Abstract: In the face of the elevated incidence and mortality rate of septic shock in the ICU, this retrospective study seeks to investigate the indicative and predictive value of high-mobility group box 1 (HMGB1) and miR-146b in patients with septic shock. Quantitative RT-PCR was employed in this study to quantify the HMGB1 and miR-146b levels in plasma samples obtained from the patient group and healthy controls. The investigation involved the comparison between the two groups and tracking changes in the patient group over time. The finding revealed that upon admission, the patient group exhibited markedly elevated relative expression levels of HMGB1, which subsequently decreased over time. Conversely, the patient group displayed significantly reduced relative expression levels of miR-146b upon admission, which subsequently increased over time compared to the control group. Receiver operating characteristic (ROC) curves showed good predictive value for HMGB1 and miR-146b. The experimental results suggest that HMGB1 and miR-146b serve as valuable and convenient biochemical markers for evaluating the severity of septic shock and predicting mortality. Additionally, it is proposed that serum miR-146b may be inducible and potentially exerts a negative regulatory effect on the expression of HMGB1.

Key words: septic shock; feedback loop; high mobility group box-1; miR-146b; disease severity

CLC number: R446

0 Introduction

Septic shock patients frequently suffer from severe and circulatory cellular metabolism disorders that cause high mortality\(^\text{[9]}\). Upon detection of inflammatory signals, the host immune system primarily generates an in-
nate response with a relative feed-forward amplification of this response and other immune response pathways. The feed-forward mechanism means that the transcription of upstream genes simultaneously activates miRNA expression to regulate target gene expression[2,3]. High mobility group box-1 (HMGB1), a macromolecular substance restricted to the cell nucleus, is released into the bloodstream of patients with sepsis and circulates at an elevated level[4,5]. HMGB1 is regarded as an alarmin that promotes the production of inflammatory mediators with a tardive and biphasic pattern[6]. This indicates that extracellular HMGB1 is involved in the initial activation of systemic inflammatory response and participates in the enduring immunosuppression that causes mortality in the later stage of sepsis[7,8]. The early source of HMGB1 is derived from platelet aggregation, and the later source is derived from injured tissue. These lines of evidence demonstrate that HMGB1 is essential in integrating the inflammatory response to cell injuries[9-12]. These results suggest that HMGB1 is a late-released and critical mediator of fatality in sepsis.

To attenuate the inflammatory response, the immune system can switch a pro-inflammatory process into the resolution phase[13,14]. Several primary anti-inflammatory reactions that inhibit the pro-inflammatory response include the inhibitory miRNAs[15], suppressor of cytokine signaling (SOCS) proteins[16], and hypothalamic-pituitary endocrine axis[17], which inhibit the expressions of pro-inflammatory genes[14]. In eukaryotes, miRNAs approximately constitute 1%-2% of the known genes and negatively regulate gene translation by targeting miRNAs[18,19]. It has been proved that the changes in miRNAs expression profile are related to the onset, progress, and response to treatment of diseases, indicating that they have potential values in diagnostic, prognostic, and predictive indicators in clinics. Recent studies have proved the association of miRNAs with the development of sepsis. It has been determined that gene-specific reprogramming through a miRNA-dependent mechanism can independently suppress the transcription and translation of proinflammatory genes[20,21]. miR-146 may play a crucial role in developing sepsis by suppressing the production of inflammatory cytokines[22]. In addition, miR-146b can reduce the expressions of inflammatory cytokines in endothelial cells[23] and improve sepsis-induced myocardial injury in mice[24]. Exceptionally, HMGB1 can be significantly downregulated by miR-146 in lipopolysaccharide (LPS) induced sepsis by targeting the key members to inhibit the inflammatory response[25]. Clinical studies suggest that miR-146a and miR-146b levels are associated with disease severity, and they might be potential biomarkers for ARDS prevention and prognosis in sepsis[26,27]. However, the roles of miRNAs and their target genes in sepsis are urgent to be illuminated.

As of now, sepsis continues to be a leading cause of morbidity and mortality in patients[28]. Despite this, only a limited number of agents have been validated for effectively treating sepsis. Genes exert their influence through networks of co-expressed genes with similar or opposite biological functions[29]. Therefore, in many instances, the interaction of the host’s genetic expressions and regulations determines the approach to treating the disease. In an effort to shed light on the role of specific genes and miRNAs in sepsis, we conducted this cohort study to investigate the potential gene HMGB1 and its associated regulatory miR-146b in context of septic shock.

1 Materials and Methods

1.1 Participants

In this study, 96 patients who suffered from septic shock were admitted to the intensive care unit (ICU) between January and December 2021 in Tongji Hospital (Wuhan, Hubei, China). Furthermore, 22 healthy controls were collected with matched gender and age. The study was approved by the Ethics Committee of Tongji Hospital (NO. TJ-IRB20211252).

1.2 Diagnosis and Treatment

The clinical criteria for diagnosis of septic, exclusive criteria of patients, the measurements of sepsis-related organ failure assessment (SOFA), and the acute physiology, age, chronic health evaluation II (APACHE-II) scores have been detailed in our prior study[30].

1.3 Sample Collection and Detection

Collecting samples and detecting serum HMGB1 and miR-146b mRNA levels at baseline (Day 0) and on Day 3, Day 5, and Day 7 in the ICU were referred to our previous study[30]. The primers utilized for quantitative RT-PCR were listed as follows (5’-3’):

HMGB1-Forward: TAACTAAACATGGGCAAAGGAG, HMGB1-Reverse: TAGCAGACATGGTCTTTCCAC;
miR-146b-Forward: TGACCC ATCCTGGGCTCAA, miR-146b-Reverse: CCAGTGCGAAGATGTTGGGCC;
β-actin-Forward: GCACCACACCTTCTACACATGAAG, 
β-actin-Reverse: GGTCTCAACATGATCTGGGG; 
U6-Forward: CTCGTTCCGACAGCATACTA, 
U6-Reverse: AACGCTTCAATTTGCGT.

1.4 Statistical Analysis

All statistical analyses were determined with GraphPad Prism 7.0 Software (GraphPad Software, San Diego, CA). Nonparametric statistical tests were used for data analysis. Mann-Whitney U test, one-way ANOVA, the post hoc test (using Tukey-Kramer’s method), receiver operating characteristic (ROC) curve, and the Spearman rank correlation coefficient were performed for statistical comparisons. Data are shown as mean ± SEM. *P*-value<0.05 indicates statistical significance.

2 Results

2.1 Clinical Characteristics of the Septic Shock Patients

Patients’ baseline information, including age, gender, disease severity scores, and clinical parameters are presented in Table 1. The demographics of the patient cohort were displayed by the age distribution [55(47-78) years] and the gender difference (65/31, male/female). The healthy controls were 16/6 (male/female) with a median age of 50 years old. Statistical tests show that there are no differences in age (*P*=0.13) and gender (*P*=0.800) between patients and healthy controls (Table 1).

The primary endpoint in this patient cohort was 28 days. This cohort was comprised of 75 survivors and 21 non-survivors, resulting in a rate of 28-day mortality of 21.9%. Statistical analysis of biochemical indices shows that the mean RBC (red blood cell) (*P*=0.013), PLT (platelet) (*P*<0.001), ALB (albumin) (*P*=0.02) and fibrinogen (*P*<0.001) were significantly elevated in survivors than that in non-survivors, while mean PCT (Procalcitonin) (*P*<0.001), CRP (C-reactive protein) (*P*=0.007), serum creatinine (Scr) (*P*=0.023), lactate and prothrombin time (PT) (*P*<0.001) were significantly decreased in survivors. Meanwhile, the mean SOFA and APACHE II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy controls (n=22)</th>
<th>All patients (n=96)</th>
<th>Survivors (n=75)</th>
<th>Non-survivors (n=21)</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) a</td>
<td>50(46-65)</td>
<td>55(47-78)</td>
<td>53(47-65)</td>
<td>63 (57-78)</td>
<td>0.13</td>
</tr>
<tr>
<td>Sex (M/F) a</td>
<td>16/6</td>
<td>65/31</td>
<td>50/25</td>
<td>15/6</td>
<td>0.800</td>
</tr>
<tr>
<td>WBC (/10^3/L)</td>
<td>6.0±0.34</td>
<td>16.3±1.13</td>
<td>15.9±1.07</td>
<td>20.5±3.48</td>
<td>0.220</td>
</tr>
<tr>
<td>RBC (/10^3/L) c</td>
<td>135.3±1.66</td>
<td>101±1.88</td>
<td>106.7±2.09</td>
<td>95.3±4.03</td>
<td>0.013</td>
</tr>
<tr>
<td>PLT (/10^3/L)</td>
<td>218.8±14.82</td>
<td>87.0±3.29</td>
<td>107.1±1.72</td>
<td>55.4±5.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCT (/ng/mL) d</td>
<td>0.03±0.002</td>
<td>35.3±2.74</td>
<td>18.9±1.13</td>
<td>62±7.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (/ng/mL) d</td>
<td>0.6±0.04</td>
<td>161.7±6.02</td>
<td>147.4±8.65</td>
<td>207.2±14.72</td>
<td>0.007</td>
</tr>
<tr>
<td>ALB (/g/L) e</td>
<td>41±0.81</td>
<td>24.8±0.40</td>
<td>25.8±0.35</td>
<td>21.9±1.14</td>
<td>0.020</td>
</tr>
<tr>
<td>Scr e</td>
<td>75±2.62</td>
<td>146.8±9.24</td>
<td>112.2±7.15</td>
<td>182.5±28.17</td>
<td>0.023</td>
</tr>
<tr>
<td>Lactate (/mmol/L) b</td>
<td>1.2±0.11</td>
<td>6.0±0.40</td>
<td>4.4±0.37</td>
<td>9.7±0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PT /a</td>
<td>13.1±0.28</td>
<td>19.1±0.32</td>
<td>17.4±0.25</td>
<td>21.1±0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (/g/L) b</td>
<td>3.0±0.23</td>
<td>4.4±0.23</td>
<td>5.5±0.18</td>
<td>3.4±0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SOFA score e</td>
<td>—</td>
<td>8.5±0.33</td>
<td>7.7±0.30</td>
<td>11.2±0.85</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APACHE II score e</td>
<td>—</td>
<td>14.3±0.43</td>
<td>20.1±0.72</td>
<td>22.1±1.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HMGB1 b</td>
<td>1.0±0.23</td>
<td>12.8±0.71</td>
<td>10.4±0.69</td>
<td>17±1.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>miR-146b b</td>
<td>0.96±0.13</td>
<td>0.8±0.07</td>
<td>0.93±0.06</td>
<td>0.36±0.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time of ICU stay /days b</td>
<td>—</td>
<td>11.4±0.49</td>
<td>12.4±0.44</td>
<td>7.7±1.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Data are presented as median (range) or number; aData are expressed as mean ±SEM
Abbreviations: WBC: white blood cell; RBC: red blood cell; PLT: platelet; PCT: procalcitonin; CRP: C-reactive protein; ALB: albumin; Scr: serum creatine; PT: prothrombin time; SOFA: sequential organ failure assessment; APACHE II: acute physiology and chronic health evaluation II; HMGB1: high mobility group box-1. *P*-values were calculated for comparisons between survivors and non-survivors, with significance set at *P*<0.05
score, which are commonly used in clinics to evaluate the severity of sepsis patients and predict the prognosis, were significantly lower in survivors ($P<0.001$, respectively).

Moreover, the time of ICU stay was longer in survivors ($P<0.001$). The detailed information on baseline and clinical characteristics of healthy controls and patients with septic shock is presented in Table 2.

### 2.2 Expressions of HMGB1 and miR-146b in Septic Shock Patients and Healthy Controls

During time series analysis, the expressions of HMGB1 and miR-146b in baseline (Day 0), Day 3, Day 5, and Day 7 significantly differed between septic shock patients and healthy controls (Fig. 1). The HMGB1 expression was significantly elevated, while the miR-146b level was obviously decreased in septic shock patients.

#### Table 2  Infection localization of septic shock

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n=96)</th>
<th>Survivors (n=75)</th>
<th>Non-survivors (n=21)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical intervention</td>
<td>20(20.8%)</td>
<td>14(18.7%)</td>
<td>6(28.6%)</td>
<td>0.370</td>
</tr>
<tr>
<td>Infection location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2(27.1%)</td>
<td>22(29.3%)</td>
<td>4(19.0%)</td>
<td>0.420</td>
</tr>
<tr>
<td>Abdominal</td>
<td>10(10.4%)</td>
<td>7(9.3%)</td>
<td>3(14.3%)</td>
<td>0.690</td>
</tr>
<tr>
<td>Liver abscess</td>
<td>3(3.1%)</td>
<td>2(2.7%)</td>
<td>1(4.8%)</td>
<td>0.520</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>4(4.2%)</td>
<td>2(2.7%)</td>
<td>2(9.5%)</td>
<td>0.210</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>23(24.0%)</td>
<td>20(26.7%)</td>
<td>3(14.3%)</td>
<td>0.260</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>9(9.4%)</td>
<td>6(8.0%)</td>
<td>3(14.3%)</td>
<td>0.410</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>5(5.2%)</td>
<td>4(5.3%)</td>
<td>1(4.8%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>CNS</td>
<td>3(3.1%)</td>
<td>2(2.7%)</td>
<td>1(4.8%)</td>
<td>0.630</td>
</tr>
<tr>
<td>Trauma</td>
<td>8(8.3%)</td>
<td>7(6.7%)</td>
<td>1(4.8%)</td>
<td>0.680</td>
</tr>
<tr>
<td>Undefined</td>
<td>5(5.2%)</td>
<td>3(5.3%)</td>
<td>2(4.8%)</td>
<td>0.300</td>
</tr>
</tbody>
</table>

Data are expressed as number of patients (ratio); $P$-value is calculated between survivors and non-survivors (significant for $P<0.05$); CNS: central nervous system

#### Fig. 1  Significant increase of HMGB1 levels (a) and significant decrease of miR-146b levels (b) in septic shock patients

***$P<0.001$; HCs: healthy controls

#### 2.3 Downward Trend of HMGB1 and Upward Trend of miR-146b over Time

To investigate the changing trend of HMGB1 and miR-146b further, consecutive time series analyses were performed among subgroups. Compared with the baseline, HMGB1 was significantly decreased on Day 3, Day 5, and Day 7 (Fig. 2(a), $P=0.003$, $P<0.001$ and $P<0.001$, respectively). However, miR-146b was significantly elevated compared to the baseline on Day 5 and Day 7 (Fig. 2(b), $P<0.001$ and $P=0.006$, respectively). Besides, miR-146b on Day 7 was slightly lower than that on Day 5, but no statistical difference was observed ($P=0.52$). Collectively, our results revealed that after standard treatment, the serum HMGB1 level showed a
downward trend, and miR-146b displayed an upward trend with time in septic shock patients.

**Fig. 2** The downward trend of HMGB1 (a) and the upward trend of miR-146b (b) over time

***$P<0.01$, ****$P<0.001$

### 2.4 HMGB1, miR-146b, SOFA, and APACHE II Scores Indicate Illness Severity and Prognosis

The 96 septic shock patients who suffered from the 28-day challenge were composed of 75 survivors and 21 deaths. The mortality rate is 21.9%. Differences in baseline HMGB1 and miR-146b levels and clinical measurements of SOFA and APACHE II scores between survivors and non-survivors were compared (Fig. 3). At admission, the mean HMGB1 and the baseline SOFA and APACHE II scores were significantly decreased in survivors (Table 1, Fig. 3(a), Fig. 3(c), and Fig. 3(d), $P<0.001$, respectively). At the same time, the miR-146b was significantly elevated in survivors (Table 1, Fig.3(b), $P<0.001$).

**Fig. 3** Correlation of septic shock with HMGB1 level (a), miR-146b(b), SOFA(c), and APACHE II scores (d)

***$P<0.001$

### 2.5 HMGB1 and miR-146b Predict Outcomes of Septic Shock

Figure 4 shows the ROC curves for predicting 28-day mortality based on baseline parameters in septic shock patients. The area under the curve (AUC) values (AUC, $P$ value) of the relative parameters were 0.67 ($P=0.02$) for HMGB1, 0.66 ($P=0.03$) for miR-146b , 0.72 ($P=0.002$) for SOFA score, and 0.73 ($P=0.001$) for APACHE II score, respectively.

### 2.6 Correlation Between miR-146b and HMGB1 in Patients with Septic Shock

Correlation analysis indicated that the serum miR-
146b expression might be negatively associated with HMGB1 level. However, no statistical significance was detected between miR-146b and HMGB1 expressions at any time point, including Day 0 (baseline) \( (r=-0.21, P=0.32) \), Day 3 \( (r=-0.14, P=0.18) \), Day 5 \( (r=-0.15, P=0.16) \), and Day 7 \( (r=-0.09, P=0.34) \).

![ROC curves of four predictors (HMGB1, miR-146b, SOFA, and APACHE II scores) for mortality](image)

**Fig. 4** ROC curves of four predictors (HMGB1, miR-146b, SOFA, and APACHE II scores) for mortality

The AUC values (with \( P \) value) of HMGB1, miR-146b, SOFA, and APACHE II scores were 0.67 \( (P=0.02) \), 0.66 \( (P=0.03) \), 0.72 \( (P=0.002) \), and 0.73 \( (P=0.001) \), respectively.

### 3 Discussion

Although retrospective, this study investigated the relative expressions, dynamic tendencies, and the correlation of HMGB1 and miR-146b in septic shock patients for the first time. HMGB1 is considered a delayed-acting mediator in sepsis since it is extracellularly released 8-12 hours after the primary response of macrophages\(^{31} \). In a study of septic patients, significant expression of serum HMGB1 was detected 24 hours after the onset of sepsis and persisted until 96 hours, suggesting that HMGB1 is not released until sepsis is well established 24 hours later and sustains the pathological progression of sepsis\(^{32} \). An earlier prospective study of septic patients has validated that HMGB1 is a late and downstream inflammatory mediator in sepsis\(^{33} \). However, in a previous multicenter trial, no correlation was observed between plasma HMGB1 levels and disease severity, including APACHE II and SOFA scores\(^{34} \). In another prospective study, plasma and sputum HMGB1 levels did not correlate with disease severity\(^{35} \). A possible explanation is that the concentration of HMGB1 was determined with Western blotting analysis in these studies.

The National Heart, Lung, and Blood Institute (NHLBI) has proposed a unified concept of sepsis as a severe syndrome of endothelial dysfunction. Intravascular or extravascular microbial infections cause it and eventually lead to multiple organ failure, which suggests the central role of endothelial dysfunction in the pathogenesis of sepsis\(^{36} \). Therefore, endothelial dysfunction has been considered a predominant hallmark of sepsis. The stability of endothelial cells and integrity of the endothelial barrier can regulate anticoagulant and anti-inflammatory properties in the bloodstream\(^{37,38} \). In response to pathogenic infections, chemokines can recruit neutrophils to infection sites for microbe clearance, and elevated endothelial adhesion molecules and loosened endothelial barrier promote cell penetration to infection sites. However, increased endothelial permeability subsequently causes microvascular leakage, leading to vascular hypotension and shock\(^{39,40} \). Though HMGB1 releases relatively later than acute phase cytokines\(^{40} \), it orchestrates excessive inflammation response to induce significant endothelial dysfunction or blood coagulation\(^{41,42} \). Besides, circulating HMGB1 can promptly bind to LPS and instruct intracellular translocation of LPS via the receptor for advanced glycation end products (RAGE). The internalization of the HMGB1-LPS complex becomes an essential step in the inflammasome response to LPS\(^{42} \). These results indicate that HMGB1 performs as a late-phase mediator of inflammation that drives the progression of sepsis, suggesting it is the potential target for the diagnostics and therapeutics of sepsis\(^{42} \).

The regulatory mechanism of miRNAs on HMGB1 is unclear. miRNAs are post-transcriptional regulators of gene translation that are involved in pathologies\(^{33,34} \), ischemia-reperfusion injury\(^{43,44} \), and inflamma-tion-related diseases\(^{45,46} \), especially sepsis\(^{40,41} \). Both miR-146a and miR-146b are negative regulators of inflammatory gene expression in various cells\(^{32,47-55} \). Validated targeted inflammation genes of miR-146 family are COX-2\(^{46} \), IRAK1\(^{52} \), TRAF6\(^{53} \), IL-1β, IL-6\(^{58} \), IL-17A\(^{59} \) and NF-κB\(^{57} \). Moreover, HMGB1 might elicit miR-146b expression in turn\(^{60} \). Since sepsis is a heterogeneous syndrome involving numerous genes, a single gene’s contribution is hard to determine with univariate tests\(^{50} \). Likewise, since expressions of miRNAs and the target genes can reciprocally regulate to form feedback loops, the role of miR-146 in sepsis or other inflammation diseases also needs to be illuminated. However, increasing studies have shown that transcriptome methods can be used to analyze potential gene networks that theoretically
regulate the occurrence and development of sepsis due to the reciprocal regulation between miRNAs and target genes.\(^{[8,12]}\)

Up to now, extensive studies on the negative regulation of inflammatory cytokines (e.g., CRP, TNF-α, IL-1β, IL-6, IL-17) and disease severity (e.g., APACHE II and SOFA scores) by miR-146 in septic patients have been carried out. In one study of 108 sepsis patients, the miR-146 relative level was higher than healthy controls.\(^{[26]}\) However, in another study of 104 septic patients, miR-146b was decreased compared to healthy controls.\(^{[27]}\) Although the measurement of miR-146 was controversial, miR-146 has attracted extensive attention from clinicians. However, there are two defects in these studies. Firstly, the dynamic trend of miR-146b was not elucidated. Secondly, the possible downstream target gene of miR-146b was not investigated. Nevertheless, these findings emphasize the critical role of miR-146b in regulating inflammation and sepsis.

To investigate the potential regulatory role of miR-146 on HMGB1, we employed quantitative RT-PCR to evaluate the transcriptional level of genes. In comparison to healthy controls, septic shock patients exhibited a notable increase in the mRNA level of HMGB1, accompanied by a significant decrease in the expression of miR-146b. Compared with non-survivors, HMGB1 levels and the baseline SOFA and APACHE II scores were significantly reduced, whereas the mean miR-146b level was significantly elevated in survivors. During time series analysis, HMGB1 levels presented a downward trend, but miR-146b levels displayed an upward trend. Our study showed higher mortality was associated with higher HMGB1 mRNA but lower miR-146b levels, SOFA and APACHE II scores. To evaluate the predictive efficiency of 28-day mortality risk, ROC curves were generated based on the baseline parameters of HMGB1, miR-146b, SOFA, and APACHE II scores. Although ROC curves showed favorable predictive values of HMGB1 and miR-146b, respectively, they were not superior to SOFA and APACHE II scores.

Furthermore, correlation analysis showed that the serum miR-146b level might be negatively associated with the HMGB1 level. However, no significant correlation was found between HMGB1 and miR-146b levels at any time within the first week after admission to ICU. The potential pathophysiological explanation is that persistent septic shock leads to profound endothelial dys-function and severe reduction in white blood cells, eventually resulting in prolonged immunosuppression. Another aspect that should be mentioned is that CRRT (continuous renal replacement therapy) has been widely applied in clinical therapy for severe sepsis, which may result in sample errors and statistical biases. In spite of these, the levels of HMGB1 and miR-146b can also reflect the direct mechanistic correlations between the host immune response and the feed-forward amplification response, which ultimately contribute to the pathogenesis of sepsis. The above results suggest that HMGB1 and miR-146b may be valuable and convenient indicators for disease severity and predictors for mortality. However, considering patient characteristics, etiology, and intervention variations, more reliable biomarkers for sepsis should be established and evaluated.

It should be noted that there are some limitations in this study. Firstly, the HMGB1 and miR-146b measurements for an extended period were not recorded. Secondly, a verification cohort was not collected to validate the correlation of miR-146b with HMGB1. Thirdly, the relatively small sample of patients might result in statistical bias. Thus, further studies will be conducted in future studies. Overall, validated indicative and predictive biomarkers are very important for clinicians to manage sepsis. Therefore, reliable indicators to evaluate endothelial function, disease severity, and treatment effectiveness should be increased for optimal application.

4 Conclusion

Our findings indicated that a majority of septic shock patients exhibited markedly elevated levels of HMGB1, coupled with notably reduced levels of miR-146b. Furthermore, our study demonstrated that the expression of miR-146b was down-regulated with time, and it may negatively regulate the expression of HMGB1. HMGB1 is a late mediator of inflammation, and miR-146b is a negative regulator of inflammation; both are critical clinical biomarkers reflecting disease severity and predictive mortality indicators in patients with sepsis.

References

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