Article

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Circ_0049271: A Novel Circular RNA Biomarker for Diagnosis and Prognostic Assessment in Acute Myocardial Infarction

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Background: Acute myocardial infarction (AMI) remains a leading cause of mortality and morbidity worldwide. Early identification of reliable biomarkers is crucial for improving diagnostic accuracy and prognostic assessment in AMI patients. Circular RNAs (circRNAs) have emerged as novel regulators in cardiovascular diseases and may serve as promising biomarkers. Our study aimed to evaluate the expression level of Circular RNA 0049271 (Circ_0049271) and its potential role in diagnosing and predicting acute ST-segment elevation myocardial infarction (STEMI).

Methods: In this prospective cohort study, 188 STEMI patients and 86 healthy controls were enrolled between July 2020 and April 2024. Clinical information, including medical history, biochemical parameters, and cardiac function scores, was collected from all participants. Circ_0049271 expression was quantified using quantitative reverse transcription polymerase chain reaction (qRT-PCR). Spearman's correlation analysis was conducted to assess the association between Circ_0049271 and cardiac troponin I (cTnI) levels. The diagnostic performance of Circ_0049271 for STEMI was evaluated using the receiver operating characteristic (ROC) curve. Additionally, logistic regression was applied to identify associations between various risk factors and STEMI. The Kaplan-Meier method estimated postoperative survival rates, and the Cox proportional hazards regression model analyzed the association between risk factors and the occurrence of major adverse cardiovascular events (MACE) after surgery.

Results: Circ_0049271 expression was significantly elevated in STEMI patients compared to healthy controls and was positively correlated with the myocardial injury marker cTnI ($r = 0.65$, $p < 0.001$). ROC curve analysis demonstrated high diagnostic accuracy for Circ_0049271 [area under the ROC curve (AUC) = 0.9099, 95% confidence interval (CI): 0.8618–0.9579]. Logistic regression identified body mass index, diastolic blood pressure, history of hypertension, low-density lipoprotein, high-sensitivity C-reactive protein, and Circ_0049271 as risk factors for STEMI. Furthermore, Kaplan-Meier analysis and the Cox proportional hazards regression model revealed that high Circ_0049271 expression was associated with an increased risk of MACE after percutaneous coronary intervention (PCI), indicating it as an independent risk factor for the occurrence of MACE.

Conclusion: Elevated Circ_0049271 levels in STEMI patients suggest its potential as a biomarker for the diagnosis and prognosis of STEMI. These findings provide valuable insights into the molecular mechanisms of AMI and suggest that Circ_0049271 could aid in developing more effective diagnostic and prognostic assessment tools.

Keywords: acute myocardial infarction; Circular RNA 0049271; logistic regression; major adverse cardiovascular events; cox proportional hazards regression

Introduction

Acute myocardial infarction (AMI) is a leading cause of cardiovascular disease-related mortality and disability worldwide. Early diagnosis and timely intervention are essential for improving the prognosis of patients with AMI [1]. Traditional biomarkers such as cardiac troponin I (cTnI) and creatine kinase isoenzymes (CK-MB) are widely used for the diagnosis of AMI. However, these biomarkers have notable limitations, including insufficient specificity and narrow diagnostic windows [2]. Additionally, major adverse cardiovascular events (MACE), including recurrent myocardial infarction, angina requiring re-intervention, heart failure, and cardiac death, are critical indicators for assessing the long-term prognosis of AMI patients [3].

With advancements in medical technology, percutaneous coronary intervention (PCI) has become the standard treatment for the acute management of AMI patients, significantly improving coronary blood flow and reducing the incidence of MACE. However, despite PCI treatment, some AMI patients continue to experience MACE, and those with

other cardiovascular conditions may remain at increased risk of in-hospital mortality after PCI. These findings indicate the limitations of current treatment strategies and highlight the need for more accurate biomarkers to predict AMI prognosis and guide personalized treatment [4,5]. Therefore, identifying novel biomarkers with higher specificity and sensitivity is crucial for enhancing the early diagnosis and prognostic assessment of AMI.

Circular RNAs (circRNAs) are a unique class of non-coding RNAs. Their covalently closed-loop structure confers exceptional stability against RNA degradation. Notably, circRNAs have been implicated in diverse biological processes and diseases, particularly in the regulation of cardiovascular pathophysiology [6]. For instance, circRNAs modulate cardiac remodeling and heart failure after myocardial infarction by regulating miRNA activity, influencing gene expression, and participating in protein synthesis [7]. Among them, Circ_0049271 has been recently identified as a circRNA with significantly altered expression in cardiovascular diseases. Although its role in other conditions has been demonstrated, its specific role and biological mechanisms in AMI remain unclear [8,9].

Therefore, this study aimed to investigate the expression level of Circ_0049271 and evaluate its diagnostic and prognostic significance in patients with acute ST-segment elevation myocardial infarction (STEMI). As a major AMI subtype, STEMI is characterized by complete coronary occlusion and distinct electrocardiographic changes. By analyzing the correlation of Circ_0049271 expression with clinical features of STEMI patients and MACE occurrence, this research aimed to provide novel insights for precise therapeutic strategies and improved clinical management of AMI.

Methods

Clinical Information

From July 2020 to April 2024, 188 STEMI patients who visited Huizhou Third People's Hospital were consecutively enrolled in this study, along with 86 age- and sex-matched healthy volunteers who underwent physical examinations at the same hospital during the same period as controls. Basic patient data were collected, including age, sex, body mass index (BMI), heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), history of diabetes, hypertension, hyperlipidemia, smoking, alcohol consumption, family history of coronary artery disease, and medication history (aspirin, clopidogrel, ticagrelor, β-blockers, statins, antihypertensive drugs, and hypoglycemic agents). The Killip classification before PCI was recorded for cardiac function assessment. Laboratory parameters included blood glucose, triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity C-reactive protein (hs-CRP), cTnI, and CK-MB.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) persistent chest pain symptoms or a history of ischemic chest pain; (2) cTnI levels above the upper normal limit; (3) electrocardiographic findings consistent with acute STEMI [10]; (4) admission within 24 hours after symptom onset; (5) age $\geq$18 years; (6) first occurrence of symptoms and undergoing first PCI treatment during hospitalization; (7) availability of complete clinical data.

Exclusion criteria were as follows: (1) previous revascularization therapy (PCI or coronary artery bypass grafting); (2) STEMI caused by coronary artery spasm, myocardial bridging, coronary artery anomalies, or secondary causes; (3) coexisting congenital heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, or rheumatic heart disease; (4) severe pericardial disease; (5) complete or incomplete bundle branch block, intraventricular conduction block, or second- or third-degree atrioventricular block; (6) implanted permanent pacemaker; (7) cardiogenic shock; (8) stent thrombosis; (9) active infection, severe systemic inflammation, or rheumatic immune diseases; (10) significant hepatic or renal dysfunction, respiratory failure, coagulation disorders, malignancies, or psychiatric disorders; (11) recent use of antibiotics, immunosuppressants, or biological enhancers; (12) pregnancy; (13) incomplete clinical data or poor compliance.

A total of 188 STEMI patients were finally included. The study was approved by the Medical Ethics Committee of Huizhou Third People's Hospital (Approval No. 2024-KY-039-01). Written informed consent was obtained from all participants before enrollment. The study was conducted following the principles outlined in the Declaration of Helsinki and its later amendments or comparable ethical standards.

Percutaneous Coronary Intervention

Upon hospital admission, patients were immediately administered 180 mg of ticagrelor (AstraZeneca UK Limited, Cambridge, UK) and 300 mg of aspirin (Bayer AG, Leverkusen, Germany) orally. A coronary angiogram was subsequently performed to identify the infarct-related artery. Following angiography, heparin was administered via the arterial sheath, and thrombi in the coronary embolization area were aspirated. After evaluating blood flow, a stent was implanted at the lesion site. Four hours postoperatively, 75 mg of enoxaparin (Sanofi-Aventis, Gentilly, France) was administered subcutaneously twice daily for seven days. Additionally, patients received 100 mg of aspirin (Bayer AG, Leverkusen, Germany) orally once daily, 90 mg of ticagrelor (AstraZeneca UK Limited, Cambridge, UK) orally twice daily for long-term use, and metoprolol starting at 25 mg/day, gradually increased to 100 mg/day. Statins and angiotensin-converting enzyme (ACE) inhibitors were also administered orally. Patients who had

been on these medications before hospitalization did not receive repeated doses.

Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)

To assess the mRNA expression level of Circ_0049271, 5 mL of venous blood was collected from each subject upon admission and processed under standardized conditions to preserve circRNA stability. After centrifugation at 3000 $\times g$ for 10 minutes at 4 °C within 30 minutes of collection, the resulting serum was used for circRNA extraction and immediately stored at –80 °C until RNA extraction. Complementary DNA (cDNA) was synthesized from circRNA using the PrimeScript RT Reagent Kit (RR036A, Takara, Kusatsu, Japan) according to the manufacturer's instructions. The reverse transcription system consisted of 10 ng of total RNA, 0.15 µL of 100 mM deoxynucleotide triphosphate mixtures (deoxyadenosine triphosphate, deoxyguanosine triphosphate, deoxycytidine triphosphate, and deoxythymidine triphosphate, each at 100 mM), 1 µL of 50 U/µL reverse transcriptase, 1.5 µL of 10× reverse transcription buffer, and 0.19 µL of 20 U/µL ribonuclease inhibitor. The total reaction volume was adjusted to 15 µL using nuclease-free water. The reverse transcription conditions were: 16 °C for 30 minutes, 42 °C for 30 minutes, and 85 °C for 5 minutes. Quantitative polymerase chain reaction (qPCR) was performed using the fluorescent PCR kit (RR820A, Takara, Kusatsu, Japan). The PCR system consisted of a mixture of 10 µL of enzymes and primers, 7.6 µL of nuclease-free water, and 1.4 µL of cDNA. PCR was conducted on a 7900HT Fast Real-Time PCR System (Applied Biosystems, Foster City, CA, USA) with *GAPDH* as the internal control. The qPCR conditions were as follows: 95 °C for 3 minutes, followed by 40 cycles of 95 °C for 15 seconds and 60 °C for 60 seconds. Each sample was tested in triplicate, and relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method. The primers used were as follows: Circ_0049271-F: ATTTTGGGGAGGTCCCTGA, Circ_0049271-R: CACCTTGTGGGCCATGAA; GAPDH-F: GTCTCCTCTGACTTCAACAGCG, GAPDH-R: ACCACCCTGTTGCTGTAGCCAA.

Postoperative Follow-Up

Patients in the STEMI group were followed for 12 months through monthly outpatient visits and weekly phone contacts. The follow-up endpoint was the occurrence of MACE events, including: (1) recurrent angina: angina symptoms with ischemic ST-T segment changes on electrocardiography; (2) recurrent myocardial infarction: myocardial infarction symptoms with electrocardiographic changes and elevated myocardial infarction biomarkers; (3) heart failure: Killip classification III or above; (4) malignant arrhythmias: sustained ventricular tachycardia or ventricular fibrillation on electrocardiography; (5) cardiac death.

Statistical Analysis

Data were analyzed using SPSS 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9.2.0 software (GraphPad Software, San Diego, CA, USA). Normality was assessed using the Shapiro-Wilk test. Data following a normal distribution were expressed as mean ± standard deviation (SD) and compared using an independent samples *t*-test, while non-normally distributed data were expressed as median (interquartile range, IQR) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as proportions (n, %) and analyzed with the Chi-square test. Spearman's correlation analysis was used to assess the association between Circ_0049271 and cTnI. Study participants were stratified into high and low expression groups based on the median gene expression level. The diagnostic efficacy of Circ_0049271 for STEMI was assessed using receiver operating characteristic (ROC) curve analysis. Logistic regression models were applied to identify risk factors for STEMI. Kaplan-Meier survival analysis was used to assess postoperative survival rates, with differences compared using the log-rank test. The life table method was recruited to calculate survival rates, and the Cox proportional hazards regression model was utilized to evaluate the predictive value of risk factors for the occurrence of MACE after surgery. A two-sided $p < 0.05$ was considered statistically significant.

Results

Clinical Information of the Study Subjects

There were no significant differences between the STEMI and the Control groups in terms of age, sex, heart rate, blood glucose, TG, TC levels, history of diabetes, smoking, alcohol consumption, family history of coronary artery disease, and medication history. However, compared to the Control group, the STEMI group had significantly higher BMI, DBP, SBP, proportions of patients with hypertension and hyperlipidemia, and levels of LDL, NT-proBNP, hs-CRP, cTnI, and CK-MB, whereas HDL levels were significantly lower. Clinical characteristics of all subjects are presented in Table 1.

Diagnostic Value of the Circ_0049271 Expression for Acute Myocardial Infarction

The serum expression level of Circ_0049271 was significantly elevated in the STEMI group compared to the Control group (Fig. 1A). Additionally, Circ_0049271 expression was positively correlated with cTnI levels ($r = 0.65$, $p < 0.001$; Fig. 1B). ROC curve analysis was performed, with Circ_0049271 expression as the predictive variable to differentiate STEMI patients from healthy controls. The results revealed that the area under the ROC curve (AUC) for distinguishing between the STEMI group and the Control group was 0.9099 [95% confidence interval (CI): 0.8618–0.9579; Fig. 1C], indicating a high diagnostic accuracy of Circ_0049271.

Table 1. Baseline clinical characteristics of study participants.

Variable	Control (n = 86)	STEMI (n = 188)	Statistics	*p*-value
Age (years)	61.83 ± 7	61.28 ± 6.98	0.598	0.551
Sex (male/female)	48/38	108/80	0.064	0.800
BMI (kg/m^2)	22.17 ± 2.1	24.61 ± 1.58	–10.645	0.000
Heart rate (bpm)	75.17 ± 4.18	75.30 ± 4.39	–0.228	0.819
SBP (mmHg)	126.73 ± 6.79	135.23 ± 7.07	–9.350	0.000
DBP (mmHg)	81.3 ± 4.53	98.48 ± 8.19	–22.262	0.000
Diabetes, n (%)	22 (25.6)	60 (31.9)	1.129	0.288
Hypertension, n (%)	25 (29.1)	89 (47.3)	8.108	0.004
Hyperlipidemia, n (%)	16 (18.6)	70 (37.2)	9.509	0.002
History of smoking, n (%)	48 (55.8)	116 (61.7)	0.851	0.356
History of alcohol consumption, n (%)	61 (70.9)	123 (65.4)	0.811	0.368
Family history of coronary artery disease, n (%)	19 (22.1)	57 (30.3)	1.992	0.158
Medication history, n			8.535	0.201
Aspirin	12	19		
Clopidogrel	7	29		
Ticagrelor	15	22		
β-blockers	11	38		
Statins	8	24		
Antihypertensive medications	15	23		
Hypoglycemic medications	18	33		
Blood glucose (mmol/L)	7.18 ± 0.24	7.18 ± 0.24	0.126	0.900
TG (mmol/L)	1.22 ± 0.21	1.24 ± 0.21	–0.813	0.417
TC (mmol/L)	4.26 ± 0.26	4.25 ± 0.24	0.295	0.768
LDL (mmol/L)	2.91 ± 0.43	3.6 ± 0.41	–12.793	0.000
HDL (mmol/L)	1.15 ± 0.28	0.97 ± 0.14	5.816	0.000
NT-proBNP (pg/mL)	346.30 (312.68–401.11)	1283.50 (638.96–1787.23)	–8.454	0.000
hs-CRP (mg/L)	9.76 (5.19–11.33)	27.41 (23.03–31.38)	–12.059	0.000
cTnI (ng/L)	22.46 (16.91–29.39)	385.33 (333.70–426.06)	–12.994	0.000
CK-MB (ng/mL)	6.63 (3.26–8.46)	21.58 (16.03–27.57)	–13.167	0.000

Note: Values are presented as mean ± SD or median (IQR) for continuous variables and n (%) for categorical variables. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; cTnI, cardiac troponin I; CK-MB, creatine kinase isoenzymes; STEMI, ST-segment elevation myocardial infarction.

Logistic Regression Analysis of Circ_0049271 Expression and Acute Myocardial Infarction

Logistic regression analysis revealed that BMI, DBP, history of hypertension, LDL, hs-CRP, and Circ_0049271 were all associated with STEMI. The relative contribution of these risk factors to STEMI, from highest to lowest, was as follows: LDL, Circ_0049271, BMI, DBP, history of hypertension, and hs-CRP [odds ratio (OR) values: 58.401, 11.666, 3.601, 3.241, 3.193, and 1.232, respectively; Table 2]. These findings indicated that Circ_0049271 (OR = 11.666, 95% CI: 2.883–154.174, p = 0.043) was an independent factor promoting the development of STEMI.

Correlation Between Circ_0049271 Expression and Clinical Characteristics in Acute Myocardial Infarction Patients

Based on Circ_0049271 expression levels in STEMI patients, those with levels above the median were classified as the high-expression group, while those below the median were classified as the low-expression group. There were no significant differences between the two groups in age, sex, BMI, heart rate, SBP, DBP, or proportions of patients with diabetes, hypertension, hyperlipidemia, smoking history, alcohol consumption, or family history of coronary artery disease. Additionally, levels of blood glucose, TG, TC, HDL, and NT-proBNP did not differ significantly. However, the high expression group exhibited significantly higher levels of LDL, hs-CRP, cTnI, and CK-MB, as well as a greater proportion of patients with Killip classification II–IV, compared to the low expression group (Table 3).

Table 2. Logistic regression analysis of risk factors for STEMI.

Variable	B	SE	Wald	*p*-value	OR	95% CI
BMI (kg/m^2)	1.281	0.583	4.827	0.028	3.601	1.148–11.295
DBP (mmHg)	1.176	0.481	5.983	0.014	3.241	1.263–8.315
SBP (mmHg)	0.523	0.312	1.263	0.126	1.236	0.569–3.236
Hypertension	1.647	1.47	1.254	0.023	3.193	1.011–13.438
Hyperlipidemia	0.62	1.675	0.137	0.711	1.859	0.07–49.577
LDL (mmol/L)	4.067	1.588	6.562	0.01	58.401	2.599–1312.052
HDL (mmol/L)	–1.28	2.756	0.216	0.642	0.278	0.001–61.704
NT-proBNP (pg/mL)	0.001	0.002	0.403	0.525	1.001	0.998–1.004
hs-CRP (mg/L)	0.208	0.091	5.243	0.022	1.232	1.03–1.472
Circ_0049271	2.457	1.317	3.479	0.043	11.666	2.883–154.174

Note: SE, standard error; OR, odds ratio; CI, confidence interval; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein.

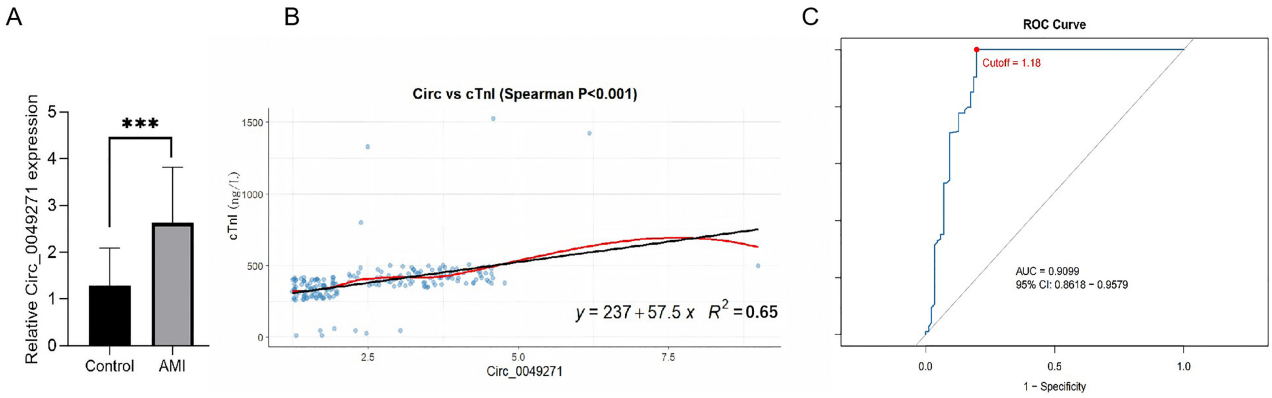

Fig. 1. Diagnostic performance of Circ_0049271 in patients with acute ST-segment elevation myocardial infarction (STEMI). (A) Relative serum expression levels of Circ_0049271 measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR). (B) Correlation between Circ_0049271 expression and cardiac troponin I (cTnI) levels assessed using Spearman's correlation analysis. The black line represents a linear regression fit (y = 237 + 57.5x, R^2 = 0.65), while the red line represents a Locally Estimated Scatterplot Smoothing (LOESS) smooth curve illustrating the non-linear trend. (C) Receiver operating characteristic (ROC) curve analysis of Circ_0049271 expression levels for differentiating STEMI patients (n = 188) from healthy controls (n = 86). The cut-off value was 1.18, with corresponding sensitivity and specificity. ***$p < 0.001$ vs. Control group. AMI, acute myocardial infarction; AUC, area under the ROC curve.

Postoperative Survival Analysis by Circ_0049271 Expression Level

Kaplan-Meier curve analysis revealed that the MACE-free survival period was significantly shorter in the high-expression group than in the low-expression group (p = 0.027, Fig. 2, Table 4).

Cox Proportional Hazards Regression Analysis of Factors Associated With MACE After PCI

Cox regression analysis identified LDL, hs-CRP, cTnI, Killip classification, and Circ_0049271 as independent risk factors for the occurrence of MACE ($p < 0.05$, Fig. 3). Notably, Circ_0049271 exhibited a hazard ratio (HR) of 3.332 (95% CI: 1.86–5.673), indicating that higher expression was significantly associated with an increased risk of MACE. Collectively, these findings suggest that Circ_0049271 may be an important risk factor for the occurrence of MACE.

Discussion

STEMI patients may experience various complications and long-term health issues that significantly impact their quality of life and prognosis [11]. Circ_0049271, as a novel circular RNA, is closely associated with the clinical characteristics and prognosis of STEMI patients. This study demonstrated its potential as a biomarker for diagnosing and predicting outcomes in STEMI.

In AMI, significant alterations in mRNA levels reflect the regulation of gene expression and related biological pro-

Table 3. Association between Circ_0049271 expression levels and clinical characteristics of STEMI patients.

Variable	Low expression group (n = 88)	High expression group (n = 100)	Statistics	*p*-value
Age (years)	61.68 ± 6.76	60.93 ± 7.18	0.736	0.463
Sex (Male/Female)	50/38	58/42	0.027	0.870
BMI (kg/m^2)	24.45 ± 1.78	24.74 ± 1.37	–1.216	0.226
Heart rate (bpm)	75.55 ± 4.4	75.09 ± 4.4	0.708	0.480
SBP (mmHg)	135.03 ± 7.48	135.41 ± 6.72	–0.363	0.717
DBP (mmHg)	97.3 ± 8.79	99.52 ± 7.51	–1.852	0.066
Diabetes, n (%)	33 (37.5)	27 (27.0)	2.374	0.123
Hypertension, n (%)	40 (45.5)	49 (49.0)	0.236	0.627
Hyperlipidemia, n (%)	31 (35.2)	39 (39.0)	0.285	0.593
History of smoking, n (%)	59 (67.0)	57 (57.0)	1.999	0.157
History of alcohol consumption, n (%)	59 (67.0)	64 (64.0)	0.192	0.661
Family history of coronary artery disease, n (%)	26 (29.5)	31 (31.0)	0.047	0.829
Blood glucose (mmol/L)	7.17 ± 0.24	7.18 ± 0.24	–0.404	0.687
TG (mmol/L)	1.22 ± 0.21	1.26 ± 0.2	–1.202	0.231
TC (mmol/L)	4.24 ± 0.24	4.26 ± 0.24	–0.715	0.475
LDL (mmol/L)	3.4 ± 0.23	3.78 ± 0.45	–7.364	0.000
HDL (mmol/L)	0.97 ± 0.14	0.97 ± 0.14	–0.368	0.713
NT-proBNP (pg/mL)	1214.43 (450.89–1794.47)	1343.61 (753.55–1788.23)	–0.717	0.473
hs-CRP (mg/L)	23.92 (20.63–28.39)	30.06 (26.96–34.78)	–6.704	0.000
cTnI (ng/L)	334.15 (286.43–376.22)	419.75 (384.49–458.17)	–8.832	0.000
CK-MB (ng/mL)	17.10 (12.09–22.47)	25.40 (20.09–31.38)	–7.325	0.000
Killip classification, n (%)			17.631	0.001
I	42	41		
II	31	16		
III	10	28		
IV	5	15		

Note: Values are presented as mean ± SD or median (IQR) for continuous variables and n (%) for categorical variables. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; cTnI, cardiac troponin I; CK-MB, creatine kinase isoenzymes.

Table 4. Number at risk for Kaplan-Meier analysis of MACE-free survival in STEMI patients stratified by Circ_0049271 expression levels.

Months	High expression	Low expression
0	100	88
3	92	83
6	82	73
9	64	66
12	49	61

Note: MACE, major adverse cardiovascular events; STEMI, ST-segment elevation myocardial infarction.

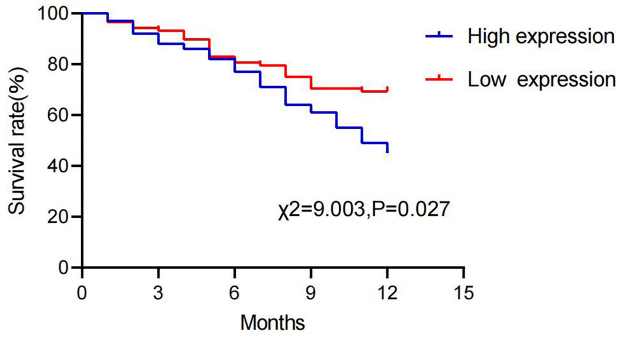

Fig. 2. Kaplan-Meier survival analysis of major adverse cardiovascular events (MACE)-free survival in acute ST-segment elevation myocardial infarction (STEMI) patients stratified by Circ_0049271 expression levels.

cesses underlying the disease [12]. Recent study has also shown that circRNAs exhibit remarkable changes in expression levels during AMI. As non-coding RNAs with a stable circular structure, circRNAs regulate mRNA stability and translation efficiency [13]. Hayward *et al.* [11] reported that circSLC8A1 and circNFIX could serve as auxiliary diagnostic markers for sudden cardiac death caused by acute ischemic heart disease. Furthermore, Shi *et al.* [6] conducted next-generation sequencing of circRNAs in the pe-

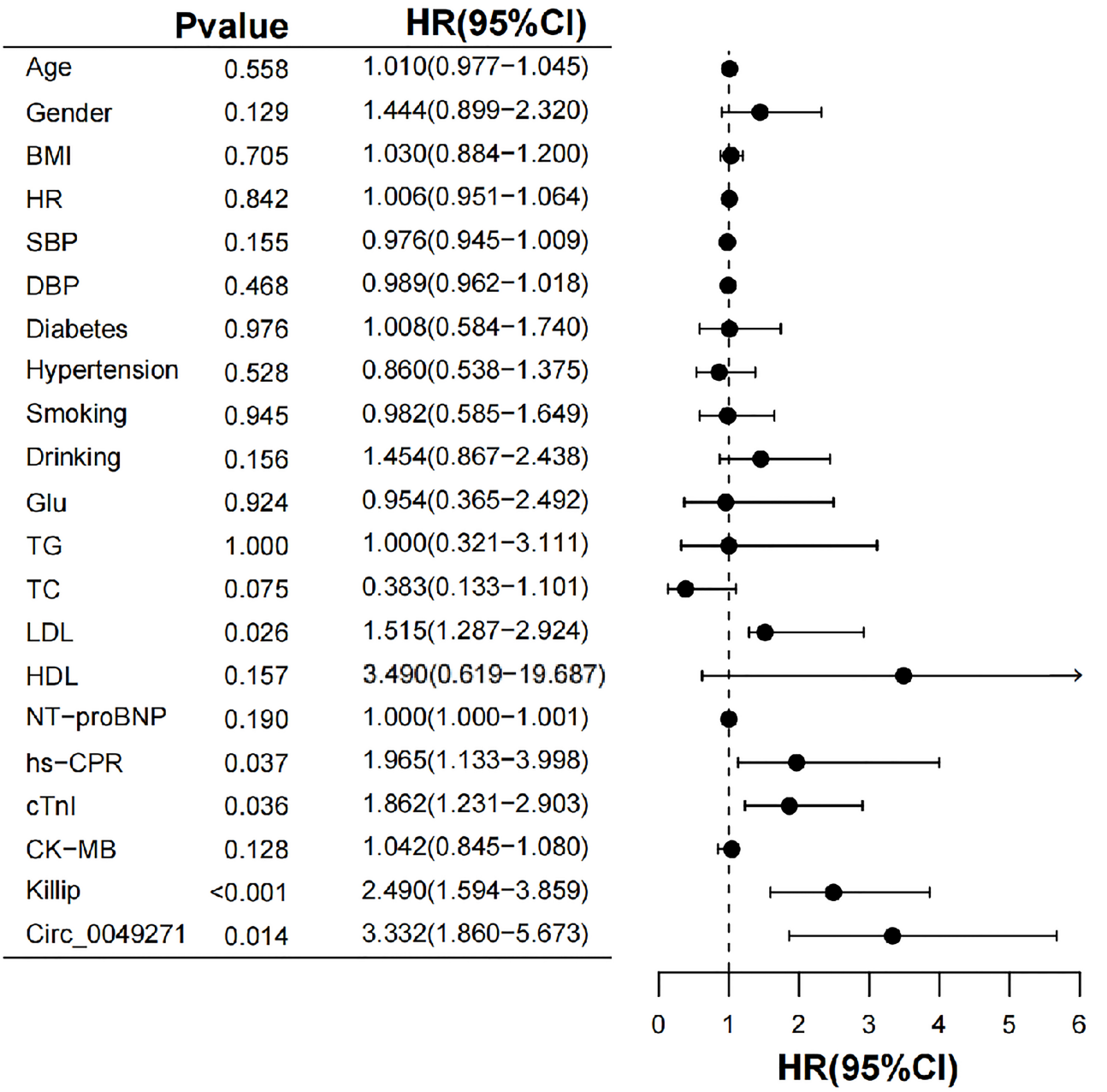

Fig. 3. Cox proportional hazards regression analysis of risk factors for major adverse cardiovascular events (MACE) in STEMI patients post-percutaneous coronary intervention (PCI).

ripheral blood of AMI patients and identified significant expression changes in 3862 circRNAs. Our findings also indicated that Circ_0049271 was highly expressed in STEMI patients, and its expression level was strongly associated with patient prognosis.

Cardiac troponin I (cTnI), a cardiac-specific troponin subtype, is a protein located in myocardial cells and widely used in the diagnosis and management of myocardial infarction (MI) [6]. During AMI, myocardial cell injury leads to the release of cTnI into the bloodstream, and its levels correlate with the severity of myocardial injury [12]. Therefore, routine cTnI testing is essential for the early diagnosis of AMI. Previous studies have explored the role of Circ_0049271 in myocardial injury. Poller *et al.* [14] demonstrated that Circ_0049271 could promote hypoxia/reoxygenation (H/R)-induced myocardial cell injury through the miR-17-3p/FZD4 signaling axis in a 1% H/R-induced AMI rat myocardial cell model. Furthermore, other studies suggest that Circ_0049271 contributes to mitochondrial stress, apoptosis, ferroptosis, angiogenesis, and myocardial remodeling in myocardial cells [15]. Our Spearman correlation analysis revealed that serum Circ_0049271 levels in AMI patients are positively correlated with cTnI levels, indicating that as myocardial injury severity in-

creases, Circ_0049271 expression also rises. This finding suggests that Circ_0049271 could complement existing cTnI testing models, improving the sensitivity and specificity of early STEMI diagnosis.

Furthermore, we examined the correlation between Circ_0049271 expression and clinical characteristics in STEMI patients. We found that patients with high Circ_0049271 expression exhibited elevated levels of LDL, hs-CRP, CK-MB, and higher Killip classification, all of which are recognized risk factors for cardiovascular diseases [16–18]. Moreover, these factors are critical in influencing the prognosis of AMI patients [19–22]. Consequently, we assessed the potential of Circ_0049271 in predicting clinical outcomes for STEMI patients. Kaplan-Meier analysis of MACE-free survival curves for post-PCI revealed significantly shorter MACE-free survival in the high-expression group compared to the low-expression group. These findings indicate that elevated Circ_0049271 expression is closely associated with poor prognosis in STEMI patients. Additionally, the Cox proportional hazards regression model confirmed the value of Circ_0049271 as an independent prognostic factor. Even after adjusting for traditional cardiovascular risk factors such as LDL and hs-CRP, Circ_0049271 expression remains an independent predictor of MACE in STEMI patients post-PCI. These findings suggest that high levels of Circ_0049271 may be associated with adverse clinical outcomes in STEMI, providing a crucial basis for personalized treatment strategies.

Nevertheless, it should be noted that in the logistic regression analysis, the association between Circ_0049271 and STEMI yielded a p-value ($p = 0.043$) close to the conventional threshold for statistical significance. This borderline result may reflect inter-individual variability in Circ_0049271 expression, the relatively limited sample size of this single-center study, and potential residual confounding factors. In contrast, LDL and hs-CRP demonstrated stronger statistical significance, consistent with their well-established roles in STEMI pathophysiology. These observations underscore the need for further validation in larger, multicenter cohorts and mechanistic investigations to validate and clarify the role of Circ_0049271. Patients with elevated Circ_0049271 levels may require more aggressive interventions and closer monitoring to mitigate MACE risk, as well as guidance for the selection and adjustment of medication dosages. Additionally, the expression profile of Circ_0049271 may provide valuable insights for targeted drug development. Researchers could use it to design more precise intervention strategies, enhancing drug efficacy and safety, thereby minimizing adverse effects and improving patient quality of life.

Despite the valuable findings, this study has several limitations. First, this was a single-center study with a relatively small sample size, and the results require validation in larger, multicenter cohorts. Second, the ORs of LDL and Circ_0049271 in the logistic regression model exhibited relatively wide confidence intervals (LDL: 95% CI 2.599–1312.052; Circ_0049271: 95% CI 2.883–154.174), likely due to the limited sample size, inter-individual variability, and the potential influence of unmeasured confounders. These findings highlight the necessity for future studies with larger populations to provide more precise effect estimates. Third, only STEMI patients were included according to our criteria, which may limit the generalizability of our findings to other AMI subtypes, such as NSTEMI. Fourth, Circ_0049271 expression was quantified only at the time of STEMI diagnosis, and its dynamic changes during disease progression (e.g., post-surgery or long-term follow-up) were not analyzed, limiting its reliability as a dynamic monitoring biomarker. Additionally, multiple comparisons were conducted for baseline characteristics without correction for alpha inflation, raising the possibility of Type I errors. Lastly, although we observed correlations between Circ_0049271 and AMI prognosis, the underlying biological mechanisms remain unclear and warrant further investigation. Future studies should investigate the longitudinal changes in Circ_0049271 expression and its potential integration into clinical decision-making for individualized treatment strategies in AMI patients.

Conclusion

This study highlights the potential role of Circ_0049271 in STEMI, proposing it as a novel biomarker to enhance diagnostic accuracy and prognostic monitoring in STEMI patients. Future research should aim to validate these preliminary findings, explore the underlying functions and mechanisms of Circ_0049271 in AMI, and assess its potential as a therapeutic target.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

Study concept and design: HL, CX; Analysis and interpretation of data: WL, WC, DX; Drafting of the manuscript: HL; Statistical analysis: WC, DX; Study supervision: all authors. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Medical Ethics Committee of Huizhou Third People's Hospital (Approval No. 2024-KY-039-01). All procedures involving human participants were conducted in accordance with

the ethical standards of the institutional research committee and with the Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants prior to inclusion in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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