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ORIGINAL RESEARCH

Expression Significance of Serum Circular RNA CDYL and Circular RNA ROBO2 in Patients with Acute Myocardial Infarction and the Value of Their Combined Prediction for Major Adverse Cardiovascular Events

Fang Wang, Rui Liu, Cuirong Zhang, Shenglin Liu

Department of Cardiology, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, 200120, People's Republic of China

Correspondence: Shenglin Liu, Email lsl0076@163.com

Objective: To investigate the expression changes of circular RNAs CDYL and ROBO2 in the serum of patients with acute myocardial infarction (AMI), explore their potential association with the occurrence of major adverse cardiovascular events (MACE), and evaluate the clinical value of their combined detection in predicting MACE after percutaneous coronary intervention (PCI).

Methods: A retrospective cohort study was conducted on 119 AMI patients who underwent PCI (observation group) between February 2023 and February 2024. Based on post-PCI MACE occurrence, patients were categorized into Group A (with MACE, n=47) and Group B (without MACE, n=72). Additionally, 100 healthy volunteers were enrolled as controls. Serum levels of circRNA CDYL and circRNA ROBO2 were measured by quantitative real-time polymerase chain reaction (qRT-PCR). Pearson correlation analysis assessed their relationship. Multivariate logistic regression identified factors independently associated with MACE. Receiver operating characteristic (ROC) curves evaluated the predictive performance of each circRNA and their combination for MACE.

Results: Serum circRNA CDYL was significantly downregulated in AMI patients, while circRNA ROBO2 was upregulated, showing a strong negative correlation ($r = -0.659$, $P<0.001$). The MACE group exhibited lower circRNA CDYL and higher circRNA ROBO2 levels than the non-MACE group ($P<0.05$). Multivariate analysis identified high circRNA ROBO2 as an independent risk factor for MACE, while high circRNA CDYL was a protective factor. The combined detection of both circRNAs predicted MACE with an area under the curve (AUC) of 0.901, significantly outperforming either marker alone (sensitivity=89.74%, specificity=80.51%).

Conclusion: Serum circRNA CDYL and ROBO2 are significantly associated with MACE risk in AMI patients after PCI. Their combined detection shows promising predictive value. However, these findings from a retrospective study are preliminary and require validation in prospective cohorts and further mechanistic investigation.

Keywords: acute myocardial infarction, circRNA CDYL, circRNA ROBO2, combined prediction, MACE

Introduction

Acute myocardial infarction (AMI) remains one of the most severe manifestations of coronary artery disease, characterized by acute coronary ischemia leading to irreversible cardiomyocyte necrosis.[1] Despite advancements in reperfusion therapies, which have reduced in-hospital mortality, AMI survivors face a substantial risk of major adverse cardiovascular events (MACE), including heart failure, recurrent infarction, and cardiac death, significantly impacting long-term prognosis and quality of life.[2,3] The identification of reliable biomarkers for early risk stratification of MACE is, therefore, a critical objective in managing AMI patients.

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Circular RNAs (circRNAs) are a class of endogenous non-coding RNAs characterized by a covalently closed loop structure, conferring high stability and resistance to degradation.[4] Their diverse functions, including acting as microRNA sponges, modulating protein interactions, and regulating transcription, have implicated them in the pathogenesis of various diseases, including cardiovascular conditions.[5,6] Accumulating evidence suggests that specific circRNAs are involved in key processes post-AMI, such as apoptosis, inflammation, and fibrosis, highlighting their potential as biomarkers and therapeutic targets.[7,8]

Among the plethora of circRNAs, CDYL and ROBO2 have emerged as molecules of interest. circRNA CDYL, derived from the chromodomain Y-like (CDYL) gene, has been preliminarily linked to protective roles in certain cellular contexts. For instance, it was reported to mitigate neuronal apoptosis in ischemic stroke models, suggesting a potential cytoprotective function.[9,10] Conversely, circRNA ROBO2, originating from the roundabout guidance receptor 2 (ROBO2) gene, has been associated with promoting pathological processes. Recent studies indicate its upregulation and pro-inflammatory role in cancers and other ischemic injuries.[11–14] However, their expression patterns, clinical significance, and potential association with MACE in the specific context of AMI remain largely unexplored.

Given the postulated but unconfirmed roles of circRNA CDYL and circRNA ROBO2 in ischemic injury, we hypothesized that their serum levels might be altered in AMI patients and associated with clinical outcomes. This study aimed to (1) investigate the serum expression levels of circRNA CDYL and circRNA ROBO2 in AMI patients compared to healthy controls, (2) analyze their association with the occurrence of MACE after percutaneous coronary intervention (PCI), and (3) evaluate their individual and combined predictive value for MACE. By addressing these questions through a retrospective analysis, we seek to provide initial clinical evidence that could guide future prospective and mechanistic investigations into the roles of these circRNAs in AMI.

Materials and Methods

Study Design and Subjects

This was a single-center, retrospective cohort study. A total of 119 patients diagnosed with AMI and treated with PCI in the Department of Cardiology of our hospital from February 2023 to February 2024 were enrolled as the observation group. Additionally, 100 healthy volunteers without a history of cardiovascular or cerebrovascular disease, who underwent routine physical examination at our hospital's Health Examination Center during the same period, were selected as the control group. Among the 119 patients in the observation group, there were 64 males and 55 females, aged 44–73 years, with a mean age of (57.82 ± 7.41) years. In the control group, there were 54 males and 46 females, aged 42–71 years, with a mean age of (57.03 ± 7.25) years. There was no statistically significant difference in gender or age between the two groups ($P > 0.05$), indicating comparability. This study was approved by the Medical Ethics Committee of Shanghai East Hospital, School of Medicine, Tongji University (Approval No.: XNLCJC2502) and strictly followed the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Inclusion and Exclusion Criteria

Inclusion Criteria

(1) Aged 18–80 years, regardless of gender; (2) Meeting the diagnostic criteria for AMI according to the 2020 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Acute Coronary Syndromes,[15] including typical clinical symptoms, ST-segment changes on ECG, and elevated cardiac biomarkers; (3) Underwent PCI within 24 hours of admission; (4) Complete clinical data and follow-up records; (5) Blood samples collected within 24 hours post-PCI and preserved appropriately; (6) Signed informed consent and voluntarily participated in the study.

Exclusion Criteria

(1) Patients with malignant tumors, active infections, autoimmune diseases, or severe liver/kidney dysfunction; (2) History of other diseases affecting cardiac function, such as heart failure, arrhythmias (eg, atrial fibrillation), or cardiomyopathy; (3) History of myocardial infarction, PCI, or coronary artery bypass grafting within the past six months; (4) Obvious cognitive impairment, mental disorders, or inability to comply with follow-up; (5) Hemolyzed,

contaminated, or improperly preserved serum samples affecting detection accuracy; (6) Lost to follow-up or with missing clinical data.

Clinical Data and Sample Collection

Demographic and clinical data, including age, gender, BMI, medical history, infarction site, blood lipid parameters, and coronary angiography findings, were collected from electronic medical records. All data were cross-verified by two independent cardiologists.

Fasting venous blood was collected from patients the morning after PCI and from healthy controls. After clotting, samples were centrifuged at 3000 rpm for 10 minutes. The serum was aliquoted into RNase-free tubes and stored at −80 °C until RNA extraction.

RNA Extraction and qRT-PCR Detection

Total RNA was extracted from serum samples using the TRIzol method, purified as per the protocol, and the concentration and purity were measured using a NanoDrop 2000 UV spectrophotometer. Equal amounts of RNA were reverse transcribed using a reverse transcription kit (Takara, Dalian, China) to synthesize cDNA, followed by qRT-PCR amplification. The total reaction volume for qRT-PCR was 20 μL, including 10 μL of 2×SYBR Green Mix, 1 μL of cDNA template, 0.4 μL each of forward and reverse primers, and RNase-free water to make up the volume. PCR conditions were as follows: pre-denaturation at 95 °C for 30s, denaturation at 95 °C for 5s, annealing/extension at 60 °C for 30s, for a total of 40 cycles. Primer sequences are shown below in Table 1 (synthesized by Sangon Biotech). Relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$ method, with GAPDH as the internal control.

Follow-up Observation and Grouping

The patients in the AMI observation group were followed up for 12 months to assess the incidence of MACE after PCI. Follow-up methods included outpatient visits, telephone follow-ups, and clinical assessments during re-hospitalization due to illness, to ensure a comprehensive record of postoperative conditions. The first follow-up was scheduled at 3 months post-discharge, followed by routine visits every 3 months, totaling four planned follow-ups. Each follow-up focused on identifying MACE events, including but not limited to recurrent myocardial infarction, persistent angina attacks, sudden cardiac death, heart failure, and severe arrhythmias. MACE diagnostic criteria: (1) Recurrent myocardial infarction was diagnosed based on: ① newly developed pathological Q waves with evolving characteristics on ECG; ② cardiac imaging showing newly developed myocardial wall motion abnormalities (eg, thinning or akinesia) not attributable to non-ischemic causes; ③ histological evidence of recent or old infarct lesions. (2) Malignant arrhythmias were diagnosed if: ① polymorphic ventricular tachycardia accompanied by loss of consciousness; ② accelerated ventricular rhythm manifesting as gradually increasing frequency (crescendo VT); ③ monomorphic VT with a frequency >230 bpm; ④ hemodynamic instability caused by ventricular tachycardia, presenting as shock or marked cardiac dysfunction. (3) Heart failure was diagnosed based on: left ventricular ejection fraction (LVEF) ≥50% with decreased cardiac pumping function, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, and clinical features consistent with heart failure. Based on MACE occurrence during follow-up, AMI patients were divided into two groups: Group A (MACE group): 47 patients, including 14 with recurrent myocardial infarction, 15 with malignant arrhythmias, 13

Table 1 Primer Sequences Used for qRT-PCR

Gene	Primer Sequence
circRNA CDYL	F: 5′-AGGTTCTCGATGGCATCCTT-3′ R: 5′-TCAGAGTTCGTGGAGGTTGA-3′
circRNA ROBO2	F: 5′-TGTCCACTTGGAGGAAGAGC-3′ R: 5′-GAGCCTTGACCTCCTCCTCT-3′
GAPDH	F: 5′-GAAGGTGAAGGTCGGAGTC-3′ R: 5′-GAAGATGGTGATGGGATTTC-3’

diagnosed with heart failure, and 5 who died due to cardiac causes. All cases involved a single MACE event, with no overlap. Group B (Non-MACE group): 72 patients with stable conditions and no MACE events during the follow-up period.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 and GraphPad Prism 9.0. Continuous data are presented as mean ± standard deviation and compared using the Student's *t*-test. Categorical data are presented as numbers (percentages) and compared using the Chi-square test. The correlation between circRNA levels was assessed using Pearson's correlation coefficient.

Given the limited number of MACE events (n=47), we acknowledge the potential for overfitting in multivariate models. To mitigate this, variable selection for the logistic regression analysis was guided by clinical relevance and univariate screening ($P < 0.1$). Multivariate logistic regression was used to identify factors independently associated with MACE, with results expressed as odds ratios (OR) and 95% confidence intervals (CI).

Receiver operating characteristic (ROC) curves were constructed to evaluate the discriminatory power of the circRNAs. The DeLong test was used to compare the areas under the curve (AUC). It is important to note that the reported performance metrics (eg, AUC, sensitivity, specificity) and the optimal cut-off values, determined by the Youden's index, were derived from this single dataset without external validation. Consequently, these results are likely optimistic and must be interpreted with caution, as they require validation in an independent, prospective cohort. A two-sided P-value < 0.05 was considered statistically significant.

Results

Baseline Expression of circRNAs in AMI Patients and Association with MACE

The serum level of circRNA CDYL was significantly lower in the AMI observation group compared to the healthy control group, while the level of circRNA ROBO2 was significantly higher ($P < 0.05$, Figure 1). Furthermore, within the AMI cohort, patients who subsequently experienced MACE (Group A) exhibited significantly lower levels of circRNA CDYL and higher levels of circRNA ROBO2 than those who did not (Group B) ($P < 0.05$, Figure 2).

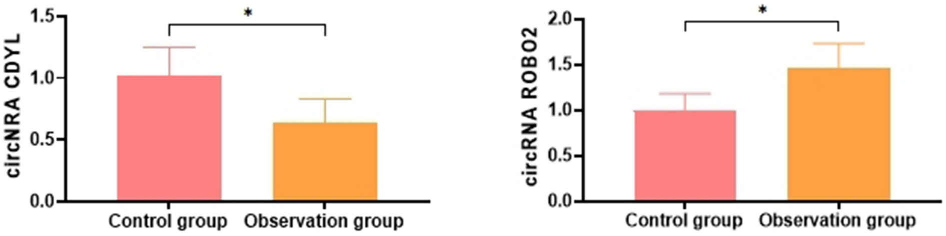

Figure 1 Comparison of circRNA CDYL and circRNA ROBO2 levels between control and observation groups.
Note: Intergroup comparison, *P<0.05.

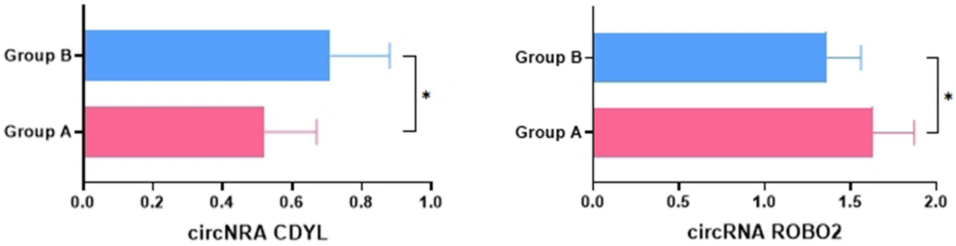

Figure 2 Comparison of circRNA CDYL and circRNA ROBO2 levels between Group A and Group B.
Note: Intergroup comparison, *P<0.05.

Correlation and Multivariate Analysis

A strong negative correlation was observed between serum circRNA CDYL and circRNA ROBO2 levels in the AMI patients ($r = -0.659$, $P < 0.001$, Figure 3). Comparisons of clinical baseline characteristics revealed that the proportion of patients with ≥2 coronary artery lesions and the incidence of intraoperative no-reflow were significantly higher in Group A than in Group B ($P < 0.05$, Table 2). Other clinical parameters, including age, gender, and lipid profiles, were not significantly different between the groups (Table 3).

Multivariate logistic regression analysis, incorporating these significant clinical factors and the circRNA levels, identified ≥2 coronary artery lesions, intraoperative no-reflow, and elevated circRNA ROBO2 as factors independently associated with an increased risk of MACE. Conversely, elevated circRNA CDYL was independently associated with a reduced risk ($P < 0.05$ for all, Table 4).

Predictive Performance and Incremental Value

The predictive performance of the circRNAs for post-PCI MACE was evaluated using ROC analysis. The areas under the curve (AUC) for circRNA CDYL, circRNA ROBO2, and their combination were 0.805, 0.816, and 0.901, respectively (Table 5, Figure 4). The combined model demonstrated superior discriminatory power compared to either circRNA alone (DeLong test: $Z_{\text{combined–circRNA CDYL}} = 2.157$, $P < 0.05$; $Z_{\text{combined–circRNA ROBO2}} = 2.474$, $P < 0.05$).

However, a critical limitation of this analysis is the lack of comparison with established clinical risk scores, such as the GRACE or TIMI scores. Our study did not systematically collect data for calculating these scores. Therefore, the claimed predictive value of the circRNAs, while promising in this cohort, is presented without demonstrating incremental value over the current clinical standard. The observed AUC for the combination model should be interpreted in this context, and its true clinical utility remains to be determined through future validation studies that include direct comparisons with validated risk models.

Discussion

Acute myocardial infarction (AMI) represents a critical manifestation of coronary artery disease, and despite advancements in percutaneous coronary intervention (PCI), the risk of major adverse cardiovascular events (MACE) remains a significant concern for long-term prognosis.[16–18] The pursuit of stable and reliable biomarkers for early risk stratification is, therefore, a key objective in cardiovascular medicine. Circular RNAs (circRNAs), with their inherent stability and tissue-specific expression, have emerged as promising candidates in this field.[19,20] While several circRNAs have been implicated in post-infarction pathological processes,[21,22] the roles of circRNA CDYL and circRNA ROBO2 in AMI are not well defined. This study aimed to preliminarily investigate their serum expression patterns and their potential association with MACE in a retrospective cohort of post-PCI AMI patients.

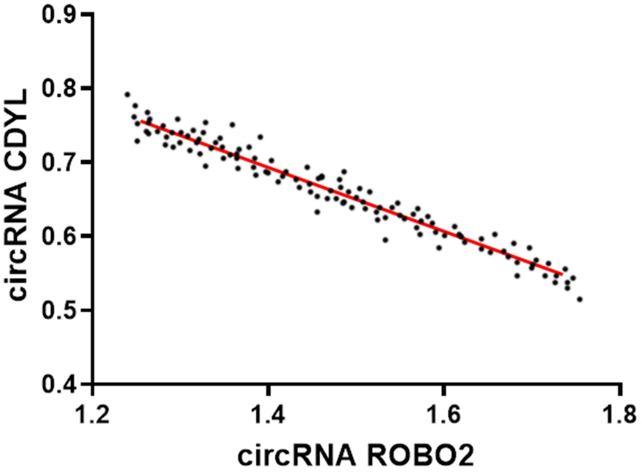

Figure 3 Scatter plot of correlation between circRNA CDYL and circRNA ROBO2.

Table 2 Comparison of Clinical Data Between Patients with (Group A) and Without (Group B) MACE

Clinical Data	MACE Status		t/x^2	*P*
	Group A (n=47)	Group B (n=72)		
Gender	–	–	0.010	0.916
Male	25 (53.19)	39 (54.17)	–	–
Female	22 (46.81)	33 (45.83)	–	–
Age (years)	58.15±7.34	57.69±7.46	0.330	0.741
BMI (kg/m²)	22.38±2.45	22.51±2.38	0.287	0.773
Smoking history	17 (36.17)	32 (44.44)	0.803	0.370
Drinking history	15 (31.91)	25 (34.72)	0.100	0.751
Hypertension	13 (27.66)	22 (30.56)	0.114	0.734
Diabetes	10 (21.28)	17 (23.61)	0.088	0.766
Infarction location	–	–	0.919	0.337
Anterior wall	18 (38.30)	27 (37.50)	–	–
Inferoposterior wall	19 (40.43)	24 (33.33)	–	–
Others	10 (21.28)	21 (29.17)	–	–
Disease type	–	–	0.405	0.524
ST-segment elevation	25 (53.19)	34 (47.22)	–	–
Non-ST-segment elevation	22 (46.81)	38 (52.78)	–	–
TC (mmol/L)	4.85±1.42	4.67±1.15	0.760	0.448
TG (mmol/L)	1.76±0.37	1.81±0.39	0.697	0.486
HDL-C (mmol/L)	0.98±0.21	1.01±0.26	0.662	0.509
LDL-C (mmol/L)	2.68±0.57	2.62±0.61	0.538	0.591
No. of coronary lesions	–	–	13.272	<0.001
<2 vessels	16 (34.04)	49 (68.06)	–	–
≥2 vessels	31 (65.96)	23 (31.94)	–	–
Intraoperative no-reflow	22 (46.81)	15 (20.83)	8.955	0.002

Table 3 Variable Assignment Table

Independent Variable	Assignment
No. of coronary lesions	<2 vessels = 0, ≥2 vessels = 1
Intraoperative reflow	Reflow = 0, No-reflow = 1
circRNA CDYL	Input original value
circRNA ROBO2	Input original value

Table 4 Multivariate Logistic Regression Analysis of Factors Associated with MACE

Factor	*β*	*SE*	*Wald*	*P*	*OR*	*95% CI*
≥2 coronary lesions	0.934	0.412	5.134	0.023	2.544	1.138–5.692
Intraoperative no-reflow	1.181	0.412	8.205	0.004	3.257	1.459–7.272
High circRNA CDYL (High)	−1.206	0.390	9.542	0.002	0.299	0.139–0.643
High circRNA ROBO2 (High)	1.372	0.389	12.441	<0.001	3.943	1.769–8.784

Our principal finding is that serum levels of circRNA CDYL were significantly downregulated, while circRNA ROBO2 were upregulated in AMI patients compared to healthy controls. More importantly, this expression pattern was more pronounced in patients who subsequently developed MACE. The significant negative correlation between them (r = −0.659) suggests a potential, though unverified, interplay and supports their combined evaluation. The functional roles of

Table 5 Predictive Value of circRNAs for MACE After PCI

Marker	Cut-off Value	AUC	95% CI	Sensitivity (%)	Specificity (%)	Youden Index
circRNA CDYL	0.62	0.805	0.727–0.882	78.72	73.61	0.5233
circRNA ROBO2	1.45	0.816	0.740–0.893	80.85	76.39	0.5724
Combined	-	0.901	0.846–0.957	89.74	80.51	0.7025

these circRNAs, as inferred from previous literature, provide a plausible biological context for our findings. circRNA CDYL, derived from the chromodomain Y-like gene, has been studied predominantly in oncology and neurology.[23,24] A study by Zhang et al suggested a protective role in a mouse AMI model, where it was reported to inhibit cardiomyocyte apoptosis via the miR-892b/PI3K/AKT pathway.[25] Our observation of its downregulation in AMI patients, particularly in those with MACE, is consistent with the hypothesis that it might function as a protective molecule, potentially through mechanisms involving anti-apoptosis or inflammation modulation. Conversely, the elevation of circRNA ROBO2 was significantly associated with adverse outcomes. The ROBO2 protein is part of the Slit/ROBO signaling pathway, implicated in angiogenesis and cell migration,[26,27] with recent evidence pointing to its involvement in atherosclerosis and myocardial remodeling.[28,30] For instance, Li et al reported that ROBO2 overexpression post-myocardial ischemia promoted inflammatory responses and worsened dysfunction.[30] Our data, showing that high serum circRNA ROBO2 is independently associated with MACE risk, align with these proposed pro-pathogenic roles.

From a predictive perspective, the ROC analysis indicated that the combination of circRNA CDYL and ROBO2 achieved an AUC of 0.901 in this cohort, which was superior to either marker alone. This suggests that these two circRNAs might capture complementary aspects of the post-AMI pathophysiology. However, the practical utility of these molecules as clinical biomarkers requires critical evaluation. Key aspects such as the long-term stability of these circRNAs in stored serum samples, the inter-assay and intra-assay reproducibility of the qRT-PCR measurements, and the cost-effectiveness of implementing such a test in routine practice were beyond the scope of this study and remain to be thoroughly investigated. Furthermore, multivariate regression identified established clinical risk factors (≥2 coronary lesions, no-reflow) alongside the circRNAs as being independently associated with MACE. While this highlights their potential relevance, it is crucial to state that our study was not designed or powered to demonstrate that these circRNAs

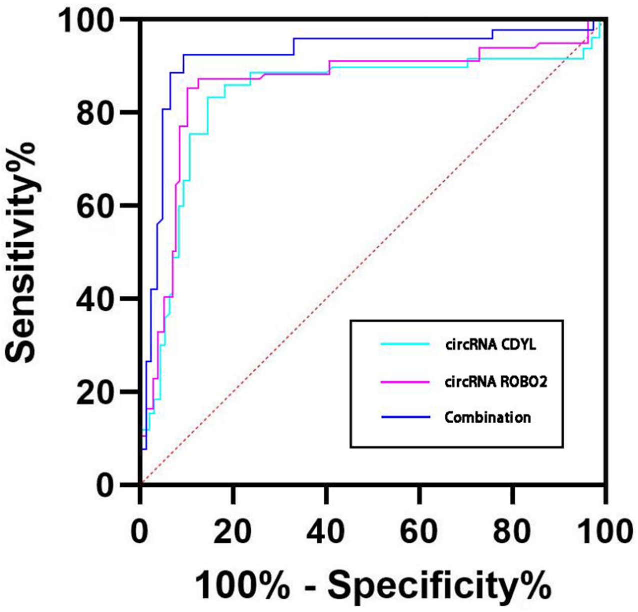

Figure 4 ROC Curves of circRNA CDYL, circRNA ROBO2 Alone and Combined for Predicting MACE After PCI in AMI Patients.

provide incremental predictive value over established clinical risk scores like GRACE or TIMI, as data for these scores were not systematically collected.

Limitations

This study has several important limitations that necessitate a cautious interpretation of the findings. First, its single-center, retrospective design with a relatively small sample size, particularly the MACE subgroup (n=47), inherently carries risks of selection bias and overfitting of the statistical models. The generalizability of our results is therefore limited and requires validation in larger, multicenter, prospective cohorts. Second, the one-year follow-up period is short for capturing the full spectrum of MACE; longer-term outcomes are needed. Third, our analysis is confined to serum measurements, and we lack direct evidence of the expression, cellular sources, or mechanistic roles of these circRNAs in myocardial tissue. Future studies incorporating RNA-protein interaction assays (eg, RIP, RNA pull-down) and functional experiments are essential to elucidate their precise molecular mechanisms. Fourth, as with any observational study, residual confounding cannot be ruled out. We did not account for all potential predictors of outcomes, such as the extent of myocardial necrosis, frailty, valvular disease, or pulmonary comorbidities, which could influence the observed associations.

Conclusions

In conclusion, this retrospective analysis provides preliminary evidence that serum circRNA CDYL and circRNA ROBO2 exhibit inverse expression patterns in AMI patients and are significantly associated with the risk of MACE after PCI. Their combined detection showed promising discriminatory performance in our dataset. However, these findings are inherently preliminary and hypothesis-generating. They should not be construed as supporting immediate clinical changes regarding monitoring or therapy. Rather, they underscore the need for further rigorous validation and mechanistic investigation to determine whether these circRNAs truly have a role in risk stratification or represent epiphenomena. If validated, they could potentially contribute to a multi-molecular risk assessment framework for AMI patients in the future.

Disclosure

The authors report no conflicts of interest in this work.

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