Association of lymphocyte-to-monocyte ratio with total coronary plaque burden in patients with coronary artery disease
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Background: Lymphocyte-to-monocyte ratio (LMR) is involved in all stages of coronary atherosclerosis and related to coronary artery disease (CAD). However, the correlation between LMR and the coronary plaque burden of CAD is not clearly elucidated. Therefore, this study aimed to investigate their correlation in patients with CAD.

Methods: A total of 1953 consecutive eligible inpatients with suspected CAD were retrospectively included in this study. They were assigned into CAD (n = 564) and non-CAD groups (n = 1389). All patients underwent coronary computed tomographic angiography to evaluate coronary stenosis and coronary artery calcification (CAC). Spearman’s tests were used to analyze the correlation between CAC score and LMR. Multivariate logistic regression models were set up to assess the risk factors of CAD.

Results: Patients with CAD had lower LMR value than patients without CAD (P = 0.001). LMR was negatively correlated with CAC score and was an independent risk factor of CAC score (P < 0.05). Multivariate logistic regression model showed that LMR ≤4.8 was a newly independent risk factor of CAD (all P < 0.05). Additionally, the new risk score model was compared with the Framingham model and showed that NRI was 4.9%, which proved that the new risk score model improved the prediction capability of CAD.

Conclusion: LMR ≤4.8 is a new independent risk factor of CAD. LMR value was negatively correlated with CAC score and could be used as a new marker to evaluate the coronary plaque burden of CAD.

Keywords: coronary artery calcification score, coronary artery disease, coronary computed tomographic angiography, lymphocyte-to-monocyte ratio

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Introduction
Coronary artery disease (CAD) remains the leading cause of global morbidity and mortality, despite considerable effort has been made to improve prevention, diagnosis, and prognosis of CAD over the past decades [1–3]. Coronary artery calcification (CAC) is still a pivotal step in the initiation and aggravation of CAD and is associated with poor cardiovascular outcomes [4,5]. CAC score could quantify coronary calcification and indicate coronary plaque burden [6].

Inflammation and oxidative stress play a key role in the pathogenesis of cardiovascular diseases and adverse cardiovascular events. Immune cells, cytokines, and other biomedical markers involved in inflammatory responses predict the progression/severity of the lesion and the pathological mechanism of CAD [7]. Accumulating experimental and clinical evidence supports that lymphocyte-to-monocyte ratio (LMR) plays a crucial role in chronic inflammation. LMR is involved in all stages of coronary atherosclerosis, from initial endothelial dysfunction and plaque disruption to acute atherothrombosis [8].

Several previous studies showed that LMR is related to cardiovascular disease and adverse cardiovascular events [5,9,10]. However, the correlation between LMR and the coronary plaque burden of CAD has never been fully elucidated. This study aimed to investigate the association of LMR with total coronary plaque burden in patients with CAD.

Methods
This study retrospectively included 1953 consecutive eligible inpatients with suspected CAD. The inpatients underwent coronary computed tomographic angiography at The Affiliated Hospital of Chengde Medical University from September 2015 to June 2017. They were assigned into CAD (n = 564) and non-CAD groups (n = 1389). Inclusion criteria were age ≥18 years and patients with...
suspected CAD. Major exclusion criteria were acute coronary syndrome, renal insufficiency, connective tissue disease, severe valvular heart disease, hypertrophic cardiomyopathy, and pregnancy. This study was carried out in accordance with the World Medical Association’s Code of Ethics (Helsinki Declaration) and was approved by the Institutional Review Boards of The Affiliated Hospital of Chengde Medical University. All subjects provided written informed consent.

The baseline demographic data including age, sex, height, and weight, as well as the risk factors for CAD including diabetes, hypertension, dyslipidemia, and ischemic stroke were carefully collected by the master’s degree students. Furthermore, heart rate, left atrium, left ventricle end-diastolic diameter, left ventricle ejection fraction, SBP, DBP, blood routine, and biochemistry were also recorded. LMR was then calculated by dividing the lymphocyte count by the monocyte count. Hypertension was defined as SBP ≥140mmHg (1 mmHg = 0.133 kPa) or DBP ≥90 mmHg at rest or previously diagnosed as hypertension in antihypertensive therapy [11]. Diabetes was defined as symptoms and random blood glucose ≥11.1 mmol/L, or fasting plasma glucose ≥7.0 mmol/L, or 2-h oral glucose tolerance test level ≥11.1 mmol/L, or no diabetes symptoms and at least twice blood glucose meets the above criteria [12]. Dyslipidemia was defined as serum total cholesterol ≥5.18 mmol/L, high-density lipoprotein cholesterol (HDL-C) ≤1.04 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥3.37 mmol/L, or triglyceride ≥1.7 mmol/L or previous diagnosis of dyslipidemia in medication [13].

Coronary computed tomographic angiography was performed using a 320-detector row computed tomography scanner (Aquilion ONE; Toshiba Medical Systems, Otawara, Japan). The CAD diagnostic criterion [14] was ≥50% stenosis by coronary computed tomographic angiography in the left main, left anterior descending, left circumflex, right coronary, or main branch. The non-CAD diagnostic criterion was without stenosis or stenosis ≤50% in the left main, left anterior descending, left circumflex, right coronary, or main branch lumen. The extent of coronary artery calcium was assessed by a dedicated offline workstation tool based on the Agatston method. This means that calcified lesions were counted if the lesions met the prespecified area of ≥1 mm², attenuation range of ≥130 HU, and ≥3 connected pixels by applying three-dimensional connectivity criteria. Agatston score was automatically calculated by multiplying the pixel area (mm²) of each lesion with weighted attenuation according to the maximum Hounsfield unit of 1 for 130–199 HU, 2 for 200–299 HU, 3 for 300–399 HU, and 4 for ≥400 HU [15]. All patients were assigned to four groups: 0, without CAC; 1, 0–100; 2, 101–400; and 3, ≥400 [16].

All statistical analyses were performed using Statistical Package for Social Sciences software, version 19 (SPSS Inc., Chicago, Illinois, USA). All continuous variables were skewness distributed by Shapiro–Wilk test and reported as quartile M, whereas categorical variables were expressed as percentages. Differences in patient characteristics between the CAD and non-CAD groups were tested using Mann–Whitney U test for continuous variables and chi-square test for categorical variables. Correlation analysis between variables and CAC score was performed using Spearman’s rank correlation coefficient. Multiple linear regression was conducted to evaluate independent predictors of CAC score. Receiver operating characteristic curve was used to determine the best diagnostic cutoff point for LMR. Binary logistic regression analyses were performed to examine the effect of the candidate predictors of CAD. Multivariable analyses were performed to select the independent risk factors of CAD in the risk score prediction models. The logistic coefficients were obtained from the multivariable logistic regression analysis, and were utilized to assign the risk scores. The new risk score model was compared with the Framingham model to test the prediction capability by calculating net reclassification index (NRI values). The level of significance was set at \( P<0.05 \).

**Results**

As shown in Table 1, patients with CAD were noted to have a lower LMR value than in patients without CAD \( (P=0.001) \). The ratio of male, age ≥65 years, smoking, and drinking were significantly higher in the CAD group than in the non-CAD group \( (P<0.001) \). The morbidity of hypertension, diabetes, and ischemic stroke were significantly higher in the CAD group than in the non-CAD group \( (P<0.05) \). Compared with the non-CAD group, pulse pressure, left atrium, left ventricle end-diastolic diameter, and hemoglobin were higher in the CAD group \( (P<0.05) \). Chest pain, peripheral arterial disease, aortic valve calcification, and abnormal wall motion were more common in the CAD group than in the non-CAD group \( (P<0.05) \). Triglycerides were higher in the CAD group, and HDL-C was lower in the CAD group \( (P<0.05) \). Uric acid, creatinine, and blood urea nitrogen were higher in the CAD group than in the non-CAD group \( (P<0.05) \). The median of CAC score in the CAD group was 96.7, but the non-CAD group had no CAC. However, no significant difference was found between the two groups in BMI, dyslipidemia, total cholesterol, and LDL-C.

In the receiver operating characteristic curve analysis, the area under the curve of the LMR was 0.589 [95% confidence interval (CI) 0.562–0.617, \( P<0.001 \)]. The optimal diagnostic cutoff point for LMR was 4.8, and the sensitivity and specificity were 65.5% and 46.5%, respectively. The positive and negative predictive values were 53.5% and 30.5%, respectively (Table 2).

The LMR value was gradually decreasing with increasing CAC score. The LMR value was significantly higher
in group 0 and significantly lower in group 3 (\(P<0.05\)). Furthermore, age, pulse pressure, and creatinine were increasing with increasing CAC score (all \(P<0.05\)) (Fig. 1).

In the Spearman correlation analysis, LMR was negatively correlated with CAC score, whereas age was significantly positively correlated with CAC score (both \(P<0.05\)). Pulse pressure, left atrium, uric acid, creatinine, and blood urea nitrogen were also positively correlated with CAC score (all \(P<0.05\)). Moreover, heart rate, left atrium, left ventricle end-diastolic diameter, and creatinine were negatively correlated with LMR (all \(P<0.05\)) (Table 3).

Multiple linear regression analysis for the association between factors and CAC score shows that LMR and ejection fraction were negatively correlated with CAC score, whereas age, pulse pressure, triglycerides, fasting blood glucose, hypertension, ischemic stroke, and smoking were positively related to CAC score (all \(P<0.05\)). All factors were independent determinants of CAC score (all \(P<0.05\)) (Table 4).

Multivariate logistic regression model analysis showed that LMR \(\leq 4.8\) was a new independent risk factor of CAD besides the classic risk factors including hypertension, diabetes, ischemic stroke, LDL-C, male, older age, and smoking (all \(P<0.05\)). Additionally, pulse pressure \(\geq 60\) mmHg was also proved to be an independent risk factor of CAD. Surprisingly, the risk of LMR was similar to the risk of hypertension and older age. It was higher than diabetes, increasing LDL-C, smoking, and pulse pressure \(\geq 60\) mmHg (Table 5).

The comparison of prediction capability of Framingham score with the new risk model showed that the area under the curve of the Framingham score was 0.630 (95% CI 0.603–0.656, \(P<0.001\)), the sensitivity and specificity were 73.2% and 47.4%, respectively. The area under the curve of the new risk score was 0.687 (95% CI 0.662–0.712, \(P<0.001\)), the sensitivity and specificity were 72.5% and 55.7%, respectively. The new risk score model was compared with the Framingham model and showed that NRI was 4.9%, which proved that the new risk score model improved the prediction capability of CAD (Table 6).

### Discussion

The main finding of the present study was that LMR was negatively correlated with CAC score and the LMR value was decreasing with increasing CAC score. To the best of our knowledge, among the current clinical studies, this is the first study to identify the correlation between

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**Table 1  Baseline characteristics of coronary artery disease and noncoronary artery disease groups**

| Variables                        | CAD group (n=564) | Non-CAD group (n=1389) | \(\chi^2/Z\) | \(P\) value |
|----------------------------------|-------------------|------------------------|--------------|-------------|
| Male (%)                         | 343 (60.8)        | 587 (42.3)             | 2.12         | <0.001      |
| Age \(>65\) (years)              | 177 (31.4)        | 280 (20.0)             | 1.816        | <0.001      |
| BMI (kg/m²)                      | 25.3 (23.4–27.5)  | 27.5 (25.1–27.5)       | -0.154       | 0.878       |
| Chest pain (%)                   | 282 (50.3)        | 549 (39.8)             | 1.53         | <0.001      |
| Smoking (%)                      | 245 (43.4)        | 391 (28.1)             | 1.96         | <0.001      |
| Drinking (%)                     | 125 (22.5)        | 227 (16.5)             | 1.472        | 0.002       |
| Hypertension (%)                 | 376 (66.9)        | 692 (50.1)             | 2.016        | <0.001      |
| Diabetes (%)                     | 190 (33.7)        | 376 (27.0)             | 1.374        | 0.003       |
| Dyslipidemia (%)                 | 394 (69.9)        | 931 (67.0)             | 1.14         | 0.225       |
| Ischemic stroke (%)              | 90 (16.0)         | 112 (8.1)              | 2.165        | <0.001      |
| Pulse pressure (mmHg)            | 55 (50–65)        | 50 (40–60)             | -5.179       | <0.001      |
| Left atrium (mm)                 | 34 (31–37)        | 33 (30–35)             | -3.441       | 0.001       |
| Left ventricle end-diastolic diameter (mm) | 49 (47–52) | 46 (47–52)             | -3.041       | 0.002       |
| Hemoglobin (g/L)                 | 142 (131–153)     | 139 (130–149)          | -2.935       | 0.003       |
| Total cholesterol (mmol/L)       | 4.24 (3.57–4.92)  | 4.19 (3.57–4.83)       | -0.048       | 0.962       |
| Triglycerides (mmol/L)           | 1.62 (1.13–2.49)  | 1.53 (1.06–2.23)       | -2.057       | 0.040       |
| HDL-C (mmol/L)                   | 1.10 (0.89–1.31)  | 1.12 (0.93–1.36)       | -3.149       | 0.002       |
| LDL-C (mmol/L)                   | 2.38 (1.80–2.89)  | 2.28 (1.72–2.81)       | -1.345       | 0.179       |
| Uric acid (mmol/L)               | 311 (264–364)     | 296 (250–354)          | -3.565       | <0.001      |
| Blood urea nitrogen (mmol/L)     | 5.4 (4.4–6.4)     | 5.2 (4.3–6.2)          | -1.979       | 0.048       |
| Creatinine (mmol/L)              | 68 (59–80)        | 64 (58–74)             | -5.891       | <0.001      |
| Peripheral arterial disease (%)  | 21 (3.8)          | 24 (1.7)               | 2.22         | 0.007       |
| Aortic valve calcification (%)   | 27 (5.2)          | 31 (2.5)               | 2.153        | 0.004       |
| Abnormal wall motion (%)         | 360 (68.8)        | 743 (59.3)             | 1.513        | <0.001      |
| CAC score                        | 96.7 (12.0–371.0) | 0 (0–0)                | -22.45       | <0.001      |
| LMR                              | 5.1 (3.9–6.9)     | 6.0 (4.6–78)           | -6.198       | 0.001       |

Data are presented as number (%) of patients, median (interquartile range).

CAC, coronary artery calcification; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMR, lymphocyte-to-monocyte ratio.

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**Table 2  Lymphocyte-to-monocyte ratio diagnostic test by coronary artery disease and noncoronary artery disease groups**

| Variables          | AUC   | 95% CI          | \(P\) value | Se (%) | Sp (%) | PPV+ (%) | PPV− (%) | Cutoff point |
|--------------------|-------|-----------------|--------------|--------|--------|----------|----------|-------------|
| LMR                | 0.589 | 0.562–0.617     | <0.001       | 65.5   | 46.5   | 53.5     | 30.5     | 4.8         |

AUC, area under the curve; CAD, coronary artery disease; CI, confidence interval; LMR, lymphocyte-to-monocyte ratio.
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The pathogenesis and progression of atherosclerotic lesions are a complex process in which immune cells and various inflammatory factors play an important role [17,18]. Previous studies addressed the role of lymphocytes and monocytes in all stages of atherosclerosis through inflammatory responses [19]. Monocytes are a subset of leukocytes, which were always activated by many growth factors and are proinflammatory; they will differentiate into macrophages when endothelial dysfunction occurs. The macrophage

phagocytotic lipids in the subendothelial space may differentiate into foam cells and lead to atherosclerotic plaque development [20,21]. Previous studies reported that monocyte count among all leukocyte types has the strongest positive and independent correlation with CAD risk in asymptomatic adults and has a fundamental role in plaque progression as well as atherosclerotic stenosis [21,22]. Several controversial hypotheses exist about how lymphocytes promote coronary atherosclerosis, such as enhanced lymphocyte apoptosis, lymphocyte proliferation, and downregulated differentiation, and how lymphocytes redistribute in the lymphocyte system [23]. Lymphocytes involved in the regulatory pathway of the immune system are inversely associated with inflammation and play a crucial role in the atherosclerosis process by regulating the inflammatory response [24,25]. Inflammation contributes to atherosclerosis plaque formation and progression; is regulated by immune cells, cytokines, and other biomedical markers; and can enhance atherosclerotic plaque progression and CAD development [25,28,29]. Atherosclerosis is a chronic inflammatory

Comparison of the variables among CAC scores 0, 1, 2, and 3 groups.

Table 3 Correlations of clinical parameters with coronary artery calcification score and lymphocyte-to-monocyte ratio

| Variables         | CAC score | LMR | LMR | CAC score |
|-------------------|-----------|-----|-----|-----------|
|                   | r         | P value | r | P value |
| CAC score         | –         | – | –1.20 | <0.001 |
| LMR               | –0.120    | <0.001 | –0.120 | <0.001 |
| Age (year)        | 0.339     | <0.001 | –0.091 | <0.001 |
| Heart rate (beat/min) | 0.056  | 0.014 | –0.103 | <0.001 |
| Pulse pressure (mmHg) | 0.183  | <0.001 | –0.043 | 0.06 |
| Left atrium (mm)  | 0.108     | <0.001 | –0.103 | <0.001 |
| Left ventricle end-diastolic diameter (mm) | 0.077 | 0.001 | –0.125 | <0.001 |
| Uric acid (mmol/L) | 0.155     | <0.001 | –0.089 | <0.001 |
| Creatinine (μmol/L) | 0.149    | <0.001 | –0.148 | <0.001 |
| Blood urea nitrogen (mmol/L) | 0.119  | <0.001 | –0.05 | 0.035 |

CAC, coronary artery calcification; LMR, lymphocyte-to-monocyte ratio.

Table 4 Multiple linear regression analysis for coronary artery calcification score

| Factors                  | β  | t    | P value |
|--------------------------|----|------|---------|
| LMR                      | –0.052 | –2.221 | 0.026 |
| Age (year)               | 0.195  | 8.052 | <0.001 |
| Pulse pressure (mmHg)    | 0.053  | 2.102 | 0.036 |
| Fasting blood glucose (mmol/L) | 0.063   | 2.683 | 0.007 |
| Triglycerides (mmol/L)   | 0.055  | 2.369 | 0.018 |
| Ejection fraction (%)    | –0.099 | –4.222 | <0.001 |
| Hypertension (mmHg)      | 0.072  | 2.906 | 0.004 |
| Ischemic stroke          | 0.053  | 2.229 | 0.027 |
| Smoking                  | 0.114  | 4.555 | <0.001 |

LMR, lymphocyte-to-monocyte ratio.

Table 5 Multiple logistic regression of coronary artery disease risk factors

| Variables | Odds ratio | 95% CI | P value | Risk score |
|-----------|------------|-------|---------|------------|
| LMR ≤ 4.8 | 1.609      | 1.282–2.020 | 0.025 | 5 |
| Male      | 1.782      | 1.354–2.345 | <0.001 | 6 |
| Age ≥ 65 (years) | 1.584  | 1.243–2.018 | <0.001 | 5 |
| Hypertension | 1.660   | 1.320–2.087 | <0.001 | 5 |
| Diabetes  | 1.352      | 1.075–1.700 | 0.01 | 4 |
| Ischemic stroke | 1.795   | 1.301–2.478 | <0.001 | 6 |
| Pulse pressure ≥ 60 mmHg | 1.352 | 1.077–1.697 | 0.009 | 4 |
| Smoking   | 1.343      | 1.020–1.769 | 0.036 | 4 |

CAD, coronary artery disease; LMR, lymphocyte-to-monocyte ratio; LDL-C, low-density lipoprotein cholesterol.
process of arteries. Therefore, low LMR, low lymphocyte count, or high monocyte count may facilitate inflammation and oxidative stress, release more inflammatory factors, promote endothelial damage, and inhibit immune response and other pathophysiological mechanisms to promote foam cell formation and subendothelial lipid precipitation [7,30,31].

Another important and new discovery of this study was that low LMR was an independent risk factor of CAD. Its risk was similar to the risk of hypertension and older age, even higher than diabetes, LDL-C, and smoking. LMR was significantly lower in patients with CAD than in patients with non-CAD. In a study by Gary et al. [20], an association was found between decreased LMR and CAD and prior myocardial infarction. Gong et al. [10] found that LMR is independently and positively related to the severity of coronary atherosclerosis, and it can be as a useful predictor of CAD. The results in this study were similar to those in previous studies. Lymphocytes and monocytes are pivotal immune cells in inflammatory response, which promote CAD development [32]. Earlier studies demonstrated that lower lymphocyte counts and higher monocyte counts are associated with cardiovascular conditions [33], cardiovascular risk and increased mortality [34,35], and adverse cardiovascular endpoints in patients with CAD [36,37]. Moreover, lymphocytes and monocytes are associated with left ventricle remodeling, myocardial healing, myofibroblast accumulation, and angiogenesis [38,39]. These conclusions further support the results of this study. Therefore, LMR value can be used as a simple predictive marker for CAD in clinical practice.

Furthermore, our results are in consensus with most previous studies that hypertension, diabetes, ischemic stroke, LDL-C, male, older age, smoking, and pulse pressure ≥60 mmHg were risk factors of CAD. An independent and positive relationship among age, pulse pressure, left atrium, uric acid, creatinine, blood urea nitrogen, and CAC score was also found in our study. Patients with high-risk factors promote inflammatory response, various cytokine release, and cardiovascular damage, and accelerate the formation and development of atherosclerosis, which is closely related to the occurrence and deterioration of CAD [40–42]. Russo et al. [43] showed that pulse pressure can be used to evaluate coronary calcification and vessel wall alterations leading to adverse outcome. Kiss et al. [44] found that serum uric acid is independently associated with CAC score. Additionally, the new risk score model was compared with the Framingham model and showed that NRI was 4.9%, which proved that the new risk score model improved the prediction capability of CAD.

The present study has several limitations. First, this is a single-center study, and the best diagnostic threshold of LMR may not be suitable for the general population. Second, this is a retrospective study with inherent limitations, which may be related to this result. Finally, our study only explored the coronary calcification burden and did not assess the severity of CAD.

In conclusion, LMR value was negatively correlated with CAC score, and LMR could be used as a new marker to evaluate the coronary plaque burden of CAD. Low LMR is a new independent risk factor of CAD. LMR is simple, cheap, and reproducible laboratory marker for the diagnosis of CAD.

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Conflicts of interest
There are no conflicts of interest.

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Table 6 Comparison of prediction capability of Framingham score and new risk model

| Prediction models | AUC   | P value | Se (%) | Sp (%) | NRI (%) |
|-------------------|-------|---------|--------|--------|---------|
| Framingham score  | 0.630 | <0.001  | 73.2   | 47.4   | 4.9     |
| New risk score    | 0.687 | <0.001  | 72.5   | 55.7   | 4.9     |

AUC, area under the curve; CI, confidence interval; NRI, net reclassification index.
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