RESEARCH ARTICLE

WILEY

A novel circulating biomarker lnc-MALAT1 for acute myocardial infarction: Its relationship with disease risk, features, cytokines, and major adverse cardiovascular events

Ruirui Li[1] | Jin Jin[2] | Enxiang Liu[2] | Jun Zhang[1]

[1]Department of Cardiovascular Disease, Cangzhou Central Hospital of Tianjin Medical University, Tianjin, China

[2]Department of Cardiovascular Disease, Cangzhou People's Hospital, Cangzhou, Hebei, China

Correspondence
Jun Zhang, Department of Cardiovascular Disease, Cangzhou Central Hospital of Tianjin Medical University, No. 16 Xinhua West Road, Cangzhou, Hebei, China.
Email: dr_zhangj@sina.com

Abstract

Objective: Long noncoding RNA MALAT1 (lnc-MALAT1) modulates atherosclerotic progression, myocardial ischemia injury, and systematic inflammation, which may be closely involved in acute myocardial infarction (AMI) pathogenesis. Thus, the current study intended to explore the relationship of lnc-MALAT1 to disease risk, features, cytokines, and prognostication in AMI patients.

Methods: This multicenter study consecutively enrolled 160 newly diagnosed AMI patients and 50 controls (angina pectoris patients). Their peripheral blood mononuclear cells were obtained to measure lnc-MALAT1 by RT–qPCR. Serum cytokines in AMI patients were detected by ELISA. In addition, AMI patients were followed up for major adverse cardiovascular event (MACE) risk evaluation.

Results: Lnc-MALAT1 was higher in AMI patients than in controls (median: 2.245 vs. 0.996, $p = 0.004$), and it also presented a good capacity for differentiating AMI patients from controls with an area under the curve of 0.823. Lnc-MALAT1 was positively related to C-reactive protein ($p = 0.005$), low-density lipoprotein cholesterol ($p = 0.022$), cardiac troponin I ($p = 0.021$), and infarct size ($p = 0.007$), but not other biochemical indexes in AMI patients. Meanwhile, lnc-MALAT1 was positively associated with tumor necrosis factor-alpha ($p = 0.001$), interleukin (IL)-6 ($p = 0.031$), IL-17A ($p = 0.042$), vascular cell adhesion molecule-1 ($p = 0.004$), and intercellular adhesion molecule-1 ($p = 0.021$) among AMI patients. Importantly, after categorization, lnc-MALAT1 high (vs. low) was related to an elevated MACE accumulation rate ($p = 0.035$); furthermore, a higher lnc-MALAT1 quartile showed a trend to be linked with an increased MACE accumulation rate ($p = 0.092$).

Conclusion: Lnc-MALAT1 may serve as a biomarker for AMI risk, infarct size, inflammation and prognosis, but further validation by large-scale studies is needed.

KEYWORDS
acute myocardial infarction, disease risk, features, lnc-MALAT1, MACE

1 | INTRODUCTION

Acute myocardial infarction (AMI) is one of the leading causes of coronary heart-related deaths worldwide, and its prevalence is still increasing partly due to the acceleration of aging, changes in lifestyle, and environmental pollution.[1,2] It's recently reported that AMI affects more than 7 million populations per year globally.[3] Currently, AMI is often combined with several complications, including arrhythmia and cardiac failure, which induce a huge burden and greatly affect the quality of life among patients.[4,5] Currently, the treatments for AMI mainly include thrombolysis and percutaneous coronary intervention.[6,7] However, the prognosis of a proportion of AMI patients is still dismal.[2,8] Thus, the exploration of potential convincing biomarkers to reflect disease risk and severity is imperative to promote the management of AMI patients.

Long noncoding RNA MALAT1 (lnc-MALAT1), situated at human chromosome 11q13, is initially discovered in cancers that acts as a well-known oncogene.[9] Recently, lnc-MALAT1 is also observed to participate in the pathophysiological process of several cerebral-cardiovascular diseases.[10–12] For instance, it has been proposed that lnc-MALAT1 has the capacity to promote heart damage by promoting cardiomyocyte cell apoptosis in an AMI rat model[11]; moreover, decreased lnc-MALAT1 inhibits the formation of atherosclerosis model cells (THP-1 macrophage-derived foam cells) in vitro; moreover, it also accelerates inflammation in atherosclerosis model mice.[12] From a clinical perspective, lnc-MALAT1 is related to increased disease risk and elevated coronary stenosis extent in coronary heart disease[13,14]; moreover, it has also been reported that lnc-MALAT1 is related to increased disease severity and poor prognosis in acute ischemic stroke.[15,16] Based on the abovementioned information, we deduced that lnc-MALAT1 could serve as a possible biomarker for disease risk and disease surveillance in AMI.

Thus, the present study intended to explore the relationship of blood lnc-MALAT1 levels with disease risk, infarct size, biochemical indexes, cytokines, and prognosis of AMI.

2 | METHODS

2.1 | Participants

The present multicenter study recruited one hundred and sixty first-ever AMI patients admitted to our hospitals from October 2020 to May 2021. The inclusion criteria for AMI patients were as follows: (1) newly diagnosed as AMI according to the 4th Common Definition of Myocardial Infarction (2018)[17]; and (2) aged more than eighteen years old. The exclusion criteria for AMI patients were as follows: (1) history of cardiothoracic surgery; (2) systemic immune or inflammatory diseases; (3) solid tumor or hematological malignancy; (4) presence of other severe cardiac conditions; and (5) pregnancy or breastfeeding. Additionally, fifty patients with angina pectoris were recruited as controls. The exclusion criteria for controls were as follows: (1) history of cardiothoracic surgery; (2) any known malignancies; (3) history of AMI; (4) immune or inflammatory disorders; and (5) pregnancy or breastfeeding. The Ethics Committee approved the study. Every participant signed written informed consent.

2.2 | Clinical data and sample collection

All participants' demographics, medical history, and biochemical indexes were recorded via a case report form. In addition, AMI patients were followed up for major adverse cardiovascular event (MACE) risk evaluation. MACE was defined as cardiovascular death, myocardial infarction, unplanned coronary revascularization, or hospital admission for cardiovascular cause according to a previous study.[18] Blood samples (15 ml) from all participants were obtained immediately after admission and stored at 4°C for later laboratory detection. On the third day of admission, the infarct size (%) of AMI patients was determined according to the methods in a previous study.[19]

2.3 | Enzyme-linked immunosorbent assay (ELISA)

After blood samples were centrifuged at $1000 \times g$ for 5 min, the AMI patients' serum was separated for ELISA. Then, the concentrations of inflammatory cytokines and cell adhesion molecules, including tumor necrosis factor-alpha (TNF-α) (Catalogue number A35601, sensitivity 0.01 pg/ml), interleukin (IL)-6 (IL-6) (Catalogue number BMS213HS, sensitivity 0.03 pg/ml), IL-10 (Catalogue number KAC1321, sensitivity 1 pg/ml), IL-17A (Catalogue number BMS2017, sensitivity 0.5 pg/ml), vascular cell adhesion molecule-1 (VCAM-1) (Catalogue number KHT0601, sensitivity 0.5 ng/ml), and intercellular adhesion molecule 1 (ICAM-1) (Catalogue number BMS241, sensitivity 0.3 ng/ml), were determined by commercial ELISA Kits (Thermo Fisher Scientific). All procedures strictly followed the manufacturer's protocols.

2.4 | Reverse transcription quantitative polymerase chain reaction (RT–qPCR) assay

Peripheral blood mononuclear cell (PBMC) isolation from AMI patients and controls was performed by density gradient centrifugation within 24 h after blood collection. RT–qPCR assays were carried out for quantitative analysis of the expression of lnc-MALAT1 in PBMCs. In brief, total RNA was extracted by PureZOL RNA isolation reagent (Bio-Rad) and reverse transcribed by a QuantiNova Reverse Transcription Kit (Qiagen). Meanwhile, qPCR was performed by TB Green™ Fast qPCR Mix (TAKARA). Furthermore, the relative expression was calculated by the $2^{-\Delta\Delta Ct}$ method, and GAPDH was used as an internal reference. In addition, primer sequences were constructed according to a previous study.[13]

2.5 | Statistical analysis

The differences between the two groups were compared using the Mann–Whitney *U* test, Chi-square test, and Student's *t* test, as appropriate. The receiver operating characteristic (ROC) curve was applied to assess the diagnostic ability of lnc-MALAT1. The correlations between two variables were evaluated via Spearman's rank correlation test. The comparison of lnc-MALAT1 between patients with or without specific medical history was carried out by the Mann–Whitney *U* test. The statistical analyses and figure plotting were performed by SPSS V 25.1 (IBM; Corp) and GraphPad Prism V 8.00 (GraphPad; Software Inc). A *p* value <0.05 was considered significant.

3 | RESULTS

3.1 | Clinical features of AMI patients and controls

The mean ages of the 50 controls and 160 AMI patients were 61.7 ± 7.2 and 61.4 ± 10.9 years, respectively. Meanwhile, there were 15 (30.0%) females and 35 (70.0%) males among the controls, as well as 39 (24.4%) females and 121 (75.6%) males among the AMI patients. By comparison, no difference was discovered in demographics and medical history between controls and AMI patients (all $p > 0.05$). In terms of biochemical indexes, the median values of C-reactive protein (CRP), cardiac troponin I (cTnI), and creatine kinase-myocardial band (CK-MB) were higher in AMI patients than controls (all $p < 0.001$), while no difference was found in other biochemical indexes between AMI patients and controls (all $p > 0.05$). Regarding the clinical presentation, there were 49 (30.6%) and 111 (69.4%) patients with non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI), respectively; meanwhile, the median symptom-to-balloon time was 280.0 (180.0–912.5) min, and the median infarct size was 21.0 (16.0–28.0)%. More detailed information is presented in Table 1.

3.2 | Comparison of lnc-MALAT1 between AMI patients and controls

Lnc-MALAT1 (median interquartile range (IQR)): 2.245 (1.515–2.728) vs. 0.996 (0.609–1.572) was increased in AMI patients compared to controls ($p < 0.001$) (Figure 1A). Furthermore, the ROC curve showed that lnc-MALAT1 had a good ability to discriminate AMI patients from controls, with an area under the curve (95% confidence interval) of 0.823 (0.756–0.890) (Figure 1B).

3.3 | Correlation of lnc-MALAT1 with biochemical indexes and medical history in AMI patients

Lnc-MALAT1 was positively linked with low-density lipoprotein cholesterol (LDL-C) ($r_s = 0.181$, $p = 0.022$) and cTnI ($r_s = 0.182$, $p = 0.021$), while it was not related to other biochemical indexes (all $p > 0.05$) (Table 2). Moreover, increased lnc-MALAT1 was associated with a history of diabetes mellitus (DM) ($p = 0.004$), while no correlation was found between lnc-MALAT1 and a history of hypertension or hyperlipidemia (both $p > 0.05$) (Table S1).

3.4 | Correlation of lnc-MALAT1 with infarct size in AMI patients

Elevated infarct size is correlated with prolonged hospitalization and high mortality among cardiovascular disease patients.[20] Thus, the association between lnc-MALAT1 and infarct size in AMI patients was explored, which showed a positive association between lnc-MALAT1 and infarct size ($r_s = 0.213$, $p = 0.007$) (Figure 2).

3.5 | Correlation of lnc-MALAT1 with inflammatory cytokines and adhesion molecules in AMI patients

Regarding the association of lnc-MALAT1 with inflammation, a positive relationship was discovered between lnc-MALAT1 and CRP ($r_s = 0.222$, $p = 0.005$) (Figure 3A), TNF-α ($r_s = 0.252$, $p = 0.001$) (Figure 3B), and IL-6 ($r_s = 0.170$, $p = 0.031$) (Figure 3C), while no correlation was found between lnc-MALAT1 and IL-10 ($r_s = -0.115$, $p = 0.146$) (Figure 3D); meanwhile, lnc-MALAT1 was also positively associated with IL-17A ($r_s = 0.161$, $p = 0.042$) (Figure 3E).

In terms of the correlation of lnc-MALAT1 with adhesion molecules, a positive association was discovered between lnc-MALAT1 and VCAM-1 ($r_s = 0.225$, $p = 0.004$) (Figure 4A) and ICAM-1 ($r_s = 0.183$, $p = 0.021$) (Figure 4B).

3.6 | Correlation of lnc-MALAT1 with the cumulative MACE rate

After categorization, it was observed that high lnc-MALAT1 expression (vs. low lnc-MALAT1 expression) was related to an increased MACE accumulation rate ($p = 0.035$, Figure 5A). Furthermore, a higher lnc-MALAT1 quartile revealed a trend to be linked with an increased MACE rate ($p = 0.092$, Figure 5B).

4 | DISCUSSION

Timely and accurate diagnosis plays an important role in the management of AMI.[2,4] Thus, it is crucial to explore a convincing biomarker to predict the disease risk of AMI. Several updated studies have proposed that the dysregulation of lnc-MALAT1 is a hallmark of disease risk in several cardiovascular and cerebrovascular diseases. For example, it has been reported that MALAT1 is increased in acute ischemic stroke compared to the healthy population[15]; moreover, an increase in lnc-MALAT1 is also discovered

TABLE 1 Clinical characteristics

Items	Controls (N = 50)	AMI patients (N = 160)	Statistics (t, χ^2, Z)	p Value
Demographics				
Age (years), mean ± SD	61.7 ± 7.2	61.4 ± 10.9	0.164	0.870
Gender, n (%)			0.631	0.427
Female	15 (30.0)	39 (24.4)		
Male	35 (70.0)	121 (75.6)		
BMI (kg/m^2), mean ± SD	24.4 ± 3.0	24.9 ± 3.2	−0.942	0.347
Current smoker, n (%)	22 (44.0)	63 (39.4)	0.338	0.561
Medical history				
History of hypertension, n (%)	34 (68.0)	111 (69.4)	0.034	0.854
History of hyperlipidemia, n (%)	21 (42.0)	63 (39.4)	0.109	0.741
History of DM, n (%)	12 (24.0)	41 (25.6)	0.053	0.817
Biochemical indexes				
WBC (10^9/L), median (IQR)	9.3 (8.2–12.2)	10.7 (8.3–13.0)	−1.376	0.169
FBG (mmol/L), median (IQR)	5.4 (4.8–6.4)	5.5 (4.6–6.5)	−0.080	0.936
Scr (umol/L), median (IQR)	77.2 (68.4–92.0)	75.3 (66.3–85.3)	−0.931	0.352
TG (mmol/L), median (IQR)	1.6 (1.4–2.2)	1.8 (1.0–2.5)	−0.129	0.897
TC (mmol/L), median (IQR)	5.2 (4.2–5.5)	4.8 (3.9–5.4)	−0.808	0.419
LDL-C (mmol/L), median (IQR)	3.4 (2.8–3.8)	3.3 (2.6–4.1)	−0.520	0.603
HDL-C (mmol/L), median (IQR)	1.0 (0.8–1.1)	0.9 (0.8–1.1)	−1.372	0.170
CRP (mg/L), median (IQR)	2.4 (1.1–3.9)	5.0 (3.5–7.3)	−6.255	<0.001
cTnI (ng/ml), median (IQR)	0.14 (0.07–0.73)	4.03 (3.01–6.02)	−10.331	<0.001
CK-MB (ng/ml), median (IQR)	9.8 (8.3–20.8)	33.5 (16.8–56.0)	−6.571	<0.001
Clinical presentation				
NSTEMI, n (%)	-	49 (30.6)	-	-
STEMI, n (%)	-	111 (69.4)	-	-
Symptom-to-balloon time (mins), median (IQR)	-	280.0 (180.0–912.5)	-	-
Infarct size (%), median (IQR)	-	21.0 (16.0–28.0)	-	-

Abbreviations: AMI, acute myocardial infarction; BMI, body mass index; CK-MB, creatine kinase-myocardial band; CRP, C-reactive protein; cTnI, cardiac troponin I; DM, diabetes mellitus; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; Scr, serum creatinine; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglyceride; WBC, white blood cell.

among coronary atherosclerosis compared to healthy subjects.[14] However, the data about lnc-MALAT1 in AMI patients are limited. In the present study, we observed that lnc-MALAT1 was elevated in AMI patients; meanwhile, it was linked with increased disease risk in AMI. The potential explanation could be that increased lnc-MALAT1 could accelerate the pathogenesis of AMI through several methods, including promoting atherosclerosis progression, myocardial ischemia–reperfusion injury, and systematic inflammation.[11,12,21] In addition, the rational for including angina pectoris patients but not health subjects as controls was that: disease controls were considered for reference in our study instead of healthy controls; therefore, angina pectoris patients were enrolled. Our discovery indicated that lnc-MALAT1 might help clinicians with the diagnosis of AMI.

The relationship of lnc-MALAT1 with disease characteristics in cardiovascular and cerebrovascular diseases (including coronary heart disease and stroke) has been investigated. For instance, interesting research proposes that lnc-MALAT1 is positively associated with coronary stenosis extent and proinflammatory cytokines among patients with coronary heart disease[13]; moreover, it has also been reported that lnc-MALAT1 is positively related to systematic inflammation among acute ischemic stroke patients.[15] However, the relationship of lnc-MALAT1 with disease characteristics in AMI patients is unclear. According to previous studies, lipid profile, cTnI, infarct size, inflammation, and adhesion molecules are viewed as hallmarks of AMI[22–24]; thus, we explored the association of lnc-MALAT1 with them among AMI patients, which showed that lnc-MALAT1 was positively linked with lipid dysregulation (reflected by LDL-C), the marker of myocardial injury (reflected by cTnI), disease severity indicator (reflected by infarct size), systematic inflammation (reflected by CRP, TNF-α, IL-6, and IL-17A), and adhesion cytokines (reflected by VCAM-1 and ICAM-1). The potential explanations might be that

FIGURE 1 Lnc-MALAT1 was elevated in AMI patients vs. controls. Comparison of lnc-MALAT1 in AMI patients and controls (A); the capacity of lnc-MALAT1 to distinguish AMI patients from controls (B).
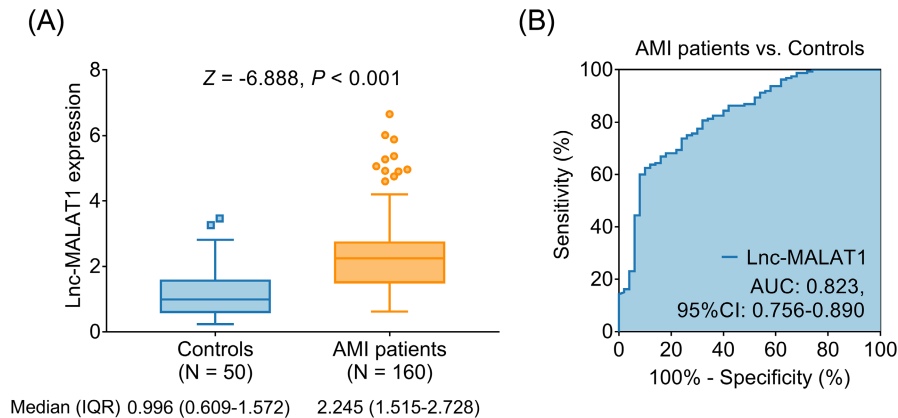
(A)

Z = -6.888, P < 0.001

Median (IQR) 0.996 (0.609-1.572)   2.245 (1.515-2.728)

(B)

AMI patients vs. Controls

Lnc-MALAT1
AUC: 0.823,
95%CI: 0.756-0.890

TABLE 2 Correlation of lnc-MALAT1 with biochemical indexes in AMI patients

Items	Lnc-MALAT1 expression	
	r_s	p Value
WBC	0.114	0.150
FBG	0.083	0.297
Scr	0.038	0.631
TG	0.147	0.064
TC	0.133	0.093
LDL-C	0.181	0.022
HDL-C	−0.058	0.463
cTnI	0.182	0.021
CK-MB	0.105	0.185

Abbreviations: AMI, acute myocardial infarction; CK-MB, creatine kinase-myocardial band; cTnI, cardiac troponin I; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lnc-MALAT1, long non-coding metastasis associated lung adenocarcinoma transcript 1; Scr, serum creatinine; TC, total cholesterol;TG, triglyceride; WBC, white blood cell.

r_s = 0.213, P = 0.007

FIGURE 2 Lnc-MALAT1 was positively linked to infarct size in AMI patients.

(1) lnc-MALAT1 could accelerate lipid metabolism and lipid oxidation in AMI, which resulted in elevated LDL-C[25]; (2) lnc-MALAT1 might promote cardiomyocyte injury through several mechanisms, such as regulating autophagy-related 3, as well as phosphatase and tensin homolog deleted on chromosome 10, which led to increased cTnI and infarct size in AMI[26,27]; (3) lnc-MALAT1 might be able to accelerate inflammation *by* regulating several signaling pathways, including Wnt/β-catenin and nuclear factor-kappa B signaling; thereby, lnc-MALAT1 was positively associated with inflammation in AMI patients[28,29]; and (4) lnc-MALAT1 could accelerate the production of adhesion molecules through several methods, such as microRNA-590 and the signal transducer and activator of transcription 3 pathway[21]; thus, a positive relation was found in lnc-MALAT1 with adhesion cytokines among AMI patients. In addition, we also discovered that higher lnc-MALAT1 was linked with a history of DM among AMI patients. The possible reason could be that lnc-MALAT1 could accelerate insulin resistance and glucose levels, which are involved in the pathogenesis of DM.[30,31] Interestingly, since lnc-MALAT1 express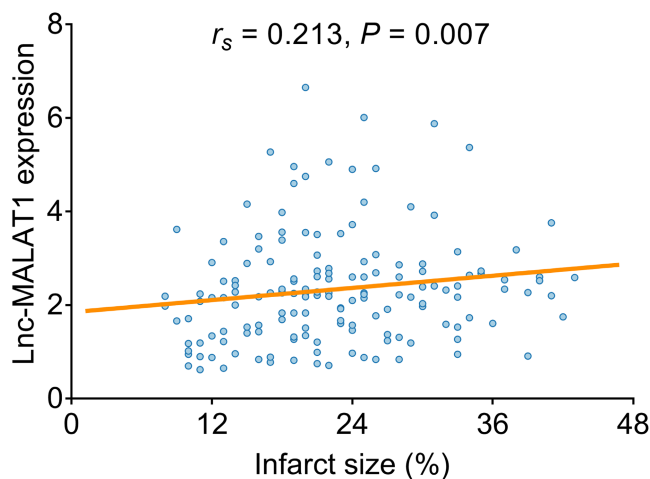ion was detected in PBMC in the current study and it closely related to inflammation, we speculated that it mainly resulted from the immune cells; besides, it was also reported previously lnc-MALAT1 promoted atherosclerotic lesion; therefore, it might come from the lesion size fall off as well.[11–13]

Interestingly, it was further identified that lnc-MALAT1 could predict accumulating MACE risk in AMI patients to some extent. The possible explanations were as follows: (1) lnc-MALAT1 accelerated atherosclerosis, myocardial damage, and inflammation, which directly increased the risk of MACE[11,12,21]; (2) lnc-MALAT1 was linked with lipid dysregulation, cTnI, infarct size, inflammatory cytokines, etc., as mentioned above and then indirectly related to an elevated risk of MACEs.

Nevertheless, some limitations could not be ignored in the present study: (1) the prognostic value of lnc-MALAT1 in AMI patients was not explored and should be investigated in the future; (2) the enrolled patients in the present study were first-ever AMI patients; thus, the clinical role of lnc-MALAT1 in recurrent myocardial infarction patients should be investigated in the future; and (3) the longitudinal change in lnc-MALAT1 in AMI patients should be measured to explore its value in monitoring disease progression. (4) The relatively small sample size limited the subgroup analyses for STEMI and NSTEMI patients individually in the current study.
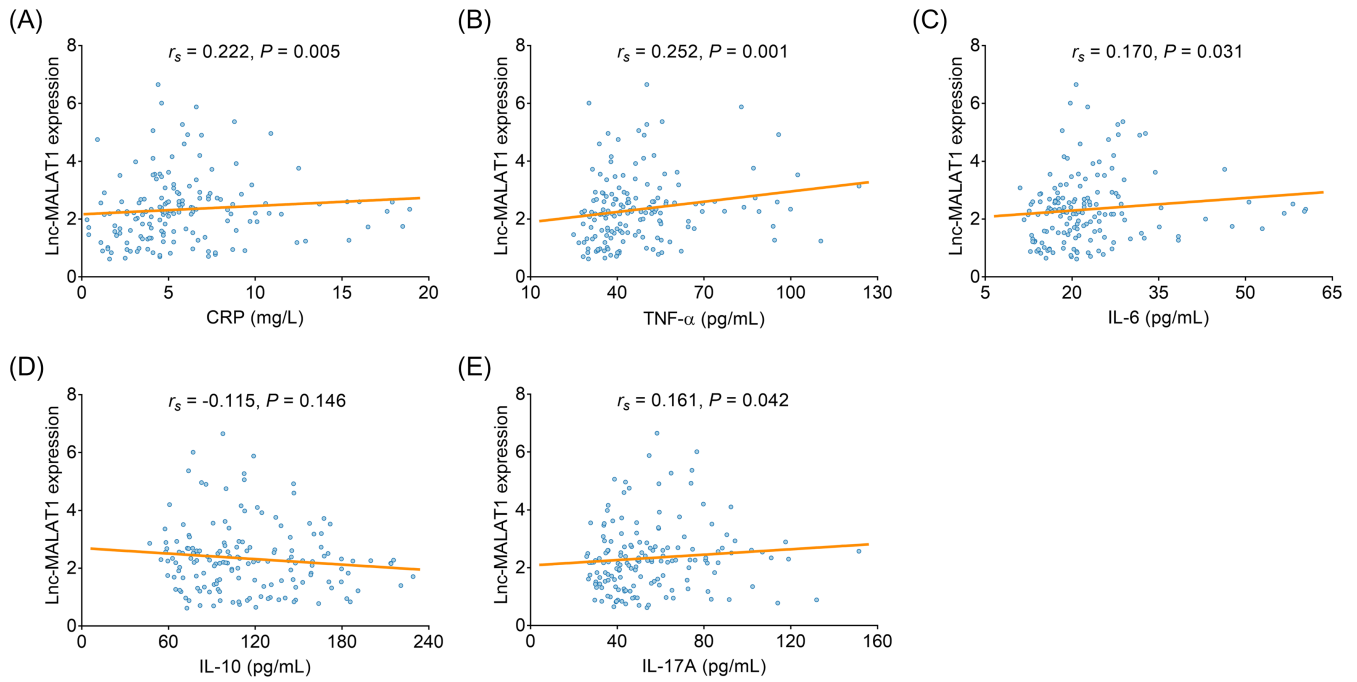
FIGURE 3 Lnc-MALAT1 was positively correlated with inflammation. Association of lnc-MALAT1 with CRP (A), TNF-α (B), IL-6 (C), IL-10 (D), and IL-17A (E) in AMI patients.
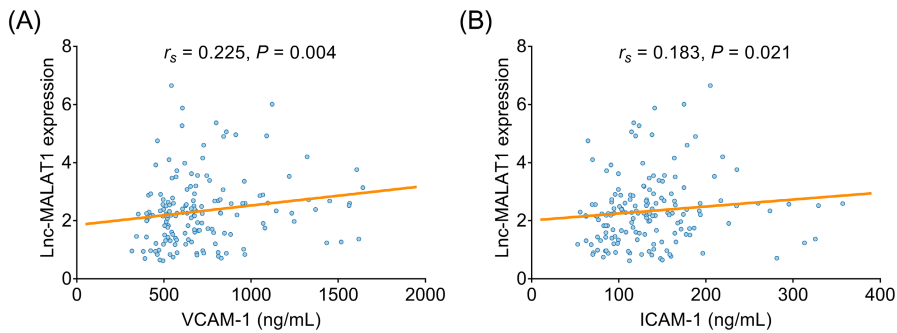

FIGURE 4 Lnc-MALAT1 was positively correlated with adhesion molecules. Relationship of lnc-MALAT1 with VCAM-1 (A) and ICAM-1 (B) in AMI patients.
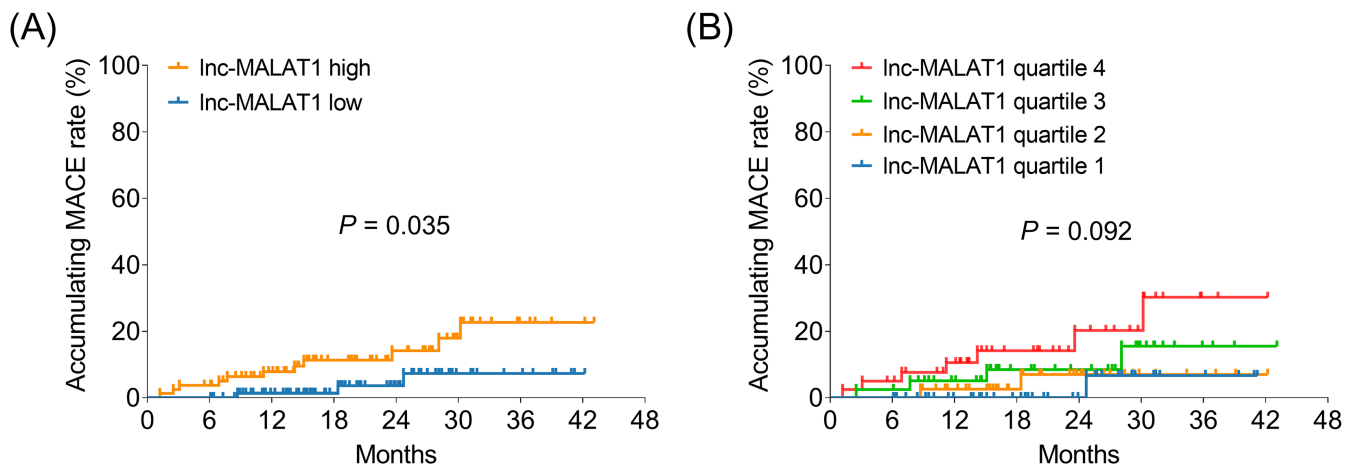

FIGURE 5 Lnc-MALAT1 predicted increased MACE risk to some extent. Correlation of lnc-MALAT1 high (vs. low) with MACE risk (A); correlation of lnc-MALAT1 quartile with MACE risk (B) in AMI patients.

To be conclusive, lnc-MALAT1 may serve as a potential biomarker for AMI reflecting disease susceptibility, infarct size, and systemic inflammation, but further validation by large-scale studies is needed.

CONFLICT OF INTEREST
None.

DATA AVAILABILITY STATEMENT
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONSENT TO PARTICIPATE
Every participant signed the written informed consent.

CONSENT FOR PUBLICATION
Not applicable.

ORCID
Jun Zhang https://orcid.org/0000-0003-3787-875X

REFERENCES

1. Toscano O, Cosentino N, Campodonico J, Bartorelli AL, Marenzi G. Acute myocardial infarction during the COVID-19 pandemic: an update on clinical characteristics and outcomes. *Front Cardiovasc Med.* 2021;8:648290.
2. Anderson JL, Morrow DA. Acute myocardial infarction. *N Engl J Med.* 2017;376(21):2053-2064.
3. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. *Lancet.* 2017;389(10065):197-210.
4. Davidson SM, Ferdinandy P, Andreadou I, et al. Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week. *J Am Coll Cardiol.* 2019;73(1):89-99.
5. Pourasghari H, Tavolinejad H, Soleimanpour S, et al. Hospitalization, major complications and mortality in acute myocardial infarction patients during the COVID-19 era: a systematic review and meta-analysis. *Int J Cardiol Heart Vasc.* 2022;41:101058.
6. He J, Liu D, Zhao L, et al. Myocardial ischemia/reperfusion injury: mechanisms of injury and implications for management (review). *Exp Ther Med.* 2022;23(6):430.
7. Atkar C. A study on Qt dispersion before and after thrombolysis in acute myocardial infarction, and its prognostic implications. *J Assoc Physicians India.* 2022;70(4):11-12.
8. Albulushi A, Giannopoulos A, Kafkas N, Dragasis S, Pavlides G, Chatzizisis YS. Acute right ventricular myocardial infarction. *Expert Rev Cardiovasc Ther.* 2018;16(7):455-464.
9. Gutschner T, Hammerle M, Diederichs S. MALAT1 — a paradigm for long noncoding RNA function in cancer. *J Mol Med (Berl).* 2013;91(7):791-801.
10. Zhang X, Hamblin MH, Yin KJ. The long noncoding RNA Malat1: its physiological and pathophysiological functions. *RNA Biol.* 2017;14(12):1705-1714.
11. Liu Z, Liu J, Wei Y, et al. LncRNA MALAT1 prevents the protective effects of miR-125b-5p against acute myocardial infarction through positive regulation of NLRC5. *Exp Ther Med.* 2020;19(2):990-998.
12. Shi Z, Zheng Z, Lin X, Ma H. Long noncoding RNA MALAT1 regulates the progression of atherosclerosis by miR-330-5p/NF-kappaB signal pathway. *J Cardiovasc Pharmacol.* 2021;78(2):235-246.
13. Lv F, Liu L, Feng Q, Yang X. Long non-coding RNA MALAT1 and its target microRNA-125b associate with disease risk, severity, and major adverse cardiovascular event of coronary heart disease. *J Clin Lab Anal.* 2021;35(4):e23593.
14. Qiu S, Sun J. lncRNA-MALAT1 expression in patients with coronary atherosclerosis and its predictive value for in-stent restenosis. *Exp Ther Med.* 2020;20(6):129.
15. Ren H, Wu F, Liu B, Song Z, Qu D. Association of circulating long non-coding RNA MALAT1 in diagnosis, disease surveillance, and prognosis of acute ischemic stroke. *Braz J Med Biol Res.* 2020;53(12):e9174.
16. Petty K, Lemkuil BP, Gierl B. Acute ischemic stroke. *Anesthesiol Clin.* 2021;39(1):113-125.
17. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol.* 2018;72(18):2231-2264.
18. Greenwood JP, Ripley DP, Berry C, et al. Effect of care guided by cardiovascular magnetic resonance, myocardial perfusion scintigraphy, or NICE guidelines on subsequent unnecessary angiography rates: the CE-MARC 2 randomized clinical trial. *JAMA.* 2016;316(10):1051-1060.
19. Yun KH, Rhee SJ, Ko JS. Comparison of the infarct size between the loading of Ticagrelor and Clopidogrel in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Korean Circ J.* 2017;47(5):705-713.
20. Stone GW, Selker HP, Thiele H, et al. Relationship between infarct size and outcomes following primary PCI: patient-level analysis from 10 randomized trials. *J Am Coll Cardiol.* 2016;67(14):1674-1683.
21. Zhou Q, Run Q, Li CY, Xiong XY, Wu XL. LncRNA MALAT1 promotes STAT3-mediated endothelial inflammation by counteracting the function of miR-590. *Cytogenet Genome Res.* 2020;160(10):565-578.
22. Mitsis A, Kadoglou NPE, Lambadiari V, et al. Prognostic role of inflammatory cytokines and novel adipokines in acute myocardial infarction: an updated and comprehensive review. *Cytokine.* 2022;153:155848.
23. Lino DOC, Freitas IA, Meneses GC, et al. Interleukin-6 and adhesion molecules VCAM-1 and ICAM-1 as biomarkers of post-acute myocardial infarction heart failure. *Braz J Med Biol Res.* 2019;52(12):e8658.
24. Liu J, Tang L, Lu Q, et al. Plasma quantitative lipid profiles: identification of CarnitineC18:1-OH, CarnitineC18:2-OH and FFA (20:1) as novel biomarkers for pre-warning and prognosis in acute myocardial infarction. *Front Cardiovasc Med.* 2022;9:848840.
25. Zhao P, Wang Y, Zhang L, Zhang J, Liu N, Wang H. Mechanism of long noncoding RNA metastasisassociated lung adenocarcinoma transcript 1 in lipid metabolism and inflammation in heart failure. *Int J Mol Med.* 2021;47(3):5.
26. Hu H, Wu J, Li D, Zhou J, Yu H, Ma L. Knockdown of lncRNA MALAT1 attenuates acute myocardial infarction through miR-320-Pten axis. *Biomed Pharmacother.* 2018;106:738-746.
27. Jing H, Wang C, Zhao L, Cheng J, Qin P, Lin H. Propofol protects cardiomyocytes from hypoxia/reoxygenation injury via regulating MALAT1/miR-206/ATG3 axis. *J Biochem Mol Toxicol.* 2021;35(10):e22880.
28. Li H, Zhao Q, Chang L, et al. LncRNA MALAT1 modulates ox-LDL induced EndMT through the Wnt/beta-catenin signaling pathway. *Lipids Health Dis.* 2019;18(1):62.
29. Bai W, Huo T, Chen X, et al. Sacubitril/valsartan inhibits oxLDL-induced MALAT1 expression, inflammation and apoptosis by suppressing the TLR4/NFkappaB signaling pathway in HUVECs. *Mol Med Rep.* 2021;23(6):402.
30. Zhou L, Xu DY, Sha WG, Shen L, Lu GY. Long non-coding RNA MALAT1 interacts with transcription factor Foxo1 to regulate SIRT1

transcription in high glucose-induced HK-2cells injury. *Biochem Biophys Res Commun*. 2018;503(2):849-855.

31. Sathishkumar C, Prabu P, Mohan V, Balasubramanyam M. Linking a role of lncRNAs (long non-coding RNAs) with insulin resistance, accelerated senescence, and inflammation in patients with type 2 diabetes. *Hum Genomics*. 2018;12(1):41.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.