Diagnostic value and significance of serum miR-132 combined with miR-223 for sepsis-induced cardiomyopathy

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Abstract. In previous studies, miR-132 and miR-223 were considered to be involved in cellular and pathological processes of diseases. However, the role of early diagnosis and prognosis evaluation in sepsis-induced cardiomyopathy (SIC) remains unknown. The present study aimed to explore the diagnostic value of combined detection of miR-132 and miR-223 for SIC and their correlation with creatine kinase-MB (CK-MB), cardiac troponin I (cTnI), tumor necrosis factor α (TNF-α), and interleukin-6 (IL)-6. SIC patients (n=80) admitted to Tianjin Medical University General Hospital were assigned to the research group (RG), while 60 healthy participants receiving physical examinations at the same period were assigned to the control group (CG). Serum expression profiles of miR-132 and miR-223 were detected by the RT-qPCR. CK-MB and cTnI were assessed using chemiluminescence assay, and TNF-α and IL-6 by enzyme-linked immunosorbent assay (ELISA). Serum miR-132 and miR-223 levels were significantly lower in the RG than in the CG (P<0.001). The sensitivity and specificity for the diagnosis of SIC were 82.50 and 71.67% for miR-132, 95.00 and 61.67% for miR-223, as well as 86.25 and 86.67% for miR-132 combined with miR-223. Serum miR-132 and miR-223 levels were significantly higher in the survivor group than in the deceased group (P<0.001). The sensitivity and specificity for the prognosis of SIC were 85.96 and 65.22% for miR-132 combined with miR-223. Serum miR-132 and miR-223 were negatively correlated with serum CK-MB, cTnI, TNF-α, and IL-6 (P<0.001). miR-132 combined with miR-223 can be used for early diagnosis and prognostic evaluation of SIC, and the two are correlated with CK-MB, cTnI, TNF-α, and IL-6.

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Introduction

Sepsis is an uncontrolled severe inflammatory response, and a common complication in patients in the ICU (1). According to statistics, the number of severe sepsis-related deaths each year is approximately 3.7 million, and the current mortality rate of sepsis in numerous countries remains high (2). Despite significant advancements in the diagnosis and treatment of sepsis over the past 30 years, sepsis remains the leading cause of death among patients, with a 30-day mortality rate of 47% (3,4). Acute organ dysfunction complicated by sepsis is termed sepsis-induced cardiomyopathy (SIC), and sepsis is aggravated once cardiac functions are impaired (5). Approximately 40% of patients with sepsis suffer from myocardial dysfunction, among which myocardial depression is a serious clinical symptom with a mortality of 70 to 90%, while the mortality for sepsis patients without cardiac dysfunction is 20% (6,7). Devoid of specific clinical symptoms in the early stage, early SIC is hard to be diagnosed (8). Thus, the identification of biomarkers involved in the occurrence and development of SIC is of great significance for the early diagnosis and prognosis evaluation of SIC.

micro-RNAs (miRNAs or miRs), non-coding RNAs with 21 to 23 nucleotides, not only regulate gene expression, but are also involved in numerous biological processes such as embryonic development, organogenesis, and human inflammatory diseases (9). Most of the studies on sepsis have centered on the screening of serum miRNA profiles in sepsis patients, and have identified several miRNAs (including miR-155, miR-223 and miR-146a) as potential diagnostic markers for severe sepsis (10,11). miR-132 is an endogenous small RNA that controls the post transcriptional regulation of gene expression through controlled degradation or transcriptional inhibition of mRNA, which can affect the pathogenesis of numerous diseases (12). miR-223 is widely involved in the regulation of cellular processes and numerous types of pathological processes, such as cancer, autoimmune and inflammatory diseases (13). In a study by Li *et al* (14), hesperidin could alleviate lipopolysaccharide-induced neuroinflammation in mice by promoting miR-132 expression. In a previous study (15), serum miR-146a and miR-223 were markedly reduced in patients with sepsis, indicating the two can function as new markers for the diagnosis of sepsis. However, the roles of miR-132 and miR-223 in SIC are not clear. The myocardial toxicity induced by sepsis is mainly related to the reduction

of cardiac energy, impaired myocardial contractility, and the process of inflammatory cytokines. The treatment of sepsis mainly includes optimizing myocardial function and improving inflammatory response (16). Therefore, markers of myocardial injury and inflammatory response are essential for detecting the occurrence and development of SIC.

The present research determined the serum expression profiles of miR-132 and miR-223 in SIC patients, analyzed the value of combined serum miR-132 and miR-223 in the early diagnosis and prognosis prediction of SIC, and investigated the correlation of miR-132 and miR-223 with myocardial injury and inflammatory response markers.

Materials and methods

General data. A total of 80 SIC patients admitted to Tianjin Medical University General Hospital (Tianjin, China) were enrolled in the research group (RG), including 45 males and 35 females, aged from 24 to 81 years, with an average age of 58.6±11.3 years. Sixty healthy participants receiving physical examinations were enrolled in the control group (CG), including 31 males and 29 females, aged from 19 to 79 years, with an average age of 56.2±9.6 years. The guardians of the participants or the patients themselves had full knowledge of this research and signed the informed consent form and had complete clinical data. With no violation of ethics and morality, this research was carried out after obtaining approval from the Ethics Committee of Tianjin Medical University General Hospital.

Inclusion and exclusion criteria. The inclusion criteria was as follows: Patients diagnosed with sepsis according to the diagnostic criteria issued by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) (17); patients aged from 19 to 81 years; patients with complete clinical data; patients with a white blood cell (WBC) count of over $12x10^9/l$, a heart index of over 3.5 l/(min · m^2), a systolic blood pressure of <90 mmHg, a mixed venous oxygen saturation of over 70%, and a mean arterial pressure of <70 mmHg according to the laboratory tests. The exclusion criteria were as follows: Patients with a history of cardiac surgery; patients with autoimmune diseases, congenital heart disease, acute pulmonary embolism, cerebrovascular disease, myocarditis, coronary heart disease, acute pulmonary heart disease, mental illness, acute coronary syndrome, malignant tumors, congestive heart failure, liver and kidney dysfunction; patients with an exposure to other myocardial toxic substances such as doxorubicin, drugs, and alcohol. The aforementioned inclusion and exclusion criteria were applied to the RG. Participants included in the CG were healthy individuals.

Detection methods. Elbow venous blood (5 ml) was obtained from participants within 24 h after admission and placed in a vacuum blood collection tube. After centrifugation at 1,500 x g and 4°C for 15 min, the serum was stored in an EP at -80°C. Serum expression profiles of creatine kinase isoenzyme (CK-MB) (cat. no. D711191), cardiac troponin I (cTnI) (cat. no. D711127), tumor necrosis factor-α (TNF-α) (cat. no. D721026) and interleukin-6 (IL-6) (cat. no. D711013)

were determined by enzyme-linked immunosorbent assay (ELISA) (18). Human TNF-α, IL-6, and ELISA kits were manufactured by Sangon Biotech (Shanghai) Co., Ltd., China and were used according to the manufacturer's instructions. The optical density (OD) of each well was measured with a SpectraMax M multi-mode microplate reader (Shanghai Molecular Devices Co., Ltd.), and the TNF-α and IL-6 levels were determined.

Reverse transcription-quantitative (RT-q)PCR detection. Total RNA extraction was performed using an TRIzol kit (cat. no. 10296010; Invitrogen; Thermo Fisher Scientific, Inc.) in line with the instructions of the manufacturer. The concentration and purity of RNA were determined by DR6000 UV-Vis spectrophotometer (Shanghai Hach Water Analysis Instrument Co., Ltd.). RNA was reversely transcribed into cDNA according to the instructions of the PrimeScript RT kit (cat. no. RR047Q; Takara Bio, Inc.) and then stored at -20°C. U6 was used as the internal reference gene. Primer sequences are presented in Table I. The primers were designed and synthesized by Thermo Fisher Scientific, Inc. The RT-qPCR reaction was performed on an ABI PRISM 7500 fluorescence quantitative PCR instrument using SYBR Green Master Mix (cat. no. A46113; Thermo Fisher Scientific, Inc.). Conditions for the amplification were as follows: 95°C for 15 sec, proceeding with 40 cycles at 60°C for 30 sec, and 72°C for 30 sec. Amplification data analysis was performed according to SDS 2.0.1 (Thermo Fisher Scientific Co., Ltd., Shanghai, China). The results were expressed using $2^{-\Delta\Delta Cq}$ (19).

Statistical analysis. Statistical analysis was performed using SPSS 22.0 (IBM Corp.) and data visualization using GraphPad Prism 8 (GraphPad Software, Inc.). The counting data were represented by [n (%)] and their intergroup comparison was analyzed by the Chi-square test. The measurement data were represented by the mean ± standard deviation and their intergroup comparison was analyzed by the independent t-test. The value of miR-132 and miR-223 single or combined detection in SIC diagnosis was analyzed by the logistic regression equation and the receiver operating characteristic (ROC) curve. The correlation of serum miR-132 and miR-223 with CK-MB, cTnI, TNF-α, ad IL-6 was determined by the Pearson correlation coefficient. P<0.05 was considered to indicate a statistically significant difference.

Results

General data of the RG and CG groups. No marked significance was observed between the RG and the CG with regard to sex ratio, body mass index (BMI), age, smoking, drinking, place of residence, educational level, alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) (P>0.05; Table II).

Expression of serum miR-132 and miR-223 in RG and CG and their diagnostic value for SIC. The relative levels of serum miR-132 and miR-223 in the CG and the RG were (1.43±0.57), (0.82±0.33) and (2.02±0.83), (1.09±0.42) respectively. The relative expression of miR-132 and miR-223 in the RG was

Table I. Primer sequences.

Gene	Forward primer	Reverse primer
miR-132	5'-TGGATCCCCCCCAGTCCCCGTCCCTCAG-3'	5'-TGAATTCGGATACCTTGGCCGGGAGGAC-3'
miR-223	5'-CAGAAAGCCCAATTCCATCT-3'	5'-GGGCAAATGGATACCATACC-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

miR, microRNA.

Table II. General information of the RG and CG [n(%)]/(mean ± SD).

Factor	RG (n=80)	CG (n=60)	t/χ^2	P-value
Sex			0.290	0.590
Male	45 (56.25)	31 (51.67)		
Female	35 (43.75)	29 (48.33)		
BMI (kg/m²)	22.68±2.05	22.76±2.16	0.223	0.824
Age (years)	58.6±11.3	56.2±9.6	1.325	0.187
Smoking			0.364	0.546
Yes	32 (40.00)	21 (35.00)		
No	48 (60.00)	39 (65.00)		
Drinking			0.713	0.399
Yes	35 (43.75)	22 (36.67)		
No	45 (56.25)	38 (63.33)		
Place of residence			0.182	0.669
Urban area	63 (78.75)	49 (81.67)		
Rural area	17 (21.25)	11 (18.33)		
Educational level			4.796	0.187
Primary school	3 (3.75)	2 (3.33)		
Middle school	9 (11.25)	15 (25.00)		
College	38 (47.50)	22 (36.67)		
University	30 (37.50)	21 (35.00)		
ALT (U/l)	24.53±11.05	23.05±10.96	0.787	0.433
AST (U/l)	26.14±12.78	24.63±13.52	0.675	0.501
HDL-C (mmol/l)	1.58±0.25	1.64±0.31	1.267	0.207
LDL-C (mmol/l)	2.31±0.57	2.25±0.36	0.715	0.476
Hospitalization time (days)	25.8±16.7	-	-	-
Primary infection site		-	-	-
Abdominal cavity	45 (56.25)	-		
Respiratory system	29 (36.25)	-		
Blood system	1 (1.25)	-		
Skin and soft tissue	5 (6.25)	-		

RG, research group; CG, control group; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

significantly lower than that in the CG (P<0.001). According to the ROC curves demonstrating the diagnosis of SIC by serum miR-132 and miR-223, the AUC of SIC diagnosis of miR-132 and miR-223 was 0.827 and 0.831, respectively; the sensitivity of miR-132 and miR-223 was 82.50 and 95.00%, respectively; the specificity of miR-132 and miR-223 was 71.67 and 61.67%, respectively; the optimal cut-off value was 1.08 for miR-132 and 1.74 for miR-223. Using miR-132 and miR-223 as independent variables, the binomial logistic regression analysis was performed to obtain a logistic regression model: Logit (P)=7.555+-3.133 miR-132+-2.655 miR-223. In the diagnosis of SIC by this model, the AUC was 0.922, the sensitivity was 86.25%, the specificity was 86.67%, and the cut-off value was 0.63 (Table III; Fig. 1).

Table III. Diagnostic value of serum miR-132 and miR-223 for SIC between the research and control groups.

Factor	miR-132	miR-223	miR-132 + miR-223
AUC	0.827	0.831	0.922
95% CI	0.754-0.899	0.760-0.903	0.876-0.968
Cut-off	1.08	1.74	0.63
Sensitivity (%)	82.50	95.00	86.25
Specificity (%)	71.67	61.67	86.67

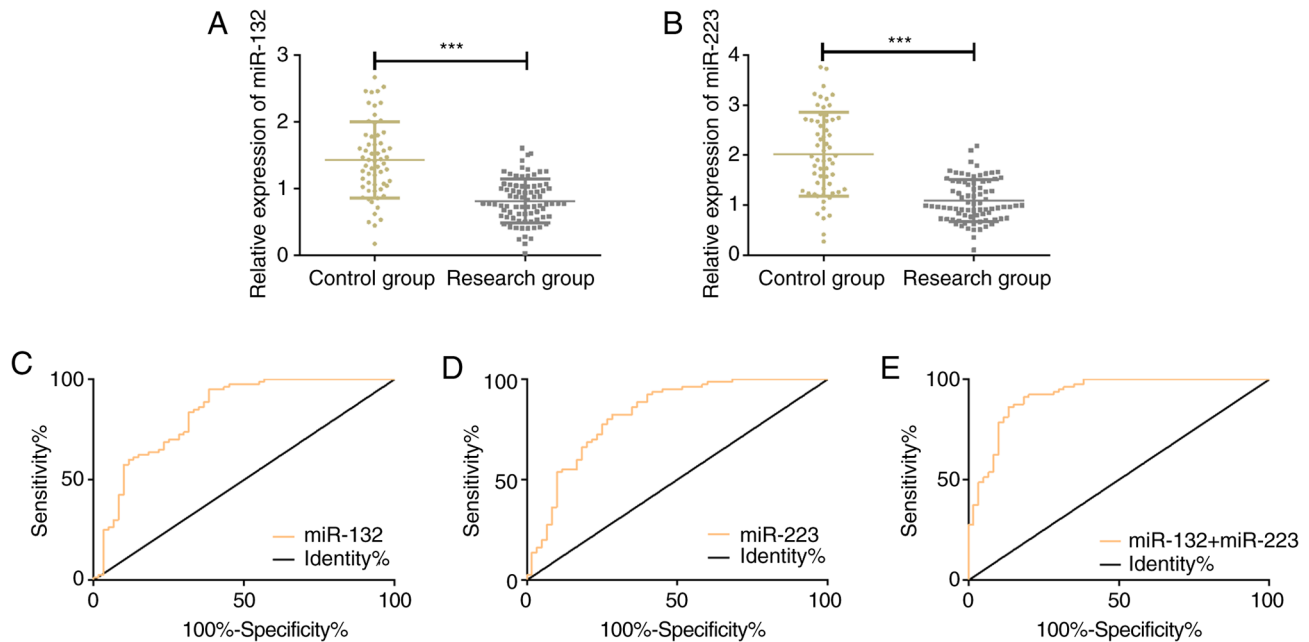miR, microRNA; SIC, sepsis-induced cardiomyopathy; AUC, area under the curve; CI, confidence interval.

Figure 1. Comparison of the relative expression of miR-132 and miR-223 in serum between RG and CG and ROC curve for diagnosis of SIC. (A) The relative expression of miR-132 in the RG was markedly lower than that in the CG. ***P<0.001. (B) The relative expression of miR-223 in the RG was significantly lower than that in the CG. ***P<0.001. (C) The sensitivity and specificity of serum miR-132 were 82.50 and 71.67%, respectively. (D) The sensitivity and specificity of serum miR-223 were 95.00 and 61.67%, respectively. (E) The sensitivity and specificity of serum miR-132 and miR-223 were 86.25 and 86.67%, respectively. miR, microRNA; SIC, sepsis-induced cardiomyopathy; RG, research group; CG, control group; ROC, receiver operating characteristic.

Serum expression profiles of miR-132 and miR-223 in the survivor group (SG) and deceased group (DC) and their prognostic value for SIC. According to the 30-day survival of SIC patients, RG was divided into the SG (n=57) and the DG (n=23). Serum miR-132 and miR-223 levels were (0.89+0.33) and (1.19+0.43) in the SG and (0.64+0.33) and (0.86+0.29) in the DG, respectively. Serum miR-132 and miR-223 levels were significantly higher in the SG than in the DG (P<0.001). According to the ROC curves demonstrating the prognosis prediction of SIC by serum miR-132 and miR-223, the AUC of prognosis prediction of miR-132 and miR-223 was 0.703 and 0.735, respectively; the sensitivity of miR-132 and miR-223 was 82.46 and 56.14%, respectively; the specificity of miR-132 and miR-223 was 60.87 and 82.61%, respectively; the optimal cut-off value was 0.64 for miR-132 and 1.06 for miR-223. Using miR-132 and miR-223 as independent variables, the binomial logistic regression analysis was performed to obtain a logistic regression model: Logit (P)=-2.725++2.124 miR-132++1.970 miR-223. In the diagnosis prediction of SIC by this model, the AUC was 0.773, the sensitivity was 85.96%, the specificity was 65.22%, and the cut-off value was 0.62 (Table IV; Fig. 2).

Correlation of serum miR-132 and miR-223 with markers for myocardial injury and inflammatory response. The serum levels of CK-MB, cTnI, TNF-α, and IL-6 were significantly higher in the RG than in the CG (P<0.001). Pearson correlation analysis revealed negative correlations of serum miR-132 and miR-223 levels with serum levels of CK-MB, cTnI, TNF-α, and IL-6 (r=-0.633, P<0.001; r=-0.532, P<0.001; r=-0.483, P<0.001; r=-0.496, P<0.001; r=-0.603, P<0.001; r=-0.616, P<0.001; r=-0.568, P<0.001; r=-0.511, P<0.001) (Figs. 3 and 4).

Discussion

SIC is a common myocardial complication in patients with sepsis, and its severity poses a threat to human health (20). Research has revealed that numerous miRNAs, including miR-146a, miR-223 and miR-21-3p, are valuable in the

Table IV. Prognostic value of serum miR-132 and miR-223 for SIC between the survivor and deceased groups.

Factor	miR-132	miR-223	miR-132 + miR-223
AUC	0.703	0.735	0.773
95% CI	0.567-0.840	0.619-0.852	0.657-0.888
Cut-off	0.64	1.06	0.62
Sensitivity (%)	82.46	56.14	85.96
Specificity (%)	60.87	82.61	65.22

miR, microRNA; SIC, sepsis-induced cardiomyopathy; AUC, area under the curve; CI, confidence interval.
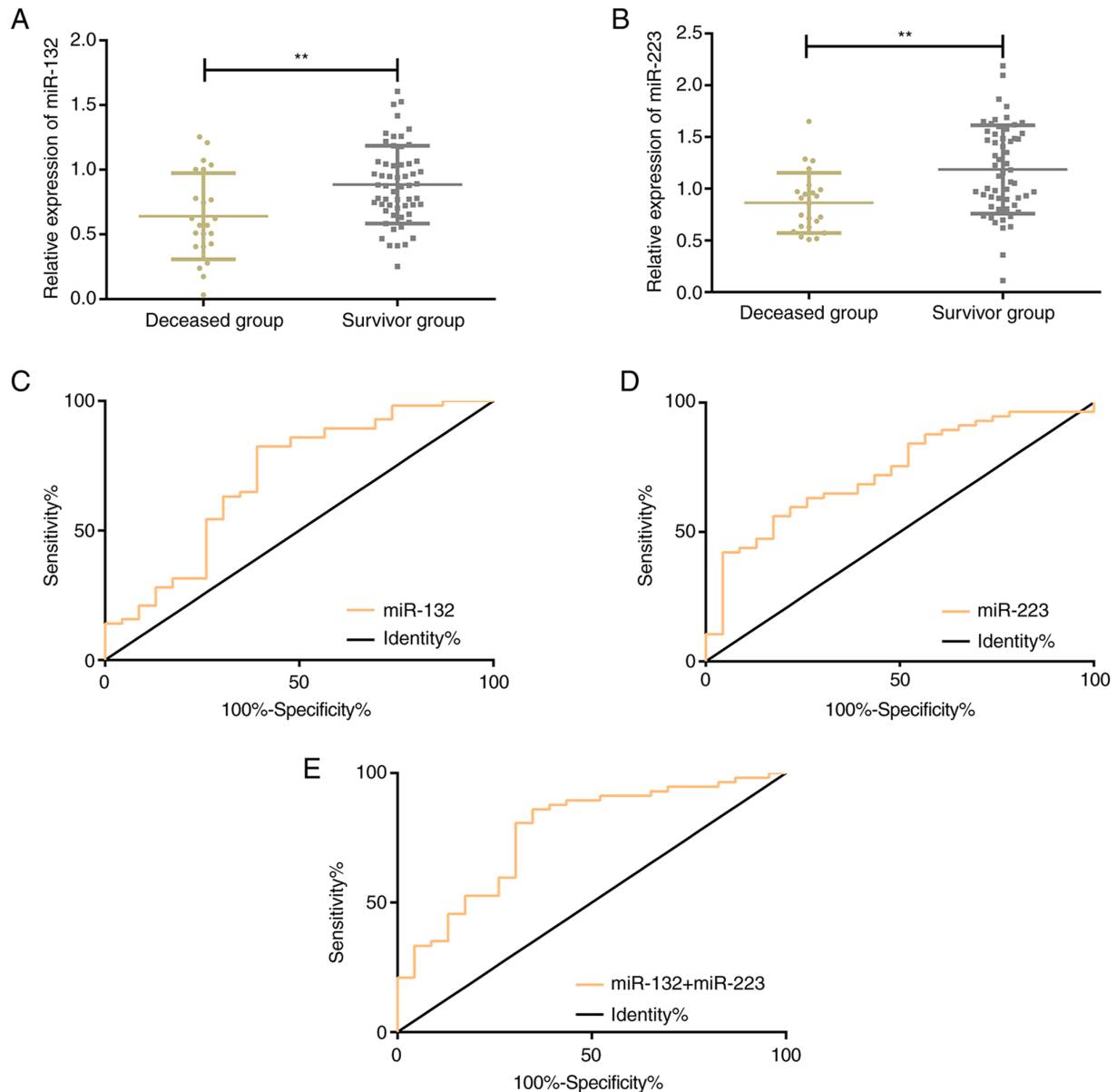

Figure 2. Expression of serum miR-132 and miR-223 in the SG and the DG and their prognostic value for SIC. (A) The relative serum miR-132 level in the SG was significantly higher than that in the DG. **P<0.01. (B) The relative serum miR-223 level in the SG was significantly higher than that in the DG. **P<0.01. (C) The sensitivity and specificity of miR-132 for the prognosis of SIC were 82.46 and 60.87%. (D) The sensitivity and specificity of miR-223 for the prognosis of SIC were 56.14 and 82.61%. (E) The sensitivity and specificity of miR-132 and miR-223 combined detection for the prognosis of SIC were 85.96 and 65.22%. miR, microRNA; SG, survivor group; DG, deceased group; SIC, sepsis-induced cardiomyopathy.

critical regulation of sepsis combined with cardiac dysfunction, although their mechanisms have yet to be elucidated (21).

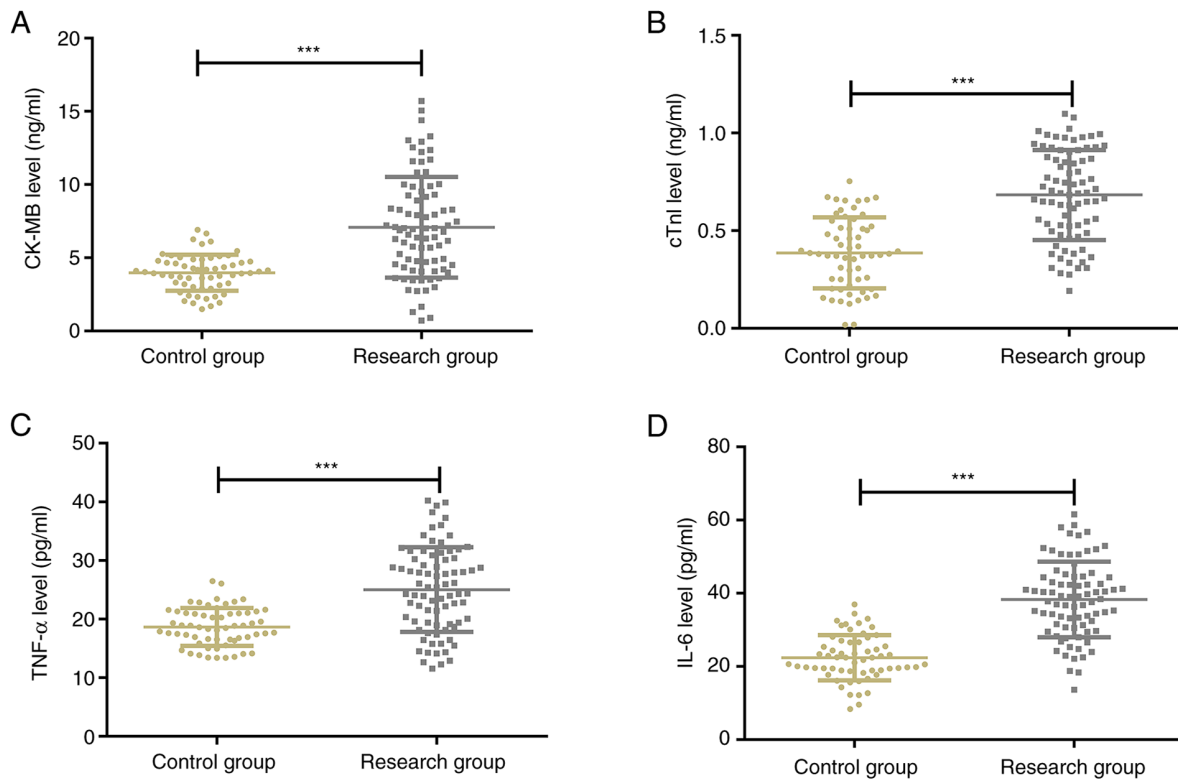Studies on miR-132 and miR-223 in sepsis are numerous. In a study by Liu et al (22), miR-132 inhibited

Figure 3. Comparison of serum levels of CK-MB, cTnI, TNF-α, and IL-6 in RG and CG. (A) Serum CK-MB level in the RG was significantly higher than that in the CG. (B) Serum cTnI level in the RG was significantly higher than that in the CG. (C) Serum TNF-α level in the RG was significantly higher than that in the CG. (D) Serum IL-6 level in the RG was significantly higher than that in the CG. ***P<0.001. RG, research group; CG, control group; CK-MB, creatine kinase-MB; cTnI, cardiac troponin I; TNF-α, tumor necrosis factor α; IL, interleukin.

inflammation responses in lung injury models induced by sepsis. Moreover, the transfection of miR-132 mimics into macrophages pre-processed with acetylcholine inhibited the pro-inflammatory response following lipopolysaccharide challenge by inhibiting NF-κB and STAT3 pathways, and the transfection of miR-132 inhibitors into macrophages pre-processed with acetylcholine promoted the production of TNF-α, IL-1β, and IL-6. A study by Essandoh and Fan (23) reported that miR-223 levels were markedly lower in surviving sepsis patients than in non-surviving sepsis patients, suggesting that a lower miR-223 expression level may result in septic death. miR-132 and miR-223 are potentially important in SIC. Previous studies have focused mostly on the mechanism of action of miR-132 and miR-223 in sepsis (24,25). The diagnostic value of the combination of miR-132 and miR-223 in SIC is unclear. In the present study, the serum levels of miR-132 and miR-223 were significantly downregulated in SIC patients. The combination of the two revealed a good diagnostic value. A previous study (26) discovered that the loss of miR-223 double-stranded (5p and 3p) aggravated the inflammatory response and myocardial dysfunction of multiple sepsis, causing higher mortality. In the present study it was hypothesized that miR-132 and miR-223 may affect the prognosis of SIC. The results revealed that miR-132 combined with miR-223 had a predictive value in the survival of SIC patients. Thus, they are both significant in the early diagnosis and prognosis prediction of SIC.

Inflammatory cytokines including TNF-α and IL-6 that are excessively released in sepsis patients are associated with

cardiac dysfunction (27). CK-MB and cTnI are markers and indicators of myocardial damage, and they can rapidly increase after myocardial damage (28). In a study by Qin *et al* (29), the myocardial enzyme indexes (including CK-MB and cTnI) and inflammation indexes (including TNF-α and IL-6,) of a rat model of myocardial injury induced by sepsis were markedly increased, and the use of erythropoietin protected the heart from sepsis-induced myocardial injury. Markers of myocardial injury and inflammatory response play an important role in SIC. In the present study, the levels of serum CK-MB, cTnI, TNF-α and IL-6 were markedly increased in SIC patients, and miR-132 and miR-223 were both negatively correlated with CK-MB, cTnI, TNF-α, and IL-6. In a previous study (30), the decrease in miR-132 expression increased the levels of TNF-α, IL-1β, and IL-6 and promoted cell apoptosis. In addition, the overexpression of miR-132 played a protective role in rat models with cerebral hemorrhage. A previous study (31) revealed that the high miR-223 level in WT-exosomes was transmitted to cardiomyocytes and in turn led to a decrease in TNF-α, IL-1β, and IL-6, protecting septic patients from myocardial damage induced by mesenchymal stem cells. Hence, the downregulation of miR-132 and miR-223 in SIC may be related to myocardial injury and upregulation of inflammatory factors, but the specific mechanism remains to be elucidated.

The present study confirmed the favorable role of miR-132 and miR-223 combined detection in the early diagnosis and prognosis evaluation of SIC. miR-132 and miR-223 exhibited an inhibitory gene effect in SIC, however, *in vivo* experiments
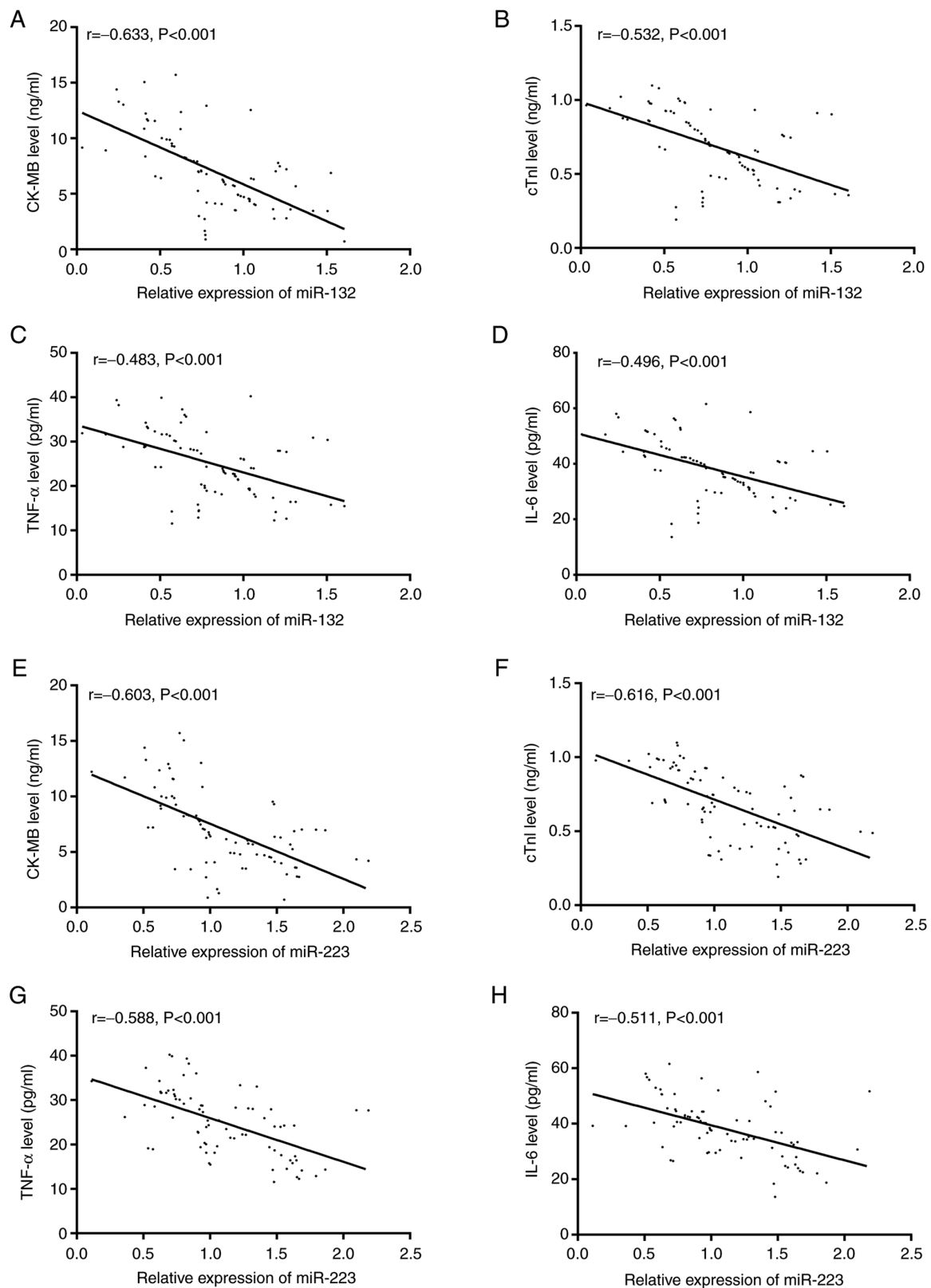
Figure 4. Correlation of serum miR-132 and miR-223 levels with serum levels of CK-MB, cTnI, TNF-α, and IL-6 in the research group. (A-D) Serum miR-132 level was negatively correlated with CK-MB, cTnI, TNF-α, and IL-6 levels (r=-0.633, P<0.001; r=-0.532, P<0.001; r=-0.483, P<0.001; r=-0.496, P<0.001). (E-H) Serum miR-223 level was negatively correlated with CK-MB, cTnI, TNF-α, and IL-6 levels (r=-0.603, P<0.001; r=-0.616, P<0.001; r=-0.568, P<0.001; r=-0.511, P<0.001). miR, microRNA; CK-MB, creatine kinase-MB; cTnI, cardiac troponin I; TNF-α, tumor necrosis factor α; IL, interleukin.

were not conducted. These two miRNAs and their target targets may function in SIC, however the specific regulatory mechanism remains to be elucidated. Furthermore, the present research included individuals undergoing health checkups instead of sepsis in the CG. These shortcomings warrant improvement in future studies to better support the results.

In summary, the combined detection of miR-132 and miR-223 can be used for early diagnosis and prognostic evaluation of SIC, and these two miRNAs were revealed to be correlated with CK-MB, cTnI, TNF-α, and IL-6 levels.

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

YL and YC designed the study and drafted the manuscript. YL, BL, MY, JZ and YY were responsible for the collection and analysis of the experimental data. JZ, YY and YC revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Tianjin Medical University General Hospital (Tianjin, China). Patients who participated in this research, signed the informed consent and had complete clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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