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# Dysregulation of Serum miR-212-3p Serves as a Biomarker to Predict Disease Onset and Short-Term Prognosis in Acute Coronary Syndrome Patients

## ABSTRACT

**Objective:** This study was conducted to investigate the clinical value of microRNA (miR)-212-3p in acute coronary syndrome (ACS) patients.

**Methods:** This study involved 128 ACS patients and 110 patients with coronary arterial atherosclerosis. Real-time fluorescence quantitative polymerase chain reaction was employed to measure serum miR-212-3p levels and assessed its correlation with disease severity. The diagnostic efficacy of miR-212-3p was evaluated through receiver operating characteristic (ROC) curve and logistic regression modeling. Furthermore, Kaplan–Meier and Cox regression analyses were utilized to determine the predictive value of miR-212-3p for the occurrence of major adverse cardiovascular events (MACE).

**Results:** The serum miR-212-3p was elevated in ACS patients, with levels in acute myocardial infarction (AMI) patients being greater than unstable angina pectoris (UAP) patients. Serum miR-212-3p demonstrated considerable diagnostic utility in the identification of ACS patients and in differentiating between AMI and UAP cases. Furthermore, miR-212-3p levels correlated with myocardial injury markers [cardiac troponin I (cTnI), high-sensitivity C-reactive protein (hs-CRP), and creatine kinase-MB (CK-MB)], as well as with coronary artery scores (Gensini and SYNTAX). Elevated levels of miR-212-3p were associated with MACE incidence. Serum miR-212-3p, cTnI, Gensini, and SYNTAX score served as independent risk factors for MACE occurrence, with higher expression of miR-212-3p being linked to a poorer clinical prognosis.

**Conclusion:** Serum miR-212-3p might serve as a non-invasive biomarker for ACS diagnosis and MACE prediction and as a supplementary molecular tool in clinical practice.

**Keywords:** Acute coronary syndrome, biomarker, diagnosis, miRNA, prognosis

ORIGINAL INVESTIGATION

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## INTRODUCTION

Cardiovascular diseases have emerged as the leading cause of mortality, with coronary heart disease (CHD) identified as the most prevalent etiology.[1] Acute coronary syndrome (ACS) represents the most severe type of CHD, primarily characterized by acute myocardial infarction (AMI) and unstable angina pectoris (UAP).[2] It is characterized by acute onset, rapid progression, elevated mortality rates, and significant inflammatory response.[3] Currently, ACS diagnosis relies on clinical symptoms, electrocardiogram (ECG) findings, and serum biomarkers.[4] Cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB) are the preferred biomarkers for ACS diagnosis; however, their late rise and low specificity hinder early detection.[5] Furthermore, percutaneous coronary intervention (PCI) is the primary therapeutic approach for ACS, effectively enhancing myocardial blood flow.[6] Nonetheless, some individuals may experience major adverse cardiovascular events (MACE) post-procedure, raising the risks of readmission and death.[7] Hence, finding fast and accurate diagnostic and prognostic markers is vital for better ACS care.

MicroRNAs (miRNAs) are endogenous, single-stranded non-coding RNAs in biological fluids. Their dysregulation is associated with cardiovascular development,

myocardial cell injury, and heart failure,[8] suggesting potential as ACS biomarkers.[9] In cardiovascular research, miRNAs impact cell processes[10] and disease progression.[11] In controlled experimental settings, individual miRNAs have demonstrated promising capabilities in disease diagnosis and prognostication. However, their instability in clinical settings limits utility. Inconsistent expression and undetected levels reduce diagnostic accuracy.[12] Consequently, there is a pressing need for the identification and development of additional miRNAs. The utilization of multiple miRNA combinations has the potential to enhance diagnostic and predictive accuracy for diseases, as well as to refine detection methodologies.[13] Given the clinical significance of miR-212-3p in relation to cardiovascular disease, for instance, the rupture of coronary arterial atherosclerosis (CAA) plaques is identified as the primary etiological factor for ACS. Notably, miR-212-3p is linked to several cardiovascular conditions. It is upregulated during coronary plaque rupture,[14] correlates with coronary artery disease (CAD) risk factors,[15] and predicts pulmonary hypertension in acute right heart failure.[16] It has also been demonstrated that miR-212-3p plays a role in regulating myocardial cell injury following myocardial infarction by targeting NR4A2 and p53/Bax.[17] Consequently, it was speculated that miR-212-3p might have analogous functions in the onset and progression of ACS, potentially serving as a non-invasive diagnostic and prognostic marker for this condition. Furthermore, this molecular marker could facilitate multi-miRNA diagnostic strategies for ACS. Nevertheless, there is a paucity of clinical studies addressing this topic at present.

Consequently, this investigation measured miR-212-3p levels in ACS patients' serum, evaluated its predictive value for ACS occurrence and MACE after PCI, and explored its potential as an auxiliary diagnostic and prognostic marker. The findings of this study offer valuable insights for early identification and timely postoperative intervention in ACS patients.

## METHODS

### AI Statement

AI was not used in the writing process of the article.

### Ethical Statement

This study was performed in line with the principles of the Declaration of Helsinki. This study received approval from the Research Ethics Committee of The First Hospital of Lanzhou University, and all participants provided informed consent.

### Study Object

A total of 128 ACS patients who underwent PCI at The First Hospital of Lanzhou University between 2021 and 2024 were designated as the experimental group. All patients were diagnosed with ACS for the first time upon admission. In accordance with the established definition of ACS, the patients were further categorized into 2 subgroups: the AMI group, which comprised 67 individuals [including 32 with ST-elevation myocardial infarction (STEMI) and 35 with non-ST-elevation myocardial infarction (NSTEMI)], and the UAP group, consisting of 61 individuals.

Additionally, a control group was formed from 110 CAA patients who received treatment during the same period. Patients classified as having CAA are individuals who exhibit no overt symptoms or clinical manifestations of CHD during the course of attendance. These patients might describe discomfort in the precordial region following intense physical activity. Subsequent imaging examinations confirmed the presence of coronary atherosclerotic plaques, with the degree of vascular stenosis not significant, measuring less than 50% or even 25%. These patients exhibit signs of coronary atherosclerosis. Not all individuals diagnosed with coronary artery disease received magnetic resonance imaging (MRI) of the chest (main) or heart (fewer than 20%); consequently, some patients were subjected to MRI, while others underwent coronary angiography. The CAA patients fulfilled the diagnostic criteria outlined in the Chinese Guidelines for the Prevention of Cardiovascular Disease (2017).[18] The exclusion criteria for this group were aligned with those for ACS.

### Inclusion and Exclusion Criteria for Acute Coronary Syndrome

The inclusion criteria for ACS were as follows: (1) adherence to the diagnostic standards outlined in the Emergency Rapid Diagnosis and Treatment Guidelines for Acute Coronary Syndrome (2019);[19] (2) the presence of clinical symptoms indicative of angina pectoris or myocardial infarction, which may present as UAP, NSTEMI, or STEMI; (3) verification of stenosis or occlusion via coronary angiography; and (4) fulfillment of the criteria for PCI and subsequent receipt of PCI treatment.

The exclusion criteria for ACS encompassed: (1) individuals with concurrent other cardiac conditions; (2) individuals experiencing chest pain attributable to alternative causes; (3) individuals exhibiting severe organ dysfunction, acute trauma, infections, or other inflammatory conditions; (4) individuals with coexisting immunodeficiency disorders or chronic systemic illnesses; (5) pregnant or breastfeeding women; and (6) individuals with incomplete clinical records.

### Baseline Data Collection

The clinical data from the initial admission of 2 patient groups were gathered, encompassing variables such as age, gender, body mass index (BMI), as well as the history of smoking, drinking, hypertension, and diabetes. Additionally, the patients' heart rate, white blood cell count (WBC), blood lipid

## HIGHLIGHTS

- miR-212-3p shows a significantly increased level in the serum of acute coronary syndrome (ACS) patients.
- miR-212-3p serves as a non-invasive biomarker for ACS diagnosis.
- miR-212-3p is a significant parameter for the severity of ACS.
- miR-212-3p has a high predictive value for the major adverse cardiovascular event occurrence.
- Low expression of miR-212-3p exhibits a more favorable prognosis.

levels [total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], and levels of serum markers of myocardial injury [cTnI, high-sensitivity C-reactive protein (hs-CRP), and CK-MB] were extracted from various diagnostic reports at the time of admission. Furthermore, scoring data for the Gensini[20] and SYNTAX scores[21] were obtained in accordance with the coronary artery scoring system.

### Follow-Up Method

The follow-up of ACS patients who have undergone PCI was carried out through various methods, including outpatient visits, readmissions, telephone consultations, and WeChat communications, over a period of 6 months. This follow-up process commenced 1 week post discharge and continued until the occurrence of MACE or 6 months had elapsed since discharge. The timing of MACE experienced by the patient was documented. The MACE indicators to be monitored include new onset myocardial infarction, new onset stroke, malignant arrhythmia, unstable angina, new-onset heart failure, cardiogenic shock, sudden death, unexpected coronary revascularization, stent thrombosis, and all-cause death. ACS patients who underwent PCI were categorized into 2 subgroups based on the occurrence of MACE: the MACE group, consisting of 37 cases, and the non-MACE group, comprising 91 cases.

### Serum Collection

Upon admission, a volume of 6 mL of venous blood was promptly obtained from patients diagnosed with ACS and CAA utilizing a procoagulant tube. The collected blood sample was allowed to incubate at room temperature for 30 minutes, followed by centrifugation in a low-temperature centrifuge for 15 minutes at 4°C and 3000 xg. The resulting supernatant was then carefully transferred to an RNase-free EP tube and subsequently stored in a freezer at −80°C.

### Real-time Quantitative Polymerase Chain Reaction

Total RNA was extracted from the serum of ACS and CAA patients utilizing an RNA extraction kit (whole blood, plasma, and serum total RNA extraction kit, HaiGene, China). The quality of the extracted RNA was assessed using a Qubit™ 4 Fluorometer (Thermo Fisher, USA). Following this, cDNA synthesis was performed using a reverse transcription kit (Hifair® Ⅱ 1st Strand cDNA Synthesis Kit, Yeasen, China), with the resulting cDNA serving as a template for RT-qPCR.

A 20 μL reaction system was prepared in accordance with the guidelines provided in the MicroRNAs qPCR Kit-SYBR Green Method (Sangon Biotech, China). Subsequently, the relative expression levels of miR-212-3p in the serum samples from all participants were conducted using a Roche LightCycler480 (Switzerland). The thermal cycling conditions were set to 30 s at 95°C, followed by 5 seconds at 95°C and 30 seconds at 60°C, with a total of 40 cycles for the latter 2 steps. The dissolution curve program referenced instrument settings. The primers for miR-212-3p were synthesized by GeneWiz Biotechnology Co., Ltd. in Suzhou, China, with the forward sequence (5′-3′) being GGTAACAGTCTCCAGTCA and the reverse sequence (5′-3′) GCAATTGCACTGGATACG. U6 was employed as an internal reference, with the forward primer (5′-3′) sequence GCTTCGGCACATATACTAAAAT and the reverse sequence (5′-3′) CGCTTCACGAATTTGCGTGTCAT. The relative expression level of miR-212-3p was calculated using the $2^{-\Delta\Delta Ct}$ method.

### Data Analysis

The experimental data were analyzed using SPSS IBM Version 23.0 (SPSS Inc., Chicago, Illinois, USA) and GraphPad Prism 9.0 (Dotmatics, Boston, Massachusetts, USA) software. The normality of continuous ratio scale data was assessed utilizing the Shapiro–Wilk test, which indicated that all continuous ratio scale data in this study adhered to a normal distribution ($P > .05$). For continuous ratio scale data, the mean ± standard deviation (SD) was employed for representation. The independent samples *t*-test was utilized for comparisons between 2 groups, while 1-way analysis of variance was applied for comparisons among multiple groups.

The diagnostic performance of miR-212-3p was assessed using receiver operating characteristic (ROC) curves. The relationship between miR-212-3p expression levels and various indicators, including blood lipids, serum myocardial injury biomarkers, and coronary artery scores, was examined using the Pearson correlation method. To identify risk factors for ACS in CAA patients, a multiple logistic regression model was employed, while the Cox proportional hazards model was utilized to determine potential risk factors for MACE following PCI. Additionally, Kaplan–Meier survival curves were generated to illustrate the MACE incidence of ACS patients stratified by different levels of miR-212-3p expression.

## RESULTS

### Comparison of General Clinical Data Between Acute Coronary Syndrome Patients and Controls

This study used the G*Power 3.1.9.7 software to estimate the sample size and ensure adequate statistical test power. At least 102 research subjects needed to be included in each group when the effect size was set at a moderate level [Cohen's *d* value = 0.5, significance level (α) = 0.05, test power (1 − β) = 0.8]. This study included 128 cases in the ACS group and 110 cases in the CAA group, with the sample sizes of both groups exceeding the threshold. Additionally, the post-hoc power analysis showed that, with an estimated effect size (d) of 0.5 and a significance level (α) of 0.05, the power (1-β) of a sample size of 238 was 0.9693, significantly higher than the standard threshold of 0.8. This suggested that this study had sufficient power to detect the expected effect.

Within the ACS group, 32 patients were diagnosed with STEMI, 35 with NSTEMI, and 61 with UAP. Statistical analysis revealed no significant differences between the 2 groups regarding age distribution, gender ratio, history (including smoking, alcohol consumption, hypertension, and diabetes), and heart rate ($P > .05$). Notably, the BMI, WBC, and lipid profile indicators, specifically TC and LDL-C levels, were significantly elevated in the ACS group compared to the CAA group ($P < 0.01$, Table 1).

Furthermore, the study performed a statistical analysis of serum myocardial injury biomarkers and coronary artery scoring indicators in ACS patients, revealing elevated

**Table 1. The Basic Information of All Subjects**

| Factors | Control (n = 110) | ACS (n = 128) | *P* |
|---|---|---|---|
| Age (years) | 57.08 ± 8.04 | 56.73 ± 8.00 | .734 |
| Gender n (%) | | | .807 |
| Male | 61 (55.45) | 73 (57.03) | |
| Female | 49 (44.55) | 55 (42.97) | |
| BMI (kg/m$^2$) | 24.69 ± 2.05 | 25.88 ± 1.81 | <.001 |
| Smoking history n (%) | | | .453 |
| Yes | 60 (54.55) | 76 (59.38) | |
| No | 50 (45.45) | 52 (40.62) | |
| Drinking history n (%) | | | .631 |
| Yes | 49 (45.55) | 61 (47.66) | |
| No | 61 (55.45) | 67 (52.34) | |
| Hypertension history n (%) | | | .396 |
| Yes | 69 (62.73) | 87 (67.97) | |
| No | 41 (37.27) | 41 (32.03) | |
| Diabetes history n (%) | | | .214 |
| Yes | 53 (48.18) | 72 (56.25) | |
| No | 57 (51.82) | 56 (43.75) | |
| Heart rate (bpm) | 75.25 ± 9.19 | 74.19 ± 6.02 | .284 |
| WBC (10$^9$/L) | 8.08 ± 1.52 | 9.62 ± 1.71 | <.001 |
| Blood lipids | | | |
| TC (mmol/L) | 4.62 ± 0.88 | 4.93 ± 0.52 | .001 |
| TG (mmol/L) | 1.48 ± 0.28 | 1.51 ± 0.30 | .546 |
| LDL-C (mmol/L) | 2.48 ± 0.27 | 2.60 ± 0.27 | .001 |
| HDL-C (mmol/L) | 1.34 ± 0.32 | 1.25 ± 0.44 | .087 |
| Myocardial injury markers | | | – |
| cTnI (ng/mL) | – | 1.01 ± 0.56 | |
| hs-CRP (mg/L) | – | 5.98 ± 1.54 | |
| CK-MB (IU/L) | – | 123.26 ± 34.83 | |
| Gensini Score | – | 49.55 ± 16.58 | – |
| SYNTAX Score | – | 28.46 ± 6.00 | – |
| Types | | | – |
| STEMI | – | 32 (25.00) | |
| NSTEMI | – | 35 (27.34) | |
| UAP | – | 61 (47.66) | |

*P* < .05 means a significant difference.

average levels. Specifically, cTnI averaged 1.01 ± 0.56 ng/mL, hs-CRP averaged 5.98 ± 1.54 mg/L, and CK-MB averaged 123.26 ± 34.83 IU/L. Additionally, the coronary artery scoring indicators, including the Gensini score and SYNTAX score, averaged 49.55 ± 16.58 and 28.46 ± 6.00, respectively (Table 1).

## Up-regulation and High Diagnostic Value of Serum miR-212-3p Expression in Acute Coronary Syndrome Patients

The expression levels of miR-212-3p in the serum of ACS patients were found to be significantly elevated, approximately double that of the CAA group (*P* < .001, Figure 1A). Serum miR-212-3p demonstrated a robust capacity for differentiating ACS patients from those with CAA, achieving

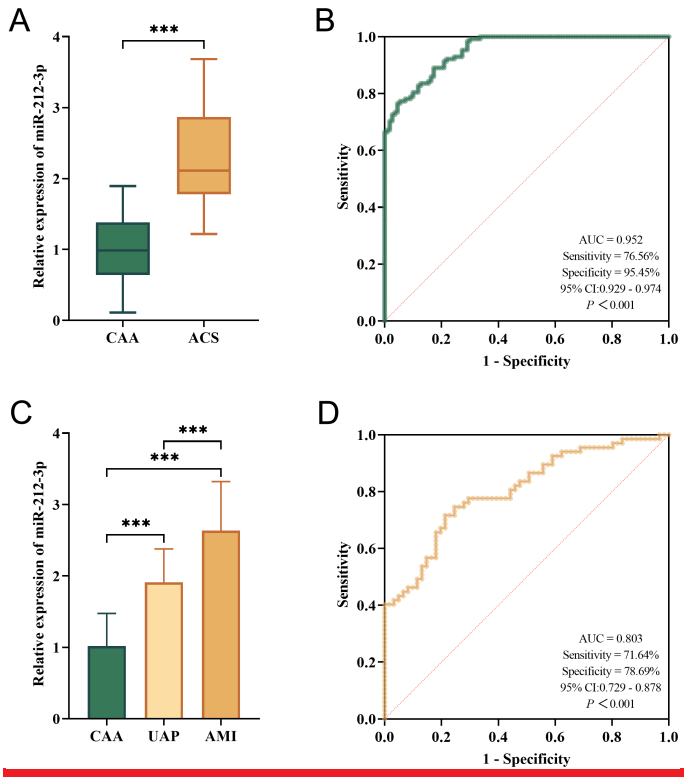


**Figure 1. The expression levels of serum miR-212-3p in CAA and ACS groups (A), and its diagnostic value for ACS (B). The expression levels of serum miR-212-3p in AMI and UAP group (C), and its discriminatory efficacy for AMI and UAP (D). ***, *P* < .001.**

an area under the curve (AUC) of 0.952 [95% CI: 0.929-0.974]. The sensitivity and specificity for this differentiation were recorded at 76.56% and 95.45%, respectively (*P* < .001, Figure 1B).

Furthermore, the levels of miR-212-3p in the serum of patients AMI and UAP were significantly higher than those observed in the CAA group (*P* < .001). Notably, the relative level of miR-212-3p in AMI patients was significantly greater than that in UAP patients (*P* < .001, Figure 1C). The AUC for serum miR-212-3p in distinguishing between AMI and UAP patients was 0.803 (95% CI: 0.729-0.878), with sensitivity and specificity values of 71.64% and 78.69%, respectively (*P* < .001, Figure 1D).

## Up-regulated Serum miR-212-3p was Significantly Associated with Diagnostic and Prognostic Indices of Acute Coronary Syndrome Patients

In ACS patients, serum levels of miR-212-3p exhibited a significant positive correlation with various lipid parameters, including TC, TG, and LDL-C. Additionally, there were notable positive correlations with serum myocardial injury biomarkers such as cTnI, hs-CRP, and CK-MB. Furthermore, significant positive correlations were observed with coronary artery scoring metrics, specifically the Gensini score and the SYNTAX score (*P* < .001). Conversely, a significant negative correlation was identified between serum miR-212-3p levels and HDL-C (*P* < .001, Table 2). Notably, the strongest

**Table 2. Correlation Between Expression Level of miR-212-3p and Various Clinical Indexes of ACS Patients**

| Factors | Correlation (r) | 95% CI | *P* value |
|---|---|---|---|
| TC (mmol/L) | 0.685 | 0.581-0.768 | <.001 |
| TG (mmol/L) | 0.746 | 0.658-0.814 | <.001 |
| LDL-C (mmol/L) | 0.875 | 0.827-0.911 | <.001 |
| HDL-C (mmol/L) | −0.886 | −0.918 to −0.841 | <.001 |
| cTnI (ng/mL) | 0.936 | 0.911-0.955 | <.001 |
| hs-CRP (mg/L) | 0.756 | 0.671-0.822 | <.001 |
| CK-MB (IU/L) | 0.762 | 0.678-0.826 | <.001 |
| Gensini Score | 0.905 | 0.868-0.933 | <.001 |
| SYNTAX Score | 0.900 | 0.861-0.928 | <.001 |

*P* < .05 means a significant difference.
ACS, acute coronary syndrome; CK-MB, creatine kinase isoenzymes; cTnI, cardiac troponin I; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

correlations were found between serum miR-212-3p and cTnI, as well as the Gensini and SYNTAX scores.

## Serum miR-212-3p Was a Risk Factor for Acute Coronary Syndrome in Coronary Arterial Atherosclerosis Patients

The demographic and clinical characteristics of patients with CAA, including age, sex, smoking history, alcohol consumption, diabetes history, heart rate, TG, LDL-C, and HDL-C, did not demonstrate a statistically significant correlation with the occurrence of ACS (*P* > .05). In contrast, BMI [odds ratio (OR) = 2.152, 95% CI: 1.060-4.479, *P* = .036], a history of hypertension (OR = 2.931, 95% CI: 1.038-8.929, *P* = .048), WBC (OR = 3.318, 95% CI: 1.682-6.758, *P* < .001), TC (OR = 2.010, 95% CI: 1.016-4.054, *P* = .047), and miR-212-3p (OR = 13.040, 95% CI: 6.595-27.320, *P* < .001) were identified as significant risk factors for ACS occurrence in CAA patients (Figure 2A). Notably, serum levels of miR-212-3p exhibited the most pronounced influence on the ACS occurrence.

## Comparison of General Clinical Data Between Non-Major Adverse Cardiovascular Events and Major Adverse Cardiovascular Events Groups in Acute Coronary Syndrome Patients

In ACS patients, 37 individuals experienced MACE, while 91 did not, resulting in an incidence rate of 28.91% for MACE. Statistical analysis revealed no significant differences in demographic and clinical characteristics, including age distribution, gender ratio, BMI, blood lipid indicators (TC, TG, LDL-C, and HDL-C), hs-CRP, and CK-MB between the 2 patient groups (*P* > .05). However, the levels of cTnI (*P* < .01), Gensini score (*P* < .05), and SYNTAX score (*P* < .05) were significantly elevated in the MACE group compared to the non-MACE group (Table 3).

## Up-regulation of Serum miR-212-3p Expression in Major Adverse Cardiovascular Events Group

The serum expression level of miR-212-3p in ACS patients experiencing MACE was found to be significantly elevated, approximately 1.67 times greater than that observed in non-MACE patients (*P* < .001, Figure 2B).

## Serum miR-212-3p Had High Prognostic Significance for Acute Coronary Syndrome Patients

In ACS patients, it was found that there was no statistically significant correlation between age, gender, BMI, blood lipid parameters (TC, TG, LDL-C, and HDL-C), and serum myocardial injury biomarkers (hs-CRP and CK-MB) with patient prognosis (*P* > .05). Notably, the cTnI [hazard ratio (HR) = 2.217, 95% CI: 1.060-4.638, *P* = .035], coronary artery scoring metrics, specifically the Gensini score (HR = 2.662, 95% CI: 1.028-6.895, *P* = .044) and the SYNTAX score (HR = 2.024, 95% CI: 1.015-4.034, *P* = .045), as well as serum miR-212-3p (HR = 5.077, 95% CI: 1.882-13.700, *P* = .001) emerged as predictors of MACE occurrence, demonstrating a significant correlation with poor prognosis in ACS patients (Figure 3A). Among them, miR-212-3p exerted the most significant influence on the occurrence of MACE.

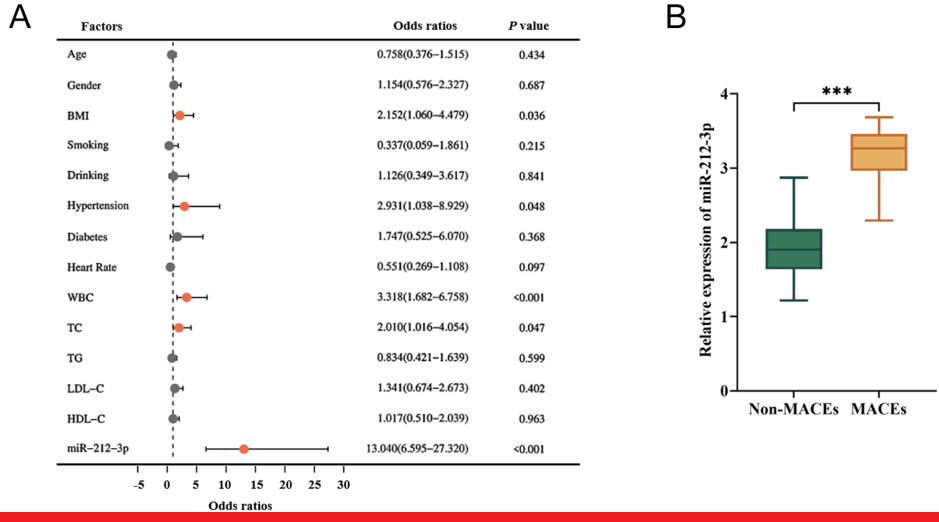


**Figure 2. The prediction of risk factors for ACS in CAA patients (A), as well as the expression levels of serum miR-212-3p in non-MACE and MACE groups (B). ***, *P* < .001.**

**Table 3. The Clinical Variables of ACS Patients in Non-MACEs and MACEs Groups**

| Factors | Non-MACEs (n = 91) | MACEs (n = 37) | *P* |
|---|---|---|---|
| Age (years) | 56.22 ± 7.73 | 57.97 ± 8.62 | .263 |
| Gender n (%) | | | .408 |
| Male | 54 (59.34) | 19 (51.35) | |
| Female | 37 (40.66) | 18 (48.65) | |
| BMI (kg/m$^2$) | 25.82 ± 1.77 | 26.02 ± 1.91 | .568 |
| Blood lipids | | | |
| TC (mmol/L) | 4.87 ± 0.47 | 5.06 ± 0.63 | .071 |
| TG (mmol/L) | 1.48 ± 0.26 | 1.57 ± 0.36 | .114 |
| LDL-C (mmol/L) | 2.58 ± 0.24 | 2.66 ± 0.33 | .136 |
| HDL-C (mmol/L) | 1.29 ± 0.41 | 1.16 ± 0.47 | .112 |
| Myocardial injury markers | | | |
| cTnI (ng/mL) | 0.93 ± 0.53 | 1.23 ± 0.57 | .005 |
| hs-CRP (mg/L) | 5.85 ± 1.47 | 6.28 ± 1.66 | .155 |
| CK-MB (IU/L) | 120.80 ± 32.41 | 129.20 ± 40.02 | .219 |
| Gensini score | 47.27 ± 16.05 | 54.08 ± 17.16 | .035 |
| SYNTAX score | 27.76 ± 5.78 | 30.19 ± 6.27 | .037 |

*P* < .05 means a significant difference.
ACS, acute coronary syndrome; BMI, body mass index; cTnI, cardiac troponin I; CK-MB, creatine kinase isoenzymes; HDL-C, high-density lipoprotein cholesterol hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACEs, major adverse cardiovascular events; TC, total cholesterol; TG, triglyceride.

Based on the average expression levels of miR-212-3p in the serum of ACS patients, individuals were categorized into high and low expression groups. The group exhibiting higher levels of serum miR-212-3p experienced a higher incidence of MACE, correlating with a poorer prognosis for ACS patients (*P* < .001, Figure 3B).

## DISCUSSION

Acute coronary syndrome is a common cardiac emergency[22] and a major cause of mortality in CHD.[23] Although coronary angiography is the "gold standard" for diagnosing ACS[24] due to its high accuracy, it is an invasive procedure that may lead to complications.[25] The ECGs are useful for dynamic monitoring but may show no significant changes in patients with severe coronary lesions or during suspected ischemic episodes.[26] Certain serum biomarkers released after myocardial necrosis have limited early diagnostic value, with a sensitivity of only 19%-43% within the first 3 hours post-event.[27] Consequently, finding new biomarkers for ACS auxiliary diagnosis remains a key clinical research priority.

The miRNAs are valuable auxiliary diagnostic markers due to their stable expression, easy detectability, and strong clinical relevance.[28] In ACS research, specific miRNAs such as miR-335-5p,[29] miR-483-5p,[3] and miR-140-3p[30] have shown potential. Recently identified, miR-212-3p is associated with atherosclerosis and early vascular inflammation.[31] As previously noted, miR-212-3p has been linked to CAA plaque rupture, CAD, and acute right heart failure.[14-16] This study revealed significantly elevated serum miR-212-3p levels in ACS patients, and even more elevated levels in AMI patients compared to UAP patients. The ROC curve is a widely utilized tool for assessing the accuracy of diagnostic biomarkers.[32] Using the ROC curve, it was demonstrated that miR-212-3p effectively discriminates ACS patients and differentiates between AMI and UAP. Logistic analysis further indicated that miR-212-3p could be a risk factor for ACS in CAA patients.

Abnormalities in blood lipid levels contribute to ACS and MACE,[33] while cTnI, hs-CRP, and CK-MB indicate myocardial injury and vascular inflammation.[34] The Gensini and SYNTAX scores assess arterial stenosis and the severity of atherosclerosis.[35] This study identified a significant correlation between serum miR-212-3p and the aforementioned factors, indicating that miR-212-3p correlates with these factors, suggesting it could reflect the severity of coronary artery disease in ACS patients and could be linked to the MACE incidence.

The PCI is a critical surgical approach for the revascularization of ACS, demonstrating a significant reduction in infarct size.[6] Nevertheless, post-PCI MACE remains common, worsening patient outcomes and healthcare burdens.[7] Identifying MACE risk factors helps target preventive strategies.[36] The Gensini and SYNTAX scores are vital for recognizing high-risk patients and forecasting MACE risk.[37] Typically,

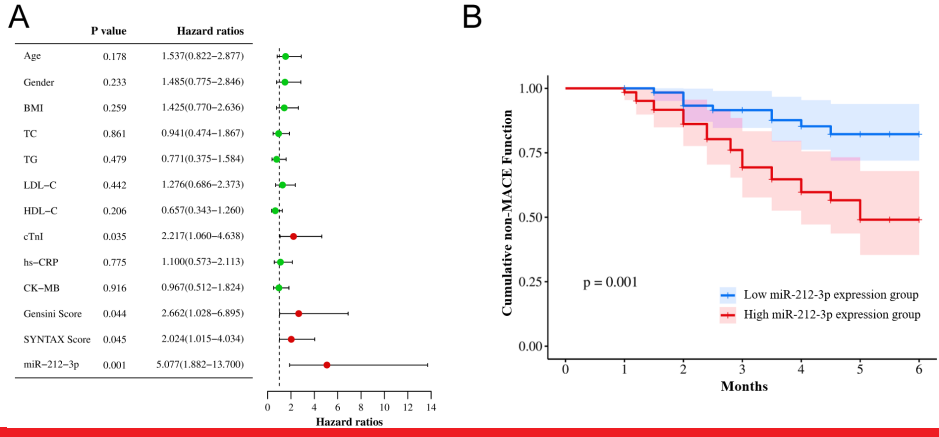


**Figure 3. The prediction of risk factors for poor prognosis in ACS patients (A), as well as the MACE incidence in groups with different levels of miR-212-3p expression (B).**

in patients whose cTnI levels continue to rise postoperatively, there is a concomitant increase in MACE incidence.[34] This study observed elevated miR-212-3p in most MACE cases. Subsequent analyses established that serum miR-212-3p, cTnI, Gensini score, and SYNTAX score serve as independent predictors of MACE occurrence in patients following PCI, with high miR-212-3p indicating poor prognosis. It was speculated that synergistically applied miR-212-3p alongside existing diagnostic and therapeutic methods could improve aspects such as early diagnosis, complex case differentiation, and precise prognosis evaluation. Specifically, during the hyperacute phase of ACS, when cTnI levels have not yet increased, abnormal fluctuations in serum miR-212-3p levels may occur earlier and can serve as an additional indicator to help identify high-risk patients at an early stage. In borderline/complex cases involving mild cTnI elevation or the presence of interfering factors, the combined detection of serum miR-212-3p can effectively overcome the limitations of relying on a single biomarker, thereby improving diagnostic specificity and reducing the risk of missed or misdiagnosis. Furthermore, combining the dynamic changes of cTnI and existing prognostic tools with changes in serum miR-212-3p can help construct a multidimensional risk assessment model to inform the development of personalized treatment strategies in clinical practice.

### Study Limitations

This study acknowledges several limitations. This study only used CAA patients as controls, omitting healthy individuals devoid of clinical or subclinical coronary artery disease. This might lead to bias in the specific evaluation of serum miR-212-3p as a biomarker and make it difficult to distinguish its diagnostic efficacy for asymptomatic early coronary artery disease. Additionally, the diagnostic thresholds established in current research might not be directly applicable for screening individuals without coronary artery disease due to the lack of healthy population data references. Therefore, subsequent studies will include a large sample size of a healthy control population and explore the specificity and clinical applicability of serum miR-212-3p through multicentric validation.

The serum samples were collected at a single time point, which may not adequately capture their temporal and dynamic patterns throughout the progression of ACS. This limitation could potentially undermine the biomarker's effectiveness in evaluating disease prognosis and restrict a comprehensive understanding of its temporal stability and expression dynamics. Future research will systematically monitor changes in serum miR-212-3p levels at key time points, such as 6 hours, 24 hours, and 72 hours after ACS onset, as well as 1 week and 1 month after PCI surgery. A dynamic prediction model will also be constructed based on patient clinical outcomes in order to accurately determine the optimal detection window for this biomarker, providing dynamic data to support its clinical application. The investigation concentrated on the association between miR-212-3p and serum markers, while omitting data pertaining to the LVEF, a cardiac function indicator. The relationship between the dynamic monitoring of miR-212-3p and LVEF and the occurrence of MACE is a noteworthy issue in future research. The potential impact of the drugs used in the development of MACE on the outcomes warrants further investigation as a significant direction for future research.

Additionally, the absence of certain clinical data pertaining to CAA patients hindered the evaluation of the combined diagnostic efficacy of serum miR-212-3p and myocardial injury markers. The small number of patients is another important limitation in this study. Future investigations will aim to broaden the sources of samples and enhance data collection. This will facilitate a more comprehensive analysis of the clinical relevance of serum miR-212-3p utilizing larger sample sizes, thereby allowing for a more comprehensive exploration of the research evidence.

## CONCLUSION

In summary, this study indicated that serum miR-212-3p might serve as a valuable diagnostic biomarker for the identification of ACS patients and differentiating between those with AMI and UAP, and was a significant parameter for the severity of coronary artery lesions. Additionally, it was a risk factor for ACS in CAA patients and demonstrated a high predictive value for the MACE occurrence in ACS patients. The prospects for clinical application of miR-212-3p are promising.

**Ethics Committee Approval:** This study was performed in line with the principles of the Declaration of Helsinki. This study protocol has been approved by the Ethics Committee of the First Hospital of Lanzhou University (No. 2021A-067, Date: March 16, 2021).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

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