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ORIGINAL RESEARCH

Association Between Inflammation Indices Derived From Complete Blood Count and Coronary Artery Calcification

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Background: Inflammation plays an important role in the pathogenesis of coronary artery calcification (CAC). This study aims to explore the potential association between inflammation indices derived from complete blood count (CBC) and CAC, including the neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), neutrophil-monocyte to lymphocyte ratio (NMLR), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), aggregate index of systemic inflammation (AISI), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR).

Methods: We systematically collected data from patients who underwent CAC scoring via cardiac CT at our hospital between July 2018 and June 2023. Patients were divided into two groups based on the presence or absence of CAC. Multivariate logistic regression analysis, smooth curve fitting, and threshold effect analysis were subsequently used to explore the potential linear or nonlinear relationships between CBC-derived inflammation indices and CAC. Subgroup analyses were conducted to examine the consistency of these findings across different subgroups.

Results: A total of 2143 participants were included in this study: the CAC group (1286 participants) and the non-CAC group (857 participants). In the four subgroups of CAC, within-group comparisons revealed that alkaline phosphatase (ALP), smoking status, and peripheral artery plaques were more prevalent in the group with CAC scores > 400. After adjusting for confounding variables, we found that the total NLR, NMLR, SIRI, and AISI were positively associated with CAC. Subsequently, we identified a nonlinear relationship between MLR and CAC, with a threshold value of 0.236. Additionally, subgroup analysis indicated that these associations remained stable across various subgroups.

Conclusion: This study indicates that the total NLR, NMLR, SIRI, and AISI are significantly positively correlated with CAC in a linear association, while MLR exhibits a nonlinear relationship with CAC. In contrast, SII, PLR, and dNLR show no significant association with CAC.

Keywords: coronary artery calcification, Agatston score, inflammation indices derived from complete blood count, association

Introduction

Atherosclerosis is the primary cause of coronary artery disease. Its natural course is prolonged and often remains in a subclinical stage, frequently going undetected until late in the disease or when cardiovascular events occur. Arterial calcification results from the deposition of calcium and phosphate in the form of hydroxyapatite within the extracellular matrix of the arterial wall. Based on the location and the arterial wall segment affected, arterial calcification is primarily classified into two types: medial calcification and intimal calcification, each with distinct etiologies and implications. Especially intimal calcification is closely linked to the progression of atherosclerosis, and coronary artery calcification (CAC) primarily reflects this type of calcification. The pathogenesis of CAC is consistent with that of arterial calcification. Therefore, further investigation into the factors associated with CAC is of great importance for the prevention and treatment of coronary artery disease.

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Inflammation plays a key role in the development and progression of atherosclerosis and CAC. Atherosclerosis is essentially a chronic inflammatory disease involving a large number of inflammatory cells and cytokines. Inflammatory indices have been shown to predict cardiovascular diseases independently of traditional risk factors.[1] For example, IL-34 has emerged as an independent predictor for slow coronary flow.[2] Atherosclerosis originates from endothelial dysfunction, accompanied by the retention and modification of low-density lipoproteins in the intima, which activates endothelial cells and leads to the recruitment of monocytes into the intima. These monocytes subsequently differentiate into macrophages, which, under the influence of various factors, can polarize into pro-inflammatory or anti-inflammatory phenotypes. When endothelial cells are damaged, pathological processes such as lipid infiltration, leukocyte adhesion, platelet activation, and oxidative stress occur in the vascular intima, thereby increasing an inflammatory response.[3] Compared to traditional inflammatory markers, hematological parameters offer the primary advantage of being more cost-effective and readily accessible through routine blood tests. Recent studies have highlighted the potential value of certain inflammation indices derived from complete blood count (CBC) in the predictive diagnosis and prognostic evaluation of cardiovascular diseases.[4] Furthermore, previous research has indicated that the levels of CBC-derived inflammation indices are valuable for predicting the prognosis of patients with moderate coronary artery stenosis.[5] Moreover, CAC testing requires advanced equipment and technical support, and the associated costs are relatively high, making it difficult to implement in resource-limited areas. The procedure also requires patients to maintain specific positions or cooperate with breath-holding, which some patients may find challenging due to anxiety or discomfort, potentially preventing them from completing the test.

Given the relationship between various CBC-derived inflammation indices and CAC, it has not yet been extensively studied. This study provides an in-depth investigation into the correlation between levels of CBC-derived inflammation indices and the prevalence of CAC, aiming to uncover the potential link between inflammation and the development of CAC.

Materials and Methods

Study Population and Design

This study is a retrospective analysis that included clinical data from patients who underwent cardiac CT and had CAC scores at our hospital between July 2018 and June 2023. The inclusion criteria were as follows: (1) complete CAC score data; (2) complete CBC data; (3) age 18 years or older. Exclusion criteria included: severe infection, malignancy, thyroid dysfunction, connective tissue diseases, hematologic disorders, severe liver or kidney dysfunction, CT image artifacts, a history of prior coronary artery stent implantation or coronary artery bypass grafting, psychiatric disorders, and incomplete clinical information. This study was approved by the Ethics Committee of the Southwest Hospital of Army Medical University (Approval No. (B)KY2023118). As the study did not involve the disclosure of patient data, written informed consent from participants was not required. All patient data were handled confidentially in accordance with relevant ethical guidelines. The procedures followed were in accordance with the regulations of the Ethics Committee and the Declaration of Helsinki of the World Medical Association.

Evaluation of CBC-Derived Inflammation Indices

CBC was performed using the Sysmex DI-60 automated cell morphology analyzer. Based on the obtained peripheral blood cell count results, we evaluated the following eight specific inflammation indices: including the neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dNLR), neutrophil-monocyte to lymphocyte ratio (NMLR), systemic inflammation response index (SIRI), systemic immune-inflammation index (SII), aggregate index of systemic inflammation (AISI), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR). The formulas for calculating these markers are as follows:

$$\mathrm{NLR} = \mathrm{Neutrophil\ count}/\mathrm{Lymphocyte\ count}$$

$$\mathrm{dNLR} = \mathrm{Neutrophil\ count}/(\mathrm{White\ blood\ cell\ count} - \mathrm{Lymphocyte\ count})$$

$$\mathrm{NMLR} = (\mathrm{Monocyte\ count} + \mathrm{Neutrophil\ count})/\mathrm{Lymphocyte\ count}$$

$$\text{SIRI} = \text{Neutrophil count} \times \text{Monocyte count}/\text{Lymphocyte count}$$

$$\text{SII} = \text{Platelet count} \times \text{Neutrophil count}/\text{Lymphocyte count}$$

$$\text{AISI} = \text{Neutrophil count} \times \text{Platelet count} \times \text{Monocyte count}/\text{Lymphocyte count}$$

$$\text{PLR} = \text{Platelet count}\ /\text{Lymphocyte count}$$

$$\text{MLR} = \text{Monocyte count}/\text{Lymphocytecount}$$

Calculation of CAC Score

During cardiac assessment, the CAC score is derived through a non-contrast, electrocardiogram-gated CT scanning. The cardiac CT imaging protocol was as follows: a tube voltage of 120 kV was applied, with the tube current adjusted automatically using CARE Dose4D technology for individualized dose optimization. The scanner rotation time was set to 0.25 seconds, and the collimation width was 0.6 mm. Retrospective electrocardiogram gating was utilized to ensure optimal image quality. The scan range extended from the tracheal bifurcation to the cardiac apex, covering a length of 12–15 cm, and was completed in a single breath-hold. The temporal resolution was 66 ms, and the Siemens Somatom Force scanner automatically adjusted the pitch according to the patient's heart rate. Acquired volumetric data were reconstructed using the Bv40 convolution kernel, generating images with a 512×512 matrix, a slice thickness of 0.75 mm, and an interslice spacing of 0.5 mm. Calcium plaques in the four major coronary arteries (left main artery, left anterior descending artery, circumflex artery, and right coronary artery) are identified by a specialized cardiothoracic radiologist, who assesses the calcified deposits in each artery. The software then automatically calculates these deposits and generates the CAC score based on the Agatston algorithm, and finally summing the scores from four coronary arteries to determine the total CAC scores.[6] Based on the severity of CAC scores, participants are classified into four groups: 0–10, 11–100, 101–400, and above 400.[7]

Statistical Analyses

Continuous variables were expressed as mean (SD), while categorical variables were presented as frequencies and percentages. Spearman's rank correlation coefficient was used to assess the correlations between baseline characteristics, and variables with a variance inflation factor>10 were excluded. Univariate and multivariate logistic regression analyses were performed to evaluate the linear association between specific inflammation indices and CAC. Subsequently, smoothing spline fitting and threshold effect analysis were employed to explore potential nonlinear relationships and identify key inflection points. Finally, subgroup analyses were conducted to assess the consistency of the results. A two-sided p-value of < 0.05 was considered statistically significant. All analyses were performed using R software (version 4.3.2).

Results

Baseline Characteristics of Participants

After a rigorous selection process, a total of 2143 participants were included in this study. The mean age of the participants was 63.51 (10.57) years, with 59.2% being female. Participants were then divided into five groups based on their CAC status: no calcification group (857 participants), CAC score <10 group (247 participants), 11–100 group (437 participants), 101–400 group (346 participants), and >400 group (256 participants). Compared to the group without CAC, the CAC group had a higher age, a lower proportion of males, and a greater number of individuals with hypertension, diabetes, peripheral artery plaques, as well as adverse lifestyle habits such as smoking and drinking (Table 1).

Logistic Regression Analysis

Table 2 presents the results of logistic regression analysis evaluating the association between CBC-derived inflammation indices and CAC. In Model 1, which did not adjust for confounding factors, total NLR, NMLR, SIRI, and MLR were

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Table 1 Baseline Characteristics of Participants

		Overall	Non-CAC	CAC Score <10	CAC Score 11–100	CAC Score 101–400	CAC Score >400	p
N		2143	857	247	437	346	256	
Sex (%)	Male	874 (40.8)	398 (46.4)	89 (36.0)	184 (42.1)	118 (34.1)	85 (33.2)	<0.001
	Female	1269 (59.2)	459 (53.6)	158 (64.0)	253 (57.9)	228 (65.9)	171 (66.8)	
Age (years)		63.51 (10.57)	60.30 (10.52)	62.21 (10.38)	65.11 (10.09)	66.90 (9.49)	68.17 (9.41)	<0.001
BMI (kg/m^2)		24.90 (5.92)	24.79 (3.69)	24.91 (3.59)	25.44 (11.01)	24.78 (3.36)	24.48 (3.58)	0.259
Hypertension (%)	No	721 (33.6)	360 (42.0)	81 (32.8)	136 (31.1)	91 (26.3)	53 (20.7)	<0.001
	Yes	1422 (66.4)	497 (58.0)	166 (67.2)	301 (68.9)	255 (73.7)	203 (79.3)	
Diabetes (%)	No	1448 (67.6)	655 (76.4)	172 (69.6)	283 (64.8)	207 (59.8)	131 (51.2)	<0.001
	Yes	695 (32.4)	202 (23.6)	75 (30.4)	154 (35.2)	139 (40.2)	125 (48.8)	
Hyperlipidemia (%)	No	1218 (56.8)	493 (57.5)	132 (53.4)	242 (55.4)	196 (56.6)	155 (60.5)	0.533
	Yes	925 (43.2)	364 (42.5)	115 (46.6)	195 (44.6)	150 (43.4)	101 (39.5)	
Peripheral artery plaque (%)	No	613 (28.6)	340 (39.7)	78 (31.6)	95 (21.7)	61 (17.6)	39 (15.2)	<0.001
	Yes	1530 (71.4)	517 (60.3)	169 (68.4)	342 (78.3)	285 (82.4)	217 (84.8)	
Smoking (%)	No	1248 (58.2)	561 (65.5)	141 (57.1)	248 (56.8)	174 (50.3)	124 (48.4)	<0.001
	Yes	895 (41.8)	296 (34.5)	106 (42.9)	189 (43.2)	172 (49.7)	132 (51.6)	
Drinking (%)	No	1339 (62.5)	574 (67.0)	154 (62.3)	274 (62.7)	199 (57.5)	138 (53.9)	0.001
	Yes	804 (37.5)	283 (33.0)	93 (37.7)	163 (37.3)	147 (42.5)	118 (46.1)	
LM CAC score		12.75 (88.06)	0.00 (0.00)	0.39 (1.38)	3.92 (11.62)	22.10 (52.52)	69.82 (238.64)	<0.001
LAD CAC score		85.88 (267.60)	0.00 (0.00)	2.47 (2.94)	28.03 (26.92)	120.28 (86.22)	506.12 (611.62)	<0.001
CX CAC score		29.09 (125.01)	0.00 (0.00)	0.47 (1.45)	5.07 (12.65)	26.52 (46.91)	198.61 (307.45)	<0.001
RCA CAC score		60.99 (234.76)	0.00 (0.00)	0.51 (1.43)	8.34 (16.27)	45.39 (65.99)	434.48 (543.55)	<0.001
Total CAC score		188.72 (549.76)	0.00 (0.00)	3.84 (2.95)	45.36 (25.75)	214.28 (85.45)	1209.03 (1137.41)	<0.001
CAC (%)	No	857 (40.0)	857 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
	Yes	1286 (60.0)	0 (0.0)	247 (100.0)	437 (100.0)	346 (100.0)	256 (100.0)	
eGFR (mL/min/1.73m^2)		87.08 (20.59)	90.42 (18.43)	89.14 (19.37)	87.66 (19.70)	83.90 (19.83)	77.26 (26.65)	<0.001
Cr (μmol/L)		86.03 (101.79)	73.58 (20.96)	79.29 (44.38)	82.27 (95.88)	87.45 (93.21)	138.71 (229.79)	<0.001
ALT (U/L)		25.94 (28.19)	26.25 (26.64)	27.41 (20.51)	27.76 (37.33)	24.44 (29.31)	22.40 (17.86)	0.107
AST (U/L)		26.54 (24.89)	26.77 (24.46)	25.35 (12.01)	26.80 (20.80)	27.16 (38.59)	25.64 (17.34)	0.872
ALP (U/L)		86.08 (47.22)	83.53 (27.46)	84.28 (33.81)	85.23 (35.16)	87.24 (47.70)	96.27 (98.83)	0.004
GGT (U/L)		39.29 (52.15)	36.96 (43.71)	41.93 (68.14)	42.82 (56.98)	38.29 (51.09)	39.85 (53.10)	0.344
HbA1c (%)		6.41 (1.67)	6.29 (2.02)	6.38 (1.30)	6.40 (1.34)	6.49 (1.34)	6.78 (1.58)	0.001
NLR		2.73 (2.54)	2.49 (1.50)	2.90 (3.12)	2.70 (2.33)	2.90 (3.64)	3.21 (3.09)	0.001
dNLR		0.86 (0.05)	0.86 (0.05)	0.87 (0.05)	0.86 (0.05)	0.86 (0.05)	0.86 (0.05)	0.123
MLR		0.28 (0.17)	0.26 (0.14)	0.27 (0.14)	0.29 (0.17)	0.30 (0.23)	0.33 (0.18)	<0.001
NMLR		3.01 (2.67)	2.74 (1.60)	3.17 (3.21)	2.99 (2.47)	3.21 (3.84)	3.54 (3.21)	<0.001
SIRI		1.29 (2.09)	1.07 (0.98)	1.35 (2.08)	1.33 (1.86)	1.57 (3.94)	1.53 (1.50)	0.001
SII		556.93 (656.96)	512.36 (361.99)	642.18 (1226.22)	582.72 (720.12)	554.65 (646.07)	582.98 (517.70)	0.057
AISI		270.01 (521.75)	224.20 (226.60)	304.44 (648.12)	298.88 (595.84)	305.78 (849.16)	292.49 (338.47)	0.025
PLR		129.73 (69.19)	129.03 (62.71)	130.44 (85.56)	132.47 (72.95)	125.77 (63.57)	132.02 (73.06)	0.697

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAC, coronary artery calcification; Cr, creatinine; CX, circumflex artery; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HbA1c, hemoglobinA1c; LAD, left anterior descending artery; LM, left main artery; RCA, right coronary artery.

positively associated with CAC, while the correlations of total SII and AISI with CAC were weaker. In Model 2, after adjusting for sex, age, and BMI, similar results were observed. Even after adjusting for multiple confounding factors (Model 3), total NLR, NMLR, and SIRI remained positively associated with CAC, with each unit increase in these indices corresponding to approximately 6%, 6%, and 11% higher odds of CAC, respectively. Furthermore, these inflammation indices were categorized into four quartile groups (Q1, Q2, Q3, Q4) based on their respective distributions. Analysis revealed that individuals in the Q3 group of dNLR had 0.35 times higher odds of CAC compared to those in the Q1 group. For SIRI, the Q3 group had 0.40 times and the Q4 group had 0.46 times higher odds compared to the Q1 group. Similarly, individuals in the Q4 group of MLR had 0.49 times higher odds of CAC than those in the Q1 group.

Table 2 Association of Total CBC-Derived Inflammation Indices and Quartiles With CAC by Logistic Regression

	Model 1	Model 2	Model 3
	OR (95% CI), p	**OR (95% CI), p**	**OR (95% CI), p**
Total NLR	1.10 (1.05–1.17), p<0.01	1.08 (1.03–1.14), p<0.01	1.06 (1.01–1.13), p=0.03
Group Q1	Ref	Ref	Ref
Group Q2	1.13 (0.89–1.45), p=0.31	1.17 (0.91–1.50), p=0.23	1.17 (0.90–1.51), p=0.24
Group Q3	1.29 (1.01–1.65), p=0.04	1.30 (1.01–1.68), p=0.04	1.29 (1.00–1.68), p=0.05
Group Q4	1.47 (1.15–1.87), p<0.01	1.32 (1.02–1.71), p=0.03	1.29 (0.99–1.68), p=0.06
Total dNLR	1.10 (1.05–1.17), p=0.28	2.07 (0.33–12.87), p=0.43	5.84 (0.83–40.96), p=0.08
Group Q1	Ref	Ref	Ref
Group Q2	0.79 (0.62–1.01), p=0.06	0.87 (0.67–1.12), p=0.27	0.87 (0.67–1.13), p=0.29
Group Q3	1.12 (0.88–1.44), p=0.36	1.34 (1.03–1.74), p=0.029	1.35 (1.03–1.76), p=0.03
Group Q4	0.78 (0.61–0.99), p=0.04	0.97 (0.75–1.25), p=0.80	1.04 (0.80–1.36), p=0.77
Total NMLR	1.10 (1.05–1.17), p<0.01	1.08 (1.03–1.13), p<0.01	1.06 (1.01–1.12), p=0.03
Group Q1	Ref	Ref	Ref
Group Q2	1.16 (0.91–1.48), p=0.23	1.15 (0.90–1.48), p=0.27	1.15 (0.89–1.49), p=0.29
Group Q3	1.30 (1.02–1.66), p=0.04	1.28 (0.99–1.65), p=0.06	1.28 (0.98–1.66), p=0.07
Group Q4	1.51 (1.18–1.93), p<0.01	1.32 (1.02–1.71), p=0.037	1.26 (0.96–1.65), p=0.09
Total SIRI	1.25 (1.14–1.38), p<0.01	1.18 (1.08–1.30), p<0.01	1.11 (1.02–1.23), p=0.03
Group Q1	Ref	Ref	Ref
Group Q2	1.26 (0.99–1.60), p=0.06	1.20 (0.93–1.54), p=0.15	1.12 (0.86–1.45), p=0.41
Group Q3	1.73 (1.35–2.21), p<0.01	1.55 (1.20–2.01), p<0.01	1.40 (1.07–1.82), p=0.01
Group Q4	1.94 (1.52–2.49), p<0.01	1.62 (1.24–2.11), p<0.01	1.46 (1.11–1.92), p=0.01
Total SII	1.00 (1.00–1.00), P=0.01	1.00 (1.00–1.00), p<0.01	1.00 (0.99–1.00), p=0.12
Group Q1	Ref	Ref	Ref
Group Q2	1.16 (0.91–1.48), p=0.25	1.24 (0.96–1.60), p=0.10	1.29 (0.99–1.68), p=0.05
Group Q3	1.07 (0.84–1.37), p=0.58	1.18 (0.92–1.53), p=0.19	1.17 (0.90–1.52), p=0.23
Group Q4	1.16 (0.91–1.48), p=0.24	1.23 (0.95–1.59), p=0.11	1.14 (0.88–1.48), p=0.33
Total AISI	1.00 (1.00–1.00), p<0.01	1.00 (1.00–1.00), p<0.01	1.00 (1.00–1.00), p=0.04
Group Q1	Ref	Ref	Ref
Group Q2	1.29 (1.01–1.65), p=0.04	1.34 (1.04–1.73), p=0.02	1.28 (0.99–1.67), p=0.06
Group Q3	1.39 (1.09–1.77), p<0.01	1.39 (1.08–1.80), p=0.01	1.31 (1.01–1.70), p=0.05
Group Q4	1.62 (1.27–2.07), p<0.01	1.57 (1.21–2.03), p<0.01	1.37 (1.05–1.80), p=0.02
Total PLR	1.00 (0.99–1.00), P=0.7	1.00 (0.99–1.00), P=0.43	1.00 (0.99–1.00), p=0.80
Group Q1	Ref	Ref	Ref
Group Q2	0.93 (0.73–1.19), p=0.57	1.03 (0.80–1.33), p=0.79	1.06 (0.81–1.38), p=0.67
Group Q3	0.85 (0.66–1.08), p=0.18	0.96 (0.74–1.24), p=0.75	0.97 (0.75–1.27), p=0.85
Group Q4	0.94 (0.73–1.20), p=0.60	1.04 (0.80–1.34), p=0.78	1.07 (0.82–1.40), p=0.62
Total MLR	5.84 (3.07–11.53), p<0.01	2.63 (1.41–5.17), p<0.01	1.67 (0.85–3.43), p=0.15
Group Q1	Ref	Ref	Ref
Group Q2	1.40 (1.10–1.79), p<0.01	1.23 (0.96–1.58), p=0.10	1.21 (0.93–1.57), p=0.15
Group Q3	1.57 (1.24–2.01), p<0.01	1.32 (1.02–1.71), p=0.03	1.27 (0.97–1.65), p=0.08
Group Q4	2.13 (1.67–2.74), p<0.01	1.54 (1.18–2.02), p<0.01	1.49 (1.12–1.98), p=0.01

Notes: Model 1: Crude. Model 2: Adjusted for sex, age, BMI. Model 3: Adjusted for sex, age, hypertension, diabetes. smoking, drinking, LDL, HDL, Tch, UA, eGFR, Cr, Alb, ALP, HbA1c, GLU, Na, K, Pi, Cl, peripheral artery plaque.
Abbreviations: Alb, albumin; GLU, glucose; HDL, high density lipoprotein; LDL, low density lipoprotein; Tch, total cholesterol; UA, uric acid.

Although the overall association between AISI and CAC remained weak, the Q3 and Q4 groups of AISI were associated with 0.31 and 0.37 times higher odds of CAC compared to the Q1 group, respectively.

Nonlinear Relationship Between CBC-Derived Inflammation Indices and CAC

Although after adjusting for confounding factors, the total dNLR did not show a significant correlation with CAC, a positive association between dNLR and CAC was observed in the Q3 group, while no such correlation was found in the Q2 and Q4 groups. Additionally, in the Q4 group of MLR, a significant positive correlation with CAC was observed, whereas no significant association was found in the Q2 and Q3 groups. To further explore the potential nonlinear relationship of MLR, smooth curve fitting and restricted cubic spline analysis were performed (Figure 1). The results showed that the p for the

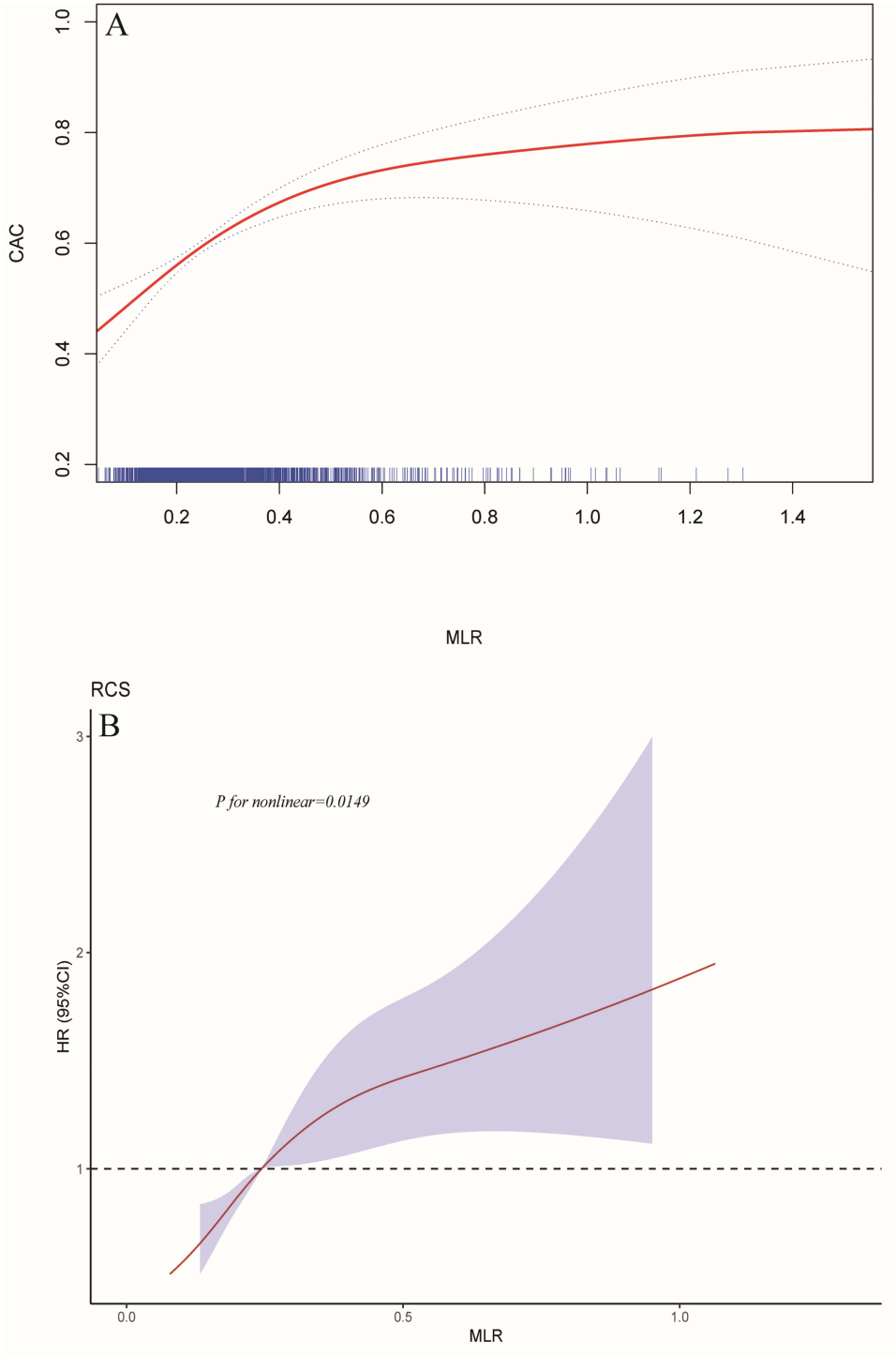

Figure 1 Nonlinear relationship between MLR and CAC. (**A**) The smooth curve fitting diagram of MLR. (**B**) The restricted cubic spline plot of MLR.

nonlinear test was 0.0149. Threshold effect analysis also supported this finding, indicating a significant nonlinear association between MLR and CAC, with a critical threshold at 0.236. When MLR values were below 0.236, a significant positive correlation with CAC was found; however, when MLR values exceeded 0.236, the relationship was no longer statistically significant (Table 3). But there is no nonlinear relationship in dNLR (Supplementary Figure 1 and Supplementary Table 1).

Subgroup Analysis

In the subgroup analysis, participants were stratified based on confounding factors. Interaction tests across these subgroups revealed no significant differences in the associations between CBC-derived inflammation indices and CAC, as all interaction p>0.05 (Table 4 and Supplementary Table 2).

Table 3 Threshold Effect Analysis of MLR on CAC Using a Two-Part Logistic Regression Model

MLR	Adjusted OR (95%), p
Model 1 Fitting model by standard linear regression	2.34 (1.21–4.77), p=0.02
Model 2 Fitting model by two-piecewise linear regression	
Inflection point	0.236
<0.236	34.51 (2.61–456.44), p<0.01
>0.236	1.53 (0.76–3.35), p=0.26
p for likelihood ratio test	p=0.03

Notes: Adjusted for sex, age, hypertension, diabetes. smoking, drinking, LDL, HDL, Tch, UA, eGFR, Cr, Alb, ALP, HbA1c, GLU, Na, K, Pi, Cl, peripheral artery plaque.

Table 4 Subgroup Analysis Results of MLR and CAC

Variable	Count	Percent (%)	OR (95% CI)	p	p for Interaction
MLR	2143	100	2.51 (1.36, 4.91)	0.005	
Age					0.207
>65	978	45.6	1.79 (0.81, 4.4)		
≤65	1165	54.4	3.79 (1.51, 10.33)		
Sex					0.562
Male	874	40.8	3.15 (0.97, 12.03)		
Female	1269	59.2	2.39 (1.17, 5.25)		
Diabetes					0.759
No	1448	67.6	2.67 (1.27, 6.01)		
Yes	695	32.4	2.31 (0.79, 8.17)		
Hypertension					0.611
No	721	33.6	2.51 (0.99, 7.74)		
Yes	1422	66.4	2.4 (1.07, 5.69)		
Smoking					0.757
No	1248	58.2	2.64 (1.12, 6.91)		
Yes	895	41.8	2.41 (1.01, 6.35)		
Drinking					0.443
No	1339	62.5	1.96 (0.89, 4.78)		
Yes	804	37.5	3.66 (1.43, 10.51)		
Hyperlipidemia					0.814
No	1218	56.8	2.46 (1.13, 5.67)		
Yes	925	43.2	2.74 (1.02, 8.99)		
Peripheral artery plaque					0.4
No	613	28.6	3.51 (1.31, 11.61)		
Yes	1530	71.4	1.96 (0.9, 4.59)		

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Discussion

This study investigates the association between various inflammation indices derived from CBC and CAC, and explores potential differences in this relationship among the various indices. After adjusting for multiple confounders, multivariable logistic regression models were employed, and the results indicated a positive association between total NLR, NMLR, SIRI, and AISI with CAC. Moreover, we identified a non-linear relationship between MLR and CAC.

Previous clinical studies have shown that calcification of atherosclerotic plaques is a relatively slow and dynamic process, closely linked to the inflammatory state of the arterial vessel walls.[8] White blood cells play a critical role in the initiation and progression of inflammation. It has been suggested that elevated white blood cell counts significantly increase the risk of cardiovascular events.[9] Histological studies have also confirmed the infiltration of white blood cells into atherosclerotic plaques. Eriksson et al used real-time in vivo imaging to observe the recruitment of white blood cells in atherosclerotic aortic plaques in mice.[10] Neutrophils, the body's most important inflammatory cells, are commonly used as indicators in inflammation studies. When activated, they release inflammatory mediators and pro-thrombotic substances, contributing to endothelial damage and platelet aggregation.[11] Reduced lymphocyte counts are often a component of acute stress responses and are closely associated with increased levels of cortisol, catecholamines, and pro-inflammatory cytokines.[12] A decrease in lymphocytes may reflect a state of physiological stress or overall poor health.[13] Given that impaired immune responses may accelerate disease progression, lymphopenia is closely associated with the progression of atherosclerosis.[14] The distribution of leukocyte subtypes is finely regulated by the autonomic nervous system. Granulocytes express adrenergic receptors, while lymphocytes possess cholinergic receptors.[15] As a result, an elevated NLR may indicate a relatively higher ratio of sympathetic to parasympathetic nervous activity. Increased sympathetic tone is positively correlated with higher oxygen consumption and elevated production of pro-inflammatory cytokines such as IL-6 and TNF-α, which play a critical role in regulating vascular wall tension. This regulation is primarily achieved by influencing the release of nitric oxide and endothelin-1 in the subendothelial space.[16] In a cross-sectional study conducted by Turkmen et al, involving 56 end-stage renal disease patients, after excluding those with acute infection, autoimmune diseases, acute heart failure, a significant correlation was found between NLR and CAC score ($r = 0.3$, $p = 0.02$). Their findings suggest that NLR can be a predictor of vascular calcification in those patients.[17] Another study by Park et al demonstrated that individuals in the highest NLR quartile had a significantly increased risk of elevated CAC score, even after adjusting for medications that could affect vascular function parameters, such as antihypertensive, antidiabetic, and lipid-lowering drugs.[18] Nam SH's team focused on a Korean population without cardiovascular disease, diabetes, or hypertension, and found that after adjusting for other cardiovascular risk factors, NLR remained significantly and independently associated with CAC score in healthy adult men.[19] Monocytes, activated through adhesion to endothelial surface molecules, play a key role in the development of atherosclerosis. These activated monocytes migrate to the vessel intima and differentiate into macrophages. After engulfing oxidized low-density lipoproteins, they form foam cells, which further secrete pro-inflammatory cytokines and oxidative components, accelerating plaque progression and destabilization.[20]

Moreover, platelets not only play a crucial role in hemostasis and thrombosis but also participate in inflammation and immune responses. Activated platelets release numerous chemokines, cytokines, and growth factors, modulating inflammatory and immune processes.[21] Platelets are also involved in vascular calcification, with exosomes and related proteins derived from platelets influencing the biological processes of vascular calcification.[22] And Yusuf Akın et al conducted a study involving 80 patients with cardiac syndrome X and found that the SII could serve as a predictive marker for this condition.[23] Although our study found no significant correlation between platelet-derived indices (such as SII and PLR) and CAC, this may be attributed to the limitation of these indices in accurately reflecting platelet activation. The degree of platelet activation and the bioactive substances they release play crucial regulatory roles in the process of vascular calcification. Furthermore, Carlos et al conducted additional research in asymptomatic patients and, through multivariate logistic regression analysis, demonstrated that PLR was not an inflammatory marker indicative of coronary artery disease severity.[24]

Our study demonstrates a non-linear relationship between MLR and CAC, suggesting that the correlation between MLR and CAC varies across different value ranges. Previous studies have indicated that the pathological process of CAC begins with small calcified lesions ranging from 0.5–15.0 μm in diameter, which gradually increase in size over time. These microcalcifications can increase shear stress at the interface between the calcified and non-calcified regions of the

plaque, contributing to plaque instability. In contrast, more extensive and larger calcifications may stabilize the plaque.[25] A study using intravascular ultrasound found that compared to non-calcified plaques, punctate calcifications are more likely to cause significant plaque volume expansion, while highly calcified plaques are less likely to continue enlarging.[26] In the early stages of atherosclerosis, the degree of plaque calcification is relatively low and often accompanied by significant inflammatory reactions, resulting in lipid-rich, thin-capped unstable plaques with a higher risk of rupture. The size of the soft-hard interface within the plaque is closely associated with the risk of plaque rupture.[27] In the early stages of inflammation, the risk of plaque rupture is relatively low due to the limited number of microcalcifications. However, as inflammation progresses, microcalcifications accumulate, increasing the size of the soft-hard interface and raising the risk of plaque rupture. When larger, more compact calcified regions form, the risk of plaque rupture decreases.[25] Therefore, the non-linear relationship between MLR and CAC may reflect the dynamic transition of atherosclerotic plaques from an unstable to a stable state.

Admittedly, our study has several limitations. First and foremost, the retrospective design inherently limits the ability to establish direct causal relationships. Secondly, this study was conducted at a single center, which may introduce selection bias. Furthermore, While we did not perform Bonferroni correction for multiple comparisons, we conducted a correlation analysis of baseline parameters and excluded variables with high collinearity to reduce the risk of multicollinearity. However, the potential impact of multiple comparisons remains. Future studies could benefit from applying more robust correction techniques to better control for this risk.

Conclusion

Despite the retrospective design of this study, which limits the ability to establish a causal relationship between CBC-derived inflammatory indices and CAC, it still reveals a positive linear correlation between total NLR, NMLR, SIRI, AISI and CAC. This suggests that elevated levels of these inflammatory indices are likely indicative of increased instability of coronary calcified plaques. Consequently, patients exhibiting elevated values of these indices should be considered high-risk individuals, warranting increased clinical attention and more aggressive treatment. Furthermore, this study also reveals a non-linear relationship between MLR and CAC, the clinical significance of which requires further exploration through additional clinical studies.

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Disclosure

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