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ORIGINAL RESEARCH

The Diagnosis and Prognosis Value of Exosomal MascRNA in Patients with Acute Coronary Syndrome

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Objective: MascRNA is involved in regulating the immune inflammatory response, but its role in acute coronary syndrome (ACS) remains unclear. This study aims to investigate the diagnostic and prognostic value of plasma exosomal mascRNA for ACS.

Methods: A total of 140 ACS patients and 50 patient with non-ACS were enrolled. Exosomes were isolated from plasma utilizing ultracentrifugation, and mascRNA expression in exosomes was quantified by qRT-PCR. Major adverse cardiovascular events (MACEs) occurring during the 1-year follow-up after stent implantation were recorded. The diagnostic value of exosomal mascRNA for ACS was evaluated utilizing receiver operating characteristic (ROC) analysis. The association between exosomal mascRNA level and MACEs was assessed by Kaplan-Meier survival analysis and Cox proportional-hazards regression.

Results: Exosomal mascRNA expression was significantly elevated in ACS patients, and positively correlated with Gensini score, white blood cells and age. Exosomal mascRNA demonstrated a diagnostic value for ACS (AUC: 0.763, 95% CI: 0.702–0.824). Combined detection of exosomal mascRNA with cTnI improved the diagnostic preformation for ACS (AUC: 0.866, 95% CI: 0.815–0.916). Exosomal mascRNA expression was higher in patients with MACEs, and patients with high mascRNA exhibited low incidence of MACE-free survival. Cox regression analysis suggested that exosomal mascRNA was independently associated with the risk of MACEs (HR: 3.710, 95% CI: 2.158–6.376, $P < 0.001$).

Conclusion: Plasma exosomal mascRNA has the potential to function as a diagnostic biomarker for ACS and as a predictor for the incidence of 1-year MACEs.

Keywords: mascRNA, exosome, acute coronary syndrome, ACS, biomarker

Introduction

Cardiovascular disease (CVD) represents the leading cause of mortality and morbidity globally, accounting for approximately 30% of all disease-related deaths each year.[1] Acute coronary syndrome (ACS) is one of the most lethal subtypes of coronary heart disease, requiring timely risk assessment and effective therapeutic interventions to improve patient outcomes.[2] Advances in medical techniques, particularly the widespread use of percutaneous coronary intervention (PCI), have significantly reduced mortality of ACS.[3,4] However, the major adverse cardiovascular events (MACEs) after PCI continue to threaten the health and quality of life of ACS patients.[5,6] Therefore, identifying biomarkers that can improve early diagnosis and predict the prognosis of ACS remains an urgent priority.[7]

Exosomes are small extracellular vesicles, with dimensions ranging from 30 to 150 nm, secreted by nearly all cell types. They function as cargo transporters, transferring nucleic acid, proteins, lipids, and other stuffs between cells.[8] Exosomes are integral to numerous biological processes and the pathogenesis of various diseases.[9] The process of exosome biogenesis enables the packaging of molecules from both membranous and cytosolic origins, making them

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reflective of the state of the releasing cell and providing valuable insights into the cellular environment. The encapsulation of proteins and RNAs within exosomes prevents their degradation, making exosomes an ideal source of biomarkers. Advances in exosome isolation techniques have garnered significant attention for their potential in clinical applications. Increasing evidence supports the potential of exosomes as valuable biomarkers for early diagnosis and prognosis assessment in cardiovascular diseases.[10]

MALAT1-associated small cytoplasmic RNA (mascRNA) originates from the nuclear long non-coding RNA MALAT1, is a tRNA-like small non-coding RNA, and is localized in the cytoplasm.[11] While MALAT1 has been extensively studied and shown to influence various cellular processes, including the development of atherosclerosis,[12,13] the function of mascRNA remains largely unknown. Recent research has detected high levels of mascRNA in circulating human peripheral blood mononuclear cells (PBMCs).[14] MascRNA suppresses the production of inflammatory cytokines in LPS-stimulated macrophages by inhibiting the activation of NF-κB and MAPK signaling pathways.[15] In murine models of atherosclerosis, mascRNA deficiency leads to hyperactivity of circulating inflammatory cells and an increased macrophage presence in atherosclerotic plaques, contributing to plaque rupture and thrombosis formation.[16] However, the expression of mascRNA in circulating exosomes remains poorly understood.

Our previous study demonstrated that MALAT1 may serve as a promising biomarker for cardiovascular disease, showing diagnostic potential for ACS patients.[17] However, limited research has evaluated the diagnostic value of mascRNA in cardiovascular disease. This study aims to explore the link between plasma-derived exosomal mascRNA and the occurrence of ACS and its association with adverse cardiovascular events.

Materials and Methods

Study Subjects

This study included 281 patients who underwent coronary angiography at Meizhou People's Hospital from Oct. 2021 to May 2024. The ACS patients were diagnosed according to the 2020 ESC Guidelines for managing acute coronary syndromes,[18] which were characterized by symptoms such as recurrent chest pain at rest or with minimal exertion, as well as severe angina that began or worsened within 4 weeks before the procedure. The exclusion criteria included severe valvular heart disease, severe arrhythmias, acute or chronic inflammation, malignant tumors, autoimmune diseases, and hematologic disorders. The non-ACS group included individuals who were diagnosed without coronary artery disease (CAD) by cardiologists as coronary angiography indicative of stenosis < 50%. This research was approved by the Ethical Committee of Meizhou People's Hospital (Approval No. MPH-HEC 2023-C-34) and was conducted in full accordance with the principles of the Declaration of Helsinki. Informed written consent was collected from each participant. Figure 1 illustrates the study flow.

Plasma Collection

A total of 5 mL of venous blood was obtained from patients prior to PCI and placed in EDTA anticoagulant tubes. The samples were maintained at 4°C for 2 hours. Subsequently, the samples were centrifuged at 300g for 10 minutes, after which the supernatant was collected and aliquoted into centrifuge tubes for exosome isolation.

Exosome Isolation

Exosomes were isolated from plasma by ultracentrifugation techniques (CP100NC, Hitachi), as shown in Figure 2A. In brief, the plasma was subjected to centrifugation at 2000g for 10 minutes, after which the supernatant was collected. This was followed by centrifugation at 10,000g for 30 minutes, and the supernatant was again collected. Subsequently, the sample was centrifuged at 120,000g for 30 minutes, and the supernatant was carefully discarded. The resulting pellet was resuspended in PBS and centrifuged once more at 120,000g for 30 minutes. The supernatant was discarded, leaving the exosomes at the bottom for subsequent experiments. All centrifugation procedures were performed at 4°C.

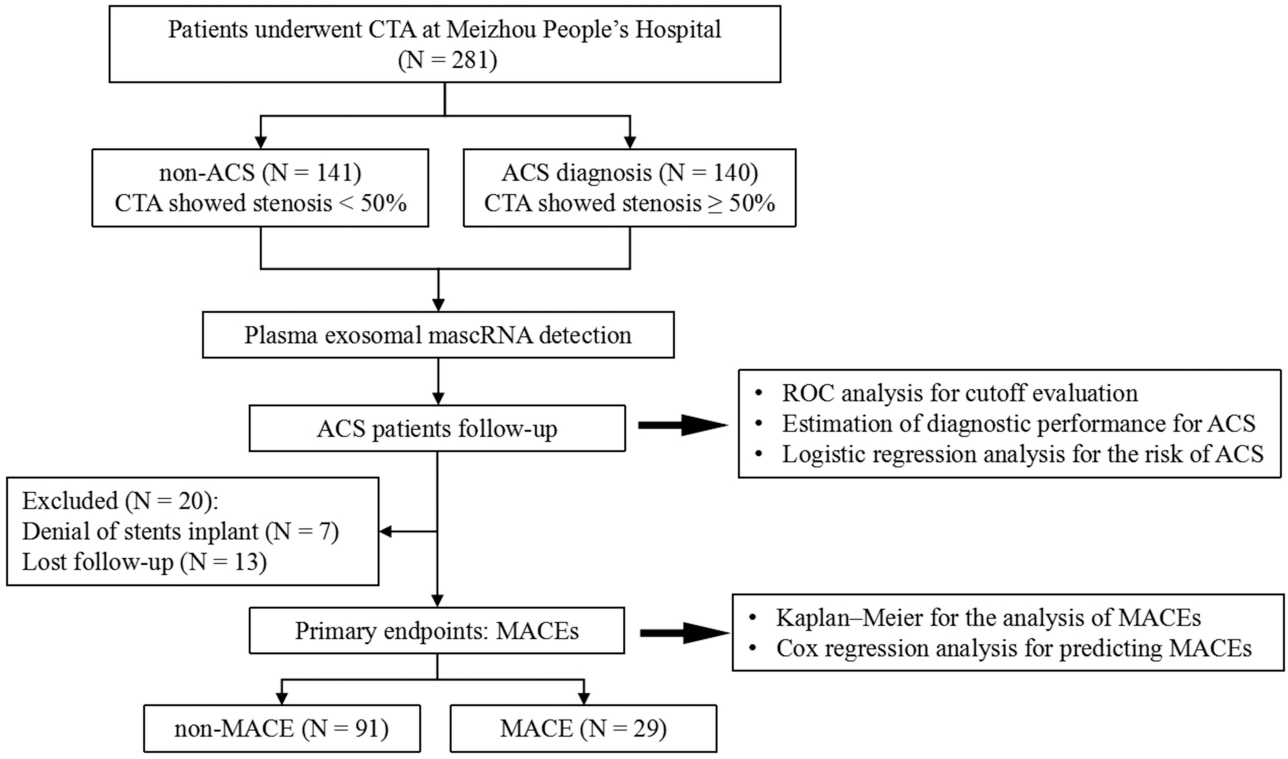

Figure 1 Study flow diagram.

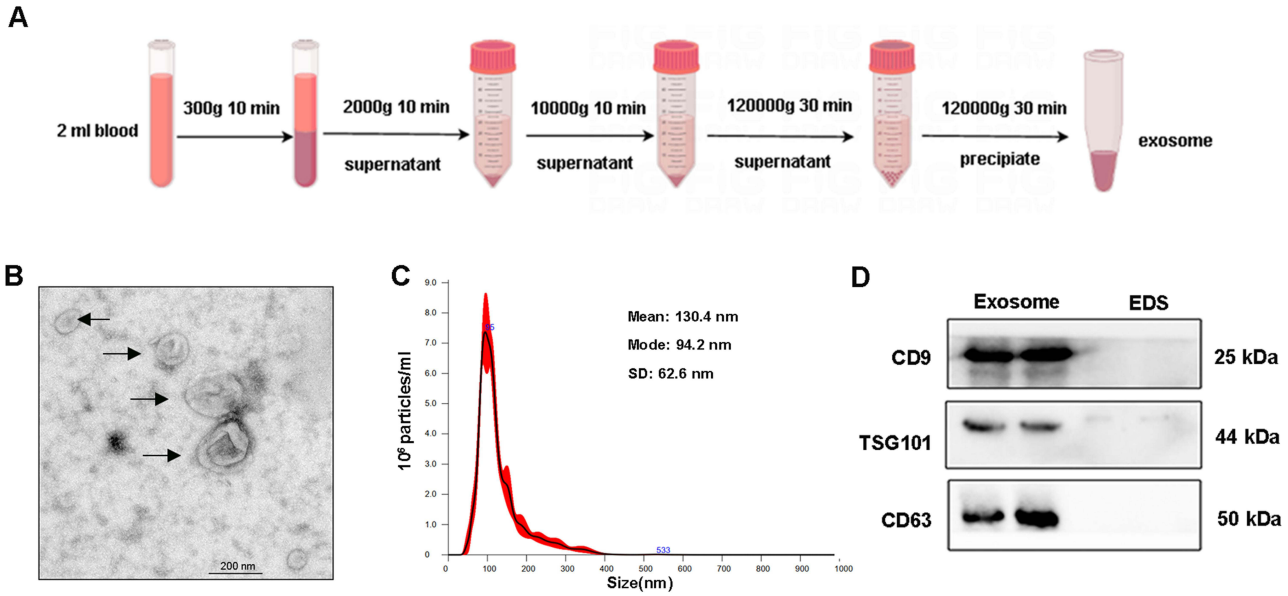

Figure 2 Isolation and characterization of exosomes from plasma. (**A**) Centrifugation protocol for enrichment of plasma exosomes; (**B**) Transmission electron microscopy (TEM) analysis of the exosome morphology. Representative exosomes are indicated by arrows; (**C**) The particle size of exosomes was measured by nanoparticle tracking analysis. (**D**) Western blot analysis of the exosomal markers.

Characterization of Exosomes

The exosomes derived from plasma were characterized using nanoparticle tracking analysis (NTA), Western blotting, and transmission electron microscopy (TEM). For the Western blot analysis, the exosomes were probed with the following primary antibodies: anti-CD9 (1:1000, Cell Signaling Technology), anti-CD63 (1:1000, Cell Signaling Technology), and

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anti-TSG101 (1:1000, Cell Signaling Technology). The NTA was conducted using a NanoSight NS300 instrument (Malvern Panalytical) to evaluate the size, distribution, and concentration of the exosomes. TEM was performed with a JEM-1400 microscope (JEOL, Japan) to examine the ultrastructural features and size of the exosomes.

RNA Isolation and Reverse Transcription-Quantitative Polymerase Chain Reaction (qRT-PCR)

Exosomal RNA was extracted utilizing the SteadyPure Small RNA Extraction Kit (Accurate Biology, China). RNA quality was assessed by measuring the A260/A280 ratio with an ultramicro-spectrophotometer (NP80, IMPLEN, Germany). Complementary DNA (cDNA) was generated by PrimeScript™ RT reagent Kit (Takara, Japan). Exosomal mascRNA expression was determined utilizing the TB Green® Premix Ex Taq™ II and normalized to U6 using the $2^{-\Delta\Delta Ct}$ method.[19] The primer sequences for qRT-PCR were as follows:

mascRNA forward, 5'-GATGCTGGTGGTTGGCACTC-3'; mascRNA reverse, 5'-TGGAGACGCCGCAGGGAT-3'; U6 forward, 5'-CTCGCTTCGGCAGCACA-3'; U6 reverse, 5'-AACGCTTCACGAATTTGCGT-3'.

Clinical Data Collection and Follow-Up

The clinical characteristics of patients were retrieved from the hospital's electronic medical records. Collected variables included age, gender, hypertension, diabetes mellitus, dyslipidemia, left ventricular ejection fraction (LVEF), blood pressure, glucose levels, lipid profiles and blood cell counts.

One-year follow-up data for ACS patients were obtained from electronic medical records or through telephone interviews. The primary outcome measure was the incidence of major adverse cardiovascular events (MACE) including all-cause mortality, nonfatal myocardial infarction, target vessel revascularization, rehospitalization for angina or heart failure, and stent thrombosis.

Statistical Analysis

Statistical analyses were conducted using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Data were presented as mean ± SD or number (percentage). The Shapiro–Wilk test checked the normality of continuous variables. Student's *t*-test was used for continuous variables, and chi-square or Fisher's exact test for categorical variables. The sample size, based on China's ACS incidence of 1%, is approximately 95, with a significance level of $\alpha = 0.05$ and a 2% margin of error. The correlation between exosomal mascRNA and clinical parameters were analyzed by Spearman correlation analysis. Logistic multivariate regression analysis was employed to assess the relationship between exosomal mascRNA and ACS risk. Receiver operating characteristic (ROC) curve analysis was employed to evaluate the diagnostic value of exosomal mascRNA for ACS. The one-year MACE-free survival was assessed using Kaplan–Meier analysis and the Log rank test, while multivariable Cox regression identified predictors of 1-year MACEs in ACS patients. A P-value < 0.05 was considered statistically significant.

Result

Characteristics of Study Subjects

The study included 140 ACS patients and 141 non-ACS, with baseline characteristics summarized in Table 1. There was no difference between the two groups regarding gender, age, hypertension, diabetes mellitus, and dyslipidemia. ACS patients exhibited higher levels of white blood cell (WBC), monocytes, neutrophils, Gensini scores, cTnI ($P < 0.05$), and lower LVEF compared to non-ACS group ($P < 0.05$).

Identification of Plasma Exosomes

Plasma exosomes were isolated utilizing multiple ultracentrifugation steps (Figure 2A). Plasma exosomes exhibited a typical double-layered vesicular structure (Figure 2B), with a mean diameter of approximately 130 nm (Figure 2C). Western blot analysis verified the expression of exosomal protein markers CD9, TSG101 and CD63 (Figure 2D).

Table 1 Baseline Characteristics of Study Subjects

Characteristics	Non-ACS (n = 141)	ACS (n = 140)	*P*
Age (years)	61.01 ± 6.40	65.30 ± 10.70	< 0.001
Sex (female/male)	57 / 84	49 / 91	0.348
Hypertension, n (%)	79 (56.02)	76 (54.28)	0.768
Diabetes mellitus, n (%)	36 (25.53)	34 (24.28)	0.809
Dyslipidemia, n (%)	34 (24.11)	50 (35.71)	0.033
LVEF (%)	61.63 ± 6.80	56.01 ± 11.53	< 0.001
SBP (mmHg)	133.46 ± 17.62	133.03 ± 19.47	0.845
DBP (mmHg)	80.56 ± 11.40	79.87 ± 12.12	0.624
Glucose (mg/dL)	5.82 ± 1.96	7.08 ± 1.32	0.001
TG (mg/dL)	1.86 ± 1.28	1.88 ± 1.30	0.875
TC (mg/dL)	4.66 ± 1.25	4.53 ± 1.17	0.396
LDL-C (mg/dL)	2.71 ± 1.02	2.89 ± 0.89	0.115
HDL-C (mg/dL)	1.19 ± 0.41	1.29 ± 0.50	0.062
WBCs (10^9/L)	724 ± 2.51	9.05 ± 3.40	< 0.001
Neutrophils (10^9/L)	4.88 ± 2.29	6.61 ± 3.20	0.001
Monocytes (10^9/L)	0.28 ± 0.48	0.44 ± 0.49	0.007
Lymphocyte (10^9/L)	1.77 ± 0.74	1.80 ± 0.95	0.739
cTnI (ng/mL)	0.04 ±0.42	11.79 ±18.38	< 0.001
CRP (mg/L)	10.83 ± 25.13	21.48 ± 42.39	0.054
ALB (g/L)	39.87 ± 3.47	38.53 ± 5.59	0.019
FAR	0.084 ± 0.02	0.101 ± 0.04	0.001
NLR	3.22 ± 2.41	4.53 ± 3.40	< 0.001
Gensini score	1.14 ± 1.77	7.50 ± 3.86	< 0.001
Stent number (n)	N.A	1.50 ± 0.66	N.A
Total stent length (mm)	N.A	35.89 ± 16.98	N.A

Abbreviations: LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; cTnI, cardiac troponin I; CRP, C reaction protein; FAR, fibrinogen to albumin ratio; NLR, neutrophil to lymphocyte ratio; N.A, not applicable.

Expression of Exosomal mascRNA in Patients with ACS

Our data suggested that exosomal mascRNA expression was elevated in ACS patients compared to the non-ACS (Figure 3A). However, exosomal mascRNA expression showed no significance between the subgroups of ACS (Figure 3B).

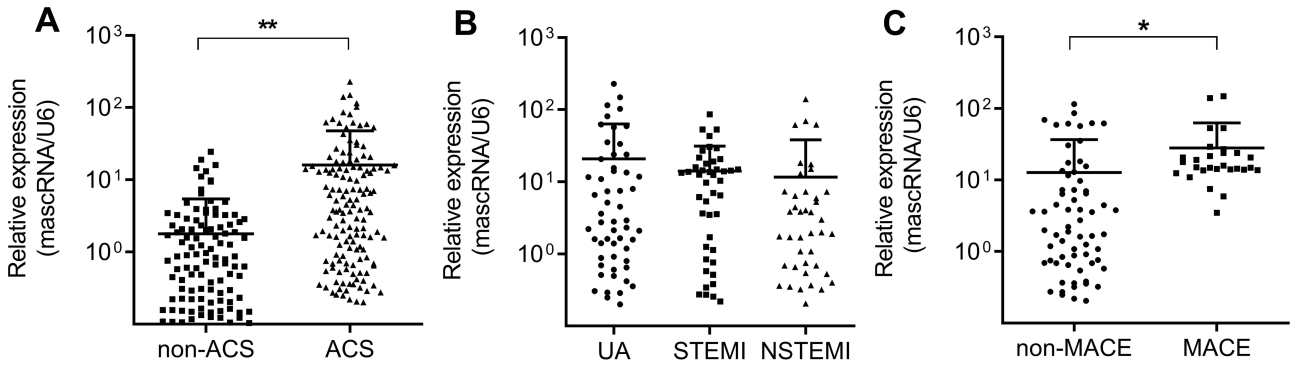

Figure 3 The expression of exosomal mascRNA in patients with ACS. (**A**) Exosomal mascRNA levels in ACS patients and non-ACS patients. $^{**}P < 0.01$, comparison was tested by Student's *t* test; (**B**) Exosomal mascRNA levels in different types of ACS patients. (**C**) Comparison of exosomal mascRNA expression in ACS patients with MACE and non-MACE during the one-year follow-up. $^{*}P < 0.05$, comparison was tested by Student's *t* test.

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We compared the expression of exosomal mascRNA in patients with or without MACEs during the 1-year follow-up period after PCI treatment. A total of 29 ACS patients developed MACEs during the follow-up. Our data showed that mascRNA expression was significantly higher in the MACE group than the non-MACE group (Figure 3C).

Association Between Exosomal mascRNA and Clinical Variables

We further analyzed the association between exosomal mascRNA and clinical parameters. As shown in Figure 4, the Spearman correlation analysis revealed a significant positive correlation between exosomal mascRNA levels and Gensini scores (r = 0.242, $P < 0.001$), LDL (r = 0.173, P = 0.019), WBC (r = 0.183, $P = 0.012$), age (r = 0.164, $P = 0.013$). No significant associations were observed between exosomal mascRNA levels and LVEF (r = −0.120, $P = 0.103$), neutrophil count (r = 0.100, $P = 0.109$), as these differences did not reach statistical significance.

The Diagnostic Value of Exosomal mascRNA for ACS

The diagnostic value of exosomal mascRNA for ACS was evaluated by ROC curve analysis. Our data revealed that exosomal mascRNA serves as a diagnostic predictor for ACS, with an AUC of 0.763 (95% CI: 0.702–0.824) and cutoff value of 1.173 (Figure 5). The predictive performance of mascRNA improved when combined with cTnI, with the AUCs increased to 0.866 (95% CI: 0.815–0.916) (Figure 5).

To illustrate the association of the exosomal mascRNA with ACS risk, its levels were categorized into quartiles (35 patients for each quartiles). Compared with patients in the first quartile for mascRNA expression, patients in the second,

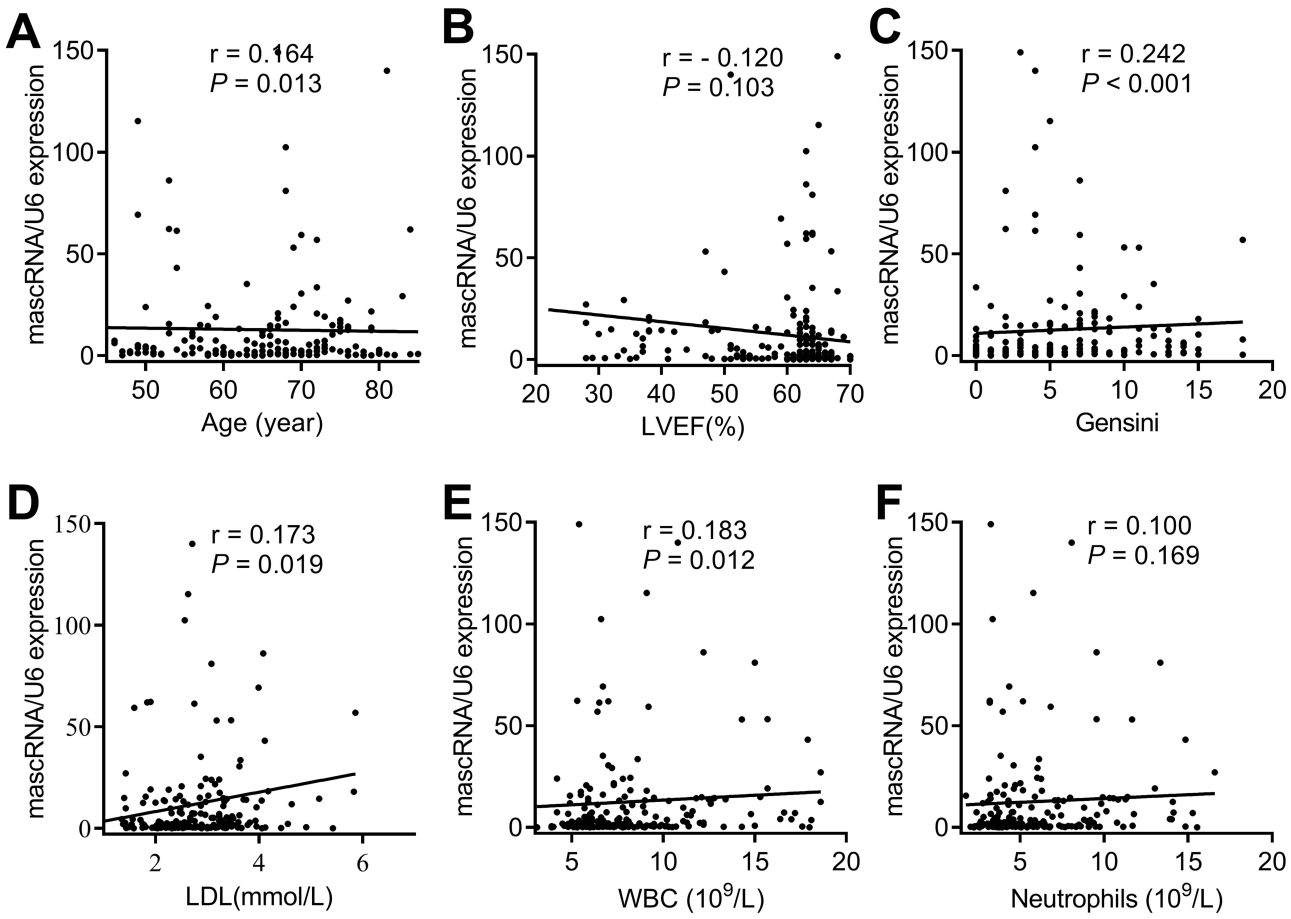

Figure 4 Correlation between exosomal mascRNA and clinical parameters. The correlation between exosomal mascRNA and age (**A**), LVEF (**B**), Gensini score (**C**), LDL level (**D**), WBC (**E**), and neutrophil (**F**) was assessed by Spearman correlation analysis.

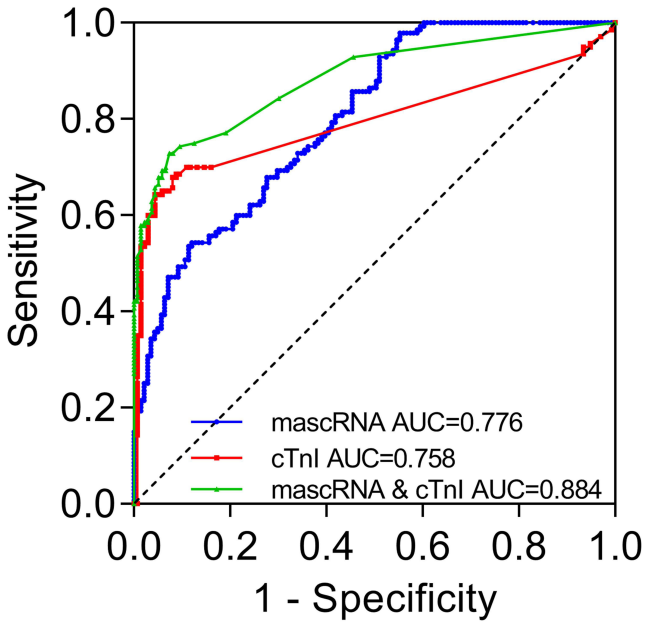

Figure 5 The diagnostic value of exosomal mascRNA for ACS.

third and fourth quartiles exhibited increased ACS risk (OR: 3.423, 95% CI: 1.427–8.213, OR: 5.542, 95% CI: 1.859–16.524 and OR: 9.288, 95% CI: 3.275–26.340, respectively; all $P < 0.01$; Table 2).

The Prognostic Value of Exosomal mascRNA for ACS

We further explored whether the expression of exosomal mascRNA predict the occurrence of MACEs. Patients were divided into high mascRNA group (≥ 3.85, n = 60) and low mascRNA group (< 3.85, n = 60). Kaplan-Meier analysis and Log rank test were utilized to assess the 1-year MACEs-free survival rate between high mascRNA and low mascRNA groups. The data revealed that patients with high mascRNA expression have a lower incidence of MACE-free survival compared to those with low mascRNA expression (long rank $P < 0.001$) (Figure 6).

A multivariate Cox regression analysis was performed to determine association between exosomal mascRNA and MACEs in ACS patients. After adjusted for age, diabetes mellitus and LVEF, mascRNA was significantly associated with the occurrence of 1-year MACEs, with a HR of 2.959 (95% CI: 1.187–4.669, $P < 0.001$) (Tables 3 and 4).

Discussion

ACS is still the leading cause of mortality despite the advances in treatment and diagnostic modalities.[2] Precise diagnosis of ACS is crucial for effective therapeutic intervention and enhancing patient survival rates. The study found that

Table 2 Association Between Exosomal mascRNA Expression and Risk of ACS

Exosomal mascRNA	OR	95% CI	*P**
mascRNA (log10)	4.559	2.970–6.997	< 0.001
mascRNA (quartiles of arbitrary units)			
Q1 (0–0.272)	Reference		
Q2 (0.273–1.250)	8.912	3.188–24.910	< 0.001
Q3 (1.251–6.140)	11.201	3.733–33.621	< 0.001
Q4 (6.141–228.034)	61.795	18.476–206.680	< 0.001

Note: *Adjusted for age, sex, hypertension, and diabetes mellitus.

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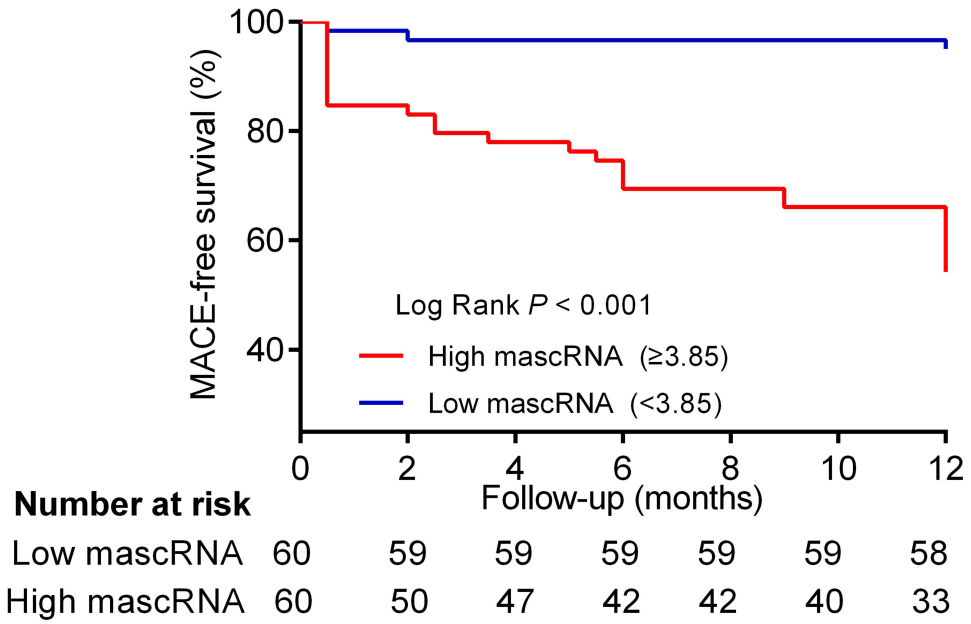

Figure 6 The prognostic value of exosomal mascRNA in patients ACS. The 1-year MACEs-free survival rate between high mascRNA and low mascRNA groups was assessed by Kaplan-Meier curves.

exosomal mascRNA levels were significantly higher in ACS patients and closely linked to ACS risk, suggesting its potential as a diagnostic and prognostic biomarker.

Cardiac troponin (cTnI) is the key plasma biomarker for detecting myocardial injury, with high sensitivity and specificity for diagnosing acute myocardial infarction (AMI). However, its specificity is low in the first 3 hours after symptoms begin, and

Table 3 Clinical Characteristics of Non-MACE and MACE Group in ACS Individuals

Characteristics	Non-MACE (n = 91)	MACE (n = 29)	*P*
Age (years)	63.74 ± 10.58	68.79 ± 11.28	0.029
Sex (male/female)	61 / 30	21 / 8	0.587
Hypertension, n (%)	52 (57.14)	14 (48.27)	0.403
Diabetes mellitus, n (%)	19 (20.87)	6 (20.68)	0.982
Dyslipidemia, n (%)	30 (32.96)	10 (34.48)	0.880
LVEF (%)	57.21 ± 10.26	50.18 ± 13.67	0.017
SBP (mmHg)	133.51 ± 19.73	129.28 ± 21.63	0.328
DBP (mmHg)	81.16 ± 12.34	76.18 ± 12.91	0.060
Glucose (mg/dL)	6.78 ± 2.85	8.55 ± 6.44	0.161
TG (mg/dL)	1.99 ± 1.37	1.56 ± 1.03	0.133
TC (mg/dL)	4.64 ± 1.13	4.30 ± 1.35	0.197
LDL-C (mg/dL)	2.92 ± 0.91	2.85 ± 0.98	0.738
HDL-C (mg/dL)	1.27± 0.44	1.26 ± 0.65	0.903
WBCs (10^9/L)	8.68 ± 3.08	10.41 ± 4.12	0.044
Neutrophils (10^9/L)	6.25 ± 2.85	7.90 ± 3.72	0.035
Monocytes (10^9/L)	0.44 ± 0.49	0.48 ± 0.50	0.404
Lymphocyte (10^9/L)	1.85 ± 0.96	1.79 ± 1.11	0.804
cTnI (ng/mL)	10.12 ± 16.80	23.21 ± 23.01	0.007
CRP (mg/L)	14.81 ± 26.09	42.65 ± 69.03	0.093
ALB (g/L)	38.63 ± 5.44	37.72 ± 6.49	0.481

(*Continued*)

Table 3 (Continued).

Characteristics	Non-MACE (n = 91)	MACE (n = 29)	*P*
FAR	0.09 ± 0.04	0.11 ± 0.05	0.186
NLR	4.11 ± 2.85	5.72 ± 4.54	0.080
Gensini score	7.77 ± 3.62	7.45 ± 3.05	0.668
Stent number (n)	1.49 ± 0.65	1.50 ± 0.66	0.970
Total stent length (mm)	35.28 ± 16.27	37.93 ± 19.36	0.480
Lipid-lowering drug, n (%)	89 (97.80)	28 (96.55)	0.707
Antihypertensive drug, n (%)	72 (79.12)	19 (65.51)	0.136
Antiplatelet drug, n (%)	91 (100)	29 (100)	1.000
Rehospitalization	N.A	8 (27.58)	N.A
Unplanned PCI, n (%)	N.A	13 (44.82)	N.A
Stent thrombosis, n (%)	N.A	0	N.A
Nonfatal MI, n (%)	N.A	6 (20.68)	N.A
Death, n (%)	N.A	2 (6.89)	N.A

Abbreviations: LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cell; cTnI, cardiac troponin I; FAR, fibrinogen to albumin ratio; NLR, neutrophil to lymphocyte ratio; N.A, not applicable.

Table 4 Multivariate Cox Regression Model Analysis of MACEs in ACS Patients

Variables	HR	95% CI	*P*	HR	95% CI	*P**
Age (years)	1.047	1.008–1.087	0.016	1.038	1.005–1.073	0.031
Sex (male/female)	1.577	0.702–3.543	0.270			
Hypertension	0.714	0.348–1.464	0.358			
Diabetes mellitus	0.873	0.357–2.136	0.766	0.529	0.198–1.412	0.204
Dyslipidemia (%)	1.024	0.479–2.188	0.951			
LVEF (%)	0.954	0.929–0.980	0.001	0.955	0.931–0.979	< 0.001
Number of stent	0.995	0.564–1.754	0.986			
Length of stent	1.008	0.986–1.030	0.494			
MascRNA (log10)	3.357	2.042–5.520	< 0.001	2.959	1.187–4.669	< 0.001

Note: *Adjusted for age, LVEF, and diabetes mellitus.

elevated levels can also indicate other conditions such as myocarditis and stress-induced cardiomyopathy.[20,21] Exosomes have attracted increasing interest in the cardiovascular field due to their potential clinical implications. More and more exosome-based biomarkers are identified for diagnosis of cardiovascular diseases.[22–25] This study found that exosomal mascRNA levels were significantly higher in ACS patients, regardless of the type of ACS (UA, STEMI, or NTEMI), and were linked to an increased risk of ACS. MascRNA levels correlated with the Gensini score, LDL, and WBC, which are related to vascular stenosis, inflammation, and lipid metabolism. Notably, although the findings are significant, the correlations are weak, thus more studies would be needed to validate the clinical relevance of mascRNA.

MascRNA is a highly conserved small non-coding RNA originating from the primary transcript of MALAT1.[11] As one of the most abundant lncRNAs, MALAT1 has been established as a crucial regulator in cardiovascular pathological processes.[26–28] Our previous study as well as studies of others suggested that MALAT1 was enriched in exosomes and serve as potential biomarker for coronary heart disease.[29,30] To the best of our knowledge, this study is the first to identify the expression of mascRNA in plasma exosomes. Our data suggested that exosomal mascRNA could distinguish ACS from non-ACS individuals, achieving an AUC of 0.776. Notably, the combination of mascRNA and cTnI markedly enhanced diagnostic performance, achieving an AUC of 0.884, surpassing the efficacy of either marker alone and underscoring its clinical utility. Further investigation is warranted to assess the optimal integration of mascRNA with other established or emerging biomarkers to improve the specificity and accuracy of ACS diagnosis.

The prediction of major adverse cardiovascular events (MACE) is crucial for optimizing treatment strategies in patients with acute coronary syndrome (ACS). Numerous inflammatory biomarkers, such as C-reactive protein (CRP), the neutrophil-lymphocyte ratio (NLR), the fibrinogen/albumin ratio (FAR), and the systemic immune-inflammation index (SII), are gaining prominence in research due to their cost-effectiveness, simplicity, and ease of application.[31–33] Although these inflammatory biomarkers demonstrated a strong correlation with the occurrence of major adverse cardiovascular events (MACEs), their specificity remains problematic. Consequently, predictive biomarkers for MACEs are still limited.[34] This study found that patients with high exosomal mascRNA levels experienced a higher rate of MACEs within a year after PCI treatment, with mascRNA being an independent risk factor (HR = 3.357). This suggests a link between mascRNA and ACS outcomes. While the typical MACE incidence post-PCI is around 10%, our one-year follow-up showed a 20.7% rate (29/140), possibly due to the MACE criteria and the predominance of AMI among ACS patients.

Although the exact mechanisms underlying how mascRNA participated in the pathology of ACS remained unclear, some research suggested that it is in part due to its function on inflammation. Sun et al[35] reported that mascRNA inhibits the activation of NF-κB and MAPK signaling, as well as the production of inflammatory cytokines in macrophages stimulated by LPS. Gast et al[16] found that selective ablation of mascRNA resulted in massive induction of TNF and IL-6 in macrophages, which significantly exacerbated vascular injury compared to wildtype macrophages. Previous studies have shown that endothelial dysfunction is linked to future MACEs. Endothelial dysfunction is a key factor in myocardial infarction and central to all ACS, contributing to atherosclerosis through vasoconstriction, macrophage migration, cellular growth, and inflammation.[36–38] Our prior research indicated that MALAT1 inhibits endothelial inflammation and the interactions between monocytes and endothelial cells through ATG5-mediated autophagy.[13] Since mascRNA is closely associated with MALAT1, mascRNA may also participate in the regulation of endothelial inflammation. Nonetheless, additional investigations are required to elucidate the underlying mechanisms.

This study is subject to several limitations. Firstly, as a single-center investigation with a relatively small sample size and a retrospective design, it is vulnerable to information and selection biases. Consequently, multicenter cohort studies are required to validate our findings. Secondly, this study did not include a comparison of mascRNA levels before and after patient treatment. Future research should assess the changes in mascRNA expression pre- and post-treatment to explore its predictive value for MACEs.

Conclusions

In summary, exosomal mascRNA levels were elevated in the plasma of ACS patients and demonstrated significant diagnostic value for ACS. Furthermore, exosomal mascRNA demonstrated a significant association with the incidence of MACEs in patients ACS, indicating its potential utility as an independent predictor of adverse clinical outcomes.

Abbreviations

ACS, Acute coronary syndrome; cDMA, Complementary DNA; CVD, Cardiovascular disease; LVEF, Left ventricular ejection fraction; MACEs, Major adverse cardiovascular events; mascRNA, MALAT1-associated small cytoplasmic RNA; NTA, Nanoparticle tracking analysis; PBMCs, Peripheral blood mononuclear cells; PCI, Percutaneous coronary intervention; qRT-PCR, Reverse transcription-quantitative polymerase chain reaction; ROC, Receiver operating characteristic; TEM, Transmission electron microscopy; WBC, White blood cell.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This research was granted by the Ethical Committee of Meizhou People's Hospital (MPH-HEC 2023-C-34).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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