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

Ruirui Li | Jin Jin | Enxiang Liu | Jun Zhang

1Department of Cardiovascular Disease, Cangzhou Central Hospital of Tianjin Medical University, Tianjin, China
2Department 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 (Inc-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 Inc-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 Inc-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, Inc-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, Inc-MALAT1 high (vs. low) was related to an elevated MACE accumulation rate \( (p = 0.035) \); furthermore, a higher Inc-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, Inc-MALAT1, MACE

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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. It’s recently reported that AMI affects more than 7 million populations per year globally. 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. Currently, the treatments for AMI mainly include thrombolysis and percutaneous coronary intervention. However, the prognosis of a proportion of AMI patients is still dismal. 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 (Inc-MALAT1), situated at human chromosome 11q13, is initially discovered in cancers that acts as a well-known oncogene. Recently, Inc-MALAT1 is also observed to participate in the pathophysiological process of several cerebral-cardiovascular diseases. For instance, it has been proposed that Inc-MALAT1 has the capacity to promote heart damage by promoting cardiomyocyte cell apoptosis in an AMI rat model; moreover, decreased Inc-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. From a clinical perspective, Inc-MALAT1 is related to increased disease risk and elevated coronary stenosis extent in coronary heart disease; moreover, it has also been reported that Inc-MALAT1 is related to increased disease severity and poor prognosis in acute ischemic stroke. Based on the abovementioned information, we deduced that Inc-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 Inc-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); 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. 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.

2.3 | Enzyme-linked immunosorbent assay (ELISA)

After blood samples were centrifuged at 1000 x 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 24h after blood collection. RT-qPCR assays were carried out for quantitative analysis of the expression of Inc-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^-ΔΔct method, and GAPDH was used as an internal reference. In addition, primer sequences were constructed according to a previous study.
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 Inc-MALAT1. The correlations between two variables were evaluated via Spearman’s rank correlation test. The comparison of Inc-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 Inc-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 Inc-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 Inc-MALAT1 with biochemical indexes and medical history in AMI patients

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

3.4 | Correlation of Inc-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 Inc-MALAT1 and infarct size in AMI patients was explored, which showed a positive association between Inc-MALAT1 and infarct size (rs = 0.213, p = 0.007) (Figure 2).

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

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

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

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

After categorization, it was observed that high Inc-MALAT1 expression (vs. low Inc-MALAT1 expression) was related to an increased MACE accumulation rate (p = 0.035, Figure 5A). Furthermore, a higher Inc-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.24 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 Inc-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 population15; moreover, an increase in Inc-MALAT1 is also discovered...
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 hallmark 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

### TABLE 1 Clinical characteristics

| Items                        | Controls (N = 50) | AMI patients (N = 160) | Statistics (t, χ², Z) | p Value |
|------------------------------|------------------|------------------------|-----------------------|---------|
| Demographics                 |                  |                        |                       |         |
| Age (years), mean ± SD       | 61.7 ± 7.2       | 61.4 ± 10.9            | 0.164                 | 0.870   |
| Gender, n (%)                |                  |                        |                       |         |
| Female                       | 15 (30.0)        | 39 (24.4)              | 0.631                 | 0.427   |
| Male                         | 35 (70.0)        | 121 (75.6)             |                       |         |
| BMI (kg/m²), 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 (10⁹/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  |

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.
(1) Lnc-MALAT1 could accelerate lipid metabolism and lipid oxidation in AMI, which resulted in elevated LDL-C; (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; (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; 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; 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. Interestingly, since Lnc-MALAT1 expression 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.

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; (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, Inc-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

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**SUPPORTING INFORMATION**

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

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