Research Square

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Diagnostic and Prognostic Value of Selected MicroRNAs in Patients with Acute Heart Failure

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Research Article

Keywords: heart failure, Biomarkers, Genetics, microRNA

Posted Date: December 9th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-117036/v1

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Abstract

Background: Measurement of the level of circulating microRNAs (miRNAs) has been introduced as a convincing diagnostic modality in a variety of diseases including acute heart failure (AHF). There are also a few encouraging results that advocate the prognostic value of miRNAs in AHF. Our aim in this study was to evaluate the diagnostic and prognostic value of selected miRNAs in patients with AHF.

Method: Forty-four patients were randomly selected from AHF patients attending the Madani Heart Center of the Tabriz University of Medical Sciences from 1st April 2018 to 31st August 2018. 58 healthy participants were included as the control group. The plasma level of selected miRNAs including miR -1, -21, -23, and -423-5-p were measured in both groups. In the second phase, patients were followed for one year and several outcomes were recorded including in-hospital mortality, one-year mortality, and the number of readmissions.

Result: An overall 102 plasma samples were evaluated. There was no significant difference in demographic characteristics between the two groups ($p > 0.05$). Mean levels of miR-1, -21, -23, and -423-5-p in AHF patients were significantly higher than the control group (p values=0.001, 0.002, 0.002, and 0.001, respectively). All selected miRNAs demonstrated high diagnostic power. The highest sensitivity and specificity were seen in miR-423-5-p which were 90% and >99%, respectively ($p = 0.001$, AUC = 0.909). The follow-up data demonstrated these miRNAs had no significant association with prognostic outcomes ($p>0.05$ for all variables).

Conclusion: The result of our study demonstrated that miR-1, -21, -23, and -423-5-p can be considered as biomarkers with high sensitivity and specificity in AHF. However, we found no evidence supporting the efficacy of these miRNAs as prognostic factors.

Introduction

Acute heart failure (AHF) is one of the most life-threatening and burdensome cardiovascular diseases in both developed and developing countries (1, 2). Currently, around six million patients have HF in the United States and it is estimated that it will rise up to more than eight million patients by 2030 (3). Timely and accurate diagnosis of AHF and distinguishing it from chronic heart failure (CHF) is of great importance. However, it is not always feasible to make a definite diagnosis merely based on history, physical examination, and echocardiogram (4). Therefore, finding novel biomarkers is warranted in this regard.

The currently-established biomarkers including brain (B-type) natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) for assigning the diagnosis of AHF and determining its prognosis have their limitations. For instance, a series of conditions such as older age, obesity, poor renal function, atrial fibrillation, thromboembolic events, etc. can affect their serum levels and may alter the results of the tests (5, 6). Moreover, a multicenter trial investigating over 1100 high-risk subjects with systolic HF reported no beneficial effect of using NT-proBNP-guided strategy within the routine outpatient management of those

patients (7). Micro-ribonucleic acids (miRNAs) are small non-coding RNAs with 21-25-nucleotide length (8). Since their discovery in 1993 in nematode Caenorhabditis elegans, their role in several physiological and pathological conditions has been widely studied (9-14). Rooij et al. revealed that miR-195 was significantly increased in the failing human heart and has an important role in cardiac remodeling in transgenic mice (15). Thereafter, a spread of biologic effects of miRNAs within the circulatory system are introduced by further studies including their role in cardiac fibrosis and hypertrophy which are essential HF pathophysiologies (16). However, few studies have investigated the role of miRNAs in the diagnosis and prognosis of AHF. Therefore, in this study, we aimed to evaluate the applicability of selected miRNAs (including miR-1, -21, -23, and -423-5-p) in the diagnosis and prognosis of AHF patients.

Materials And Methods

This study consisted of two phases (supplementary figure 1). In the first phase with a case-control design, the plasma samples of the AHF patients and healthy control group were evaluated for the level of selected miRNAs including miR -1, -21, -23, and -423-5-p. Also, baseline demographic and clinical characteristics were recorded and investigated in association with the level of miRNAs. In the second phase, patients were followed for one year after admission and several outcomes were recorded including in-hospital mortality, one-year mortality, number of readmissions, administration of implantable cardioverter-defibrillator (ICD), and NYHA function class (FC) after one year. The study was conducted in accordance with the ethical guidelines of the declaration of Helsinki and the protocol was approved by the ethics committee of the university. Patients or healthy participants were not included unless they give written informed consent after a brief description of the aim of the study.

Patients' inclusion:

AHF patients were included who were admitted with either acute decompensation of CHF or de novo AHF according to Framingham-based criteria and confirmation of two attending cardiologists to a tertiary care hospital during a 5 months period. Patients with heart failure with reduced ejection fraction (HfrEF: at least one major Framingham-based criteria/two minor criteria and ejection fraction [EF] <40%) and those with heart failure with preserved ejection fraction (HfpEF: at least one major criteria/two minor criteria and EF ≥50%) were included and those with midrange EF (40% ≤EF <50%) were excluded. An overall, 44 patients were randomly selected from included AHF patients and 58 healthy control participants were selected from the hospital staff or accompanying relatives of the patients.

Plasma sample:

5ml Blood samples were obtained within 24 hours after admission by a direct venous puncture into sodium citrate containing tubes. The samples were stored at -80°C and were subjected to freeze-thawing once.

RNA isolation:

RNA was extracted by Tripura isolation reagent (Roche Inc., cat no.11667165001) according to the manufacturer's protocol. The integrity of the extracted RNA was evaluated by agarose gel electrophoresis. NanoDrop 2000c UV-Vis spectrophotometer (Thermo, MA, USA) was used for further assessment of extracted RNA.

Complementary DNA syntheses & real-time PCR:

In this study, real-time PCR was used to quantitate the relative miRNA levels in samples. A miRCURY™ LNA™ miRNA RT Kit (Exiqon, cat no. 40023301) was used for cDNA synthesis according to the manufacturer's instructions. Approximately 10 ng of the extracted RNA was used for this purpose. The reactions were carried out in a T100 Thermocycler system (Bio-Rad, CA, USA) at a final volume of 10 µl. The cDNA synthesis kit exerted in the investigation was to reverse-transcribe the RNA of mature miRNAs. The quantification of the mature miRNAs was performed at a light cycler 96 system (Roche, Germany) using the ExiLENT SYBR Green master mix (Exiqon,Cat no. 400203421) and miRNAs specific primer sets (Cat.numbers are summarized in Table 3). PCR was carried out in duplicates and normalized by U6 expression levels considering the required controls (such as non-template control and no reverse transcription) The relative expression levels of target miRNAs were determined by $2^{-\Delta Ct}$ method (ΔCt = Ct target gene – Ct U6).

Statistical Analyses:

GraphPad Prism and SPSS version 22 were used for statistical analysis. All data are reported as mean ± SD/frequency and percentage unless indicated otherwise. The level of selected miRNAs is presented as fold-change relative to controls. Student t-test was used for comparison between two groups in data with normal distribution and Mann-Whitney test for non-normal data or small sample size. ANOVA test or Kruskal-Wallis tests were used in comparisons between more than two groups in data with normal and non-normal distributions or small sample sizes, respectively.

Receiver operating characteristic (ROC) curves were generated to estimate the area under the curve, sensitivity and specificity.

Results

An overall 102 plasma samples were evaluated including the plasma samples from 44 AHF patients and 58 healthy participants (supplementary figure 1). The baseline characteristics of the groups are described in Table 1. No significant difference was seen between two groups in terms of the baseline characteristics including age, sex, body mass index (BMI), and place of residence ($p>0.05$ for each). The data regarding the patients' medical history and addiction are summarized in Table 2. The three most frequent concomitant diseases in AHF patients in our study were ischemic heart disease (65.9 %), hypertension (38.64 %), and diabetes (27.27 %). Mean EF in all AHF patients was 21.75 ± 10.3 percent. Forty patients (90.9%) had HFrEF and the majority of patients had an NYHA FC of III (Table 3). Twenty-nine patients (65.9 %) had AHF due to ischemic causes and de novo AHF was detected in 16 patients (36.4%).

Table 1. Baseline characteristics of groups

		AHF group (n=44)	Control (n=58)	P value
Age, mean ± SD		20 ± 55	14 ± 47	0.162
Sex, n (%)	Male	33 (75%)	46 (79.3%)	0.606
	Female	11 (25%)	12 (20.7%)	
Place of residence, n (%)	Urban	31 (70.5%)	48 (82.8%)	0.141
	Rural	13(29.5%)	10 (17.2%)	
Body mass index, mean ± SD		6.14 ± 23.55	4.47 ± 26.8	0.168

Table 2. Medical and addiction history of included patients

		n (%)
Concomitant disease	Hypertension	17 (38.64)
	DM	12 (27.27)
	IHD	8 (18.18)
	CABG	1 (2.27)
	Parkinson	1 (2.27)
	BPH	1 (2.27)
	COPD	3 (6.82)
	TB	1 (2.27)
	Congenital myopathy	2 (4.55)
	Acute rheumatic fever	2 (4.55)
	CRF	2 (4.55)
	ICD	1 (2.27)
	Hepatitis	1 (2.27)
	CVA	2 (4.55)
	Asthma	1 (2.27)
Addiction	Smoking	12 (27.27)
	Alcohol	2 (4.55)

Table 3

Properties	Characteristics	n (%)
NYHA function class at admission	I	0 (0)
	II	10 (22.7)
	III	15 (34.1)
	IV	19 (43.2)
Type of heart failure (based on EF)	Reduced EF	40 (90.9)
	Preserved EF	4 (9.1)
Type of heart failure (based on history)	Acute on chronic	28 (63.6)
	de novo	16 (36.4)
Cause	Ischemic	29 (65.9)
	Non-ischemic	15 (34.1)
EF= Ejection fraction		

The mean relative level of miR-1 in the AHF group was 1.930 ± 0.830 (p<0.001) (Figure 1). Its sensitivity and specificity for the values above 1 were 84% and >99%, respectively (p =0.001, AUC = 0.841, supplementary Figure 1). Relative miR-21 level in AHF patients was on average 1.445 ± 0.534 (P = 0.002) with the sensitivity and specificity of the values above 1 of 79.5% and >99%, respectively (p = 0.001, AUC = 0.807). The mean relative level of miR-23 AHF was 1.490 ± 0.545 (p=0.002). Its sensitivity and specificity for the values above 1 were 86.4% and >99%, respectively (p =0.001, AUC = 0.874). Relative miR-423-5-p level in AHF patients was on average 1.681 ± 0.546 (P <0.001) with the sensitivity and specificity for the values above 1 of 90% and >99%, respectively (p = 0.001, AUC = 0.909, supplementary Figure 2).

The levels of miR-21 and miR-423-5-p were higher in patients with HFpEF than those with HFrEF, although these differences were not statistically significant (p = 0.775, p=0.760, respectively). The levels of miR-1 and miR-23 were lower in patients with HFpEF than those with HFrEF, also these differences were not statistically significant (p = 0.353, p=0.420, respectively) (Figure 2).

The levels of miR-21 and miR-23 were significantly lower in patients with HF due to ischemic causes than those in non-ischemic causes (p = 0.027. p = 0.029). However, no significant differences were seen in the levels of miR-1 and miR-423-5-p between those with HF due to ischemic and those with non-ischemic causes (Figure 3). Also, no significant difference in the levels of selected miRNAs was detected between AHF patients with de novo and acute on chronic HF (Figure 4).

Patients' follow-up results:

Thirty-five patients were followed up (loss to follow up = 20%). Of these patients, 3 patients (8.5%) died at their initial hospitalization and 7 patients (20%) were deceased 1 to 7 months after discharge (median = 1 month). The cause of death was the decompensation of HF in all patients. Of the surviving patients, 9 patients (25.7%) had not been hospitalized in one year after admission, and 16 patients (45.7%) had readmission for an average of 3 times. An ICD was administered in 3 patients (8.5%). Four patients (16%) were candidates for heart transplantation but no cardiac transplant was performed. Patients' NYHA FC after one year is reported in Table 4. The majority of the surviving patients had an FC of I (44%).

Table 4. The level of miRNAs with respect to their outcomes in follow up

		n	mir1 Mean ± SD	mir21 Mean ±SD	mir23 Mean ± SD	mir423-5-p Mean ± SD
General Condition	bad	8	2.179 ± 0.765	1.360 ± 0.346	1.575 ± 0.276	1.461 ± 0.343
	good	17	1.957 ± 0.908	1.441 ± 0.658	1.502 ± 0.684	1.732 ± 0.663
P value*			0.511	0.887	0.588	0.288
In hospital mortality	No	23	1.818 ± 0.819	1.474 ± 0.571	1.462 ± 0.589	1.728 ± 0.589
	Yes	3	1.940 ± 0.937	1.213 ± 0.240	1.533 ± 0.387	1.837 ± 0.150
P value*			0.759	0.405	0.571	0.436
readmission	No	9	1.957 ± 0.656	1.643 ± 0.782	1.682 ± 0.821	1.970 ± 0.740
	Yes	16	2.068 ± 0.967	1.287 ± 0.381	1.438 ± 0.393	1.463 ± 0.399
P value*			0.598	0.187	0.598	0.065
Alive/Dead	Dead	10	2.082 ± 0.920	1.350 ± 0.282	1.429 ± 0.407	1.742 ± 0.344
	Alive	25	2.028 ± 0.855	1.415 ± 0.570	1.526 ± 0.579	1.646 ± 0.586
P value*			0.957	0.733	0.733	0.186
ICD	Yes	3	2.036± 0.712	1.499± 0.598	1.578± 0.653	1.675± 0.645
	NO	21	0.884± 0.779	1.147± 0.248	1.303± 0.075	1.720± 0.361
P value*			**0.030**	0.191	0.265	0.718
FC in F/U	1	11	1.993 ± 0.848	1.595 ± 0.689	1.638 ± 0.746	1.859 ± 0.740
	2	6	2.150 ± 0.702	1.100 ± 0.547	1.253 ± 0.521	1.613 ± 0.524
	3	3	1.254 ± 01.047	1.273 ± 0.323	1.533 ± 0.237	1.263 ± 0.249
	4	5	2.422 ± 0.869	1.482 ± 0.279	1.600 ± 0.321	1.444 ± 0.183
P value#			0.335	0.352	0.699	0.288

* Mann-Whitney U test, # Kruskaw-Wallis test

At patients' follow up, we detected no significant differences in the level of miRNAs in association with evaluated outcomes (Table 4), except for a significantly higher level of miR-1 in patients who received ICD

during the follow up (2.036± 0.712 vs 0.884± 0.779, p = 0.030). However, it had relatively low power in the prediction of ICD implementation (AUC = 0.114, p = 0.035).

Discussion

Even though miRNAs are considered as novel biomarkers for diagnosis of AHF, they are not established in clinical setting yet. These biomarkers have some advantages as compared to the established biomarkers such as NT-proBNP. The confounding factors which were indicated to affect the level of NT-proBNP such as age, obesity, sex, and renal function, do not have any significant influence on the level of miRNAs (17). Moreover, miRNAs can be detected in a variety of body fluids including blood, saliva, urine, milk, amniotic fluid, etc. (18). The current study investigated the applicability of selected miRNAs (including miR-1, -21, -23, and -423-5-p) in the diagnosis and prognosis of AHF patients. We found a significant elevation of these miRNAs in the plasma samples of AHF patients as compared to healthy control subjects. They also demonstrated impressive diagnostic power and significantly high sensitivity and specificity. The highest sensitivity and specificity in our study were seen in miR-423-5-p. However, we did not find any evidence supporting the prognostic value of these miRNAs. Even though, it does not rule out their applicability due to some limitations of our study which is discussed below. As far as the authors of the present study investigated, this is the first study that provides evidence for the diagnostic role of miR-21 in AHF patients. However, the diagnostic utility of miR-1, -23 and -423-5-p has been demonstrated in some previous studies (19-23), as well as, but there are some controversies. Corsten et al. (17) failed to detect any elevation in the level of miR-1 and -21 in AHF as compared to healthy controls. Also, Seronde et al. (20) postulated that the levels of miR-21 and miR-23 were similar among patients with AHF, stable CHF, and non-AHF with dyspnea. Moreover, miR-1 was significantly lower in AHF or stable CHF patients as compared to non-AHF with dyspnea. Zhang et al. (24) demonstrated a significant diagnostic value of miR-21 for CHF with a sensitivity of >99 percent, a specificity of 97.5 percent. A recent meta-analysis revealed that miR-423-5-p is an appropriate diagnostic biomarker for HF with a pooled sensitivity of 81 percent and a pooled specificity of 67 percent (25). Therefore, our study provided further confirmation on the diagnostic value of these miRNAs in AHF.

In the current study, we also investigated the levels of selected miRNAs in association with the cause of AHF and HF type based on EF and history of chronic HF (de novo or acute on chronic). However, we did not detect any significant differences in the levels of selected miRNAs in association with these outcomes, except for miR-21 and miR-23 which were significantly lower in patients with HF due to ischemic causes than those with non-ischemic causes. Previously, some similar unsuccessful results have been reported by other investigators. Elis et al. (19) also did not find any significant differences in the levels of miR-23 and miR-423-5-p between patients with HFrEF and HFpEF. Likewise, Seronde et al. (20) demonstrated no significant differences between de novo and acute on chronic AHF patients in terms of selected miRNAs including miR-1, -21, -23, and -423-5-p.

One year follow up of AHF patients in our study showed no applicability of these selected miRNAs in a one-year prognosis. Previously, Seronde et al. (20) also failed to detect any prognostic value for miR-1,

-21, -23, and -423-5-p in terms of predicting readmission and one-year mortality. Cakmak et al. (26) postulated an upregulation of miR-21 in HF but reported that it had no significant prognostic value. However, Zhang et al. (10) demonstrated a significant correlation of miR-21 with patients' two-year mortality but not with readmission rate. Schneider et al. (27) reported that increased level of miR-21 at the time of clinical compensation was associated with better two-year survival and longer rehospitalization-free. Furthermore, they demonstrated that higher miR-423-5p between the time of admission and clinical compensation was associated with fewer hospital readmissions in two-years. Therefore, the time of acquisition of plasma samples may affect the prognostic applicability of miRNAs.

Our study had some limitations. Although epidemiologic studies report that there are higher proportions of patients with HFpEF, there were few patients with HFpEF in our study. However, the inclusion of the patients in this study was completely random and we did not select the patients based on their HF type. Additionally, relatively small sample size in our study prevented us to evaluate accurately the level of miRNAs among AHF patients with different characteristics. Also, we had a relatively high rate of loss to follow up (20%), therefore, the same problem existed in the analysis of the patients' follow up data. Even though, 20 percent is suggested to be an acceptable rate for loss to follow up (28). However, financial limitations prevented us to include more patients. Furthermore, it was better to compare AHF with other patients with dyspnea instead of healthy control. Moreover, a two-gated study design can be assumed as another source of bias for our study which should be avoided in future studies. Finally, although the diagnosis of the patients was assigned by two attending cardiologists and we tried to meticulously evaluate patients to assign the diagnosis according to the current established guidelines, it was better to confirm the patients' diagnosis with an objective test such as NT-proBNP. However, performing this test was not feasible for us.

Conclusions

Our study demonstrated a significantly high diagnostic power of four selected miRNAs (miR-1, -21, -23, 423-5-p). Although considering some limitations of our study, further studies are warranted to confirm it. Moreover, our results do not provide adequate evidence for the prognostic value of these miRNAs in AHF.

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the ethical guidelines of the declaration of Helsinki and the protocol was approved by the ethics committee of the university. Written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: All Data and material collected during this study are available from the corresponding author upon reasonable request.

Conflicts of interest/Competing interests: None declared.

Funding: This study was supported by the Tabriz University of Medical Sciences.

Authors' contributions: Conceptualization: SRSE, MA, RB; Methodology: SRSE, NA, HZ, VZ; Formal analysis and investigation: SRSE, DS, EE, HT, RB, NA; Writing (original draft preparation): SRSE, EE, VZ; Writing (review and editing): NA, RB, HT, VZ; Funding acquisition: NA, RB; Resources: NA, RB; Supervision: NA, RB

Acknowledgements: None.

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Figures

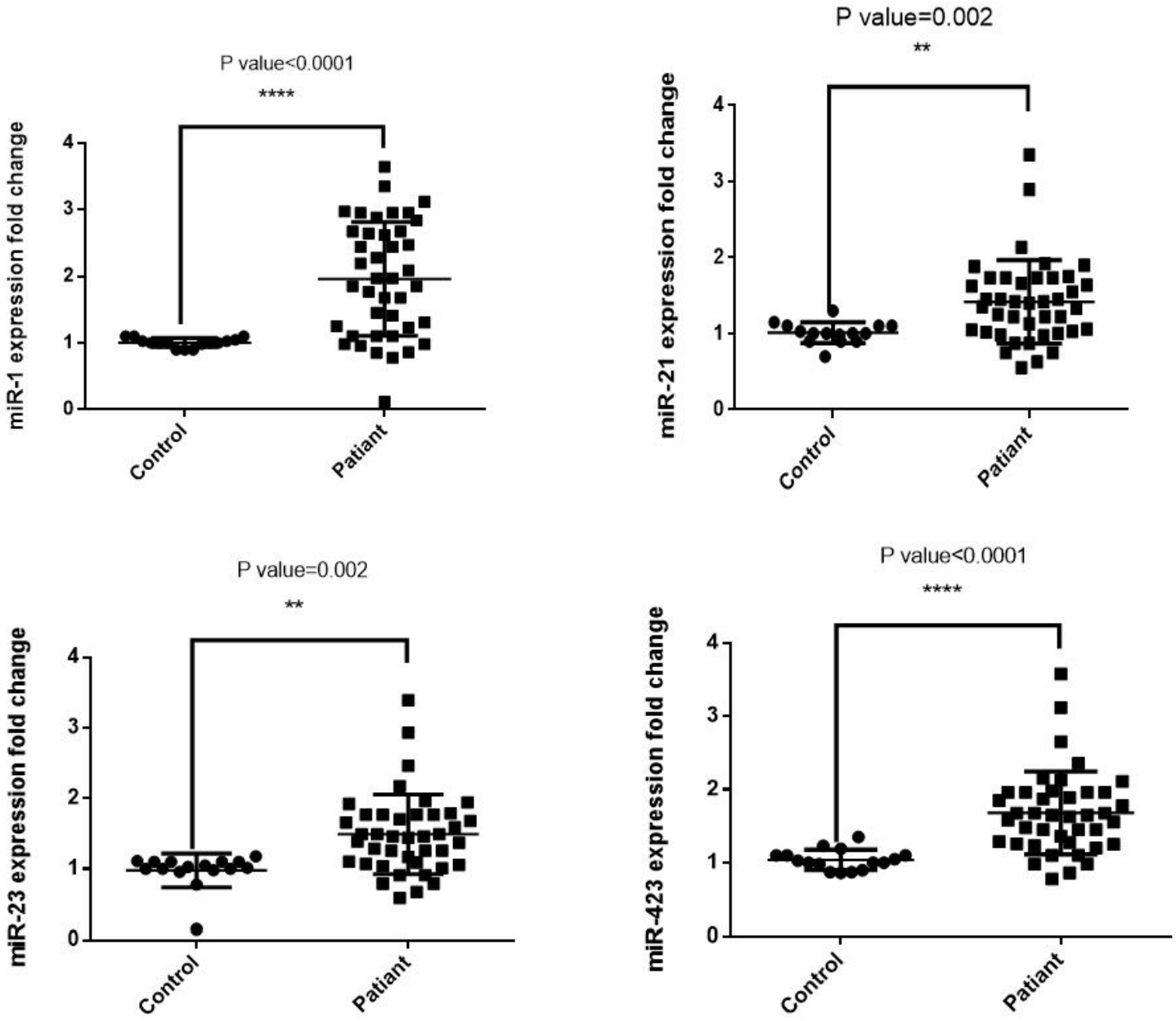

Figure 1

The levels of four selected miRNAs in two groups

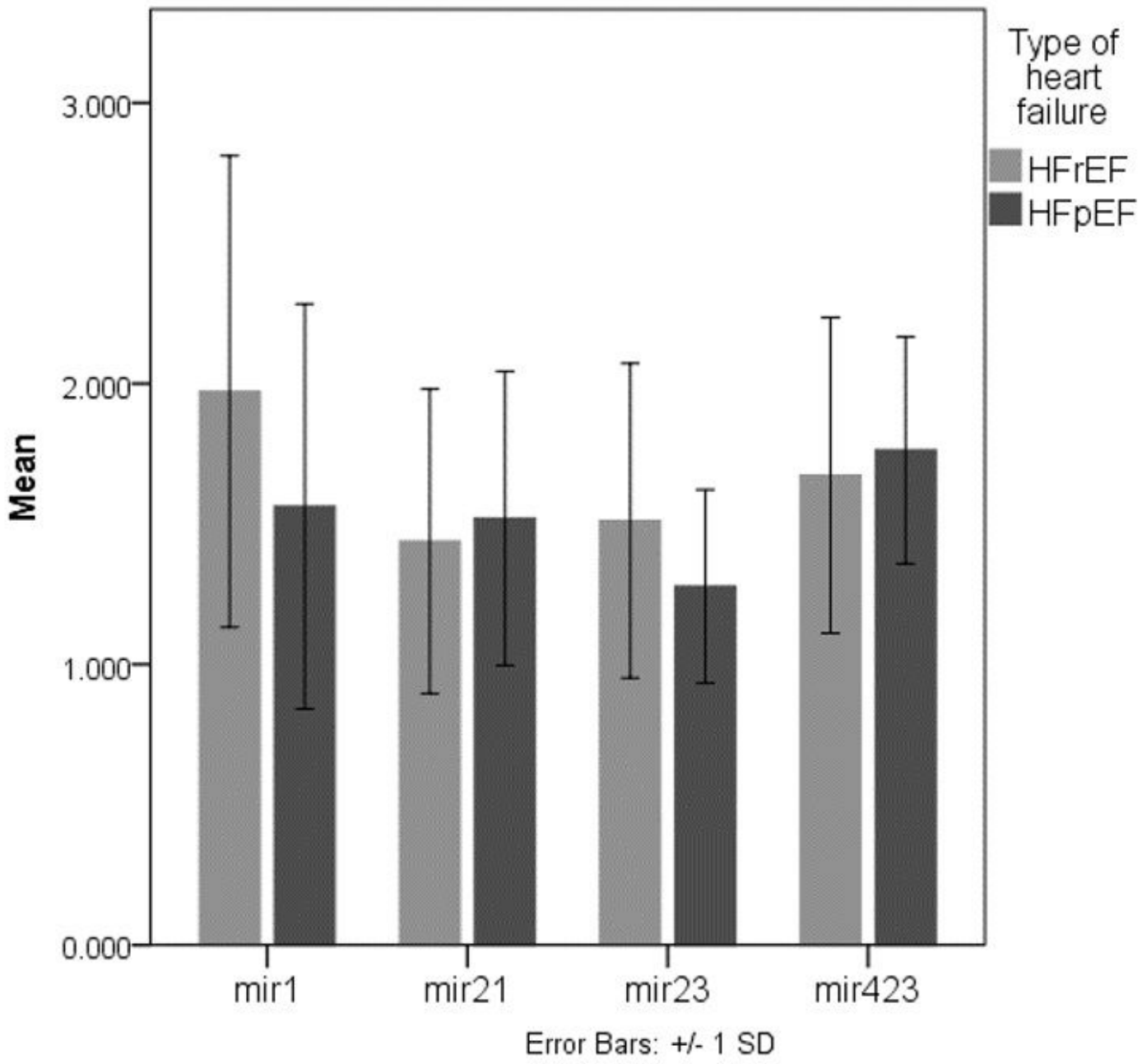

Figure 2

The levels of selected miRNAs in two types of heart failure (heart failure with reduced ejection fraction [HfrEF] and with heart failure with preserved ejection fraction (HfpEF])

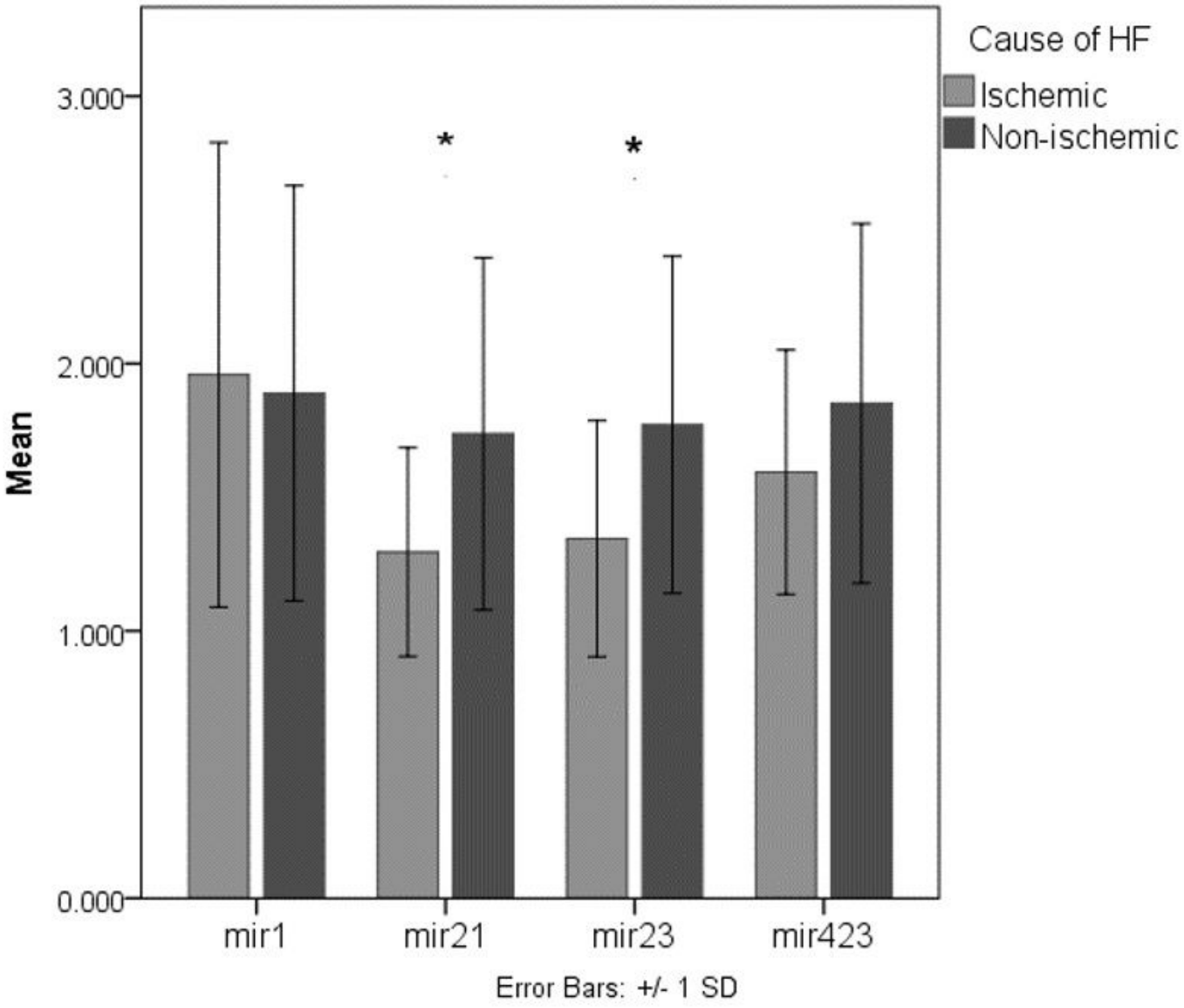

Figure 3

The levels of selected miRNAs with respect to the cause of heart failure

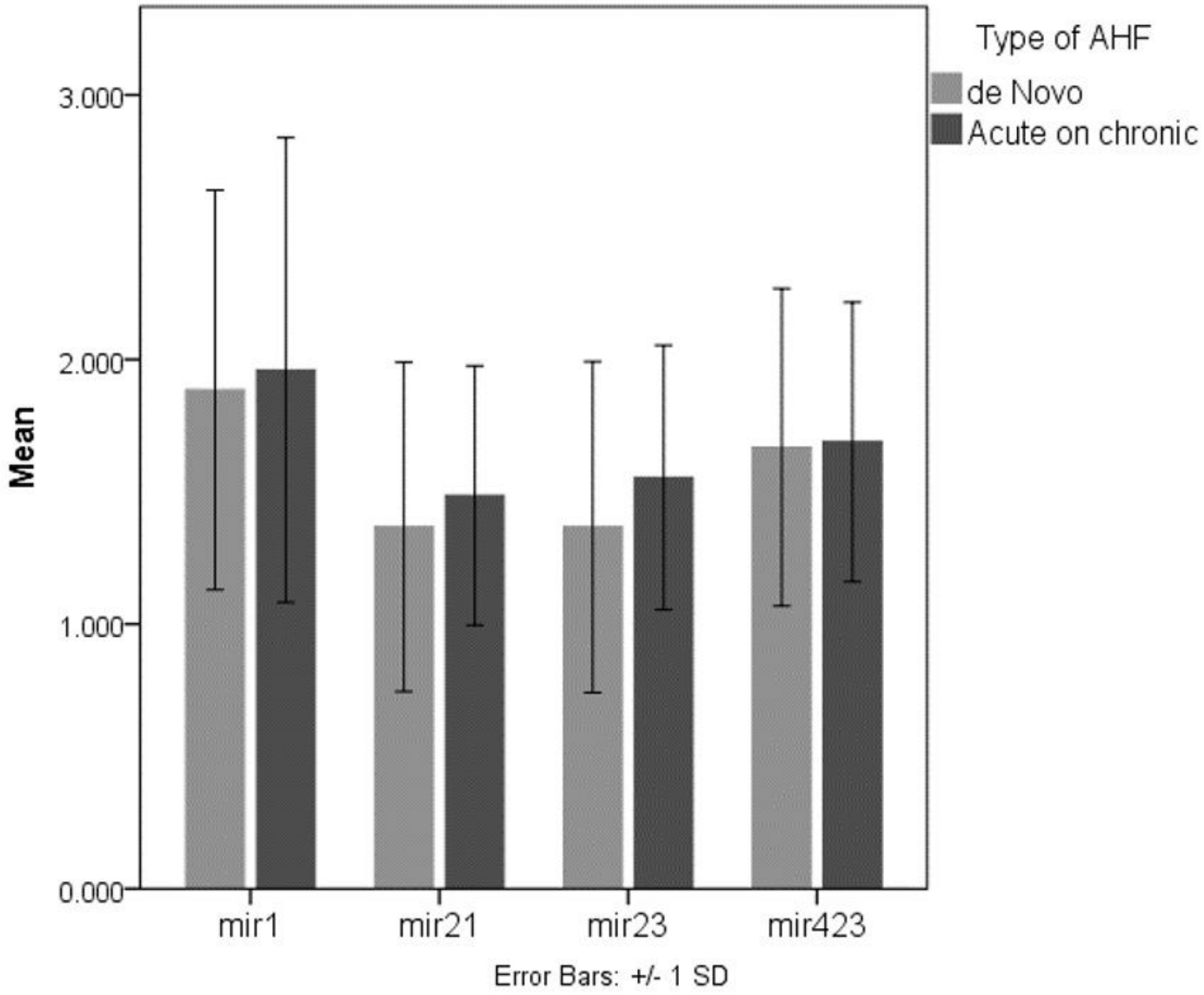

Figure 4

The levels of selected miRNAs with respect to the type of heart failure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Sup.docx