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Diagnostic and prognostic value of microRNA423-5p in patients with heart failure

Xiaohua Guo[1†], Yi Zhou[2†], Honghao Huang[2], Zhen Zong[2], Mei Xin[2*] and Ke Yang[2*]

Abstract

Objectives MicroRNAs are considered as a class of potential biomarkers for HF. This study aimed to retrospectively evaluate the diagnostic and prognostic value of microRNA423-5p in patients with HF.

Methods The observational group comprised 98 patients diagnosed with HF due to coronary atherosclerotic heart disease ($n=45$), hypertension ($n=26$), or cardiac valve insufficiency ($n=27$). Conversely, the control group consisted of 30 healthy volunteers without any history of HF. These patients were further classified into heart function class II ($n=33$), class III ($n=32$), and class IV ($n=33$) according to the NYHA classification. Of these patients, 33 were diagnosed with HF with mid-range ejection fraction (HFmrEF) and the remaining 65 with HF with reduced ejection fraction (HFrEF). The diagnostic and prognostic significance of microRNA423-5p in patients with HF was assessed through laboratory parameter assessments (microRNA423-5p and B-type natriuretic peptide test, BNP), cardiac ultrasound evaluations (left ventricular ejection fraction, LVEF), and subsequent follow-up assessments.

Results In this study, we found that patients with HF exhibited notably elevated levels of microRNA423-5p and BNP, as well as significantly lower LVEF values. A significant positive correlation between microRNA423-5p and BNP indicators was validated. In addition, our study also revealed an elevation in the level of microRNA423-5p correlating with the progression of the HF. The combined evaluation of LEVF, BNP, and microRNA423-5p demonstrated superior diagnostic efficacy in comparison to the solitary use of BNP.

Conclusions Elevated levels of microRNA423-5p in the serum of patients with HF suggest its potential utility as a novel biomarker for both the diagnosis and prognosis of this condition.

Keywords Heart failure, MicroRNA423-5p, Biomarker

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Introduction

Heart failure (HF) represents the final stage in the progression of several severe cardiovascular conditions. Globally, there are over 15 million new cases of HF annually, with a one-year all-cause mortality rate of 25.7% following disease onset [1, 2]. Given its high rates of hospitalization, morbidity, and mortality, early detection and prognostic assessment of HF are essential for informing treatment strategies and enhancing patient survival rates. HF markers, including plasma B-type natriuretic peptide (BNP) and N-terminal proB-type natriuretic peptide (NT-proBNP), are currently important for the diagnosis and prognostic evaluation of HF. BNP has great diagnostic value in acute HF, but its concentration in nonacute HF patients is often lower than the critical value, significantly reducing its diagnostic performance [3]. Although NT-proBNP is recommended as an exclusion indicator for nonacute HF, it is difficult to classify subtypes such as HF with preserved ejection fraction (HFpEF) or HF with reduced ejection fraction (HFrEF), limiting its clinical guiding role [4]. Hence, the identification of new biomarkers with enhanced diagnostic utility for the prompt detection, management, and prognostic assessment of individuals with HF has emerged as a significant focus of research.

MicroRNAs are intrinsic noncoding RNAs implicated in various pathological mechanisms of HF, such as myocardial hypertrophy, myocardial cell apoptosis, and fibrosis. Several investigations have demonstrated the presence of microRNAs, including microRNA423-5p, microRNA-21, and microRNA-132, in HF patients [5–7], with aberrant expression levels observed across different concentrations. MicroRNA-21 shields cardiomyocytes from oxidative stress by gene suppression [8]. The GISSSI HF study linked microRNA-132 levels to HF severity [9]. MicroRNA-423-5p, produced during myocardial apoptosis in HF, may induce apoptosis via the PI3K/AKT pathway and inhibit OGT [10]. MicroRNAs like microRNA-221/222 are associated with atherosclerosis and myocardial remodeling [11]. Despite numerous reports, significant variability exists in the effects of microRNAs on HF. A meta-analysis has indicated that microRNA-423-5p may serve as a reliable biomarker for HF, as evidenced by prior studies [12]. Consequently, we selected microRNA-423-5p as the focal point of this study. Research has indicated that the concurrent assessment of multiple microRNAs and NT-proBNP in blood samples can significantly enhance the specificity and precision of early HF diagnosis [4]. Additionally, several studies have demonstrated the high predictive accuracy of utilizing molecular levels of HF-related microRNAs to forecast all-cause mortality in patients [13]. These findings introduce a novel concept for diagnosing and evaluating the prognosis of HF. However, the above studies are still at the preliminary stage, and the predictive value of microRNA molecules for the prognosis of HF still needs further study. Therefore, this study aimed to investigate the predictive value of microRNA423-5p for the prognosis of patients with HF and to provide a theoretical basis for its further clinical application.

Materials and methods

Study design

Data retrospectively were collected from 98 patients with HF between January 2022 and January 2023 at the Cardiovascular Surgery Department of the General Hospital of Western Theater Command. The inclusion criteria were: (1) patients with HF diagnosed according to the relevant diagnostic criteria in the "Chinese Guidelines for the Diagnosis and Treatment of HF 2018"; (2) patients with a stable condition post-treatment for over six months, as indicated by echocardiography showing a left ventricular ejection fraction (LVEF) of less than 50%. Of these patients, 33 were diagnosed with HF with mid-range ejection fraction (HFmrEF) and the remaining 65 with HF with reduced ejection fraction (HFrEF); (3) all patients were adults aged between 18 and 80 years. These patients were categorized into heart function class II (n=33), class III (n=32), and class IV (n=33) groups based on New York Heart Association (NYHA) classification. Thirty healthy volunteers without HF were selected as the control group. The exclusion criteria were: (1) patients who underwent severe heart disease such as acute myocardial infarction, (2) patients who underwent special conditions such as pregnancy, tumor, immune diseases or coagulation disorders, (3) missing patient data or duplicate medical records. Additionally, a control group consisting of 30 healthy volunteers who did not exhibit signs of HF during physical examinations at our hospital within the same timeframe was included in the study. This study was approved by the Medical Ethics Committee of the Western Theater General Hospital (approval number: 2022xjsxxm019).

Laboratory index measurement

Ten milliliters of blood specimens were obtained from all participants at the euvolemic condition. For patients diagnosed with HF, constituting the observation group, venous blood samples were procured during the early morning hours of the day subsequent to their admission, in a fasting state. Conversely, the blood collection from the control group was conducted on the day of their medical examination. The blood samples were utilized for routine blood tests, liver and kidney function assessments, BNP measurements, and microRNA423-5p experiments. These analyses were conducted in the Laboratory Department of the Second Affiliated Hospital of Army Military Medical University. All subjects also

underwent Cardiac ultrasound testing with a color Doppler ultrasound system to measure LVEF. Routine blood tests were conducted utilizing an automated hematology analyzer (Mindray BC-6800), liver and kidney function tests were carried out using an automated biochemical analyzer (Beckman AU5800), and BNP analysis was conducted using a fully automated luminescence immunoassay analyzer (Triage® BNP Test Kit, reference value for BNP ranges from 0 to 100 ng/L).

MicroRNA423-5p was detected using real-time fluorescence quantitative PCR (SLAN-96P) after centrifugation of blood samples at 4000 rpm for 5 minutes and aliquoting 100 μl of each serum sample into centrifuge tubes. Total miRNA was subsequently extracted from the sera using the Simply *P* RNA Extraction Kit (Bio-Flux, USA). The RNA concentration was measured with the ND-2000 C. The miRNAs mentioned above were reverse transcribed into cDNA utilizing the ABScript Neo RTMaster Mix for quantitative PCR with Gdna Remover (ABdonal Wuhan Biotechnology Co., Ltd.). The expression level of microRNA423-5p was assessed using 2X Universal SYBR Green Fast q PCR Mix (ABdonal Wuhan Biotechnology), and its relative expression level was determined utilizing the $2^{-\Delta\Delta Ct}$ method with GAPDH as an internal reference. The sequence of the microRNA423-5p PCR forward primer was 5′-ATA AAG GAA GTT AGG CTG AGG G-3′, and the reverse primer sequence was 5′-GAA GCA AGA CTG AGG GGC C-3′. The internal reference gene GAPDH PCR forward primer sequence was 5'-AAG GTC ATC CAT GAC AAC TTT G-3', and the reverse primer sequence was 5'-GTC CAC CAC CCT GTT GCT GTA G-3'.

Patient follow-up data

Two independent researchers perform regular monthly follow-up calls and mandate monthly hospital visits to monitor biochemical indicators, respectively. The patients in the observation group were monitored monthly for a duration of one year, with the primary outcome being rehospitalization due to HF or all-cause mortality. Subsequently, the patients were categorized into either the event group or the nonevent group. A comparison was then made between the microRNA423-5p levels in both groups at the time of enrollment, along with differences in BNP and LVEF indicators.

Statistical analysis

SPSS 25.0 software was used for the statistical analysis.α value of 0.05 was used for comparisons between groups, and $P<0.05$ indicated that the difference was statistically significant. Normally distributed data were used, nonnormally distributed data were described as medians (25th percentile, 75th percentile), and categorical data were expressed as the number of patients and percentages (%). The normally distributed data were compared between the two groups, and the Mann–Whitney U test was performed. Multiple groups of normally distributed data were compared using the variance F test, and the Kruskal–Wallis H test was used if the data were not normally distributed. Intergroup comparisons of count data were performed using the chi-square test. The correlation between the measurement data was analyzed by Spearman correlation. ROC curves were used to evaluate the diagnostic performance of the indicators. The larger the area under the curve (AUC), the better the diagnostic performance. ROC models were also compared using Delong Test.

Results

Baseline demographic and clinical characteristics

The baseline demographic and clinical characteristics of the patients are listed in Table 1. No significant difference was observed among the four groups, regarding all characteristics ($p>0.05$). The comparison of HF phenotypes among the three groups revealed a statistically significant difference ($p<0.05$), with the heart function class II being of the HFmrEF, and the heart function class III and IV being of the HFrEF; No significant differences were observed in the etiology and comorbidity of HF among the three groups ($p>0.05$).

Comparison and correlation analysis of microRNA423-5p, BNP, and LVEF in each group

In comparison to the control group, patients with class II, III, and IV cardiac dysfunction exhibited significantly higher levels of microRNA423-5p and BNP, as well as a significantly lower LVEF ($p<0.05$). Levels of microRNA423-5p and BNP significantly increased with worsening HF across the three groups of heart function class II, class III, and class IV. Pairwise comparisons indicated significant differences in heart function classes ($p<0.05$). Concurrently, LVEF decreased as the disease worsened, with levels in class III and class IV groups significantly lower than those in class II group ($p<0.05$), as detailed in Table 2. Additionally, Spearman correlation analysis revealed a strong positive correlation between microRNA423-5p and BNP ($rs=0.850$, $p<0.001$), a significant negative correlation with LVEF ($rs=-0.825$, $p<0.001$), and a similarly strong negative correlation between BNP and LVEF ($rs=-0.832$, $p<0.001$).

Comparison of microRNA423-5p, BNP, and LVEF between the event group and the non-event group

The patients within the observation group were monitored for a duration of one year, with the primary outcome being rehospitalization due to HF or mortality from any cause. Subsequently, the patients were categorized into an event group ($n=35$) and a non-event

Table 1 Baseline demographic and clinical characteristics of patients

Parameters	Class II (*n* = 33)	Class III (*n* = 32)	Class IV (*n* = 33)	Control group (*n* = 30)	F/χ^2/Fisher	*P*
Gender, *n* (%)					0.159#	0.984
Female	14(42.4)	15(46.9)	15(45.5)	13(43.3)		
Male	19(57.6)	17(53.1)	18(54.5)	17(56.7)		
Age (years)	63.21 ± 5.19	61.28 ± 5.75	64.15 ± 6.19	63.03 ± 7.54	1.209*	0.309
Body weight (kg)	61.45 ± 5.46	60.98 ± 3.63	63.46 ± 4.32	62.31 ± 3.89	1.997*	0.118
BMI (kg/m^2)	23.19 ± 1.60	23.56 ± 1.63	23.45 ± 1.51	23.14 ± 1.78	0.486*	0.693
TBIL (μmol/L)	26.97 ± 4.09	27.73 ± 6.01	29.90 ± 4.53	27.94 ± 6.54	1.796*	0.151
ALT (U/L)	61.40 ± 9.30	62.15 ± 11.95	60.26 ± 12.72	57.31 ± 11.23	1.073*	0.363
AST (U/L)	47.98 ± 11.16	52.48 ± 13.47	53.27 ± 10.62	46.57 ± 11.43	2.517*	0.061
CREA (μmol/L)	154.82 ± 28.79	165.46 ± 31.11	169.01 ± 31.10	163.25 ± 29.57	1.317*	0.272
HCT (%)	42.51 ± 2.13	43.51 ± 1.97	42.04 ± 3.70	42.88 ± 2.69	1.699*	0.171
Phenotype, *n* (%)					98.000 #	0.000
HFmrEF	33(100)	0(0)	0(0)	-		
HFrEF	0(0)	32(100)	33(100)	-		
Etiology, *n* (%)						
Coronary heart disease	15(45.5)	13(40.6)	17(51.5)	-	0.780#	0.677
Hypertension	11(33.3)	9(28.1)	6(18.2)	-	2.005#	0.367
Heart valve insufficiency	7(21.2)	10(31.3)	10(30.3)	-	1.009#	0.604
Comorbidity, *n* (%)						
Malignant arrhythmia	5(15.2)	6(18.8)	9(27.3)	-	1.573#	0.455
Renal insufficiency	2(6.1)	1(3.1)	2(6.1)	-	0.416#	0.812
Liver dysfunction	1(3.0)	0(0)	1(3.0)	-	1.222Δ	1.000
Thrombus	0(0)	1(3.1)	1(3.0)	-	1.284Δ	0.771

Note: *: *F* test; #: Chi-square test, Δ: Fisher's exact test

Table 2 Comparison of microRNA423-5p, BNP, and LVEF

Groups	*n*	microRNA423-5p	BNP (ng/L)	LVEF (%)
Class II	33	0.42(0.39,0.45) a	579.23(460.85,644.88) a	46.92(44.31,48.14) a
Class III	32	0.80(0.78,0.82) ab	946.59(874.33,1086.38) ab	36.18(33.75,38.34) ab
Class IV	33	1.18(1.16,1.21) abc	2500.23(1920.60,2917.24) abc	33.09(30.16,35.63) ab
Control group	30	0.34(0.32,0.37)	77.60(60.04,83.93)	62.32(57.24,66.26)
Z		109.658	108.675	102.726
P		0.000	0.000	0.000

Note: Compared with the control group, $^a p < 0.05$; compared with the Class II group, $^b p < 0.05$; compared with the Class III group, $^c p < 0.05$

Table 3 Comparison of microRNA423-5p, BNP, and LVEF between the event group and the nonevent group

Groups	*n*	microRNA423-5p	BNP (ng/L)	LVEF (%)
Non-event group	63	0.76(0.42,0.82)	760.66(552.33,1083.87)	39.37(35.28,47.58)
Event group	35	1.16(0.79,1.19)	1957.27(1000.37,2696.74)	34.50(30.86,39.43)
Z		-4.518	-4.845	-3.440
P		0.000	0.000	0.001

group ($n = 63$). Upon conducting a comparative analysis between the two groups, statistically significant variances were observed ($p < 0.05$); specifically, elevated levels of microRNA423-5p and BNP were noted, alongside a reduced LVEF in the event group (Table 3).

ROC curve analysis of microRNA423-5p for the evaluation of the prognosis

As shown in Fig. 1; Table 4, ROC curve analysis was utilized to assess the prognostic significance of microRNA423-5p, BNP, and LVEF individually, as well as in combination (microRNA423-5p + BNP, microRNA423-5p + LVEF, and microRNA423-5p + BNP + LVEF) for patients diagnosed with HF. The findings indicated that both microRNA423-5p + BNP + LVEF and microRNA423-5p + BNP exhibited strong predictive capabilities, with respective areas under the curve of 0.839 and 0.814. Of the individual indicators examined, BNP demonstrated the highest predictive value, with an AUC of 0.796, followed by microRNA423-5p at 0.776, and the LVEF indicator at 0.710. According to the Delong test, there was no significant difference between

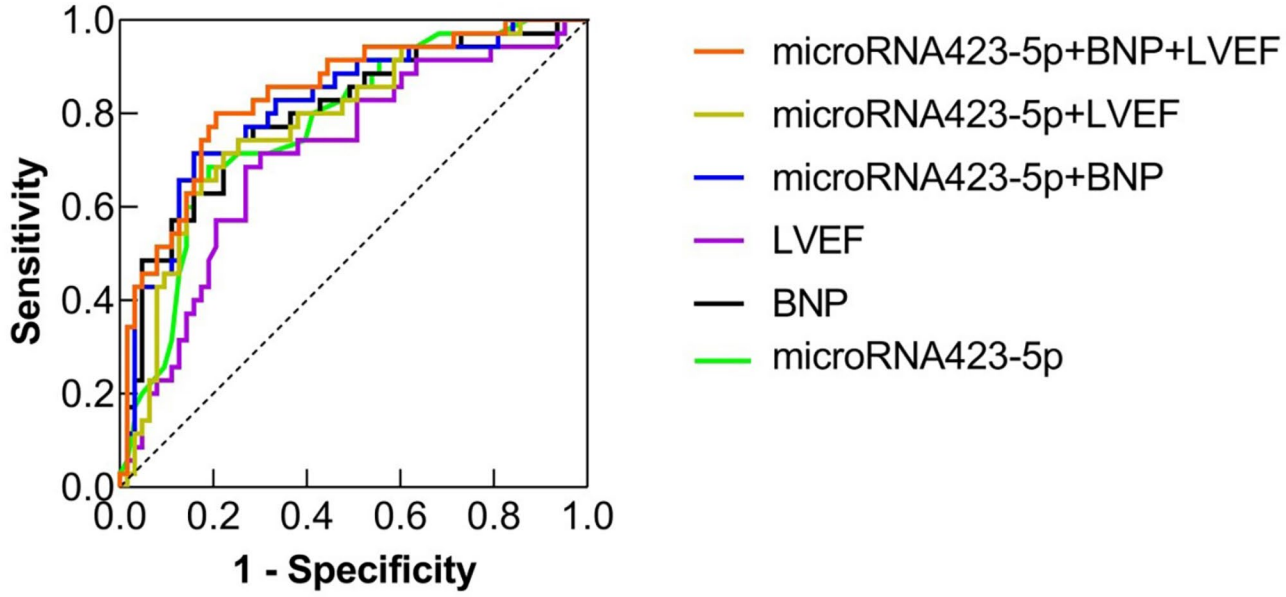

Fig. 1 ROC curve analysis of microRNA423-5p for the evaluation of the prognosis

Table 4 Assessment parameters of microRNA423-5p for the evaluation of the prognosis

Parameters	AUC	SE	*P*	95%CI	Cut off point	Sensitivity	Specificity
microRNA423-5p	0.776	0.048	0.000	0.682–0.871	1.0850	0.657	0.841
BNP	0.796	0.048	0.000	0.702–0.891	1085.620	0.714	0.778
LVEF	0.710	0.055	0.001	0.603–0.818	35.915	0.730	0.686
microRNA423-5p + BNP	0.814	0.046	0.000	0.723–0.904	3.795	0.714	0.841
microRNA423-5p + LVEF	0.779	0.049	0.000	0.683–0.875	3.371	0.714	0.778
microRNA423-5p + BNP + LVEF	0.839	0.042	0.000	0.757–0.922	4.444	0.800	0.794

microRNA423-5p+BNP and microRNA423-5p+LVEF ($Z=1.027$, $P=0.304$), and there was no significant difference between microRNA423-5p+BNP+LVEF and microRNA423-5p+BNP and microRNA423-5p+LVEF ($Z=1.509$, 1.862, $P=0.131$, 0.063, respectively).

Discussion

HF represents the terminal phase of several cardiovascular conditions. Despite the availability of numerous strategies for enhancing the identification and management of HF, the rates of hospitalization and mortality among individuals with this condition persist at elevated levels. BNP and NT-proBNP are well-established clinical indicators of HF, however, their diagnostic and prognostic efficacy can be influenced by factors such as the underlying disease, patient age, and genetic predisposition [12, 14]. The investigation of microRNA molecules as potential biomarkers for a range of diseases has been the subject of extensive research. Numerous research studies have demonstrated the presence of microRNAs in a diverse range of bodily fluids, including serum, plasma, whole blood, cerebrospinal fluid, urine, and saliva, with the concentration of microRNAs in these fluids being indicative of the pathological status of the disease [15, 16]. In studies related to HF, the presence of the microRNA423-5p [5], along with microRNA-21 [6] and microRNA-132 [7], has been identified in patients. In this study, we found that patients with HF exhibited notably elevated levels of microRNA423-5p and BNP, as well as significantly lower LVEF values. A significant positive correlation between microRNA423-5p and BNP indicators was validated. In addition, our study also revealed an elevation in the level of microRNA423-5p correlating with the progression of the HF. The combined evaluation of LEVF, BNP, and microRNA423-5p demonstrated superior diagnostic efficacy in comparison to the solitary use of BNP. Consequently, microRNA423-5p plays a pivotal role in the diagnosis and prognostic assessment of HF.

Our study corroborated the findings of another study that also posited that microRNA-423-5p is significantly upregulated in patients with HF and serves as a reliable diagnostic biomarker [14]. Additionally, we demonstrated a significant positive correlation between microRNA423-5p and BNP, and a significant negative correlation with LVEF. Similarly, a significant negative correlation was observed between BNP and LVEF. A meta-analysis on the prognostic significance of BNP changes in HF indicated that variations in BNP levels can predict the prognosis of

HF patients [17]. Given the positive correlation observed in this study between microRNA423-5p and BNP levels, we assumed that the changes in BNP levels when using microRNA423-5p have strict similarity in predicting HF.

We subsequently utilized the ROC curve to assess the joint diagnostic and prognostic evaluation of BNP, LVEF, and microRNA423-5p in patients with HF. The results indicated that, among the individual markers, BNP exhibited the best predictive value, followed by microRNA423-5p, with LVEF having the least. Both combinations of microRNA423-5p plus BNP and LVEF showed significant prognostic predictive value. This result is consistent with the conclusion of a previous study. Their research demonstrated that the detection of HF using microRNA423-5p exhibits high sensitivity and specificity, and when combined with BNP, it can further enhance diagnostic efficacy [5]. However, a study examining microRNA423-5p as a biomarker for post-myocardial infarction prognosis concluded that microRNA423-5p is not significantly correlated with left ventricular function recovery or BNP levels in patients one-year post-infarction [18]. This finding contradicts our observations of a significant positive correlation between BNP and microRNA423-5p in HF patients, which could enhance the diagnostic efficacy of a combined biomarker approach. We attribute this discrepancy to the administration of maximal doses of medications, including antiplatelets, statins, ACE inhibitors, and β-blockers.

The limitations of this study lie in its single-center research. Due to the limited sample size, this study focused on a single microRNA that is highly expressed in HF, rather than analyzing the entire genome expression profile. In the current study, several microRNAs including microRNA21, microRNA-132, microRNA-221, and microRNA-222, which are known to be dysregulated in heart diseases, were not included, compromising the accuracy of the research findings. Concurrently, research has indicated the joint diagnosis of multiple microRNAs will help distinguish patients with HFpEF and patients with HFrEF [12]. Therefore, to more precisely assess the potential role of microRNAs in HF, further research involving HFpEF patients is necessary. The study cohort comprised 98 patients diagnosed with heart failure (HF), all of whom exhibited a left ventricular ejection fraction (LVEF) of less than 50%. The patients with class II heart function were all HFmrEF type, while those with class III and IV were both HFrEF type. Subsequent comparative analysis of etiological factors (including coronary artery disease, hypertension, and valvular heart insufficiency), comorbid conditions (such as malignant arrhythmias, renal and hepatic insufficiency, and thrombosis), as well as demographic variables such as age, weight, and body mass index (BMI) across the three groups, revealed no statistically significant differences (Table 1). Actually, the type of HF, etiology and a presence of the metabolic conditions, such as overweight, obesity are all the factors to intervene in microRNA423-5p and BNP levels. A multiple factor regression analysis may further elucidate their impact in future work. Despite these limitations, this study is anticipated to provide a foundation for subsequent multicenter studies with larger samples. Based on the above results, we believe that microRNA423-5p has the potential to become a new biomarker for the diagnosis and prognostic evaluation of HF.

Conclusions

Our research indicates that elevated serum microRNA423-5p in HF patients is predictive of the condition. While BNP demonstrates the optimal predictive efficacy as a standalone marker, joint detection of BNP and microRNA423-5p shows higher sensitivity and specificity compared to using BNP alone. This suggests that microRNA423-5p holds predictive value for HF patients and could potentially serve as a novel biomarker for combined detection, aiding in the diagnosis and prognostic assessment of HF.

Abbreviations

HF	Heart failure
BNP	B-type natriuretic peptide
NT-proBNP	N-terminal proB-type natriuretic peptide
HFpEF	Heart failure with preserved ejection fraction
HFmrEF	Heart failure with mid-range ejection fraction
HFrEF	Heart failure with reduced ejection fraction
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
BMI	Body Mass Index
ROC	Receiver operating characteristic
AUC	Area under the curve
OGT	O-type N-acetyl glucosyltransferase
CI	Confidence interval

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Author contributions

X.H.G. and Y.Z. contributed equally to this work. Xiaohua Guo: Conceptualization, Investigation, Writing-original draft contributed equally to this work. Yi Zhou: Investigation, Writing-original draft contributed equally to this work. HongHao Huang: Investigation, Methodology. Zhen Zong: Investigation. Xin Mei: Writing-review & editing, Funding acquisition. Ke Yang: Conceptualization, Supervision, Writing-review & editing, Project administration, Funding acquisition.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Statement of Ethics
This research was conducted in compliance with the Declaration of Helsinki and was approved by the Institutional Ethical Review Board of the General Hospital of Western Theater Command approved the study (2022xjsxxm019). Each recruited patient provided written informed consent.

Conflict of interest
The authors declare not conflict of interest.

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