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Circulating microRNA-29 Reflects Remodeling-Related Ventricular Changes in Ischemic Dilated Cardiomyopathy

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SOUHRN

Kontext: Fibrotická remodelace je typickou známkou ischemické dilatační kardiomyopatie (IDKM). Z několika malých nekódujících molekul RNA (microRNA, miR) podílejících se na regulaci extracelulární matrix byla v experimentu miR-29 spojena s expresí kolagenu a transformujícího růstového faktoru β/skupiny proteinů podílejících se na transdukci signálů a regulaci transkripce (transforming growth factor-β/mothers against decapentaplegic homolog 3 related signaling). Profil cirkulující miR-29 při IDKM u člověka a její vztah se strukturou a funkcí dosud nebyly dostatečně popsány. Smyslem této studie bylo kvantifikovat hodnoty miR-29 v plazmě pacientů s IDKM a zjistit, zda se cirkulující miR-29 shodují se zavedenými echokardiografickými ukazateli nepříznivé remodelace komor.
Metody: Do této studie bylo zařazeno 46 pacientů s angiograficky potvrzenou IDKM a 30 zdravých jedinců. Exprese miR-29 v plazmě se určovala metodou RT-qPCR s normalizací miR-103. Při echokardiografickém vyšetření se měřily ejekční frakce (EF), průměr levé komory na konci diastoly (left-ventricular end-diastolic diameter, LVEDD) a průměr levé komory na konci systoly (left-ventricular end-systolic diameter, LVESD). Srovnali jsme obě skupiny, použili Spearmanovy korelace a provedli analýzu ROC a multivariační regresní analýzu.
Výsledky: Hodnoty miR-29 v plazmě byly vyšší při IDKM než u kontrol ($p < 0,001$). Diskriminační analýza prokázala příznivou schopnost odlišení skupiny s IDKM od kontrolní skupiny (AUC = 0,87; 95% CI 0,78–0,94). Ve skupině pacientů s IDKM korelovaly hodnoty miR-29 negativně s EF (r = –0,34; $p = 0,021$) a pozitivně s LVEDD (r = +0,557; $p < 0,001$) i LVESD (r = +0,571; $p < 0,001$). V multivariačních modelech zůstávala hodnota log10(miR-29) nezávisle spojena s EF (β = –1,05 % na každé zvýšení 1-log10; $p = 0,0227$) a s LVEDD (β = +2,14 mm na každé zvýšení 1-log10; $p < 0,001$).
Závěry: Při ischemické dilatační kardiomyopatii je cirkulující miR-29 spojena s nepříznivou dilatací komory a sníženou systolickou funkcí. Tato zjištění ukazují, že cirkulující miR-29 odráží molekulární aktivitu související s remodelací a je spojena regulací extracelulární matrix; uvedená zjištění mohou tak umožnit přesnější poznání remodelační biologie a posloužit jako základ pro formulaci hypotéz budoucích studií zkoumajících stratifikaci pacientů a léčebných postupů zaměřených na signální dráhy.

Keywords:
Extracellular matrix
Echocardiographic indices
Ischemic dilated cardiomyopathy
miR-29
Ventricular remodeling

ABSTRACT

Background: Fibrotic remodeling is a hallmark of ischemic dilated cardiomyopathy (IDCM). Among microRNAs (miR) implicated in extracellular matrix regulation, miR-29 has been experimentally linked to collagen expression and transforming growth factor-β / mothers against decapentaplegic homolog 3 related signaling. However, its circulating profile in human IDCM and its relationship with ventricular structure and function remain insufficiently characterized. The purpose of this study is to quantify plasma miR-29 in patients with IDCM and examine whether circulating miR-29 aligns with established echocardiographic indices of adverse ventricular remodeling.
Methods: This study included 46 angiographically confirmed IDCM patients and 30 healthy individuals. Plasma miR-29 expression was assessed using RT-qPCR with miR-103 normalization. Echocardiographic measurements included ejection fraction (EF), left-ventricular end-diastolic diameter (LVEDD), and left-ventricular end-systolic diameter (LVESD). Group comparisons, Spearman correlations, ROC analysis, and multivariable regression were performed.

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Results: Plasma miR-29 levels were higher in IDCM compared with controls (p <0.001). Discriminatory analysis demonstrated good discriminative performance between IDCM group and control (AUC = 0.87, 95% CI 0.78 – 0.94). Within IDCM patients, miR-29 correlated inversely with EF (r = –0.34, p = 0.021) and positively with LVEDD (r = +0.557, p <0.001) and LVESD (r = +0.571, p <0.001). In multivariable models, $\log_{10}$(miR-29) remained independently associated with EF (β = –1.05% per 1-log10 increase, p = 0.0227) and LVEDD (β = +2.14 mm per 1-$\log_{10}$ increase, p <0.001).
Conclusions: Circulating miR-29 is associated with adverse ventricular dilation and reduced systolic function in ischemic dilated cardiomyopathy. These findings indicate that circulating miR-29 reflects remodeling--related molecular activity linked to extracellular matrix regulation and may provide additional molecular insight into remodeling biology, serving as a hypothesis-generating signal for future studies exploring patient stratification and pathway-directed therapeutic approaches.

Introduction

Heart failure (HF) remains a major global health burden, and despite therapeutic progress, its rates of hospitalization, morbidity, and mortality continue to rise worldwide.[1,2] Among the principal causes of chronic HF, IDCM occupies a central position.[3] IDCM develops from recurrent or unresolved myocardial ischemia, culminating in necrosis, scar formation, and diffuse fibrosis that ultimately promote left-ventricular (LV) dilation and impaired systolic function.[3,4] Fibrotic remodeling represents a key determinant of structural deterioration and clinical outcome in ischemic heart disease, yet detecting early or evolving fibrosis remains challenging because conventional tools rely primarily on advanced imaging or invasive sampling.[5,6] These limitations have intensified interest in circulating molecular biomarkers capable of identifying fibrosis-driven remodeling in a non-invasive and clinically applicable manner.[7]

MicroRNAs (miRNAs) are short, non-coding RNAs that regulate gene expression post-transcriptionally by binding to target mRNAs and influencing translation and stability, reflecting changes in regulatory networks rather than simply downstream protein release.[8,9] They participate in many of the cellular responses that shape cardiac injury and repair including inflammation, angiogenesis, necrosis, hypertrophy, and matrix remodeling and influence multiple pathways involved in post-ischemic ventricular adaptation.[10,11] Their stability in the circulation and predictable detectability makes plasma miRNAs promising indicators of underlying myocardial pathology offering potential insight into underlying myocardial dysfunction.[12,13]

miR-29 is one of several circulating microRNAs detectable in peripheral blood that exhibit remarkable stability, often through encapsulation within extracellular vesicles or binding to protective proteins, making it feasible indicator of gene-regulatory programs engaged during disease progression.[14] Preclinical and cellular studies demonstrate that miR-29 directly represses multiple profibrotic ECM genes, including collagens such as Collagen Type I Alpha 1 (COL1A1) and Collagen Type III Alpha 1 (COL3A1), and that its downregulation is associated with increased collagen expression in fibrotic models, supporting an antifibrotic regulatory role.[15,16] miR-29 expression is tightly modulated by the transforming growth factor-β (TGF-β) / mothers against decapentaplegic homolog 3 (Smad3) signaling axis, a central pathway involved in maladaptive myocardial fibrotic remodeling.[17] Importantly, while these mechanistic data establish miR-29 as a regulator of ECM-related pathways at the tissue level, the extent to which circulating miR-29 reflects myocardial remodeling processes in human cardiomyopathy remains uncertain with previous studies focused on diagnostic classification or heterogeneous heart-failure populations.[13,15,18] To our knowledge, no prior study has specifically examined the association between circulating miR-29 and echocardiographic markers of remodeling severity in IDCM.

Given this consideration, we evaluated circulating miR-29 expression in patients with angiographically confirmed IDCM. The objective of this study was to examine the relationship between plasma miR-29 levels and echocardiographic indices of left-ventricular structure and systolic function, in order to assess whether circulating miR-29 is associated with remodeling patterns commonly linked to fibrotic processes in patients with IDCM.

Material and methods

Study setting and design

The objective of this study was to determine circulating miR-29 levels in patients with IDCM and examine their association with echocardiographic indicators of ventricular remodeling.

Study population

A total of 76 participants were included and allocated into the following groups:

1. **IDCM Group (n = 46)**
   All IDCM patients had prior coronary angiography confirming significant obstructive coronary artery disease consistent with an ischemic etiology. Patients who had undergone revascularization were included, provided that angiographic evidence of prior infarction or residual disease was present. Cases with recent or acute myocardial infarction were excluded to avoid acute--phase changes in circulating miRNAs. IDCM patients had left ventricular ejection fraction (EF) <40% with echocardiographic evidence of chamber dilation (LV end-diastolic diameter [LVEDD] >58 mm, consistent with echocardiographic reference values).

2. **Control Group (n = 30)**
   Controls consisted of healthy, age- and sex-matched volunteers with normal clinical examination and echocardiography.

Exclusion criteria

Exclusion criteria included EF >40%, LVEDD <58 mm, recent or acute myocardial infarction, significant valvular pathology, hypertrophic or restrictive cardiomyopathy, drug-induced or chemotherapy-related cardiomyopathy, isolated right-sided failure, chronic renal or hepatic dysfunction, hematologic and autoimmune diseases, and any acute or chronic inflammatory condition.

Echocardiographic evaluation

All subjects underwent transthoracic echocardiography according to standardized imaging protocols.

- EF was calculated using biplane Simpson method.
- LVEDD and LVESD were measured using M-mode imaging in the parasternal long-axis view.

Measurements adhered to American Society of Echocardiography guidelines, and sonographers were blinded to miRNA results.[19]

Blood collection and sample handling

Peripheral venous blood (10 mL) was withdrawn from each participant.

- Plasma was isolated from EDTA tubes, centrifuged, and stored at –80 °C.
- Serum was collected separately for routine biochemical assessment.

Only plasma samples were used for miRNA analyses. Samples demonstrating hemolysis or poor quality were excluded before processing.

miRNA extraction and quantification

Total circulating miRNA was isolated using the miRNeasy Serum/Plasma Kit (Qiagen, Germany). RNA concentration and purity were verified spectrophotometrically; only samples with acceptable A260/A280 and A260/A230 ratios (1.8–2.1) were included.

cDNA synthesis was performed with the miRCURY LNA miRNA PCR Starter Kit (Qiagen). Quantitative real-time PCR (qRT-PCR) was conducted on the Rotor-Gene Q platform using miRCURY SYBR Green Master Mix. Circulating miR-29 was quantified using a miRCURY LNA–based qRT-PCR assay (Qiagen) specific for hsa-miR-29a-5p according to the manufacturer's instructions. All reactions were duplicated, with repeat analysis performed when replicate Ct values differed by more than 0.3. Melt-curve profiles confirmed specificity, and no-RT and no-template controls were included in each run.

Normalization and data processing

miR-29 expression was normalized to miR-103, selected for its validated stability across study groups. Relative expression was calculated using the 2^–ΔΔCt method (ΔCt = Ct_target – Ct_reference; ΔΔCt = ΔCt_sample – mean ΔCt_controls).[20]

Given the right-skewed nature of circulating miRNA data, log10-transformed values were used for correlation and ROC analyses, whereas untransformed 2^–ΔΔCt values were used for group comparisons for ease of interpretation. All qPCR procedures followed MIQE recommendations.21

Bias minimization

To reduce selection bias, consecutive eligible patients were enrolled, and stringent inclusion and exclusion criteria were applied. Control subjects were clinically screened to exclude any cardiovascular or inflammatory disease.

Laboratory personnel were blinded to clinical grouping. All assays were performed under uniform laboratory conditions. Hemolyzed or suboptimal samples were excluded. Data completeness was ensured before analysis, and missing data (<5%) were handled by case-wise exclusion.

Statistical analysis

Analyses were performed using IBM SPSS Statistics v27 (IBM Corp., NY, USA). Continuous variables were expressed as mean ± SD or median (IQR), depending on distribution; categorical variables were presented as counts and percentages.

Group differences were assessed using:

- independent t-test for normally distributed variables,
- Mann–Whitney U test for non-normal variables, and
- chi-square for categorical comparisons.

Associations between circulating miR-29 and echocardiographic measures (EF, LVEDD, LVESD) were explored using Spearman correlation.

Diagnostic performance of miR-29 for distinguishing IDCM from controls was evaluated using ROC analysis, reporting AUC, sensitivity, specificity, and optimal cutoff (Youden index). Bonferroni correction was applied where appropriate. A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline clinical and echocardiographic characteristics of the study population are summarized in **Table 1**. A total of 76 participants were enrolled, including 46 patients with angiographically confirmed IDCM and 30 healthy controls. IDCM patients exhibited reduced EF and enlarged LV dimensions on echocardiography. Demographic and risk-factor distributions, as well as blood pressure, heart rate, and chamber measurements, are presented in **Table 1.**

Circulating miR-29 expression in IDCM vs controls

Plasma miR-29 expression was markedly higher in IDCM than controls (p <0.001). Because miR-29 values were right-skewed, $\log_{10}$ transformation confirmed stable group separation, indicating robust up-regulation. The median miR-29 level was 14.7 (IQR: 1.11–312.99) in IDCM and 2.96 (IQR: 0.740–4.756) in controls (**Table 2, Fig. 1**).

ROC analysis of circulating miR-29

ROC curve analysis demonstrated a good discriminatory ability of circulating miR-29 between IDCM patients and controls (AUC = 0.87, 95% CI: 0.78–0.94; **Table 3, Fig. 2**). An optimal cut-off value of 1.10 yielded a sensitivity of 74.1% and a specificity of 73.3%.

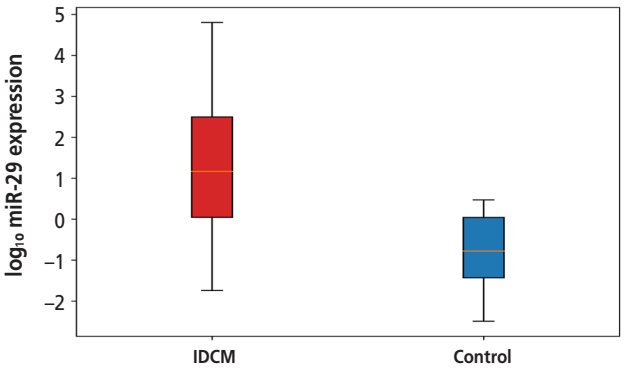

Fig. 1 – Comparison of circulating miR-29 between IDCM and control groups on log_{10} scale

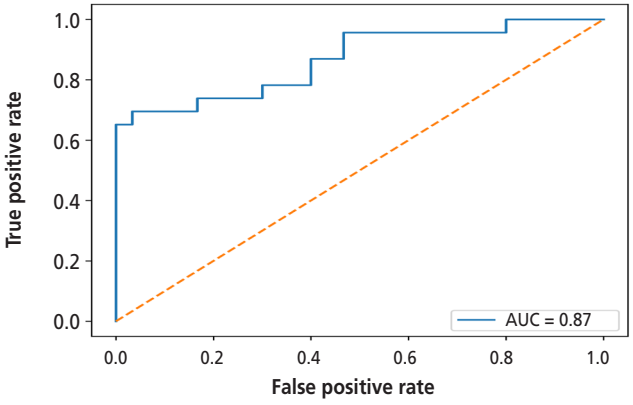

Fig. 2 – Receiver operating characteristic (ROC) analysis for circulating miR-29 in discriminating IDCM patients from healthy controls.

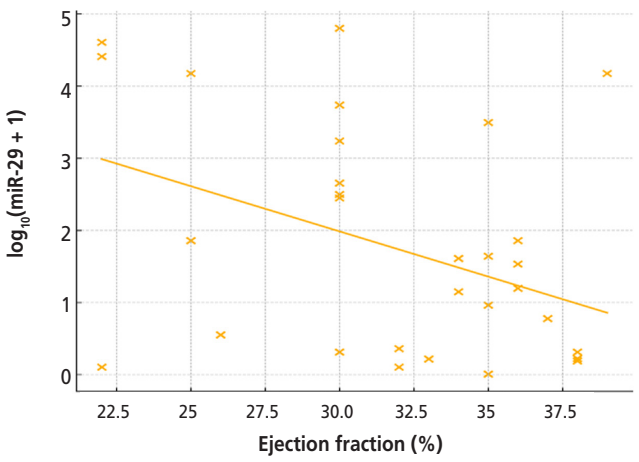

Fig. 3 – Relationship between log_{10}-transformed plasma miR-29 expression and EF in IDCM.

Table 3 – Discriminative (ROC) value of circulating miR-29 for diagnosis of ischemic IDCM

Parameter	Value
AUC (95% CI)	0.87 (0.62–0.85)
Optimal cutoff (miR-29)	1.10
Sensitivity (%)	74.1
Specificity (%)	73.3

The optimal cutoff value was determined using Youden's index. AUC – area under the ROC curve.

Table 1 – Baseline characteristics of IDCM patients and healthy controls

Variable	IDCM (n = 46)	Controls (n = 30)	*p*-value
Age (years), mean ± SD	58.61 ± 7.20	53.10 ± 7.90	0.03
Male sex, n (%)	30 (65.2%)	18 (60.0%)	0.63
HTN, n (%)	34 (73.9%)	0 (0.0%)	<0.001
DM, n (%)	18 (39.1%)	0 (0.0%)	<0.001
Current smoking, n (%)	30 (65.2%)	0 (0.0%)	<0.001
Heart rate (bpm), mean ± SD	81.22 ± 9.77	79.23 ± 12.54	0.47
Systolic BP (mmHg), mean ± SD	128.22 ± 12.09	112.83 ± 13.48	<0.001
Diastolic BP (mmHg), mean ± SD	80.26 ± 6.08	69.52 ± 7.38	<0.001
IVS thickness (mm), mean ± SD	8.9 ± 2.1	7.2 ± 2.5	0.003
LVEDD (mm), mean ± SD	66.43 ± 5.80	45.55 ± 5.67	<0.001
LVESD (mm), mean ± SD	56.54 ± 6.11	26.68 ± 9.32	<0.001
LVEF (%), mean ± SD	32.59 ± 4.57	62.45 ± 6.97	<0.001

Values are presented as mean ± SD or n (%). Continuous variables were compared using independent-samples t test. Categorical variables were compared using chi-square test.

Table 2 – Comparison of circulating miR-29 between IDCM and control groups

miR-29	Median (IQR)	IDCM (n = 46)	Control (n = 30)	*p*-value
		14.7 (1.11–312.99)	0.17 (0.04–1.10)	<0.001

Values expressed as median (IQR). Mann–Whitney U test was used to assess *p*-value.

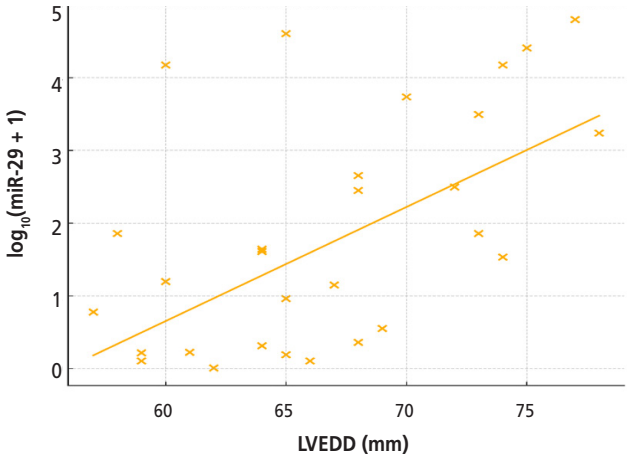

Fig. 4 – Relationship between log_{10}-transformed plasma miR-29 expression and LVEDD in IDCM.

Correlation with echocardiographic parameters

Table 4, and Figure 3 and 4 showed that miR29 was correlated negatively with EF (r = –0.340, p = 0.021) and positively with LVEDD (r = +0.557, p <0.001) and LVESD (r= +0.571, p <0.001).

These findings demonstrate a consistent remodeling pattern: higher miR-29 levels accompany greater chamber dilation and reduced systolic performance.

Multivariable analysis

To evaluate whether these associations were independent of clinical factors, multivariable linear regression models were constructed. After adjustment for age, HTN, DM, and sex, log_{10}(miR-29) remained significantly associated with both systolic function and chamber size. Each 1-log_{10} increase in miR-29 corresponded to a 1.05% lower EF (β = –1.05, p = 0.0227) and a 2.14-mm greater LVEDD (β = +2.14, p <0.001). None of the covariates showed significant associations with EF or LVEDD (**Table 5**).

Association with cardiovascular risk factors

Circulating miR-29 levels did not differ significantly according to the presence or absence of HTN (p = 0.43), DM (p = 0.69), or smoking (p = 0.22) (**Table 6**). These findings indicate that the elevation of circulating miR-29 in IDCM is independent of conventional cardiovascular risk factors.

Table 4 – Correlation between circulating miR-29 and echocardiographic parameters among IDCM patients

Parameter	Spearman r	*p*-value
Ejection fraction (EF)	–0.340	**0.021**
Left ventricular end-diastolic diameter (LVEDD)	+0.557	**<0.001**
Left ventricular end-systolic diameter (LVESD)	+0.571	**<0.001**

Associations evaluated using Spearman's rank correlation. Negative and positive correlation coefficients (r) indicate inverse and direct relationships, respectively.

Table 5 – Multivariable regression models showing independent predictors of EF and LVEDD

Model A: EF as outcome			
Variable	**Coefficient (β)**	**Std. error**	***p*-value**
Intercept	59.4743	7.2497	**<0.001**
log_{10}(miR-29)	–1.0503	0.4481	**0.0227**
Age	–0.0934	0.0893	0.3025
HTN	–1.3446	1.3572	0.3276
DM	–0.8829	1.3121	0.5088
Male sex	–0.5955	1.2363	0.6271
Model B LVEDD as outcome			
Variable	**Coefficient (β)**	**Std. error**	***p*-value**
Intercept	37.0922	3.8814	**<0.001**
log_{10}(miR-29)	+2.1402	0.2646	**<0.001**
Age	+0.0280	0.0471	0.5524
HTN	–0.1727	0.7158	0.8101
DM	–0.0777	0.6930	0.9114
Male sex	+0.5980	0.6487	0.3637

Table 6 – Comparison of circulating miR-29 levels according to clinical risk factors among IDCM patients

Risk Factor	Median (IQR) – yes	Median (IQR) – no	*p*-value
HTN	13.1 (1.0–313.0)	55.3 (2.5–322.7)	0.430
DM	8.2 (1.3–313.0)	23.9 (0.6–322.7)	0.693
Smoking	14.7 (0.7–227.9)	25.5 (4.1–6654.5)	0.217

Data are presented as median (interquartile range, IQR). Comparisons were performed using the Mann–Whitney U test).

Discussion

In our study, circulating miR-29 was significantly elevated in patients with IDCM and showed statistically significant associations with key echocardiographic indices of adverse remodeling. Its inverse correlation with LVEF, together with positive correlations with LVEDD and LVESD, suggests that higher circulating miR-29 levels are observed in parallel with greater ventricular dilation and more advanced systolic impairment.

Although direct fibrosis quantification with cardiac MRI or histology was unavailable, structural indices such as LV dilation and reduced EF are well-established indicators of chronic ischemic remodeling. In longstanding ischemic cardiomyopathy, chamber enlargement and systolic impairment are commonly associated with accumulated scar burden and altered ECM turnover.[3,22]

Circulating miR-29 levels do not necessarily mirror myocardial expression, as they are influenced by signals originating from multiple cell types and injury-related pathways.[23] Rather than serving as a direct surrogate for myocardial expression, circulating miR-29 may reflect the broader molecular environment of post-ischemic remodeling, integrating contributions from fibrosis, inflammation, and ECM turnover.[24,25] Experimental data show that

miRNAs can be exported via extracellular vesicles, released during apoptosis, or actively secreted in response to biomechanical stress or inflammatory signaling.[26,27] Such mechanisms have been described during cardiac injury and fibrosis, supporting the concept that elevations in plasma miR-29 may relate to enhanced ECM turnover or myocardial stress signaling rather than direct tissue expression.[28,29] In this context, circulating miR-29 provides complementary molecular insight into remodeling activity that is not fully captured by clinical assessment, echocardiographic indices, or conventional circulating biomarkers alone.[30]

The elevation of circulating miR-29 in IDCM is biologically plausible given its regulatory influence on major ECM components, including COL1A1, COL3A1, Fibrillin-1, and Elastin, with multiple experimental models demonstrating that suppressing miR-29 promotes collagen accumulation, whereas augmenting its activity can reduce fibrosis burden.[14,15] Chronic ischemia, neurohormonal activation, and scar maturation intensify TGF–β/Smad-mediated fibrotic signaling, which is a major upstream regulator of miR-29 expression.[3,31] Together, these mechanisms provide a coherent biological rationale for why circulating miR-29 may increase in parallel with fibrosis-linked remodeling in IDCM. Importantly, such elevations may reflect engagement of ECM–regulatory signaling or passive release from stressed myocardial tissue

The positive correlations between miR-29 and LVEDD/LVESD, together with its inverse relationship with EF, represent the most clinically relevant observations of this study. Ventricular dilation and systolic impairment are established downstream manifestations of chronic ischemic remodeling, in which ECM disorganization and fibrotic accumulation contribute to adverse chamber geometry and functional decline.[3,32] Ventricular dilation reflects progressive ECM disorganization, impaired architectural integrity, and maladaptive remodeling,[33,34] while lower EF in IDCM reflects both replacement fibrosis from prior infarction and diffuse interstitial fibrosis,[35,36] pathways that are plausibly influenced by ECM-modulating miRNAs such as miR-29. Accordingly, the observed associations between circulating miR-29 levels and LV geometry or systolic function support the concept that circulating microRNAs may serve as accessible indicators of underlying remodeling-related molecular pathways, rather than direct measures of myocardial fibrosis burden.

ROC analysis demonstrated good overall discriminatory performance of circulating miR-29 in distinguishing patients with IDCM from healthy controls. The observed sensitivity and specificity are consistent with the behavior of circulating microRNAs as biologically informative markers reflecting pathway-specific remodeling activity rather than broad disease screening tools.[37,38] In this context, the ROC findings support the interpretation of circulating miR-29 as a remodeling-associated, pathway-informative biomarker.

Circulating miR-29 levels were not significantly influenced by major clinical covariates, including HTN, DM, smoking status, or age. This relative independence from common cardiovascular risk factors reduces the likelihood that the observed associations are driven by systemic confounding, a known limitation in circulating miRNA research.[39] Importantly, the persistence of miR-29's associations with LVEDD and EF after multivariable adjustment strengthens the interpretation that circulating miR-29 relates to ventricular remodeling severity rather than nonspecific clinical burden.

While echocardiography remains central to phenotypic characterization, it does not capture the regulatory pathways driving remodeling progression. In this context, miR-29 provides insight into disease-relevant molecular signaling and ECM regulation, complementing structural and functional assessment without replacing established imaging or clinical markers.

In clinical terms, circulating miR-29, by reflecting engagement of ECM related regulatory pathways, may therefore serve as a molecular indicator of remodeling activity rather than a diagnostic or prognostic marker per se. Importantly, defining such molecular signatures may inform future studies aimed at stratifying patients according to dominant remodeling pathways and exploring pathway-directed therapeutic interventions.

Conclusions

Circulating miR-29 levels were significantly higher in patients with IDCM and were closely associated with indices of adverse ventricular remodeling, including LV dilation and reduced systolic function, independent of major clinical covariates. These findings suggest that miR-29 reflects remodeling-related molecular activity linked to ECM regulation and may provide additional molecular insight into remodeling biology, serving as a hypothesis-generating signal for future studies exploring patient stratification and pathway-directed therapeutic approaches.

Conflict of interest

The authors declare that they have no competing interests.

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Ethical statement

The study was approved by Ethics Committee of the National Research Centre – Ethics Committee: Medical Research Ethics Committee (MREC), National Research Centre (Approval number: 130601109).

Informed consent

Written informed consent was obtained from all individual participants included in the study.

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