



Unraveling MINOCA: The hidden impact of inflammation on myocardial infarction without coronary obstruction

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Abstract

Myocardial infarction with non-obstructive coronary arteries (MINOCA) accounts for 5% to 15% of myocardial infarction (MI) cases; it presents with clinical signs of MI without significant coronary artery obstruction. Unlike MI with obstructive coronary artery disease (MICAD), which is primarily caused by atherosclerotic plaque rupture, MINOCA arises from mechanisms such as coronary vasospasm, coronary microvascular dysfunction (CMD), thromboembolism, plaque disruption, and spontaneous coronary artery dissection (SCAD). Inflammation plays a key role in both conditions, though its mechanisms differ; MICAD is driven by atherosclerosis-related inflammation, while MINOCA is associated with endothelial dysfunction, oxidative stress, and immune activation. Elevated biomarkers such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) highlight systemic inflammation in MINOCA, correlating with adverse outcomes. Despite the absence of significant coronary obstruction, MINOCA is not benign, and has a significant mortality rate and a high risk of recurrent cardiovascular events. Imaging modalities such as cardiac magnetic resonance (CMR) and intravascular ultrasound (IVUS) improve diagnosis, while emerging therapies targeting inflammation, including IL-1 β inhibitors and colchicine, may offer benefits. Future research should focus on personalized treatment strategies addressing the inflammatory and microvascular components of MINOCA to enhance risk stratification and improve long-term outcomes.

Keywords

MINOCA, MICAD, inflammation, endothelial dysfunction, prognosis

Rezumat

Infarctul miocardic cu artere coronare non-obstructive (MINOCA) reprezintă 5-15% dintre cazurile de infarct miocardic (IM) și se caracterizează prin semne clinice de IM fără o obstrucție semnificativă a arterelor coronare. Spre deosebire de infarctul miocardic cu boală coronariană obstructivă (MICAD), care este cauzat în principal de ruptura plăcii aterosclerotice, MINOCA apare ca urmare a unor mecanisme precum vasospasmul coronarian, disfuncția microvasculară coronariană (CMD), tromboembolismul, disrupția plăcii și disecția spontană a arterei coronare (SCAD). Inflamația joacă un rol esențial în ambele afecțiuni, însă prin mecanisme diferite; MICAD este determinat de inflamația asociată aterosclerozei, în timp ce MINOCA este legat de disfuncția endotelială, stresul oxidativ și activarea imună. Biomarkerii crescuți, precum proteina C reactivă cu sensibilitate înaltă (hs-CRP), interleukina-6 (IL-6) și factorul de necroză tumorală alfa (TNF- α), evidențiază o inflamație sistemică în MINOCA, corelată cu evoluții nefavorabile. Deși nu există o obstrucție coronariană semnificativă, MINOCA nu este o afecțiune benignă, venind cu un risc semnificativ de mortalitate și un risc crescut de evenimente cardiovasculare recurente. Modalitățile imagistice, precum rezonanța magnetică cardiacă (CMR) și ecografia intravasculară (IVUS), îmbunătățesc diagnosticul, iar terapiile emergente care vizează inflamația, inclusiv inhibitorii IL-1 β și colchicina, pot oferi beneficii. Cercetările viitoare ar trebui să se concentreze pe strategii terapeutice personalizate care să abordeze componentele inflamatorii și microvasculare ale MINOCA pentru a îmbunătăți stratificarea riscului și rezultatele pe termen lung.

Cuvinte cheie

MINOCA, MICAD, inflamație, disfuncție endotelială, prognostic

Introduction

Myocardial infarction (MI) is a leading cause of morbidity and mortality worldwide, traditionally associated with obstructive coronary artery disease (CAD). However, 5% to 15% of all MI cases present with myocardial infarction with non-obstructed coronary arteries

(MINOCA), a condition characterized by clinical signs of myocardial infarction but without significant stenosis (>50%) in the epicardial coronary arteries upon angiography¹. Unlike myocardial infarction with obstructive coronary artery disease (MICAD), the primary reason for which is atherosclerosis and consequent plaque rupture leading to intravascular thrombosis and obstruction, MINOCA is characterized by the absence of significant coronary obstruction, with a heterogeneous pathophysiology, which may include plaque disruption, coronary microvascular dysfunction, coronary vasospasm, and thrombosis.² Increasing evidence suggests that inflammation plays a central role in both MINOCA and MICAD,

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potentially through different mechanisms. In MICAD, inflammation is well established as a key driver of atherosclerotic progression, plaque destabilization, and thrombosis, with elevated inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) correlating with worse cardiovascular outcomes^{3,4}. In contrast, MINOCA is increasingly recognized as an inflammatory condition, with studies demonstrating elevated inflammatory markers in affected patients^{5,6}. Moreover, imaging techniques such as pericoronary fat attenuation index and FDG-PET have provided further evidence of heightened coronary inflammation in MINOCA⁷. Given the prognostic implications of inflammation in both conditions, a deeper understanding of its role in MINOCA compared to MICAD may improve diagnostic accuracy, risk stratification, and therapeutic strategies. This review aims to explore the pathways and mechanisms of inflammation in MINOCA, draw comparisons with MICAD, and highlight emerging biomarkers and imaging modalities that may aid in clinical decision-making.

Inflammation in myocardial infarction with coronary artery disease (MICAD)

1. The mechanics of inflammation in MICAD

Inflammation is now widely recognized as a central contributor to the pathogenesis of MICAD. Over the past decades, researchers have explored the roles of both systemic and local inflammatory processes, employing biochemical assays, advanced imaging modalities, and interventional studies to elucidate the role of inflammation, showing its duality by its participation in plaque formation and destabilization, contributing to atherothrombosis, but also influencing myocardial healing post-infarction.^{7,8}

At the molecular level, the inflammatory process is often initiated by endothelial dysfunction. Risk factors such as hyperlipidemia, hypertension, and smoking lead to endothelial injury, which leads to vascular permeability that allows low-density lipoprotein (LDL) to get into the intima. Subsequent oxidative modification of LDL particles triggers an inflammatory response by activating resident macrophages, which release cytokines such as IL-6 and TNF- α . These cytokines activate transcription factors such as nuclear factor-kappa B (NF- κ B), resulting in the upregulation of multiple pro-inflammatory genes.⁹

Immune cell recruitment is another critical component of the inflammatory process in MICAD. Monocytes migrate to the area of endothelial injury and, upon entering the intima, differentiate into macrophages that engulf oxidized LDL to form foam cells and secrete additional cytokines and matrix metalloproteinases that break down the fibrous cap of atherosclerotic plaques, increasing their vulnerability^{10,11}. Neutrophils also contribute by releasing reactive oxygen species (ROS), which amplify oxidative stress and further damage the vascular endothelium, reinforcing the inflammatory response¹².

Another key molecule that has recently gained attention is the NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome which plays a critical role in the inflammatory

processes underlying MICAD. As a cytosolic sensor, NLRP3 detects various stress signals, including oxidative stress, cholesterol crystals, and mitochondrial dysfunction, which are common in atherosclerosis and ischemic heart disease¹³. Activated NLRP3 triggers a cascade of inflammatory responses that contribute to plaque instability, myocardial injury, and adverse post-infarction remodeling by combining with apoptosis-associated speck-like protein (ASC) and caspase-1, leading to the cleavage and maturing of the pro-inflammatory cytokines interleukin-1 β (IL-1 β) and interleukin-18 (IL-18). These cytokines amplify the local inflammatory response, exacerbating endothelial dysfunction and accelerating plaque destabilization¹⁴. In macrophages within atherosclerotic plaques, NLRP3 activation also promotes foam cell formation and necrotic core expansion, two key contributors to plaque rupture and acute coronary events¹⁵. Beyond its role in plaque instability, the NLRP3 inflammasome is actively involved in post-MI myocardial remodeling. Its sustained activation following myocardial infarction leads to excessive fibrosis, cardiomyocyte apoptosis, and impaired cardiac repair, which contribute to ventricular dysfunction and an increased risk of heart failure¹⁵.

All these mechanisms make NLRP3 inflammasome an intriguing factor in "acute on chronic" inflammation in MICAD. This concept reflects the interplay between long-standing low-grade inflammation and the sudden inflammatory rise during an acute ischemic event. Patients with chronic CAD often exhibit persistent low-level inflammation, characterized by CRP, IL-6, and TNF- α , which contribute to plaque progression and vulnerability^{12,16}. However, during an acute MI, an increase in inflammatory response occurs, exacerbating myocardial injury and increasing the risk of complications such as infarct expansion, adverse ventricular remodeling, and heart failure³. Chronic NLRP3 activation in macrophages in atherosclerotic plaques promotes low-grade inflammation and plaque instability. Upon plaque rupture, NLRP3 is further activated, triggering the release of IL-1 β and IL-18, which intensify myocardial damage and recruit neutrophils to the infarcted area¹⁷. The sudden inflammatory surge results in a paradoxical effect: while inflammation is necessary for tissue repair, excessive or prolonged inflammation can worsen ischemic injury and lead to fibrosis and heart failure³.

Targeting the NLRP3 inflammasome has been proposed as a therapeutic approach to mitigate both chronic and acute inflammatory responses in myocardial damage and to reduce post-MI complications, positioning it as a promising therapeutic target in MICAD¹⁸. Inhibitors like MCC950 and Dapansutrile have been shown to reduce infarct size and preserve cardiac function^{19,20}. These findings suggest that modulating the inflammatory response—particularly during the transition from chronic to acute inflammation—may improve post-MI outcomes and prevent adverse remodeling¹⁸.

2. Systemic Inflammatory Markers and Their Prognostic Significance in MICAD

The clinical relevance of inflammation in MICAD extends beyond its mechanical role. Several studies have examined systemic inflammatory markers, such as CRP, IL-6, and TNF- α , and their

correlation with disease severity and outcomes in MICAD patients. Elevated IL-6 levels have been consistently linked to a higher risk of recurrent cardiovascular events, suggesting that systemic inflammation is not merely a consequence but an active driver of plaque progression and myocardial damage resulting in residual risk.^{16, 21}

A number of studies demonstrated that hs-CRP levels were predictive of recurrent ischemic events even after adjusting for traditional risk factors, putting into focus the clinical value of inflammatory biomarkers in risk stratification²². This aligns with findings from the aforementioned studies^{16, 21} that identified IL-6 and TNF- α as independent predictors of infarct size and left ventricular dysfunction post-MI. When comparing these findings, it is evident that hs-CRP provides an accessible measure of systemic inflammation, while IL-6 and TNF- α offer deeper insights into active inflammatory processes contributing to myocardial injury. These biomarkers could be integrated into clinical risk models to improve MICAD prognosis and guide treatment strategies.

Interestingly, in the CANTOS trial, a study that used IL-1 β inhibitor canakinumab, results showed that reducing inflammation without altering lipid levels significantly lowered the incidence of recurrent myocardial infarction⁸. This landmark study put into clinical perspective that targeting inflammation directly could yield clinical benefits, paving the way for novel anti-inflammatory interventions in MICAD.

3. The Role of Local Coronary Inflammation and Imaging Findings

While systemic markers reflect generalized inflammation, studies have increasingly focused on localized coronary inflammation which is increasingly recognized as a more precise indicator of plaque instability and cardiovascular risk. Advances in imaging techniques have facilitated the non-invasive assessment of coronary artery inflammation, particularly through pericoronary fat attenuation index (FAI) and FDG-PET imaging.

One study that used coronary computed tomography angiography (CCTA) with pericoronary FAI analysis demonstrated that an increased pericoronary fat attenuation, especially above -70.1 Hounsfield units (HU), localized in the proximal segment of the right coronary artery or on the left descending artery correlated with plaque vulnerability and increased risk of major adverse cardiovascular events (MACE)²³. These findings are consistent with another imaging-based study that identified higher coronary artery inflammation using FDG-PET in patients' acute settings compared to more stable CAD patients²⁴.

A systemic review published in 2022 by Sagris et al. suggests that pericoronary inflammation may provide additional prognostic value beyond traditional risk factors and systemic inflammatory markers²⁵. Moreover, the same meta-analysis has highlighted the heterogeneous distribution of inflammation in MICAD patients, with some plaques exhibiting high inflammatory activity, thus making them more hemodynamically significant despite minimal luminal stenosis with every increase in the value of FAI²⁵. These findings challenge the traditional view that plaque burden alone dictates ischemic risk, emphasizing the importance of plaque composition

and inflammatory status. While blood-derived biomarkers offer systemic insights into inflammation, CCTA-based fat attenuation provides direct visualization of localized coronary inflammation, making it a promising tool for early risk stratification in MICAD.

4. Acute-on-Chronic Inflammation in MICAD: A Dual-Phase Model

The "acute on chronic" inflammation model has gained attention as a framework for understanding the interplay between pre-existing low-grade inflammation and the acute inflammatory surge during MI. Chronic CAD patients often exhibit persistent low-level inflammation, which serves as a pro-inflammatory baseline that primes the vascular environment for an exaggerated immune response following plaque rupture^{3, 26}.

LATITUDE-TIMI 60 study found that patients with elevated IL-6 and TNF- α levels at four weeks post-randomization experienced worse outcomes following an acute MI, likely due to enhanced leukocyte infiltration and prolonged inflammatory activity²¹. This is further supported by findings demonstrating that monocyte activation and neutrophil infiltration that are mainly driven by the chemokine MCP-1 were significantly higher in MICAD patients compared to those with stable angina^{27, 28}.

Comparing these findings, it is evident that chronic inflammation not only predisposes plaques to rupture but also exacerbates myocardial injury once an infarction occurs. This dual-phase inflammatory response may explain why MICAD patients with high baseline inflammation often experience larger infarcts and worse ventricular remodeling post-MI²⁶.

5. Targeting Inflammation in MICAD: Therapeutic Perspectives

Given the well-established role of inflammation in MICAD, several studies have tried to move the research in the direction of finding anti-inflammatory therapies to improve patient outcomes. Statins, colchicine, and IL-1 β inhibitors have shown promising results in modulating the inflammatory response, but their clinical efficacy varies depending on the phase of inflammation (chronic vs. acute)¹⁷.

The Colchicine Cardiovascular Outcomes Trial (COLCOT) found that administering low-dose colchicine significantly reduced cardiovascular events in MICAD patients²⁹. Similar results are being detailed in another study, and also showed that 0.5mg of colchicine daily to patients with chronic CAD correlates with a decreased risk for MACE events.³⁰

The CANTOS study, which analyzed the effects of IL-1 β inhibition via canakinumab, had promising results, further supporting inflammation as a therapeutic target. In this study patients showed a decrease in risk for MACE events by 15% and also a 24% lower risk of a recurring MI. The risk for cardiovascular death was lowered by 10% when administering canakinumab in patients post-MI.⁸

Another anti-inflammatory therapy that has been studied in the context of post-MI patients is anakinra. One of the main findings on the effect of anakinra in this population was described in a pooled analysis of the VCUART clinical trials; these showed that patients that had received the treatment for 14 days post-STEMI had a

reduced risk of heart failure at 1 year compared to the placebo group.³¹ Behind the clinical findings it can also be seen that anakinra leads to lower levels of CRP³¹ and a lower leukocyte count³², which demonstrates the critical role the inflammation process plays in the prognostic of these patients.

Moreover, while statins exhibit anti-inflammatory effects beyond lipid-lowering, their impact on plaque-specific inflammation remains limited³³, reinforcing the need for targeted therapies such as NLRP3 inhibitors. One of the molecules studied in NLRP3 inhibition is MCC950. One study done on mice that had induced MI by ligaturing the left descending artery showed that the administration of MCC950 for 14 days decreased the amount of fibrosis post-MI and alleviated cardiac function.³⁴

However, challenges remain. Some studies have noted that while reducing inflammation improves outcomes, excessive suppression may impair myocardial healing, suggesting a need for personalized anti-inflammatory strategies³⁵.

Mechanisms of myocardial infarction with non-obstructed coronary arteries (MINOCA)

MINOCA is a distinct clinical entity characterized by myocardial infarction (MI) in the absence of significant coronary artery obstruction (>50% stenosis) on angiography, underlying that behind the clinical manifestations of a myocardial infarction lies a wide spectrum of mechanisms, far beyond the well-known atherothrombotic process¹. Despite the clinical similarities between MINOCA and MI-CAD, such as ECG findings (Fig. 1, Fig. 2), elevated cardiac enzymes and symptoms, MINOCA has a diverse pathophysiological spectrum, including coronary vasospasm, thromboembolism, coronary microvascular dysfunction (CMD), spontaneous coronary artery dissection (SCAD), and myocardial disorders such as myocarditis and takotsubo cardiomyopathy³⁶, which angiographically present as non-obstructed coronary arteries compared to the obstruction seen in MI-CAD (Fig. 1, Fig. 2).

The heterogeneity of MINOCA makes it difficult to manage using standard MI protocols. Unlike ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) due to atherosclerotic occlusion MINOCA may not respond to conventional antiplatelet therapy in the same way³⁷. The growing understanding of imaging, biomarker analysis, and pathophysiological research has improved our approach to diagnosing and managing this condition.

1. Coronary vasospasm

Coronary vasospasm is a significant mechanism underlying MINOCA, leading to transient myocardial ischemia due to reversible vasoconstriction of coronary arteries. Unlike atherosclerotic obstructions, vasospasm results in dynamic narrowing that can be triggered by endothelial dysfunction, oxidative stress, or autonomic nervous system dysregulation. Coronary vasospasm is categorized into epicardial vasospasm, affecting large coronary arteries, and microvascular dysfunction, involving the smaller coronary arterioles that regulate myocardial perfusion³⁸.

Epicardial vasospasm is characterized by a temporary, reversible constriction of major coronary arteries, which can lead to myocardial ischemia, angina, and even infarction. This condition is frequently associated with endothelial dysfunction, as the nitric oxide-dependent vasodilatory response is impaired, resulting in an exaggerated vasoconstrictive reaction to stimuli such as acetylcholine, cold exposure, and emotional stress³⁹. Studies have demonstrated that patients with MINOCA often exhibit a heightened vasospastic response to acetylcholine provocation testing, supporting the role of endothelial dysfunction in its pathogenesis⁴⁰.

A key contributor to endothelial dysfunction in MINOCA is oxidative stress, which disrupts nitric oxide synthesis and bioavailability, thereby impairing vasodilation. Hung et al. highlighted that vascular inflammation, oxidative stress, and autonomic imbalance play a crucial role in increasing coronary vasoreactivity, predisposing individuals to vasospasm⁴¹.

Beyond epicardial involvement, CMD is also a major contributor to vasospastic MINOCA. CMD results in impaired vasomotor control, abnormal coronary flow regulation, and increased microvascular resistance, leading to inadequate perfusion despite angiographically normal epicardial arteries. Recent studies suggest that CMD is one of the predominant mechanisms of MINOCA, with up to 30% to 50% of cases involving some form of microvascular dysfunction⁴². The dysfunction in CMD is often related to endothelial-independent mechanisms, such as smooth muscle hypercontractility and heightened sympathetic nervous system activity³⁸. CMD may coexist with epicardial vasospasm, compounding ischemic risk and making diagnosis more complex.

2. Coronary Thromboembolism and Plaque Disruption in MINOCA

Coronary thromboembolism and plaque disruption are other important mechanisms in MINOCA, and was found in around 30% to 40% of patients with MINOCA⁴³. These conditions result in myocardial ischemia due to either embolization of thrombotic material into the coronary circulation or disruption of a vulnerable plaque that does not lead to complete luminal occlusion. The pathophysiology of these mechanisms is diverse, involving factors such as thrombophilia, atrial fibrillation (AF), left ventricular thrombi, paradoxical embolism, and minor plaque erosion.

Coronary thromboembolism refers to the embolization of thrombotic material into the coronary arteries, which may originate from cardiac or extracardiac sources. Cardiac sources include atrial fibrillation, left ventricular thrombi, infective endocarditis, and prosthetic heart valves, while extracardiac sources involve paradoxical embolism via a patent foramen ovale (PFO) or aortic atheromas⁴⁴.

Opolski et al. demonstrated that some MINOCA cases, even if they were less than MICAD cases, involve embolic occlusions without evidence of coronary atherosclerosis⁴⁵, emphasizing the need for thrombophilia screening in high-risk patients. Other studies looked further into the correlation between thrombophilic diseases and their connection to MINOCA, and found that patients who suffered from such an event had higher rates of thrombophilia.^{46, 47} Additionally,

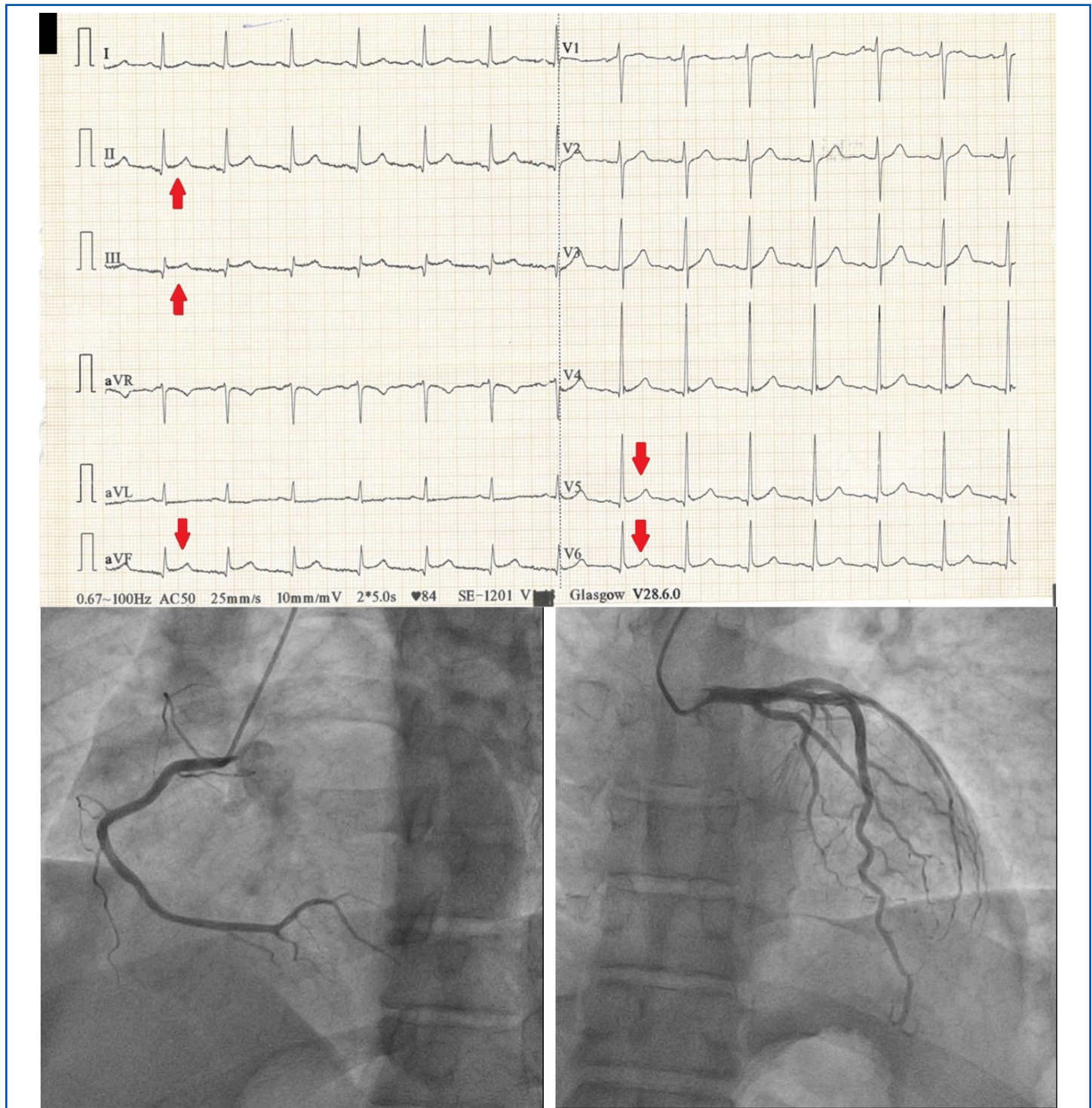


Figure 1 - 38- year old patient presenting to the E.R. with recent onset chest pain. ECG shows ST elevation in DII, DIII, aVF V5 and V6 (red arrows), suggesting a inferolateral STEMI. Patient undergoes coronary angiogram which reveals normal coronary arteries with no significant stenosis.

Reynolds et al. used OCT and CMR to identify thromboembolic sources in MINOCA, finding that a significant subset of patients had embolic infarcts ⁴³.

Because coronary embolism can be transient, angiographic imaging may fail to detect evidence of an obstruction. This highlights the importance of multimodal imaging, including transesophageal echocardiography (TEE) and contrast-enhanced cardiac MRI,

to detect embolic sources that may not be evident with standard coronary angiography ⁴².

Unlike coronary embolism, plaque disruption in MINOCA occurs when an atherosclerotic plaque erodes or ruptures without leading to total occlusion. This mechanism is more commonly associated with younger patients and women, who often present with MINOCA without significant obstructive disease. Plaque disruption is typically

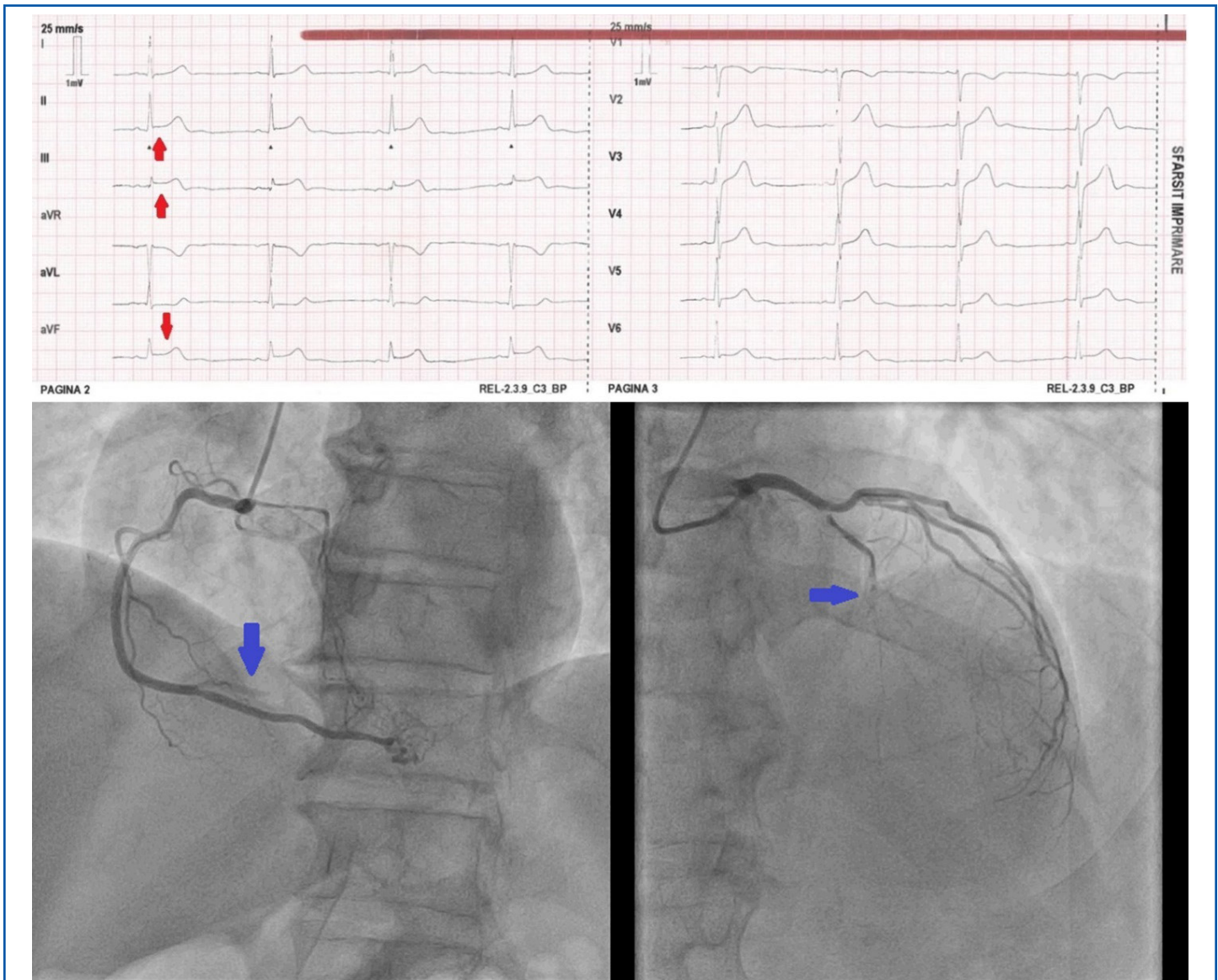


Figure 2 - 63-year old patient presenting with a day old chest pain. ECG shows ST elevation in inferior leads DII, DIII, aVF (red arrows) consistent with an inferior STEMI. Angiogram shows acute occlusion on the right coronary artery (blue arrow – left image) and chronic occlusion of the left anterior descending coronary artery (blue arrow – right image).

classified into two main forms: plaque rupture characterized by a fibrous cap rupture that leads to exposure of lipid-rich plaque contents, triggering thrombosis and ischemia, and plaque erosion in which the endothelial surface becomes disrupted without rupture, leading to localized thrombus formation^{48, 49}. The ability to detect subtle plaque disruption using these imaging techniques highlights the importance of intracoronary imaging in MINOCA evaluation.

3. Spontaneous coronary artery dissection (SCAD)

SCAD is an important but underrecognized cause of MINOCA. It primarily affects younger women and is associated with hormonal fluctuations, fibromuscular dysplasia, and extreme emotional or physical stress. Unlike atherosclerotic coronary artery disease, SCAD occurs due to spontaneous tearing of the arterial wall, leading to an intramural hematoma that compresses the lumen and results

in myocardial ischemia⁵⁰. This phenomenon has been seen in patients who also had associated systemic inflammatory diseases or connective tissue disorders⁴⁹.

SCAD is often misdiagnosed due to its transient and dynamic nature, with angiographic findings sometimes appearing normal or inconclusive. CMR imaging and intracoronary imaging techniques such as OCT and IVUS are essential for diagnosing SCAD in MINOCA patients⁴². The use of OCT has been highlighted as particularly effective in identifying wall abnormalities and distinguishing SCAD from other causes of MINOCA, such as myocarditis or takotsubo cardiomyopathy⁵¹.

SCAD-related MINOCA differs from other MINOCA etiologies in terms of management. Unlike classic acute coronary syndrome (ACS), the use of anticoagulation, thrombolytics, and aggressive percutaneous coronary intervention (PCI) can be detrimental

and may worsen the dissection. Unless the patient presents with hemodynamic instability, a conservative approach is often preferred, with beta-blockers, lifestyle modifications, and close monitoring being the mainstay of treatment ⁵².

The role of inflammation in MINOCA

MINOCA is a complex cardiovascular condition involving diverse pathophysiological mechanisms. Among these, inflammation plays a crucial role in its onset and progression. Inflammatory molecules and pathways have been increasingly implicated in MINOCA, from the shared mechanisms with MICAD to finding specific key factors in MINOCA. Understanding the involvement of key inflammatory markers, cytokines, and pathways is essential for elucidating the underlying mechanisms and improving diagnostic strategies.

1. Inflammatory Markers in MINOCA

Several inflammatory markers that were found to play a role in MICAD have been also linked to MINOCA, including hs-CRP, interleukins, and TNF- α . Elevated levels of hs-CRP are frequently found in MINOCA patients, suggesting a systemic inflammatory state ⁵³.

A study identified IL-6 as a crucial mediator of vascular inflammation, which plays a role in endothelial dysfunction and microvascular dysfunction, both key features of MINOCA. IL-6 has been associated with increased coronary microvascular resistance and impaired vasodilation, contributing to ischemia even in the absence of epicardial obstruction ⁵⁴. Furthermore, hs-CRP, a well-established marker of systemic inflammation, is significantly elevated in MINOCA patients, indicating ongoing vascular and myocardial inflammation. Elevated hs-CRP levels are associated with increased cardiovascular risk and worse clinical outcomes ⁵.

2. Cytokine Activation and Endothelial Dysfunction

Endothelial dysfunction is a hallmark of MINOCA, often driven by pro-inflammatory cytokines. Studies have demonstrated that TNF- α induces endothelial damage, reduces nitric oxide bioavailability, and promotes vascular inflammation ⁵³. These effects contribute to CMD, a primary mechanism in MINOCA.

Another crucial inflammatory pathway involved in MINOCA is the IL-1 signaling cascade. IL-1 β has been shown to promote endothelial activation, leading to increased expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), which facilitate leukocyte infiltration and perpetuate vascular inflammation ⁵⁵. Increased IL-1 activity has also been linked to myocardial fibrosis, suggesting that chronic inflammatory activation contributes to long-term structural changes in the myocardium ⁵⁶.

In addition to IL-1, IL-18, a member of the IL-1 superfamily, has been shown to amplify the inflammatory response by promoting monocyte and macrophage activation, which enhances the release of additional pro-inflammatory cytokines and increases oxidative stress. These inflammatory cascades collectively lead to a sustained

pro-thrombotic environment, increased endothelial permeability, and microvascular dysfunction, all of which are crucial mechanisms in MINOCA pathogenesis ⁵⁷.

A newer published review ⁵⁸ highlights the role of the cytokine trio – visfatin, placental growth factor (PIGF), and fractalkine in MINOCA-related inflammation and vascular dysfunction. Visfatin, secreted by adipose tissue and immune cells, acts as a pro-inflammatory mediator by activating NF- κ B, increasing cytokine production, and promoting endothelial dysfunction. PIGF, part of the vascular endothelial growth factor (VEGF) family, enhances monocyte infiltration and neovascularization but also induces oxidative stress and plaque destabilization. Fractalkine, a chemokine, binds to CX3CR1 receptors on monocytes and T cells, amplifying vascular inflammation and endothelial activation.

These cytokines collectively worsen microvascular dysfunction and inflammatory injury, making them potential therapeutic targets. Visfatin amplifies PIGF and fractalkine signaling: by activating NF- κ B, visfatin upregulates the expression of VEGFR-1 and CX3CR1, increasing the sensitivity of endothelial cells to PIGF and fractalkine-induced inflammation. This synergy enhances monocyte adhesion and infiltration into the vessel wall, worsening vascular inflammation. PIGF-induced oxidative stress reinforces fractalkine activation: PIGF-mediated ROS production exacerbates endothelial dysfunction, leading to increased shedding of fractalkine from endothelial cells. This results in heightened monocyte and macrophage recruitment, fueling a persistent inflammatory state. Fractalkine sustains visfatin and PIGF-driven inflammation by maintaining leukocyte adhesion and activation, fractalkine ensures sustained production of visfatin and PIGF, creating a chronic inflammatory milieu that contributes to microvascular instability, endothelial damage, and impaired coronary perfusion. ⁵⁸

3. Role of Oxidative Stress and Immune Activation

Inflammation and oxidative stress are closely intertwined in MINOCA. Oxidative stress exacerbates endothelial dysfunction by increasing ROS, impairing nitric oxide production, and enhancing vascular inflammation ⁵⁸. Elevated ROS levels have been linked to platelet hyperactivation, endothelial apoptosis, and increased thrombotic risk, all of which may contribute to the ischemic events seen in MINOCA ¹⁴.

Moreover, immune cell infiltration into coronary microcirculation has been observed in MINOCA patients. Macrophages and neutrophils, key players in the immune response, contribute to vascular inflammation and endothelial disruption. A study using CMR imaging showed that patients with MINOCA had increased myocardial inflammation, supporting the role of immune activation in the disease process. Additionally, activated monocytes and neutrophils secrete matrix metalloproteinases (MMPs), which degrade the extracellular matrix and contribute to microvascular instability ¹⁴.

4. Microvascular Dysfunction and Chronic Inflammation

As discussed in the MICAD mechanisms, chronic low-grade inflammation is a major contributor to CMD ⁵⁹ which is one of the leading causes of MINOCA. Inflammatory cytokines and oxidative

stress induce microvascular constriction, capillary rarefaction, and impaired coronary flow reserve, leading to ischemia even in the absence of obstructive coronary artery disease⁵⁶. CCTA studies have confirmed that patients who do not present obstructive CAD often exhibit microvascular inflammation and endothelial swelling, further supporting the role of chronic inflammation in disease progression⁶⁰.

Additionally, autoimmune conditions, including systemic lupus erythematosus and rheumatoid arthritis, have been associated with an increased prevalence of MINOCA. Autoimmune-mediated vasculitis and endothelial injury may contribute to coronary microvascular dysfunction and ischemia in these patients⁴⁹. This further raises the question of whether elevated levels of circulating immune complexes and autoantibodies suggest an autoimmune-driven component in MINOCA pathogenesis, highlighting the need for investigation into the immune mechanisms of MINOCA.

All the information presented earlier lead to the fact that inflammation plays a pivotal role in the pathogenesis of MINOCA, and the identification of inflammatory pathways involved in MINOCA not only enhances our understanding of its mechanisms but also paves the way for improved diagnostic approaches. Future research should focus on biomarker-guided personalized treatment strategies to improve outcomes in MINOCA patients.

What we know about the prognosis in MINOCA?

As stated before, MINOCA is a complex and heterogeneous condition that accounts for approximately 6% to 15% of all MI cases. Unlike obstructive CAD, MINOCA lacks significant stenotic lesions on angiography, making prognosis assessment and management strategies particularly challenging. While previously considered a benign condition, recent studies have shown that MINOCA patients face substantial risks of recurrent cardiovascular events, heart failure, and mortality⁶¹. We aim to do an analysis of the prognosis of MINOCA based on the findings of multiple studies, emphasizing mortality rates, recurrence risks, biomolecular markers, and the impact of inflammatory and metabolic factors.

1. Clinical factors for MACE and mortality risk in MINOCA

Several studies have evaluated the long-term survival of MINOCA patients, with mortality rates varying significantly depending on underlying pathophysiological mechanisms and comorbidities. According to a meta-analysis published in 2022 that look at 44 articles which comprised 36,932 showed that the mortality rate was 2.0%⁶². Another later study published in European Heart Journal found that the 5-year mortality rate was approximately 8.5%, with higher mortality among elderly individuals and those with systemic inflammatory disorders⁶, and the mortality rate went up to 16% at three-year follow-up in a study by Zhang et al⁶¹.

Sex differences in MINOCA outcomes have also been noted. In one study of MINOCA cases women were represented more, with 168 (65.9%) vs. 87 male patients, while in another larger retrospective study women made up 62% of all cases recorded⁶³. But

as far as the mortality rate between the two sexes, multiple studies didn't find any significant differences between the two groups^{64, 65}. Additionally, age has emerged as a significant predictor of mortality, with individuals over 70 years old having a higher mortality rate than younger patients, especially in female patients who had a mortality rate of 20.7% compared to 2.6% for those under 70 years.⁶⁴

Further research has suggested that the presence of systemic inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, may contribute to the onset of MINOCA, but it doesn't correlate with an increase in mortality for these patients after a median follow-up period of 28 months. One study reported that MINOCA patients had a higher incidence of pro-inflammatory conditions, but the occurrence of MACE or mortality didn't correlate with the these conditions.⁵⁹

As stated before, MINOCA is not a benign condition. The risk of major adverse cardiovascular events (MACE) has been studied in MINOCA-only cohorts as well as in comparison to MI-CAD. A study published in *International Journal of Cardiology* that included 2147 patients with MINOCA found that at 4.5 years, 24% of the patients have experienced MACE.⁶³ Out of all MACE, deaths represented most of the events, with a total of 1,254, of which 1,165 happened after the first 30 days and only 497 (42.7%) had a cardiovascular cause.⁶³

The aforementioned study by Chaudhary et al. has shown that even though the mortality rate doesn't differ between genders, the MACE risk is higher in women: 10.1% compared to 9.1%, and even more women displayed higher rates of recurrent ischemic events: 3.5% vs. 2.2%, indicating potential disparities in disease mechanisms and responses to treatment⁶⁵. These findings are supported by another study that also showed that the incidence of MACE in women, especially under 70 years of age, was higher than in men.⁶⁴ Even though this study has not seen any differences in MACE when analyzing it by age, there are more studies published that show age as an independent factor in the appearance of MACE in MINOCA patients. A large retrospective study that looked at 1,544 patients over a period of seven years has found that age does correlate with the risk of MACE, but the end point was only comprised of all-cause mortality and MI recurrence.⁶⁶ In support of these findings comes the Nordenskjöld et al. study that compared 10-year-difference age groups, and showed that the risk of MACE increased alongside the increase in age.⁶³

Another traditional risk factor that is looked at in most of the studies that followed the outcomes of MINOCA patients is the lipid profile. And even though dyslipidemia has been less observed in MINOCA patients, it is still an important factor in the prognosis. In one study LDL-C has been linked to a higher risk of MACE⁶⁷, and in another study it was shown that residual cholesterol is a factor that contributes to an adverse prognosis for patients with MINOCA⁶⁸. A newer direction for study is the effect of lipoprotein (a) [Lp(a)] in MINOCA, given its known effect on poor outcome in MICAD patients. One study focusing on the effect of Lp(a) analyzed the risk of MACE appearance in 1,179 patients with MINOCA and showed that higher levels of Lp(a) defined as over 30mg/dL, correlated with a higher rate of MACE over a median follow-up period of 41.7 months. Even

Table 1 - Biomarkers in MINOCA.

Biomarkers	Mechanisms	Changes in MINOCA	Effect on prognosis
C-reactive protein (CRP) ^{5, 6, 73}	Vascular and myocardial inflammation	In MINOCA vs. MI-CAD	Elevated risk of mortality and MACE
Tumor necrosis factor α (TNF- α) ⁵³	- induces endothelial damage, - reduces nitric oxide bioavailability promotes vascular inflammation	In MINOCA vs MI-CAD	Unknown
Interleukin-6 (IL-6) ^{21, 54}	- increases coronary microvascular resistance - impairs coronary vasodilatation	In CMVD	Elevated risk of recurrent myocardial infarction
Interleukin-1 (IL-1) ^{55, 56}	- pro-thrombotic effect - increases expression of adhesion molecules - increases endothelial permeability	In MINOCA	Unknown
Visfatin ⁵⁸	- promotes endothelial dysfunction - inflammation	In MINOCA	Unknown
Placental growth factor (PIGF) ⁵⁸	- monocyte infiltration - angiogenesis	In MINOCA	Unknown
Fractalkine ⁵⁸	- vascular inflammation - endothelial activation	In MINOCA	Unknown
Fibrinogen-on-albumin ratio (FAR) ⁷⁴	coagulation cascade	-	Higher risk of MACE and hospitalization for heart failure
sVCAM-1 ⁵⁵	- leukocyte infiltration - vascular inflammation	In MINOCA vs MI-CAD	Progression of atherosclerosis
Soluble urokinase-type plasminogen activator receptor (suPAR) ⁸⁰	inflammation	In MINOCA vs. healthy control	Increase in MACE and all-cause deaths.
Uric acid ⁷⁹	inflammation	-	Higher risk of MACE and heart failure
Lipoprotein(a) ^{69, 70}	lipid metabolism	In MINOCA vs MI-CAD	Increase in MACE
Ratio of neutrophils, monocytes, lymphocytes, platelet to HDL (NHR, MHR, LHR, PHR) ⁷⁵	oxidative stress		Increase in MACE
Systemic inflammation response index (SIRI) ⁷⁶	-	-	Higher rates of MACE
Neutrophil-to-lymphocyte ratio (NLR) ⁷⁷	inflammation	In MINOCA	Increased risk of all-cause mortality
White blood cell count to mean platelet count ratio (WMR) ⁷⁸	inflammation	-	Higher rates of MACE
Neutrophil-to-platelet ratio ⁷⁸	inflammation	-	Higher rates of MACE

more, it described an increase in risk paralleled with the increase in Lp(a) levels. ⁶⁹ In addition to this, a newer study published in 2023 showed that beside the already mentioned risk factors such as age, a Lp(a) level higher than 60mg/dL was considered an independent risk factor for worse outcomes in MINOCA patients. ⁷⁰

Other traditional risk factors seen to play a factor in MI-CAD prognosis, such as diabetes, chronic kidney disease, and a low left ventricular ejection fraction (LVEF) <40%, were also found to impact the outcome of patients that suffered a MINOCA, by increasing the risk of MACE as well as the risk of mortality. ⁷¹

2. The impact of inflammation biomarkers on prognosis

Inflammation plays a critical role in the prognosis of MINOCA, influencing both acute and long-term cardiovascular outcomes. Unlike obstructive myocardial infarction, MINOCA is characterized by coronary microvascular dysfunction, endothelial inflammation, and pro-thrombotic activity, which contribute to persistent ischemia,

recurrent events, and increased mortality risk. Numerous studies have demonstrated that inflammatory markers, including CRP, IL-6, fibrinogen, and oxidative stress-related molecules, serve as significant predictors of prognosis in MINOCA patients.

CRP levels have been one of the first to be studied when looking into inflammation and the effect it has on the outcomes of patients with MINOCA. A *Journal of the American Heart Association* (JAHA) study highlighted that CRP levels decreased faster over a month in MINOCA patients than in MI-CAD patients, correlating with a lower extent of the MI. ⁷² A post-hoc of the PLATO study has found that higher levels of CRP were an independent factor that predicted all-cause mortality, and it also correlated with a higher risk for MACE ⁷³, results that are also seen in a retrospective study from *European Heart Journal* which looks at 706 patients over a median of five years and has showed that the CRP at admission was an independent factor for all-cause mortality. ⁶ Elevated IL-6 levels, a key pro-inflammatory cytokine, have also been linked to

an increased risk of recurrent myocardial infarction, emphasizing the contribution of endothelial injury and immune activation to long-term cardiovascular complications²¹. Another study reported that patients with persistent inflammation had a significantly higher risk of long-term cardiovascular mortality, suggesting that chronic systemic inflammation plays a crucial role in the pathophysiology of MINOCA and its long-term outcomes.⁵

The impact of fibrinogen, an acute-phase reactant involved in coagulation, has also been well established. One study published in the *International Journal of Cardiology* looked at fibrinogen-on-albumin ratio (FAR) and reported that patients with MINOCA who had high FAR levels demonstrated a higher risk of major MACE, with a 22% rate of occurrence compared to 9.3%, and also greater rate of hospitalization for heart failure.⁷⁴

A growing body of research has also identified oxidative stress and endothelial dysfunction as key contributors to poor prognosis in MINOCA. In one study the progression of atherosclerosis over a period of one year in MINOCA patients has been closely linked to sVCAM-1 and CCL-21, indicating a multifaceted underlying mechanism. These markers suggest that atherosclerosis progression may be driven by a combination of structural plaque alterations and microcirculatory dysfunction, highlighting the complex interplay between vascular inflammation and endothelial integrity.⁵⁵ Further supporting these findings, asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthesis, was significantly elevated in MINOCA patients, correlating with endothelial dysfunction and increased long-term cardiovascular risk.⁵³

A study published in *Frontiers in Cardiovascular Medicine* looked at the role of multiple inflammatory biomarkers: ratio of neutrophil count to HDL level (NHR), ratio of monocyte count to HDL level (MHR), ratio of lymphocyte count to HDL level (LHR), ratio of platelet count to HDL level (PHR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI). The results demonstrated that the MACE group had increased oxidative stress markers and the association of NHR, MHR, PHR, SII, SIRI, and AISI are a good predictor for the recurrence of MACE, reinforcing the role of inflammation in MINOCA.⁷⁵ SIRI biomarker has also been researched in correlation with the role of N-terminal Pro-B-type natriuretic peptide (NT-proBNP) and showed that high levels of SIRI correlate strongly with worse outcomes and higher rates of MACE, and can be a good indicator for risk, especially when combined with NT-proBNP levels.⁷⁶

Another significant biomarker that has been shown to have increased levels and also play a role in the prognosis of patients with MINOCA is neutrophil-to-lymphocyte ratio (NLR). In one study that analyzed MINOCA patients versus control patients that had normal angiographic coronary arteries, patients presenting with MINOCA had significantly higher levels of NLR and that these levels correlated with an increase in mortality over a median period of 21 months.⁷⁷ These results correlate with the findings of another study that has investigated the impact of white blood cell count to mean platelet volume ratio (WMR) and neutrophil-to-platelet ratio (NPR). It followed 274 patients with MINOCA that were classified considering

the medians of WMR and NPR. The results showed that the group with higher values of these biomarkers had higher rates of MACE, making WMR and NPR independent predictors of MACE.⁷⁸

Additionally, research published in *Nutrition and Metabolism* identified hyperuricemia as an independent predictor of poor prognosis in MINOCA patients, with serum uric acid levels ≥ 420 $\mu\text{mol/L}$ in men or ≥ 357 $\mu\text{mol/L}$ in women being associated with an increased risk of MACE of 18.7% compared to 12.8%, and also higher rates of heart failure.⁷⁹ This association is thought to arise from oxidative stress, endothelial inflammation, and platelet hyperactivation, all of which contribute to recurrent cardiovascular events and impaired myocardial recovery. Similarly, the soluble urokinase-type plasminogen activator receptor (suPAR) and high-sensitivity troponin I (hsTnI) have been found to be a robust inflammatory predictor, with patients exhibiting suPAR >2523 pg/ml and a hsTnI >2.7 pg/ml demonstrating a 24 and 19-fold increased likelihood of adverse cardiovascular events as well as all-cause adverse events.⁸⁰

Given the strong correlation between inflammation and prognosis in MINOCA, there is growing interest in targeted anti-inflammatory strategies and risk stratification approaches to improve long-term outcomes. Future research should focus on developing biomarker-based risk assessment models and personalized treatment protocols to mitigate inflammation-driven myocardial injury and recurrent ischemic events.

3. Prognostic Value of Imaging Modalities

Advanced imaging techniques, including CMR, IVUS, and OCT, have enhanced risk stratification in MINOCA. A study published in *JACC: Cardiovascular Imaging* found that patients with higher percentage of late gadolinium enhancement (LGE) on CMR had an increased risk of MACE at three years.⁸¹ Furthermore, OCT studies have detected occult atherosclerotic plaque disruptions in 52.1% of MINOCA patients, demonstrating that underlying coronary pathology is more common than initially believed. Also it has shown that the MACE risk for atherosclerotic group of MINOCA patients was higher than in the non-atherosclerotic group, especially for revascularization and rehospitalization.⁸² These imaging findings correlate with higher long-term cardiovascular risk, underscoring the importance of multimodal assessment.

Conclusions

MINOCA and MICAD represent distinct yet overlapping clinical entities, each with unique underlying mechanisms, inflammatory profiles, and prognostic implications. Inflammation is a key driver of both MINOCA and MICAD, but its role in these conditions differs significantly. The presence of biomarkers such as sVCAM-1, CCL-21, and FAR further supports the role of endothelial inflammation and microvascular remodeling in MINOCA, distinguishing it from MICAD in terms of inflammatory pathology. Prognostically, both MINOCA and MICAD are associated with substantial long-term cardiovascular risks, though their trajectories differ. While MICAD patients have a

higher short-term mortality risk due to acute coronary obstruction, MINOCA patients face increased risks of recurrent ischemic events, heart failure, and persistent microvascular dysfunction over time. Given the inflammatory underpinnings of both conditions, targeted anti-inflammatory therapies and risk stratification approaches may improve long-term outcomes. A deeper understanding of these mechanisms will enable personalized treatment strategies, reducing morbidity and mortality in both MINOCA and MICAD populations.

List of abbreviations

ACS - acute coronary syndrome
 AF - atrial fibrillation
 AISI - aggregate index of systemic inflammation
 ASC - apoptosis-associated speck-like protein
 CCTA - coronary computed tomography angiography
 CMD - coronary microvascular dysfunction
 CMR - cardiac magnetic resonance
 COLCOT - Colchicine Cardiovascular Outcomes Trial
 CRP - C-reactive protein
 FAI - fat attenuation index
 FAR- fibrinogen-on-albumin ratio
 hs-CRP - high-sensitivity C-reactive protein
 hsTnI - high-sensitivity troponin I
 HU - Hounsfield units
 ICAM-1 - intercellular adhesion molecule-1
 IL-18 - interleukin-18
 IL-1 β - interleukin-1 β
 IL-6 - interleukin-6
 IVUS - intravascular ultrasound
 LDL - low-density lipoprotein
 LGE - late gadolinium enhancement
 LHR - ratio of lymphocyte count to HDL level
 Lp(a) - lipoprotein (a)
 LVEF - left ventricular ejection fraction
 MACE - major adverse cardiovascular events
 MHR - ratio of monocyte count to HDL level

MI - Myocardial infarction
 MICAD - myocardial infarction with coronary artery disease
 MINOCA – myocardial infarction with non-obstructive coronary arteries
 NF- κ B - nuclear factor-kappa B
 NHR - ratio of neutrophil count to HDL level
 NLR - neutrophil-to-lymphocyte ratio
 NLRP3 - NOD-, LRR-, and pyrin domain-containing protein 3
 NPR - neutrophil-to-platelet ratio
 NSTEMI - non-ST-elevation myocardial infarction
 NT-proBNP - N-terminal Pro-B-type natriuretic peptide
 PCI - percutaneous coronary intervention
 PFO - foramen ovale
 PHR - ratio of platelet count to HDL level
 PIGF - placental growth factor
 ROS - reactive oxygen species
 SCAD - spontaneous coronary artery dissection
 SCAD - spontaneous coronary artery dissection.
 SII - systemic immune-inflammation index
 SIRI - systemic inflammation response index
 STEMI - ST-elevation myocardial infarction
 suPAR - soluble urokinase-type plasminogen activator receptor
 TEE - transesophageal echocardiography
 TNF- α - tumor necrosis factor-alpha
 VCAM-1 - vascular cell adhesion molecule-1
 VEGF - vascular endothelial growth factor
 WMR - white blood cell count to mean platelet volume ratio

Conflict of interests

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