Relationship of Neutrophil–Lymphocyte Ratio with coronary artery disease and plaque composition of coronary artery

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Abstract

Evidence suggests that the neutrophil-lymphocyte ratio (NLR) has been considered as useful marker for identifying individuals under risk of coronary artery disease (CAD) and associated events, a more powerful predictor than any other leukocyte subtypes. In this study, we aimed to evaluate association of NLR with CAD and plaque composition of coronary artery analyzed from coronary CT angiography (CCTA). The study population consisted of 469 patients who underwent CCTA due to stable typical or atypical chest pain. The enrolled patients were divided into two groups and three groups according to coronary artery stenosis and tertiles of NLR, respectively. The plaque burden, volume and ratio of calcified, lipid and fibrous components of plaques were measured based on CCTA images. Chi-square, Student’s test, ANOVA, Mann–Whitney U test, KruskalWallis test and multiple logistic regression were used for statistical analysis. Compared with non-CAD group, NLR was significantly higher in CAD group (P = 0.001). The non-calcified plaque volume, fibrotic plaque volume and lipid plaque volume increased with the NLR (P<0.05). Multivariate logistic regression analysis showed that NLR was an independent risk factor for CAD (OR: 1.792, 95CI 1.067–3.011, P<0.05). The present study demonstrated that NLR is associated with both the CAD and non-calcified plaque volume of coronary artery.

Introduction

Atherosclerosis remains the primary cause of coronary artery disease (CAD), the leading cause of mortality worldwide[1]. Atherosclerosis, an inflammatory process that is based on the interaction between immune mechanisms and metabolic risk factors[2]. Leukocytes has been shown to be an independent indicator for adverse cardiovascular events and all-cause mortality[3]. Neutrophil-lymphocyte ratio (NLR), calculated as the ratio of absolute neutrophil count and absolute lymphocyte count, was considered as a potential marker for identifying individuals with a risk of cardiovascular disease (CVD) and associated events[4, 5]. Lipid-enriched non-calcified plaques (NCP) are associated with increased coronary event rates and plaque volume progression; therefore, they are considered to be more prone to rupture and high risk for poor outcomes[6, 7]. Previous researches have shown that NLR is associated with the severity of coronary stenosis, NCP burden, and calcium score[8–10]. Patients with NCP had a higher risk of worse prognosis compared with those without coronary plaque or who had calcified plaques [11]. However, there is no research to explore the correlation of coronary plaque composition quantitative analysis and NLR based on coronary CT angiography (CCTA). Therefore, this study used CCTA plaque quantitative analysis software to obtain quantitative indicators of plaque components, explore the relationship of NLR with coronary artery disease and the quantitative characteristics of each plaque component based on it. The results of our study provide strong evidence for the risk assessment of patients with coronary atherosclerosis, and then guide early intervention to reduce the occurrence of major adverse cardiovascular events.

Methods

Study Design and Population
We retrospectively included consecutive patients who had CCTA due to stable typical or atypical chest pain from January 2020 to October 2020 in Shandong Provincial Hospital affiliated to Shandong First Medical University (Jinan, China). Clinical and laboratory data were collected. Exclusion criteria were: (1) Complete clinical and laboratory data are not available; (2) factors influencing total and differential leukocyte counts (infection, autoimmune disease or use of anti-inflammatory drugs); (3) Leukocytes >10×10⁹ cells/L due to concern for other factors that may affect leukocytes count; (4) Other diseases: such as heart failure, hematological disease, cancer, and severe renal or liver disease. The study protocol was approved by the hospital ethics committee (nr. 2021-302).

Baseline definitions and risk factor assessment

The recorded clinical characteristics of the patients included age, gender and risk factors for CAD (hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, alcohol consumption). Hypertension was defined as a previously established diagnosis, systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or currently receiving antihypertensive treatment. Dyslipidemia was defined as total cholesterol ≥ 200 mg/dL, low-density lipoprotein (LDL) cholesterol ≥ 130 mg/dL, high-density lipoprotein (HDL) cholesterol ≥ 30 mg/dL or currently receiving lipid modifying agents. Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or currently receiving hypoglycemic treatment (insulin, oral hypoglycemic therapy, or dietary advice). Smoking was classified as current smoking if the patient smoked or quit in the last 30 days, or not smoking if the patient never smoked or smoked in the remote past.

Biochemical and hematologic measurements

Record the biochemical and hematologic indexes of patients within 48 hours before and after CCTA. Total leukocytes count, including neutrophils and lymphocytes count analysis, was performed in the hematology laboratory of our hospital, and NLR values were calculated. The levels of fasting blood glucose (FBG), lipids including triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and uric acid, creatinine were measured using an Olympus AU5400 system. All blood samples were collected from the cubital vein at least 8 hours after fasting.

Scan protocol and image reconstruction

CCTA was performed by Siemens third generation dual source CT (SOMATOM Force CT, Germany). Before scanning, all patients (except hypotension) were given sublingual nitroglycerin to dilate coronary artery, and training breathing to reduce respiratory motion artifacts. Use of high-pressure syringe (Ulrich Medical Co., Ltd. Germany), 30.0-55.0 ml of iohexol (containing 350 mg / ml iodine, Beijing Beilu Pharmaceutical Co., Ltd. China) and 30.0-55.0 ml of 0.90% sodium chloride were injected at a flow rate of 3.5-5.5 ml/s. The CT attenuation was monitored by selecting the region of interest in the aortic root with contrast tracer method. When the CT attenuation reached 100 Hu, the scan was automatically triggered 5s later. The scanning range was from 1cm above the aortic arch to 1cm below the diaphragmatic
surface of the heart. The scanning parameters are set as follows: collimator 192 × 6 mm, layer thickness 0.75 mm, rotation time 0.25 s, tube voltage ranges from 70 ~ 120 kV according to weight. Prospective ECG gated spiral scanning mode was used according to the heart rate and respiratory control. 0.75 mm slice thickness and BV40 convolution kernel, the best diastolic and systolic data were automatically reconstructed, and the position of the reconstruction window is adjusted to minimize the artifacts. All data are transmitted to the post-processing workstation for image analysis.

**Coronary plaque quantitative analysis**

Image quality was assessed by Likert scale, signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) [12]. The quality assessment of all images was completed by 2 experienced radiologists.

Coronary atherosclerotic plaque was defined as tissue structures >1 mm² that existed either within or adjacent to the coronary artery lumen and that could be discriminated from surrounding pericardial tissue, epicardial fat, and the vessel lumen itself [13]. Importing CCTA images to the workstation (Syngo.via Siemens Force, Germany) and apply semi-automated plaque quantification software (Coronary Plaque Analysis 5.0.0 syngo. via FRONTIER™ Siemens Force® Germany). Specific CT thresholds of each plaque component: calcified plaque was defined as CT value more than 350Hu; lipid plaque CT values ranged from −30 to 130 Hu; fibrous plaque CT values ranged from 130 to 350 Hu. Both ends of the plaque were manually identified, and the software automatically identified the lumen centerline, intraluminal contours, and extravascular contours. Manual correction is required if the automatically annotated vessel centerline do not correspond to the actual vessel or inaccurate intravascular contours. The software automatically calculated the quantitative parameters of each component of plaque (Fig.1).

Quantitative indicators of plaque components include total plaque volume (TPV), total plaque burden (TPB), calcified plaque volume (CPV), calcified plaque ratio (CPR), non-calcified plaque volume (NCPV), non-calcified plaque ratio (NCPR), fibrous plaque volume (FPV), fibrous plaque ratio (FPR), lipid plaque volume (LPV), lipid plaque ratio (LPR). The proportion of plaque components was defined as the percentage of plaque volume of different components in total plaque volume (plaque volume of different components / total plaque volume × 100%).

Inter-and intra-class correlation coefficients (ICCs) were calculated to estimate the inter-observer reliability and intra-observer reproducibility of plaque measurement. 20 cases of CCTA images were randomly chosen; region-of-interest segmentation was drawn by one radiology resident (Reader 1) and one radiologist (Reader 2) independently. Reader 1 then repeated the contouring procedure 8 weeks after the initial analysis to assess the agreement of plaque measurement. The remaining image segmentation was performed by Reader 1.

**Statistical analysis**

SPSS 26.0 was used for data analysis, a value of less than 0.05 was deemed statistically significant. The distribution of the different variables was examined for normality by the Kolmogotov-Smirnov test.
Categorical variables were expressed in percentages and continuous variables in mean (SD) or geometric mean (95% confidence interval). Between-group differences with respect to categorical variables were assessed using a Chi-square test. Between-group differences with respect to continuous variables of normal distribution were assessed using Student’s test, one-way ANOVA, and continuous variables of non-normal distribution were assessed using Mann–Whitney U test or Kruskal–Wallis test. Inter-and intra-observer variability were analyzed with ICCs. Multivariate logistic regression analysis was used to calculate the odds ratios (ORs) and 95% confidence intervals (CI) of incident CAD for each investigated indicator tertiles compared with the lowest tertiles, with adjustment for some confounding factors. All methods mentioned were carried out in accordance with relevant guidelines and regulations.

Results

The study population consisted of 469 patients undergoing CCTA (average age: 62.81±9.28 years; 59.9% male). They were divided into coronary heart disease (CAD) group and non-coronary heart disease (non-CAD) group based on whether the coronary artery stenosis was more than 50%. The overall prevalence of CAD was 38.8%. Baseline clinical and laboratory data of the 2 groups are shown in the Table 1. The proportion of male, drinking and smoking in CAD group were higher than those in non-CAD group(70.3 vs 53.3%, 37.4 vs 25.1%, 29.1 vs 19.2%, P<0.05), and the proportion of participants with hypertension was higher(62.6 vs 52.3%, P<0.05). In addition, there were significant differences in total cholesterol (TC), high density lipoprotein (HDL), creatinine and uric acid between non-CAD group and CAD group (P<0.05). In the CAD group, the inflammatory biomarkers such as leukocytes, neutrophil, C-reactive protein (CRP) and NLR increased, whereas lymphocyte count decreased. However, only the CRP, neutrophil count and NLR reached significant difference (P < 0.05) (Fig.2).

Table 1 Baseline clinical and laboratory characteristics of the study patients stratified by the CAD
### Clinical characteristics

|                      | Non-CAD (n=287) | CAD (n=182) | P        |
|----------------------|-----------------|-------------|----------|
| Male, n (%)          | 153(53.3%)      | 128(70.3%)  | <0.001   |
| Age, y               | 62.68±9.28      | 63.03±9.29  | 0.685    |
| Currently drinking, n (%) | 72(25.1%)      | 68(37.4%)   | 0.005    |
| Currently smoking, n (%) | 55(19.2%)      | 53(29.1%)   | 0.013    |
| Diabetes mellitus, n (%) | 66(23%)        | 41(22.5%)   | 0.906    |
| Hypertension, n (%)  | 150(52.3%)      | 114(62.6%)  | 0.027    |
| Dyslipidemia, n (%)  | 10(3.5%)        | 13(7.1%)    | 0.074    |
| Systolic BP, mm Hg   | 135(125,150)    | 139(126,150) | 0.276    |
| Diastolic BP, mm Hg  | 81(75,90)       | 82(74.75,90) | 0.797    |

### Biochemical parameters

|                      | Non-CAD (mmol/L) | CAD (mmol/L) | P        |
|----------------------|------------------|--------------|----------|
| Triglyceride         | 1.14(0.87,1.70)  | 1.20(0.91,1.69) | 0.481    |
| Total cholesterol    | 4.81±1.17        | 4.51±1.12    | 0.005    |
| HDL cholesterol      | 1.33(1.13,1.58)  | 1.21(1.00,1.46) | <0.001   |
| LDL cholesterol      | 2.85(2.25,3.42)  | 2.72(2.10,3.27) | 0.087    |
| VLDL cholesterol     | 0.93(0.71,1.21)  | 0.90(0.70,1.14) | 0.182    |
| Fasting glucose      | 5.42(4.90,6.34)  | 5.38(4.93,6.23) | 0.688    |

### Hematologic parameter

|                      | Non-CAD (umol/L) | CAD (umol/L) | P        |
|----------------------|------------------|--------------|----------|
| Creatinine           | 61(51.9,71.4)    | 67.8(58.78.55) | <0.001   |
| Uric acid            | 320.36±89.41     | 341.11±90.05 | 0.015    |
| CRP                  | 1.11(0.65,1.83)  | 1.17(0.68,2.91) | 0.037    |
| Leukocytes           | 5.76(4.88,6.84)  | 6.04(5.06,7.12) | 0.061    |
| Neutrophils          | 3.29(2.62,4.04)  | 3.61(2.86,4.47) | 0.005    |
| Lymphocytes          | 1.83(1.45,2.19)  | 1.72(1.40,2.14) | 0.220    |
| NLR                  | 1.71(1.31,2.35)  | 1.96(1.59,2.69) | 0.001    |

CAD: coronary artery disease, HDL: high density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, CRP: C-reactive protein
To investigate the correlation of the NLR with CAD and plaque composition of coronary artery, the enrolled patients were divided into 3 groups according to NLR tertiles. The NLR were 1.26(1.07,1.40), 1.84(1.70,2.04) and 2.87(2.49,3.81) in groups I (lowest), II, and III (highest), respectively. As shown in Table 2, the percentage of male gradually increased from 50% in tertile 1 to 66% in tertile 3 (P=0.008), and the proportion of participants with hypertension gradually increased from 44.9% in tertile 1 to 64.1% in tertile 3 (P=0.002). The triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) significantly decreased with raising of NLR. Furthermore, creatinine significantly elevated with increasing NLR (P < 0.05).

Quantitative indicators of plaque were shown having a good inter- and intra-observer agreement, with ICCs > 0.75 for all (Table 3). The results of quantitative analysis of coronary atherosclerotic plaque are shown in Table 4. With the increase of NLR, the NCPV showed an upward trend (Fig. 3). Patients with higher NLR had larger FPV and LPV (P < 0.05 for all).

Table 2 Baseline clinical and laboratory characteristics of the study patients according to the NLR tertiles
|                  | T1(lowest)       | T2(n=157)       | T3(highest)     | P      |
|------------------|------------------|-----------------|-----------------|--------|
| **Clinical characteristics** |                  |                 |                 |        |
| Male, n (%)      | 78(50%)          | 100(63.7%)      | 103(66%)        | 0.008  |
| Age, y           | 61.59±8.70       | 64.35±9.49      | 62.49±9.48      | 0.027  |
| Currently drinking, n (%) | 43(27.6%)       | 53(33.8%)       | 44(28.2%)       | 0.420  |
| Currently smoking, n (%) | 42(26.9%)      | 35(22.3%)       | 31(19.9%)       | 0.323  |
| CAD, n (%)       | 44(28.2%)        | 69(43.9%)       | 69(44.2%)       | 0.004  |
| Diabetes mellitus, n (%) | 36(23.1%)       | 30(19.1%)       | 41(26.3%)       | 0.317  |
| Hypertension, n (%) | 70(44.9%)       | 94(59.9%)       | 100(64.1%)      | 0.002  |
| Dyslipidemia, n (%) | 9(5.8%)         | 9(5.7%)         | 5(3.2%)         | 0.485  |
| Systolic BP, mm Hg | 134(124,146)    | 138(125,149)    | 137.5(127,156.75) | 0.037  |
| Diastolic BP, mm Hg | 80(74,89)       | 82(73.5,90)     | 82.5(76,92)     | 0.155  |
| **Biochemical parameters** |                  |                 |                 |        |
| Triglyceride, (mmol/L) | 1.25(0.93,1.81) | 1.24(0.92,1.70) | 1.11(0.81,1.51) | 0.012  |
| Total cholesterol, (mmol/L) | 4.78(4.16,5.64) | 4.76(3.83,5.47) | 4.34(3.56,5.26) | 0.001  |
| HDL cholesterol, (mmol/L) | 1.36(1.13,1.59) | 1.24(1.07,1.46) | 1.28(1.05,1.55) | 0.073  |
| LDL cholesterol, (mmol/L) | 2.95(2.42,3.47) | 2.87(2.23,3.40) | 2.52(1.91,3.24) | 0.001  |
| VLDL cholesterol, (mmol/L) | 1.00(0.81,1.23) | 0.92(0.71,1.22) | 0.86(0.62,1.07) | <0.001 |
| Fasting glucose, (mmol/L) | 5.23(4.87,5.96) | 5.47(4.90,6.31) | 5.46(4.97,6.46) | 0.349  |
| **Hematologic parameter** |                  |                 |                 |        |
| Creatinine, (umol/L) | 61(52.53,70.75) | 65.2(53.95,77.70) | 66.3(54.40,75.35) | 0.025  |
| Uric acid, (umol/L) | 326.96±80.96     | 336.28±97.97    | 321.94±90.60    | 0.361  |
| CRP, mg/L         | 1.05(0.63,1.77)  | 1.11(0.58,2.28) | 1.17(0.68,2.72) | 0.135  |
| Leukocytes (× 10^9/L) | 5.45(4.54,6.58) | 5.81(4.97,6.83) | 6.34(5.51,7.37) | <0.001 |
| Neutrophils (× 10^9/L) | 2.64(2.17,3.23) | 3.35(2.84,3.92) | 4.21(3.61,5.44) | <0.001 |
Lymphocytes (× 10^9/L) 2.19(1.79,2.59) 1.83(1.50,2.12) 1.42(1.13,1.67) <0.001

NLR 1.26(1.07,1.40) 1.84(1.70,2.04) 2.87(2.49,3.81) <0.001

CAD: coronary artery disease, HDL: high density lipoprotein, LDL: low-density lipoprotein, VLDL: very low-density lipoprotein, CRP: C-reactive protein

Table 3 Inter-and intra-class correlation coefficients (ICCs) of quantitative indicators of plaque

|        | ICC⁹ (95%CI) | ICC⁹ (95%CI) |
|--------|-------------|-------------|
| TPV    | 0.978 (0.896-0.993) | 0.975 (0.919-0.991) |
| TPB    | 0.939 (0.840-0.976) | 0.946 (0.871-0.978) |
| CPV    | 0.976 (0.905-0.992) | 0.974 (0.917-0.991) |
| CPR    | 0.970 (0.926-0.988) | 0.979 (0.947-0.991) |
| NCPV   | 0.979 (0.907-0.993) | 0.977 (0.927-0.992) |
| NCPR   | 0.970 (0.926-0.988) | 0.979 (0.947-0.991) |
| LPV    | 0.954 (0.878-0.982) | 0.920 (0.811-0.967) |
| LPR    | 0.943 (0.865-0.977) | 0.902 (0.770-0.960) |
| FPV    | 0.979 (0.912-0.993) | 0.977 (0.925-0.992) |
| FPR    | 0.965 (0.915-0.986) | 0.966 (0.916-0.986) |

a: Inter-class correlation coefficients b: Intra-class correlation coefficients

TPV: total plaque volume, TPB: total plaque burden, CPV: calcified plaque volume, CPR: calcified plaque ratio, NCPV: non-calcified plaque volume, NCPR: non-calcified plaque ratio, LPV: lipid plaque volume, LPR: lipid plaque ratio, FPV: fibrotic plaque volume, FPR: fibrotic plaque ratio.

Table 4 Plaque component characteristics of the study patients according to the NLR tertiles
To determine independent predictors of the incidence of CAD, multivariate logistic regression analysis was performed, and results showed in table 5. Patients with higher NLR, leukocytes, neutrophils, and CRP significantly increased the incidence of CAD (P < 0.05 for all). After adjusting for age and sex, leukocyte count was no longer independent predictor of CAD (model 1). whereas the associations between NLR, neutrophils, CRP, and incident CAD had no change, and continued to maintain even after further adjustments were made for drinking, smoking, diabetes, hypertension, and dyslipidemia (model 2). However, in the model 3 after further adjustment for other confounding factors such as TG, TC, fasting blood glucose (FBG), HDL, LDL, VLDL, creatinine and uric acid, only NLR was the independent predictors of the incidence of CAD. In the final model, the subjects with the highest tertiles of NLR had a 1.792-fold increased incidence of CAD (P<0.05).

Table 5. Associations of inflammatory markers and risk of CAD incidence
| Tertile | T1(lowest) | T2 | T3(highest) | P for trend |
|---------|------------|----|-------------|-------------|
| **NLR** |            |    |             |             |
| Range   | ≤1.59      | 1.59-2.18 | ≥2.18       |             |
| No adjusted | 1.000      | 1.996(1.247-3.193) | 2.019(1.261-3.232) | 0.004      |
| Model 1 | 1.000      | 1.806(1.116-2.924) | 1.824(1.130-2.946) | 0.016      |
| Model 2 | 1.000      | 1.782(1.088-2.920) | 1.871(1.138-3.077) | 0.016      |
| Model 3 | 1.000      | 1.692(1.018-2.813) | 1.792(1.067-3.011) | 0.031      |
| **Leukocytes** |    |    |             |             |
| Range   | ≤5.24      | 5.24-6.54 | ≥6.54       |             |
| No adjusted | 1.000      | 1.344(0.846-2.135) | 1.633(1.031-2.587) | 0.037      |
| Model 1 | 1.000      | 1.342(0.832-2.164) | 1.557(0.970-2.500) | 0.068      |
| Model 2 | 1.000      | 1.294(0.797-2.101) | 1.510(0.928-2.457) | 0.098      |
| Model 3 | 1.000      | 1.340(0.814-2.207) | 1.491(0.898-2.475) | 0.125      |
| **Neutrophils** |    |    |             |             |
| Range   | ≤2.94      | 2.94-3.85 | ≥3.85       |             |
| No adjusted | 1.000      | 1.230(0.772-1.960) | 1.828(1.155-2.892) | 0.010      |
| Model 1 | 1.000      | 1.138(0.702-1.843) | 1.680(1.049-2.690) | 0.028      |
| Model 2 | 1.000      | 1.110(0.678-1.815) | 1.678(1.029-2.734) | 0.035      |
| Model 3 | 1.000      | 1.100(0.662-1.829) | 1.573(0.950-2.604) | 0.074      |
| **Lymphocytes** |    |    |             |             |
| Range   | ≤1.52      | 1.52-2.02 | ≥2.02       |             |
| No adjusted | 1.000      | 0.800(0.509-1.257) | 0.744(0.472-1.173) | 0.202      |
| Model 1 | 1.000      | 0.883(0.554-1.408) | 0.767(0.480-1.226) | 0.268      |
| Model 2 | 1.000      | 0.892(0.553-1.437) | 0.733(0.453-1.186) | 0.206      |
| Model 3 | 1.000      | 0.935(0.568-1.537) | 0.729(0.439-1.211) | 0.225      |
| **CRP** |            |    |             |             |
| Range   | ≤0.81      | 0.81-1.71 | ≥1.71       |             |
| No adjusted | 1.000      | 0.836(0.524-1.322) | 1.717(1.089-2.708) | 0.019      |
Data are expressed as ORs (95% CI).

Model 1: adjusted for age, sex

Model 2: Model 1 adjusted further for drinking, smoking, diabetes, hypertension, and dyslipidemia

Model 3: Model 2 adjusted further for TG, TC, HDL, LDL, VLDL, creatinine and uric acid

Discussion

Cardiovascular events have been considered as the most common reason for death in Europe and America, which, especially in North American, accounts for 38% of all deaths [14]. Recently, the incidence of CAD has increased dramatically among developing countries [15]. Inflammation plays an important role in atherosclerosis leading to CAD, angina, and myocardial infarction (MI). Total leukocyte and differential counts represented cheap, widely available indicators of the inflammatory response. Horne et al. found that elevated leukocyte predicted an increased risk of death or MI in CAD patients. However, both neutrophilia and lymphopenia were more strongly associated with poor long-term outcomes compared to the leukocyte alone [16].

As a potential biomarker, NLR represents the balance between neutrophils and lymphocytes[17], and has significance for identifying patients at high cardiovascular risk. Neutrophils are found within the thrombus of coronary arteries among patients with myocardial infarction[18]. Unlike neutrophils, as a part of the adaptive immune system, lymphocytes play a critical role in suppressing inflammation. Lower lymphocyte count is associated with advanced atherosclerosis and heart failure [19]. Moreover, current studies reported that NLR correlated with the atherosclerotic risk factors, such as age, hypertension[20], diabetes[21], and hypercholesterolemia[22], which also means that NLR could be affected by those risk factors[23].

Arbel et al. demonstrated for the first time that NLR was independently associated with CAD severity in patients undergoing conventional coronary angiography[24]. Ahmet et al found that NLR is associated with both the severity and morphology of coronary atherosclerotic disease[25]. Park et al. show that a higher NLR was independently associated with arterial stiffness and coronary calcium score[9]. In patients with clinically suspected CAD without history of myocardial infarction, who were evaluated with coronary angiography and followed up for a definite time course, it was shown that higher NLR levels independently predicted mortality and future myocardial infarction risk[26, 27]. NLR has also been associated with in-hospital major adverse cardiovascular events (MACE) and long-term mortality in patients with ST-segment elevated myocardial infarction undergoing primary percutaneous coronary
intervention (PCI)[28–30]. In this study, we retrospectively collected the clinical and laboratory data of 469 consecutive patients undergoing CCTA and found that the highest NLR among CAD group. Additionally, multivariate regression analysis showed that NLR was an independent risk factor for the presence of CAD.

Non-calcified plaque, compared with calcified plaque, is more vulnerable and more frequently present in the culprit lesions of patients with ACS[11]. Hou et al. further demonstrated that patients with non-calcified plaque had a 3 times higher risk of 3-year major adverse cardiac events, in 5007 outpatients with suspected CAD[11]. Therefore, early identification non-calcified plaque of is clinically relevant. However, CCTA is not suitable for routine examination due to radiation exposure and high cost whereas NLR as an easily measured and cheaper biomarkers might provide valuable information[7]. In our study, semi-automatic plaque quantitative analysis software was used to explore the relationship between plaque components and NLR. The results showed that the non-calcified plaque volume added with the increase of NLR. The results in the present study were similar to previous studies, while our research methods are different. This is the first time to study the relationship between coronary atherosclerotic plaque and NLR based on quantitative analysis. our findings confirmed and extended previous studies. However, further studies need to validate this phenomenon.

Noticeably, this study showed that the NLR was significantly negatively correlated with the levels of TG, TC, LDL, and VLDL. Previous studies had shown that the cardiovascular drugs (especially statins) could decrease the level of TG, TC, LDL, and VLDL, while they had no effect on the NLR, which could partly explain that why NLR levels were negatively correlated with the levels of lipids profiles[7].

Limitations

Some limitations were present in our study. First, the number of enrolled was small, which could result in biased. Secondly, the cross-sectional observation study was used in the research, and the causal relationship between the NLR and CAD could not be evaluated. Thirdly, the development of plaque is a dynamic and complex process. The patients have not been followed up for a long time, it is difficult to evaluate the development and outcome. Therefore, in future studies, we need to conduct long-term follow-up of the study population to explore the relationship between the final cardiovascular events and NLR, plaque characteristics.

Conclusions

In summary, NLR is an independent marker of the presence of CAD. With the increase of NLR, the incidence of CAD and non-calcified plaque volume of coronary artery increased. As a simple and inexpensive marker that can help identifying individuals with CAD or those at risk of developing ACS. Ultimately, NLR may prove to be a novel component of an important risk stratification scoring system, which could positively impact the ability to diagnose and treat CAD.
Declarations

Authors' contributions RPW: Study concept and design, Analysis and interpretation of data, Statistical analysis, Drafting of the manuscript. HG: Study concept and design, Analysis and interpretation of data, Statistical analysis, Critical revision of the manuscript. CSJ, YG: Study concept and design, Acquisition of data, Critical revision of the manuscript. LG, SNQ: Acquisition of data, Critical revision of the manuscript. XMW: Study concept and design, Acquisition of data, Analysis and interpretation of data, Critical revision of the manuscript, Study supervision. All authors read and approved the final manuscript.

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Availability of data and material The data underlying this article will be shared on reasonable request to the corresponding author.

Code availability Not applicable

Conflict of interest All authors declare that there is no conflict of interest.

Consent to participate Written informed consent was waived because this study was retrospective.

Ethical approval The ethics committee of hospital approved this study (SWYXNO.2021-302).

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Figures
Figure 1

Plaque quantitative analysis software was used to quantitatively analyze coronary CT angiography. a: The software automatically identifies the coronary artery tree, manually identifies the diseased vessels and determines the location of the plaque. The lesion is located in the circumflex branch of the left coronary artery. b: The long axis of the diseased vessel (circumflex branch), in which blue represents lipid plaque, green represents fibrous plaque and yellow represents calcified plaque. c: The software
automatically calculates the quantitative indexes of each component of plaque, including TPV, TPB, CPV, CPR, NCPV, NCPR, FPV, FPR, LPV, LPR. d: The narrowest section of the lesion lumen. The meaning of different colors is the same as that in Figure B.

**Figure 2**

The levels of NLR and other inflammatory markers according to whether suffering from CAD (a: NLR; b: Leukocytes; c: Neutrophils; d: Lymphocyte; e: CRP)
Figure 3

Comparison non-calcified plaque volume of according to NLR group

P = 0.002