BMC Cardiovascular Disorders

RESEARCH

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The potential value of microRNA-409-5p-mediated negative regulation of USP7 in the diagnosis and treatment of acute myocardial infarction

Xuemei Fu[1,2†], Xi Zhang[1,3†], Lixing Wang[4], Juan Zhang[5], Waiqiong Li[2], Shaoxi Qin[2], Min Zhang[2], Xiaotian Zheng[2], Ying Li[2], Shaobo Yang[2*] and Qiang Xue[1,3*]

Abstract

Purpose This study aimed to explore the effects of ubiquitin-specific peptidase 7 (USP7) on acute myocardial infarction (AMI) and the negative regulation of USP7 by microRNA-409-5p (miR-409-5p).

Methods Clinical data were collected from patients admitted to the Cardiology Department of Yan'an Hospital of Kunming City between July 2020 and July 2021. The participants included patients with AMI (AMI; $n=30$), stable angina pectoris (SAP; $n=30$), and chest pain syndrome (CPS; $n=30$) and healthy controls ($n=30$). The expression levels of miR-409-5p and USP7 were analysed using Quantitative real-time polymerase chain reaction (qRT–PCR) and Western blotting (WB). Finally, a dual-luciferase assay was performed to verify the interaction between miR-409-5p and USP7.

Results The expression level of miR-409-5p was significantly lower (all $p<0.05$), whereas the expression level of USP7 was elevated in patients with AMI compared with those in the other three groups (all $p<0.05$). A dual-luciferase assay demonstrated that miR-409-5p binds to USP7 3'UTP to inhibit luciferase expression. Compared with cells transfected with mutation fragments and a luciferase reporter vector with microRNA-409-5p mimics and USP7 3'UTR binding and mutation sites, the luminescence level of cells with miR-409-5p was approximately 40% lower. Additionally, miRNA-409-5p was inversely correlated with cTnI ($p=0.004$).

Conclusion USP7 plays a significant role in AMI via negative regulation by miR-409-5p. Both miR-409-5p and USP7 hold key potential as early diagnostic biomarkers and therapeutic targets for AMI in the future.

Keywords USP7, Myocardial infarction (MI), MiR-409-5p, Apoptosis

†Xuemei Fu and Xi Zhang contributed equally to this work and share first authorship.

*Correspondence:
Shaobo Yang
qjyangshaobo@163.com
Qiang Xue
xueqiang3513@126.com
Full list of author information is available at the end of the article

Introduction

Cardiovascular disease remains the leading cause of death worldwide, with acute myocardial infarction (AMI) being particularly detrimental; however, a timely diagnosis and rapid primary revascularization of the culprit vessel are critical for improving the prognosis under current treatment strategies [1–4]. AMI arises mainly from acute thrombosis caused by plaque erosion and rupture due to coronary artery atherosclerosis, resulting in a sharp reduction in or interruption of the coronary blood supply, leading to severe and lasting ischaemia and myocardial necrosis [3, 4]. At present, AMI treatments emphasise the early revascularization and timely restoration of blood flow to the culprit vessels to minimise myocardial cell death and save patients' lives. In contrast, the early diagnosis of AMI relies on a comprehensive diagnosis of symptoms, electrocardiograms, and myocardial enzyme profiles [5, 6]. For many patients who present with nonspecific chest pain and atypical electrocardiograms, physicians often rely on key essential markers such as myocardial enzymes. However, some studies have shown that plasma cardiac troponin I (cTnI) concentrations may be abnormally elevated in severe heart failure, chronic kidney disease, etc. [7, 8]. Consequently, many scholars have focused on identifying novel biomarkers of myocardial damage and targeting molecular substances to treat myocardial infarction (MI).

MicroRNAs are small, noncoding RNAs involved in posttranscriptional regulation and influence the transcription of approximately 60% of the mammalian genome [9]. Numerous microRNAs participate in myocardial apoptosis and remodelling by inhibiting the expression of target genes that play decisive roles in the growth or apoptosis of myocardial cells and extracellular matrix remodelling, thus contributing to heart failure [10, 11]. In the acute phase of AMI, many circulating microRNAs are abnormally expressed [12–15]. Interestingly, miRNAs are present in the blood and/or plasma in a strikingly stable way and might be reasonable biomarkers for the diagnosis of AMI [16]. In an animal study by Xue et al., the expression of microRNA-409-5p (miR-409-5p) in the serum of experimental mice was downregulated, and artificial supplementation of mice with miR-409-5p analogues alleviated myocardial damage [10]. Posttranslational protein modifications are emerging as critical regulators of myocardial cell protection and endogenous regeneration, indicating that protein modifications may be promising treatments for MI [17].

Deubiquitination is a highly regulated process that plays a pivotal role in the progression of heart disease [18, 19]. Ubiquitin-specific peptidase 7 (USP7) is one of the most characteristic ubiquitination enzymes, and many proteins have been identified as potential substrates and binding partners of USP7. USP7 regulates several target proteins through its deubiquitination activity and participates in the programming of various cell types [20–22]. Many studies have examined the proteins on which USP7 acts. As a well-known proapoptotic factor, p53 promotes myocardial cell apoptosis and plays a vital role in regulating myocardial apoptosis after AMI [23, 24]. USP7 stabilises p53 and MDM2 through deubiquitinating enzymatic activity, thus playing an essential role in the regulation of p53 and MDM2 levels under normal and stress conditions [25, 26].

A previous study revealed that post-MI downregulation of circulating miR-409-5p abnormally increases the expression of USP7, which subsequently promotes cardiomyocyte injury [10]. Circulating levels of miR-409-5p and USP7 are significantly correlated with serum biomarkers and echocardiographic indicators of heart failure and left ventricle remodelling, suggesting that they contribute to the occurrence and evolution of left ventricle remodelling and dysfunction following AMI [27].

However, it is unclear whether circulating miR-409-5p and USP7 play similar roles in humans during AMI. Therefore, this study investigated the levels of circulating miR-409-5p and USP7 in the serum of patients with AMI, stable angina pectoris (SAP), and chest pain syndrome (CPS) and healthy controls (H) to provide clinical evidence for future applications.

Methods

Research participants

One hundred twenty patients admitted by the Cardiology Department of Yan'an Hospital of Kunming City due to chest pain and distress for the first time from July 2019 to July 2021 were selected as the research participants. The participants were patients with AMI ($n=30$), SAP ($n=30$), or CPS ($n=30$) and healthy volunteers (no history of cardiovascular disease and normal electrocardiographic findings, $n=30$). Briefly, the inclusion criteria for patients with AMI were based on increased cTnI or/and electrocardiogram (ECG) findings, such as new pathological Q waves or ST-segment elevation or depression, from the 2018 Fourth Universal Definition of Myocardial Infarction of the European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF). The diagnostic criteria for SAP patients were based on the Guidelines for Diagnosis and Treatment of Stable Coronary Heart Disease formulated by the Chinese Medical Association Cardiovascular Branch in 2018. CPS patients were defined as those who had ruled out coronary heart disease or who had been diagnosed with other diseases causing chest pain, including reflux oesophagitis, pneumothorax, and intercostal

neuralgia. Patients with the following conditions were excluded: heart failure, congenital heart disease, valvular heart disease, secondary MI, history of cerebrovascular diseases, thyroid disease, various acute and chronic infections, COPD, liver or kidney insufficiency, autoimmune diseases, blood diseases, and malignant tumours. This observational study complied with medical ethics requirements and was approved by the Ethics Committee of Yan'an Hospital of Kunming City. All procedures performed on patients followed the Helsinki Declaration. All patients provided informed consent before blood samples were taken.

miRNA extraction and quantification

Serum miRNAs were extracted using the miRNeasy Extraction Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The concentration of the extracted miRNA was quantified using a NanoDrop spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). The miRNA-409-5p and USP7 mRNA expression levels were measured using the Bulge-Loop™ miRNA qRT–PCR Primer Kit (RiboBio Co., Guangzhou, China) following the manufacturer's instructions. *Caenorhabditis elegans* miRNA was used as an internal control.

For reverse transcription, 0.5 μg of total RNA from each sample was transcribed using microRNA-specific primers and M-MLV reverse transcriptase (Promega, Madison, WI, USA). Complementary DNA (cDNA) was synthesised using the use of the miR-409-5p primer. Quantitative real-time polymerase chain reaction (qRT–PCR) was performed using a PRISM 7900HT sequence detection system (Applied Biosystems, Carlsbad, CA, USA). All the assays were conducted in triplicate.

The expression levels of circulating miR-409-5p were normalised to those of U6, and miRNA quantification was conducted using the TaqMan MicroRNA Analysis Kit and TaqMan Universal Master Mix (Applied Biosystems). The primer sequences for miR-409-5p were as follows: forward primer 5'-ACA CTC CAG CTG GGA GGT TAC CCG AGC AAC T-3', reverse primer 5'-TGG TGG GGA GGT TAC CCG AGC AAC T-3'. For U6, the forward primer was 5'-CTC GCT TCG GCA GCA CA-3', and the reverse primer was 5'-AAC GCT TGT CGT GGA GTC G-3'.

USP7 and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA levels were also quantified via qRT–PCR. The primers for USP7 were forward primer 5'-GTC CTT AGC CCT CCG TGT TT-3', reverse primer 5'-CAA ATG ACT GCT GCA GCA CA-3'. For GAPDH, the forward primer was 5'-GGA AGC TTG TCA TCA ATG GAA ATC-3', and the reverse primer was 5'-TGA TGA CCC TTT TGG CTC CC-3'.

All the experiments were performed by an investigator (Z.X.) who was blinded to the patients' clinical characteristics. The threshold cycle (Ct) values were defined as the number of cycles required for fluorescence to exceed a specified threshold. Relative expression values for miRNAs were calculated using the $2^{-\Delta\Delta Ct}$ method.

Western blot

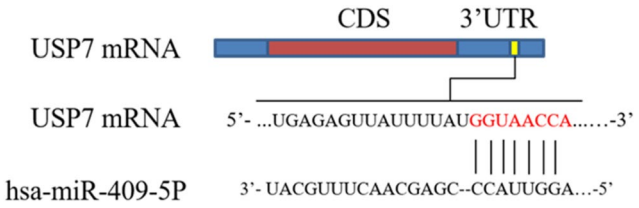
Proteins were extracted from the peripheral blood mononuclear cells of patients using RIPA buffer (P0013B, Baiyoushi, China) supplemented with a mixture of protease inhibitors. The lysates were resolved by 10% SDS–PAGE and subsequently transferred electrophoretically to PVDF membranes. The membranes were blocked with 5% milk and incubated overnight at 4 °C with a specific USP7 primary antibody (1:20,000, 66,514–1-Ig, Proteintech, China). Afterwards, the membranes were incubated with an appropriate secondary antibody. Chemiluminescence detection was performed via an enhanced chemiluminescence (ECL) kit (PK10003, Proteintech, China) according to the manufacturer's instructions. Signal detection was performed via a chemiluminescence imaging system (5200 Multi, Tanon, China).

cTnI measurement

Plasma cTnI levels were determined by electrochemiluminescence using an Elecsys 2010 immunoanalyzer (Roche Diagnostics, Switzerland) according to the manufacturer's protocol.

Dual-luciferase detection

First, the binding site fragment was synthesised with miR-409-5p mimics. For biological prediction, the binding site (BS) and the flanking fragment of miR-409-5p contained in the human USP7 3'UTR were cloned and inserted into the luciferase vector psiCHECK2. The fragment sequence used is shown in Fig. 1 (the underlined part is the binding site, and SacI and HindIII restriction enzyme cutting sites were added at both ends of the sequence). Second, the single-stranded DNA sequence was renatured and recovered, and the recovered double-stranded DNA and vector were subjected to double digestion with SacI and HindIII, respectively. The enzyme digestion products of the double-stranded DNA and vector after electrophoresis detection and concentration determination were recovered, connected, identified after transformation, and then transfected according to the manufacturer's instructions. The transfection-grade ultrapure plasmid was extracted via an E.Z.N. endotoxin-removing ultrapure plasmid extraction kit (Omega). The obtained plasmid was required to have A260/280 ratios of 1.8 and 2.0 and an A160/230 ratio > 2. Luciferase activity was measured 48 h after transfection.



Name	Sequence
psiCHECK 2-STAT3	5'-CGAGCTCGUGAGAGUUAUUUUAUGGUAACCAGGATCTAAGGACA AGCTTG-3'
psiCHECK 2-STAT3-Mut	5'-CGAGCTCGUACGUUUCAACGAGCCCAUUGGAGGATCTAAGGACAA GCTTG -3'

Fig. 1 Sequence and SacI and HindIII restriction enzyme cutting sites of the fragment

Statistical method

SPSS ver. 23.0 was used for statistical analysis. All the clinical characteristics of the patients are presented as the means ± SDs, and the other data are presented as the means ± SEMs. The data on age, USP7, miRNA, and cTnI were analysed via the Kolmogorov–Smirnov test to examine whether they followed a normal distribution. One-way ANOVA was performed to compare four groups with normally distributed data. When significant differences were found, post hoc pairwise comparisons were conducted using either the least significant difference (LSD) method or Tamhane's T2 test, depending on the assumption of homogeneity of variance. For data that did not follow a normal distribution, the Kruskal–Wallis H test was used for between-group comparisons, and the Mann–Whitney U test was applied for pairwise comparisons when applicable. Comparisons of categorical variables were made using the $\chi 2$ test. Correlation analysis was performed via linear regression analysis. All p values were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study population

The clinical characteristics of the study groups are summarised in Table 1. The mean ages of the AMI group (61.23 ± 11.74) and the SAP group (57.53 ± 10.69) were similar ($p = 0.751$) but significantly greater than those of the CPS group (45.37 ± 16.41) and H group (47.27 ± 15.87), with p values < 0.05 for these

Table 1 Comparison of clinical data among the four groups

Index	AMI ($n = 27$)	SAP ($n = 28$)	CPS ($n = 27$)	H ($n = 27$)	*P* value
Age, years	61.23 ± 11.74**	57.53 ± 10.69*	45.37 ± 16.41	47.27 ± 15.87	< 0.0001
Male, n (%)	21 (70.0)	19 (63.3)	15 (50.0)	13 (43.3)	0.145
Hypertension, n (%)	17 (56.7)	13 (43.3)	9 (30.0)	16 (53.3)	0.170
Diabetes, n (%)	4 (13.3)	2 (6.7)	1 (3.3)	2 (6.7)	0.625
Smoking, n (%)	19 (63.3)	18 (60.0)	11 (36.7)	14 (46.7)	0.169
Drinking, n (%)	8 (26.7)	13 (43.3)	9 (30.0)	6 (20.0)	0.286
SCr, mmol/L	82.17 ± 17.92	76.97 ± 15.84	73.83 ± 17.16	76.63 ± 14.11	0.259
cTnI, ng/mL	1.20 ± 0.17**	0.60 ± 0.13	0.59 ± 0.20	0.59 ± 0.11	< 0.0001

AMI Acute myocardial infarction group, *SAP* Stable angina pectoris group, *CPS* Chest pain syndrome group, *H* Healthy volunteer group, *TC* Total cholesterol, *SCr* serum creatinine, *cTnI* cardiac troponin I

** $p < 0.001$

* $p < 0.05$ versus healthy controls

comparisons. All groups were predominantly male, with 21/30 in the AMI group, 19/30 in the SAP group, 15/30 in the CPS group, and 13/30 in the H group ($p=0.145$). Compared with those in all the other groups, the mean cTnI level in the AMI patients was markedly elevated (1.20 ± 0.17 ng/mL) (all $p<0.0001$; Fig. 2A). No significant differences in other clinical parameters were observed between the AMI group and the other groups.

Circulating cardiac-associated microRNA levels in AMI patients

As shown in Fig. 2B, the expression of miR-409-5p was significantly decreased in the AMI group (all $p<0.05$). However, no significant differences in the expression of miR-409-5p were observed among the SAP, CPS, and H groups (all $p>0.05$). This finding confirms that the plasma miR-409-5p levels were specifically downregulated in the AMI group, distinguishing this group from the other groups. Furthermore, correlation analysis revealed a significant negative correlation between circulating miR-409-5p levels and cTnI concentrations in AMI patients (Fig. 2C).

Detection of USP7 expression via WB

Compared with those in the other three groups, the expression levels of USP7 in the AMI group were significantly greater ($p<0.001$, Fig. 3). However, no statistically significant differences in USP7 expression were detected among the SAP, CPS, and H groups (all $p>0.05$; Fig. 3).

Luciferase reporter assay

The dual-luciferase reporter assay demonstrated that miR-409-5p binds to the 3′UTR of USP7, thereby inhibiting luciferase expression. Compared with cells transfected with mutation fragments and luciferase reporter vector cells with miR-409-5P mimics and USP7 3'UTR and mutation binding sites, the luminescence level of

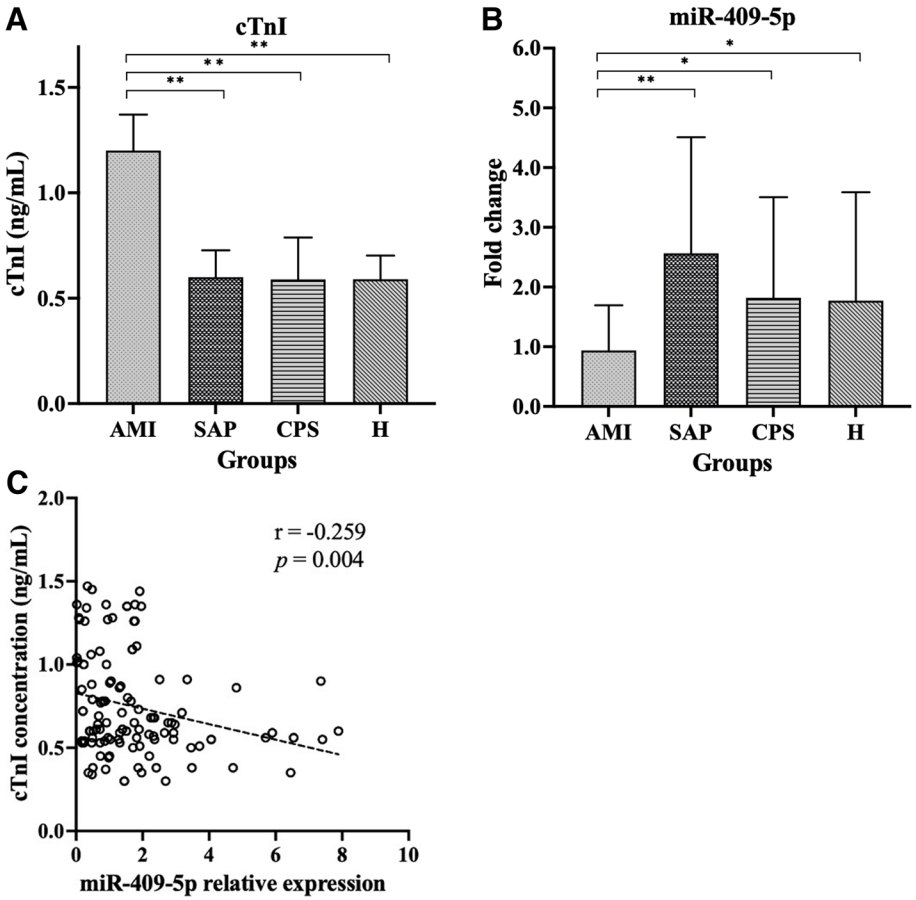


Fig. 2 Expression patterns of circulating cTnI and miR-409P-5P in Each Group. **A** The expression of circulating cTnI in the four groups (AMI vs. H, $p<0.0001$; AMI vs. SAP, $p<0.0001$; AMI vs. CPS, $p<0.0001$; SAP vs. CPS, $p=0.788$; SAP vs. H, $p=0.796$; and CPS vs. H, $p=0.996$). **B** The expression of circulating miR-409P-5P in the four groups (AMI vs. H, $p=0.048$; AMI vs. SAP, $p<0.0001$; AMI vs. CPS, $p=0.037$; SAP vs. CPS, $p=0.071$; SAP vs. H, $p=0.065$; CPS vs. H, $p=0.943$). **C** The correlation between miR-409P-5P and cTnI in plasma. AMI, acute myocardial infarction; SAP, stable angina pectoris; CPS, chest pain syndrome; H, healthy volunteers; *: $p<0.05$; **: $p<0.001$

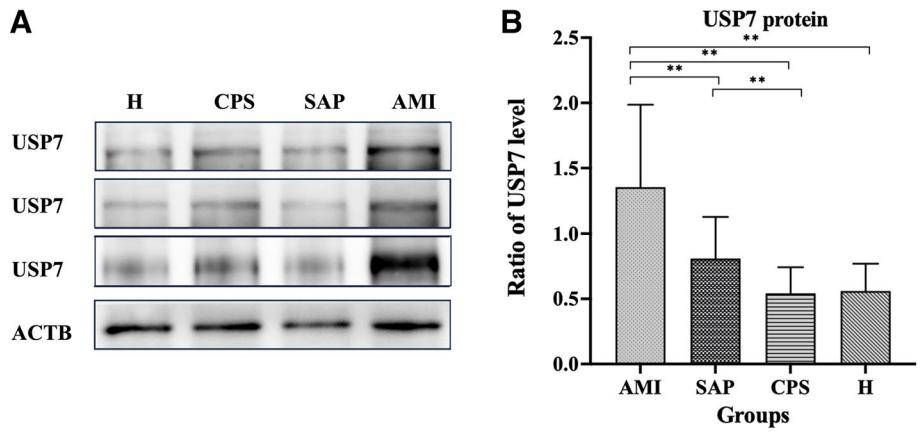


Fig. 3 Grey Values of USP7 Expression and Expression Quantity (**B**) in Each Group. **A** Detection of USP7 expression by WB; (**B**) Relative expression of USP7 protein/ACTB (AMI vs. H, $p < 0.0001$; AMI vs. SAP, $p < 0.0001$; AMI vs. CPS, $p < 0.0001$; SAP vs. CPS, $p = 0.788$; SAP vs. H, $p = 0.796$; CPS vs. H, $p = 0.994$); AMI, acute myocardial infarction; SAP, stable angina pectoris; CPS, chest pain syndrome; H, healthy volunteers; **: $p < 0.001$ versus healthy controls

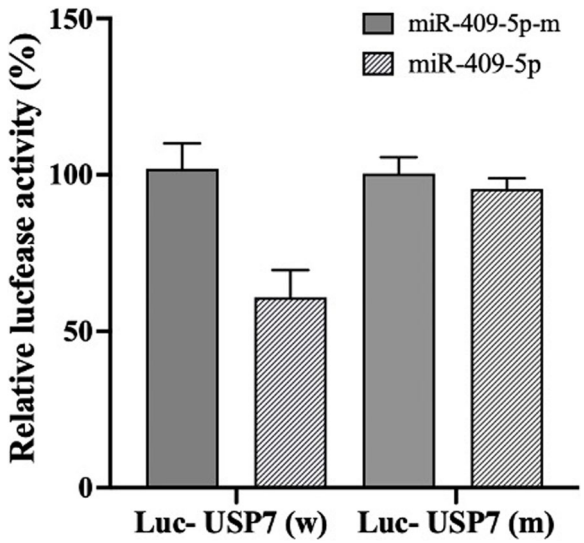


Fig. 4 Luciferase detection

cells with miR-409-5p was approximately 40% lower (Fig. 4).

Discussion

This study yielded the following main findings: (1) miRNA-409-5p expression was downregulated and USP7 expression was upregulated in AMI patients compared with the other three groups; (2) USP7 was negatively regulated by miR-409-5p; and (3) miRNA-409-5p levels were inversely correlated with plasma cTnI concentrations.

AMI is a life-threatening cardiovascular disease owing to its severity, high complication rates, sudden onset, and extremely high mortality and disability rates [3, 4]. cTnI is widely recognised as the gold standard biomarker for diagnosing AMI [3, 4]. However, plasma cTnI levels may increase in both cardiac and noncardiac conditions, including atrial fibrillation, severe heart failure, and chronic kidney disease [7, 8]. This raises concerns about the specificity of cTnI as a diagnostic tool.

Several recent studies have emphasised the regulatory roles of endogenous miRNAs in the pathogenesis of MI, in which the levels of certain miRNAs, such as miRNA-331 and miRNA-499, increase or decrease significantly during the occurrence and development of MI [12–15]. Interestingly, miRNAs can exist in exosomes, microbubbles, or apoptotic bodies and are protected from degradation by endogenous RNA enzyme activity; for these reasons, they can exist stably in biological fluids such as blood, tissue fluid, and urine [16, 27]. This stability renders miRNAs promising reasonable biomarkers for diagnosing AMI.

The miRNA-409 family is closely associated with the occurrence and development of cardiac diseases, including atrial fibrillation and MI; however, few studies have been conducted on the diagnosis and treatment of the miRNA-409 family for cardiovascular diseases [27, 28].

Our previous studies in animal models demonstrated that miRNA expression was significantly reduced and that USP7 expression was elevated in the AMI model, which is consistent with the findings of this study involving distinct patient cohorts (Fig. 2C-B) [10, 27]. Notably, the miR-409-5p levels in the CPS group did not significantly differ from those in the H group, likely because the CPS group did not have combined myocardial injury and necrosis. In contrast, SAP patients presented higher miR-409-5p expression than did the other groups. We speculate that this may be partially due to a protective cardiac feedback mechanism in response to chronic

micromyocardial ischaemia. However, further research is necessary to validate this hypothesis. In addition, we confirmed via bioinformatics and luciferase assays that miR-409-5p inhibits USP7 expression by binding to the 3'UTR; conversely, it promotes USP7 expression [10].

Currently, USP7 is widely used in MI research. USP7 has been implicated in promoting inflammation and cardiomyocyte apoptosis, with concurrent increases in the secretion of the cytokines IL-1b, TNF-a, and IL-6, which exacerbate myocardial ischaemic injury and increase circulating cTnI levels [10, 29, 30]. Similarly, the observed inverse correlation between miRNA-409-5p expression and cTnI levels further underscores their interconnected roles in AMI pathology (Fig. 2C) [31, 32]. Targeting miRNA- and USP7-based therapies could represent a promising approach to mitigate myocardial infarction.

Moreover, the miR-409-5p expression level decreased within one hour of AMI onset, preceding changes in serum cTnI levels, which suggests that miR-409-5p levels respond faster in AMI and that the low expression in the serum appeared earlier than that of cTnI. It is well known that pathological changes such as myocardial ischaemia, hypoxia, oedema, and necrosis occur rapidly during the early stages of AMI, followed by the release of necrotic products, including cTnI, CKMB, BNP, and miRNAs, into the bloodstream. However, unlike cTnI, which binds primarily to myofibrils, miRNAs are predominantly associated with cytoplasmic protein complexes [33–35]. We hypothesised that these differences may influence the pattern of cTnI and miRNA release patterns during the progression of myocardial necrosis. Undoubtedly, understanding these dynamics could enhance our ability to differentiate between miRNA- and cTnI-mediated diagnostic pathways in AMI, shedding light on their promising roles as novel diagnostic biomarkers and tailored therapeutic targets.

Despite its promising and compelling potential to facilitate rapid diagnostic and therapeutic decisions, this study inevitably has several limitations. First, this was a single-centre study with a small sample size. Second, longitudinal monitoring of plasma miRNA fluctuations is lacking because the study design did not perform a continuous, comprehensive assessment of miRNA expression levels in AMI patients. Future research with a larger cohort is essential to clearly validate the diagnostic value of miRNA-409-5p as a practical reliable biomarker compared with other markers. Moreover, miR-409-5p plays a pivotal role in regulating the gene expression and metabolism of myocardial cells after AMI through multiple pathways. Thus, identifying related cytokines and metabolic pathways could pave the way for innovative therapeutic strategies targeting AMI. Although the early diagnostic utility and specific therapeutic practicability require validation, the underlying evidence and potential benefits for rapid decision-making are promising.

Conclusion

miR-409-5p negatively regulates USP7 and plays a crucial role in the pathophysiology of acute myocardial infarction. miR-409-5p and USP7hold significant promise as significant early diagnostic markers and therapeutic targets for acute myocardial infarction, warranting further exploration in future research.

Abbreviations

AMI	Acute myocardial infarction
MI	Myocardial infarction
cTnI	Cardiac troponin I
USP7	Ubiquitin-specific protease 7
miR-409-5p	MicroRNA-409-5p
qRT–PCR	Quantitative real-time polymerase chain reaction
WB	Western blotting
SAP	Stable angina pectoris
CPS	Chest pain syndrome
ECG	Electrocardiogram

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04590-2.

Supplementary Material 1.

Acknowledgements

Not applicable.

Authors' contributions

QX and SBY designed the research study. The research was performed by XZ, XMF, JZ, MZ, XZ, YL, SXQ, WQL, and LXW. XZ, XMF, and JZ analysed and interpreted the data. XMF and XZ wrote the manuscript. All the authors contributed to editorial changes in the manuscript. All the authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Funding

This study was supported by funds from Kunming Cardiovascular Interventional Imaging Institute [grant numbers 2023-SW-01]; funds from the Yunnan Provincial Department of Education Science Research Program [grant number 2024J0280]; and funds from the Yunnan Provincial Science and Technology Program Project-Biomedical Special Project [grant number 202102AA310003-25].
The funding organization played no role in designing the study and did not participate in its execution, analysis, interpretation of the data, or decision to submit the results for publication.

Data availability

The data supporting this study's findings are available from the Yan'an Hospital of Kunming City Medical Record System, but restrictions apply to their availability. These data were used under licence for the current study and are not publicly available.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Yan'an Hospital of Kunming City approved the study. Because the data were collected retrospectively, informed consent for the use

of coronary angiography was waived, given the institutional ethics regulations concerning the observational study's nature.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiology, Yan'an Hospital of Kunming City, Yan'an Hospital Affiliated with Kunming Medical University, Kunming 650051, China. [2]Department of Cardiology, Qujing Second People'S Hospital of Yunnan Province, Qujing 655099, China. [3]Kunming Cardiovascular Interventional Imaging Institute, Kunming 650051, China. [4]Department of Gastrointestinal Surgery, Second Affiliated Hospital of Kunming Medical University/Second Faculty of Clinical Medicine, Kunming Medical University, Kunming 650101, China. [5]Department of Otolaryngology, Qujing Second People'S Hospital of Yunnan Province, Qujing 655099, China.

Received: 29 November 2023 Accepted: 18 February 2025
Published online: 08 March 2025

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