Clinical significance of the long non-coding RNA NEAT1/miR-129-5p axis in the diagnosis and prognosis for patients with chronic heart failure

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Abstract. Chronic heart failure (CHF) is the leading cause of death worldwide. The regulatory interactions of long non-coding RNA (lncRNAs) and microRNAs (miRs) have important roles in multiple diseases. However, the clinical significance of the nuclear-enriched abundant transcript 1 (NEAT1)/miR-129-5p axis in CHF has remained elusive. The present study explored whether the NEAT1/miR-129-5p axis may be a suitable diagnostic and prognostic marker for CHF. The expression of lncRNA NEAT1 and miR-129-5p in the serum of patients with CHF was analyzed by reverse transcription-quantitative PCR. Furthermore, inter-indicator correlations were assessed by Pearson correlation coefficient analysis. Receiver operating characteristic (ROC) curves were generated to evaluate the ability of NEAT1, miR-129-5p and brain natriuretic peptide (BNP) to identify patients with CHF. The prognostic value of the NEAT1/miR-129-5p axis was analyzed by drawing Kaplan-Meier survival curves and by Cox logistic regression analysis. Baseline data were not significantly different between CHF (n=70) and control subjects (n=62). The serum level of NEAT1 was increased and the expression level of miR-129-5p was decreased in patients with CHF (all P<0.001). The ROC curves suggested that serum NEAT1 and miR-129-5p were of diagnostic value in patients with CHF and the combined diagnostic accuracy of NEAT1, miR-129-5p and BNP was significantly improved. Kaplan-Meier and multivariate Cox regression analysis suggested that low NEAT1 and high miR-129-5p were able to predict overall survival of patients with CHF (all P<0.01). In conclusion, the present study indicated that patients with CHF had increased NEAT1 and decreased miR-129-5p expression. The deregulated NEAT1/miR-129-5p axis may provide novel non-invasive biomarkers for the diagnosis and prognosis of CHF.

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Introduction

Heart diseases cause more deaths than all types of cancer combined (1). In effect, cardiac diseases, such as chronic heart failure (CHF), are the leading cause of hospitalization in numerous regions of the world (2). The occurrence of CHF is closely related to various other clinical diseases, such as hypercholesterolemia, hypertension and diabetes mellitus (3). The goal of the treatment of heart failure is not only to improve symptoms and quality of life, but also to delay and prevent the development of cardiac remodeling and reduce hospitalization and mortality of patients with heart failure (4). Brain natriuretic peptide (BNP) is a cardiac hormone with diuretic, natriuretic and vasodilator properties. Measurement of plasma B-type natriuretic peptide concentrations is increasingly used to aid the diagnosis, assess prognosis and tailoring treatment in adults with congestive heart failure (5). However, it may also be significantly altered in other diseases, such as hepatitis (6) and renal failure (7). Although the left ventricle ejection fraction (LVEF) is frequently used to assess cardiac function in patients with CHF (8), a certain proportion of patients may have normal LVEFs. Therefore, novel markers for the diagnosis and prognosis of CHF remain to be explored and developed.

Long non-coding RNAs (lncRNAs) are a group of non-protein coding RNAs that are >200 nucleotides in length. Increasing evidence indicates that lncRNAs have a crucial role in the pathophysiology of human diseases (9) and certain lncRNAs are also aberrantly expressed in CHF. LncRNA nuclear-enriched abundant transcript 1 (NEAT1) is an lncRNA known to be closely related to myocardial function. Interfering with NEAT1 levels protects myocardial cells from hypoxia injury (10). NEAT1 is able to competitively bind to microRNA (miR)-129-5p in myocardial cells, thereby promoting apoptosis and inhibiting cell proliferation (11). Studies have indicated that miR-129-5p is able to improve cardiac function in rats with CHF (12) and has a biological function of inhibiting apoptosis of cardiomyocytes (13). However, the expression

levels of the NEAT1/miR-129-5p axis in patients with CHF and its clinical significance in the diagnosis and prognosis of CHF have remained to be determined.

In the present study, the expression of lncRNA NEAT1 and miR-129-5p in the serum of patients with CHF was analyzed using reverse transcription-quantitative (RT-q)PCR. Furthermore, inter-indicator correlations were determined using Pearson correlation coefficient analysis. Receiver operating characteristic (ROC) curves were obtained to analyze the predictive ability of NEAT1, miR-129-5p and BNP for the onset of CHF. In addition, the prognostic value of the NEAT1/miR-129-5p axis was analyzed by drawing Kaplan-Meier survival curves and performing Cox regression analysis. The results suggested that patients with CHF have increased NEAT1 and decreased miR-129-5p expression. The NEAT1/miR-129-5p axis may provide novel non-invasive biomarkers for CHF diagnosis and prognosis.

Patients and methods

Study population and sample collection. A total of 70 patients with CHF and 62 age- and sex-matched controls were collected from Weifang People's Hospital (Weifang, China) between May 2016 and April 2018. The diagnosis of CHF was made according to the criteria of the 2013 American College of Cardiology Foundation/American Heart Association Guidelines for the Management of Heart Failure and the 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of Acute and CHF (14,15). The control subjects were obtained from a population of individuals referred for physical examination at Weifang People's Hospital (Weifang, China) during a same time period and were determined to not have any CHF. The patients with CHF had an LVEF <40% and were clinically stable, with the New York Heart Association (NYHA) stage ranging from II to IV based on the 1928 and 1994 revised version of NYHA staging system (16). The exclusion criteria for both the patients and controls were as follows: i) Presence of infection; ii) cancer; iii) history of surgery within 1 year; iv) history of cerebral vascular events within 6 months; v) heart assist devices; or vi) liver or renal failure. To avoid fibrin interference in plasma, serum was used as the experimental sample in this experiment. Venous blood samples were collected from the participants to ensure the accuracy of the analytical results, serum separation was performed by centrifugation immediately after blood sample collection to avoid hemolysis and the samples were stored at -20˚C for further use. The experimental protocols were approved by the Ethics Committee of Weifang People's Hospital (Weifang, China) and written informed consent was provided by each participant.

Therapy of patients and follow-up survey. The 70 patients with CHF were treated with conventional drugs, including diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β-blockers. All patients underwent monthly telephone follow-up for a total of 24 months and survival information was collected and analyzed for all patients in this study to record the deaths of patients with CHF.

RNA extraction and RT-qPCR. Total RNA was extracted from fresh serum samples using the GenElute Total RNA Purification Kit (Sigma-Aldrich; Merck KGaA), and the concentration and quality of total RNA were analyzed using a NanoDrop 2000 (Thermo Fisher Scientific, Inc.). RNA with an optical density at 260 nm (OD260)/OD280 ratio close to 2.0 was used for subsequent RT. RT was performed using the Applied Biosystems High-Capacity complementary (c)DNA RT Kit (Thermo Fisher Scientific, Inc.) with the following reaction conditions: 42˚C for 30 min, 85˚C for 5 sec, and the resulting cDNA was stored at -20˚C for later use.

The expression levels of NEAT1 and miR-129-5p were measured by qPCR, which was performed using a SYBR green I Master Mix kit (Invitrogen; Thermo Fisher Scientific, Inc.) on a 7500 Real-Time PCR System (Applied Biosystems; Thermo Fisher Scientific, Inc.), according to the manufacturer's protocol. U6 was used as an endogenous control for miR-129-5p and GAPDH was used as an endogenous control for NEAT1. The following thermocycling conditions were used for the qPCR: Initial denaturation at 95˚C for 10 min; followed by 40 cycles of 95˚C for 20 sec, 60˚C for 15 sec and 72˚C for 20 sec. The following primer sequences were used for the qPCR: miR-129-5p forward: 5'-GCCGAGCTTTTT GCGGTCTGGG-3' and reverse, 5'-CTCAACTGGTGTCGT GGA-3'; NEAT1 forward, 5'-CTTCCTCCCTTTAACTTA TCCATTCAC-3' and reverse, 5'-CTCTTCCTCCACCATTAC CAACAATAC-3'; U6 forward, 5'-GCTTCGGCAGCACAT ATACTAAAAT-3' and reverse, 5'-CGCTTCACGAATTTG CGTGTCAT-3' and GAPDH forward, 5'-TGCACCACCAAC TGCTTAGC-3' and reverse: 5'-GGCATGCACTGTGGTCAT GAG-3'; The final expression value was calculated using the $2^{-\Delta\Delta Cq}$ method (17).

Statistical analysis. Values are expressed as the mean ± standard deviation and analyzed using SPSS 21.0 (IBM Corp.) and GraphPad 7.0 (GraphPad Software, Inc.). Each experiment was performed for at least three times. Differences between groups were analyzed with an unpaired Student's t-test or one-way ANOVA followed by Tukey's multiple-comparisons test. Pearson correlation analysis was used to determine the correlation between various indicators. ROC curves for the predictive value of the expression values of BNP, NEAT1 and miR-129-5p regarding CHF were plotted using SPSS software. The area under the ROC curve (AUC) was calculated and the sensitivity and specificity were obtained at the optimal cutoff value. To evaluate the synthetic role of BNP, NEAT1 and miR-129-5p to distinguish CHF patients, logistic analysis was used to calculate the probability values of the combination of the parameters. Survival analysis was performed using the Kaplan-Meier method and a log-rank test was used to determine statistically significant differences between curves for high and low expression. The prognostic value of NEAT1 and miR-129-5p was evaluated by Cox logistic regression analysis, in which the clinical data, NEAT1 and miR-129-5p were included to evaluate their relationship with the survival of patients.

Results

Baseline characteristics and clinical parameters of the participants. In the present study, 70 patients with CHF and 62 matched controls were enrolled. The CHF patients included 37 males and 33 females with an average age of

Table I. Baseline characteristics and clinical parameters of the participants.

Feature	Controls (n=62)	CHF (n=70)	P-value
Age (years)	66.71±1.65	67.24±1.60	0.061
Sex (male/female)	34/28	37/33	0.820
BMI (kg/m^2)	25.04±0.377	24.95±0.360	0.171
Smoking history (never/ever)	43/19	44/26	0.432
Drinking history (never/ever)	40/22	40/30	0.387
TC (nM)	4.65±0.16	4.63±0.19	0.779
TG (nM)	1.37±0.65	1.44±0.63	0.476
LDL-C (nM)	2.97±0.13	3.00±0.14	0.153
HDL-C (nM)	1.19±0.31	1.16±0.03	0.542
UA (μM)	353.76±15.15	356.31±13.69	0.312
BNP (ng/l)	67.24±20.66	1,519.83±853.73	<0.001
LVEF (%)	59.89±0.63	30.17±3.44	<0.001
Complication (no/yes)			
Hypertension	26/36	22/48	0.210
Diabetes	30/32	24/46	0.100
COPD	-	58/12	-
Anemia	-	62/8	-
Fluid and electrolyte imbalance	-	39/31	-
NYHA stage			
II	-	36	-
III	-	19	-
IV	-	15	-

Values are expressed as the mean ± standard deviation or n. BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; BNP, brain natriuretic peptide; LVEF, left ventricle ejection fraction; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; CHF, chronic heart failure.

67.24±1.60 years and the control included 34 males and 28 females with an average age of 66.71±1.65 years. Their basic information is listed in Table I. The results suggested that there were no differences in age, sex, body mass index, smoking history, drinking history, total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or uric acid between the two groups. In terms of complications, there were no differences in hypertension and diabetes between the two groups. The CHF group had significantly higher levels of BNP and significantly lower levels of LVEF compared to the controls (both P<0.001).

Expression of NEAT1 and miR-129-5p in patients with CHF. To further understand the role of NEAT1 and miR-129-5p in CHF, their serum levels in patients with CHF were quantified by RT-qPCR. It was observed that compared to the healthy control, patients with CHF had upregulated serum NEAT1 (P<0.001; Fig. 1A) and downregulated serum miR-129-5p (P<0.001; Fig. 1B), and serum NEAT1 and miR-129-5p levels were significantly negatively correlated in patients with CHF (r=-0.801, P<0.001; Fig. 1C). In addition, the expression level of NEAT1 was upregulated with the increase of the NYHA stage (all P<0.01; Fig. 1D), while the expression level of miR-129-5p decreased with the increase of the NYHA stage (all P<0.01; Fig. 1E).

Correlation of the NEAT1/miR-129-5p axis with BNP and LVEF in patients with CHF. The results of the Pearson correlation analysis indicated that the expression level of NEAT1 was positively correlated with BNP (r=0.666, P<0.001; Fig. 2A) and negatively correlated with LVEF (r=-0.611, P<0.001; Fig. 2B) in patients with CHF. The expression level of miR-129-5p was negatively correlated with the BNP level (r=-0.570, P<0.001; Fig. 2C) and positively correlated with the LVEF (r=0.454, P<0.001; Fig. 2D).

Diagnostic performance of the NEAT1/miR-129-5p axis in patients with CHF. As a traditional diagnostic marker for CHF, the BNP-based ROC curve was first drawn and the diagnostic value of NEAT1 and miR-129-5p was further evaluated, which indicated that both NEAT1 and miR-129-5p had a certain diagnostic value (Fig. 3). ROC analysis revealed that the AUC of BNP was 0.982. The AUC of the ROC curve based on serum NEAT1 was 0.868 with a sensitivity and specificity of 62.9 and 96.8%, respectively, at a cutoff value of 0.465. miR-129-5p had a good diagnostic value with an AUC of 0.921, and the sensitivity was 95.7% and the specificity was 77.4% at a cutoff value of 1.130. Of note, the combination of NEAT1 and miR-129-5p had high diagnostic accuracy (AUC=0.970) and the combination of NEAT1, miR-129-5p and BNP had the best diagnostic value (AUC=0.998), indicating

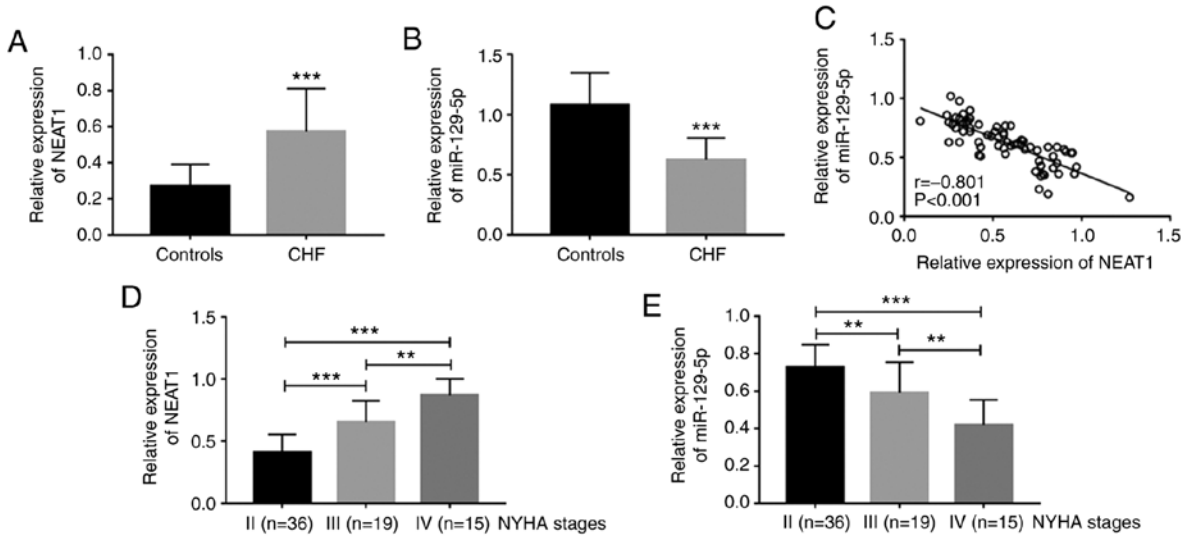

Figure 1. Expression of NEAT1 and miR-129-5p in patients with CHF. (A) The expression of NEAT1 was higher in patients with CHF than that in the control group. (B) miR-129-5p levels were lower in patients with CHF. (C) Serum NEAT1 and miR-129-5p levels were significantly negatively correlated in CHF patients. (D) NEAT1 expression level increase with the increase of NYHA stages. (E) miR-129-5p expression level decrease with the increase of NYHA stages. **P<0.01, ***P<0.001 vs. control or as indicated. CHF, chronic heart failure; miR, microRNA; NYHA, New York Heart Association; NEAT1, nuclear-enriched abundant transcript 1.

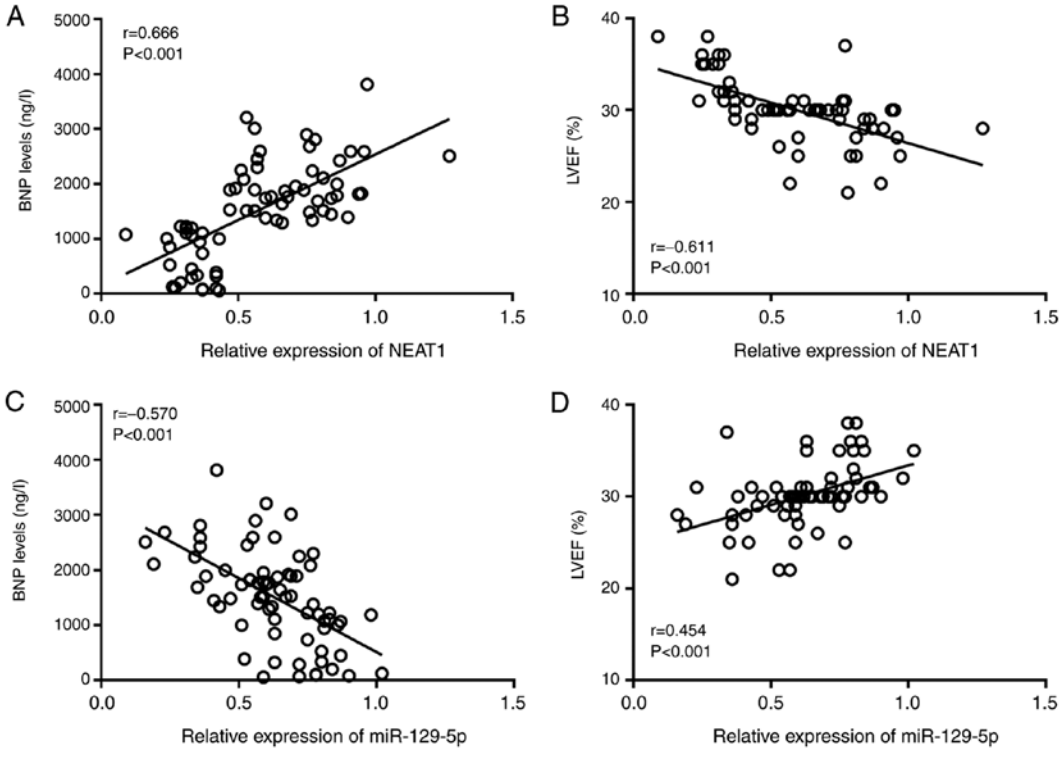

Figure 2. Correlation of the NEAT1/miR-129-5p axis with BNP and LVEF in patients with chronic heart failure. (A) Correlation between NEAT1 and BNP (r=0.666, P<0.0001). (B) Correlation between NEAT1 and LVEF (r=-0.611, P<0.0001). (C) Correlation between miR-129-5p and BNP (r=-0.570, P<0.0001). (D) Correlation between miR-129-5p and LVEF (r=0.454, P<0.0001). BNP, brain natriuretic peptide; NEAT1, nuclear-enriched abundant transcript 1; LVEF, left ventricle ejection fraction; r, Pearson correlation coefficient.

that this combination resulted in a significant increase in the diagnostic power compared with BNP alone (Table II).

Prognostic value of NEAT1/miR-129-5p in predicting survival rates of patients with CHF. The association of NEAT1 and miR-129-5p expression with the overall survival of patients was estimated by plotting the Kaplan-Meier survival curves (Fig. 4). The Kaplan-Meier curves indicated that patients with low NEAT1 expression levels had better overall survival than those with high NEAT1 expression levels (log-rank P=0.001) and patients with low miR-129-5p expression levels had lower overall survival than those with high miR-129-5p expression

Table II. ROC curve analysis results for patients with chronic heart failure.

Variable	AUC	Cutoff value	Sensitivity (%)	Specificity (%)
BNP	0.982	127.455	92.9	98.4
NEAT1	0.868	0.465	62.9	96.8
miR-129-5p	0.921	1.130	95.7	77.4
NEAT1+miR-129-5p	0.970	-	94.3	88.7
BNP+NEAT1+miR-129-5p	0.998	-	98.6	96.8

BNP, brain natriuretic peptide; ROC, receiver operating characteristic; miR, microRNA; AUC area under the ROC curve; NEAT1, nuclear-enriched abundant transcript 1.

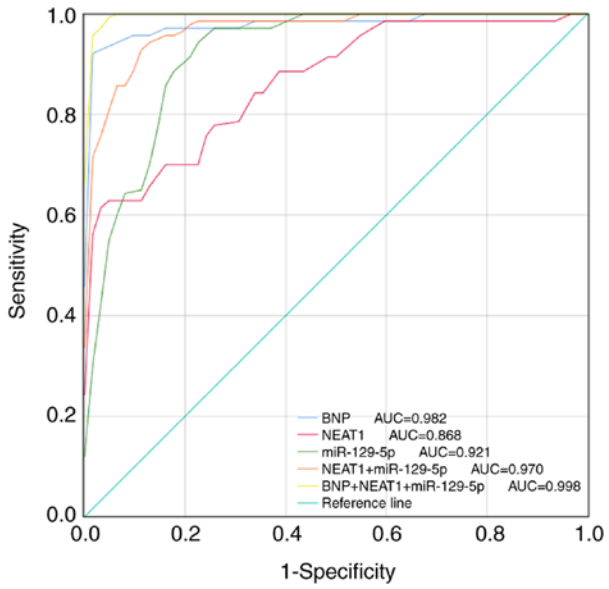

Figure 3. ROC analysis of the diagnostic performance of the NEAT1/miR-129-5p axis for CHF. The AUC of BNP, NEAT1, miR-129-5p, NEAT1+miR-129-5p and BNP+NEAT1+miR-129-5p to diagnose CHF were 0.982, 0.868, 0.921, 0.970 and 0.998, respectively. CHF, chronic heart failure; miR, microRNA; NEAT1, nuclear-enriched abundant transcript 1; BNP, brain natriuretic peptide; AUC, area under the ROC curve; ROC, receiver operating characteristic.

levels (log-rank P=0.002). Furthermore, the multivariate Cox analysis demonstrated that BNP [hazard ratio (HR)=3.998, 95% CI=1.752-6.874, P=0.022], NYHA stage (HR=3.597, 95% CI=1.884-6.496, P=0.016), NEAT1 (HR=3.197, 95% CI=1.702-5.879, P=0.006) and miR-129-5p (HR=3.549, 95% CI=1.975-6.365, P=0.012) were independent prognostic factors for the survival of patients with CHF (Table III).

Discussion

Numerous studies have indicated that NEAT1 overexpression may improve diseases by downregulating miR-129-5p, including epilepsy (18) and alcoholic steatohepatitis (19). In the present study, the clinical value of NEAT1 and miR-129-5p in patients with CHF was investigated. It was confirmed that NEAT1 expression was upregulated and miR-129-5p expression was downregulated in CHF, and they may serve as two non-invasive diagnostic and prognostic biomarkers for CHF.

CHF is the end stage of multiple heart diseases. The diagnosis and prognostication of patients with CHF remain a challenge (4). With efforts to improve the treatment and prevention of CHF, the mortality rate of sudden death among patients with CHF have markedly decreased over the past decades (20). However, the overall mortality of these patients remains high (21). In recent years, BNP in the diagnosis, treatment and prognosis of cardiovascular diseases has become a research focus (22). It was indicated that in the clinic, certain cases presented with symptoms of CHF with normal BNP values. There are also cases with heterophile antibody interference on immunodetection, resulting in false elevation of BNP. These issues all influence the diagnostic yield of BNP (23). Therefore, it is important to identify patients with CHF with a high risk of death, improve their diagnosis and prognostic efficacy and increase the survival of those patients. Certain lncRNAs are abnormally expressed during the development of diseases and lncRNAs may thus become novel biomarkers for prognosis and diagnosis (24). For instance, Song *et al* (25) provided an innovative lncRNA expression signature that may be a useful biomarker for the prognosis of patients with gastric cancer based on bioinformatics analysis. Furthermore, lncRNA-D16366 was identified to be decreased in hepatocellular carcinoma and may be an independent diagnostic and prognostic indicator for this disease (26). In cervical cancer, upregulated expression of lncRNA focally amplified lncRNA on chromosome 1 may serve as a noninvasive diagnostic and prognostic biomarker (27). However, studies on the clinical significance of lncRNAs in CHF are currently limited.

LncRNA NEAT1 is transcribed from multiple endocrine neoplasia sites and is involved in cancer progression (28). Aberrant overexpression of the long non-coding RNA NEAT1 has been demonstrated in different types of disease and its abnormal expression levels were associated with diagnosis and prognosis (29). For instance, in colorectal cancer, high expression of NEAT1 may serve as a novel biomarker for diagnosis and prognostication of patients (30). LncRNA NEAT1 may also be used as a diagnostic biomarker for ovarian cancer (31). Huang *et al* (32) indicated that lncRNA NEAT1 correlates with increased unfavorable prognosis in patients with sepsis. However, the effect of NEAT1 on the CHF process has remained elusive. Previous studies have indicated that lncRNA NEAT1 is able to competitively bind to miR-129-5p in cardiomyocytes, thereby promoting apoptosis and inhibiting cell proliferation (11). In the present study, the RT-qPCR results

Table III. Multivariate Cox regression analysis for patients with chronic heart failure.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age (≥67 years vs. <67 years)	1.311	0.702-2.213	0.485	1.281	0.672-2.120	0.551
Sex (male vs. female)	1.248	0.589-2.096	0.669	1.201	0.531-1.705	0.732
BMI (≥24 kg/m^2 vs. <24 kg/m^2)	1.587	0.781-2.406	0.326	1.658	0.730-2.888	0.256
Smoking (ever vs. never)	1.401	0.728-1.757	0.384	1.389	0.657-2.218	0.408
Drinking (ever vs. never)	1.399	0.697-2.188	0.455	1.497	0.687-2.240	0.469
TC (high vs. low)	1.502	0.759-2.337	0.412	1.584	0.726-2.553	0.352
TG (high vs. low)	1.608	0.714-2.587	0.287	1.822	0.796-2.854	0.246
LDL-C (high vs. low)	1.912	0.951-3.841	0.062	2.077	0.906-3.895	0.069
HDL-C (low vs. high)	1.857	0.912-2.816	0.118	1.912	0.856-3.511	0.130
UA (high vs. low)	2.022	0.979-4.005	0.059	1.923	0.859-3.687	0.072
BNP (high vs. low)	4.106	1.855-6.304	0.014	3.998	1.725-6.874	0.022
LVEF (low vs. high)	2.027	1.612-2.419	0.038	2.114	0.982-3.763	0.059
Complication (yes vs. no)	2.409	0.989-3.205	0.055	2.541	0.984-4.167	0.064
NYHA stage (high vs. low)	3.995	1.974-6.207	0.008	3.597	1.884-6.496	0.016
NEAT1 (high vs. low)	3.228	1.846-4.789	<0.001	3.197	1.702-5.879	0.006
miR-129-5p (low vs. high)	3.666	2.017-5.294	0.002	3.549	1.975-6.365	0.012

BMI, body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; UA, uric acid; BNP, brain natriuretic peptide; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; HR, hazard ratio; NEAT1, nuclear-enriched abundant transcript 1; miR, microRNA.

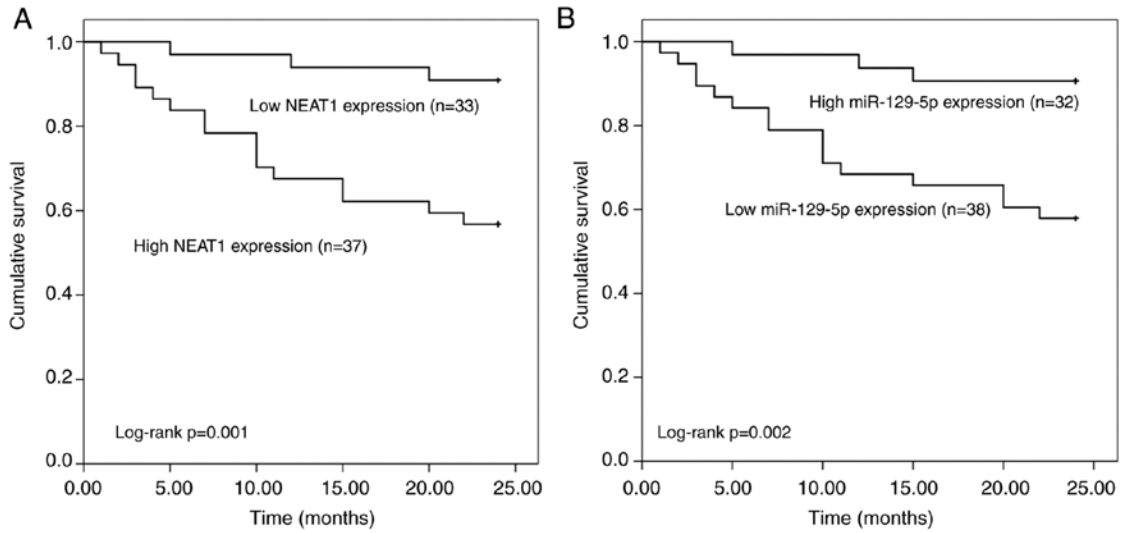

Figure 4. Prognostic value of the NEAT1/miR-129-5p in predicting survival rates of patients with CHF. (A) Kaplan-Meier curves demonstrated that the survival rate of patients with CHF with higher circulating NEAT1 (n=33) was significantly lower than that of patients with CHF with lower NEAT1 (n=37; P=0.001). (B) Kaplan-Meier curves demonstrated that the survival rate of patients with CHF with lower circulating miR-129-5p levels (n=38) was significantly lower than that of patients with CHF with higher miR-129-5p levels (n=32). CHF, chronic heart failure; miR, microRNA; NEAT1, nuclear-enriched abundant transcript 1.

revealed that NEAT1 was significantly upregulated, while miR-129-5p was downregulated in the serum of patients with CHF when compared to normal controls. Pearson correlation coefficient analysis indicated a significant negative correlation between NEAT1 and miR-129-5p expression levels in patients with CHF. Furthermore, with the increase of the NYHA stage, the expression level of miR-129-5p was downregulated and the expression level of NEAT1 was upregulated. The results all suggested that NEAT1 and miR-129-5p may have a role in CHF. This may provide an approach to improve the treatment of CHF, namely by screening out patients at the early stage of NYHA based on the expression levels of NEAT1 and miR-129-5p.

The NEAT1/miR-129-5p axis has an important role in the occurrence and development of numerous diseases. For instance, lncRNA NEAT1 suppression was able to

inhibit papillary thyroid cancer progression by upregulating miR-129-5p (33). In breast tumorigenesis, dysregulation of the BRCA1/NEAT1/miR-129-5p/WNT4 signaling axis has a promotive role (34). Fu *et al* (35) indicated that NEAT1 expression was aberrantly increased in hepatoblastoma and that it may promote the metastasis of hepatoblastoma cells by inhibiting miR-129-5p. In addition, certain studies investigated the potential mechanisms of NEAT1 and miR-129-5p. For instance, NEAT1 was indicated to regulate the expression of inflammatory chemokines and cytokines to affect the MAPK pathway in systemic lupus erythematosus (36). Zhang *et al* (13) determined that miR-129-5p was able to partially inhibit hydrogen peroxide-induced cell autophagy and apoptosis by downregulating autophagy related 14 expression levels through activation of the PI3K/AKT/mTOR pathway. miR-129-5p was able to regulate hydrogen peroxide-induced injury of cardiomyocytes by mediating NEAT1. However, the clinical application of NEAT1 and miR-129-5p remains to be established (11). Based on the above, it is indicated that the NEAT1/miR-129-5p axis has an important role in CHF and may be of clinical value. In the present study, correlation analyses suggested that both NEAT1 and miR-129-5p had linear correlations with diagnostic markers (BNP, LVEF) of CHF. Thus, the NEAT1/miR-129-5p axis may serve as a novel CHF marker, and it is suggested that a high level of NEAT1 and low level of miR-129-5p are closely associated with poor prognosis of patients with CHF. The present study determined that the diagnostic power of NEAT1 and miR-129-5p for CHF was high; the good diagnostic value of NEAT1 was demonstrated by an ROC curve with an AUC of 0.868 and miR-129-5p also has a high diagnostic value with an AUC of 0.921. Of note, compared with BNP alone, the combination of NEAT1, miR-129-5p and BNP had the best diagnostic value and significantly improved the diagnostic accuracy. Thus, NEAT1 and miR-129-5p may be potential diagnostic biomarkers for CHF and may be used to enhance the diagnostic accuracy of BNP in CHF. The Kaplan-Meier survival curves indicated that patients with high NEAT1 or low miR-129-5p expression had poor overall survival. Multivariate Cox analysis revealed that NEAT1 and miR-129-5p were independent prognostic factors for survival in patients with CHF. These results demonstrated that NEAT1 and miR-129-5p may be used as ideal biomarkers for the diagnosis and prognosis of CHF.

In conclusion, the present study was the first to demonstrate the deregulation of serum NEAT1 and miR-129 and their clinical significance in patients with CHF. The results of the ROC analysis indicated that NEAT1 and miR-129-5p had high diagnostic accuracy and considerable potential to improve the diagnostic accuracy of BNP in CHF. Higher NEAT1 and lower miR-129-5p were predictive of poor prognosis for patients with CHF. Therefore, the NEAT1/miR-129-5p axis may provide noninvasive diagnostic and prognostic biomarkers for CHF. However, the present study has certain limitations, such as the limited sample size and the follow-up time to assess prognosis may have been relatively short. In addition, the underlying mechanisms of the implication of the NEAT1/miR-129-5p axis in CHF were not fully explored in the present study and in a future study by our group, the roles of the NEAT1/miR-129-5p axis in relation to CHF will be further investigated in cardiomyocytes using a well-established experimental protocol.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HZ and XL designed the present study and were responsible for writing and revising the manuscript. NZ and WJ collected the clinical samples and data. HZ and XL analyzed the data and confirmed the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from each patient and the experimental procedures were approved by the Ethics Committee of Weifang People's Hospital (Weifang, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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