

# Long noncoding RNA MIAT: A potential role in the diagnosis and mediation of acute myocardial infarction

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**Abstract.** The long noncoding RNA myocardial infarction associated transcript (MIAT) has been shown to be a risk allele for myocardial infarction in a previous study. However, there is still controversy about whether MIAT can be used as a biomarker for acute myocardial infarction (AMI). Peripheral blood from patients with AMI and non-AMI patients was collected to detect the expression levels of MIAT by reverse transcription-quantitative PCR. Correlation analysis and receiver operating characteristic (ROC) curve analysis were performed to calculate the diagnostic value of MIAT. A rat AMI model was established to detect the expression of MIAT in plasma and cardiac samples. Neonatal rat cardiomyocytes were isolated and exposed to hypoxia, and MIAT small interfering RNAs were transfected into cells to test the expression levels of MIAT and to perform apoptosis-related assays. The results showed that the plasma levels of MIAT were significantly increased in patients with AMI compared with non-AMI patients. Correlation analysis showed that MIAT was positively associated with creatine kinase-MB and cardiac troponin T (cTnT). ROC analysis indicated that MIAT had the same diagnostic value as cTnT. In addition, MIAT was expressed at low levels in the normal rat heart and was highly expressed in AMI hearts. Knockdown of MIAT significantly inhibited cardiomyocyte apoptosis. The present

study demonstrated that MIAT may act as a novel potential biomarker for the diagnosis of AMI.

## Introduction

Acute myocardial infarction (AMI) is one of the top three causes of mortality and disability in the world (1). The pathological process of AMI is myocardial necrosis due to persistent myocardial ischemia and hypoxia, caused by coronary plaque rupture or paralysis. At present, biomarkers reflecting myocardial injury, such as cardiac troponins, creatine kinase (CK)-MB and lactate dehydrogenase (LDH), and electrocardiogram (ECG) findings, are the most common diagnostic methods for AMI in clinical practice. However, the aforementioned biomarkers are not sensitive enough for the early diagnosis of AMI in the emergency room, thereby increasing the risk of complications and mortality (2). The low specificity of elevated cardiac troponins also affects the diagnosis of AMI, as these elevated levels may result from other non-cardiac issues (3). In order to develop practical surveillance tools, there is a clear need to identify new biomarkers for the diagnosis of AMI.

Noncoding RNAs (ncRNAs) are classified into small ncRNAs and long ncRNAs (lncRNAs) based on size, and play a variety of roles in cell cycle regulation, gene expression regulation, cellular differentiation, transcription, translation and chromatin modification (4,5). Emerging evidence has indicated that lncRNAs participate in multiple physiological and pathological processes of cardiovascular disease (6). Circulating RNAs have been described as being relatively stable in different human bodily fluids, such as serum, plasma and urine (7-9), making them suitable for the clinical assessment and monitoring of pathological conditions. Circulating mitochondrial lncRNA uc022bqs.1 has been proven to be a novel biomarker of cardiac remodeling and predicts future mortality in patients with heart failure (10). lncRNA urothelial carcinoma-associated 1 was found to be aberrantly expressed in AMI patients (11).

A previous study demonstrated that the lncRNA myocardial infarction associated transcript (MIAT) is associated with myocardial infarction through single-nucleotide polymorphism (SNP) association experiments (12). The present study aimed to detect the plasma level of MIAT in patients with AMI

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**Abbreviations:** lncRNAs, long noncoding RNAs; AMI, acute myocardial infarction; MIAT, myocardial infarction associated transcript; LDH, lactate dehydrogenase; ECG, electrocardiogram; cTnT, cardiac troponin T; CK-MB, creatine kinase-MB

**Key words:** lncRNA MIAT, AMI, biomarker, apoptosis

to determine whether it can be used as a potential biomarker to monitor myocardial pathological changes, and to explore its function at the cellular level.

## Materials and methods

**Patients.** Between August 2016 and December 2017, 260 patients aged 40-70 years treated in the emergency department of The First Affiliated Hospital of Xinjiang Medical University within 3 h of the onset of chest pain were recruited. In the present study, 58 patients diagnosed with ST-segment elevated myocardial infarction (STEMI) were selected as the observer group and 50 patients with unstable angina (UA) as the control group. A total of 72 patients were excluded due to a lack of four serial time samples, or the presence of cardiomyopathy, myocarditis, heart failure, chronic renal failure, pulmonary infection or psychiatric problems. The other 80 patients diagnosed with non-ST segment elevation myocardial infarction were not included in the study. A total of 180 patients were included in the present study (49 female and 59 male). All of the patients received a clinical assessment by an experienced cardiologist, which included medical history, physical examination, renal function assessment, and ECG and cardiac enzyme monitoring at 0, 3, 6, 12 and 24 h after the onset of chest pain. The inclusion criteria for STEMI were based on the 2017 European Society of Cardiology (ESC) guidelines (13) and the diagnostic parameters included ischemic symptoms, an elevated ST-segment on ECG, and evidently increased cardiac troponin T (cTnT) and CK-MB. The inclusion criteria for UA were also based on the 2017 ESC guidelines, including recent episodes of angina, and onset of or new angina at rest lasting >20 min, with or without ECG ST-T changes at onset. Written informed consent was obtained from all enrolled subjects and the study protocol was approved by the ethics committee of The First Affiliated Hospital of Xinjiang Medical University.

**Plasma collection and determination of myocardial enzymes.** Plasma was collected at 0, 3, 6, 12 and 24 h after the chest pain episode, and the concentrations of myocardial enzymes (cTnT; cat. no. MAB18742; and CK-MB; cat. no. MAB9076; R&D Systems, Inc.) at the different times were detected using ELISA. Fasting venous blood was collected from all subjects on the morning following admission. Samples were placed in heparin-coated anticoagulant tubes and centrifuged at 3,000 x g for 15 min at room temperature to separate the plasma. The supernatant was obtained and stored at -80°C.

**Animals and establishment of the rat AMI model.** All animal procedures were approved by the Experimental Animal Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. Male 8 week old Wistar rats (n=40; 200-250 g) were purchased from the laboratory animal center of Xinjiang Medical University. All animals were fed a standard rat diet and subjected to 1 week of adaptive feeding. The animals were allowed free access to drinking water and feed at a temperature of 23-25°C and a humidity of 55-70% with a 12 h light/dark cycle. In total, 10 normal rats were sacrificed after 1.0% isoflurane anesthesia and the heart, liver, spleen, lungs

and kidneys were removed. In total, 50 g of tissue homogenate was obtained and the expression of MIAT was detected by reverse transcription-quantitative (RT-q)PCR.

The remaining 30 rats were divided into a sham group (n=15) and an AMI group (n=15). AMI surgery was performed according to a previously published procedure (14). Briefly, rats were deeply anaesthetized with 1.0% isoflurane using a rodent ventilator, fixed onto the operating table, and connected to a standard limb lead II ECG. Thoracotomy and pericardiotomy in the 3rd to 4th ribs were performed to expose the heart, and then a segment of saline-soaked 7/0 suture was looped around the left anterior descending (LAD) coronary artery. When the left ventricular myocardium turned white, and the ECG ST-segment was elevated >0.1 mv, the model was considered to have been successfully established. In the sham group, the LAD was encircled without ligation. Post-operative blood samples were collected at 0, 3, 6, 12 and 24 h.

**Neonatal rat cardiomyocyte culture and treatment.** Neonatal Wistar rats (1-2 days old) were purchased from the laboratory animal center of Xinjiang Medical University. The rats were deeply anesthetized with 1.0% isoflurane, and the ventricles were cut into small pieces and transferred into a digestion solution containing 0.1% collagenase and 0.25% trypsin at 37°C for 30 min. The cells were then cultured in Dulbecco's Modified Eagle's medium/F12 (Gibco; Thermo Fisher Scientific, Inc.) with 10% fetal bovine serum (Thermo Fisher Scientific, Inc., MA, USA), 100 U/ml penicillin and 100 mg/ml streptomycin in an incubator at 37°C. Cells were cultured in a culture flask and exposed to normoxic conditions in a humidified atmosphere of 5% CO<sub>2</sub> and 95% O<sub>2</sub>, or hypoxic conditions in 5% CO<sub>2</sub> and 95% N<sub>2</sub> in a hypoxic incubator chamber for 24 h and then subjected to further experiments.

**Cell transfection.** lncRNA MIAT small interfering (si) RNA (si-MIAT-1 and si-MIAT-2) and si-negative control (NC) were synthesized by Shanghai GenePharma Co., Ltd. Cardiomyocytes were transfected with 100 nM of si-NC, si-MIAT-1 or si-MIAT-2 when the cells reached ~80% confluence in 24-well plates using Lipofectamine® 2000 reagent (Life Technologies; Thermo Fisher Scientific, Inc.). After 48 h, cells were harvested for further experiments. The sequences of the siRNAs are as follows: si-NC, 5'-CCCACG CACTTCCTGCAA-3'; si-MIAT-1, 5'-CCTCTCATCTTT CATTCCAATCCTTA-3'; and si-MIAT-2, 5'-UCCUCCGAA CCUGGCACGU-3'.

**TUNEL assay.** The TUNEL assay was performed followed instructions of the *in situ* apoptosis detection kit (Roche Diagnostics). The detection procedure was in accordance with a previous study (15). Cells were exposed to normoxic or hypoxic conditions, and fixed with 4% paraformaldehyde at room temperature for 20 min. After permeabilization with 0.1% Triton-X 100 for 2 min, cells were added to the TUNEL reaction mixture (including TdT and fluorescein-dUTP) and incubated at 37°C for 1 h. After washing with PBS, cells were incubated with 10 µg/ml DAPI (Solarbio, Beijing) for 10 min at room temperature. The rate of apoptosis was expressed as the ratio of TUNEL-positive cardiomyocyte nuclei to the total number of cardiomyocyte nuclei.

Table I. Demographic and clinical baseline characteristics.

Variable	UA group (n=50)	AMI group (n=58)	P-value
Age, years	60.4	61.64	0.41
Male/female, n/n	26/24	33/25	0.69
Currently smoking, n (%)	18 (36)	33 (56.8) <sup>a</sup>	0.02
Heart rate, beats/min	72.2 (67.3, 76.9)	75.4 (71, 83)	0.37
SBP, mmHg	120 (115, 125)	118 (110, 127)	0.61
DBP, mmHg	73.64±4.39	72.2±11.36	0.53
Hypertension, n (%)	12 (24)	16 (27.3)	0.14
Diabetes mellitus, n (%)	8 (16)	22 (37.9)	0.03
Coronary artery disease, n (%)	25 (50)	48 (82.5) <sup>a</sup>	<0.01
LVEF, %	60.72	52.44 <sup>a</sup>	<0.01
CK-MB (U/l)	3.2	38.65 <sup>a</sup>	<0.01
cTnT, ng/ml	0.12	0.49 <sup>a</sup>	<0.01
eGFR, ml/min/1.73 m <sup>2</sup>	91.5 (83.5, 102.8)	96.7 (86.3, 104)	0.35

Data are presented as the mean ± SD, median (interquartile range) or %. P<0.05 was considered to indicate a statistically significant difference.

<sup>a</sup>P<0.05 vs. UA group. UA, unstable angina; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase MB; cTnT, cardiac troponin T; eGFR, estimated glomerular filtration rate.

**RNA extraction and reverse transcription-quantitative PCR (RT-qPCR).** Total RNA was extracted using TRIzol<sup>®</sup> reagent (Invitrogen; Thermo Fisher Scientific, Inc.). RT was performed using a Prime Script<sup>™</sup> RT reagent kit (Takara Bio, Inc.) with the following conditions: 42°C for 15 min and 95°C for 3 min. The specific primers were synthesized by Sangon Biotech Co., Ltd., and the sequences of the primers were as follows: MIAT forward, 5'-TAGCTCGAGTCTTTTAGCTA CTTGACTACGGC-3' and reverse, 5'-TCAAGAATGCGG ACGCGACAGGATAGGCCACTTTGTC-3'; and GAPDH forward, 5'-TGTGTCCGTCGTGGATCTGA-3' and reverse, 5'-CCTGCTTACCACCTTCTTGA-3'. The lncRNA levels were quantified via a standard RT-qPCR protocol with SYBR Premix Ex Taq (Takara Bio, Inc.). The thermal cycling conditions were as follows: 95°C for 15 min, followed by 40 cycles of 95°C for 10 sec, 60°C for 30 sec and 72°C for 60 sec. The lncRNA levels were calculated based on the Cq values and were normalized to GAPDH in each sample. The data were analyzed using the 2<sup>-ΔΔCq</sup> method (16).

**Western blotting.** Total protein was extracted from tissues or cells using RIPA lysis buffer containing protease inhibitor and PMSF (Nanjing KeyGen Biotech Co., Ltd.). The supernatant protein concentration was detected using a standard BCA assay (Nanjing KeyGen Biotech Co., Ltd.). Protein samples (60 μg) were loaded into the wells of 10 or 15% SDS-PAGE gels for electrophoresis, and transferred to PVDF membranes. The membranes were blocked with 5% nonfat milk at room temperature for 2 h and then incubated with primary antibodies at 4°C overnight. The primary antibodies used were as follows: Anti-caspase 3 (1:1,000; Cell Signaling Technology, Inc.; cat. no. 9662), anti-cleaved caspase 3 (1:1,000; Cell Signaling Technology, Inc.; cat. no. 9661), anti-Bax (1:1,000; Cell Signaling Technology, Inc.; cat. no. 2772), anti-Bcl2

(1:1,000; Abcam; cat. no. ab196495) and anti-GAPDH (1:5,000; Abcam; cat. no. ab9484) were used in this study. After washing with PBS three times, the membranes were incubated with HRP-conjugated secondary antibody (1:8,000; Abcam; cat. no. ab7090) for 2 h at room temperature. ECL (EMD Millipore) was used to detect the protein bands. The western blot bands were captured using a ChemiDoc MP Imager (ChemiDoc<sup>™</sup> MP imaging system; Bio-Rad, Laboratories, Inc.) and analyzed with ImageJ v14.0 software (National Institutes of Health).

**Statistical analysis.** All data are presented as the mean ± SD of three independent experiments. Differences between groups were analyzed using SPSS 19.0 (IBM Corp.) and GraphPad 6.0 (GraphPad Software, Inc.) software with a Student's t-test or one-way ANOVA. Comparisons between groups were performed using Tukey's or Dunnett's tests, based on whether the variances were consistent. Spearman's rho correlation coefficient was used to assess the relationships among biomarkers. The sensitivity and specificity of biomarkers were assessed using a receiver operating characteristic (ROC) curve. P<0.05 was considered to indicate a statistically significant difference.

## Results

**Pattern of plasma lncRNA MIAT levels in the patients with AMI.** A total of 58 patients with AMI and 50 subjects with UA were included for the detection of circulating MIAT levels. The baseline characteristics of the subjects are shown in Table I. There were significant differences in smoking status, coronary artery disease, left ventricular ejection fraction, CK-MB and cTnT (P<0.05). As shown in Fig. 1A, the plasma level of MIAT in the AMI group was significantly upregulated

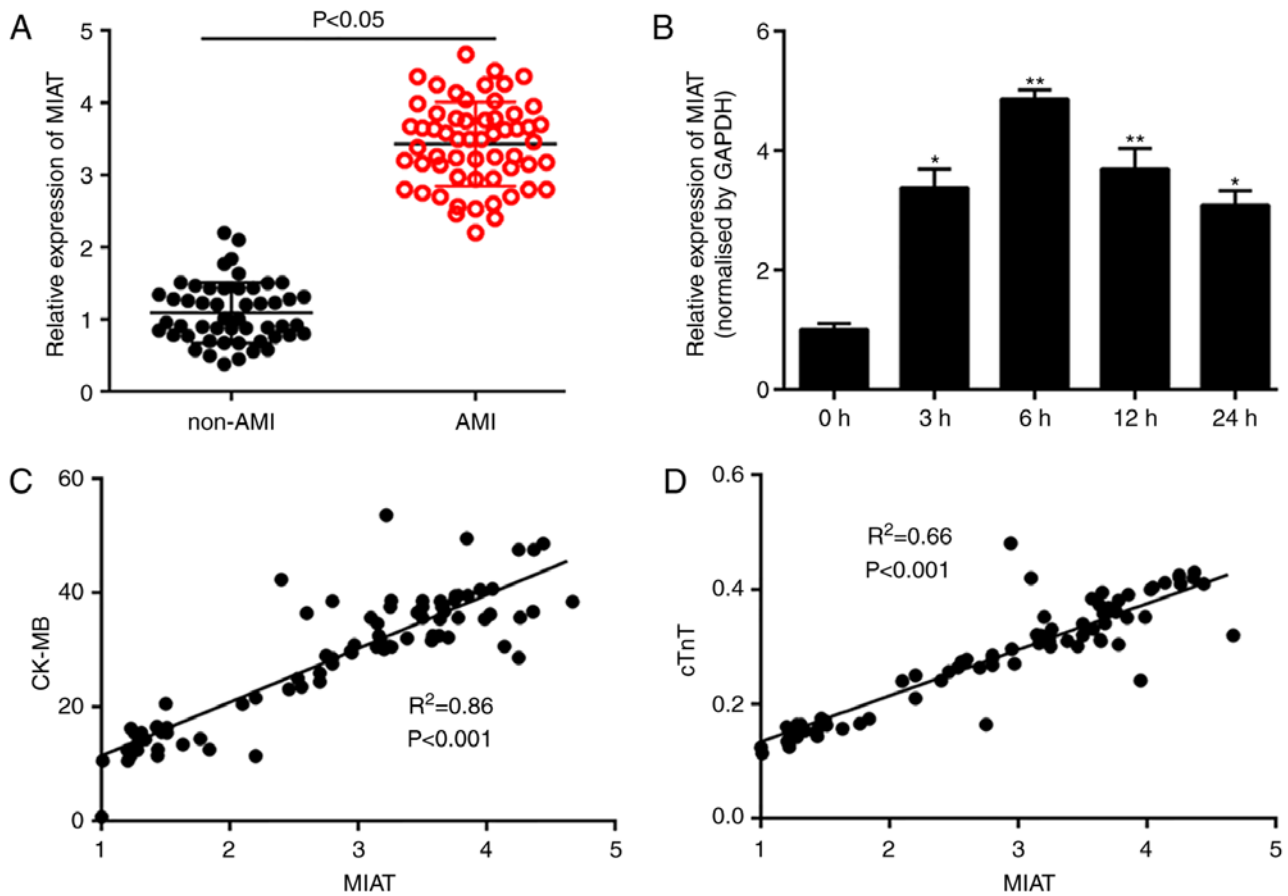


Figure 1. Pattern of plasma long noncoding RNA MIAT levels in the patients with AMI. (A) Relative expression of MIAT in the plasma of every subject. (B) Relative expression of MIAT at 0, 3, 6, 12 and 24 h after the onset of AMI. Comparisons between groups were performed using Dunnett's test. (C) Correlation analysis of CK-MB and MIAT. (D) Correlation analysis of cTnT and MIAT. The data are presented as the mean  $\pm$  SD. \* $P < 0.05$ , \*\* $P < 0.01$  vs. 0 h group. MIAT, myocardial infarction associated transcript; AMI, acute myocardial infarction; cTnT, cardiac troponin T; CK-MB, creatine kinase-MB.

by approximately three times compared with that of the UA group. In addition, dynamic monitoring showed that MIAT was significantly upregulated within 3 h of the onset of ischemic symptoms, and reached its highest level at 6 h, making it more sensitive than cTnT or CK-MB (Fig. 1B) (17). Moreover, correlation analysis indicated that the expression trend of MIAT was positively correlated to those of CK-MB and cTnT, particularly with CK-MB ( $r = 0.86$ ;  $P < 0.01$ ; Fig. 1C and D). These results suggested that the expression level of MIAT is closely related to myocardial injury, and that circulating MIAT may be detected within hours of the onset of chest pain.

**lncRNA MIAT is a sensitive biomarker that reflects the extent of myocardial injury.** To validate the expression trend of MIAT, a rat AMI model was established. As presented in Fig. 2A, the expression level of MIAT was significantly increased within 3 h, indicating that the dynamic trend of MIAT expression in rat plasma is similar to that in humans. In addition, the expression levels of MIAT were detected in different organs to further understand its potential as a biomarker of myocardial damage. As expected, MIAT was expressed at the lowest level in the normal myocardium, which was obviously opposite in AMI tissues (Fig. 2B). The results indicated that the expression level of MIAT reflects the state of myocardial injury. Monitoring the level of MIAT may be beneficial for understanding the condition of patients with myocardial infarction.

**Diagnostic value of lncRNA MIAT in patients with AMI.** ROC curve analysis was performed to test the reliability of MIAT as a biomarker for diagnosing AMI. As shown in Fig. 3, CK-MB provided the greatest diagnostic value [area under the curve (AUC) = 0.86; 95% CI, 0.814–0.92], while cTnT and MIAT obtained AUC values of 0.76 and 0.78, respectively. These results indicated that MIAT has the same value as cTnT in the diagnosis of AMI.

**Knockdown of MIAT alleviates cardiomyocyte apoptosis.** To characterize the functional role of MIAT in myocardial injury, a loss-of-function approach was used in neonatal rat cardiomyocytes. As shown in Fig. 4A, the expression of MIAT was significantly increased after exposure to hypoxia for 24 h, and this result was consistent with the results in the plasma of patients with AMI and AMI rats. Subsequently, MIAT siRNAs were transfected into cell and the expression of MIAT was significantly decreased in the si-MIAT-1 and si-MIAT-2 groups (Fig. 4B). Moreover, the TUNEL assay showed that MIAT knockdown significantly repressed cardiomyocyte apoptosis (Fig. 4C and D). Caspases are a family of cysteine proteases that play essential roles in cell apoptosis. Cleaved caspase 3 was increased when cells were exposed to hypoxia, and MIAT knockdown significantly decreased caspase 3 activity. Besides, the pro-apoptotic protein Bax and the anti-apoptotic protein Bcl2 were detected using western

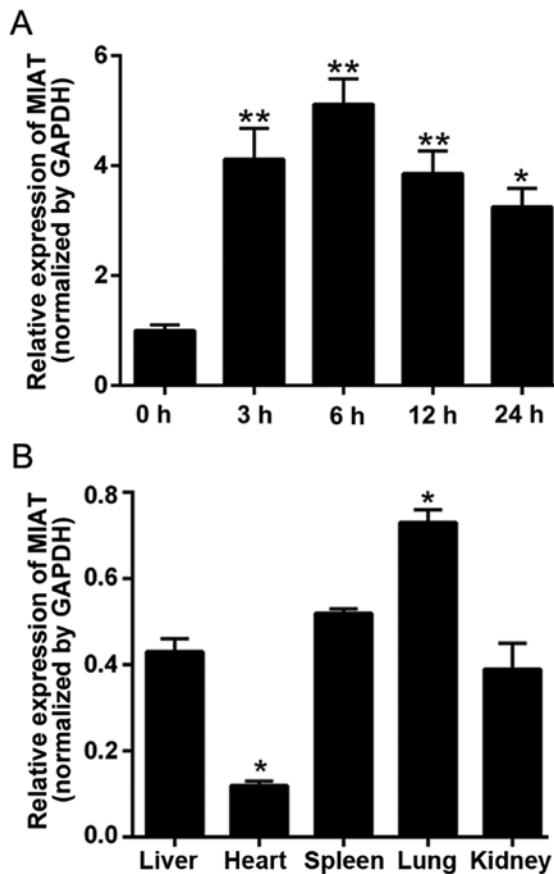


Figure 2. IncRNA MIAT is a myocardium-specific lncRNA. (A) Expression pattern of plasma MIAT in acute myocardial infarction rats. Comparisons between groups were performed using Dunnett's test. \* $P < 0.05$ , \*\* $P < 0.01$  vs. 0 h group. (B) Expression levels of MIAT in the liver, heart, spleen, lung and kidney. The data are presented as the mean  $\pm$  SD. \* $P < 0.05$  vs. liver. MIAT, myocardial infarction associated transcript; lncRNA, long noncoding RNA.

blotting. The results indicated that knockdown of MIAT significantly decreased the expression of Bax and increased the expression of Bcl2 (Fig. 4E and F). These results indicated that MIAT knockdown may prevent the apoptosis of cardiomyocytes by regulating the expression of Bcl2 family proteins.

## Discussion

AMI has become a major public health problem, owing to its high mortality and morbidity. Therefore, there is an urgent need to discover new biomarkers for better and faster diagnosis of AMI. The present study found enough advantages of MIAT as a novel biomarker to diagnose AMI. Firstly, MIAT was rapidly upregulated by two times within 3 h of ischemic symptom onset, and reached a peak at 6 h. Secondly, correlation analysis and ROC analysis demonstrated that MIAT had the same diagnostic value as cTnT. Thirdly, MIAT is specifically expressed at low levels in the heart, and rapidly increases during the onset of MI, which may be beneficial for monitoring the condition of the myocardium in patients with AMI. A previous study reported that the expression level of MIAT was correlated with a high risk of mortality from AMI, suggesting that MIAT may play a role in promoting cardiomyocyte apoptosis and even mortality (12).

Several lncRNAs have been implicated as regulators of the cardiovascular system. lncRNA-p21 is induced by p53 to inhibit smooth muscle cell proliferation and apoptosis (18). lncRNA Mhrt, as a cardiac-specific lncRNA, plays an important role in preventing cardiac remodeling and hypertrophy by regulating the chromatin-binding protein transcription activator BRG1 (19). MIAT, also known as RNCR2, AK028326 or GOMAFU, was first reported to be expressed in mitotic progenitors and post-mitotic retinal precursor cells (20). Subsequent studies have confirmed that MIAT is correlated with the progression of multiple diseases, including tumor proliferation and apoptosis (21), a high risk of mortality from AMI (12,22), microvascular dysfunction (23) and neuronal activity (24).

A large clinical trial (25) compared MIAT levels in peripheral blood cells between patients with MI and healthy subjects, and the results indicated that there was no statistical difference in MIAT levels between the two groups. However, the difference in expression of MIAT appears between patients with STEMI and those with non-ST-segment elevated myocardial infarction. Ishii *et al* (12) identified that the aberrant expression of MIAT with SNP rs2301523 was related to the pathogenesis of MI, which is consistent with the present results. Yan *et al* (23) demonstrated that the upregulation of MIAT induced by high glucose leads to diabetic microvascular dysfunction. In the present study, the proportion of patients with concomitant diabetes was higher in the AMI group than in the non-AMI group, which may be a reason for the difference in MIAT expression between the two groups.

Early rescue of apoptosis in cardiomyocytes induced by ischemia and hypoxia is the key to the treatment of AMI. With more in-depth study of lncRNAs, their influence on cardiomyocyte apoptosis and pathological mechanisms may be further revealed, which will provide a theoretical basis for the role of lncRNAs in clinical cardiovascular disease and anti-atherosclerosis therapies. The pro-apoptotic effect of MIAT in cardiomyocytes, by affecting the expression of death-associated protein kinase 2 (DAPK2), has been demonstrated in a rat diabetic cardiomyopathy model (26). Specifically, it may act as a competitive endogenous RNA, upregulating DAPK2 expression by sponging miR-22-3p, which leads to cardiomyocyte apoptosis.

There are some limitations to the present study. A larger sample size would allow for investigating the possibility of using MIAT as an AMI biomarker. Animal experiments are needed to further verify the role of MIAT in promoting cardiomyocyte apoptosis, and its regulatory mechanism at the transcriptional level.

The present study evaluated the plasma levels and functional role of lncRNA MIAT in the process of AMI to investigate the potential of MIAT as a biomarker for diagnosing AMI. Moreover, *in vivo* and *in vitro* experimental results showed that MIAT was able to sensitively reflect the degree of myocardial injury and that MIAT knockdown markedly suppressed cardiomyocyte apoptosis. These findings provide a new insight into the potential role of MIAT in the diagnosis of AMI, and its functional role in AMI pathogenesis.

## Acknowledgements

Not applicable.

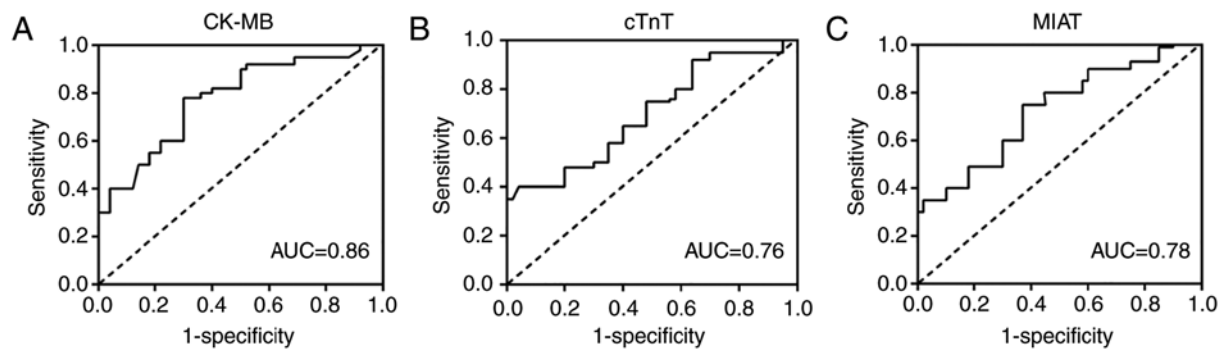


Figure 3. Receiver operating characteristic curve analysis. (A) Expression profiles of CK-MB in patients with non-AMI and AMI. (B) Expression profiles of cTnT in patients with non-AMI and AMI. (C) Expression profiles of MIAT in patients with non-AMI and AMI. AUC, area under the curve; AMI, acute myocardial infarction; cTnT, cardiac troponin T; CK-MB, creatine kinase-MB; MIAT, myocardial infarction associated transcript.

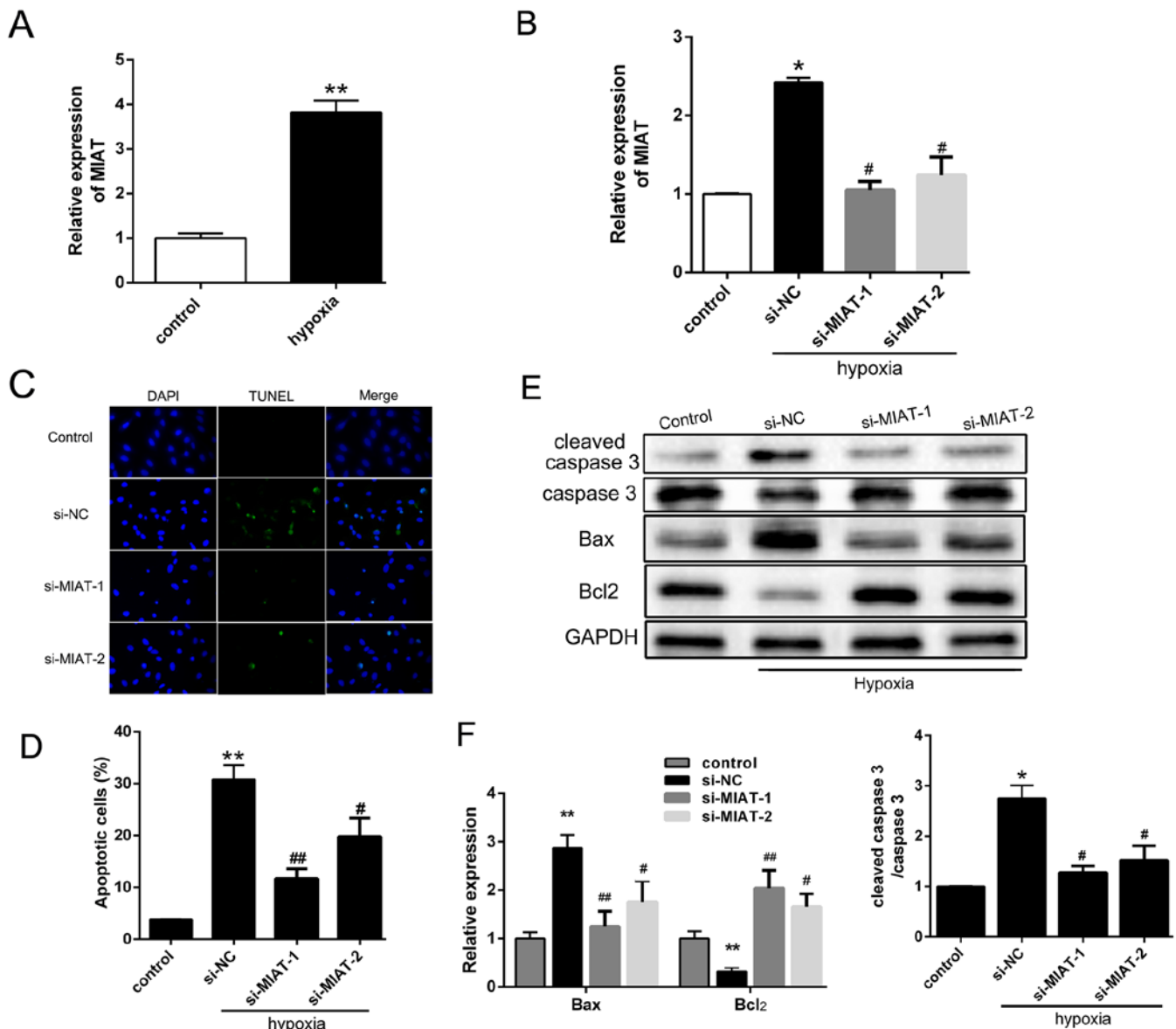


Figure 4. Knockdown of MIAT alleviates cardiomyocyte apoptosis. (A) Cardiomyocytes were exposed to hypoxia for 24 h, and the expression of MIAT was measured using RT-qPCR. (B) Cells were transfected with MIAT siRNAs, and relative expression of MIAT was detected using RT-qPCR. Comparisons between groups were performed using Tukey's test. (C) Cells were incubated with TUNEL reaction mixture and DAPI stain, and representative images indicated that condensed nuclei were present (magnification, x200). (D) The relative apoptotic cell percentages were calculated at least three times. Comparisons between groups were performed using Tukey's test. (E) Cells were collected and expression levels of cleaved caspase 3, caspase 3, Bax and Bcl2 were detected using western blotting. (F) Relative protein quantitative differences were calculated in the different treatment groups. Comparisons between groups were performed using Tukey's test. The data are presented as the mean  $\pm$  SD. \* $P$ <0.05, \*\* $P$ <0.01 vs. respective control group; # $P$ <0.05, ## $P$ <0.01 vs. respective si-NC group. RT-qPCR, reverse transcription-quantitative PCR; siRNA, small interfering RNA; NC, negative control; MIAT, myocardial infarction associated transcript.

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## Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

## Authors' contributions

MA was responsible for drafting the manuscript, analysis and interpretation of data. AA and XH were responsible for acquisition of data. RG was responsible for searching documents and acquisition of data. PP was responsible for the design of the study and revising it critically for important intellectual content.

## Ethics approval and consent to participate

Written informed consent was obtained from all enrolled subjects and the study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University. All animal procedures were approved by the Experimental Animal Ethics Committee of The First Affiliated Hospital of Xinjiang Medical University.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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