

The Interplay of Inflammatory Cytokines, Epigenetic Biomarkers and Cardiac Imaging Features in Coronary Artery Disease Progression: A Multimarker Approach

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Abstract This study evaluated the significance of a multibiomarker model, including an epigenetic marker (miR-155), inflammatory cytokines (TNF- α , IL-1 β) and noninvasive cardiac imaging patterns, for assessing the risk of progressive coronary artery disease (CAD). A comprehensive assessment of correlations between the parameters of coronary atherosclerosis according to contrast MSCT angiography (coronary calcium score, degree of stenosis, remodeling index, segment involvement score -SIS, density, volume and mass of plaques) and biomarker levels was carried out in 152 patients with stable and unstable forms of coronary artery disease. miR-155 expression was determined using a Rotor-Gene Q device by real-time polymerase chain reaction (qRT-PCR), and concentrations of proinflammatory cytokines were determined by enzyme-linked immunosorbent assay (ELISA). We hypothesized that the combined assessment of these biomarkers would improve risk stratification compared to the analysis of individual biomarkers. There were fairly close positive correlations of miR-155 with IL-1 ($r=0.54$; $p<0.01$) and TNF- α ($r=0.57$; $p<0.01$). It is noteworthy that the nature and strength of these associations varied depending on the clinical form of CAD. The study revealed significant correlations between the levels of inflammatory markers (TNF- α , IL-1 β , IL-4), miR-155, and MSCT angiography in patients with various forms of CAD. In patients with unstable angina (UA), TNF- α , IL-1 β , and miR-155 levels showed strong positive correlations with signs of the prevalence and vulnerability of atherosclerosis: SIS index, degree of stenosis, remodeling index (RI), plaque volume and mass (r up to 0.88; $p<0.001$), and They are also negative with plaque density ($r=-0.80$; $p<0.001$). On the contrary, IL-4 had reverse bonds, especially pronounced in HC (RI: $r=-0.70$; plaque volume: $r=-0.71$), confirming its protective role. The inflammatory response index (IRI = (IL-1 β + TNF- α)/IL-4) showed high prognostic value in HC, correlating with the main signs of plaque instability. The expression of miR-155 was also closely associated with active forms of atherosclerosis. In the stable angina group, similar associations persisted, but were less pronounced. The data obtained emphasize the importance of assessing the inflammatory profile and miR-155 in combination with MSCT data for risk stratification and detection of signs of atherosclerotic plaque instability in patients with CAD. These results highlight the key role of inflammatory and epigenetic mechanisms in the destabilization of atherosclerotic plaques and their morphological expression. The data obtained indicate that this multibiomarker panel can become a valuable tool for early detection, risk assessment, and the development of individual management strategies for patients with CAD.

Keywords Coronary artery disease, Cardiac imaging, MSCT-CA, Coronary calcium index, Degree of stenosis, Remodeling index, Plaque density (HU), Segment involvement score (SIS), Cytokines, TNF- α , IL-1 β , IL-4, Epigenetic markers, miR-155 expression

1. Introduction

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Cardiovascular diseases (CVDs) remain the leading cause of mortality globally, accounting for approximately 17.9 million deaths in 2019—nearly 32% of all deaths—with over 75% occurring in low- and middle-income countries [1]. Ischemic heart disease (IHD), also known as coronary artery disease (CAD), is the most critical component of this burden, responsible for about 18.6% of global mortality in

2019 [2]. Despite improvements in age-adjusted mortality from CAD, the absolute number of deaths attributed to CAD is growing, likely due to factors such as an aging global population and increased risk factor risk factors such as obesity, diabetes, and smoking, particularly in low- and middle-income countries [3], underscoring the urgent need for effective prevention and treatment strategies tailored to diverse socioeconomic contexts.

Atherosclerosis, the pathological hallmark of CAD, evolves through a multifactorial interplay of genetic susceptibility, epigenetic regulation, metabolic stress, and chronic inflammation. Unstable atherosclerotic plaques—characterized by large lipid cores, thin fibrous caps, and significant inflammatory infiltrates—are the primary triggers of acute coronary syndromes (ACS), myocardial infarction (MI), and sudden cardiac death [4]. Therefore, early detection and precise evaluation of atherosclerotic changes in the coronary arteries are essential for predicting adverse outcomes and improving patient management.

Chronic systemic inflammation plays a pivotal role in the etiopathogenesis of atherosclerosis [5]. Elevated levels of proinflammatory cytokines, including tumor necrosis factor- α (TNF- α) and interleukin-1 beta (IL-1 β), alongside reduced levels of anti-inflammatory cytokines such as interleukin-4 (IL-4), are strongly linked to plaque progression, destabilization, and a heightened risk of cardiovascular events [6–7]. Studies have demonstrated that elevated TNF- α and IL-1 β levels are associated with increased plaque burden and vulnerability in CAD patients, while diminished IL-4 levels correlate with a higher incidence of acute events [8–9]. Correlating cardiac imaging markers—particularly those obtained through multislice computed tomography coronary angiography (MSCT-CA)—with cytokine levels and clinical manifestations of CAD can enhance our understanding of inflammation's role in atherosclerosis and help identify valuable prognostic markers.

Beyond inflammation, epigenetic mechanisms also contribute significantly to the pathophysiology of CAD. Recent research has identified over 50 miRNAs as critical regulators of vascular homeostasis and CAD progression, playing significant roles in atherosclerotic plaque development, endothelial cell senescence, and impaired vascular repair. Certain miRNAs have been found to influence inflammatory pathways within atherosclerotic plaques, contributing to plaque instability and rupture, which are key events in ACS, such as MI and unstable angina (UA). Furthermore, circulating miRNAs have emerged as promising non-invasive biomarkers for early detection, risk assessment, and therapeutic targeting in CAD [10].

Among them, microRNA-155 (miR-155) has emerged as a key regulator of inflammation and vascular cell function, including that of endothelial cells, macrophages, and smooth muscle cells. Overexpression of miR-155 is associated with intensified inflammatory responses, lipid accumulation, necrotic core formation, and thinning of the fibrous cap—hallmarks of vulnerable plaques prone to rupture [11–12]. Thus, miR-155 may serve as an important molecular indicator

of inflammatory activity and a predictor of plaque instability, which can be reflected in cardiac imaging profiles.

Multislice computed tomography coronary angiography (MSCT-CA) is becoming increasingly valuable as a noninvasive imaging modality for diagnosing CAD. In addition to visualizing anatomical abnormalities, MSCT-CA provides quantitative assessments of atherosclerotic burden, including coronary calcium score (CCS), degree of stenosis (DS), remodeling index (RI), plaque composition and density in Hounsfield units (HU), segment involvement score (SIS), and plaque number, volume, and mass [13–14]. These imaging parameters offer insights into the pathomorphological features of atherosclerosis and enable more individualized disease monitoring.

Several large-scale international investigations have recently examined the association between inflammatory biomarkers and plaque characteristics using advanced imaging modalities. The PROSPECT trial, involving patients undergoing percutaneous coronary intervention, demonstrated that elevated levels of systemic inflammatory markers (e.g., hs-CRP, IL-6) independently predicted high-risk plaque morphology—such as large lipid cores and thin fibrous caps—visualized via intravascular ultrasound and near-infrared spectroscopy. These vulnerable features corresponded to an increased risk of future cardiovascular events [15].

Randomized trials targeting the IL-1 β pathway, such as CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), confirmed that inhibiting proinflammatory cytokines stabilizes atherosclerotic plaques. Treatment not only reduced systemic inflammation but also attenuated plaque progression as measured by serial CT angiography, resulting in significantly fewer recurrent cardiovascular events [6].

Cohort studies across Europe and North America, including the GENES and ACC Science studies, evaluated circulating miRNAs—especially miR-155—and their relation to plaque composition. Notably, higher miR-155 levels showed strong positive associations with lipid-rich necrotic core plaques and predicted acute ACS events [16–17].

A meta-analysis pooling data from multiple observational studies confirmed that miR-155 levels are significantly elevated in CAD patients compared to healthy controls, with greater expression linked to severe atherosclerotic burden and high-risk plaque phenotypes identified by CT angiography [18].

A Chinese multi-ethnic study on miRNA biomarkers of CAD found that miR-155, alongside miR-130a and miR-221, independently predicted coronary stenosis severity, as determined by invasive angiography—highlighting its role across diverse populations [6].

Although these studies have significantly advanced our understanding of individual biomarker–imaging relationships, most investigations have focused primarily on either proinflammatory cytokines (such as IL-1 β or TNF- α) or epigenetic regulators like miR-155. Anti-inflammatory mediators—particularly interleukin-4 (IL-4), which plays a crucial counter-regulatory role—have received considerably

less attention in this context. Furthermore, prior studies often assessed isolated imaging parameters, neglecting the full spectrum of multislice computed tomography angiography (MSCT-CA) metrics such as coronary calcium score, segment involvement score, remodeling index, plaque volume, mass, and density. Importantly, few studies have systematically stratified patients by clinical CAD phenotype (stable vs. unstable angina), which is essential for identifying biomarker-imaging patterns predictive of acute events. Addressing these limitations could improve the precision of multi-marker risk stratification and support more targeted interventions.

In light of these gaps, the present study aims to investigate the relationships between comprehensive MSCT-CA parameters (including CCS, DS, RI, HU, SIS, number, volume, and mass of plaques) and circulating levels of both pro- and anti-inflammatory cytokines (TNF- α , IL-1 β , IL-4), along with the expression of the epigenetic biomarker miR-155, in patients with CAD. By evaluating these associations across distinct clinical presentations—namely stable and unstable angina—the study seeks to clarify how inflammatory and epigenetic imbalances contribute to coronary atherosclerosis progression and plaque destabilization. The findings may help refine patient-specific risk stratification strategies and inform personalized approaches to CAD management.

2. Materials and Methods

The study involved 152 patients of both sexes who received inpatient treatment at the 1st and 2nd cardiology departments. The mean age of the cohort was 60.9 ± 1.46 years. The main group included 73 patients diagnosed with unstable angina pectoris (UAP), while the comparison group comprised 79 patients with stable angina pectoris (SAP), functional class III. No statistically significant differences in age, sex, duration of CAD, or comorbidity prevalence were observed between the two groups at baseline.

To investigate the epigenetic mechanisms involved in CAD and evaluate coronary atherosclerosis destabilization, quantitative measurement of microRNA-155 (miR-155) levels in blood plasma was performed. miRNA expression analysis was carried out via real-time reverse transcription polymerase chain reaction (RT-qPCR) using a Rotor-Gene Q system. Total miRNA was extracted using the miRNeasy Mini Kit (QIAGEN, USA), in accordance with the manufacturer's protocol. The high stability of the miR-155 molecular ion ($[M+H]^+=281.171$) under analysis conditions ensured reliable quantification, even at nanomolar concentrations and with a minimal sample volume (0.5 μ L).

Serum concentrations of pro- and anti-inflammatory cytokines — interleukin-1 beta (IL-1 β), interleukin-4 (IL-4), and tumor necrosis factor alpha (TNF- α) — were determined by enzyme-linked immunosorbent assay (ELISA) using commercially available standard kits. All assays were conducted strictly following the manufacturer's guidelines, including the use of

standardized reagents and reference ranges. These procedures were performed at the Molecular Genetics Laboratory of the Centre for Biomedical Technologies.

Assessment of coronary atherosclerosis imaging characteristics was conducted via MSCT-CA. Scans were performed at the Republican Specialized Scientific and Practical Centre of Cardiology using a 64-slice CT scanner. A breath-hold protocol with ECG synchronization was employed to ensure high spatial resolution with a slice thickness of 0.75–2 mm. Intravenous administration of a non-ionic iodine-based contrast agent (350 mg iodine/mL) was carried out via an automatic injector at 4.5–5 mL/s, with parameters optimized individually for each patient.

A low-dose non-contrast MSCT was initially performed to assess the CCI using the Agatston scoring system. This was followed by ECG-gated contrast-enhanced scanning during the optimal phase of the cardiac cycle. Post-processing was conducted using advanced cardiology-specific software and included automatic or semi-automatic segmentation of the coronary arteries and quantitative evaluation of the following parameters:

- Coronary calcium score (CCS), per Agatston scoring
- Segment involvement score (SIS), indicating the extent of atherosclerosis
- Degree of coronary artery stenosis (DS)
- Remodeling index (RI) of coronary vessels
- Plaque density in Hounsfield units (HU)
- Volume and mass of atherosclerotic plaques
- Identification of high-risk plaques, based on morphological instability features (e.g., lipid core, ulceration, irregular surface, signs of thrombosis), evaluated via both visual inspection and algorithm-based tools [20].

To provide a comprehensive assessment of coronary atherosclerosis severity and predict cardiovascular event risk, all MSCT-CA findings were interpreted according to the CAD-RADS (Coronary Artery Disease - Reporting and Data System) classification. This included evaluation of coronary calcification (CCI), global left ventricular function, SIS, high-risk plaque features, epicardial fat volume, and pericoronary adipose tissue density [21].

Statistical analysis was conducted using STATISTICA 6.0 and SAS 6.3. An electronic database was developed in Microsoft Excel (Office 2020). The Wald test was used to compute p-values, with statistical significance set at $p < 0.05$. Spearman's rank correlation coefficient was used to assess associations between variables.

3. Research Results and Discussion

In contemporary clinical cardiology, the multi-biomarker model entails the simultaneous use of several biomarkers — including epigenetic and inflammatory indicators — to assess the severity of coronary artery disease (CAD), as well as to aid in its diagnosis and prognosis. Unlike single-marker approaches, the multi-biomarker strategy integrates data from multiple biological systems, thereby providing a more

comprehensive and precise diagnostic profile. This synergy improves both sensitivity and specificity, significantly reducing the probability of false-positive or false-negative results — a critical factor in the assessment of complex, multifactorial conditions such as CAD.

To implement this approach, we conducted a comprehensive analysis of selected epigenetic (miR-155) and inflammatory (IL-1 β , TNF- α) markers in patients diagnosed with CAD. The prognostic relevance of miR-155 overexpression in plasma — in conjunction with elevated levels of pro-inflammatory cytokines — was validated through correlation analysis.

The results demonstrated a strong positive correlation between miR-155 expression and the concentration of IL-1 β ($r=0.54$, $p<0.01$), and an even stronger correlation with TNF- α levels ($r=0.57$, $p<0.01$). These findings suggest a significant interplay between epigenetic regulation and systemic inflammation in the pathogenesis and progression of CAD.

The graphical distribution of the data (Figure 1) illustrates the high correlation through a distinct elongation of the data point cloud along the trend line, consistent with the principles of scatterplot interpretation. This linear relationship underscores the potential of miR-155 as a sensitive biomarker, especially when used in combination with inflammatory markers, for identifying patients at high risk of acute cardiovascular events or plaque destabilization.

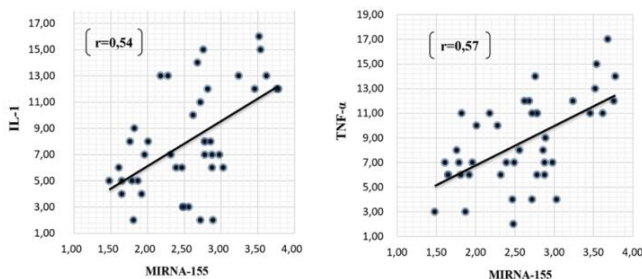


Figure 1. Evaluation of the correlation between the concentration of miR-155 and the level of proinflammatory cytokines

In this study, special attention was paid to the relationship between systemic proinflammatory markers and cardiac imaging patterns of coronary atherosclerosis, which allows for a deeper understanding of the mechanisms underlying the progression of coronary heart disease and the destabilization of atherosclerotic plaques. The analysis of correlations between the levels of proinflammatory cytokines (TNF- α and IL-1 β) and the parameters of MSCT angiography of the coronary arteries revealed significant differences between patients with UAP and SAP emphasizing the dynamics of the inflammatory process.

In the group of patients with unstable angina, significant and strong direct correlations were observed between the levels of proinflammatory cytokines and markers of the prevalence and activity of the atherosclerotic process. Thus, the involvement index (SIS – Segment Involvement Score), reflecting the overall spread of atherosclerosis in the coronary bed, demonstrated a significant positive correlation with

TNF- α ($r=0.60$, $p<0.001$) and a fairly close one with IL-1 β ($r=0.75$, $p<0.001$). The degree of coronary artery stenosis also showed significant positive relationships with TNF- α ($r=0.64$, $p<0.001$) and IL-1 β ($r=0.66$, $p<0.001$). These findings are pathogenetically supported by the fact that TNF- α and IL-1 β are key inflammatory mediators stimulating smooth muscle cell proliferation, extracellular matrix synthesis, and lipid accumulation, which contribute to the growth of atherosclerotic plaques and the progression of stenosis. Particularly strong correlations with IL-1 β can be explained by its central role in initiating and amplifying the inflammatory cascade in atherosclerosis.

The coronary calcium score, on the other hand, showed only a weak positive correlation with TNF- α ($r=0.15$, $p<0.05$) and IL-1 β ($r=0.25$, $p<0.01$), which can be attributed to the fact that calcification is a more chronic and delayed process, reflecting cumulative inflammation rather than the acute phase characteristic of UAP.

The relationships with parameters characterizing plaque vulnerability deserve special attention. The coronary artery remodeling index (RI), which is often associated with positive remodeling and the formation of vulnerable plaques, showed fairly close positive correlations with TNF- α ($r=0.70$, $p<0.001$) and strong ones with IL-1 β ($r=0.80$, $p<0.001$). These findings indicate that the active inflammatory process mediated by these cytokines is directly involved in pathological arterial remodeling. This process creates conditions for plaque expansion without significant luminal narrowing, which, in turn, contributes to plaque instability.

Similarly, the volume and mass of atherosclerotic plaques demonstrated robust positive correlations with TNF- α ($r=0.76$, $p<0.001$) and IL-1 β ($r=0.84$, $p<0.001$), confirming the role of these cytokines in promoting plaque growth. Conversely, the density of atherosclerotic plaques (Hounsfield units, HU) showed notable negative correlations with TNF- α ($r=-0.55$, $p<0.001$) and IL-1 β ($r=-0.60$, $p<0.001$). This inverse relationship suggests that elevated proinflammatory cytokine levels are associated with lower plaque density, a hallmark of lipid-rich, necrotic, and inflammation-infiltrated plaques—morphological features characteristic of vulnerable and unstable lesions.

In contrast, in the comparison group (SAP), correlations were less pronounced but remained statistically significant, reflecting a more chronic and less aggressive inflammatory process. The coronary calcium index demonstrated moderate positive correlations with TNF- α ($r=0.30$, $p<0.001$) and IL-1 β ($r=0.35$, $p<0.001$), which is expected, as calcification is a marker of long-standing atherosclerosis. The segment involvement score (SIS) showed moderate positive correlations with TNF- α ($r=0.40$, $p<0.001$) and IL-1 β ($r=0.45$, $p<0.001$). The degree of coronary artery stenosis also demonstrated moderate and significant positive associations with TNF- α ($r=0.44$, $p<0.001$) and IL-1 β ($r=0.50$, $p<0.001$). The coronary artery remodeling index (RI) showed moderate positive correlations with TNF- α ($r=0.30$, $p<0.001$) and IL-1 β ($r=0.40$, $p<0.001$). The volume/mass of atherosclerotic plaques also correlated moderately positively with TNF- α ($r=0.47$,

$p < 0.001$) and IL-1 β ($r = 0.50$, $p < 0.001$). At the same time, atherosclerotic plaque density (HU) had only a weak negative correlation with TNF- α ($r = -0.20$, $p < 0.05$) and IL-1 β ($r = -0.20$, $p < 0.05$). These less pronounced relationships in SAP patients suggest that, although inflammation is present in stable CAD, it is not as acute and does not result in the dramatic changes in plaque morphology and arterial remodeling observed in UAP.

Thus, the comparative analysis indicates that the levels of proinflammatory cytokines, especially IL-1 β , in combination with MSCT-CA parameters reflecting plaque activity (RI, plaque density, plaque volume/mass), serve as key predictors of atherosclerosis destabilization and can be used for risk stratification in patients with CAD.

This study also evaluated the anti-inflammatory cytokine interleukin-4 (IL-4), known for its role in limiting the inflammatory response and stimulating reparative processes. Pathogenetically, increased IL-4 levels are associated with macrophage polarization toward the M2 phenotype, suppression of proinflammatory cytokine secretion, and enhanced collagen synthesis. In the context of atherosclerosis, these mechanisms may contribute to plaque stabilization and slow disease progression. Accordingly, inverse correlations were anticipated between IL-4 levels and markers of the prevalence, severity, and vulnerability of the atherosclerotic process, as well as a direct correlation with features of a more stable plaque phenotype (e.g., higher density).

In the main group of patients with unstable angina (UAP), IL-4 levels demonstrated noticeable and fairly strong negative correlations with most cardiac imaging parameters characterizing the extent and vulnerability of atherosclerosis. The segment involvement score (SIS) correlated with IL-4 at $r = -0.60$ ($p < 0.001$), indicating a significant inverse relationship. Similarly, the degree of coronary artery stenosis also showed a marked negative correlation ($r = -0.65$, $p < 0.001$). The coronary artery remodeling index (RI), often associated with positive arterial remodeling and plaque instability, demonstrated a strong negative correlation with IL-4 ($r = -0.70$, $p < 0.001$). The strongest negative correlation was observed with the volume/mass of atherosclerotic plaques ($r = -0.71$, $p < 0.001$). These results are pathogenetically consistent with the notion that higher IL-4 levels are associated with a lower plaque burden and less pathological arterial remodeling, supporting the cytokine's protective role. A weak negative correlation with the coronary calcium index ($r = -0.10$, $p < 0.05$) aligns with the fact that this index reflects a more chronic and stable process, on which IL-4 likely has a limited impact. Conversely, atherosclerotic plaque density (HU) demonstrated a moderate positive correlation with IL-4 ($r = +0.40$, $p < 0.001$), indicating that elevated IL-4 levels are associated with denser (i.e., less lipid-rich, more fibrous or calcified) plaques—morphological features indicative of greater plaque stability, even under conditions of acute destabilization.

In the comparison group of patients with SAP, the negative correlations with IL-4 were less pronounced than in the UAP group but remained statistically significant. The involvement

index (SIS) showed a moderate negative correlation ($r = -0.30$, $p < 0.01$), and the degree of coronary artery stenosis also demonstrated a moderate inverse correlation ($r = -0.40$, $p < 0.001$). The remodeling index (RI) had a moderate negative correlation ($r = -0.50$, $p < 0.001$), while the volume/mass of atherosclerotic plaques displayed a moderate negative correlation ($r = -0.45$, $p < 0.001$). These findings confirm the role of IL-4 in inhibiting atherosclerotic progression and promoting plaque stability in chronic coronary artery disease. The coronary calcium index also showed a weak negative correlation with IL-4 ($r = -0.20$, $p < 0.05$). Atherosclerotic plaque density (HU) demonstrated only a weak positive correlation ($r = +0.15$, $p < 0.05$), indicating a less pronounced effect of IL-4 on plaque structure in stable CAD compared to its role during acute inflammation.

A comparative analysis of IL-4 correlations between the UAP and SAP groups allows us to conclude that, although IL-4 is an anti-inflammatory cytokine and its elevated levels are generally associated with reduced severity of atherosclerotic changes, the strength of these correlations is significantly higher in the UAP group. This may suggest that in unstable angina, against the background of an acute inflammatory process, compensatory anti-inflammatory mechanisms mediated by IL-4 are activated more intensively in an attempt to counteract plaque destabilization. However, despite their activation, the dominant influence of proinflammatory cytokines and the aggressiveness of the pathological process do not allow for complete plaque stabilization, ultimately resulting in the clinical manifestation of unstable angina. In the SAP group, where inflammation is more chronic, the influence of IL-4, although present, is not as pronounced and does not aim to urgently restrain pathological changes. Thus, IL-4 levels, especially when combined with MSCT parameters reflecting plaque morphology, may serve as an important marker of the balance between inflammatory and anti-inflammatory forces and contribute to a more accurate assessment of the risk of atherosclerotic plaque destabilization.

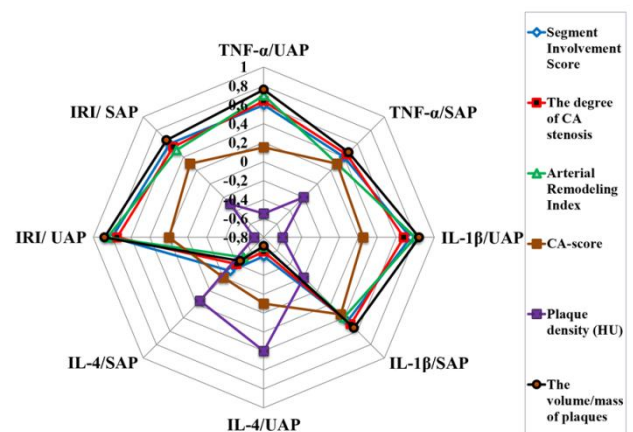


Figure 2. Correlation of inflammatory biomarkers with MSCT-AG patterns depending on the clinical form of CAD

To gain a deeper understanding of the role of inflammatory imbalance in the progression of coronary atherosclerosis and the development of cardiac imaging patterns, this study

utilized the Inflammatory Response Index (IRI), calculated as the ratio $(IL-1\beta + TNF-\alpha) / IL-4$. Pathogenetically, a high IRI indicates the dominance of proinflammatory cytokines over anti-inflammatory ones, which is a critical factor in the initiation, progression, and especially the destabilization of atherosclerotic plaques. Accordingly, direct correlations between IRI and imaging parameters indicative of the extent and vulnerability of atherosclerosis, as well as inverse correlations with markers of plaque stability, were anticipated.

In the main group of patients with UAP, exceptionally strong and significant positive correlations were found between the Inflammatory Response Index and cardiac imaging parameters indicating high activity and aggressiveness of the atherosclerotic process. The segment involvement score (SIS), reflecting the overall extent of atherosclerotic lesions, showed a strong positive correlation with IRI ($r=0.80$, $p<0.001$). The degree of coronary artery stenosis also demonstrated a close positive correlation ($r=0.75$, $p<0.001$). The strongest correlations were observed with parameters directly indicating plaque vulnerability: the coronary artery remodeling index (RI), often associated with positive remodeling and the formation of "vulnerable" plaques, showed a strong positive correlation ($r=0.85$, $p<0.001$), while the volume/mass of atherosclerotic plaques exhibited a very strong positive correlation with IRI ($r=0.88$, $p<0.001$). These findings convincingly confirm that a pronounced proinflammatory imbalance (high IRI) is a powerful driver of atherosclerotic plaque growth, pathological remodeling, and, consequently, an increase in stenosis severity and total lesion burden—key morphological substrates of unstable angina. The coronary calcium score (Ca scoring) showed only a weak positive correlation with IRI ($r=0.20$, $p<0.05$), which may be explained by the fact that calcification represents a more chronic, cumulative process less directly and immediately influenced by acute inflammation, as captured by the IRI, compared to dynamic plaque characteristics.

Of particular note is the inverse relationship between the Inflammatory Response Index (IRI) and atherosclerotic plaque density (measured in Hounsfield Units, HU) in the UAP group. A significant negative correlation was observed ($r=-0.70$, $p<0.001$), indicating that higher IRI values are associated with lower plaque density—i.e., more negative HU values. This pattern is characteristic of lipid-rich, necrotic, and macrophage-infiltrated plaques, which are highly vulnerable and prone to rupture. Pathogenetically, pronounced inflammation, as reflected by elevated IRI, promotes enlargement of the lipid core, thinning of the fibrous cap, and accumulation of inflammatory cells, particularly macrophages. These changes lead to a reduction in plaque density and substantially increase the risk of destabilization.

In the comparison group, consisting of patients with SAP, the correlations between IRI and cardiac imaging parameters were statistically significant, though less pronounced than those in the UAP group. The involvement index (SIS) showed a moderate positive correlation ($r=0.60$, $p<0.001$), while the degree of coronary artery stenosis was also positively correlated ($r=0.55$, $p<0.001$). The remodeling

index (RI) and the volume/mass of atherosclerotic plaques demonstrated moderate correlations ($r=0.50$, $p<0.001$ and $r=0.65$, $p<0.001$, respectively). The coronary calcium score exhibited a weak but statistically significant correlation ($r=0.30$, $p<0.01$). Plaque density (HU) was inversely correlated with IRI ($r=-0.30$, $p<0.01$), although this relationship was less pronounced compared to that observed in the UAP group.

These weaker but consistent associations in the SAP group suggest that chronic, low-grade inflammation also contributes to atherosclerosis progression, albeit with a more modest impact on plaque morphology and without leading to acute destabilization. Comparative analysis thus supports the conclusion that the Inflammatory Response Index, reflecting the balance between pro- and anti-inflammatory mediators, is a robust predictor of atherosclerotic activity and plaque vulnerability. The stronger correlations between IRI and imaging markers of "soft" plaques and pathological remodeling in the UAP group further underscore its prognostic value in identifying patients at elevated risk of acute coronary events.

In this study, we analyzed the expression level of micro RNA-155 (miR-155), a key epigenetic biomarker actively involved in the regulation of inflammatory processes and the progression of atherosclerosis. Pathogenetically, miR-155 functions as a proinflammatory microRNA that promotes the proliferation and activation of immune cells, stimulates cytokine release, and contributes to endothelial dysfunction, ultimately leading to the formation and destabilization of atherosclerotic plaques. Consequently, we expected to observe direct correlations between miR-155 expression levels and MSCT angiography parameters reflecting the prevalence, severity, and vulnerability of atherosclerotic lesions, as well as an inverse correlation with plaque density, which serves as an indicator of plaque stability.

Table 1. Correlation relationship of cardiac imaging patterns MSCT-AG with the level of miR -155 in the blood of patients with CAD

MSCT-AG indicators	The expression level of miRNA -155 in the main group with UAP		The expression level of miRNA -155 in the main group with SAP	
	r	r	r	r
Number of atherosclerotic plaques	0.55	<0.05	0.5	<0.05
Atherosclerotic plaque volume (mm ³)	0.68	<0.001	0.48	<0.05
Atherosclerotic plaque mass (mg)	0.43	<0.05	0.35	<0.05
Atherosclerotic plaque density (HU)	-0.80	<0.001	-0.60	<0.001
SIS Engagement Score	0.72	<0.001	0.55	<0.01
Ca scoring (Agatston scale)	0.38	<0.05	0.5	<0.05
Degree of coronary artery stenosis (%)	0.6	<0.001	0.45	<0.05
Coronary artery remodeling index (RI)	0.7	<0.001	0.42	<0.05

In the main group of patients with unstable angina (UAP), the expression level of miR-155 demonstrated significant positive correlations with cardiac imaging parameters reflecting the prevalence and activity of the atherosclerotic process. The involvement index (SIS — Segment Involvement Score) showed a strong positive correlation with miR-155 expression ($r=0.72$, $p<0.001$), indicating a close relationship between this epigenetic marker and the overall burden of coronary atherosclerosis. The degree of coronary artery stenosis also exhibited a notable positive correlation ($r=0.60$, $p<0.001$). The coronary artery remodeling index (RI), often associated with vulnerable plaque formation and pathological vessel dilation, showed a strong positive correlation ($r=0.70$, $p<0.001$) with miR-155 levels. Additionally, the volume of atherosclerotic plaques correlated positively ($r=0.68$, $p<0.001$), while plaque mass demonstrated a moderate positive correlation ($r=0.43$, $p<0.05$). These findings are pathogenetically supported by the role of increased miR-155 expression in promoting vascular inflammation, which drives plaque growth, pathological remodeling, and stenosis, serving as a key factor in the pathogenesis of unstable angina. The coronary calcium score (Ca scoring) showed a moderate positive correlation ($r=0.38$, $p<0.05$), potentially reflecting the chronic inflammatory influence of miR-155 on vascular calcification processes.

Of particular importance is the strong negative correlation observed between miR-155 expression and atherosclerotic plaque density (HU) in the UAP group ($r=-0.80$, $p<0.001$). This indicates that higher miR-155 levels are associated with plaques of lower density (more negative HU values), characteristic of lipid-rich, inflamed, and rupture-prone lesions. Elevated miR-155 expression contributes to plaque destabilization by enhancing inflammation, promoting extracellular matrix degradation, and enlarging the necrotic core, all of which reduce plaque density and increase vulnerability.

In the comparison group of patients with SAP, correlations between miR-155 expression and cardiac imaging parameters were statistically significant but less pronounced than in the UAP group. The coronary calcium score showed a significant positive correlation ($r=0.50$, $p<0.05$), while the involvement index (SIS) correlated positively ($r=0.55$, $p<0.01$). The degree of coronary artery stenosis and remodeling index (RI) demonstrated moderate positive correlations ($r=0.45$ and $r=0.42$, respectively; $p<0.05$ for both). Similarly, atherosclerotic plaque volume and mass exhibited moderate positive correlations ($r=0.48$ and $r=0.35$, respectively; $p<0.05$). Plaque density (HU) showed a significant negative correlation ($r=-0.60$, $p<0.001$), though less strong than that observed in unstable angina. These results suggest that miR-155 plays a role in the chronic progression of atherosclerosis and stable coronary artery disease, promoting plaque growth and reducing plaque density, albeit to a lesser degree than in acute plaque destabilization.

Comparative analysis underscores that miR-155 expression is a significant marker of atherosclerotic plaque activity and vulnerability, with its impact especially pronounced in unstable angina. The strong correlations between miR-155

levels and parameters reflecting plaque destabilization highlight its potential as a diagnostic and prognostic biomarker in the progression of coronary heart disease.

4. Conclusions

The study demonstrated a significant association between the progressive course of CAD and increased expression of the epigenetic marker miR-155, alongside the activation of proinflammatory cytokines IL-1 and TNF- α in the peripheral blood of patients. These findings underscore the predictive value of these biomarkers for clinical deterioration in patients with CAD. Furthermore, the results highlight the critical importance of data obtained via MSCT-CA. Key imaging parameters indicative of atherosclerosis progression include the number and volume of atherosclerotic plaques, degree of stenosis, as well as plaque density and mass. Many of these parameters exhibit positive correlations with levels of miR-155 and proinflammatory cytokines, reflecting their integrative role in the inflammatory processes and destabilization of atherosclerotic plaques.

Specifically, an increase in the number of hemodynamically significant stenoses combined with a decrease in plaque density may serve as markers of heightened inflammatory activity, associated with elevated miR-155 and proinflammatory cytokine levels. Thus, a multi-biomarker approach incorporating quantitative assessment of inflammatory, epigenetic, and cardiac imaging markers emerges as a promising strategy for predicting CAD progression and identifying patients at high risk for plaque destabilization. This approach paves the way for developing novel therapeutic interventions and monitoring protocols, enabling more personalized treatment strategies grounded in the integration of inflammatory, epigenetic, and imaging data. The implementation of multi-biomarker analysis in clinical practice has the potential to substantially enhance CAD prevention and treatment outcomes, reduce cardiovascular complications, and improve patient quality of life. Future research should focus on establishing optimal biomarker threshold values and creating clinically applicable algorithms to enable precise and individualized risk stratification for patients with coronary heart disease.

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