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Review Article

Serum MiR-155 and MiR-143 can be used as prognostic markers for severe sepsis/septic shock in the elderly

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Abstract: Objective: To probe the value of serum miR-155 and miR-143 in the prognosis of severe sepsis/septic shock (SSSS) in the elderly. Methods: Two hundred and three patients with SSSS treated in Shanghai Fengxian District Central Hospital from June 2014 to July 2018 were selected as the research group (RG), and another 100 healthy elderly subjects who underwent physical examination during the same period were included as the control group (CG). The serum levels of miR-155 and miR-143 were detected by qRT-PCR. The clinical data of the patients were collected, and they were classified into a death group and a survival group according to whether they died within 28 days. The area under the curve (AUC) of death diagnosed by miR-155 and miR-143 was determined by ROC. Peason correlation coefficient was employed to analyze the correlation of miR-155 and miR-143 with tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), creatine kinase-MB isoenzyme (CK-MB) and cardiac troponin I (cTnI). Results: Compared with the healthy elderly, miR-155 and miR-143 were over-expressed in those with SSSS. The sensitivity of sepsis patients diagnosed with serum miR-155 were 66.99%, and the specificity was 89.00%; while the corresponding sensitivity and specificity of serum miR-143 in diagnosing sepsis patients were 76.35% and 99.00%. The miR-155 and miR-143 levels in the survival group were notably down-regulated compared to those in the death group ($P<0.05$). Serum miR-155 and miR-143 were positively related to serum TNF-α, IL-6, CK-MB and cTnI concentrations ($P<0.05$). Conclusion: Serum miR-155 and miR-143 can be used as useful prognostic markers for SSSS in the elderly, both of which are related to TNF-α, IL-6, CK-MB and cTnI.

Keywords: miR-155, miR-143, severe sepsis/septic shock, prognosis

Introduction

Severe sepsis/septic shock (SSSS) is a lethal organ dysfunction triggered by the host's maladjusted response to infection, and is a leading cause of death [1, 2]. Moreover, studies have shown that SSSS also leads to honeycomb/metabolic abnormalities, and its incidence increases steadily with the aging of the population [3]. Therefore, early identification and diagnosis of the disease is crucial; however, the diagnosis of early sepsis is very complicated due to the unknown source of infection and the vague definition of sepsis syndrome [4]. Hence, understanding biomarkers in the occurrence and development of sepsis makes a great difference in the early diagnosis and prognostic evaluation of sepsis.

MiRNA is a kind of non-coding RNA that participates in many important biological processes, and there is evidence showing that miRNA is functionally important to the occurrence and development of various complex diseases [5, 6]. For example, studies have reported that a variety of miRNAs, such as miR-25, miR-133a, miR-146, may be potential biomarkers of sepsis [7, 8]. In the study of Lan C, et al. [9], miR-155-5p rose in parallel with the aggravation of sepsis patients, indicating its potential as an independent influencing factor to evaluate the prognosis of sepsis in patients. In addition, Möhnle P et al. [10] revealed that miR-143 was up-regulated in the serum of sepsis patients while miR-150 was down-regulated, suggesting that both could be used as markers for detection of whole blood T cell immunosuppression and may be helpful to develop a new miRNA-based diagnostic method for sepsis. However, little research has been done on the role of miR-155 and miR-143 in SSSS. Severe sepsis often leads to death due to shock: which is

caused by the release of toxins from pathogens that trigger the release of inflammatory mediators; thus reducing systemic or local inflammation can prevent intestinal damage caused by sepsis shock [11]. Therefore, inflammatory response markers act a vital part in the development of SSSS.

In this study, the serum miR-155 and miR-143 levels in SSSS patients were detected to explore their diagnostic value and the potential treatment of this disease.

Materials and methods

General information

Consisting of 117 males and 86 females, a total of 203 patients with SSSS treated in Shanghai Fengxian District Central Hospital from June 2014 to July 2018 were selected as the research participants in the research group (RG).

Inclusion and exclusion criteria: Inclusion criteria: Patients who were over 60 years old; Patients who met the diagnostic criteria for sepsis of the SCCM/ESICM/ACCP/ATS/SIS [12]; Patients with at least one organ dysfunction defined as severe sepsis; Patients with septic shock, which was defined under the condition that adequate fluid was given, but patients still needed to be treated with a booster drug. Exclusion criteria: Patients with an expected survival time of less than 28 days; Patients with lack of major clinical medical records; Patients with malignant tumors; Patients who had taken drugs that may affect the indicators of this study within the past half a year; Patients who were lost to follow up. In addition, another 100 healthy elderly controls, including 64 males and 36 females, who underwent physical examination during the same period were included, and their physical indications proved to be normal after examination. The research was approved by the Medical Ethics Committee of Shanghai Fengxian District Central Hospital. This study was carried out under the full understanding of the participants, with written informed consent obtained from each of them and their guardians.

Sample collection

Venous blood (5 mL) was extracted from the research participants within 24 h after admission, and placed in an anticoagulant-free vacuum blood collection tube before it was centrifuged in a centrifuge of 1500 g for 15 min. Then the serum was collected and stored in an EP tube and stored in at -80°C for later use. Serum TNF-α and IL-6 levels were measured by enzyme-linked immunosorbent assay (ELISA) [13], with the detection kits of human TNF-α and IL-6 ELISA obtained from Hengfei Biotechnology Co., Ltd., Shanghai, China. Sample wells, standard wells and blank wells were set up. The sample wells were given 50 μL of the sample to be tested, the standard wells had 50 μL of the standard, and the blank wells did not have any reagents. Then, 100 μL of horseradish peroxidase-labeled detection antibody was put into the sample and standard wells; the plate was sealed and incubated at 37°C for 60min. The liquid was then discarded, dried and washed repeatedly 5 times. After the substrates A and B (1:1) were thoroughly mixed, 100 μL of the substrate mixture was added to each well, and the plate was sealed for incubation at 37°C for 15 min. Finally, each well was added with 50 μL stop solution, its absorbance (OD) was read by SpectraMax M multi-function board reader (Meigu Molecular instrument Co., Ltd., Shanghai, China), and the TNF-α and IL-6 levels were calculated. ACCESS chemiluminescence instrument was adopted to detect the levels of serum CK-MB and cTnI. The instruments and kits were purchased from Beckman Coulter Trading (China) Co., Ltd. The detection process was carried out strictly in accordance with the instructions of the instrument and kit.

RT-qPCR detection

Total serum RNA was extracted with reference to the instructions of the Ambion kit (Thermo Scientific, Willmington, DE, USA). The concentration and purity of RNA were detected by a DR6000 UV-vis spectrophotometer (HACH water quality analysis Instrument Co., Ltd., Shanghai, China), and cDNA was prepared by referring to the instructions of the miRNA RT-qPCR Detection Kit (Bio-Rad, Hercules, CA, USA). The synthesized cDNA samples were stored at -20°C for later use. With U6 as the internal reference gene, the prime sequence is shown in **Table 1**. The primers were designed and synthesized by Thermo Fisher Scientific (China) Co., Ltd. MiR-132 and miR-223 were quantitatively detected with reference to miRNA RT-qPCR Detection Kit reverse transcription kit

Table 1. Primer sequence

Gene	Upstream primer sequence	Downstream primer sequence
miR-155	5'-ACCCTGCTGGATGAACGTAG-3'	5'-CATGTGGGCTTGAAGTTGAG -3'
miR-143	5'-GGGTGAGATGAAGCACTGTAGCTC-3'	5'-GCTGTCAACATACGCTACGTAACG-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

Table 2. General data of patients in the two groups [n (%)] (x ± sd)

Categories	RG (n=203)	CG (n=100)	t/χ^2 value	*P* value
Gender			1.128	0.28
Male	117 (57.64)	64 (64.00)		
Female	86 (42.36)	36 (36.00)		
Age (years old)			1.060	0.289
	58.18±12.27	56.58±12.52		
BMI (kg/m^2)			0.720	0.472
	21.95±2.15	22.14±2.18		
Educational level			0.756	0.384
≥ High school	107 (52.71)	58 (58.00)		
< High school	96 (47.29)	42 (42.00)		
Ethnicity			0.037	0.845
Han	93 (45.81)	47 (47.00)		
Ethnic minorities	11 (54.19)	53 (53.00)		
Place of residence			1.062	0.302
Urban	105 (51.72)	58 (58.00)		
Rural	98 (48.28)	42 (42.00)		
Drinking history			0.384	0.535
Yes	137 (67.49)	71 (71.00)		
No	66 (32.51)	29 (29.00)		
ALT (U/L)			0.997	0.319
	23.47±11.02	22.15±10.43		
AST (U/L)			1.077	0.282
	25.84±11.73	24.28±12.12		
SBP (mmHg)			1.124	0.262
	115.68±8.59	114.52±8.16		
DBP (mmHg)			0.965	0.335
	74.24±6.78	73.45±6.53		
HDL-C (mmol/L)			1.729	0.084
	1.52±0.23	1.57±0.25		
LDL-C (mmol/L)			0.717	0.473
	2.11±0.51	2.15±0.32		

on ABI PRISM 7500 fluorescence quantitative PCR instrument. Amplification cycle conditions: 95°C, 15 s, 60°C, 30 s, 72°C, 30 s, with a total of 40 cycles. The manufacturer's software was used for amplification data analysis, and the results were represented by $2^{-\Delta CT}$ [14].

Statistical analysis

The collected data were statistically analyzed using SPSS 22.0 (IBM Corp, Armonk, NY, USA), and the required pictures were plotted by GraphPad Prism 8 (IBM Corp, Armonk, NY, USA). The counting data were described in [n (%)], and the measurement data were represented by mean ± standard deviation (x ± SD). The inter-group comparison of the counting data was carried out by the chi-square test, and the inter-group comparison of the measurement data were conducted by the t-test. The receiver operating characteristic curve (ROC) was responsible for the evaluation of the diagnostic value of serum miR-155 and miR-143 in patients with sepsis. Pearson correlation coefficient was used to analyze the correlation of serum miR-155 and miR-143 with TNF-α, IL-6, CK-MB, cTnI. P<0.05 denoted that the difference statistically significant.

Results

General data

The baseline data represented by gender, age, body mass index (BMI), educational level, ethnicity, place of residence, drinking history, alanine transaminase (ALT), aspartate aminotransferase (AST), diastolic blood pressure (DBP), systolic blood pressure (SBP), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) did not reveal any statistically significance differences between the two groups (P>0.05) (**Table 2**).

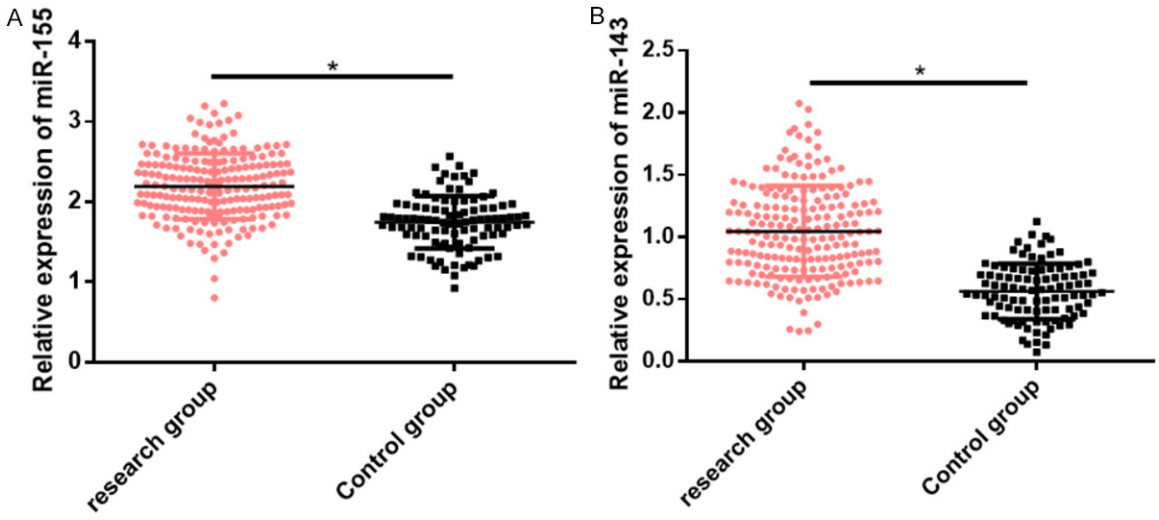

Figure 1. Results of relative expression levels of serum miR-155 and miR-143 in the RG and the CG. A. The RG showed significantly higher serum miR-155 level than the CG (P<0.05). B. The RG showed significantly higher serum miR-143 level than the CG (P<0.05). Note: * indicated P<0.05.

Table 3. ROC parameters of serum miR-155 and miR-143 in patients with sepsis

Diagnostic indexes	AUC	95% CI	Standard error	Cut-off value	Sensitivity (%)	Specificity (%)
miR-155	0.811	0.764-0.857	0.023	2.098	66.99	89.00
miR-143	0.885	0.845-0.923	0.019	0.798	76.35	99.00

Serum miR-155 and miR-143 expression levels in sepsis

The relative expression levels of serum miR-155 and miR-143 in the RG were (2.21±0.41) and (1.08±0.45), respectively; while those in the CG were (1.76±0.25) and (0.59±0.13), respectively. The serum miR-155 and miR-143 levels in the RG were significantly higher than those in the CG (P<0.05) (**Figure 1**).

Value of serum miR-155 and miR-143 in diagnosing sepsis

The ROC curve of serum miR-155 and miR-143 for the diagnosis of sepsis was drawn to determine the optimal cut-off value, with both sensitivity and specificity taken into account. The AUC value of serum miR-155 in diagnosing sepsis was 0.811, the sensitivity was 66.99%, the specificity was 89.00%, and the optimal cut-off was 2.098. While the AUC value of serum miR-143 in the diagnosis of sepsis was 0.885, the sensitivity was 76.35%, the specificity was 99.00%, and the optimal cut-off was 0.798 (**Table 3**; **Figure 2**).

Diagnostic value of serum miR-155 and miR-143 in the survival and death groups for the prognosis of sepsis patients

Patients in the RG were classified into a survival group (148 cases) and a death group (55 cases) according to whether they survived for 28 days. The relative serum miR-155 and miR-143 levels in the survival group were (1.89±0.28) and (0.76±0.21) respectively; while those in the death group were (2.34±0.43) and (1.23±0.44), respectively. The relative serum miR-155 and miR-143 levels in the survival group were noticeably lower than those in the CG. What's more, the prognostic ROC curve of the two for the diagnosis of sepsis was plotted. The AUC value of serum miR-155 in diagnosing sepsis was 0.769, the sensitivity was 87.83%, the specificity was 61.81%, and the cut-off value was 2.237. While the AUC value, sensitivity, specificity and cut-off value of patients diagnosed with sepsis by serum miR-155 were 0.844, 91.21%, 72.72%, and 1.033, respectively (**Table 4**; **Figure 3**).

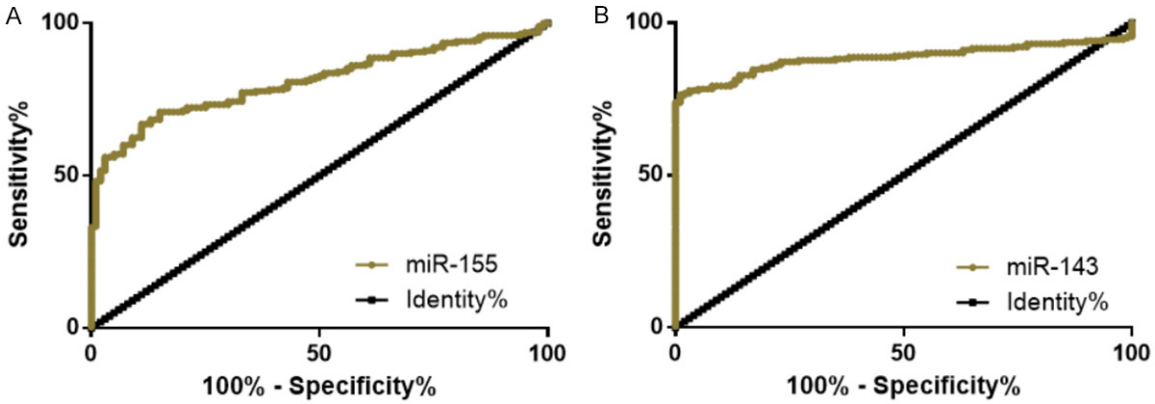

Figure 2. ROC parameters of serum miR-155 and miR-143 in patients with sepsis. A. The sensitivity of serum miR-155 in the diagnosis of sepsis was 66.99%, and the specificity was 89.00%. B. The sensitivity of serum miR-143 in diagnosing sepsis patients was 76.35%, and the specificity was 99.00%.

Table 4. Diagnostic value of serum miR-155 and miR-143 in the prognosis of sepsis patients

Diagnostic indexes	AUC	95% CI	Standard error	Cut-off value	Sensitivity (%)	Specificity (%)
miR-155	0.769	0.682-0.856	0.044	2.237	87.83	61.81
miR-143	0.844	0.768-0.9519	0.038	1.033	91.21	72.72

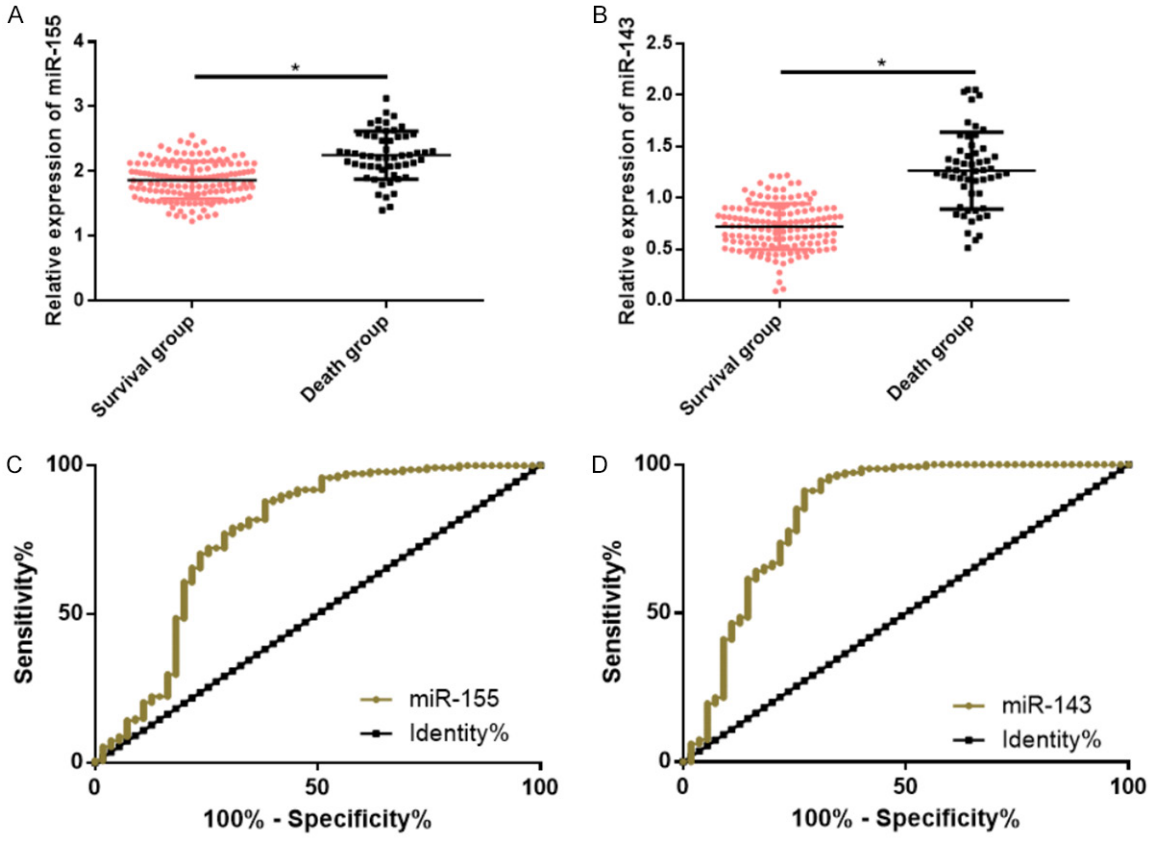

Figure 3. Diagnostic value of serum miR-155 and miR-143 in the survival and death groups for the prognosis of sepsis patients. A. Compared with the death group, the serum miR-155 in the survival group was significantly lower ($P<0.05$). B. Compared with the death group, the serum miR-143 in the survival group was significantly

lower (P<0.05). C. The sensitivity and specificity of serum miR-155 in prognosis diagnosing of sepsis patients were 87.83% and 61.81% respectively. D. The sensitivity and specificity of serum miR-134 in diagnosing the prognosis of patients with sepsis were 91.21% and 72.72%, respectively. Note: * indicates P<0.05.

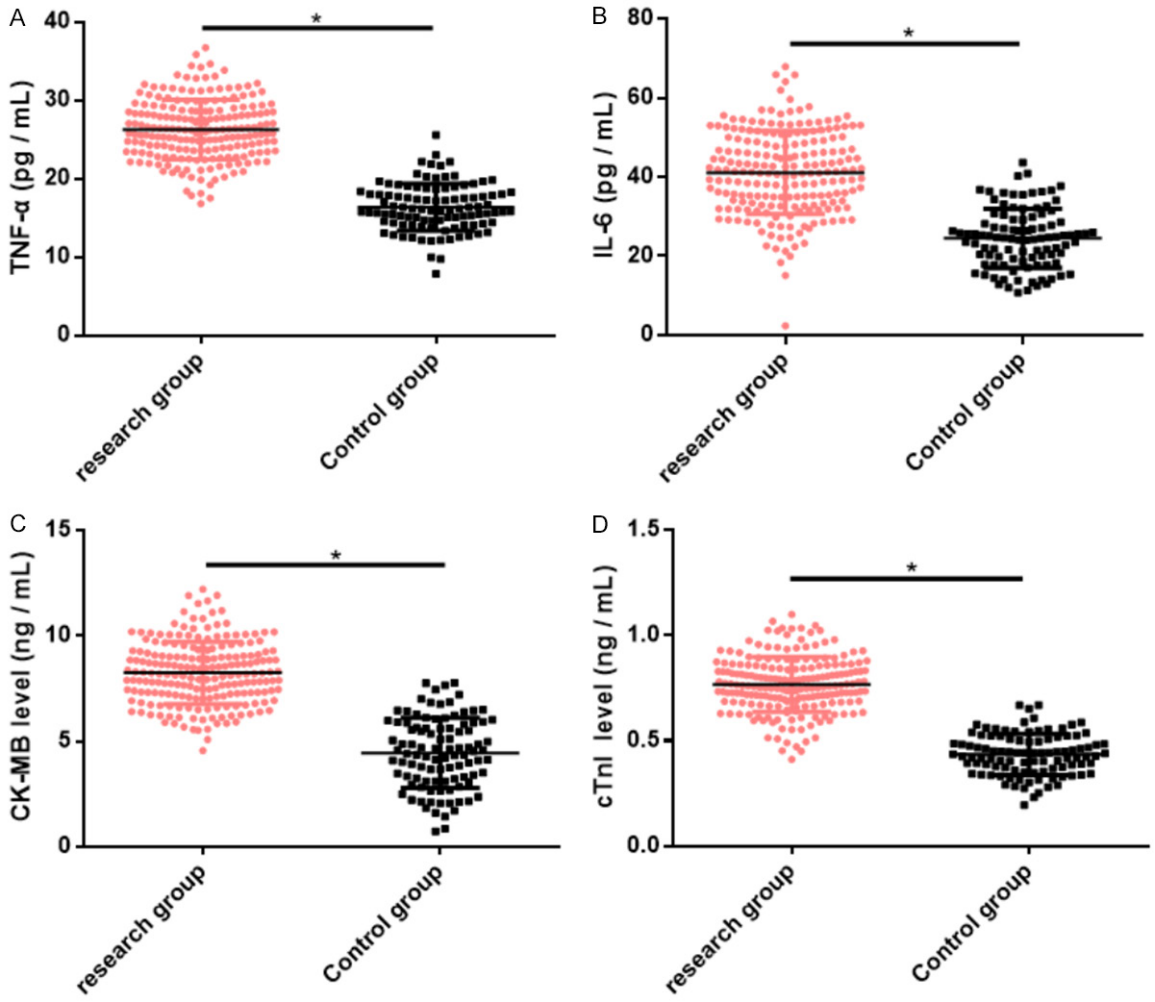

Figure 4. Comparison of serum TNF-α, IL-6, CK-MB and cTnI levels between the RG and the CG. A. The serum TNF-α level in the RG was significantly higher than that in the CG. B. Compared with the CG, the serum IL-6 level was significantly higher in the RG (P<0.05). C. The serum CK-MB level was significantly higher in the RG Compared with the CG (P<0.05). D. Compared with the CG, the serum cTnI level was significantly higher in the RG (P<0.05). Note: * indicated P<0.05.

Correlation of serum miR-155 and miR-143 with markers of inflammatory response and myocardial injury

Serum TNF-α, IL-6, CK-MB and cTnI presented significantly higher levels in the RG than in the CG (P<0.05). The results of Pearson correlation analysis showed that serum miR-155 and miR-143 were positively correlated with the concentrations of serum TNF-α, IL-6, CK-MB and cTnI (r=0.602, P<0.001; r=0.601, P<0.001; r=0.605, P<0.001; r=0.601, P<0.001; r=0.681, P<0.001; r=0.697, P<0.001; r=0.644, P<0.001 r=0.629, P<0.001) (**Figures 4**, **5**).

Discussion

Sepsis is the most serious form of infection in clinical practice, which also involves endothelial dysfunction. In the early stage, sepsis often ignites the cascade of immune responses, which triggers the automatic amplification of

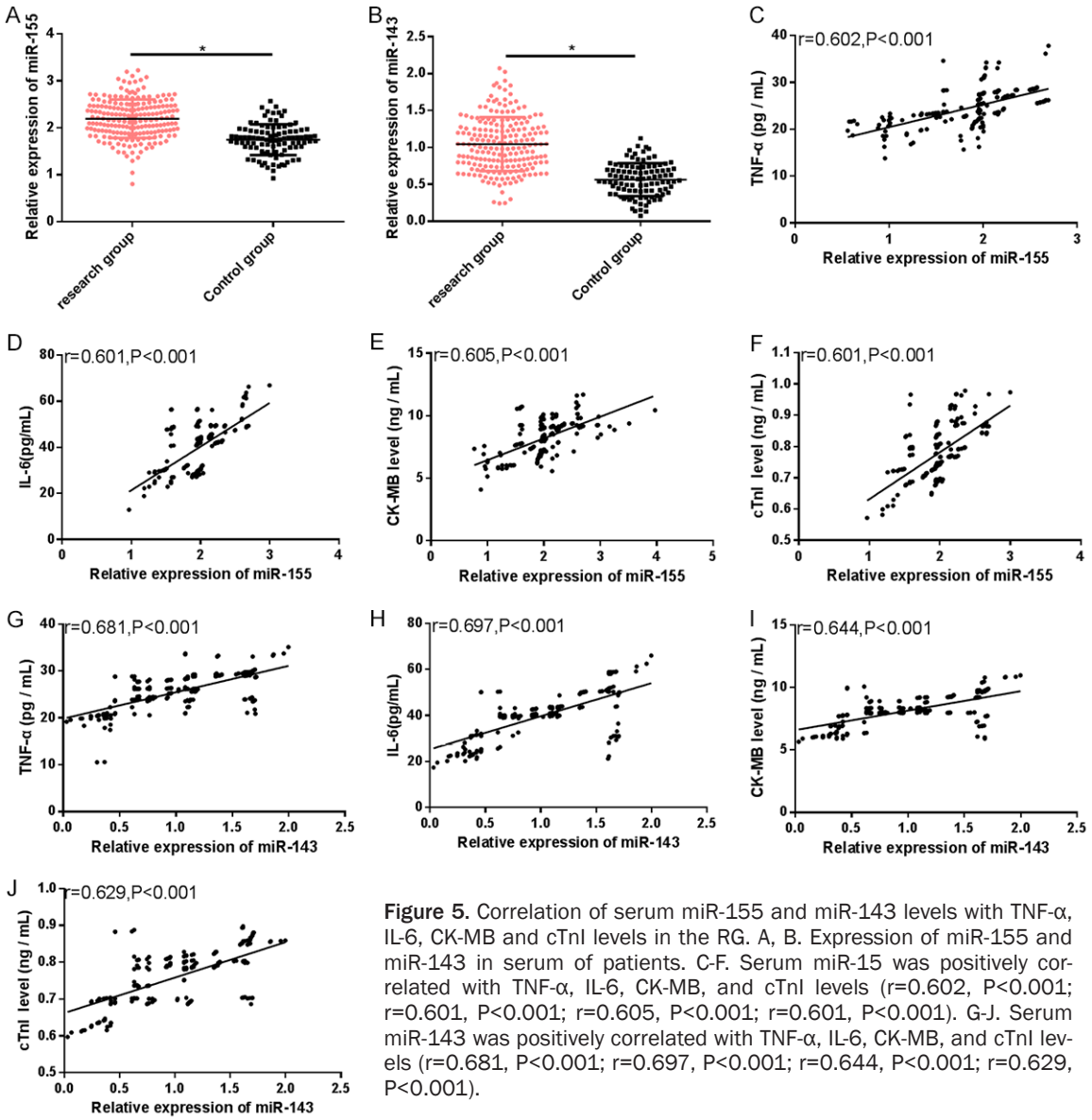

Figure 5. Correlation of serum miR-155 and miR-143 levels with TNF-α, IL-6, CK-MB and cTnI levels in the RG. A, B. Expression of miR-155 and miR-143 in serum of patients. C-F. Serum miR-15 was positively correlated with TNF-α, IL-6, CK-MB, and cTnI levels (r=0.602, P<0.001; r=0.601, P<0.001; r=0.605, P<0.001; r=0.601, P<0.001). G-J. Serum miR-143 was positively correlated with TNF-α, IL-6, CK-MB, and cTnI levels (r=0.681, P<0.001; r=0.697, P<0.001; r=0.644, P<0.001; r=0.629, P<0.001).

cytokines, and ultimately leads to organ failure in patients [15, 16]. While septic shock is the most severe period of sepsis, often accompanied by refractory hypotension or hyperlactic acidemia with fluid resuscitation, it eventually leads to death of patients [17, 18]. However, due to the lack of specificity in early clinical manifestations of patients with sepsis, early diagnosis is difficult [19]. It is therefore particularly important to explore biomarkers closely related to the diagnosing and prognosis of SSSS.

Increasing studies have shown that multiple miRNAs such as miR-182, miR-143, and miR-155 play a potential role in the key regulation of sepsis, although the mechanism has not yet been elucidated [20]. In the study of Liu J, et al. [21], the high expression of miR-155 indicated that patients with sepsis were in a serious condition with a poor prognosis, and those with high miR-155 levels were always accompanied by a lower 28-day survival. As reported by Yang Z B et al. [22], silencing miR-155 inhibited TNF-α and IL-6 in the serum of patients with sepsis, and promoted IL-10. It also inhibited the oxidative stress-mediated ER activation by targeting Nrf-2, and alleviated the liver damage caused by sepsis, indicating that miR-155 could be used as a target treatment for patients

with septic liver damage. According to Zhao X et al. [23], TLR3 could improve the survival rate of sepsis induced by cecal ligation by activating mesenchymal stem cells, while overexpressed serum miR-143 could affect the effectiveness of this result. In this study, serum miR-155 and miR-143 levels of elderly SSSS patients were noticeably up-regulated compared with those in the CG, and the AUC of serum miR-155 and miR-143 in the OG were 0.811 and 0.885, respectively; indicating that the two had good predictive value in elderly patients with SSSS, and they can be used as biomarkers for this disease. Furthermore, we divided the patients into a death group and a survival group according to whether the patients survived for 28 days. The results exhibited that the serum miR-155 and miR-143 levels in the survival group were clearly lower compared with the death group, and the AUC of the patients diagnosed with serum miR-155 and miR-143 was 0.769 and 0.844, respectively; suggesting that both of them have some certain predictive value for the death of elderly SSSS patients. Therefore, miR-155 and miR-143 may play a vital part in the early diagnosis and prognosis of elderly patients with SSSS.

Sepsis is a systemic inflammation caused by infection that gives rise to elevated levels of TNF-α, IL-6, which can also lead to cardiac dysfunction in patients [24, 25]. Both CK-MB and cTnI are biomarkers of myocardial injury, and their levels can rapidly increase after myocardial injury [26]. Studies have revealed that the levels of cTnI, CK-MB, TNF-α, and IL-6 in serum of patients with myocardial injury caused by sepsis increase significantly [27], suggesting that both inflammatory markers and myocardial markers may be related to SSSS in the elderly. Back to our study, the serum TNF-α, IL-6, CK-MB and cTnI levels in the RG were higher than those in the CG, and miR-155 and miR-143 were positively correlated with these indicators; indicating that miR-155 and miR-143, which were highly expressed in collagen-induced arthritis (CIA) in myocardial injury and inflammatory environments, may be associated with the onset and progression of SSSS in the elderly.

The research participants were screened in strict accordance with inclusion and exclusion criteria in the present study, and there was no marked difference in general clinical baseline data such as gender and age between the RG and the CG, which ensured the rigor and reliability of the study. Although here we have confirmed that miR-155 and miR-143 have good predictive value in the diagnosis of SSSS in the elderly, there were still some deficiencies. First of all, no basic experiments have been carried out in this study, and the specific regulatory mechanism of miR-155 and miR-143 in SSSS in the elderly remains unclear. In addition, it is not known whether miR-155 and miR-143 are factors of death in elderly patients with SSSS. These deficiencies will be addressed in the future research, so as to further support the results of this study.

Taken together, serum miR-155 and miR-143 are promising prognostic markers for elderly patients with SSSS, both of which are related to TNF-α, IL-6, CK-MB, and cTnI.

Disclosure of conflict of interest

None.

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