

Correlation Analysis of Carotid Plaque in Young Patients With Newly Diagnosed Type 2 Diabetes and Platelet to Lymphocyte Ratio (PLR) and Neutrophil-Lymphocyte Ratio (NLR)

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Research

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Abstract

Background

PLR and NLR had been reported that they may be related to carotid atherosclerotic. The relationship between PLR, NLR and carotid atherosclerotic plaque in young patients with newly diagnosed type 2 diabetes had not been clinically reported.

Objectives

To analyzed the relationship between platelet to lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and carotid plaques in young patients with newly diagnosed type 2 diabetes.

Methods

The patients were divided into intima-media thickening (IMT)group and plaque group. The plaque group was divided into grade I, grade II and grade III groups. The counts of platelets, neutrophils, and lymphocytes were determined.

Results

The diagnostic effect of PLR and NLR was evaluated by Receiver Operating Characteristic Curve (ROC) and areas under the curve (AUC). The PLR and NLR values in observation group were higher than control group; two values in plaque group were higher than IMT group. The two values in t grade III plaque group were higher than in grade II. The two values in grade II plaque group were higher than grade I plaque group. The ROC of PLR and NLR were 0.722 and 0.653, the AUC of PLR and NLR were 111.086 and 2.240. PLR yielded a sensitivity of 0.789 and a specificity of 0.612.

Conclusion

NLR yielded a sensitivity of 0.809 and a specificity of 0.511. The PLR and NLR may be related to carotid inflammation in patients and positively correlated with carotid plaque.

1 Background

Diabetes mellitus is a group of metabolic diseases caused by multiple etiologies, which are clinically characterized by chronic pathological changes in blood vessels and nerves [1]. Diabetic patients constantly suffer from chronic inflammatory reactions [2], so they are at two to four times higher risk of developing a cerebral infarction than non-diabetic patients [3]. Previous research [4] shows that diabetes

itself is an inflammatory disease, and atherosclerosis is the pathological basis of diabetic macroangiopathy. Chronic inflammation is the main reason for its occurrence and development. The adhesion of activated neutrophils on the surface of endothelial cells can cause endothelial dysfunction in patients, and simultaneously pro-inflammatory factors can further aggravate the vascular inflammation. Therefore, long-term inflammation will cause microvascular formation and arteriosclerosis in such patients [5].

Platelet-induced inflammatory response plays an important role in the development of atherosclerosis in diabetic patients. The mitogenic substances and inflammatory mediators released by activated platelets can recruit more platelets and leukocytes to the inflammatory site, which leads to the occurrence of atherosclerosis [6].

The values of PLR and NLR are easily obtainable, repeatable, and widely used as markers of inflammation. These two are quick and simple parameters for assessing the state of inflammation and are closely related to the severity of atherosclerosis [7]. Some recent studies have shown that NLR can predict carotid artery stenosis and stroke, which emphasizes the role of NLR as an immunosensor during the process of atherosclerosis. This marker is a powerful predictor of the presence and number of carotid atherosclerotic plaques [6–9].

PLR may represent the pre-thrombotic inflammation status in patients with acute ischemic stroke. The increase in PLR value is closely related to the poor prognosis and the size of cerebral infarction volume [10]. It has been reported that PLR and NLR, as new inflammation indicators, are closely related to the arterial stiffened indiabetic retinopathy and diabetic nephropathy [11, 12]. At present, there are few clinical reports on the relationship between PLR, NLR, and carotid atherosclerotic plaques in young patients with newly diagnosed type 2 diabetes.

Therefore, this study aimed to explore the relationship between carotid plaque and values of PLR and NLR in newly diagnosed young type 2 diabetic patients. The cervical vascular ultrasound was used to judge the existence of carotid atherosclerosis, a semi-quantitative method was used to determine the severity of the plaque, and at the same time, routine and related biochemical indicators of blood were determined [13].

2 Methods

2.1 Subjects

By reviewing the medical history, the clinical records of 268 young non-consecutive patients with newly diagnosed type 2 diabetes and 104 patients with normal arterial intima who were admitted to the Diabetic Medical Department of Baoji Municipal Central Hospital from March 2014 to November 2019 were retrospectively collected. All procedures in this study were approved by the ethics committee of Baoji Municipal Central Hospital.

The inclusion criteria included the following conditions: random venous blood glucose > 11.1 mmol/L or fasting blood glucose > 7.0 mmol/L, OGTT 2-hour blood glucose > 11.1 mmol/L and with diabetes symptoms, according to the standards of the “Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2017 Revision)” [14] within 48 h from admission, without dietary control or oral hypoglycemic drugs, age of onset between 18 and 45 years old, carotid ultrasound examination conducted within 48 h of admission.

The exclusion criteria included: other types of diabetes (such as gestational diabetes, type 1 diabetes and other special types of diabetes), combined with severe underlying diseases such as severe heart, liver, kidney function damages, with autoimmune diseases, thyroid and parathyroid diseases, malignant tumors, and other endocrine diseases, those receiving glucocorticoid therapy or hormone replacement therapy, patients with previous diabetes medical history, incomplete clinical data and previous medical history.

2.2 Study group

According to the test results of carotid intima-media thickness, young patients (observation group) newly diagnosed with type 2 diabetes were divided into intima-media thickening group (116 cases) and plaque group (152 cases). The semi-quantitative method [13] was used to assess the severity of plaque to divide the plaque group into grade I plaque group (62 cases), grade II plaque group (47 cases), and grade III plaque group (43 cases). One hundred four young people with normal arterial intima during the same period were selected as the control group. The data of gender, age, and carotid atherosclerosis-related risk factors (such as hypertension, hyperlipidemia, hyperhomocysteinemia, obesity, smoking, drinking, and family history) were collected. The platelet to lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) between the groups were compared.

2.3 Calculation of carotid intima-media thickness and plaque grade

According to the literature [15], the thickness of carotid intima-media is determined by the standard, which is: $IMT < 1.0$ mm is carotid ultrasound negative, $IMT \geq 1.0$ mm is carotid ultrasound positive, wherein 1.0 mm $< IMT \leq 1.2$ mm is intima-media thickening, $IMT \geq 1.3$ mm is plaque formation. The observed group was divided into intimal thickening group (116 cases) and plaque group (152 cases),

The severity of arterial plaque was assessed by the semi-quantitative method [13]. The patients in the plaque group were further divided into 62 cases of grade I plaque, 47 cases of grade II plaque, and 43 cases of grade III plaque by the standard that grade I is unilateral plaque ≤ 2.1 mm, grade II is unilateral plaque > 2.1 mm or both sides have plaque, and at least one of them is ≤ 2.1 mm, grade III is bilateral plaque > 2.1 mm. In addition, 104 healthy young people who underwent carotid B-ultrasound examination for normal carotid intima-media thickness during the same period were selected as the control group. The comparison of baseline data between the groups is shown in Table 1.

Table 1
Comparison of demographic and biochemical data between the observation and control groups

	Observation group (268)	Control group (104)	t/ χ^2	P
Sex (F/M)	176/92	65/39	0.090	0.894
Age	36.8 ±7.4	35.9 ±8.1	1.876	0.119
BMI (kg/m ²)	26.4 ±3.2	22.9 ±2.6	4.526	0.038
Hypertension (n, %)	94(35.1)	16(15.4)	5.473	0.035
Smoking (n, %)	85(31.7)	21(20.2)	4.357	0.039
Alcohol (n, %)	68(25.4)	14(13.5)	2.158	0.056
CAD (n, %)	26(9.7)	9(8.6)	2.051	0.063
WBC (10 ⁹ ·L ⁻¹)	6.28 ±1.39	5.97 ±1.26	1.536	0.621
PLT (10 ⁹ ·L ⁻¹)	269.26 ±45.19	234.11 ±38.46	1.156	0.053
NEUT (10 ⁹ ·L ⁻¹)	5.14 ±1.07	4.15 ±1.12	2.103	0.056
LYM (10 ⁹ ·L ⁻¹)	1.16 ±0.43	1.56 ±0.34	1.934	0.061
TC (mmol·L ⁻¹)	4.30 ±1.05	4.08 ±1.14	1.413	0.097
TG (mmol·L ⁻¹)	1.76 ±0.68	1.45 ±0.72	0.685	0.538
HDL-C (mmol·L ⁻¹)	1.38 ±0.49	1.29 ±0.43	0.822	0.415
LDL-C (mmol·L ⁻¹)	3.16 ±0.67	2.13 ±0.48	3.802	0.031
FBG (mmol·L ⁻¹)	7.83 ±1.42	4.56 ±0.75	24.37	0.000
HCY (μmol·L ⁻¹)	18.21 ±11.53	14.13 ±9.18	1.293	0.059
NLR	3.31 ±0.79	1.79 ±0.48	10.162	0.021
PLR	152.13 ±51.69	72.30 ±31.59	15.286	0.009

2.4 Diagnostic criteria for related risk factors

2.4.1 Diagnostic criteria for hypertension

According to the standards of the Chinese Guidelines for the Prevention and Treatment of Hypertension (2010 Revision) [16], without taking blood pressure-lowering drugs, by continuous monitoring of arterial blood pressure twice, that is, the arterial systolic blood pressure 140 mmHg and/or the arterial diastolic

blood pressure 90 mmHg, was diagnosed as hypertension. In the case of previously diagnosed hypertension, the relevant drugs to control blood pressure were continued to be used.

2.4.2 Diagnostic criteria for dyslipidemia

According to the Guidelines for the Prevention and Control of Dyslipidemia in Chinese Adults (2007) [17], it was important that one of the following conditions was satisfied: Total cholesterol (TC) ≥ 220 mmol/L; TG ≥ 2.6 mmol/L; HDL-C ≤ 1.04 mmol/L; LDL-C ≥ 4.14 mmol/L, can be diagnosed as dyslipidemia.

2.4.3 Diagnostic criteria for hyperhomocysteinemia

Hyperhomocysteinemia can be diagnosed on the basis of the following criteria: blood homocysteine > 15.0 mmol/L; homocysteine-lowering drugs were being used; or doctor-diagnosed hyperhomocysteinemia [18].

2.4.4 Smoking

Previous or current regular smoking and smoking > 10 cigarettes/d time > 1 year or smoking cessation < 10 years [19]

2.4.5 Drinking

Average alcohol consumption every day, average alcohol intake > 50 g/day [20]

2.4.6 Obesity

The formula of Body Mass Index (BMI) is the weight (kg) divided by the square of height (m) ($BMI = \text{kg}/\text{m}^2$), when the $BMI \geq 27.5 \text{ kg}/\text{m}^2$, it is classified as obesity [21].

2.5 Statistical processing

SPSS 20.0 software was used for statistical analysis. Measurement data were expressed as mean \pm standard deviation ($\bar{x} \pm s$). An independent Student's *t*-test or Chi-square test was used for comparing the differences between the two groups. One-way ANOVA was used for comparing the differences among three or more than three groups, following LSD method as a post-hoc test. Variables were put into univariate analysis using logistic regression. Pearson's and Spearman's correlations were determined for normally distributed data and non-normally distributed data, respectively. The receiver operating characteristic curve (ROC) was used to evaluate the diagnostic values of PLR and NLR. $P < 0.05$ was considered as a statistical significance.

3 Results

3.1 Logistic regression analysis of related factors of carotid intima-media thickening in the observation group

Firstly, we analyzed the risk factor of type 2 diabetes using t-test (Table 1), and the factors that showed statistical significance were added into the following logistic regression analysis. The results showed that diabetes, hypertension, hyperlipidemia, smoking, obesity, PLR values, and NLR values were all related to the incidence of carotid atherosclerosis (Table 2).

Table 2
Logistic regression analysis of the risk factors of carotid atherosclerosis

Related factors	OR	95%CI	P
FBG(mmol·L ⁻¹)	2.641	1.230~5.514	0.014
Hypertension (n)	3.487	1.612~7.783	0.009
LDL-C (mmol·L ⁻¹)	3.541	1.132~4.896	0.038
Smoking (n)	2.593	1.469~4.487	0.026
BMI (kg/m ²)	4.731	1.897~5.269	0.041
PLR	1.021	1.003~1.053	0.023
NLR	2.349	1.034~5.357	0.039

3.2 Comparison of PLR and NLR values of patients at admission between the intima-media thickening group and plaque group

Independent student's *t*-test was used to compare if there is a statistically significant difference between intima-media thickening group and plaque group. Results showed that the levels of PLR and NLR in the plaque group were higher than those in the intima-media thickening group ($t = 7.189, 5.387, P = 0.024, 0.037$). The differences were statistically significant ($P < 0.05$) and are summarized in Table 3.

Table 3
Comparison of the PLR and NLR level between the observation groups at admission

Groups	PLR	NLR
Intima-media Thickening group (116)	103.28 ± 35.46	2.11 ± 0.57
Plaque group (152)	153.19 ± 32.58	3.09 ± 0.62
<i>F</i>	7.189	5.387
<i>P</i>	0.024	0.037

3.3 Correlation analysis of PLR and NLR values of patients with different plaque grades

One-way ANOVA was used to analyze the difference among three plaque subgroups. Results showed that the PLR and NLR values of patients in grade III plaque group were higher than those in grade II plaque group ($P=0.030, 0.033$) and grade I plaque group ($P=0.021, 0.027$). The levels of PLR and NLR in patients with grade II plaque were higher than those in grade I plaque ($P=0.036, 0.041$), as shown in Table 4. With the increase in the plaque grade, the values of PLR and NLR also increased. Therefore, there was a positive correlation between PLR and NLR values and plaque grade ($r=0.687, P=0.012$) (Fig. 1).

Table 4
Correlation analysis of PLR and NLR in patients with different plaque grades

Plaque grades	PLR	NLR
grade I (62)	136.34 ± 43.72 ^{a, b}	2.41 ± 0.71 ^{d, e}
grade II (47)	149.57 ± 39.58 ^c	2.98 ± 0.83 ^f
grade III (43)	168.28 ± 41.30	3.81 ± 0.59

Note: a: Comparison of PLR values between grade I plaque group and grade II plaque group, $P=0.036$. b: Comparison of PLR values between grade I plaque group and grade III plaque group, $P=0.021$. c: Comparison of PLR values between grade II plaque group and grade III plaque group, $P=0.030$

3.4 Analysis of the ROC curve

The area under the PLR curve is 0.722 (95% CI 0.663–0.790), the cutoff value is 111.086; the sensitivity and specificity are 0.789 and 0.612, respectively. On the other hand, the area under the NLR curve is 0.653 (95% CI: 0.586–0.723), the cutoff value 2.240, the sensitivity and specificity are 0.809 and 0.511, respectively (Table 5 and Fig. 2).

Table 5
The diagnostic value of PLR and NLR in young people with newly diagnosed type 2 diabetes mellitus and carotid atherosclerosis

Index	Area under curve	Sensitivity	Specificity	Truncation value	95% CI	P
PLR	0.722	0.789	0.612	111.086	0.663~0.790	0.017
NLR	0.653	0.809	0.511	2.240	0.586~0.722	0.009

4 Discussion

With the increasing complexity of the modern life style, the work pressure in young people is increasing. The trend of diabetes mellitus in youth is gradually emerging due to the disruption of sleep and circadian rhythms [22]. Especially in youth, the fluctuating hyperglycemia can increase the risk of carotid

atherosclerosis and other complications compared to persistent hyperglycemia [23, 24]. The incidence of diabetes combined with carotid atherosclerosis is growing fast. Chronic inflammation plays a decisive role in the development of diabetic vasculopathy [25]. An earlier study had shown that diabetes itself is an inflammatory disease [2], and the occurrence and development of carotid atherosclerosis are also closely related to the vascular inflammatory reactions.

The increased incidence of type 2 diabetes mellitus in youth is closely related to the gene factors and environmental factors, such as the family history of diabetes, unhealthy diet, overweight, excessive fat intake, low frequency of physical activity, long sit-in time, alcohol intake, etc. [26]. Some studies have pointed out that hyperlipidemia in pre-diabetic patients is an important risk factor after the thickening of carotid artery intima-media [27]. Among young people, IMT thickening is associated with systolic blood pressure [28], while smoking also exacerbates atherosclerosis. Therefore, the overall risk of stroke and ischemic stroke has significantly increased [29]. A study found that the majority of young type 2 diabetes mellitus patients were obese [30], and the increased IMT in young adults was associated with obesity [31]. Type 2 diabetes mellitus in youth becomes quickly aggressive after onset, as the rate of functional impairment in the islet B cells is swift. Therefore, the risk of comorbidities and death is higher [32]. The reported foreign studies indicated that the incidence of carotid plaque in type 2 diabetes mellitus is 64.3% [33]. The result of this study showed that the risk factors for carotid atherosclerosis in young patients with newly diagnosed type 2 diabetes were mainly hypertension, hyperlipidemia, smoking, and obesity. These outcomes were consistent with the results of previous studies.

Some studies have shown that the basic pathophysiological changes in carotid atherosclerosis plaque (CAP) caused by diabetes are arterial vascular injury and following an inflammatory response [34]. Diabetes mellitus is recognized as an important harmful factor in the formation of CAP [35]. Therefore, the detection of the body's inflammatory response is of considerable significance to judge the development and prognosis of atherosclerosis [36, 37].

PLR is considered to be a new biomarker that reflects the degree of systemic inflammation [38–41]. A high platelet count and low lymphocyte count or high PLR value may contribute to the progression of atherosclerosis and could be associated with adverse events of ischemic prognosis of cardiovascular and cerebrovascular diseases, which reflects the high risk of plaque shedding [10, 42, 43]. NLR is a risk factor for atherosclerotic plaque formation and arterial stenosis [44, 45]. Studies have reported that NLR is associated with blood glucose regulation, insulin resistance (IR), diabetes with acute myocardial infarction, diabetic retinopathy (DR), and diabetic nephropathy (DN) [46, 47].

The results of this study showed that the PLR value and NLR value of newly diagnosed type 2 diabetes young patients were significantly higher than those in normal youth. A series of inflammatory responses caused by hyperglycemia leads to abnormalities of vascular endothelium and blood vessels, thereby mediating the abnormal functional metabolism of the smooth muscle cells [2, 35]. The inflammatory factors will then result in significantly elevating of PLR and NLR values. Abnormal immune function can easily lead to the formation of vascular plaque, while unstable plaque can lead to cerebral infarction [47].

Logistic regression showed that PLR and NLR values were significantly related to the onset of arterial plaque in newly diagnosed type 2 diabetes patients. The possible mechanisms are as follows. When oxidative stress and inflammation occur, the release of corticosteroids and catecholamines in the plasma increases and leads to bone marrow suppression. The lymphocyte apoptosis can be observed during plaque formation, rupture, and thrombosis [48]. Under the action of atherosclerosis risk factors, granular proteins released by neutrophils cause endothelial dysfunction. The released proteases can also aggravate endothelial erosion and induce the monocyte accumulation to the atherosclerotic lesions. This event can stimulate macrophage maturation and foam cell formation, and promote the atherosclerotic plaque formation [49]. The rapid increase in the number of platelets can change the blood flow rate, promote the synthesis of C-reactive protein and fibrinogen. It can also facilitate the endothelial cells and lymphocytes to produce more inflammatory substances, which in turn can enhance the inflammatory response and the progress of atheromatous plaques [50]. This shows that the PLR and NLR values can be used as novel inflammation indicators to assess the severity of plaque. They can clinically assist the early and rapid screening of patients with high-risk carotid atherosclerosis to make timely and effective treatment strategies.

In this study, ultrasound Doppler was used to evaluate the thickness of IMT. The results showed that the PLR and NLR values of patients in grade III plaque group were higher than those in grade II plaque group and in the grade I plaque group. The level of PLR and NLR in the patients of the plaque group II was higher than that in the grade I plaque group. With the increase of plaque grade, PLR and NLR values of patients also increased due to the aggravation of chronic inflammation. Along with the increased release of inflammatory mediators, the platelets were activated. Various enzymes, receptors, and cytokines prompt further platelet activation [5], which would cause platelets in the blood to rise quickly [51]. On the contrary, some studies have shown that lymphocytes are usually reduced during the pathogenesis of inflammatory reactions, which is a relatively common manifestation of the body's stress response, normally accompanied by increased corticosteroids [44], which may be related to the role of lymphocytes in protecting plaque stability [52]. Through direct contact and the secretion of soluble mediators, platelets and lymphocytes interact and form intercellular aggregates. At the same time, platelets can also promote the recruitment of lymphocytes in the injured blood vessel wall [6]. An increase in platelet count reflects a potential inflammatory response. Some inflammatory mediators stimulate megakaryocyte proliferation to cause the associated increase in platelets. In addition, high platelet count indicates a high tendency to form platelet-rich thrombocytes on atherosclerotic plaques. However, lymphocytes represent the inactive state of the inflammation control process [53]. The decrease in the total number and a relative number of circulating lymphocytes during an ischemic event may be related to that the physiological stress that leads to the increase in cortisol and catecholamine levels, causing the lymphocyte redistribution [54].

The results of this study suggest that the PLR value and NLR value are related to the plaque grade, indicating that the change in these values may reflect the severity of carotid plaque. In clinical work, the PLR and NLR values can be used as effective indicators to measure the severity of carotid artery and inflammatory response. It provides evidence for assessing the condition and guiding treatment modality.

At the same time, it is of far-reaching significance to conduct personalized out-of-hospital antiplatelet and anti-arteriosclerotic drugs therapy based on different PLR values and NLR values.

However, this study has certain limitations. Firstly, due to time, funding, personnel, and other constraints, this study did not follow up on the selected young patients with newly diagnosed type 2 diabetes, making it hard to understand the dynamic evolution between the CAP and PLR, NLR values. Therefore, it could not fully evaluate the relationship between PLR and NLR values and carotid atherosclerosis in young people. Secondly, the blood routine test has more variability in different periods, and it is arbitrary to make a judgment based on the result of only one blood draw. It may be necessary to test the results multiple times and calculate the average value, which may increase the reliability of the results. Lastly, the number of cases included in this study is relatively small.

5 Conclusion

The PLR and NLR may be related to carotid inflammation in patients and positively correlated with carotid plaque. However, the relationship and exact mechanism between PLR, NLR values and intracranial atherosclerosis in young patients with newly diagnosed type 2 diabetes are not yet clear. Large-scale basic and clinical studies are still needed to draw a reliable conclusion.

Declarations

Ethics approval and consent to participate

The study procedure conformed to the ethical guidelines of the Declaration of Helsinki, and the approval for the study was obtained from the Medical Ethics Committee of Baoji Municipal Central Hospital. A written informed consent was obtained from patients enrolled.

Consent for publication

A written informed consent was obtained from patients to publish this paper.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WHJ conducted statistical analysis and drafted the manuscript. YH conceived the research, participated in the research design and coordination, and provided suggestions on the writing of the manuscript. All authors read and approved the final manuscript.

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Figures

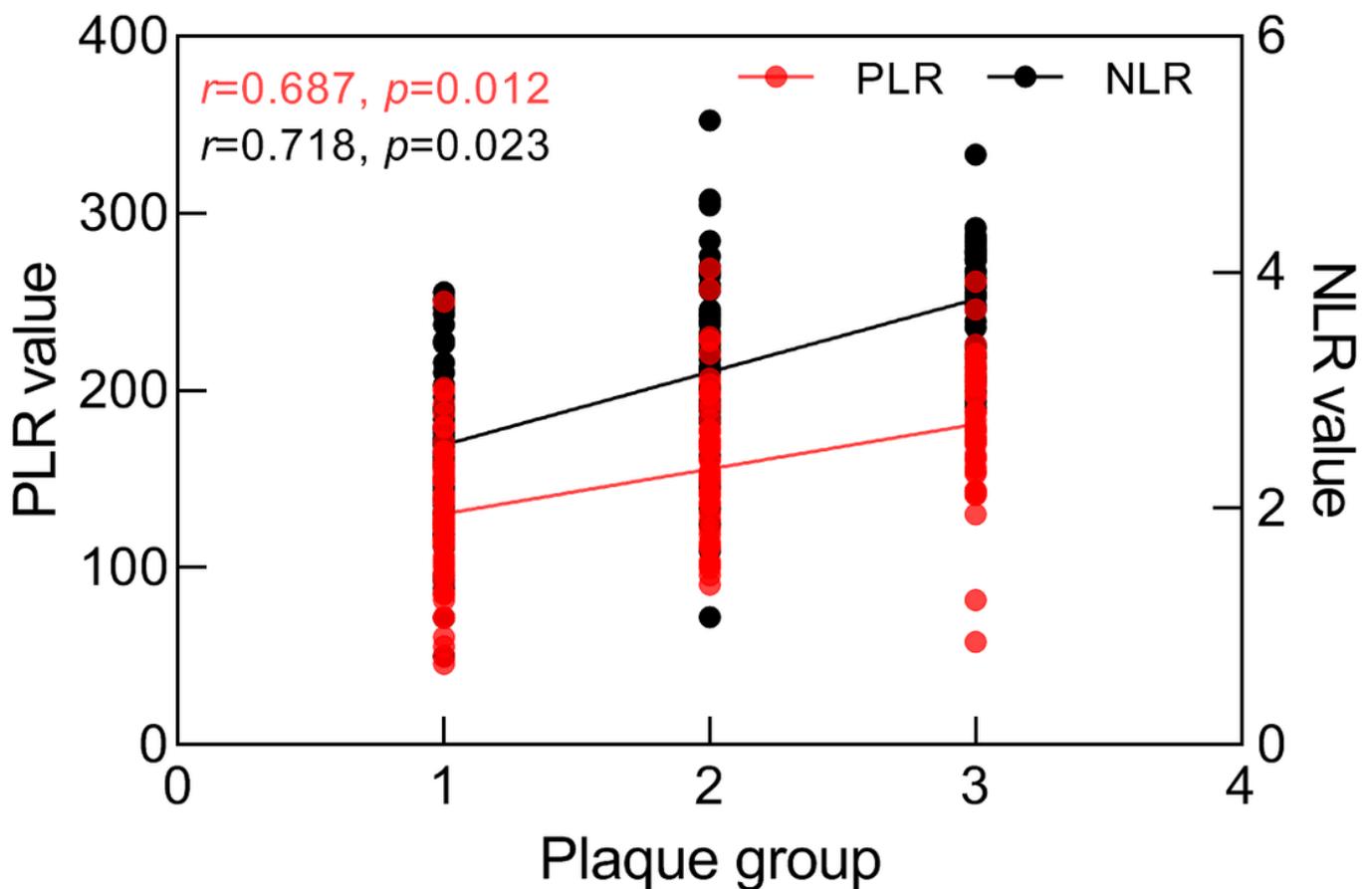


Figure 1

A positive correlation between PLR and NLR values and plaque grade ($r = 0.687$, $P = 0.012$)

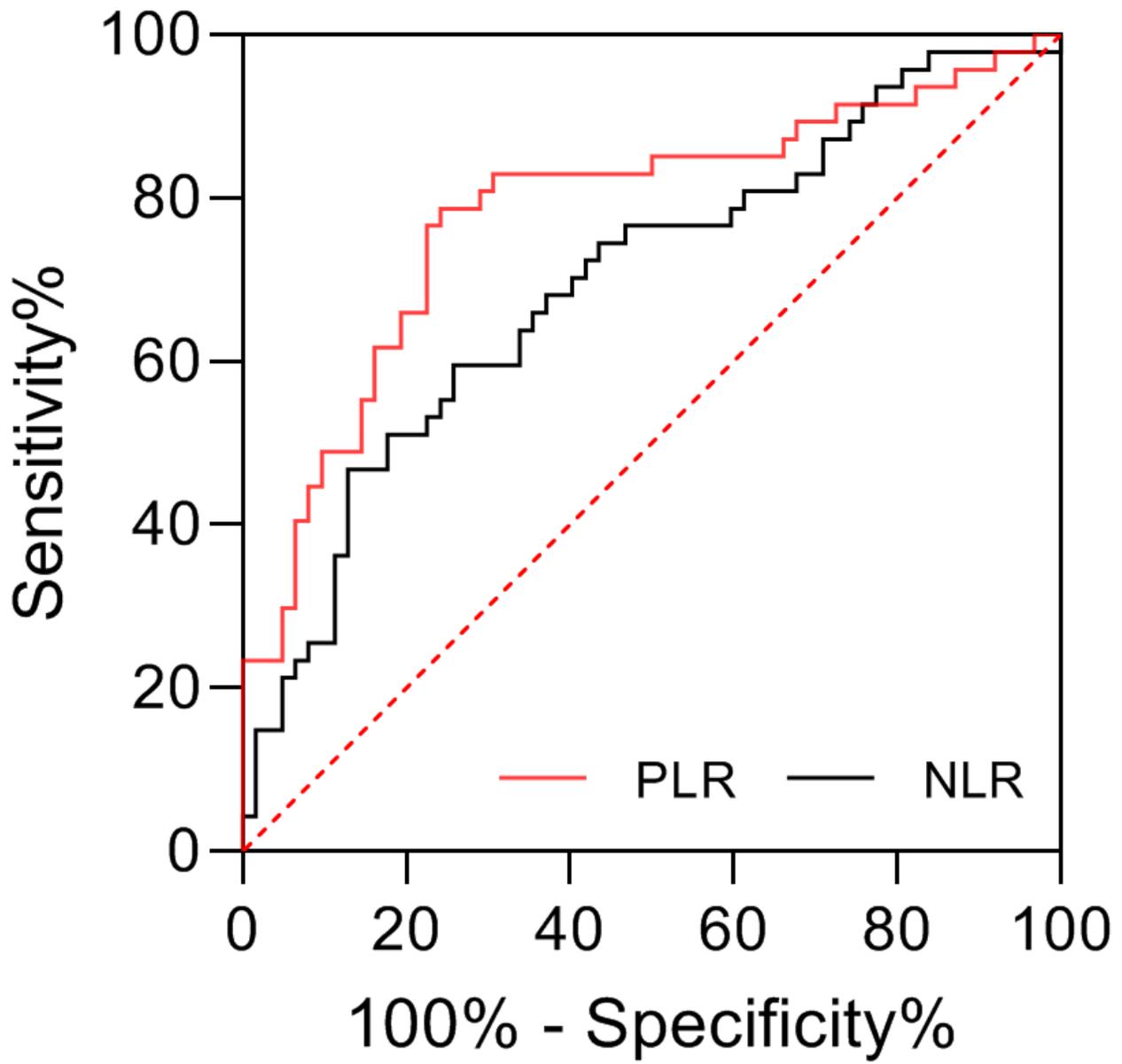


Figure 2

ROC curve