

Plasma miRNA-223 correlates with risk, inflammatory markers as well as prognosis in sepsis patients

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Abstract

The purpose was to evaluate the role of plasma microRNA-223 (miRNA-223) in risk and prognosis in sepsis patients, and its correlation with inflammatory markers.

In this study, 187 sepsis patients from July 2015 to December 2016 were consecutively enrolled. Blood samples from septic patients and healthy controls (HCs) were collected, and plasma was separated for miRNA-223 expression detected by quantitative real-time PCR (qPCR). Enzyme-linked immune sorbent assay (ELISA) was performed to detect inflammatory markers.

The results were as follows: miRNA-223 was highly expressed in sepsis patients compared to HCs ($P < .001$). Receiver operating characteristic (ROC) curve revealed miRNA-223 disclosed a good diagnostic value of sepsis with area under curve (AUC) of 0.754, 95% CI: 0.706–0.803. Sensitivity and specificity were 56.6% and 86.6% at the best cut-off point, respectively. Multivariate logistic analysis indicated that miRNA-223 could predict sepsis risk independently. Spearman's correlation disclosed that miRNA-223 relatively expression positively correlated with APACHE II score ($r = 0.459$, $P < 0.001$), CRP ($r = 0.326$, $P < 0.001$), TNF α ($r = 0.325$, $P < 0.001$), IL-1 β ($r = 0.165$, $P = 0.024$), IL-6 ($r = 0.229$, $P = 0.002$) and IL-8 ($r = 0.154$, $P = 0.035$), while it was negatively correlated with IL-10 ($r = -0.289$, $P < 0.001$). miRNA-223 expression in non-survivor was higher than that in survivor ($P < 0.001$). ROC curve revealed miRNA-223 could distinguish sepsis non-survivor from survivor with AUC of 0.600, 95% CI: 0.505–0.695. Sensitivity and specificity were 83.5% and 38.9% respectively at the best cut-off point.

In conclusion, plasma miRNA-223 correlates with disease severity and inflammatory markers levels, and it might serve as a novel diagnostic and prognostic biomarker in sepsis patients.

Abbreviations: AHR = aryl hydrocarbon receptor, APACHE = Acute Physiology and Chronic Health Evaluation, ARNT = aryl hydrocarbon nuclear translocator, AUC = area under curve, BMI = body mass index, CRP = C-reactive protein, DAMP = damage-associated molecular patterns, ELISA = enzyme linked immune sorbent assay, FOXO3 = forkhead box O3, HCs = healthy controls, HIV-1 = human immunodeficiency virus-1, IBDs = inflammation bowel diseases, ICU = intensive care unit, IKK α = I κ B kinase α , miRNA-223 = microRNA-223, NF- κ B = nuclear factor-kappa B, PAMPs = pathogen-associated molecular patterns, PRRs = pattern recognition receptors, qPCR = quantitative real-time PCR, ROC = receiver operating characteristic, Scr = serum creatinine, SzS = seziary syndrome, TB = tuberculosis, WBC = white blood cell.

Keywords: inflammatory markers, miRNA-223, plasma, prognosis, risk, sepsis

1. Introduction

Sepsis, one of the most common, fatal and expensive diseases, is defined as the constellation of symptoms due to infection from

bacterial, viral or fungal, resulting in systemic inflammatory response syndrome (including fever, leukocytosis, or leukopenia) and reducing vascular resistance to cause hypotension (septic shock), organ dysfunction (severe sepsis), or even death.^[1] During last four decades, the incidence of sepsis has been reported to be increased, and its incidence ranges from 0.4/1000 to 1/1000 of the population in the United States, Europe, and the United Kingdom.^[2] Furthermore, the mortality of sepsis is also relatively high, ranging from 17% to 56% worldwide.^[3–5] Therefore, exploring novel and convincing biomarkers in sepsis to improve diagnosis and prognosis is greatly needed.

microRNAs (miRNAs), a class of small, endogenously expressed and non-protein-coding RNAs with length at approximately 19 to 23 nucleotides, regulate post-transcriptional silencing via binding to complementary sequences of the 3'-untranslated region (3'-UTR) in the target messenger RNAs.^[6] Accumulating evidence has proven that miRNAs play critical roles in various inflammatory diseases through affecting cells activities during pathological processes, such as cells proliferation, differentiation, apoptosis as well as migration.^[6–8]

miRNA-223, a critical miRNA related to hematopoietic system and expresses in the myeloid compartment, has been identified as a novel biomarker in some inflammatory and infection diseases,

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such as inflammation bowel diseases (IBDs), psoriasis as well as chronic kidney disease.^[9–11] However, little is known about the role of miRNA-223 in sepsis, which is one of the inflammatory diseases. Therefore, the purpose of this study was to evaluate the role of plasma miRNA-223 in risk and prognosis in sepsis patients, and its correlation with inflammatory markers.

2. Methods

2.1. Sepsis patients and healthy controls

In the present study, totally 187 sepsis patients who were admitted to intensive care unit (ICU) at the Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology during the period from July 2015 to December 2016 were consecutively enrolled. Inclusion criteria were as follows: diagnosed as sepsis according to the American College of Chest Physicians/Society of Critical Care Medicine consensus definition,^[12] age ≥ 18 years. Patients who had history or suffered from solid cancer, leukopenia, current hematologic malignancy, severe chronic diseases of the heart, liver, kidney or lung, HIV-infected diseases, stem cell transplantation, treated with immunosuppressive medication within 3 months, and were in pregnancy or lactation were excluded from this study. In this study, all healthy volunteers were aged 18 years or older from the Health Screening Center of the The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology who intended to do physical examination. According to the results of physical examination, 186 age and sex matched healthy volunteers were screened for eligibility and recruited as healthy controls (HCs) during the same period from July 2015 to December 2016. HCs with the following conditions were excluded: had any symptoms of active infection, severe kidney or hepatic dysfunction, or had any history of systematic inflammatory disease, solid cancer or hematological malignancies, or were on current chronic steroid therapy or immunosuppressive therapy.

2.2. Ethics

The study was approved by the Research Ethics Committee of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, and all subjects or statutory guardians had provided the signed informed consents.

2.3. Data collection

After enrolment in the study, sepsis patients' demographic information, clinical characteristics and laboratory indexes including age, gender, body mass index (BMI), serum creatinine (Scr) level, albumin level, white blood cell count (WBC) and C-reactive protein (CRP) level were recorded. Meanwhile, Acute Physiology and Chronic Health Evaluation (APACHE) II scores in sepsis patients were assessed by senior physicians. Moreover, basic information, which was the same with sepsis patients, was collected in HCs as well.

2.4. APACHE II score assessment

The APACHE II system was a severity of disease classification system, which used a point score based upon initial values of 12 routine physiologic measurements, age and previous health status to provide a general measure of severity of disease.^[13] 12 routine physiologic measurements included PaO₂, temperature, mean

arterial pressure, arterial pH, heart rate, respiratory rate, sodium, potassium, creatinine, hematocrit, leucocyte count, and Glasgow Coma Scale. The worst parameters for each physiological variable in the first 24 hours of patient admittance were selected and calculated into an integer score from 0 to 71. Higher score represented a more severe disease and a higher hospital mortality risk.

2.5. Blood samples

Blood samples from septic patients were collected within 24 hours of admission to the ICU, and the blood sample from each patient was divided into two parts: one was used for plasma separation for detection of miRNA-223 expression; another part was used for serum separation for evaluation of inflammation markers. In addition, after achieving informed consents, every HCs received blood test at the Health Screening Centre, and blood samples were collected for further detection. Plasma were separated.

2.6. Total RNA isolation and quantitative real-time PCR (qPCR)

According to the instructions of the manufacturer, total RNA was extracted from the samples using TRIzol reagent (Invitrogen, Waltham, Massachusetts). The PrimerScript Real-time reagent kit (TaKaRa, Kusatsu, Shiga, Japan) was performed for total RNA reverse transcription, and then SYBR Premix Ex Taq™ II (TaKaRa, Japan) was used for the quantitation analysis of miRNA-223 expression. Considering the special structure of miRNAs, we designed the stem-loop with miRNA-223 sequence (which was used to the primer of reverse transcription) and used stem-loop to complete reverse transcription. The primer sequences for primer source were performed as follows: miRNA-223: Forward 5'ACACTCCAGCTGGGCGTGTATTTGACAAGCTG3' Reverse 5' TGTCGTGGAGTCGGCAATTC; U6: Forward 5' CTCGCTTCGGCAGCACATA3' Reverse 5'CTCGCTTCGGCAGCACATA3'; 2^{- $\Delta\Delta$ ct} method was used for the calculation of miRNA-223 expression, and U6 was served as the internal reference.

2.7. Enzyme-linked immune sorbent assay (ELISA)

According to the instructions of the manufacturer, commercial ELISA kit (R&D, Minneapolis, Minnesota) was used for detecting the expressions of serum CRP, tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β (IL-1 β), IL-6, IL-8, and IL-10.

2.8. Statistical analysis

Statistical analysis was performed using SPSS22.0 software (SPSS Inc., IBM, Armonk, New York) and GraphPad Prism 6.0 (GraphPad Prism 6 (San Diego, California)). Data were mainly displayed as mean \pm standard deviation, median (quartile 25th–75th) or count (%). The differences in baseline characteristics between sepsis patients and HCs were determined by *t* test or χ^2 test. Differences in miRNA levels were determined using Wilcoxon rank-sum test. Spearman's correlation was used to analyse the correlation of miRNA-223 levels with disease severity or inflammation markers levels. Univariate and multivariate logistic regression analyses were performed to analyse the predictive value of miRNA-223 level for sepsis risk. Receiver operating characteristic (ROC) curve was used to assess the diagnostic value of miRNA-223 level for sepsis vs HCs and the predictive value of miRNA-223 level for non-survivor vs. survivor. *P* < .05 was considered statistically significant.

Table 1
Basic characteristics of sepsis patients and HCs.

Parameters	Sepsis patients (N=187)	HCs (N=186)	P
Age, ys	57.87 ± 8.081	56.71 ± 9.033	.191
Gender, n/%			.183
Male	125 (66.8)	112 (60.2)	
Female	62 (33.2)	74 (39.8)	
BMI, kg/m ²	24.89 ± 3.83	24.35 ± 3.73	.170
Scr, mg/dL	1.494 (1.007–1.921)	–	–
Albumin, g/L	25.778 (22.207–34.879)	–	–
WBC, × 10 ⁹ /L	12.367 (3.656–27.856)	–	–
CRP, mg/L	42.291 (25.207–62.371)	–	–
APACHE II score	16 (12–20)	–	–

Data was presented as mean value ± standard deviation, median (quartile 25th–75th) or count (%). Comparison was determined by *t* test or χ^2 test. *P* < .05 was considered significant. APACHE=acute physiology and chronic health evaluation, BMI=body mass index, CRP=C-reactive protein, HCs=healthy controls, Scr=serum creatinine, WBC=white blood cell.

3. Results

3.1. Basic characteristics

As listed in Table 1, no difference was found in age (*P*=.191), gender (*P*=.183) as well as BMI (*P*=.170) between sepsis patients and HCs. For sepsis patients, median values of Scr, albumin, WBC and CRP were 1.494 (1.007–1.921) mg/dL, 25.778 (22.207–34.879) g/L, 12.367 (3.656–27.856) × 10⁹/L, and 42.291 (25.207–62.371) mg/L, respectively. The median APACHE II score was 16 (12–20).

3.2. The diagnostic value of miRNA-223 for sepsis

High expression of plasma miRNA-223 was found in sepsis patients compared to HCs (*P* < .001, Fig. 1A), and the median

values of miRNA-223 expression were 3.187(1.217–4.818) and 1.137(0.519–2.116), respectively. In addition, ROC curve was performed to investigate the value of miRNA-223 level in sepsis diagnosis, which revealed that miRNA-223 disclosed a good diagnostic value of sepsis with area under curve (AUC) 0.754, 95% CI: 0.706–0.803. Sensitivity and specificity were 56.6% and 86.6% respectively at the best cut-off point (Fig. 1 B).

3.3. All factors affecting sepsis risk

Univariate logistic regression analysis was performed to evaluate all factors affecting sepsis risk (Table 2). miRNA-223 expression was positively correlated with sepsis risk (*P* < .001). Multivariate logistic regression analysis was carried out to evaluate further the

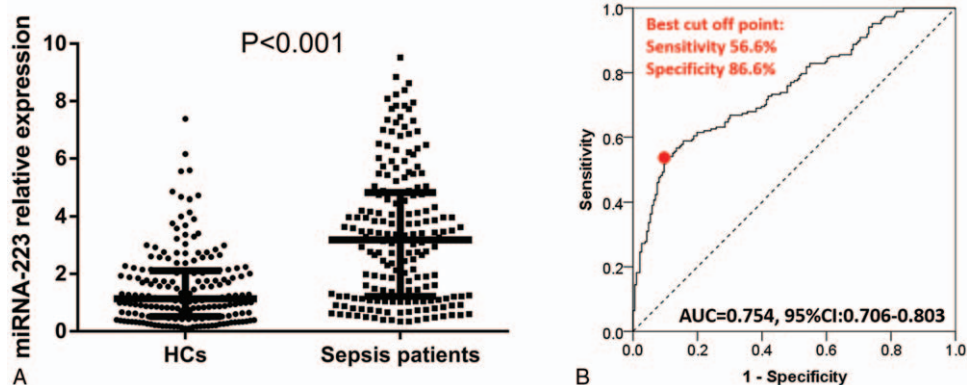


Figure 1. miRNA-223 expression and its diagnostic value between sepsis patients and HCs. High expression of miRNA-223 was in sepsis patients compared to HCs (*P* < .001) (A), miRNA-223 disclosed a good diagnostic value of sepsis (B). Wilcoxon rank-sum test was used to evaluate differences in miRNA level. Receiver operating characteristic (ROC) curve was used to assess the diagnostic value of miRNA-223 level for sepsis. *P* value < .05 was considered statistically significant.

Table 2
Logistic regression analysis of factors for sepsis risk.

	Univariate logistic regression (N=373)				Multivariate logistic regression (N=373)			
	<i>P</i>	OR	95% CI		<i>P</i>	OR	95% CI	
			Lower	Higher			Lower	Higher
miRNA-223	<.001	1.784	1.538	2.070	<.001	1.778	1.531	2.065
Age	.191	1.016	0.992	1.041	.640	1.006	0.980	1.033
Gender (male)	.184	1.332	0.873	2.033	.239	1.331	0.827	2.142
BMI	.170	1.039	0.984	1.096	.397	1.027	0.966	1.093

Data was presented as *P* value, OR (odds ratio) and 95% CI. Significance was determined by univariate and multivariate logistic regression analysis. *P* < .05 was considered significant. BMI=body mass index, CI = confidence interval, OR = odds ratio.

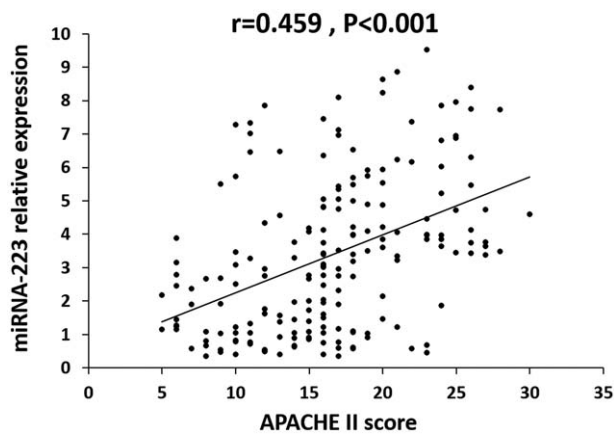


Figure 2. Correlation between miRNA-223 expression and APACHE II score. miRNA-223 relative expression was positively correlated with APACHE II score ($r=0.459$, $P<.001$). Spearman's correlation was used to analyze the relationship between miRNA-223 levels and disease severity. $P<.05$ was considered statistically significant.

independent factor of sepsis risk, which indicated that miRNA-223 could predict sepsis risk independently.

3.4. Correlation between miRNA-223 expression and APACHE II score

Spearman's correlation was used to assess the association between plasma miRNA-223 levels and APACHE II score, as shown in Fig. 2, miRNA-223 relative expression was positively correlated with APACHE II score ($r=0.459$, $P<.001$).

3.5. Correlation between miRNA-223 expression and inflammation markers levels

Plasma miRNA-223 expression was positively associated with the levels of CRP ($r=0.326$, $P<.001$) (Fig. 3 A), TNF- α ($r=0.325$, $P<.001$) (Fig. 3 B), IL-1 β ($r=0.165$, $P=.024$) (Fig. 3 C), IL-6 ($r=0.229$, $P=.002$) (Fig. 3 D), and IL-8 ($r=0.154$, $P=.035$) (Fig. 3 E), while it was negatively correlated with IL-10 expression ($r=-0.289$, $P<.001$) (Fig. 3 F).

3.6. The predictive value of miRNA-223 for survivor

The median value of miRNA-223 expression in non-survivors was (4.898(2.591–7.327)), which was higher than that in survivors 2.727(1.043–4.017) ($P<.001$) (Fig. 4 A). After that, ROC curve was performed to assess the value of miRNA-223 expression in distinguishing non-survivor from survivor, which revealed that the expression of miRNA-223 could distinguish sepsis non-survivor from survivor with AUC 0.600, 95% CI: 0.505–0.695. Sensitivity and specificity were respectively 83.5% and 38.9% at the best cut-off point (Fig. 4 B). The predictive values of other inflammation markers on outcomes of sepsis were shown in Supplementary Figure 1, <http://links.lww.com/MD/C322>.

4. Discussion

In the present study, we observed that higher expression of miRNA-223 was in sepsis patients compared to HCs, and ROC curve revealed that miRNA-223 disclosed a good diagnostic value for sepsis risk, and multivariate logistic analysis indicated that miRNA-223 could predict sepsis risk independently. miRNA-223 relative expression was positively correlated with APACHE II score and most inflammation markers levels. Higher expression of miRNA-223 was found in non-survivors compared

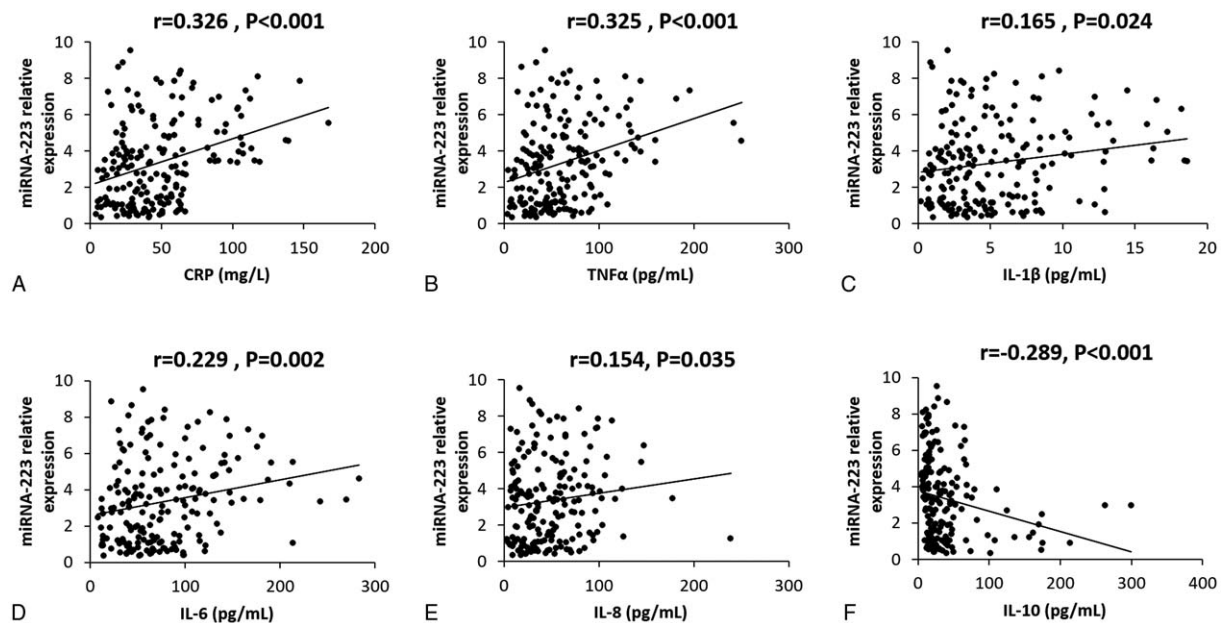


Figure 3. Correlation between miRNA-223 expression and inflammation markers level. Plasma miRNA-223 expression was positively associated with CRP ($r=0.326$, $P<.001$) (A), TNF α ($r=0.325$, $P<.001$) (B), IL-1 β ($r=0.165$, $P=.024$) (C), IL-6 ($r=0.229$, $P=.002$) (D), IL-8 ($r=0.154$, $P=.035$) (E), while it was negatively correlated with IL-10 ($r=-0.289$, $P<.001$) (F). Spearman's correlation was used to analyze the correlation between miRNA-223 levels and inflammation markers levels. $P<.05$ was considered statistically significant.

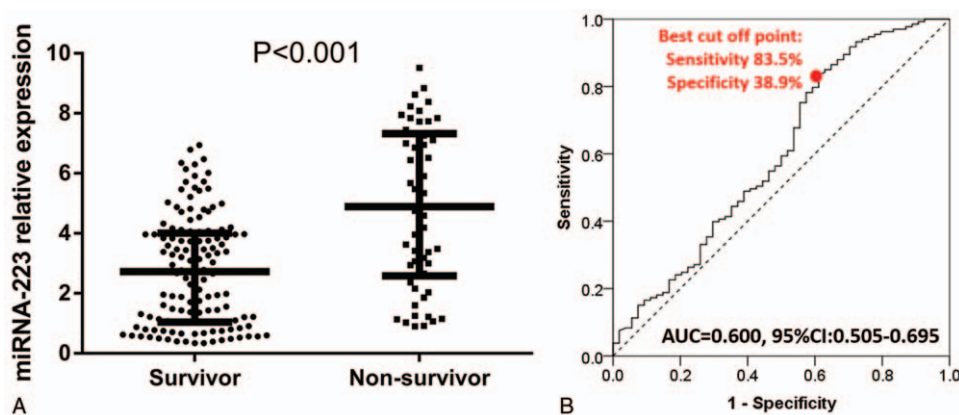


Figure 4. miRNA-223 expression and its predictive value between non-survivor and survivor. The miRNA-223 expression in non-survivor was higher than that in survivor (A). miRNA-223 could distinguish sepsis non-survivor from survivor (B). Wilcoxon rank-sum test was used to evaluate differences in miRNA levels. Receiver operating characteristic (ROC) curve was used to assess the predictive value of miRNA-223 levels for non-survivors vs. survivors. $P < .05$ was considered statistically significant.

to survivors, and ROC curve revealed that miRNA-223 could distinguish sepsis non-survivor from survivor.

Sepsis, a severe form of infection characterized by inflammatory clinical symptoms, is related to strong activation of the innate immune system and inflammatory reactions regulated by the activation of pathogen-associated molecular patterns (PAMPs) via an assortment of pattern recognition receptors (PRRs) and damage-associated molecular patterns (DAMP).^[14]

miRNA-223, located on X-chromosomes and transcribed genes independently, has been identified to devote to the regulation of inflammation disorders, immune response, and haematopoiesis.^[6,15] Among these, miRNA-223 is considered as a pro-inflammatory factor in several diseases. For instance, miRNA-223 promotes inflammatory responses in IBDs through directly inhibiting claudin-8 (CLDN8) genes or upregulating inflammatory cytokine IL-7; in rheumatoid arthritis (RA) via suppressing aryl hydrocarbon receptor (AHR)/aryl hydrocarbon nuclear translocator (ARNT) pathway; also in activated macrophages of leucocytopenia through targeting I κ B kinase α (IKK α) to regulate the release and translocation of nuclear factor-kappa B (NF- κ B) signals.^[16-19] As to infection, miRNA-223 has been reported to repress forkhead box O3 (FOXO3) to inhibit macrophages apoptosis in tuberculosis (TB).^[20] These previous studies suggest that miRNA-223 plays an important role in inflammatory responses and infection reactions through regulating several genes or pathways.

According to some previous studies, aberrant expression of miRNA-223 is observed in various inflammatory diseases, including sepsis, RA or viral infections likes' human immunodeficiency virus-1 (HIV-1), serving as a novel potential diagnostic biomarker in these diseases related to inflammatory disorders.^[15,21-23] Although there is one previous study investigating the role of miRNA-223 in sepsis, which illustrates that serum miRNA-223 serves as a new diagnostic biomarker for sepsis patients, while just 50 sepsis patients and 30 systemic inflammatory response syndrome patients are recruited in that study, the sample size is relatively small, possibly resulting in relatively low statistical efficiency.^[23] In the current study, we had a relatively larger sample size which included 187 sepsis patients and 186 HCs, and we observed that over-expression of miRNA-223 was in sepsis patients compared to HCs, and ROC curve revealed that it could be an independent diagnostic factor in

sepsis patients. For the correlation of miRNA-223 with inflammation markers, few clinical studies have been performed. In the present study, we further evaluated the correlation of miRNA-223 expression with disease severity as well as inflammation markers levels, and found that miRNA-223 expression was positively associated with APACHE II score and most inflammation markers levels. The possible explanations were that miRNA-223 targets several genes or signaling pathways to activate inflammatory responses, thereby increasing the levels of most inflammatory factors and aggravating disease severity of sepsis.

As for prognostic value, some previous studies have validated the prognostic role of circulating miRNA-223 in RA, adipocyte inflammatory and sezary syndrome (SzS).^[24-26] Some studies have disclosed that miRNA-143, miRNA-15a and miRNA-16 could serve as useful biomarkers for diagnosis of sepsis.^[27,28] However, few studies have performed to assess the role of miRNA-223 in sepsis patients. Hence, we investigated the prognostic value of miRNA-223 in sepsis patients and found that miRNA-223 expression was increased in non-survivor compared to survivor, and it could distinguish non-survivors from survivors in sepsis. The possible reasons were as follows: miRNA-223 contributes to the regulation of multiple genes and pathways to induce inflammation disorder and infection, thereby causing a high risk of death.

Although there were interesting results, some limitations still existed in this study. A number of sepsis patients were only 187, hence, the sample size in this study was relatively small, which may cause insufficient statistical power. The detailed mechanism of miRNA-223 in sepsis was not investigated. All patients enrolled in this study were from monocentric, further study with more patients from multicentre is necessary. The effects of other miRNAs on diagnosis in sepsis patients were not investigated. Hence, the uniqueness of miRNA-223 as a marker for sepsis diagnosis was not evaluated compared to other miRNAs. Although the enrolment time of sepsis group (from July 2015 to December 2016) and HCs (from October 2016 to December 2016) was nearly same, but in order to match age and gender between groups, different enrolment time still existed.

In conclusion, plasma miRNA-223 is correlated with disease severity and levels of inflammatory markers, and it might serve as a novel diagnostic and prognostic biomarker in sepsis patients.

Author contributions

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