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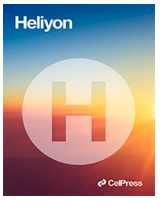

Research article

# Neutrophil-to-HDL-C Ratio as an inflammatory biomarker in patients with anxiety and obstructive coronary artery disease: A retrospective study

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ABSTRACT

*Background:* Anxiety is a common comorbidity with coronary artery disease (CAD). The neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-high-density lipoprotein cholesterol (HDL-C) ratio (NHR), lymphocyte-to-HDL-C ratio (LHR), and monocytes-to-lymphocyte ratio (MLR) can predict the severity of CAD. This retrospective study aimed to explore the relationship between NLR, NHR, LHR, and MLR and the presence of obstructive or severe CAD (OCAD, SCAD) in patients with comorbid anxiety and chest pain.

*Methods:* A total of 1063 patients with anxiety and chest pain were divided into an NOCAD group and OCAD group according to computed topography angiography (CCTA). The 455 patients in the OCAD group were further divided into the NSCAD group (n = 216) and SCAD group (n = 239) according to coronary angiography (CAG) results, and the Gensini score (GS) was calculated. Demographic and laboratory data were collected.

*Results:* Multiple regression analysis showed that higher NLR, NHR, and LHR served as independent risk factors for OCAD in patients with anxiety and chest pain (OR 1.37, 95%CI: 1.13–1.65, $p = 0.001$; OR 2.24, 95%CI: 1.89–2.65, $p < 0.001$; OR 2.47, 95%CI: 1.87–3.62, $p < 0.001$), and both were significantly associated with SCAD (OR 1.93, 95%CI: 1.44–2.59, $p < 0.001$; OR 4.45, 95%CI: 3.28–6.31, $p < 0.001$; OR 2.86, 95%CI: 1.93–4.25, $p < 0.001$). Area under the receiver operating characteristic curve analysis showed that NHR had the highest predictive value for OCAD and SCAD compared with NLR and LHR (AUC 0.71, sensitivity 57.14 %, specificity 68.20 %; AUC 0.86, sensitivity 83.68 %, specificity 74.54 %, respectively). When NHR and GS were combined, the predictive value for SCAD further increased compared to other parameters (AUC 0.94, sensitivity 92.05 %, specificity 87.05 %).

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*Conclusion:* NLR, NHR, and LHR were associated with severity of coronary stenosis in patients with comorbid anxiety and chest pain. Among these systemic inflammatory markers, NHR served as a more effective independent predictor of OCAD and SCAD in these patients.

## 1. Introduction

With changes in lifestyle and the acceleration of life's rhythm, the incidence rates of coronary heart disease (CAD) and anxiety are increasing worldwide [1]. Patients with CAD often have comorbid anxiety, which is a risk factor for CAD development and poor prognosis [2,3]. Anxiety can induce systemic inflammation [4], thus affecting blood vessel function, which may eventually lead to the onset of CAD [5]. Neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-high-density lipoprotein cholesterol (HDL-C) ratio (NHR), monocyte-to-lymphocyte ratio (MLR), and lymphocyte-to-HDL-C ratio (LHR) are systemic inflammatory markers that could be promptly and inexpensively analyzed during routine blood examination. These markers can effectively predict the occurrence and development of tumors, cardiovascular diseases, psychiatric disorders, and surgery treatment outcomes [6–9]. These markers offer the advantages of being non-invasive, inexpensive, and convenient compared to traditional CAD examination methods like coronary angiography (CAG) and computed topography angiography (CCTA) [10]. In patients with chest pain with controlled low-density lipoprotein cholesterol (LDL-C), NHR and LHR correlate with the degree of coronary artery stenosis [11]. MLR has been proven useful in predicting heart rupture in acute myocardial infarction [12]. NLR has also been shown to be associated with anxiety. However, in patients with comorbid chest pain and anxiety, it is not clear whether these systemic inflammatory markers correlate with the severity of obstructive CAD (OCAD). In this study, we examined whether NLR, NHR, MLR, or LHR can predict OCAD and severe CAD (SCAD) in patients with comorbid anxiety and chest pain.

## 2. Materials and methods

### 2.1. Study population

This study retrospectively analyzed hospital records of patients with anxiety who were admitted to the Second Affiliated Hospital of Dalian Medical University for treatment of chest pain from August 1, 2017 to October 31, 2022. The inclusion criteria were as follows: age $\geq$18 years old, clinical diagnosis of anxiety state, and had undergone CCTA examination. The exclusion criteria were as follows: pregnancy, tumors, severe hepatic or renal dysfunction, history of autoimmune diseases, rheumatic heart disease, blood disorders, current acute or chronic infection, and not receiving a CAG examination when the degree of coronary stenosis was $\geq$50 % based on CCTA results. A total of 1063 patients were enrolled in the present study. This study was approved by the hospital ethics committee (approval #: 2022-159). As this is a retrospective study, informed consent was waived by the ethics committee.

### 2.2. CCTA, CAG, OCAD, and SCAD

All enrolled patients received CCTA examination. According to CCTA results, patients with $<$50 % of stenosis of the left main trunk (LM), left anterior descending branch (LAD), left circumflex branch (LCX), or right coronary artery (RCA) were defined as the non-OCAD (NOCAD) group. The remaining patients were allocated to the OCAD group, and all patients underwent CAG.

According to CAG results, patients with LM stenosis greater than 50 % or patients with stenosis greater than 75 % in any other coronary arteries were allocated to the SCAD group; otherwise patients were included in the non-SCAD (NSCAD) group. The results of CCTA and CAG were independently assessed by two doctors and, in case of disagreement, determined by consensus.

### 2.3. Gensini score

As a supplement to measuring the degree of coronary stenosis, the Gensini score (GS) of OCAD patients was calculated based on CAG results. The GS was calculated according to the segment and degree of stenosis: 1 for 1%–25 % stenosis, 2 for 26%–50 %, 4 for 51%–75 %, 8 for 76%–90 %, 16 for 91%–99 %, and 32 for complete occlusion. The score was then multiplied by the following coefficient according to the segment of the lesion: main left coronary artery $\times$ 5; proximal LAD and proximal left circumflex artery (LCX) $\times$ 2.5; mid-segment of LAD $\times$ 1.5; distal segment of LAD, distal segment of LCX, right coronary artery, D1 diagonal branch and posterior descending branch $\times$ 1; and D2 diagonal branch and other small branches $\times$ 0.5. The final score was the sum of the scores for all lesions [13].

### 2.4. Laboratory examinations

Patient blood was collected for laboratory examinations after a 10–12 h overnight fast. The following markers were analyzed in the blood serum: lymphocytes, monocytes, neutrophils, total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, albumin (ALB), alanine transaminase (ALT), aspartate aminotransferase (AST), uric acid (UA) apolipoprotein AI (APOAI), and apolipoprotein B (APOB). NLR, NHR, MLR, and LHR were calculated as follows: neutrophil count ( $\times 10^9$/L)/lymphocyte count ( $\times 10^9$/L), neutrophil count ( $\times 10^9$/L)/HDL-C (mmol/L), monocyte count ( $\times 10^9$/L)/lymphocyte count ( $\times 10^9$/L), and lymphocyte count ( $\times 10^9$/L)/HDL-C (mmol/L),

respectively.

### 2.5. Statistical analysis

All statistical analyses were performed using the SPSS V.29.0 software. Categorical variables are presented as frequencies and percentages, and continuous variables are presented as median with 25$^{th}$ and 75$^{th}$ percentiles or mean with standard deviation. The Chi-squared test was used for categorical variables, whereas the Student's *t*-test and Mann-Whitney *U* test were used for continuous variables. Spearman's and Pearson's correlation analyses were used to measure the correlation between GS and NLR, NHR, MLR, and LHR, depending on the distribution of the variables. Logistic regression analysis was used to assess the association between NLR, NHR, and LHR and OCAD and SCAD, respectively. Multivariate logistic regression analysis was used to adjust for age, diabetes, smoking, hypertension, family history, and UA. Subgroup analyses were then performed based on sex, age (young age <55 years old), smoking, and family history. Area under the receiver operating characteristic (ROC) curve analysis was performed to evaluate the abilities of various parameters to predict OCAD and SCAD. The DeLong test (MedCalc) was used to evaluate differences between parameters on the ROC curves. All *p*-values were two-sided, and $p < 0.05$ was considered significant.

## 3. Results

### 3.1. Baseline characteristics of the participants

We enrolled a total of 1063 patients, including 608 subjects with NOCAD and 455 individuals with OCAD. In the OCAD group, there were 216 patients with NSCAD and 239 individuals with SCAD (Fig. 1). Compared to patients with NOCAD, those with OCAD were more often male, were smoking, had a family history of CAD, were older, and had a higher body mass index (BMI). Subjects with OCAD had a higher proportion of comorbidity with diabetes and hypertension, and had higher serum levels of ALT, LDH, APOB, LDL-C, and UA, but lower APOAI levels (Table 1). Older age, higher BMI, and presence of hypertension, smoking, and family history of CAD were more prevalent among patients with SCAD than those with NSCAD. In addition, individuals with SCAD had the highest neutrophil count and lowest HDL-C levels, while those with NOCAD had the lowest neutrophil count and highest HDL-C levels. Although the lymphocyte count was higher in patients with OCAD than in NOCAD patients, no statistical difference was observed between patients with SCAD and NSCAD. Finally, patients with OCAD had higher NLR, NHR, MLR, and LHR than NOCAD patients (Fig. 1A and C), and those with SCAD had higher appeal indicators than NSCAD patients (Fig. 1B and C) (Table 2, Supplementary Table 1).

### 3.2. The correlation between NLR, NHR, MLR, and LHR and GS

To explore the correlation between NLR, NHR, MLR and LHR and the severity of stenosis, Spearman's correlation analysis was conducted. As shown in Fig. 2, only LHR ($r = 0.202$ $p < 0.001$) (Fig. 2B)and NHR ($r = 0.255$, $p < 0.001$) (Fig. 2C) significantly correlated with GS (NLR ($r = 0.038$, $p = 0.42$) (Fig. 2A)and MLR ($r = 0.070$, $p = 0.135$) (Fig. 2D)were not significant.

### 3.3. Associations between NLR, NHR, MLR, and LHR and the presence of OCAD and SCAD in patients with chest pain and anxiety

To further investigate the relationship between NLR, NHR, MLR, and LHR and the presence of OCAD and SCAD in patients with chest pain and anxiety, we performed a logistic regression analysis, which showed that higher NLR, NHR, and LHR were risk factors for

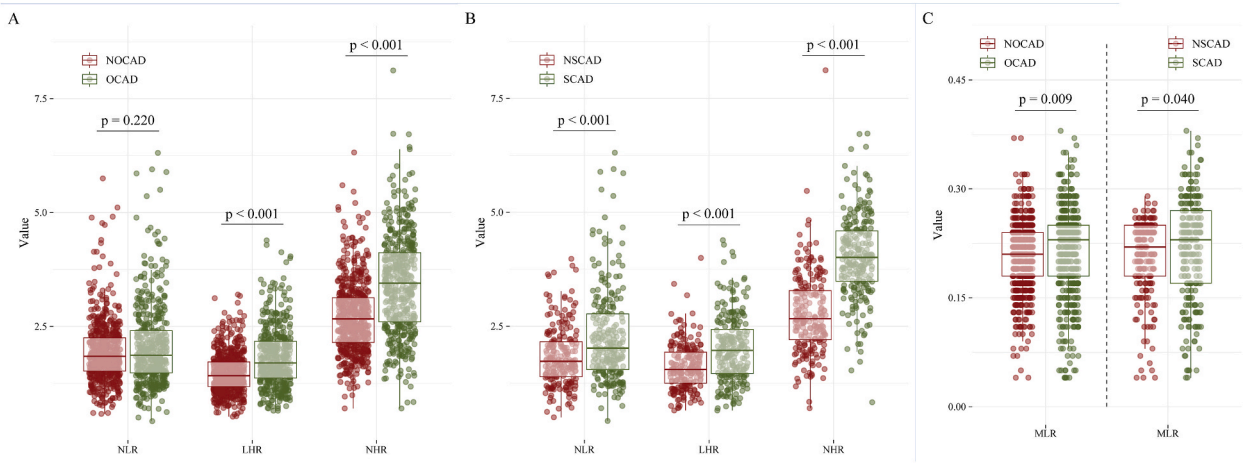


**Fig. 1.** Box plots showing the distribution of patients with OCAD and NOCAD (A) and patients with SCAD and NSCAD (B) related to LHR, NHR, NLR and MLR(C). (LHR, lymphocyte-to-HDL-C ratio; NHR, neutrophil-to-HDL-C ratio; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-HDL-C).

**Table 1**
Baseline characteristics of the study population.

| | All n = 1063 | NOCAD n = 608 | OCAD n = 455 | *p*-value |
|---|---|---|---|---|
| Male | 529(49.76) | 300(49.34) | 299(65.71) | 0.047 |
| Age, years | 55(47–62) | 51(43–61) | 57(50–64) | <0.001 |
| Hypertension | 283(26.62) | 126(20.72) | 157(34.51) | <0.001 |
| Diabetes | 196(18.44) | 120(19.74) | 76(16.70) | 0.029 |
| Smoking | 318(29.92) | 181(29.77) | 137(30.11) | 0.054 |
| Family history | 449(46.94) | 202(33.22) | 247(54.29) | <0.001 |
| BMI, kg/m2 | 22.12(3.28) | 21.70(3.25) | 22.67(3.24) | <0.001 |
| ALT, U/L | 26.22(8.23) | 25.10(6.69) | 27.71(9.72) | <0.001 |
| AST, U/L | 29.58(6.13) | 29.82(5.10) | 29.25(7.23) | 0.156 |
| LDH, U/L | 181.86(21.77) | 177.26(20.83) | 188.00(21.51) | <0.001 |
| ApoAI, g/L | 1.53(0.38) | 1.59(0.42) | 1.46(0.31) | <0.001 |
| ApoB, g/L | 0.78(0.66–0.89) | 0.72(0.62–0.82) | 0.83(0.73–0.94) | <0.001 |
| TC, mmol/L | 3.07(0.71) | 3.08(0.73) | 3.06(0.69) | 0.672 |
| TG, mmol/L | 1.26(0.45) | 1.25(0.42) | 1.29(0.49) | 0.160 |
| LDL-C, mmol/L | 2.58(0.49) | 2.43(0.30) | 2.79(0.60) | <0.001 |
| HDL-C, mmol/L | 1.22(0.24) | 1.29(0.23) | 1.12(0.22) | <0.001 |
| UA, μmol/L | 357.57(30.56) | 346.12(27.72) | 372.87(27.35) | <0.001 |
| Neutrophils, $\times 10^9$/L | 3.53(3.06–4.02) | 3.40(2.94–3.84) | 3.74(3.23–4.33) | <0.001 |
| Lymphocytes, $\times 10^9$/L | 1.85(1.56–2.20) | 1.83(1.57–2.12) | 1.95(1.55–2.35) | 0.001 |
| Monocytes, $\times 10^9$/L | 0.38(0.32–0.44) | 0.38(0.33–0.42) | 0.40 (0.13) | <0.001 |

Data are presented as median (with 25th and 75th percentiles) or mean (standard deviation) for continuous variables and as number (percentage) for categorical variables.

**Table 2**
Comparison NLR, NHR, MLR, and LHR in all enrolled patients.

| | All n = 1063 | NOCAD n = 608 | OCAD n = 455 | *p*-value |
|---|---|---|---|---|
| NLR | 1.85(1.50–2.33) | 1.85(1.52–2.25) | 1.87(1.48–2.41) | 0.22 |
| NHR | 2.89(2.32–3.64) | 2.67(2.15–3.13) | 3.43(1.09) | <0.001 |
| LHR | 1.52(1.23–1.93) | 1.42(1.18–1.73) | 1.70(1.37–2.18) | <0.001 |
| MLR | 0.22(0.18–0.25) | 0.22(0.18–0.24) | 0.23(0.18–0.25) | 0.009 |
| | All n = 455 | NSCAD n = 216 | SCAD n = 239 | P value |
| NLR | 1.87(1.48–2.41) | 1.73(1.39–2.16) | 2.02(1.55–2.77) | <0.001 |
| NHR | 3.43(1.09) | 2.67(2.20–3.29) | 4.03(0.91) | <0.001 |
| LHR | 1.70(1.37–2.18) | 1.55(1.25–1.93) | 1.97(1.45–2.45) | <0.001 |
| MLR | 0.23(0.18–0.25) | 0.22(0.18–0.25) | 0.23(0.18–0.28) | 0.04 |

Data are presented as median (with 25th and 75th percentiles) or mean (standard deviation).

OCAD and SCAD. After adjusting for age, smoking, family history, hypertension, diabetes, and UA, elevated NLR, NHR and LHR remained as independent risk factors for OCAD [1.37 (95%CI:1.13–1.65, $p = 0.01$); 2.24 (95%CI:1.89–2.65, $p < 0.001$); and 2.47 (95% CI:1.87–3.62, $p < 0.001$), respectively]. After adjustments, NLR, NHR, and LHR remained significantly associated with the presence of SCAD. GS was also an independent risk factor for SCAD [1.93 (95%CI:1.44–2.59, $p < 0.001$) vs 4.59 (95%CI:3.28–6.31, $p < 0.001$) vs 2.86 (95%CI:1.93–4.25, $p < 0.001$)] (Table 3). In addition, subgroup analysis revealed that family history affected the ability of NLR to predict OCAD, and gender affected the ability of NHR to predict SCAD (Supplementary Tables 2–4).

### *3.4. The ability of NLR, NHR, LHR, and GS to predict OCAD and SCAD in patients with chest pain and anxiety*

The ROC analysis showed that NHR had the highest predictive value for OCAD, while MLR displayed the smallest predictive value (NHR vs MLR, $z = 6.503$, $p < 0.001$). In addition, NHR had the highest sensitivity (57.14 %) in predicting OCAD, and NLR had the highest specificity (91.45 %) in predicting OCAD (Fig. 3A). Moreover, in patients experiencing anxiety and chest pain with OCAD, GS demonstrated the highest predictive value for SCAD. However, NHR still had the highest predictive value for SCAD among NLR, NHR, LHR, and MLR, with MLR exhibiting the smallest predictive value for SCAD. Notably, both NLR and LHR had comparable predictive values for SCAD, which were both smaller than that of NHR (GS vs NHR, $z = 7.954$, $p < 0.001$; LHR vs NLR, $z = 0.984$, $p = 0.325$; NLR vs MLR, $z = 2.349$, $p = 0.019$). Application of the combined NHR and GS resulted in the largest AUC in prediction analysis for SCAD (GS + NHR vs NHR, $z = 5.923$, $p < 0.001$; GS + NHR vs GS, $z = 4.099$, $p$=<0.001) compared to other parameters (Fig. 3B) (Table 4, Supplementary Table 5).

## 4. Discussion

CAD is a major healthcare problem and cause of death worldwide. Comorbidity of CAD and anxiety is common, and CAD patients

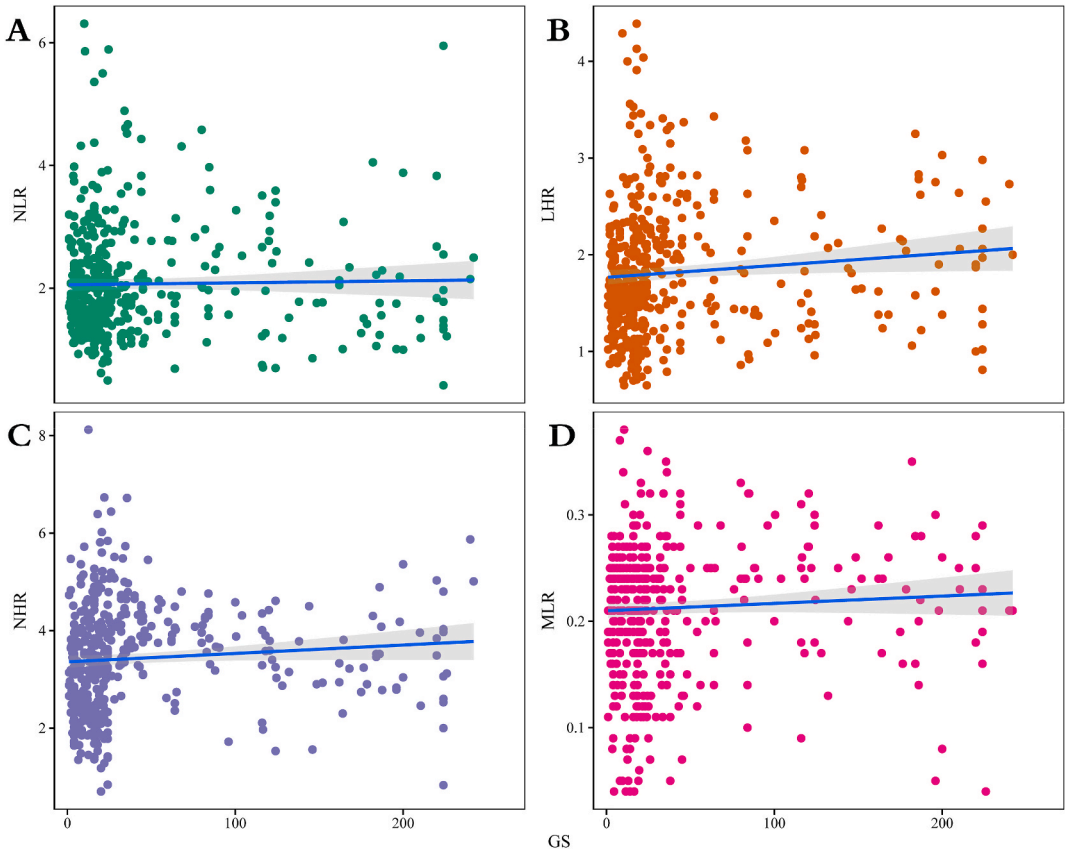


**Fig. 2.** Relationship between different parameters and GS. (A) Relationship between GS and NLR. (B) Relationship between GS and LHR. (C) Relationship between GS and NHR. (D) Relationship between GS and MLR.

**Table 3**
Logistic regression analysis of the relationship between different parameters and the occurrence of OCAD and SCAD.

| | OCAD | | SCAD | |
|---|---|---|---|---|
| | OR (95%CI) | *p*-value | OR (95%CI) | *p*-value |
| Univariate analysis | | | | |
| NLR | 1.25 (1.07–1.46) | 0.006 | 1.88 (1.47–2.41) | <0.001 |
| NHR | 2.31 (1.99–2.69) | <0.001 | 5.11 (3.77–6.95) | <0.001 |
| LHR | 3.13 (2.44–4.02) | <0.001 | 2.93 (2.09–4.11) | <0.001 |
| MLR | 4.80 (0.84–6.71) | 0.17 | 4.98 (0.72–7.34) | 0.12 |
| GS | – | – | 1.06 (3.04-1.07) | <0.001 |
| Multivariate analysis | | | | |
| NLR | 1.37 (1.13–1.65) | 0.01 | 1.93 (1.44–2.59) | <0.001 |
| NHR | 2.24 (1.89–2.65) | <0.001 | 4.55 (3.28–6.31) | <0.001 |
| LHR | 2.47 (1.87–3.62) | <0.001 | 2.86 (1.93–4.25) | <0.001 |
| GS | – | – | 1.02 (1.04–1.07) | <0.001 |

Adjusted for age, smoking, family history, hypertension, diabetes, and UA.

with anxiety are 2–3 times more likely to experience an adverse cardiovascular event than those without anxiety. Previous studies indicated that mental stress, such as anxiety and depression, is an independent risk factor for CAD development. Furthermore, mental stress may induce systemic inflammatory responses, which is a known trigger of CAD.

In response to inflammation, neutrophils mainly secrete pro-inflammatory mediators. Patients with CAD exhibit elevated levels of interleukin IL-6, IL-8, IL-1β, and other inflammatory factors released by neutrophils. Similarly, patients with anxiety also have higher serum concentrations of IL-6, IL-8, and IL-1β, and these inflammatory factors may increase the risk of CAD onset or promote the development of CAD. Therefore, comorbidity of anxiety and CAD can stimulate a feed-forward loop of chronic systemic inflammation.

In this study on leukocyte and HDL-C levels, neutrophil counts were higher in patients with anxiety and OCAD compared to those with NOCAD and were further elevated in individuals with SCAD. Lymphocyte counts were also higher in patients with OCAD than in

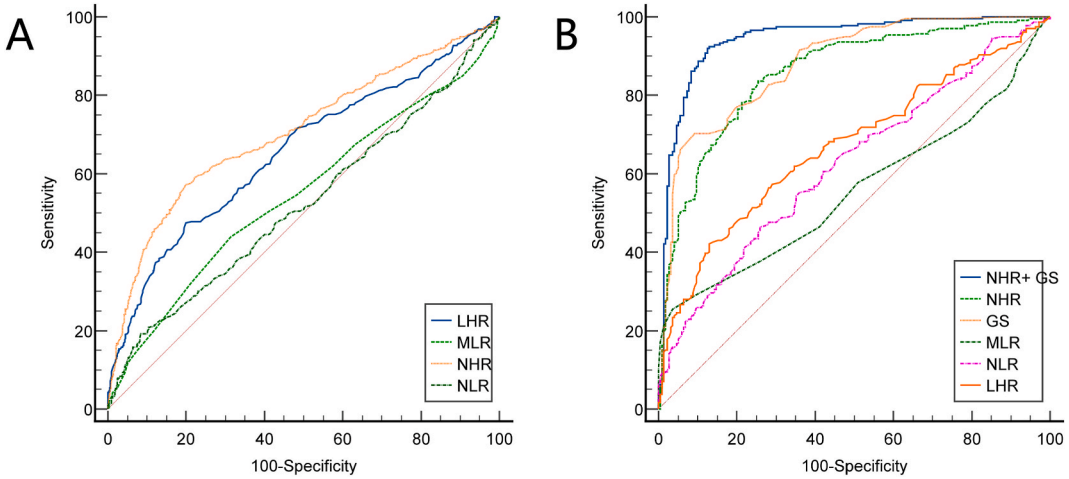


**Fig. 3.** Receiver operating characteristic curve (ROC) analysis of NLR, NHR, MLR and LHR in predicting OCAD (A) and NLR, NHR, MLR LHR and GS in predicting SCAD (B) in patients with anxiety and chest pain.

**Table 4**
Predictive performance of different parameters for OCAD and SCAD among patients with comorbid anxiety and chest pain.

| Group and Parameters | AUC | Cutoff Value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| OCAD | | | | | | |
| NLR | 0.52 | 2.72 | 19.34 | 91.45 | 62.90 | 60.20 |
| NHR | 0.71 | 3.24 | 57.14 | 68.20 | 71.40 | 71.50 |
| LHR | 0.66 | 1.79 | 47.47 | 79.93 | 63.90 | 67.00 |
| MLR | 0.55 | 0.23 | 43.96 | 68.59 | 51.20 | 62.10 |
| SCAD | | | | | | |
| NLR | 0.63 | 2.212 | 46.44 | 74.07 | 66.50 | 55.60 |
| NHR | 0.86 | 3.26 | 83.68 | 74.54 | 79.00 | 76.50 |
| LHR | 0.67 | 2.10 | 42.26 | 87.04 | 78.30 | 57.70 |
| MLR | 0.56 | 0.26 | 25.52 | 96.30 | 88.40 | 53.90 |
| GS | 0.88 | 23.00 | 70.29 | 90.74 | 89.40 | 73.40 |
| NHR + GS | 0.94 | 0.48 | 92.05 | 87.05 | 89.10 | 90.90 |

those with NOCAD; however, they were not different between patients with SCAD and NSCAD. We observed that lymphocyte counts exhibited a milder difference in range than neutrophil counts in all study groups. As a typical lipid-related biomarker, HDL-C plays a protective role in atherosclerosis and inflammation. In this study, the highest concentration of HDL-C was observed in the serum of NOCAD patients, while those with SCAD had lower HDL-C levels than those with OCAD.

Regarding markers of systemic inflammation, the highest indices of NLR, NHR, MLR, and LHR were observed in patients with SCAD, while patients with NOCAD demonstrated the lowest values of these ratios. In OCAD and anxiety states, the body is in a highly chronic inflammatory state; research has confirmed the correlation between inflammation, cardiovascular diseases, and mood disorders. Regarding NLR, neutrophils, as the initiating cells of inflammation, can regulate the activity of lymphocytes and monocytes [14]. Neutrophils are activated or egressed by inflammatory factors, while monocytes can mediate tissue damage and expand the inflammatory response by releasing proteolytic enzymes [12]. Lymphocytes represent the body's immune regulatory response [15,16]. In an inflammatory activated state, cortisol levels in the blood increase, which may lead to a decrease in lymphocyte levels [17]. Therefore, an increase in NLR and MLR can effectively reflect the increase in chronic inflammation caused by CAD and anxiety in the body. For NHR and LHR, the pathological process of CAD is influenced by inflammatory metabolism and lipid metabolism. Opting for NHR allows for a more comprehensive reflection of the inflammatory status and lipid metabolism [8]. In states of elevated inflammation, higher counts of neutrophils and monocytes can lead to a decrease in HDL [18]. Conversely, HDL can also regulate the activation of neutrophils and monocytes [19]. A high NHR in a patient indicates the presence of high neutrophil count or low HDL-C concentration, or both. Therefore, using NHR as a marker to connect inflammation and abnormal lipid metabolism may be more effective than relying on a single-source marker [20]. Collectively, these data suggest that as key markers of systemic inflammation, NLR, NHR, MLR, and LHR can rapidly and cost-effectively reflect the status of both inflammatory responses and lipid metabolism in the body.

We observed a significant but weak correlation between LHR and NHR with the GS score in SCAD patients. We speculate that this mild correlation may stem from variations in the scoring proportions assigned to each vessel with different degrees of stenosis in the GS scoring system. While the GS score effectively evaluates the severity of coronary artery stenosis, the degree of chronic inflammation in the body may not be necessarily linked to the specific coronary branch affected, but rather to the overall severity of coronary artery

stenosis. Consequently, the correlation coefficient is lower, which is consistent with the results of similar studies [8,11]. Additionally, the presence of anxiety in our study may introduce interference, potentially contributing to the observed low correlation. However, the results of regression analysis results indicate that NLR, NHR, and LHR serve as independent risk factors for both OCAD and SCAD in patients experiencing anxiety and chest pain. This is likely due to the relatively minor differences in lymphocyte counts among study groups. Only NHR displayed a strong ability to predict SCAD, suggesting that the underlying mechanism of OCAD and SCAD in patients with anxiety may not be primarily related to lymphocytes, but is rather mediated by HDL-C levels and neutrophils. This is further supported by the fact that both HDL-C levels and neutrophils can change the endothelial function of coronary arteries. Therefore, this study provides a rationale for clinical use of NLR, NHR, and LHR in screening for OCAD and SCAD in patients with comorbid anxiety and chest pain, whereas NHR demonstrates the highest performance among these markers. In clinical scenarios where obtaining detailed CAG results is challenging, the combined use of GS score and NHR for screening SCAD patients demonstrates improved performance compared to using each alone.

CAD is an underlying reason for presentation of chest pain, but CAD could also be a somatic symptom of anxiety. Therefore, it would be of great clinical significance to screen patients with OCAD and SCAD in order to adjust clinical treatment strategies. Biomarkers such as NLR, NHR, and LHR can be used in daily clinical practice as an inexpensive and rapidly available tool to more accurately screen for suspected OCAD in cohorts of patients with anxiety accompanied by chest pain. After such screening, only high-risk patients would be recommended to undergo additional CCTA or expensive and invasive CAG examinations, thereby reducing the healthcare costs and medical risks associated with radiation exposure and catheter insertion for many patients.

This study has several limitations. First, it was a single center retrospective study with inherent selection bias. Second, the sample size of this study was rather small. Our results require further validation using multicenter, prospective, and larger cohort studies. Third, in addition to NLR, NHR, MLR, and LHR, other blood biomarkers may also have strong predictive value and will be investigated in our future studies. Finally, due to the retrospective nature of this study, we did not have access to information on anxiety levels of the study participants. Therefore, we will further explore the relationship between anxiety level and related inflammatory indicators in future prospective studies.

## 5. Conclusion

NHR has the highest predictive potential to detect OCAD and SCAD compared to NLR, MLR, and LHR in patients with comorbid anxiety and chest pain. NHR is also an effective independent predictor of OCAD and SCAD in these patients. Therefore, these markers, and NHR in particular, can be used to screen for OCAD and SCAD in patients with comorbid anxiety and chest pain before resorting to costly CCTA and invasive CAG tests. Further research is warranted to explore the relationship between these markers and the degree of anxiety in such patients, as well as the ability of these markers to evaluate the efficacy of treatments for anxiety and CAD.

## Ethics approval

Ethics Committee of the Second Hospital of Dalian Medical University approved the study protocol (approval number: 2022-159). As this is a retrospective study, informed consent was waived by the ethics committee.

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None.

## Data availability

The datasets generated and analyzed in the present study are available from the corresponding author upon reasonable request.

## CRediT authorship contribution statement

**Aodan Zhang:** Writing – original draft, Visualization, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Weihang Sun:** Writing – original draft, Visualization, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lingjun Mei:** Writing – original draft, Visualization, Data curation. **Miaomiao Bai:** Methodology, Investigation, Data curation. **Wenyu Shi:** Supervision, Project administration, Methodology, Investigation. **Chuang Sun:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **Xiaofeng Qu:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38829.

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