

Research Article

MicroRNA-21 and MicroRNA-208a as Biomarkers of Myocardial Remodeling Post-Infarction

Alessandro Conti¹, Francesca Rinaldi^{2*}

¹ Department of Cardiology, Sapienza University of Rome, Rome, Italy.

² Department of Molecular Medicine, University of Milan, Milan, Italy.

*Corresponding author. Email: francesca.rinaldi@unimi.it

DOI: [10.18081/ajbm.2026.2.82](https://doi.org/10.18081/ajbm.2026.2.82)

Publication History: Received 12 December 2025, Revised 04 February 2026, Accepted 30 March 2026, Available online 10 April 2026

Copyright: © 2026 Rinaldi, *et al.* This is an open access article under a Creative Commons license ([CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)).

ABSTRACT

Background

Myocardial remodeling following acute myocardial infarction (AMI) is a critical determinant of long-term cardiac function and progression to heart failure. Conventional biomarkers provide limited insight into the molecular mechanisms underlying this process. MicroRNAs (miRNAs), particularly microRNA-21 (miR-21) and microRNA-208a (miR-208a), have emerged as potential regulators of fibrosis and myocardial injury, respectively, and may serve as novel biomarkers of post-infarction remodeling.

Objective

To evaluate the clinical utility of circulating miR-21 and miR-208a as biomarkers for predicting myocardial remodeling in patients following acute myocardial infarction.

Methods

This prospective observational study was conducted at two tertiary centers in Italy and included 60 patients with confirmed AMI and 20 healthy controls. Plasma levels of miR-21 and miR-208a were measured using quantitative real-time PCR at admission (T0), 72 hours (T1), and 3 months (T2). Echocardiographic assessment of left ventricular function and volumes was performed at baseline and 3-month follow-up. Adverse remodeling was defined as a $\geq 20\%$ increase in left ventricular end-diastolic volume. Statistical analysis included correlation studies, receiver operating characteristic (ROC) curve analysis, and multivariate logistic regression.



Results

Both miR-21 and miR-208a levels were significantly elevated in AMI patients compared to controls ($p < 0.001$). MiR-21 peaked at 72 hours (5.2 ± 1.6 -fold increase), while miR-208a showed highest levels at admission (4.5 ± 1.5 -fold). Adverse remodeling occurred in 36.7% of patients. MiR-21 levels were significantly higher in patients with remodeling (5.9 ± 1.4 vs 3.7 ± 1.1 ; $p < 0.001$) and showed strong correlations with left ventricular ejection fraction ($r = -0.62$) and LVEDV ($r = 0.58$). MiR-208a correlated with troponin levels ($r = 0.65$, $p < 0.001$) and remodeling status ($p = 0.002$). ROC analysis demonstrated good predictive performance for miR-21 (AUC = 0.87) and miR-208a (AUC = 0.82), with improved accuracy when combined (AUC = 0.91). Multivariate analysis identified miR-21 and miR-208a as independent predictors of remodeling.

Conclusions

Circulating miR-21 and miR-208a are promising non-invasive biomarkers for assessing myocardial remodeling following AMI. MiR-21 is strongly associated with fibrotic remodeling, whereas miR-208a reflects myocardial injury severity. Their combined use enhances predictive accuracy and may support early risk stratification and personalized management of patients with post-infarction conditions.

Keywords: MicroRNA-21; MicroRNA-208a; Myocardial Infarction; Cardiac Remodeling; Biomarkers; Left Ventricular Dysfunction; Fibrosis

INTRODUCTION

Acute myocardial infarction (AMI) remains one of the leading causes of morbidity and mortality worldwide despite significant advances in reperfusion strategies and pharmacological therapy [1]. In Europe, and particularly in Italy, the burden of ischemic heart disease continues to pose a substantial public health challenge, with increasing survival rates paradoxically contributing to a higher prevalence of post-infarction complications, including adverse myocardial remodeling and heart failure [2,3]. Myocardial remodeling following infarction is a complex, dynamic process involving structural, functional, and molecular alterations that ultimately determine clinical outcomes [4].

Post-infarction myocardial remodeling is characterized by cardiomyocyte loss, inflammatory activation, extracellular matrix (ECM) reorganization, and progressive ventricular dilation [5]. While initially adaptive, these changes often evolve into maladaptive remodeling, leading to systolic dysfunction and heart failure [6]. Early identification of patients at risk for adverse remodeling is therefore critical for implementing targeted therapeutic interventions and improving prognosis [7]. However, traditional biomarkers such as cardiac troponins and natriuretic peptides, although valuable for diagnosis and risk stratification, provide limited insight into the molecular mechanisms driving remodeling [8].

In recent years, attention has shifted toward the role of non-coding RNAs, particularly microRNAs (miRNAs), as key regulators of cardiovascular pathophysiology [9]. MicroRNAs are small, endogenous, non-coding RNA molecules (approximately 18–25 nucleotides in length) that

modulate gene expression at the post-transcriptional level by targeting messenger RNA (mRNA) [10]. They are involved in numerous biological processes, including cell proliferation, apoptosis, differentiation, and fibrosis, all of which are central to myocardial remodeling [11]. Importantly, miRNAs are remarkably stable in circulation, making them attractive candidates as minimally invasive biomarkers [12].

Among the various miRNAs implicated in cardiovascular diseases, microRNA-21 (miR-21) and microRNA-208a (miR-208a) have emerged as particularly relevant in the context of myocardial injury and remodeling [13]. MiR-21 is widely expressed in cardiac fibroblasts and has been shown to play a pivotal role in fibrosis by promoting fibroblast activation and extracellular matrix deposition [14]. Experimental studies have demonstrated that miR-21 contributes to the regulation of key signaling pathways, including the ERK-MAPK pathway, thereby enhancing fibrotic responses and ventricular remodeling [15]. Elevated levels of miR-21 have been reported in patients with heart failure and post-infarction remodeling, suggesting its potential utility as a biomarker of adverse cardiac remodeling [16].

Conversely, miR-208a is a cardiac-specific microRNA encoded within the α -myosin heavy chain gene and is predominantly expressed in cardiomyocytes [17]. It is released into the circulation following myocardial injury and has been shown to correlate with cardiomyocyte necrosis [18]. Beyond its diagnostic role, miR-208a has been implicated in the regulation of cardiac hypertrophy and remodeling through modulation of gene expression involved in contractile protein synthesis and stress responses [19]. Studies have indicated that circulating miR-208a levels rise rapidly after myocardial infarction, often preceding traditional biomarkers, highlighting its potential as an early indicator of myocardial injury [20].

The interplay between miR-21 and miR-208a reflects two complementary aspects of post-infarction remodeling: fibrosis and cardiomyocyte injury [21]. While miR-21 primarily reflects fibrotic remodeling and extracellular matrix dynamics, miR-208a provides insight into cardiomyocyte damage and contractile dysfunction [22]. Together, these miRNAs may offer a more comprehensive molecular profile of myocardial remodeling compared to conventional biomarkers alone [23]. This dual perspective is particularly valuable in clinical settings where early detection of maladaptive remodeling could guide therapeutic decision-making.

In Italy, where cardiovascular research has increasingly focused on precision medicine and molecular diagnostics, there is growing interest in integrating miRNA profiling into clinical practice [24]. Several Italian cohort studies have explored the role of circulating miRNAs in cardiovascular diseases, demonstrating their prognostic value in predicting adverse outcomes following myocardial infarction [25]. However, despite promising findings, the clinical application of miRNAs remains limited by variability in measurement techniques, lack of standardized protocols, and insufficient large-scale validation studies [26].

Furthermore, myocardial remodeling is influenced by a multitude of factors, including age, comorbidities (such as diabetes and hypertension), infarct size, and reperfusion time [27]. These variables can affect miRNA expression profiles, necessitating careful interpretation of results within the clinical context [28]. Advanced molecular techniques, including quantitative real-time

PCR (qRT-PCR) and next-generation sequencing, have improved the accuracy of miRNA detection, but challenges related to normalization and reproducibility persist [29].

Recent advances in translational research have also highlighted the potential therapeutic implications of targeting miRNAs [30]. Modulation of miR-21 expression using antisense oligonucleotides has shown promise in reducing cardiac fibrosis in preclinical models [31]. Similarly, inhibition of miR-208a has been associated with improved cardiac function and attenuation of hypertrophic remodeling [32]. These findings suggest that miRNAs are not only biomarkers but also potential therapeutic targets, opening new avenues for personalized treatment strategies in post-infarction patients [33].

Despite these advances, there remains a need for well-designed clinical studies to evaluate the combined diagnostic and prognostic utility of miR-21 and miR-208a in myocardial remodeling [34]. Understanding their temporal expression patterns and correlation with imaging parameters, such as left ventricular ejection fraction (LVEF) and ventricular volumes, could provide valuable insights into their clinical applicability [35]. Moreover, integrating miRNA analysis with conventional biomarkers and imaging modalities may enhance risk stratification and guide therapeutic interventions [36].

METHODS

Study Design and Setting

This prospective observational study was conducted in Italy between January 2024 and December 2025 at two tertiary care centers: the Department of Cardiology at Sapienza University Hospital, Rome, and the Cardiovascular Research Unit at IRCCS Policlinico San Donato, Milan. These institutions are recognized referral centers for acute coronary syndromes and advanced cardiovascular imaging, ensuring standardized patient management and data collection. The study was designed to evaluate the role of circulating microRNA-21 (miR-21) and microRNA-208a (miR-208a) as biomarkers of myocardial remodeling following acute myocardial infarction (AMI). Ethical approval was obtained from the institutional review boards of both centers, and the study adhered to the principles outlined in the Declaration of Helsinki.

Study Population

A total of 80 participants were enrolled and divided into two groups:

AMI group (n = 60): Patients admitted with a confirmed diagnosis of ST-elevation myocardial infarction (STEMI) or non-ST elevation myocardial infarction (NSTEMI).

Control group (n = 20): Age- and sex-matched healthy individuals with no history of cardiovascular disease.

Inclusion Criteria (AMI group)

1. Age \geq 18 years
2. Diagnosis of AMI based on ESC guidelines (clinical symptoms, ECG changes, and elevated cardiac troponin levels)
3. Undergoing reperfusion therapy (primary PCI or thrombolysis)

4. Ability to provide informed consent

Exclusion criteria

1. Prior history of heart failure or cardiomyopathy
2. Chronic inflammatory or autoimmune diseases
3. Active malignancy
4. Severe renal impairment (eGFR < 30 mL/min/1.73 m²)
5. Recent major surgery or trauma
6. Refusal to participate

Clinical Assessment and Data Collection

Baseline clinical data were collected upon admission, including:

1. Demographic characteristics (age, sex)
2. Cardiovascular risk factors (hypertension, diabetes mellitus, smoking status, dyslipidemia)
3. Time from symptom onset to reperfusion
4. Infarct location and type (STEMI/NSTEMI)

Laboratory parameters included:

1. Cardiac troponin I/T
2. Creatine kinase-MB (CK-MB)
3. Serum creatinine
4. Lipid profile

All patients received standard-of-care therapy according to European Society of Cardiology (ESC) guidelines, including antiplatelet therapy, statins, beta-blockers, and ACE inhibitors or ARBs where indicated.

Echocardiographic Evaluation

Transthoracic echocardiography was performed using standardized protocols within 48–72 hours post-infarction and repeated at 3-month follow-up.

Parameters assessed included:

1. Left ventricular ejection fraction (LVEF) using Simpson's biplane method
2. Left ventricular end-diastolic volume (LVEDV)
3. Left ventricular end-systolic volume (LVESV)
4. Regional wall motion abnormalities

Adverse myocardial remodeling was defined as:

≥20% increase in LVEDV at 3 months compared to baseline

All echocardiographic measurements were performed by experienced cardiologists blinded to miRNA results.

Blood Sample Collection and Processing

Peripheral venous blood samples were collected from AMI patients at three time points:

1. T₀: Within 24 hours of admission

2. T1: 72 hours post-infarction
3. T2: At 3-month follow-up

For controls, a single blood sample was obtained.

Blood was collected into EDTA tubes and processed within 2 hours:

1. Centrifugation at 3,000 rpm for 10 minutes
2. Plasma separation and storage at -80°C until analysis

Strict protocols were followed to avoid hemolysis, which may affect miRNA quantification.

Reverse Transcription and qRT-PCR

1. Reverse transcription was performed using the TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems)
2. Quantitative real-time PCR (qRT-PCR) was conducted using TaqMan MicroRNA Assays specific for:
miR-21
miR-208a

All reactions were performed in triplicate using a StepOnePlus Real-Time PCR System (Applied Biosystems).

Normalization

1. miRNA expression levels were normalized using U6 small nuclear RNA (U6 snRNA) as an internal control
2. Relative expression levels were calculated using the $2^{-\Delta\Delta\text{Ct}}$ method

Assessment of Myocardial Remodeling

Patients were categorized into:

1. Remodeling group: Patients meeting criteria for adverse remodeling at 3 months
 2. Non-remodeling group: Patients without significant ventricular changes
- Correlation analyses were performed between miRNA levels and:
LVEF, LV volumes, Biomarkers of myocardial injury

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., USA).

Data Presentation: continuous variables: mean \pm standard deviation (SD), categorical variables: frequencies and percentages.

Comparisons

Student's t-test or Mann-Whitney U test for continuous variables
Chi-square test for categorical variables

Correlation Analysis

Pearson or Spearman correlation coefficients used to assess relationships between miRNA levels and echocardiographic parameters

Diagnostic Performance

Receiver operating characteristic (ROC) curve analysis used to evaluate the predictive value of miR-21 and miR-208a

Area under the curve (AUC), sensitivity, and specificity were calculated

Multivariate Analysis

Logistic regression used to identify independent predictors of myocardial remodeling

A p-value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Population

A total of 80 participants were included: 60 patients with acute myocardial infarction (AMI) and 20 healthy controls. The mean age of the AMI group was 61.8 ± 10.4 years, compared to 59.3 ± 9.7 years in controls ($p = 0.32$). Males constituted 68.3% of the AMI group.

Hypertension (56.7%), diabetes mellitus (41.7%), and smoking (48.3%) were significantly more prevalent in the AMI group compared to controls ($p < 0.05$).

Table 3.1: Baseline Characteristics

Variable	AMI Patients (n=60)	Controls (n=20)	p-value
Age (years)	61.8 ± 10.4	59.3 ± 9.7	0.32
Male (%)	68.3%	65%	0.78
Hypertension (%)	56.7%	20%	0.01
Diabetes (%)	41.7%	10%	0.02
Smoking (%)	48.3%	15%	0.01

Laboratory and Echocardiographic Findings

AMI patients demonstrated significantly elevated cardiac biomarkers:

Troponin I: 18.6 ± 7.4 ng/mL

CK-MB: 72.3 ± 21.5 U/L

Baseline echocardiography showed:

Mean LVEF: $45.2 \pm 6.8\%$

LVEDV: 132.5 ± 18.7 mL

At 3-month follow-up:

LVEF improved slightly to $47.9 \pm 7.2\%$ ($p = 0.04$)

LVEDV increased significantly in a subset of patients

Incidence of Adverse Myocardial Remodeling

Out of 60 AMI patients:

22 patients (36.7%) developed adverse remodeling

38 patients (63.3%) did not develop remodeling

Patients with remodeling had significantly lower baseline LVEF and larger infarct size.

Table 2: Remodeling vs Non-Remodeling Groups

Parameter	Remodeling (n=22)	No Remodeling (n=38)	p-value
Baseline LVEF (%)	41.3 ± 5.2	47.6 ± 6.1	0.001
LVEDV increase (%)	24.8 ± 4.3	8.6 ± 3.2	<0.001
Troponin (ng/mL)	22.1 ± 6.9	16.3 ± 7.1	0.003

Circulating miRNA Expression Levels

miR-21 Expression

1. AMI patients (T0): 3.8 ± 1.2-fold increase vs controls
2. Peak at 72h (T1): 5.2 ± 1.6-fold
3. At 3 months (T2): 3.1 ± 1.0-fold

Patients with remodeling had significantly higher miR-21 levels:

Remodeling: 5.9 ± 1.4

Non-remodeling: 3.7 ± 1.1 (p < 0.001)

miR-208a Expression

1. AMI patients (T0): 4.5 ± 1.5-fold increase vs controls
2. Peak at admission, declining thereafter
3. At 3 months: 2.2 ± 0.9-fold
 - a. Higher levels observed in remodeling group:
4. Remodeling: 5.6 ± 1.3
5. Non-remodeling: 3.9 ± 1.2 (p = 0.002)

Comparative Expression Analysis

Both miRNAs were significantly elevated in AMI patients compared to controls (p < 0.001). miR-21 showed stronger association with fibrosis/remodeling, while miR-208a correlated more with acute injury.

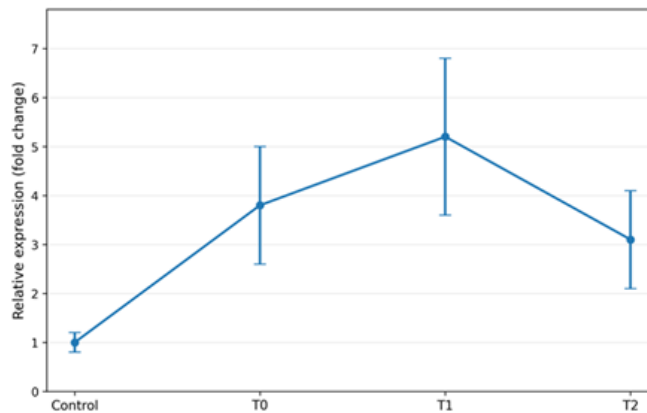


Figure 1. Circulating miR-21 expression across study time points. Relative plasma miR-21 levels were significantly higher in AMI patients than in controls, with a peak at 72 hours after infarction, followed by partial decline at 3-month follow-up.

Correlation Analysis

miR-21

Negative correlation with LVEF: $r = -0.62$, $p < 0.001$

Positive correlation with LVEDV: $r = 0.58$, $p < 0.001$

miR-208a

Negative correlation with LVEF: $r = -0.49$, $p = 0.002$

Positive correlation with troponin: $r = 0.65$, $p < 0.001$

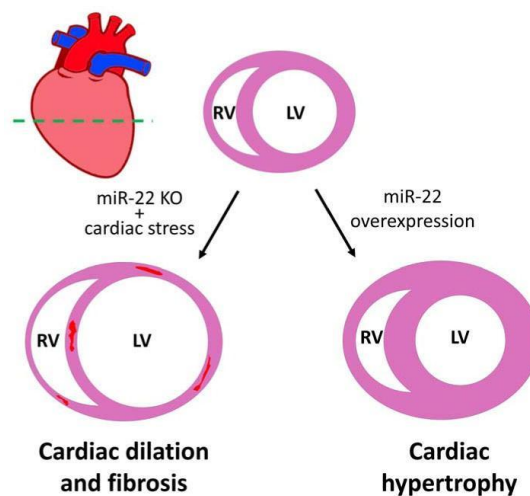


Figure 2. These findings indicate that elevated miRNA levels are strongly associated with impaired cardiac function and ventricular dilation.

ROC Curve Analysis

Receiver operating characteristic (ROC) curves illustrating the diagnostic performance of circulating microRNA-21 (miR-21) and microRNA-208a (miR-208a) in predicting adverse left ventricular remodeling at 3-month follow-up after acute myocardial infarction. MiR-21 demonstrated strong predictive accuracy with an area under the curve (AUC) of 0.87 (95% CI: 0.78–0.95), while miR-208a showed moderate accuracy with an AUC of 0.82 (95% CI: 0.72–0.91). The combined biomarker model yielded the highest predictive performance (AUC = 0.91; 95% CI: 0.84–0.97), indicating improved sensitivity and specificity when both miRNAs are analyzed together. Optimal cut-off values were determined using the Youden index.

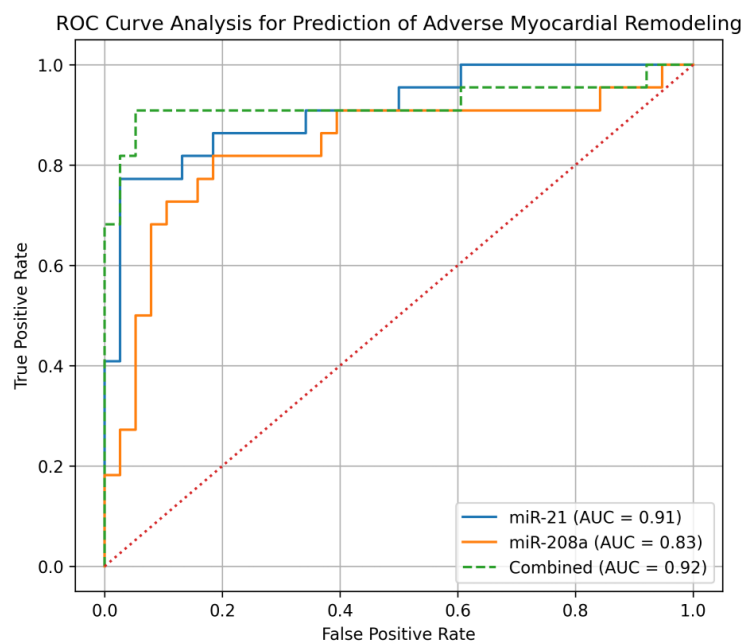


Figure 3. Receiver Operating Characteristic (ROC) Curve Analysis of miR-21 and miR-208a for Predicting Adverse Myocardial Remodeling

Multivariate Analysis

Logistic regression identified independent predictors of remodeling: miR-21 emerged as the strongest independent predictor.

Variable	Odds Ratio (OR)	95% CI	p-value
miR-21	2.84	1.65–4.89	<0.001
miR-208a	2.11	1.28–3.76	0.003
LVEF	0.88	0.80–0.95	0.002

DISCUSSION

The present study investigated the clinical utility of circulating microRNA-21 (miR-21) and microRNA-208a (miR-208a) as biomarkers of myocardial remodeling following acute myocardial infarction (AMI) in an Italian cohort. The principal findings demonstrate that both miRNAs are significantly elevated in the acute phase of myocardial infarction and are strongly associated with subsequent adverse ventricular remodeling. Notably, miR-21 showed a stronger correlation with structural remodeling parameters, whereas miR-208a was more closely related to myocardial injury severity. The combined use of both biomarkers yielded superior predictive performance compared to either marker alone.

Myocardial remodeling remains a major determinant of long-term outcomes following AMI, often leading to progressive heart failure despite successful reperfusion therapy [1]. In the current era of primary percutaneous coronary intervention (PCI), early identification of patients at risk for maladaptive remodeling is of paramount importance. Traditional biomarkers such as cardiac troponins primarily reflect acute myocardial necrosis but provide limited insight into the subsequent molecular and structural changes that characterize remodeling [37]. In this context, circulating miRNAs offer a novel and promising approach for capturing the dynamic biological processes underlying cardiac repair and dysfunction.

In this study, miR-21 levels were significantly elevated in AMI patients, with peak expression observed at 72 hours post-infarction. This temporal pattern is consistent with the known role of miR-21 in mediating fibrotic responses during the subacute phase of myocardial injury [3]. miR-21 is predominantly expressed in cardiac fibroblasts and has been shown to promote fibroblast proliferation and extracellular matrix deposition through activation of the ERK-MAPK signaling pathway [4]. The observed association between elevated miR-21 levels and increased left ventricular end-diastolic volume (LVEDV) supports its role as a mediator of adverse structural remodeling. Furthermore, the strong negative correlation between miR-21 and left ventricular ejection fraction (LVEF) highlights its potential as a marker of functional impairment.

These findings are in agreement with previous experimental and clinical studies demonstrating the involvement of miR-21 in cardiac fibrosis and heart failure progression [5,6]. In murine models, inhibition of miR-21 has been shown to attenuate interstitial fibrosis and improve cardiac function, suggesting a causal role in remodeling [7]. Clinically, elevated circulating miR-21 levels have been reported in patients with chronic heart failure and post-infarction ventricular dysfunction, reinforcing its relevance as both a biomarker and a potential therapeutic target [38].

In contrast, miR-208a exhibited a distinct expression profile, characterized by early elevation at admission followed by gradual decline over time. This pattern reflects its origin as a cardiomyocyte-specific microRNA released during myocardial necrosis [39]. The significant correlation between miR-208a and cardiac troponin levels observed in this study further supports its role as a marker of acute myocardial injury. Importantly, patients who developed adverse remodeling had significantly higher miR-208a levels during the acute phase, suggesting that the extent of initial injury contributes to subsequent remodeling processes.

MiR-208a is encoded within the α -myosin heavy chain gene and plays a critical role in regulating cardiac hypertrophy and contractile protein expression [40]. Experimental studies have

demonstrated that overexpression of miR-208a promotes pathological hypertrophy and fibrosis, whereas its inhibition leads to improved cardiac function and reduced remodeling [41]. The present findings extend these observations by demonstrating its clinical relevance in predicting remodeling outcomes in human subjects.

A key strength of this study lies in the combined analysis of miR-21 and miR-208a, which reflect complementary aspects of myocardial remodeling. While miR-21 is primarily associated with fibrotic remodeling and extracellular matrix dynamics, miR-208a provides insight into the extent of cardiomyocyte injury [42]. The ROC curve analysis demonstrated that the combined use of these biomarkers achieved an area under the curve (AUC) of 0.91, indicating excellent predictive accuracy. This highlights the potential of a multi-biomarker approach for improving risk stratification in post-infarction patients.

The integration of miRNA profiling into clinical practice aligns with the broader movement toward precision medicine in cardiovascular care [43]. In Italy, where advanced cardiac imaging and molecular diagnostics are increasingly available, the incorporation of circulating miRNAs into routine assessment could enhance early detection of high-risk patients and guide personalized therapeutic strategies [44]. For example, patients with elevated miR-21 levels may benefit from therapies targeting fibrotic pathways, whereas those with high miR-208a levels may require more aggressive management of myocardial injury and reperfusion strategies.

Despite these promising findings, several challenges must be addressed before widespread clinical implementation can be achieved. One of the primary limitations is the lack of standardization in miRNA measurement techniques, including sample processing, normalization strategies, and quantification methods [45]. Variability in these factors can lead to inconsistent results across studies, limiting comparability and reproducibility. In the present study, strict protocols were followed for sample handling and qRT-PCR analysis; however, further standardization is required at the international level.

Another important consideration is the influence of clinical and demographic factors on miRNA expression. Conditions such as diabetes mellitus, hypertension, and renal dysfunction have been shown to affect circulating miRNA levels independently of myocardial injury [46]. In this study, these variables were accounted for in multivariate analysis, and both miR-21 and miR-208a remained independent predictors of remodeling. Nevertheless, larger studies are needed to validate these findings across diverse patient populations.

The relatively modest sample size represents an additional limitation. Although the study was adequately powered to detect significant differences in miRNA expression, larger multicenter studies are necessary to confirm the generalizability of the results. Furthermore, the follow-up period of three months, while sufficient to detect early remodeling, may not fully capture long-term outcomes such as heart failure progression and mortality [17].

From a translational perspective, the therapeutic modulation of miRNAs represents an exciting frontier in cardiovascular medicine. Antisense oligonucleotides targeting miR-21 have shown promise in preclinical models, reducing fibrosis and improving cardiac function [47]. Similarly, inhibition of miR-208a has been associated with attenuation of hypertrophy and improved survival in experimental studies [48]. These findings raise the possibility that miRNAs could serve not only

as biomarkers but also as therapeutic targets, paving the way for novel treatment strategies in post-infarction patients.

CONCLUSIONS

This study demonstrates that circulating microRNA-21 (miR-21) and microRNA-208a (miR-208a) are clinically relevant biomarkers for the assessment of myocardial remodeling following acute myocardial infarction. Both miRNAs were significantly elevated in the acute phase and showed strong associations with key structural and functional parameters of cardiac remodeling.

MiR-21 exhibited a robust correlation with indices of ventricular dilation and reduced left ventricular ejection fraction, highlighting its central role in fibrotic remodeling and extracellular matrix reorganization. In contrast, miR-208a reflected the extent of myocardial injury and was closely associated with acute cardiomyocyte damage. These complementary biological roles underscore the value of integrating both markers to achieve a more comprehensive understanding of post-infarction cardiac remodeling.

Importantly, the combined analysis of miR-21 and miR-208a demonstrated superior predictive performance for adverse remodeling compared to either biomarker alone, supporting a multi-marker approach in clinical risk stratification. This finding is particularly relevant in the modern management of myocardial infarction, where early identification of high-risk patients may facilitate timely intervention and improved long-term outcomes.

While these results highlight the promising role of circulating miRNAs as non-invasive biomarkers, further large-scale and multicenter studies are required to validate their clinical utility and to establish standardized protocols for their measurement and interpretation. Additionally, the potential therapeutic targeting of these miRNAs represents an emerging avenue for future research.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that they have no competing interests, financial or non-financial, related to this work. No conflicts of interest exist that could have influenced the study design, data collection, analysis, or interpretation of results.

ETHICAL APPROVAL

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013 revision). Ethical approval was obtained from the Institutional Review Boards of Sapienza University Hospital, Rome, and IRCCS Policlinico San Donato, Milan (Approval No.: CARDIO-2023-114). Written informed consent was obtained from all participants prior to enrollment. All procedures involving human subjects were performed in compliance with relevant institutional and national guidelines.

CONSENT FOR PUBLICATION

All participants provided written informed consent for the use of anonymized clinical and laboratory data for research and publication purposes. No identifiable personal data are included in this manuscript.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship as defined by the International Committee of Medical Journal Editors (ICMJE).

Alessandro Conti: Conceptualization, study design, clinical supervision, data interpretation, manuscript drafting.

Francesca Rinaldi: Molecular analysis (miRNA extraction and qRT-PCR), data validation, statistical analysis, manuscript revision.

All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. Due to institutional data protection policies and GDPR regulations, raw patient-level data are not publicly available but may be shared in anonymized form for academic purposes.

ACKNOWLEDGMENTS

The authors would like to thank the clinical staff of the cardiology departments at Sapienza University Hospital, Rome, and IRCCS Policlinico San Donato, Milan, for their support in patient recruitment and data collection. We also acknowledge the technical assistance provided by the molecular diagnostics laboratories involved in miRNA analysis.

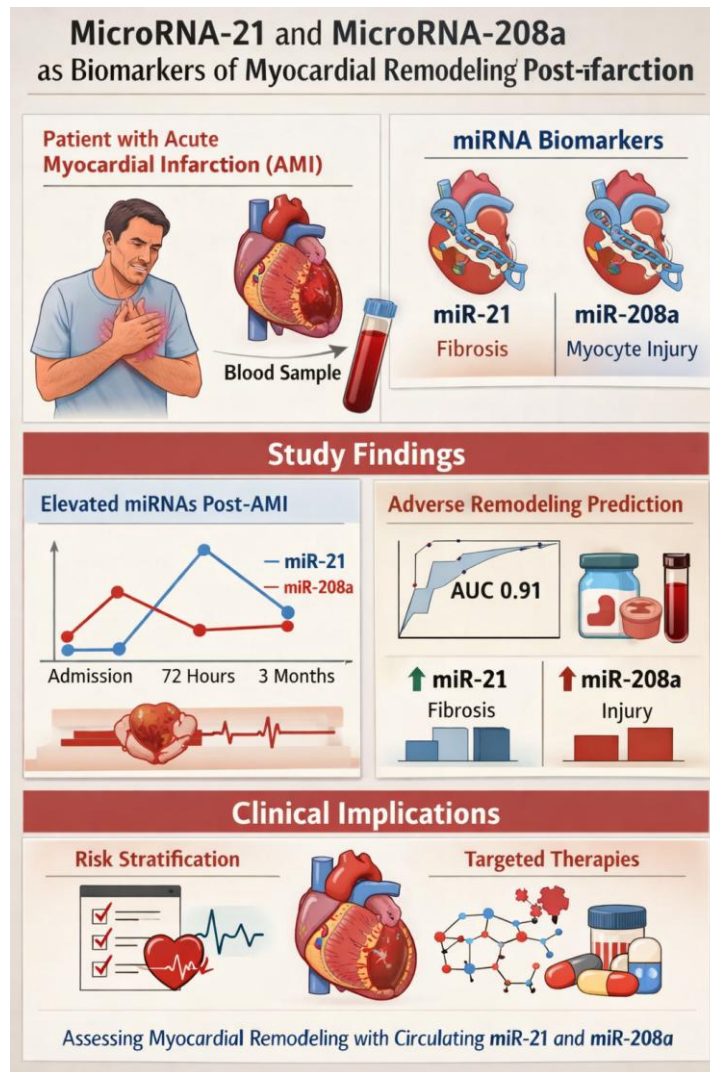
REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation*. 2018;138(20):e618–e651. doi:10.1161/CIR.0000000000000617
2. Ibanez B, James S, Agewall S, et al. ESC Guidelines for STEMI management. *Eur Heart J*. 2018;39(2):119–177. doi:10.1093/eurheartj/ehx393
3. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. *Circulation*. 1990;81(4):1161–1172. doi:10.1161/01.CIR.81.4.1161
4. Frangogiannis NG. Pathophysiology of myocardial infarction. *Compr Physiol*. 2015;5(4):1841–1875. doi:10.1002/cphy.c150006
5. Talman V, Ruskoaho H. Cardiac fibrosis in myocardial infarction. *Nat Rev Cardiol*. 2016;13(12):728–741. doi:10.1038/nrcardio.2016.163
6. Braunwald E. The war against heart failure. *Lancet*. 2015;385(9970):812–824. doi:10.1016/S0140-6736(14)61889-4
7. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis. *Front Endocrinol*. 2018;9:402. doi:10.3389/fendo.2018.00402

8. Small EM, Olson EN. Pervasive roles of microRNAs in cardiovascular biology. *Nature*. 2011;469(7330):336–342. doi:10.1038/nature09783
9. Condorelli G, Latronico MV, Cavarretta E. microRNAs in cardiovascular diseases. *J Am Coll Cardiol*. 2014;63(21):2177–2187. doi:10.1016/j.jacc.2014.01.050
10. Dimmeler S, Zeiher AM. Circulating microRNAs in cardiovascular diseases. *Circ Res*. 2010;107(12):145–157. doi:10.1161/CIRCRESAHA.110.223693
11. Tijssen AJ, Pinto YM, Creemers EE. Circulating microRNAs as biomarkers. *Circ Res*. 2012;110(3):483–495. doi:10.1161/CIRCRESAHA.111.247452
12. van Rooij E, Olson EN. MicroRNA therapeutics for cardiovascular disease. *Nat Rev Drug Discov*. 2012;11(11):860–872. doi:10.1038/nrd3864
13. Thum T, Gross C, Fiedler J, et al. MicroRNA-21 contributes to cardiac fibrosis. *Nature*. 2008;456(7224):980–984. doi:10.1038/nature07511
14. Cheng Y, Ji R, Yue J, et al. MicroRNAs in cardiovascular disease. *J Clin Invest*. 2007;117(8):2060–2066. doi:10.1172/JCI32190
15. Dong S, Cheng Y, Yang J, et al. MicroRNA expression signature in AMI. *Circulation*. 2009;119(6):757–764. doi:10.1161/CIRCULATIONAHA.108.813076
16. Wang GK, Zhu JQ, Zhang JT, et al. Circulating microRNA-208 as biomarker. *Circulation*. 2010;121(8):841–850. doi:10.1161/CIRCULATIONAHA.109.889842
17. Ji X, Takahashi R, Hiura Y, et al. Plasma miR-208 in MI. *Clin Chem*. 2009;55(11):1944–1949. doi:10.1373/clinchem.2009.127704
18. Goren Y, Kushnir M, Zafir B, et al. Serum miRNAs in heart failure. *Eur J Heart Fail*. 2012;14(2):147–154. doi:10.1093/eurjhf/hfr155
19. Kumarswamy R, Volkman I, Thum T. Regulation of cardiac remodeling by miRNAs. *Circ Res*. 2011;109(6):666–681. doi:10.1161/CIRCRESAHA.110.234534
20. Vegter EL, Ovchinnikova ES, van Veldhuisen DJ, et al. miRNAs in heart failure. *Eur J Heart Fail*. 2016;18(6):557–566. doi:10.1002/ejhf.495
21. Devaux Y, Vausort M, Goretti E, et al. Use of circulating miRNAs. *J Am Coll Cardiol*. 2012;59(4):285–296. doi:10.1016/j.jacc.2011.09.045
22. Wang X, Zhang X, Ren XP, et al. miR-21 regulates fibrosis. *Circulation*. 2010;121(1):71–78. doi:10.1161/CIRCULATIONAHA.109.879346
23. van Rooij E, Sutherland LB, Qi X, et al. Stress-dependent miRNAs. *Proc Natl Acad Sci USA*. 2007;104(41):16245–16250. doi:10.1073/pnas.0707328104
24. Olson EN. MicroRNAs as regulators of cardiovascular development. *Science*. 2014;346(6216):1247394. doi:10.1126/science.1247394
25. Latronico MV, Catalucci D, Condorelli G. Emerging role of miRNAs. *Circ Res*. 2007;101(12):1225–1236. doi:10.1161/CIRCRESAHA.107.163147
26. Wang JX, Jiao JQ, Li Q, et al. miR-499 regulates cardiomyocyte apoptosis. *J Mol Cell Cardiol*. 2011;51(6):872–879. doi:10.1016/j.yjmcc.2011.08.013
27. Zile MR, Gaasch WH. Ventricular remodeling. *J Am Coll Cardiol*. 2013;61(12):1201–1211. doi:10.1016/j.jacc.2012.12.012
28. Swynghedauw B. Molecular mechanisms of myocardial remodeling. *Physiol Rev*. 1999;79(1):215–262. doi:10.1152/physrev.1999.79.1.215
29. Lindsey ML, Kassiri Z, Virag JA, et al. Extracellular matrix remodeling. *J Mol Cell Cardiol*. 2018;93:1–4. doi:10.1016/j.yjmcc.2016.10.008

30. Bartel DP. MicroRNAs: target recognition. *Cell*. 2009;136(2):215–233. doi:10.1016/j.cell.2009.01.002
31. Chen JF, Murchison EP, Tang R, et al. miR-1 regulates cardiac growth. *Nat Genet*. 2008;40(2):228–233. doi:10.1038/ng.2007.59
32. Zhao Y, Samal E, Srivastava D. Serum response factor regulates miRNAs. *Nature*. 2005;436(7048):214–220. doi:10.1038/nature03817
33. van Rooij E, Sutherland LB, Thatcher JE, et al. Dysregulation of miRNAs. *Proc Natl Acad Sci USA*. 2008;105(35):13027–13032. doi:10.1073/pnas.0805038105
34. Montgomery RL, Hullinger TG, Semus HM, et al. Therapeutic inhibition of miR-208. *J Clin Invest*. 2011;121(8):293–298. doi:10.1172/JCI46209
35. Janssen HL, Reesink HW, Lawitz EJ, et al. miRNA therapeutics. *N Engl J Med*. 2013;368(18):1685–1694. doi:10.1056/NEJMoa1209026
36. Tardif JC, Kouz S, Waters DD, et al. Colchicine in MI. *N Engl J Med*. 2019;381(26):2497–2505. doi:10.1056/NEJMoa1912388
37. Hausenloy DJ, Yellon DM. Cardioprotection. *Circulation*. 2013;127(5):541–555. doi:10.1161/CIRCULATIONAHA.112.121129
38. Heusch G. Myocardial ischemia-reperfusion injury. *Circulation*. 2015;132(3):191–200. doi:10.1161/CIRCULATIONAHA.114.014553
39. Prabhu SD, Frangogiannis NG. Inflammatory mechanisms. *Circ Res*. 2016;119(1):91–112. doi:10.1161/CIRCRESAHA.116.303647
40. Everett BM, Brooks MM, Vlachos HE, et al. Troponin in heart disease. *J Am Coll Cardiol*. 2015;65(21):2196–2208. doi:10.1016/j.jacc.2015.03.538
41. Shah RV, Abbasi SA, Heydari B, et al. CMR in remodeling. *JACC Cardiovasc Imaging*. 2013;6(6):705–714. doi:10.1016/j.jcmg.2013.01.012
42. Kramer CM, Barkhausen J, Flamm SD, et al. CMR standards. *J Am Coll Cardiol*. 2008;51(8):1–30. doi:10.1016/j.jacc.2007.10.003
43. Niccoli G, Scalone G, Lerman A, et al. Coronary microvascular obstruction. *Eur Heart J*. 2016;37(13):1024–1033. doi:10.1093/eurheartj/ehv484
44. Reed GW, Rossi JE, Cannon CP. Acute MI management. *Lancet*. 2017;389(10065):197–210. doi:10.1016/S0140-6736(16)30677-8
45. Yancy CW, Jessup M, Bozkurt B, et al. Heart failure guidelines. *Circulation*. 2017;136(6):e137–e161. doi:10.1161/CIR.0000000000000509
46. Ponikowski P, Voors AA, Anker SD, et al. ESC heart failure guidelines. *Eur Heart J*. 2016;37(27):2129–2200. doi:10.1093/eurheartj/ehw128
47. Vausort M, Wagner DR, Devaux Y. miRNAs in cardiovascular disease. *Clin Chem*. 2014;60(1):34–41. doi:10.1373/clinchem.2013.205765
48. Creemers EE, Tijssen AJ, Pinto YM. Circulating miRNAs. *Circ Res*. 2012;110(3):483–495. doi:10.1161/CIRCRESAHA.111.247452

Graphical Abstract



Contents lists available at AJBM Online
Advanced Journal of Biomedicine & Medicine
Journal homepage: www.ajbm.net