Cardiovascular Topics

Association of ratios of monocyte/high-density lipoprotein cholesterol and neutrophil/high-density lipoprotein cholesterol with atherosclerotic plaque type on coronary computed tomography

Taha Okan, Caner Topaloglu

Abstract

Objectives: The monocyte/high-density lipoprotein cholesterol (HDL-C) ratio (MHR) and neutrophil/HDL-C ratio (NHR) are markers for inflammation and dyslipidaemia, which are important factors in atherosclerosis. Studies have linked MHR and NHR to the prediction, severity and prognosis of coronary artery disease. However, no study has explored their connection to plaque stability, specifically its calcific or soft/mixed content.

Methods: Monocyte, neutrophil and HDL-C levels were examined in 99 patients who had coronary computed tomographic angiography (CTA) between January and August 2023. They were divided into three groups: a group of 42 healthy individuals (group 0) with no coronary artery plaque and an Agatson score of 0, an unstable plaque group (group 1) with 31 patients displaying mixed and/or soft plaque on CTA, and a stable plaque group (group 2) with 26 patients showing only calcific plaque.

Results: White blood cell (WBC), monocyte and neutrophil counts were significantly higher in group 1 patients compared to group 0 patients (group 0: WBC = 6.31 ± 0.97 × 10^3 cells/µl, monocytes = 0.40 ± 0.09 × 10^3 cells/µl, neutrophils = 3.32 ± 0.81 × 10^3 cells/µl; and group 1: WBC = 7.61 ± 1.95 × 10^3 cells/µl, monocytes = 0.50 ± 0.11 × 10^3 cells/µl, neutrophils = 4.19 ± 1.36 10^3 cells/µl; $p < 0.05$). MHR and NHR were significantly higher in group 1 patients compared to group 0 patients (group 0: MHR = 0.0079 ± 0.0029, NHR = 0.063 ± 0.023 and group 1: MHR = 0.0102 ± 0.003, NHR = 0.085 ± 0.036, $p < 0.05$).

Conclusion: The significant differences in MHR and NHR between the three groups were due to the differences between groups 0 and 1. MHR and NHR were significantly higher in group 1 patients, although there was no statistically significant difference between groups 1 and 2.

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Cardiovascular disease is the leading cause of death and morbidity worldwide, with a significant proportion occurring in low- and middle-income countries.[1] Vascular inflammation and dyslipidaemia are pivotal factors contributing to the onset and progression of atherosclerosis.[2]

Atherosclerosis is a complex, progressive, inflammatory process. It is characterised by the formation and build-up of atherosclerotic plaques, which are composed of distinct elements including lipids, necrotic cores, calcified areas, inflamed smooth muscle cells, endothelial cells, immune cells and foam cells.[3] Macrophages, which constitute the primary immune cell population found within arterial plaques, are widely recognised as a key factor in both the immune response and the progression of atherosclerosis.[4]

Macrophages primarily arise from circulating monocytes and resident tissue. Their recruitment to the lesion site occurs as they adhere to activated endothelial cells and subsequently migrate into the subendothelial cell space.[5] In the plaque, macrophages can take up particles of lipid deposits and become transformed into foam cells, which are one of the hallmark events of early atherosclerotic lesions.[6] These foam cells further induce a cascade of inflammatory responses that promote increased lipoprotein retention, extracellular matrix modification, and sustained chronic inflammation.[4-6]

A high monocyte count is associated with the development of atherosclerotic plaques. Monocytes are key components of the inflammatory process in atherosclerosis. Neutrophils also play an important role in various stages of atherosclerosis. They contribute to the instability of atherosclerotic plaques by increasing endothelial dysfunction, monocyte–macrophage activation and foam cell production.[7]

There is a strong inverse association between high-density lipoprotein cholesterol (HDL-C) and atherosclerosis. HDL-C

plays a central role in reverse cholesterol transport by providing the transfer of excess cholesterol from the adipocytes or macrophages back to the liver. HDL-C plays a significant anti-inflammatory and antioxidant role by controlling the activation of monocytes, preventing macrophage migration, and inhibiting the oxidation of low-density lipoprotein cholesterol (LDL-C). It accomplishes this by blocking the 12-lipoxygenase enzyme, which produces lipid hydroperoxides, and thereby prevents oxidation of LDL-C through interaction with transition metal ions. As a result, HDL-C protects the endothelium of arteries from the detrimental effects of LDL-C.[8,9]

The monocyte count to HDL-C ratio (MHR) is used as an indicator of inflammation. Recent studies have shown that MHR indicates the extent of oxidative stress and is used as a prognostic marker for cardiovascular disease.[10] Similarly, the neutrophil to HDL-C ratio (NHR) reflects inflammation status and dyslipidaemia, both of which play significant roles in coronary artery disease (CAD).[11]

MHR and NHR have undergone evaluation to predict the severity and extent of CAD in both stable CAD and acute coronary syndromes (ACS). There is a direct correlation between CAD and MHR levels. Previous studies have shown that MHR levels play a role in the prediction of CAD.[12-17] Furthermore, they have been investigated for their predictive capabilities regarding outcomes in patients with ACS, such as stent restenosis and mortality.[18-22] Additionally, their potential in detecting subclinical atherosclerosis has been explored through the assessment of the relationship between MHR and intima–media thickness (IMT).[23] However, the role of MHR and NHR in predicting plaque composition, specifically, identifying vulnerable soft plaques with a high risk for ACS or calcific plaques with a low risk for ACS, has not been studied.

The objective of this study was to perform a comparative analysis of MHR and NHR values among individuals with CAD who displayed either soft or calcific plaques, as well as among those without CAD. Our aim was to explore the relationship between MHR, NHR and the specific type of atherosclerotic plaques in patients whose coronary arteries were visualised through coronary computed tomography angiography (CCTA).

Methods

This retrospective study included 99 consecutive patients as revealed by CCTA. All patients underwent an examination between January and August 2023. The study protocol adhered to the principles of the 1975 Declaration of Helsinki. The study received approval from the ethics committee of the Izmir Bakırcay University (trial no: 1135, decision no: 1155).

A CCTA was performed on all patients utilising a 128-slice single-source scanner (Somatom Go Top; Siemens Healthcare, Forchheim, Germany). Coronary artery calcium scoring was conducted, and the Agatston score was quantified using the same CT scanner.

Patients with conditions such as known CAD, ACS, severe congestive heart failure, atrial fibrillation, severe valvular disease, hypertrophic cardiomyopathy, malignancies, autoimmune diseases and severe renal or liver failure were excluded from the study.

Diabetes mellitus was defined as having a fasting plasma glucose level greater than 126 mg/dl (6.99 mmol/l) or currently being treated with antidiabetic medication. Hyperlipidaemia was defined as having a fasting serum LDL-C level greater than 130 mg/dl (3.37 mmol/l) or receiving lipid-lowering drugs. Patients with a resting blood pressure of 140/90 mmHg or higher on at least two measurements or those taking antihypertensive medication were considered to have hypertension.

We defined the three patient groups as follows, based on the CCTA results. Group 0: a normal coronary artery group comprised individuals without atherosclerotic plaques and their Agatson score was 0 (Fig. 1). Group 1: the vulnerable plaque group included individuals with mixed atherosclerosis with or without calcific plaques (Figs 2, 3). Group 2: the stable plaque group consisted of individuals who had only calcific plaques (Fig. 4).

Patient gender, age, medical history, co-morbidities, routine biochemistry results, 12-lead electrocardiography, transthoracic

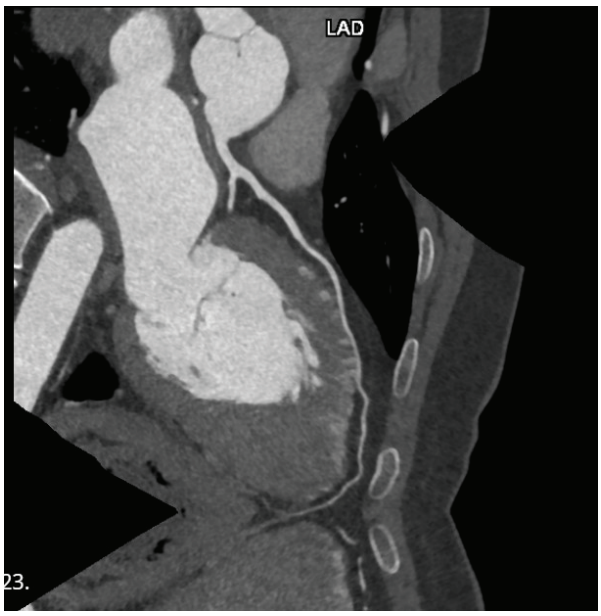

Fig. 1. Normal coronary artery.

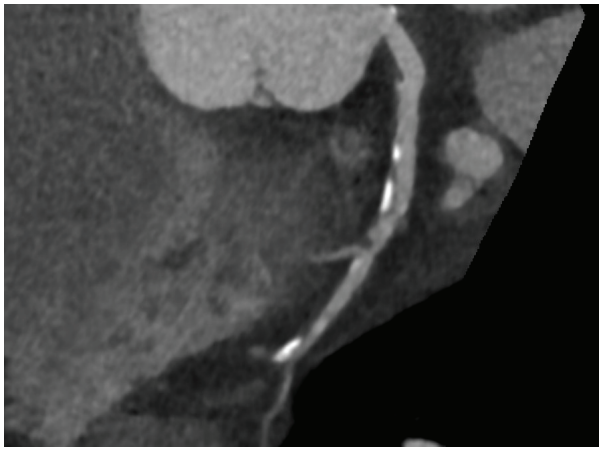

Fig. 2. Soft atherosclerotic plaque with calcification (mixed).

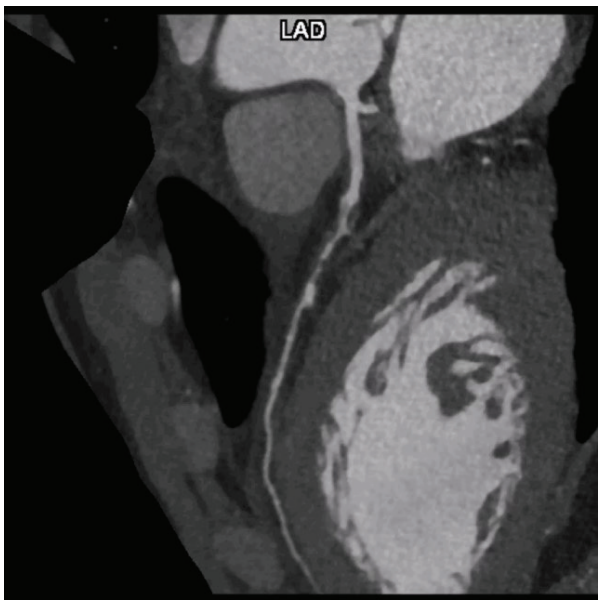

Fig. 3. Soft atherosclerotic plaque.

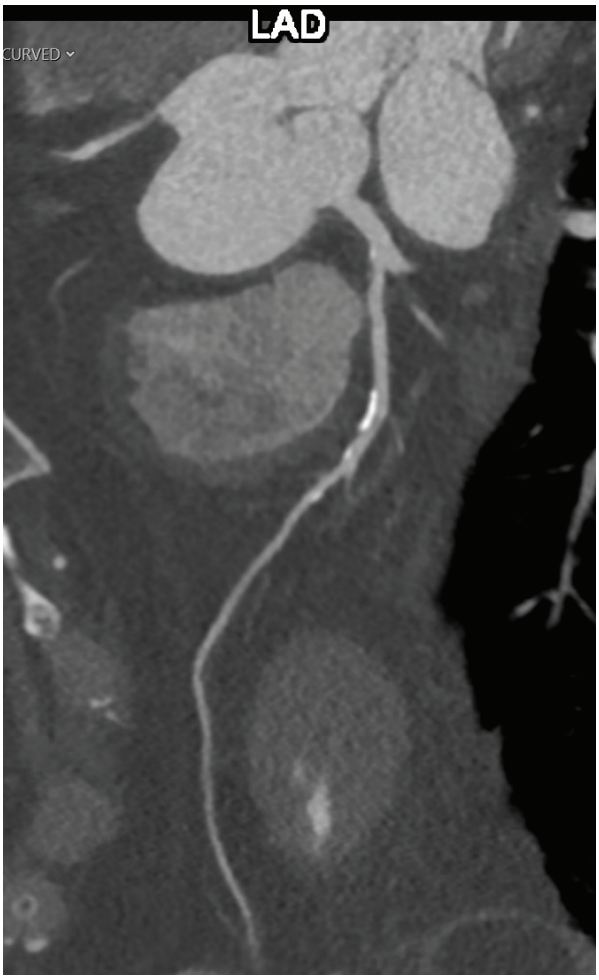

Fig. 4. Stable calcific plaque.

echocardiography and CCTA were retrieved from the medical records at our medical centre.

Statistical analysis

Statistical analyses were performed with IBM SPSS for Windows Version 25.0 software. Numerical variables are expressed as mean ± standard deviation (SD). Categorical variables are summarised as numbers and percentages. The Kolmogorov–Smirnov test was used to test normality of distribution. Pearson's chi-squared test was performed for categorical data analyses. We compared parametric values among the groups by one-way ANOVA. Bonferroni's correction test was used as a *post hoc* test for multiple comparisons among the groups. Comparisons of non-parametric values among the groups were performed by the Kruskal–Wallis test. A p-value < 0.05 was considered to reflect statistical significance.

Results

Age, gender, body mass index and smoking status did not exhibit significant differences among the three groups. Additionally, lipid profiles showed similarity across all the groups and blood pressure did not significantly differ between them. The lower diastolic blood pressure observed in group 2 may have been the result of marked calcification of the arterial endothelium (Table 1).

Haemoglobin levels were significantly higher in group 1 compared to group 2. Platelet and lymphocyte counts, red blood cell distribution width and mean platelet volume were not significantly different between all groups. WBC, monocyte and neutrophil counts were highest in group 1, and they were significantly higher in group 1 than in group 0. This pattern was also observed between group 0 and group 2, as well as between group 1 and group 2, although it did not reach statistical significance.

Neutrophil-to-lymphocyte ratio (neutrophil/lymphocyte) and monocyte-to-lymphocyte ratio (monocyte/lymphocyte) were not statistically significantly different between the groups. The MHR and NHR were significantly higher in group 1. In group 0, the

Table 1. Demographic and blood cholesterol values between the groups

Variables	*Group 0 (control,* n = *42)*	*Group 1 (vulnarable plaque,* n = *31)*	*Group 2 (stable plaque,* n = *26)*	p-*value*
Age (years)	59.80 ± 8.63	56.54 ± 9.43	62.61 ± 8.08	0.361
Female, *n* (%)	9 (21.4)	8 (18.6)	7 (16.3)	0.764
Smoking, *n* (%)	12 (28.5)	10 (32.2)	8 (30.7)	0.532
BMI, kg/m^2	26.84 ± 4.10	28.35 ± 4.31	26.29 ± 3.87	0.376
HT, *n* (%)	32 (76.1)	25 (80.6)	21 (80.8)	0.234
HL, *n* (%)	27 (64.2)	21 (67.7)	18 (69.2)	0.102
DM, *n* (%)	13 (30.9)	11 (35.4)	8 (30.7)	0.156
SBP (mmHg)	132.14 ± 14.01	137.58 ± 13.83	131.73 ± 16.05	0.351
DBP (mmHg)	80.28 ± 9.86	82.58 ± 9.82	76.38 ± 9.91	0.061
TC (mg/dl)	216.47 ± 42.13	235.94 ± 53.15	225.12 ± 44.55	0.240
LDL-C (mg/dl)	132.78 ± 38.21	148.96 ± 48.65	139.34 ± 40.41	0.328
HDL-C (mg/dl)	55.59 ± 14.66	53.32 ± 12.65	54.07 ± 12.87	0.940
TG (mg/dl)	143.28 ± 57.92	168.96 ± 65.33	154.01 ± 66.92	0.322

BMI: body mass ındex, HT: hypertension, HL: hyperlipidaemia, DM: diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, TG: triglycerides.
Values are *n* (%) or mean ± SD, $p \leq 0.05$ represents statistical significance.

Table 2. Agatson score and blood parameter values between the groups

Variables	*Group 0 (control,* n = *42)*	*Group 1 (vulnarable plaque,* n = *31)*	*Group 2 (stable plaque,* n = *26)*	p-*value*
Agatson score	0	148.56 ± 218.15	266.46 ± 360.28	0.016
Hb (g/dl)	13.88 ± 1.41	14.65 ± 1.40	13.66 ± 1.22	0.024
WBC (× 10³ cells/µl)	6.31 ± 0.97	7.61 ± 1.95	6.73 ± 1.62	0.002
Platelets (× 10³ cells/µl)	245 ± 59	260 ± 56	254 ± 56	0.55
Lymphocytes (× 10³ cells/µl)	2.35 ± 0.61	2.60 ± 0.77	2.33 ± 0.56	0.200
Monocytes (× 10³ cells/µl)	0.40 ± 0.09	0.50 ± 0.11	0.47 ± 0.12	0.001
Neutroplils (× 10³ cells/µl)	3.32 ± 0.81	4.19 ± 1.36	3.66 ± 1.08	0.005
Neutrophils/lymphocytes	1.55 ± 0.75	1.67 ± 0.51	1.59 ± 0.41	0.702
Monocytes/lymphocytes	0.18 ± 0.08	0.20 ± 0.06	0.20 ± 0.05	0.426
Platelets/lymphocytes	111.08 ± 42.54	107.54 ± 36.99	113.85 ± 36.45	0.826
SII [(platelets × neutrophils)/ lymphocytes]	385.56 ± 233.09	443.28 ± 183.38	414.11 ± 175.63	0.492
RDW	13.55 ± 1.01	13.69 ± 1.39	13.71 ± 0.71	0.824
MPV	10.30 ± 1.39	9.88 ± 1.08	9.58 ± 1.37	0.081
MHR	0.0079 ± 0.0029	0.0102 ± 0.003	0.0095 ± 0.003	0.013
NHR	0.063 ± 0.023	0.085 ± 0.036	0.073 ± 0.032	0.012

Hb: haemoglobin, WBC: white blood cells, SII: systemic immune–inflammation index, RDW: red blood cell distribution width, MPV: mean platelet volume, HDL-C: high-density lipoprotein cholesterol, MHR: monocyte to HDL-C ratio, NHR: neutrophyl to HDL-C ratio.
Values are mean ± SD, $p \leq 0.05$ represents statistical significance.

MHR was 0.0079 ± 0.0029, while in group 1 it was 0.0102 ± 0.003 (p = 0.013). Similarly, the NHR in group 0 was 0.063 ± 0.023, while in group 1 it was 0.085 ± 0.036 (p = 0.012). Group 2 exhibited a higher MHR and NHR level compared to group 0 but a lower MHR and NHR level than group 1. However, these differences did not reach statistical significance. Systemic inflammatory index (SII) was higher in group 1, but this differentiation was not statistically significant (Table 2).

Discussion

The current European Society of Cardiology guidelines for stable coronary artery syndrome recommend utilising either non-invasive functional imaging to detect ischaemia or anatomical imaging via CCTA as the primary diagnostic test for CAD.[24] CCTA has shown promise in imaging the properties and morphology of coronary plaques. Studies have shown that CCTA can assess the burden of atherosclerosis and plaque morphology, and yields results comparable to those obtained with intravascular ultrasound.[25]

Histological studies suggest that plaque composition plays a central role in the pathogenesis and clinical consequences of coronary artery atherosclerotic lesions. Expert consensus indicates that the morphology, composition and degree of inflammation of coronary atherosclerotic plaques are more important than the degree of luminal stenosis.[26] In atherosclerotic heart disease, intimal thickening, which is composed of smooth muscle cells and is affected by increased macrophage and lipid influx, is observed early in the disease process.

The next phase is represented by the formation of a necrotic core and the development of a fibrous cap atheroma. The necrotic core contains a certain amount of lipids and apoptotic macrophages. Intraplaque haemorrhages are also frequently seen in this entity and lead to further enlargement of the lipid core. A stable fibrous cap may prevent the lesion from developing. If the fibrous cap loses matrix proteins and smooth muscle cells, a thin cap atheroma can result. Fibrocalcific plaques might represent an end stage of the atherosclerosis process and can contain extensive calcifications. Due to a stable fibrous cap and low lipid content, these lesions rarely cause thrombosis. However, they may cause chronic ischaemic symptoms due to narrowing of the lumen.

The most devastating consequences of atherosclerosis, such as ACS and stroke, result from thrombosis. Plaque rupture is the leading cause of coronary thrombosis. Ruptured plaques exhibit distinctive characteristics, including a sizable lipid-rich core, a thin fibrous cap containing few smooth muscle cells but numerous macrophages, angiogenesis, adventitial inflammation and outward remodelling. The term 'vulnerable plaque' should be universally reserved for plaques that closely resemble the underlying causes of luminal thrombosis. Typically, it is specifically used to refer to rupture-prone plaques. The non-thrombosed lesion that most closely resembles the acute plaque rupture and subsequently represents its precursor is known as the thin-cap fibro-atheroma.[27,28]

Previous studies have demonstrated that the morphology of plaques in coronary angiography has had a significant impact on outcomes. The mortality rate has shown a progressive increase, rising from 1.4% for calcified plaques to 3.3% for mixed plaques, and significantly higher at 9.6% for non-calcified plaques. The risk-adjusted hazard ratios for all-cause mortality were 3.2 (95% confidence interval: 1.3–8.0, p = 0.001) for individuals with mixed plaques and 7.4 (95% confidence interval: 2.7–20.1, p = 0.0001) for those with non-calcified plaques when compared to those with calcified plaques. This study clearly reveals that the presence of non-calcified and mixed coronary plaques is associated with worse long-term clinical outcomes compared to those with calcified plaques, independent of cardiovascular risk factors and the number of diseased coronary arteries.[29]

The results of the present study indicate that MHR and NHR were significantly higher in subjects with CAD. These differences can be attributed to the soft and mixed plaque groups, which carry a higher risk of ACS. These markers concurrently reflect inflammation status and dyslipidaemia, which are the primary causes of atherosclerosis and are more pronounced in vulnerable plaques.[11]

Vulnerable plaques can lead to thrombotic events, resulting in ACS and stroke.[27,28] This phenomenon can help explain the predictive capabilities of MHR and NHR for mortality and stent restenosis in patients with ACS.[18-22] MHR and NHR possess predictive value for the severity and extent of CAD in both stable CAD and ACS. This can be explained by the proportional relationship between atherosclerotic plaque burden and vulnerable plaque quantity. MHR and NHR are positively correlated with the prevalence and severity of CAD. This variability may be explained by the composition of the patient groups, which may exhibit different amounts of sensitive plaque.[12-17]

The MHR correlates significantly with carotid IMT values, allowing the detection of subclinical atherosclerosis. Early in the disease process, intimal thickening is observed, characterised by smooth muscle cell involvement, increased macrophages, predisposition to lipid influx and aggravated inflammation. Importantly, during this period, there is no evidence of calcification.[23,27] This situation can be explained by our trial results, which indicate a significantly higher MHR in soft and

mixed plaques without calcification.

Atherosclerotic plaque type is of great importance in determining the treatment strategy and prognosis. Among non-invasive methods, CCTA stands out as the most promising approach with the potential to comprehensively characterise coronary artery plaque volume. Studies have demonstrated that CCTA is capable of identifying non-calcified plaques, which are notably influenced by aggresive statin therapy and, consequently, contribute to the therapeutic benefits.[30] Studies using CCTA indicate that the combination of statins with angiotensin converting enzyme inhibitors or angiotensin receptor blockers may be more effective for anti-atherosclerotic therapy than using statins alone, even in patients with CAD. This suggests that combination therapy has an inhibitory effect on vascular remodelling.[31]

Limitations

The primary limitation of this study lies in the restricted number of participants. Patients with autoimmune conditions impacting on inflammatory markers, individuals using anti-inflammatory medications, and those on statins, acknowledged for their efficacy in managing inflammation in atherosclerosis, were not incorporated into the research. Additionally, the presence of co-morbidities and drug therapies influencing MHR and NHR could not be entirely mitigated. However, rigorous efforts were made to ensure that factors such as smoking status, gender, age and prevalence of chronic diseases, such as hypertension and diabetes mellitus, and the frequency of drug usage (including antihypertensive drug categories and quantities) potentially affecting MHR and NHR were comparable between the patient and control groups.

Conclusion

There is a growing number of studies investigating the utility of MHR and NHR in patients with CAD. These suggest that MHR and NHR may be valuable markers for assessing the prevalence and severity of CAD, classifying risk and predicting prognosis. Our study is the first to establish a relationship between MHR and NHR and atherosclerotic plaque types. MHR and NHR levels were significantly higher in patients with vulnerable plaques, which could lead to ACS and sudden cardiac death. We propose that MHR and NHR can be used as cost-effective and simple markers of inflammation to predict the presence of vulnerable plaque in patients undergoing invasive coronary angiography. Invasive coronary angiography is insufficient to demonstrate atherosclerotic plaque content. MHR and NHR may be helpful in determining treatment options and their intensity after invasive coronary angiography.

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