Correlation of microRNA-146a/b with disease risk, biochemical indices, inflammatory cytokines, overall disease severity, and prognosis of sepsis

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Abstract

Background: Previous studies have indicated the association of microRNA-146a/b (miR-146a/miR-146b) with pro-inflammatory cytokines production, lipopolysaccharide-mediated injuries and organ dysfunction, however, the correlation of miR-146a/miR-146b with disease risk, disease severity, biochemical indices, inflammatory cytokines and mortality of sepsis has not been explored, which was investigated in the present study.

Methods: In total, 180 sepsis patients and 180 healthy controls were enrolled. The peripheral blood samples were collected from sepsis patients within 24 hours after admission and from healthy controls at enrolment. Furthermore, MiR-146a/miR-146b expressions in plasma were detected by reverse transcription quantitative polymerase chain reaction.

Results: MiR-146a and miR-146b expressions were higher in sepsis patients compared to healthy controls. MiR-146a (AUC: 0.774, 95%CI: 0.727–0.820) and miR-146b (AUC: 0.897, 95%CI: 0.865–0.929) were both of good value in predicting increased sepsis risk. MiR-146a was positively associated with miR-146b expression. Besides, MiR-146a and miR-146b expressions were positively correlated with acute pathologic and chronic health evaluation II score, sequential organ failure assessment score, serum creatinine, C-reactive protein, tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-17, while negatively correlated with albumin. Based on the survival status in 28-day follow-up, MiR-146a and miR-146b expression were both increased in survivors compared to deaths. MiR-146b presented relatively good predictive for increased 28-day mortality risk (AUC: 0.703, 95%CI: 0.617–0.788), but MiR-146a was of poor value in predicting increased 28-day mortality risk (AUC: 0.599, 95%CI: 0.511–0.688).

Conclusion: MiR-146b presents superior potential as a prognostic biomarker in sepsis patients compared to MiR-146a, which implies the clinical application of miR-146b in disease management of sepsis.

Abbreviations: APACHE II = acute pathologic and chronic health evaluation II, AUC = area under the curve, BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, IL-1β = interleukin-1β, LPS = lipopolysaccharide, MiR-146a = microRNA-146a, miR-146b = microRNA-146b, ROC = receiver operating characteristic, RT-qPCR = reverse transcription quantitative polymerase chain reaction, Scr = serum creatinine, SOFA = sequential organ failure assessment, TNF-α = tumor necrosis factor-α, WBC = white blood cell.

Keywords: disease severity, inflammation, microRNA-146a/b, sepsis, survival

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, which is considered to be a common contributor to mortality for hospitalized patients in the intensive care unit and a serious healthcare issue affecting millions of people globally every year.[1,2] Current treatments for sepsis include antimicrobial therapy, source control, fluid therapy, vasoactive medications, etc, however the prognosis of sepsis patients is still unfavorable because of delayed identification of infection source and inappropriate management in the
initial hours.\textsuperscript{[3–6]} Therefore, it is important to investigate novel biomarkers, which can help to identify the sepsis risk timely and monitor prognosis in sepsis patients.

MicroRNA-146a (MiR-146a) and microRNA-146b (miR-146b) are identified to be crucial mediators in innate immune and inflammatory responses, and their association with pro-inflammatory cytokines production, lipopolysaccharide (LPS)-mediated, injuries and even organ dysfunction has been revealed by several studies.\textsuperscript{[7–10]} For example, MiR-146a is reported to regulate the release of various inflammatory cytokines (IL-1β, TNF-α, IL-1α) by activating pro-inflammatory transcriptional signaling (the NF-κB signaling pathway), which further associates with sepsis-induced multiple organ injury, including kidney, lung, and myocardia.\textsuperscript{[11–14]} Furthermore, prior studies indicate that miR-146b is capable of modulating inflammatory responses via regulating p38MAPK and NF-κB signaling, and the association of miR-146b with LPS-mediated inflammation-related apoptotic injury has been reported to result in the pathology of acute renal injury and intestinal injury.\textsuperscript{[8,15,16]} According to these previous studies, MiR-146a and miR-146b were both able to regulate the LPS-stimulated systematic inflammation and sepsis-induced multiple organ injuries, moreover sepsis was characteristic of cytokine storm, multiple organ failures, therefore we hypothesized that MiR-146a/miR-146b might participate in the pathology of sepsis, and conducted the present study to explore the potential application of MiR-146a/miR-146b in clinical management of sepsis. In detail, we investigated the association of MiR-146a/miR-146b level with disease risk, disease severity, biochemical indices, inflammatory cytokines, and prognosis of sepsis.

2. Methods

2.1. Participants

One hundred eighty sepsis patients who were admitted to our hospital from January 2016 to July 2019 were consecutively enrolled in the present study. The inclusion criteria were:

(1) diagnosed as sepsis according to the criteria of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3);\textsuperscript{[17]}
(2) age ≥ 18 years;
(3) not complicated with hematological malignancies, solid tumors, or autoimmune disorders;
(4) no history of stem cell transplant.

The exclusion criteria were:

(1) received immunosuppressive therapy (such as cyclosporine, azathioprine, or cancer chemotherapy) within 1 month before enrollment;
(2) transferred from other hospitals if they had spent more than 24 hours after symptom onset;
(3) infected with human immunodeficiency virus;
(4) pregnant or lactating woman. Between January 2019 and July 2019, 180 healthy gender-and age-matched subjects were enrolled as healthy controls in this study. The healthy controls were defined as healthy subjects who had no obvious abnormalities in biochemical indices and no history of malignancies, severe infection, or sepsis. Written, informed consents were provided by all participants or their guardians. The study was approved by the Ethics Committee of our hospital.

2.2. Data collection

After the sepsis patients were admitted to our hospital, the clinical characteristics were recorded, which included:

(1) demographic characteristics such as age, gender and body mass index (BMI);
(2) biochemical indices such as serum creatinine (Scr), albumin, white blood cell (WBC) and C-reactive protein (CRP);
(3) chronic comorbidities such as chronic obstructive pulmonary disease, cardiomyopathy, chronic kidney failure and cirrhosis. In addition, the assessment of severity and organ dysfunction for sepsis patients was performed within 24 hours after admission, which was evaluated by acute pathologic and chronic health evaluation II (APACHE II) score and sequential organ failure assessment (SOFA) score, respectively. For the healthy controls, the clinical characteristics including age, gender, BMI, and biochemical indices (Scr, albumin, WBC and CRP) were recorded after enrollment.

2.3. Sample collection

Within 24 hours after admission, the peripheral blood samples of sepsis patients were collected. The separation was performed as follows: first, the peripheral blood samples were separated at 3000 g under 4°C, then the supernatants were collected and further centrifuged at 10,000 g for 10 min under 4°C, finally, the plasma were isolated and stored at –80°C for determination. Besides, peripheral blood samples of healthy controls were collected on the enrolment, and the plasma was obtained and stored as the same method described above.

2.4. Inflammatory cytokines measurement

For the sepsis patients, the level of inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and IL-17 in plasma were measured by enzyme-linked immunosorbent assay with the use of enzyme-linked immunosorbent assay Kits (Thermo Fisher Scientific, Waltham, MA). All procedures were performed according to the instructions provided by manufacturer, which were briefly summarized as follows: The plasma samples were added to the wells of antibody pre-coated microplate. After incubation, the wells were washed to remove the unbound materials, and then the second antibody was added. Subsequently, the wells were added with tetramethylbenzidine substrate and incubated at room temperature. Following stop solution was added, the optical density was measured at 450 nm wavelengths using a microplate reader (BioTek, Winskoy, VT).

2.5. MiR-146a and miR-146b detection

For the sepsis patients and healthy controls, the relative MiR-146a and miR-146b expressions in plasma samples were detected by reverse transcription quantitative polymerase chain reaction (RT-qPCR). Total RNA was extracted from plasma using TRizol Reagent (Invitrogen, Waltham, MA) and then reversely transcribed using ReverTra Ace qPCR RT Kit (Toyobo, Osaka, Kansai, Japan). Following that, qPCR was performed using KOD SYBR qPCR Mix (Toyobo, Osaka, Kansai, Japan) to quantify MiR-146a/miR-146b expressions. In addition, the expression level of MiR-146a/miR-146b were calculated using $2^{-\Delta\Delta C_T}$. 

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method with U6 as an internal reference. The experiments were conducted in triplicate with coefficient variation ≤10% and intra-assay coefficient variation ≤5%. Primers used in our study were listed in Supplementary Table 1, http://links.lww.com/MD/E267.

### 2.6. Treatment and follow-up

All sepsis patients received conventional therapies (such as initial resuscitation, antimicrobial therapy, inotropic therapy, fluid therapy, infection prevention, vasopressor therapy, and so on) based on their clinical conditions and guideline. Daily follow-up was conducted for all sepsis patients until death or 28 days after admission. During follow-up, the deaths were recorded to calculate the 28-day mortality. All sepsis patients were classified as survivors and deaths according to the data of the survival status in 28-day follow-up. In addition, accumulating survival was calculated from the date of hospital admission to the date of death.

### 2.7. Statistical analysis

The continuous variables were presented as mean ± standard deviation or median and interquartile range, while the categorical variables were displayed as count (percentage). Comparison between 2 groups was determined by Student t test, Chi-squared or Wilcoxon rank-sum test. Correlation between 2 continuous variables was analyzed by Spearman rank-correlation test. Receiver operating characteristic (ROC) curve and the area under the curve (AUC) with 95% confidence interval (CI) were used to assess the performance of variables in discriminating sepsis patients from healthy controls or in predicting 28-day mortality risk. Kaplan–Meier curve was plotted to display accumulating survival, and the difference of accumulating survival between 2 groups was determined by Log-rank test. All statistical analyses were performed using SPSS 24.0 software (IBM, Chicago, IL), and all figures were made with the used of GraphPad Prism 7.01 software (GraphPad Software, San Diego, CA). P value <.05 was considered significant.

### 3. Results

### 3.1. Clinical characteristics

The average age was 56.5 ± 10.4 years and 57.2 ± 12.0 years in sepsis patients (N = 180) and healthy controls (N = 180) (Table 1). There were 74 (41.1%) females and 106 (58.9%) males in sepsis patients, and 63 (35.0%) females and 117 (65.0%) males in healthy controls. No difference of age (P = .523), gender (P = .235) between sepsis patients and healthy controls was observed. Regarding biochemical indices, the median Scr (P < .001), WBC (P = .011) and CRP (P < .001) were higher in sepsis patients than that in healthy controls, while median albumin (P < .001) was lower in sepsis patients than that in healthy controls. Furthermore, in sepsis patients, the mean APACHE II score was 13.8 ± 6.1, and the mean SOFA score was 6.2 ± 2.8. More detailed information of clinical characteristics in patients with sepsis and healthy controls were presented (Table 1).

| Table 1 | Clinical characteristics of sepsis patients and healthy controls. |
|---------|---------------------------------------------------------------|
|         | Sepsis patients (N = 180) | Healthy controls (N = 180) | P value |
| Age (yr), mean ± SD | 56.5 ± 10.4 | 57.2 ± 12.0 | .523 |
| Gender, No. (%) | 232 | 232 | 232 |
| Female | 74 (41.1) | 63 (35.0) | .232 |
| Male | 106 (58.9) | 117 (65.0) | .232 |
| BMI (kg/m²), mean ± SD | 23.1 ± 4.9 | 22.6 ± 3.1 | .235 |
| Biochemical indices, median (IQR) | | | |
| Scr (mg/dL) | 1.6 (1.2–2.3) | 0.8 (0.7–1.0) | <.001 |
| Albumin (g/L) | 27.3 (21.8–36.1) | 42.5 (39.6–46.5) | <.001 |
| WBC (>10³/μL) | 11.9 (2.8–26.2) | 6.5 (5.5–7.6) | .011 |
| CRP (mg/L) | 102.6 (57.5–154.3) | 1.8 (1.1–2.9) | <.001 |
| APACHE II score, mean ± SD | 13.8 ± 6.1 | – | – |
| SOFA score, mean ± SD | 6.2 ± 2.8 | – | – |
| Inflammatory cytokines, median (IQR) | | | |
| TNF-α (pg/mL) | 204.2 (124.3–314.8) | – | – |
| IL-1β (pg/mL) | 9.3 (4.2–19.9) | – | – |
| IL-6 (pg/mL) | 89.8 (46.5–165.7) | – | – |
| IL-17 (pg/mL) | 180.8 (90.0–270.0) | – | – |
| Chronic comorbidities, No. (%) | | | |
| COPD | 24 (13.3) | – | – |
| Cardiomyopathy | 62 (34.4) | – | – |
| Chronic kidney failure | 17 (9.4) | – | – |
| Cirrhosis | 34 (18.9) | – | – |

Comparison was determined by Student t test, Chi-squared or Wilcoxon rank-sum test. APACHE II = acute pathologic and chronic health evaluation II, BMI = body mass index, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, IL = interleukin, IQR = interquartile range, Scr = serum creatinine, SD = standard deviation, SOFA = sequential organ failure assessment, TNF = tumor necrosis factor, WBC = white blood cell.

Figure 1. MicroRNA-146a/microRNA-146b (MR-146a/miR-146b) expression in sepsis patients and healthy controls. Comparison of MiR-146a (A)/MiR-146b (B) relative expression between sepsis patients and healthy controls (Y-axes units: 2-ΔΔCt value). The performance of MiR-146a (blue line)/miR-146b (red line) in predicting sepsis risk (C) (X-axes units: 1-specificity value; Y-axes units: sensitivity value). MiR-146a, MiR-146a; miR-146b, microRNA-146b.
3.2. Correlation of microRNA-146a/b expression with sepsis risk

MiR-146a relative expression was higher in sepsis patients (2.092 (1.099–3.471)) compared to healthy controls (0.897 (0.389–1.641)) \((P < .001)\) (Fig. 1A). Meanwhile, miR-146b relative expression was increased in sepsis patients (2.470 (1.844–4.243)) compared to healthy controls (0.987 (0.662–1.422)) \((P < .001)\) (Fig. 1B). And ROC curve indicated that MMiR-146a (AUC: 0.774, 95%CI: 0.727–0.820) and miR-146b (AUC: 0.897, 95%CI: 0.865–0.929) were of relatively good value in differentiating sepsis patients from healthy controls, among them miR-146b was of better predictive value compared to MMiR-146a in sepsis risk (Fig. 1C).

3.3. Correlation between MiR-146a and miR-146b in sepsis patients

Since MMiR-146a and miR-146b were both from miR-146 family, therefore we assessed their correlation and found that MiR-146a relative expression was positively associated with miR-146b relative expression \((r = 0.490, P < .001)\) (Fig. 2).

3.4. Correlation of microRNA-146a/b with APACHE II score and SOFA score in sepsis patients

MiR-146a relative expression was positively correlated with APACHE II score \((r = 0.489, P < .001)\) (Fig. 3A) and SOFA score \((r = 0.417, P < .001)\) (Fig. 3B) in sepsis patients. MiR-146b relative expression was also positively associated with APACHE II score \((r = 0.383, P < .001)\) (Fig. 3C) and SOFA score \((r = 0.355, P < .001)\) (Fig. 3D) in sepsis patients.
3.5. Correlation of microRNA-146a/b with biochemical indices and inflammatory cytokines in sepsis patients

MiR-146a was positively associated with Scr ($r = 0.170$, $P = .022$), CRP ($r = 0.283$, $P < .001$), TNF-$\alpha$ ($r = 0.181$, $P = .015$), IL-1$\beta$ ($r = 0.237$, $P = .001$), IL-6 ($r = 0.188$, $P = .012$), IL-17 ($r = 0.194$, $P = .009$), while negatively correlated with albumin ($r = -0.411$, $P < .001$) in sepsis patients (Table 2). In addition, miR-146b was positively associated with increased systemic inflammation, including Scr ($r = 0.273$, $P < .001$), CRP ($r = 0.494$, $P < .001$), TNF-$\alpha$ ($r = 0.368$, $P < .001$), IL-1$\beta$ ($r = 0.330$, $P < .001$), IL-6 ($r = 0.188$, $P = P < .001$) and IL-17 ($r = 0.194$, $P = P < .001$), while negatively correlated with albumin ($r = -0.198$, $P = .008$) in sepsis patients.

| Items   | $P$ value | Correlation coefficient ($r$) | $P$ value | Correlation coefficient ($r$) |
|---------|-----------|-------------------------------|-----------|-------------------------------|
| Scr     | <.001     | 0.170                         | <.001     | 0.273                         |
| Albumin | <.001     | 0.283                         | <.001     | 0.494                         |
| WBC     | .221      | 0.002                         | .199      | 0.069                         |
| CRP     | <.001     | 0.283                         | <.001     | 0.494                         |
| TNF-$\alpha$ | .015 | 0.181                         | <.001     | 0.368                         |
| IL-1$\beta$ | .001 | 0.237                         | <.001     | 0.330                         |
| IL-6    | .012      | 0.188                         | <.001     | 0.408                         |
| IL-17   | .009      | 0.194                         | <.001     | 0.393                         |

Correlation was determined by Spearman’s rank correlation test. CRP = C-reactive protein, IL = interleukin, MiR-146a = microRNA-146a, miR-146b = microRNA-146b, Scr = serum creatinine, TNF = tumor necrosis factor, WBC = white blood cell.

3.6. The predicting factor of 28-day mortality risk in sepsis patients

All sepsis patients were classified as survivors ($n = 132$) and deaths ($n = 48$) based on the survival status in 28-day follow-up. MiR-146a relative expression was decreased in survivors (1.871 (1.050–3.385)) compared to deaths (2.339 (1.667–3.739)) ($P = .042$) (Fig. 4A). MiR-146b relative expression was also reduced in survivors (2.288 (1.623–3.659)) compared to deaths (3.375 (2.177–6.705)) ($P < .001$) (Fig. 4B). Further ROC analysis found that MiR-146a was of poor value in predicting 28-day mortality risk (AUC: 0.599, 95%CI: 0.511–0.688), while miR-146b was of relatively good predictive value in 28-day mortality risk (AUC: 0.703, 95%CI: 0.617–0.788) in sepsis patients.
expression compared to those with MiR-146b low expression was also decreased in sepsis patients with MiR-146b high expression (P = 0.001) (Fig. 5B). Similarly, accumulating survival was also decreased in sepsis patients with miR-146b high expression compared to those with miR-146b low expression (P < 0.001) (Fig. 5B).

3.7. Correlation of microRNA-146a/b with accumulating survival

Accumulating survival was reduced in sepsis patients with MiR-146a high expression compared to those with MiR-146a low expression (P = 0.038) (Fig. 5A). Similarly, accumulating survival was also decreased in sepsis patients with miR-146b high expression compared to those with miR-146b low expression (P < 0.001) (Fig. 5B).

4. Discussion

From the data of our study, we found that

1. MiR-146b presented a better predictive value for elevated sepsis risk compared to miR-146a.
2. In sepsis patients, MiR-146a was positively associated with miR-146b; meanwhile, MiR-146a/miR-146b were both positively correlated with disease severity and systemic inflammation.
3. miR-146b but not MiR-146a presented relatively good predictive value for elevated 28-day mortality risk in sepsis patients.

MiR-146a is indicated to be involved in secretion of inflammatory factors during the progression of inflammatory diseases and associated with inflammation-induced injuries.\(^\text{[19-21]}\) For example, MiR-146a regulates IL-1β and IL-10 via mediating NF-κB in kidney tissues, which associates with the progression of the glomerular injury and renal vascular injury.\(^\text{[19]}\) Besides, MiR-146a is upregulated in lung tissues of asthma, and its overexpression enhances the release of inflammatory factors, contributing to the injury of lung tissue and further resulting in advanced disease severity in asthma.\(^\text{[20]}\) As for miR-146b, it appears to serve as a central regulator of inflammatory signaling and correlates with LPS-induced injuries by mediating pro-inflammatory transcriptional signaling.\(^\text{[8,10,22]}\) For instance, miR-146b increases cell viability, promotes colony number, decreases apoptotic cell rate, and regulates the production of inflammatory factors, which exerts regulatory effect on LPS-induced damage, and LPS-mediated injuries have been observed in acute lung injury, sepsis-induced renal function impairment, and etc.\(^\text{[8,21,23]}\) In addition, miR-146b is correlated with intestinal inflammation through NF-κB signaling.\(^\text{[10]}\) In our present study, we observed that MiR-146a and miR-146b relative expressions were both higher in sepsis patients compared to healthy controls, and ROC curve exhibited that MiR-146a (AUC: 0.774, 95%CI: 0.727–0.820) and miR-146b (AUC: 0.897, 95%CI: 0.865–0.929) were of relatively good value in predicting sepsis risk, and the predictive value of miR-146b was superior to MiR-146a. The possible reasons behind might include that

1. MiR-146a and miR-146b might promote inflammation processes via stimulating production of pro-inflammatory cytokines and activating inflammatory pathways (such as: NF-κB signaling), which enhanced the level of inflammation and organ injuries induced by LPS, driving sepsis onset.
2. MiR-146a/b might aggravate cell damage by inducing inflammatory cascades, increasing tissue edema, leukocyte adhesion, and even microvascular coagulation, which further contributed to microcirculatory failure, multiple organ injuries and sepsis risk.\(^\text{[20]}\)

In addition, we investigated the correlation between MiR-146a and miR-146b, and further explored their correlation with APACHE II score, SOFA score, biochemical indices, and inflammatory cytokines in sepsis patients. We observed that MiR-146a was positively associated with miR-146b, and MiR-
MiR-146a/miR-146b was positively correlated with APACHE II score, SOFA score, Scr, CRP, TNF-α, IL-1β, IL-6, IL-17, while negatively correlated with albumin. The possible reasons might include that

(1) MiR-146a/b might increase the production of pro-inflammatory cytokines via mediating pro-inflammatory transcriptional signaling, exacerbating the severity of organ dysfunction, which led to enhanced disease severity in sepsis patients.

(2) MiR-146a/miR-146b might facilitate endothelial activation via promoting the release of endothelial nitric oxide, which potently promoted leukocyte adhesion and further enhanced the transcriptional and post-transcriptional activation of inflammatory responses in sepsis patients.

Besides, our study also revealed that MiR-146a presented a poor value in predicting 28-day mortality risk (AUC: 0.599, 95% CI: 0.511–0.688), while miR-146b was of relatively good value in predicting 28-day mortality risk (AUC: 0.703, 95% CI: 0.617–0.788) in sepsis patients. Interestingly, we also found that the predictive value of miR-146b for 28-day mortality risk in sepsis patients was similar to several commonly used prognostic indices (APACHE II score, SOFA score), however, MiR-146a was less effective compared to those prognostic indices. The possible reasons might include that:

(1) according to the previous findings in our study, miR-146b was associated with disease severity and systematic inflammation, which might lead to multiple organ failure and unfavorable prognosis, suggesting the potential value of miR-146b in predicting 28-day mortality in sepsis patients.

(2) Considering that the numerical value of correlation coefficient for MiR-146a with inflammatory cytokines was relatively small, the association of MiR-146a with systemic inflammation might be weaker compared to miR-146b; therefore, the predictive value of MiR-146a in mortality risk of sepsis was weaker. Some prior studies indicate that some miRNA have potential to be generalized to vast population and be applied in the sepsis management, as for the application of MiR-146a/miR-146b in sepsis management, more studies with larger population was still needed to validate the generalizability.[12,26]

The limitations in our study were as follows:

(1) The present study was double-centered with relatively small sample size, which might reduce statistical power, therefore, more patients from multiple regions were needed for validation.

(2) We assessed the association of MiR-146a/miR-146b with 28-day mortality, however, the long-term predictive value of MiR-146a/miR-146b on survival in sepsis patients needed further exploration.

(3) As the causative pathogens (such as gram positive, gram negative, fungal, MDR pathogens, and the site of infection, CNS/cardiac involvement) is not involved in the present study, which might lead to confounders.

(4) Considering that the peripheral blood samples of sepsis patients and healthy controls were collected once within 24 hours after admission and on the enrolment, respectively, serial sampling should be warranted in the future study to detect the best time for sampling, when the gene level was in the peak serum level/bottom serum level.

5. Conclusion

The present study detected MiR-146a/miR-146 expression in plasma samples from the sepsis patients and healthy controls; meanwhile, the level of inflammatory cytokines as well as survival profiles were documented in all sepsis patients. These data indicate that both MiR-146a and miR-146b are associated with higher sepsis risk, disease severity and systemic inflammation, while miR-146b presents superior potential predictive value for increased sepsis risk and mortality compared to MiR-146a. These provide insights into the novel potential biomarkers for the management of sepsis.

Author contributions

Conception and design: LC, LY and WS; Administrative support: RZ; Provision of study materials or patients: RZ and LZ; Collection and assembly of data: RZ, LZ and WS; Data analysis and interpretation: LC, LY and WS; Manuscript writing: All authors. Final approval of manuscript: All authors.

References

[1] Braun D. A retrospective review of the sepsis definition after publication of sepsis-3. Am J Med 2019;132:382–4.

[2] Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303–10.

[3] Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 2017;43:304–77.

[4] Faux JD. Biomarkers of sepsis. Crit Rev Clin Lab Sci 2013;50:2:3–36.

[5] Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med 2006;34:1389–96.

[6] De Backer D, Creteur J, Silva E, et al. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: which is best? Crit Care Med 2003;31:1659–67.

[7] Pfeiffer D, Rosemann E, Lang I, et al. MiR-146a, miR-146b, and miR-153 increase expression of IL-6 and IL-8 and support HSP10 in an in vitro sepsis model. PLoS One 2017;12:e0179850. doi: 10.1371/journal.pone.0179850.

[8] Wang Q, Li D, Han Y, et al. MicroRNA-146 protects A549 and H1975 cells from LPS-induced apoptosis and inflammation injury. J Biosci 2017;42:637–45.

[9] Li X, Zhang W, Xiao M, et al. MicroRNA-146b-5p protects oligodendrocyte precursor cells from oxygen/glucose deprivation-induced injury through regulating Keap1/Nrf2 signaling via targeting bromodomain-containing protein 4. Biochem Biophys Res Commun 2019;513:875–82.

[10] Nara T, Fujiya M, Ueno N, et al. MicroRNA-146b improves intestinal injury in mouse colitis by activating nuclear factor-kappaB and improving epithelial barrier function. J Gene Med 2013;15:249–60.

[11] Wu ZW, Liu YF, Wang S, et al. MicroRNA-146a induces vascular smooth muscle cell apoptosis in a rat model of coronary heart disease via NF-kappaB pathway. Genet Mol Resh 2015;14:18703–12.

[12] An R, Feng J, Xi C, et al. MiR-146a attenuates sepsis-induced myocardial dysfunction by suppressing IRAK1 and TRAF6 via targeting ERBB4 expression. Oxid Med Cell Longev 2018;2018:7163057. doi: 10.1155/2018/7163057.

[13] Funahashi Y, Kato N, Masuda T, et al. MiR-146a targeted to splenic macrophages prevents sepsis-induced multiple organ injury. Lab Invest 2019;99:1130–42.

[14] Han Y, Li Y, Jiang Y. The prognostic value of plasma microRNA-155 and microRNA-146a level in severe sepsis and sepsis-induced acute lung injury patients. Clin Lab 2016;62:2355–60.

[15] Jin H, Zhang H, Ma T, et al. Resveratrol protects murine chondrogenic ATDC5 cells against LPS-induced inflammatory injury through up-regulating MiR-146b. Cell Phys Biochem 2018;47:972–80.

[16] Zhu Y, Yu J, Yin L, et al. MicroRNA-146b, a sensitive indicator of mesenchymal stem cell repair of acute renal injury. Stem Cells Transl Med 2016;5:1406–15.
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[17] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315:801–10.

[18] Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med 2013;39:165–228.

[19] Fu HX, Fan XP, Li M, et al. MiR-146a relieves kidney injury in mice with systemic lupus erythematosus through regulating NF-kappaB pathway. Eur Rev Med Pharmacol Sci 2019;23:7024–32.

[20] Shi ZG, Sun Y, Wang KS, et al. Effects of MiR-26a/MiR-146a/miR-31 on airway inflammation of asthma mice and asthma children. Eur Rev Med Pharmacol Sci 2019;23:5432–40.

[21] Zhou C, Zhao L, Wang K, et al. MicroRNA-146a inhibits NF-kappaB activation and pro-inflammatory cytokine production by regulating IRAK1 expression in THP-1 cells. Exp Ther Med 2019;18:3078–84.

[22] Chen P, Li Y, Li L, et al. Circulating microRNA146b-5p is superior to C-reactive protein as a novel biomarker for monitoring inflammatory bowel disease. Aliment Pharmacol Therap 2019;49:733–43.

[23] Jin J, Xu W, Wan B, et al. Topotecan alleviates lipopolysaccharide-mediated acute lung injury via the NF-kappaB signaling pathway. J Surg Res 2019;235:83–92.

[24] Jiang Q, Wu C, Zhang Q. microRNA-34a participates in lipopolysaccharide mediated sepsis related renal function impairment via Kruppel-like factor 4. Zhonghua wei zhong bing ji jiu yi xue 2018;30:351–4.

[25] Reithmair M, Buschmann D, Marte M, et al. Cellular and extracellular miRNAs are blood-compartment-specific diagnostic targets in sepsis. J Cell Mol Med 2017;21:2403–11.

[26] Sandquist M, Wong HR. Biomarkers of sepsis and their potential value in diagnosis, prognosis and treatment. Expert Rev Clin Immunol 2014;10:1349–56.