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Functional Significance of Cardiac Rehabilitation-Regulated Expression of Circulating MicroRNA-423-5p in Hypertensive Patients with Heart Failure with a Moderately Reduced Ejection Fraction

ORIGINAL INVESTIGATION

ABSTRACT

Background: Hypertension is a vital risk factor for heart failure, while cardiac rehabilitation can effectively improve cardiac function of heart failure patients. This study aimed to determine the impact of cardiac rehabilitation on microRNA-423-5p in hypertensive patients with heart failure with a moderately reduced ejection fraction.

Methods: Sixty hypertensive patients with heart failure with a moderately reduced ejection fraction were randomly divided into cardiac rehabilitation group and positive control group with 30 cases per group, while 30 hypertensive patients without heart failure were recruited as negative control group. The cardiac rehabilitation group and positive control group were treated with 1-month cardiac rehabilitation combined with the routine treatment and routine treatment only, respectively. The New York Heart Association classification, 6-minute walking test, and color Doppler echocardiography were adopted to detect cardiac function. Meanwhile, the expression of microRNA-423-5p and N-terminal pro-B-type natriuretic peptide was determined via Real-Time Fluorescence Quantitative PCR and electrochemiluminescence immunoassay. The diagnostic potential of microR-423-5p and N-terminal pro-B-type natriuretic peptide was assessed by ROC curve analysis and multivariate linear regression model.

Results: Patients in cardiac rehabilitation group displayed significantly lower expression of microR-423-5p and better results of New York Heart Association classification, 6-minute walking test, and color Doppler echocardiography than those in positive control group ($P < .05$). ROC analysis showed that microR-423-5p (AUC = 0.785; 95% CI: 0.686-0.865; sensitivity = 73.33%; specificity = 73.33%) had better specificity and accuracy than N-terminal pro-B-type natriuretic peptide (AUC = 0.721; 95% CI: 0.617-0.811; sensitivity = 81.67%; specificity = 63.33%).

Conclusion: MicroR-423-5p was implicated in left ventricular hypertrophy and might be a potential biomarker for assessing the therapeutic effect of cardiac rehabilitation on hypertensive patients with heart failure with a moderately reduced ejection fraction.

Keywords: MicroRNAs, hypertension, heart failure, cardiac rehabilitation, biological markers

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INTRODUCTION

Heart failure (HF) is the terminal stage of most cardiovascular diseases, which has become a serious epidemic and is the leading cause of hospitalization, morbidity, and mortality in most countries, including China.[1] Di Palo and Barone[2] have clarified that hypertension may be a vital risk factor for HF. Hypertension is a common cardiovascular disease, and long-term elevated blood pressure can eventually lead to the occurrence of progressive HF.[2] At present, the traditional biomarkers including brain natriuretic peptide (BNP) and N-terminal brain natriuretic peptide precursor (NT-proBNP) can facilitate the clinical management of HF, but they are also vulnerable to other factors including age, gender, and renal insufficiency.[3,4] Therefore, a more reliable and objective detection method is required for the treatment of HF.

Several studies have reported that cardiac rehabilitation elicits a marked reduction in the risk of cardio-cerebrovascular events and HF-related hospitalization rate, improves cardiac function and exercise tolerance, repairs endothelial injury, and decreases BNP.[5,6] Polakovičová et al[5] have revealed obvious changes in the expression of several microRNAs (miRNAs) in peripheral blood after cardiac rehabilitation in HF patients. MicroRNAs are a class of endogenous non-coding single-stranded regulatory small RNAs that participate in the occurrence and progression of HF.[7] Compared with traditional protein biomarkers, miRNAs have various advantages of low complexity, high sensitivity and specificity, good measurability, noninvasiveness, long half-life, good stability, and correlation with numerous diseases.[3]

A review found that only 5 miRNAs were identified as biomarkers of HF in more than one study, namely miR-1228, miR-122, miR-423-5p, miR-142-3p, and exosomal miR-92b-5p.[8] The miR-423-5p has been shown to be significantly associated with several clinical diagnostic criteria for HF.[8] Circulating miR-423-5p is a new marker that indicates the progression and prognosis of HF in ischemic cardiomyopathy and dilated cardiomyopathy, and mediates the protective effect of cardiac rehabilitation on cardiovascular diseases.[9-11] Cardiac rehabilitation is a medical intervention designed to improve patient care that not only reduces mortality and morbidity but also improves the life quality of the patients.[12] However, few studies have been conducted to assess the role of miR-423-5p in hypertensive patients with heart failure with a moderately reduced ejection fraction (HFmrEF), and it remains to be determined how cardiac rehabilitation affects circulating miR-423-5p in these patients.

Herein, this study measured and analyzed plasma miR-423-5p levels in hospitalized HFmrEF patients before and after cardiac rehabilitation treatment to investigate the effect of cardiac rehabilitation on plasma miR-423-5p in those patients and its clinical significance.

METHODS

Patients and Data Collection

Totally 60 hospitalized HFmrEF patients from January 2018 to September 2019 were recruited. These participants were divided into cardiac rehabilitation group and positive control group, with 30 cases for each. Depending on the individual patient, one or more antihypertensive drugs were used. We cross-matched the two groups of patients for medication use. Meanwhile, 30 hypertensive patients without HF were selected as the negative control group. The inclusion criteria of both the cardiac rehabilitation and positive control groups were as follows: patients diagnosed with HFmrEF according to the 2016 European Society of Cardiology guidelines[13]; patients had no previous history of HF at the time of hypertension diagnosis; and patients met the Framingham criteria for HF at the time of the study. The inclusion criteria for subjects in the negative control group were a definite diagnosis of hypertension, no previous history of HF, and failure to meet the Framingham criteria for HF at the time of the study. The exclusion criteria for all three groups were as follows: patients with coronary heart disease, pulmonary heart disease, rheumatic heart disease, pregnancy, hemodialysis, severe endocrine disease, severe liver and kidney dysfunction, severe infectious disease, or malignant disease; patients who could not cooperate with the medical staff to complete the examination that needs to be conducted; and patients with unstable medical conditions requiring close monitoring. Demographics and clinical history of all participants were recorded at baseline, including age, gender, smoking, diabetes mellitus, NT-pro-BNP, low-density lipoprotein cholesterol (LDL-C), systolic blood pressure (SBP), and diastolic blood pressure (DBP). The current study was approved by the Ethics Committee, and written informed consent were obtained from all patients, and was conducted in accordance with the 1964 Helsinki Declaration.

Intervention Process

In this study, the cardiac rehabilitation group was treated with 1-month cardiac rehabilitation combined with the routine treatment, while the negative control and positive control groups received the routine treatment only. The course of intervention was 1 month for all three groups.

The cardiac rehabilitation in the study consists of two stages. In the first stage, the medical staffs evaluated patients' general condition, including nutrition, physical condition, and psychological status, before conducting the education and management of physical health, social psychology, and exercise training. During this period, patients were treated with external counterpulsation for 30 minutes once a day. In the second stage, the medical staffs formulated a self-management plan for patients, which involves health education, dietary intervention, behavioral intervention, psychological intervention, and exercise rehabilitation, while providing individualized guidance for patients seeking professional support. Notably, the procedures in the first and second stages were carried out in the hospital and at home, respectively.

Cardiac Function Assessment

The New York Heart Association (NYHA) classification and 6-minute walking test (6MWT) were utilized to evaluate cardiac function in cardiac rehabilitation and positive control groups at baseline and after the intervention.

HIGHLIGHTS

- Cardiac rehabilitation reduces the expression of circulating microRNA-423-5p in patients with hypertension secondary to heart failure.
- Cardiac rehabilitation is beneficial for patients with hypertension secondary to heart failure.
- MiR-423-5p was implicated in left ventricular hypertrophy.
- MiR-423-5p might be a potential biomarker for assessing the therapeutic effect of cardiac rehabilitation on hypertensive patients with heart failure with a moderately reduced ejection fraction.

The NYHA classification includes the following four levels: patients of class I have heart disease but no resulting limited physical activity. Regular physical exercise does not lead to discomfort or pain; patients of class II suffer from cardiac disease, resulting in slight restriction of physical activity; patients of class III have cardiac disease that severely restricts their physical activity; and patients of class IV have cardiac disease, which prevents them from doing any physical activity. Symptoms of HF or anginal syndrome can occur even at rest, while physical activity leads to an increased discomfort.

The 6MWT measures the distance that a patient can walk rapidly on a flat and hard surface within 6 minutes and evaluates the global and integrated responses of various systems involved in the exercise, including cardiovascular systems. Moreover, the 6MWT has been used extensively to assess the sub-maximum level of functional exercise capacity in patients. Given that most patients did not achieve maximum exercise capacity in the test, 6MWT allowed patients to set their own exercise intensity and stop or rest if needed during the process. Since most activities of daily living are conducted at sub-maximum exercise levels, this test can be a better measure for the functional exercise capacity of daily physical activities.[14]

Echocardiography

Echocardiography was adopted to quantitatively evaluate left ventricular functional status and left ventricular hypertrophy (LVH) of all subjects at baseline and after intervention, respectively. The acquired cardiac functional parameters included left ventricular end-diastolic dimension (LVDD), left ventricular ejection fraction (LVEF), and end-systolic volume (ESV). The modified Simpson`s method was used to determine LVEF and ESV.

Real-Time Fluorescence Quantitative PCR (RT-qPCR)

Real-Time Fluorescence Quantitative PCR was used to detect plasma miR-423-5p in all patients at baseline and after the intervention. The whole blood of patients in the cardiac rehabilitation and positive control groups was collected from their elbow veins before and after intervention. Total RNA was extracted from plasma via TRIzol LS® kit (Invitrogen, Carlsbad, USA), and *U6* was utilized as the reference gene. The expression level of miR-423-5p was determined by reverse transcription and subsequent PCR assay in accordance with the manufacturer's protocols.

Electrochemiluminescence Immunoassay

Electrochemiluminescence immunoassay was performed to measure NT-proBNP using Cobase411 platform (Roche Diagnostics, Basel, Switzerland) at baseline and after the intervention. The immunoassay was performed as described in the protocol from the manufacturer. The detection range was 5-35 000 ng/L.

Enzyme-Linked Immunosorbent Assay (ELISA)

Membrane-type-1 matrix metalloproteinase (MT1-MMP), vascular endothelial growth factor (VEGF), and B-cell lymphoma-2 (Bcl-2) at baseline were measured using ELISA detection kits (Amersham Biosciences, Pittsburg, Pa, USA) according to the manufacturer's instructions.

Statistical Analysis

SPSS 16.0 statistical software was adopted for data analysis. Kolmogorov–Smirnov (K–S) method and Levene method were employed for the homogeneity test of variance and normality test, respectively. If the continuous data meet the normality and homogeneity of variance, *t*-test was used for comparison of group means; otherwise, non-parametric test was applied. The continuous data conforming to the normal distribution and skewed data were presented as mean ± SD and medians (interquartile range), respectively. The categorical data were shown as frequency or percentage and were analyzed by χ^2 test and Fisher's exact test. The receiver operation characteristic (ROC) curve method was used to detect the differences between miR-423-5p and traditional biological indicators for predicting HFmrEF, while correlation analysis of rank data was conducted by using the Spearman rank correlation test. Multiple regression analysis was applied in the analysis of factors affecting miR-423-5p expression level. $P < .05$ indicated a statistical significance.

RESULTS

Patient Characteristics

The baseline characteristics of participants were presented in Table 1. No significant differences in age, gender, smoking history, diabetes, LDL-C, SBP, and DBP were noticed among the three groups ($P > .05$).

Table 1. Clinic Characteristics of Patients in Three Groups

Variables	Cardiac Rehabilitation Group (n = 30)	Positive Control Group (n = 30)	Negative Control Group (n = 30)	*P*
Age (years) (mean ± SD)	64.73 ± 8.81	65.17 ± 8.10	63.93 ± 7.81	.842
Gender, n (%)				
Male	15 (50.0)	15 (50.0)	14 (46.7)	.957
Female	15 (50.0)	15 (50.0)	16 (53.3)	
Smoking, n (%)	17 (56.7)	18 (60.0)	17 (56.7)	.955
Diabetes, n (%)	12 (40.0)	14 (46.7)	14 (46.7)	.835
LDL-C (mmol/L)	3.28 ± 1.03	3.23 ± 1.00	3.25 ± 1.15	.982
SBP (mmHg)	140.93 ± 24.21	139.30 ± 24.99	140.73 ± 24.10	.961
DBP (mmHg)	80.33 ± 13.83	82.13 ± 16.62	81.67 ± 14.47	.891

LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Cardiac Function Assessment and LVH Degree

New York Heart Association classification results showed that most patients (73.3%) in the cardiac rehabilitation and positive control groups at baseline were identified as class III-IV patients. Moreover, there were no noticeable differences in 6MWT scores and left ventricular functional parameters between the two groups ($P > .05$). Notably, the treatments led to significant improvements in the NYHA classification, 6MWT scores, and left ventricular functional parameters of patients in the two groups ($P < .05$). After the intervention, only 40.0% of patients in the cardiac rehabilitation group were classified as NYHA class III-IV, while the patients of class III-IV accounted for 56.7% of cases in the positive control group. Meanwhile, compared with the positive control group, significantly more improvements in the 6MWT scores and left ventricular functional parameters were detected in the cardiac rehabilitation group ($P < .05$) (Table 2).

The Expression Levels of HF-Related Factors

From Table 2, both the interventions caused a decrease in VEGF and MT1-MMP, but an enhancement in Bcl-2. Patients in the cardiac rehabilitation group displayed more obvious changes than those in the positive control group ($P < .05$).

The Expression of Circulating miR-423-5p

As shown in Figure 1, the expression of circulating miR-423-5p was noticeably upregulated in cardiac rehabilitation and positive control groups compared with the negative control group ($P < .05$). In addition to improving cardiac function, both the interventions also downregulated circulating miR-423-5p level in the blood of patients in the cardiac rehabilitation and positive control groups, and the reduction in the cardiac rehabilitation group was more significant than that in the positive control group ($P < .05$).

The ROC Curve of Circulating miR-423-5p

To determine whether miR-423-5p and NT-proBNP serve as predictive indicators of HFmrEF, the ROC curve was performed in this study. ROC curve analyses identified an AUC (the areas under the ROC curve) of 0.785 (95% CI: 0.686-0.865; $P = .005$) and 0.721 (95% CI: 0.617-0.811; $P = .019$) for miR-423-5p and NT-proBNP, respectively, suggesting that both factors could be valuable biomarkers for distinguishing HFmrEF patients from healthy individuals (Figure 2). Moreover, circulating miR-423-5p displayed higher predictive specificity and accuracy, but lower sensitivity than NT-proBNP (Table 3).

Association of miR423-5p with Risk Factors of HF and LVH

The association of plasma miR-423-5p level with the risk factors of LVH and HF was analyzed using multivariate linear regression model. The analyses revealed that plasma miR-423-5p was related to following parameters, including NT-proBNP ($\beta = 0.251$, 95% CI = 0-0.001, $P = .012$), 6MWT ($\beta = 0.286$, 95% CI = 0.001-0.014, $P = .024$), NYHA ($\beta = 0.257$, 95% CI = 0.006-0.539, $P = .045$), LVEF ($\beta = 0.324$, 95% CI = 0.019-0.082, $P = .002$), LVDD ($\beta = 0.155$, 95% CI = 0.002-0.051, $P = .034$), and EVS ($\beta = 0.268$, 95% CI = 0.032-0.006, $P = .006$) (Table 4).

DISCUSSION

MiR-423-5p plays a key role in cardiac development and acts as a biomarker of cardiac injury.[9] It can also be used as a diagnostic biomarker for HF in dilated cardiomyopathy[15] and acute HF.[16] In the present study, the ROC analysis showed that circulating miR-423-5p had better specificity and accuracy in response to HFmrEF than NT-proBNP.

In this study, we detected the blood levels of circulating miR-423-5p in the participants before and after intervention

Table 2. Cardiac Function Assessment and LVH Degree of Patients in Two Groups Before and After Treatment

	Cardiac Rehabilitation Group			Positive control group		
Variables	**Before Intervention**	**After Intervention**	***P***	**Before Intervention**	**After Intervention**	***P***
NYHA, n (%)			<.001			.001
I	0 (0)	5 (16.7)		0 (0)	2 (6.7)	
II	8 (26.7)	13 (43.3)		8 (26.7)	11 (36.7)	
III	12 (40.0)	8 (26.7)		13 (43.3)	13 (43.3)	
IV	10 (33.3)	4 (13.3)		9 (30.0)	4 (13.3)	
LVEF	40.00 ± 3.87	50.83 ± 8.45[a]	<.001	40.83 ± 6.37	45.57 ± 5.80	<.001
LVDD	46.83 ± 6.25	39.53 ± 4.58[a]	<.001	44.70 ± 6.09	44.03 ± 5.05	<.001
ESV	63.77 ± 13.75	52.23 ± 12.58[a]	<.001	62.93 ± 13.60	58.93 ± 13.17	<.001
6MWT	394.17 ± 25.02	446.67 ± 35.97[a]	<.001	398.00 ± 25.75	422.33 ± 41.95	<.001
NT-proBNP	1839.60 ± 394.07	915.33 ± 224.35[a]	<.001	1928.77 ± 353.25	1536.23 ± 320.02	<.001
miR-423-5p	2.81 ± 0.85	1.55 ± 0.46[a]	<.001	2.68 ± 0.79	2.04 ± 0.63	<.001
VEGF (ng/L)	146.2 ± 21.8	113.5 ± 19.9[a]	<.001	152.1 ± 20.3	135.2 ± 22.1	<.001
Bcl-2 (ng/mL)	3.2 ± 1.0	6.1 ± 1.2[a]	<.001	3.3 ± 1.2	4.5 ± 1.3	<.001
MT1-MMP (ng/mL)	421.3 ± 63.2	267.4 ± 56.7[a]	<.001	452.7 ± 66.7	375.6 ± 60.5	<.001

[a]$P < .05$ versus positive control group.
NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; ESV, end-systolic volume; 6MWT, 6-minute walking test; miR-423-5p, microRNA-423-5p; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VEGF, vascular endothelial growth factor; Bcl-2, B-cell lymphoma-2; MT1-MMP, membranetype 1 matrix metalloproteinases.

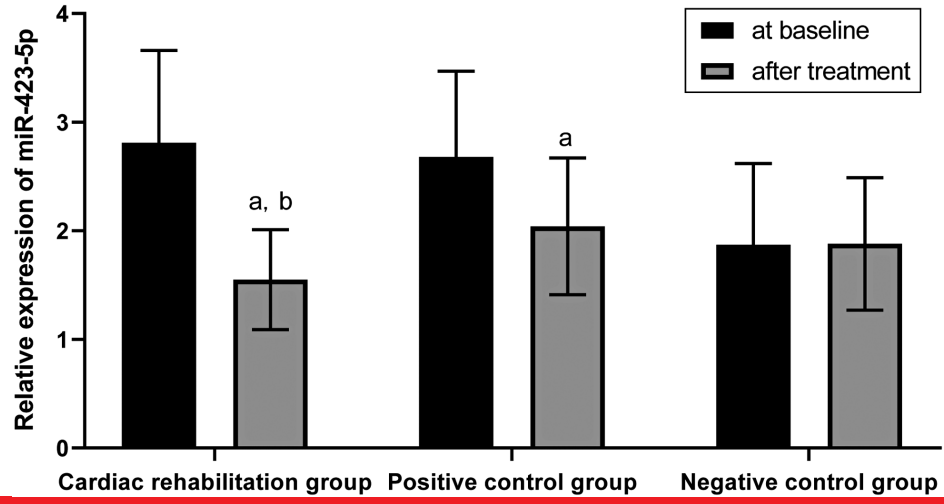

Figure 1. Relative expression levels of miR-423-5p in the three groups at baseline and after the treatment. miR-423-5p, microRNA-423-5p; [a]$P<.05$ vs. before treatment, [b]$P<.05$ vs. the positive control group.

and found that miR-423-5p expression was upregulated in HFmrEF patients, but downregulated in those with improved cardiac function. Multivariate linear regression analysis revealed the association between miR-423-5p expression and NT-proBNP. These findings showed that miR-423-5p could effectively indicate the cardiac function of hypertensive patients. However, a previous study excluded circulating miR-423-5p as a biomarker of systemic ventricular function after atrial repair in adults with transposition of the great arteries.[17] The above observations suggest that miR-423-5p may only be effective in detecting the cardiac function of patients with HF. Consistent with the present study, Tijsen et al[10] pointed out that serum miR-423-5p level in HF patients was higher than that in healthy individuals, while being markedly correlated with NT-proBNP level and NYHA classification, suggesting that serum miR-423-5p might be a potential biomarker of chronic HF (AUC = 0.91). Herein, this study showed that miR-423-5p was remarkably associated with the NYHA classification and 6MWT scores, as well as LVH parameters including LVEF, LVDD, and EVS. Given that the left ventricle is the primary target of hypertension end-organ damage,[18] and hypertension often causes LVH and secondary HF, our results further demonstrated that miR-423-5p could be a predictor of HFmrEF.

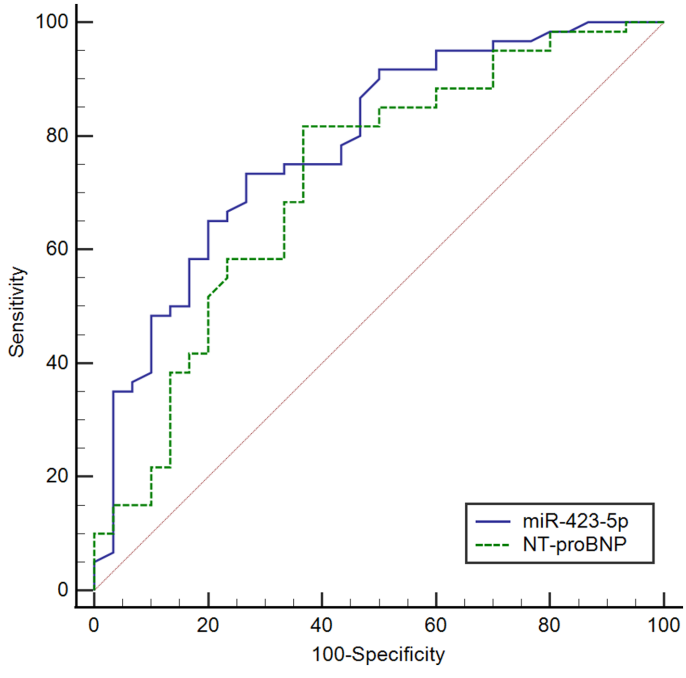

Figure 2. The ROC curve analysis of miR-423-5p and NT-proBNP for diagnosis of HF secondary to hypertension. miR-423-5p, microRNA-423-5p; NT-proBNP, N-terminal pro-B-type natriuretic peptide

In this case, compared with the routine treatment only, the cardiac rehabilitation combined with the routine treatment could better improve cardiac function of HFmrEF patients. Besides, similar results were found in the expression levels of HF-related factors. In hypertensive patients, reduced cardiac function was accompanied by marked changes in VEGF, Bcl-2, and MT1-MMP. With improved cardiac function and decreased miR-423-5p expression level, the above factors changed accordingly. Numerous studies have shown that MT1-MMP is related to blood pressure and HF, while being involved in tissue remodeling and inducing cardiomyocyte fibrosis.[19] Abnormal regulation of MT1-MMP can lead to collagen accumulation in the extracellular matrix, thereby triggering myocardial fibrosis.[20] Vascular endothelial growth factor, a powerful indicator of vascular endothelial permeability and proliferation, participates in microvascular remodeling in hypertension. Studies have shown that VEGF expression in HF patients is noticeably upregulated, which may be attributed to impaired endothelial function, blood hypercoagulability, and tissue hypoxia.[21,22] B-cell lymphoma-2 is an anti-apoptotic protein localized in the outer mitochondrial membrane and participates in HF progression.[23,24] Analysis of the expression of VEGF, Bcl-2, and MT1-MMP in this research revealed that miR-423-5p was a good predictor of HFmrEF, which could accurately indicate an improved cardiac

Table 3. The ROC Curve Characteristics of Two Biological Indicators for Diagnosis of Heart Failure Secondary to Hypertension

	AUC	95% CI	*P*	Sensitivity (%)	Specificity (%)
miR-423-5p	0.785	0.686-0.865	.005	73.33	73.33
NT-proBNP	0.721	0.617-0.811	.019	81.67	63.33

ROC, receiver operating characteristic; miR-423-5p, microRNA-423-5p; NT-proBNP, N- terminal pro-B-type natriuretic peptide; AUC, area under the ROC curve.

Table 4. Multiple Linear Regression Analysis of miR-423-5p Expression Level with the Parameters of Left Ventricular Hypertrophy and Heart Failure

	β (95% CI)	*t*	*P*
NT-proBNP	0.251 (0-0.001)	2.614	.012
6MWT	0.286 (0.001-0.014)	2.327	.024
NYHA	0.257 (0.006-0.539)	2.053	.045
LVEF	0.324 (0.019-0.082)	3.204	.002
LVDD	0.155 (0.002-0.051)	2.177	.034
ESV	0.268 (0.032-0.006)	−2.884	.006

NT-proBNP, N-terminal pro-B-type natriuretic peptide; 6MWT, 6-minute walking test; NYHA, New York heart association; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; ESV, end-systolic volume.

function in those patients following cardiac rehabilitation treatment. Combined with previous studies, our data suggest that miR-423-5p may induce cardiomyocyte apoptosis by regulating the PI3k/AKT pathway[25] and inhibiting O-type *N*-acetylglucosaminyltransferase (OGT).[26] Meanwhile, cardiac rehabilitation may improve cardiac function, promote physiological structural changes in the heart, and inhibit cardiac physiological remodeling[27] by regulating endothelial progenitor cells via miR-423-5p.[28]

CONCLUSION

The present study suggests that increased levels of plasma miR-423-5p are associated with the risk factors of HFmrEF. Cardiac rehabilitation combined with routine treatment improves cardiac function of those patients with HF more effectively than routine treatment only. Circulating miR-423-5p could potentially serve as a biomarker for evaluating the therapeutic effect of cardiac rehabilitation while being valuable in predicting the progression of HFmrEF.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Minzu Hospital of Guangxi Zhuang Autonomous Region (approval No: [2020] No. 14).

Informed Consent: The identity of the individuals participating in the study is anonymous and confidential, specific informed consent was obtained for its publication.

Peer-review: Externally peer-reviewed.

Author Contributions: Y.H. conceived the study concept and design. Y.Z. and W.N. were responsible for the data collection. Y.Z. and B.L. were taken part in the data analysis and interpretation, while D.Z. completed the manuscript writing. All authors critically revised the manuscript, and agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Declaration of Interests: The authors declare that they have no conflicts of interest with the contents of this article.

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