Regulatory Role of Non-Coding RNAs on Immune Responses During Sepsis

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Sepsis is resulted from a systemic inflammatory response to bacterial, viral, or fungal agents. The induced inflammatory response by these microorganisms can lead to multiple organ system failure with devastating consequences. Recent studies have shown altered expressions of several non-coding RNAs such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs) during sepsis. These transcripts have also been found to participate in the pathogenesis of multiple organ system failure through different mechanisms. NEAT1, MALAT1, THRIL, XIST, MIAT and TUG1 are among lncRNAs that participate in the pathoetiology of sepsis-related complications. miR-21, miR-155, miR-15a-5p, miR-494-3p, miR-218, miR-122, miR-208a-5p, miR-328 and miR-218 are examples of miRNAs participating in these complications. Finally, tens of circRNAs such as circC3P1, hsa_circRNA_104484, hsa_circRNA_104670 and circVMA21 and circ-PRKCI have been found to affect pathogenesis of sepsis. In the current review, we describe the role of these three classes of noncoding RNAs in the pathoetiology of sepsis-related complications.

Keywords: IncRNA, miRNA, sepsis, expression, biomarker

INTRODUCTION

Sepsis is a systemic inflammatory response to different infections, namely bacterial, viral, or fungal agents. This condition is the principal source of mortality in intensive care units (1). These infectious microorganisms can stimulate inflammatory reactions through induction of cytokines release. These reactions lead to multiple organ system failure. Other factors that contribute in this
devastating condition during sepsis are systemic hypotension and abnormal perfusion of the microcirculatory system (2). No specific treatment modality has been suggested for prevention of multiple organ system failure during sepsis (2). Thus, identification of sepsis-related changes at cellular and biochemical levels is important. Currently, there is no effective pharmacological therapy for sepsis. Thus, early diagnosis, resuscitation and instant administration of suitable antibiotics are essential steps in decreasing the burden of this condition (Thompson, 2019 #562).

Lipopolysaccharide (LPS) as the main constituent of the cell wall of Gram-negative bacteria has been found to stimulate apoptotic pathways in tubular epithelial cells of kidney (3). Moreover, it can prompt acute inflammatory responses through activation of NF-κB during the course of acute kidney injury (4). This molecular pathway is an important axis in mediation of immune-related organ damage.

Recent studies have shown altered expressions of several non-coding RNAs such as long non-coding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs (circRNAs) during sepsis. These transcripts have also been found to participate in the pathogenesis of multiple organ system failure through different mechanisms. In the current review, we describe the role of these three classes of noncoding RNAs in the pathoetiology of sepsis-related complications.

**LncRNAs and Sepsis**

LncRNAs are transcripts with sizes larger than 200 nucleotides. These transcripts regulate gene expression through modulation of chromatin configuration, regulation of splicing events, serving as decoys for other transcripts and making structures for recruitment of regulatory proteins (5). These transcripts participate in the regulation of immune reactions and pathoetiology of several immune-related disorders (6).

Experiments in animal model of acute lung injury have shown down-regulation of TUG1 and induction of apoptosis and inflammation. Up-regulation of TUG1 in these animals could ameliorate sepsis-associated lung injury, apoptosis and inflammatory reactions. TUG1 could also protect lung microvascular endothelial cells from deteriorative effects of LPS. In fact, TUG1 inhibits cell apoptosis and inflammatory reactions in LPS-stimulated microvascular endothelial cells through sponging miR-34b-5p and releasing GAB1 from its inhibitory effects. Cumulatively, TUG1 ameliorates sepsis-associated inflammation and apoptosis through miR-34b-5p/GAB1 axis (7). Another study has demonstrated down-regulation of TUG1 while up-regulation of miR-223 in the plasma samples of sepsis patients. They have also reported a negative correlation between expressions of TUG1 and miR-223 in sepsis patients. Besides, expression levels of TUG1 have been negatively correlated with respiratory infection, serum creatinine, white blood cell, C-reactive protein, APACHE II score, and SOFA score. Based on these results, TUG1 has been suggested as a biomarker for prediction of course and prognosis of sepsis (8). TUG1 has also been shown to interact with miR-27a. Over-expression of TUG1 has resulted in down-regulation of TNF-α, while up-regulation of miR-27a has enhanced expression of TNF-α in cardiomyocytes. TNF-α and miR-27a up-regulation could enhance LPS-induced apoptosis of cardiomyocytes. On the other hand, TUG1 up-regulation has exerted opposite effects (9).

MALAT1 is another lncRNA that affects immune responses of rats with LPS-induced sepsis through influencing the miR-146a/NEAT1 axis (10). Moreover, MALAT1 could increase apoptosis skeletal muscle cells and sepsis-associated immune responses through down-regulating BRCA1 levels via recruitment of EZH2 (11). The miR-150-5p/NEAT1 axis is another axis that mediates the effects of MALAT1 in sepsis-associated cardiac inflammation (12). In addition, the protective effects of Ulinastatin against LPS-associated dysfuncion of heart microvascular endothelial cells have been shown to be exerted through down-regulation of MALAT1 (13). Most notably, MALAT1/miR-125a axis has been shown to discriminate sepsis patients based on their severity of diseases, organ damage, levels of inflammatory responses and mortality (14). Figure 1 depicts function of MALAT1 in sepsis-related events.

NEAT1 is another lncRNA whose participation in the pathophysiology of sepsis has been vastly investigated. This lncRNA could promote inflammatory responses and aggravate sepsis-associated hepatic damage through the Let-7a/TLR4 axis (15). Moreover, NEAT1 can accelerate progression of sepsis via miR-370-3p/TSP-1 axis (16). This lncRNA could also promote LPS-induced inflammatory responses in macrophages through regulation of miR-17-5p/TLR4 axis (17). NEAT1 silencing could suppress immune responses during sepsis through miR-125/MCEMP1 axis (18). Figure 2 shows the function of NEAT1 in sepsis-related events. Several other lncRNAs have also been found to influence course of sepsis through modulation of immune responses (Table 1).

**miRNAs and Sepsis**

miRNAs have sizes about 22 nucleotides and regulate expression of genes through binding with different regions of target mRNAs, particularly their 3’ UTR. They can either degrade target mRNA or suppress its translation. Several miRNAs have been found to influence course of sepsis. Altered expression of these small-sized transcripts has been reported in sepsis by numerous research groups. For instance, plasma levels of miR-494-3p have been shown to be decreased in sepsis patients compared with healthy controls in correlation with up-regulation of TLR6. Expression level of miR-494-3p has been decreased in LPS-induced RAW264.7 cells, parallel with up-regulation of TLR6 and TNF-α. Forced over-expression of miR-494-3p in RAW264.7 cells could reduce TNF-α level and suppress translocation of NF-κB p65 to the nucleus.
Several other lncRNAs have also been found to influence the course of sepsis through modulation of immune responses (Table 1).
TLR6 has been shown to be targeted by miR-494-3p. Taken together, miR-494-3p could attenuate sepsis-associated inflammatory responses through influencing expression of TLR6 (132). miR-218 is another miRNA which participates in the pathoetiology of sepsis. This miRNA could reduce inflammatory responses in the sepsis through decreasing expression of VOPP1 via JAK/STAT axis (133).

miR-122 is another important miRNA in the sepsis which has superior diagnostic power compared with CRP and total leucocytes count for distinguishing sepsis from wound infection. miR-122 has also been found to be a prognostic marker for sepsis, albeit with poor specificity and accuracy values (134).

In the mouse model of sepsis, decreased levels of miR-208a-5p and increased levels of SOCS2 has been associated with enhanced activity of SOD, while reduction in LDH and MDA activities. and increased levels of SOCS2 has been associated with enhanced values (134).

miR-12-2 is another miRNA whose role in sepsis has been investigated by several groups. Down-regulation of miR-21 has been shown to inhibit inflammasome activation, ASC pyroptosome, LPS-induced pyroptosis and septic shock in one study (136). On the other hand, another study in animal models of sepsis has shown that up-regulation of miR-21 reduced inflammation and apoptosis (137). Similarly, βMSCs-derived exosomes have been shown to reduce symptoms in septic mice and improve their survival rate through up-regulation of miR-21 (138).

miR-328 is another miRNA which is dysregulated in sepsis patients as well as animal models of sepsis. Serum levels of this miRNA could properly differentiate sepsis from normal conditions. Thus, miR-328 has been suggested as a diagnostic biomarker for sepsis. Moreover, down-regulation of miR-328 could amend sepsis-related heart dysfunction and inflammatory responses in this tissue (139). miR-452 is another miRNA with diagnostic applications in sepsis. Notably, serum and urinary levels of this miRNA have been suggested as possible markers for early diagnosis of sepsis-associated acute kidney injury, since expression of this miRNA has been higher in sepsis patients with acute kidney injury compared with those without this condition (140) (Table 2). Figure 3 depicts miRNAs that are down-regulated in sepsis.

CircRNAs AND SEPSIS

CircRNAs are a recently appreciated group of non-coding RNAs with enclosed circular configuration formed by covalent bonds between two ends of linear transcripts. However, some of these transcripts have been shown to produce proteins. They mostly exert regulatory functions in the transcriptome. Impact of circRNAs in the sepsis has been assessed by several groups (303). For instance, circC3P1 has been shown to attenuate production of inflammatory cytokines and decrease cell apoptosis in sepsis-associated acute lung injury via influencing expression of miR-21 (304).

A microarray-based has shown differential expression of 132 circRNAs between sepsis patients and healthy controls among them have been hsa_circRNA_104484 and hsa_circRNA_104670 whose up-regulation in sepsis serum exosomes has been verified been RT-PCR. Expression levels of these two circRNAs have been suggested as diagnostic biomarkers for sepsis (305).

CircVMA21 is another circRNA that has been shown to ameliorate sepsis-related acute kidney injury through modulation of oxidative stress and inflammatory responses via miR-9-3p/SMG1 axis (306). Circ_0114428/miR-495-3p/CRBN axis is another molecular axis which is involved in the pathoetiology of sepsis-related acute kidney injury (307). Moreover, expression levels of circPRKCI have been correlated with sepsis risk, severity of sepsis and mortality during a period of 28 days (308). Table 3 summarizes the role of circRNAs in sepsis.

DISCUSSION

A vast body of literature points to the involvement of lncRNAs, miRNAs and circRNAs in the pathoetiology of sepsis-related complications. NEAT1, MALAT1, MEG3, THRIL, XIST, CRNDE, ZFAS1, HULC, MIAT and TUG1 are among IncRNAs with the strongest evidence for their participation in this process. NEAT1 as the mostly assessed IncRNA in this regard has been shown to act as a molecular sponge for let-7a, let-7b-5p, miR-370-3p, miR-124, miR-125, miR-17-5p, miR-16-5p, miR-93-5p, miR-370-3p, miR-144-3p, miR-944, miR495-3p, miR-22-3p, miR-31-5p and miR-590-3p. Through sequestering these miRNAs, NEAT1 can affect several molecular pathways in the course of sepsis. It can enhance immune responses and the related injury in target organs, thus participating in sepsis-related multiple organ damage.

Similar to lncRNAs, circRNAs influence course of sepsis mainly through acting as molecular sponges for miRNAs. circC3P1/miR-21, circVMA21/miR-9, circVMA21/miR-199a-5p, circ_PRKCI/miR-545, circPRKCI/miR-106b-5p, circDNMT3B/miR-20b-5p, circ_0114428/miR-495-3p, circ_Ttc3/miR-148a, circPRKCI/miR-454, circ-Fryl/miR-490-3p, circ_0091702/miR-182, circTLK1/miR-106a-5p, circFADS2/miR-15a-5p, circ_0091702/miR-545-3p, hsa_circ_0068888/miR-21-5p, circPTK2/miR-181c-5p, circFANCA/miR-93-5p and circANKRD36/miR-330 are among circRNA/miRNA axes which are involved in the pathophysiology of sepsis-related conditions.
| LncRNA   | Expression Pattern | Clinical Samples/ Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|----------|--------------------|--------------------------------|---------------------|----------------------|-------------------|----------------------------------------------------------------------------|-----------|
| TUG1     | ↓                  | 35 ARDS patients and 68 HCs, male CS7BL/6 mice | PMVECs              | † miR-34b-5p, GAB1    | ↓                 | TUG1 reduces sepsis-induced pulmonary injury, apoptosis and inflammation in ALI. | (7)       |
| TUG1     | ↓                  | 122 patients with sepsis and 122 HCs | -                   | † miR-223            | -                 | Low levels of TUG1 was correlated with respiratory infection. TUG1 expression was negatively associated with Scr, WBC, SOFA score, and CRP levels and 28-day deaths, but positively associated with albumin levels. | (8)       |
| TUG1     | ↓                  | 70 patients with sepsis and 70 HCs rats with and without LPS-induced sepsis | AC16                | miR-27a, ↓ SLIT2      | ↑                 | Up-regulation of TUG1 reduced apoptosis, autophagy, and inflammatory response. | (19)      |
| MALAT1   | †                  | BALB/c male mice                 | HSMKMC 3500         | ↓ miR-146a, ↑ P65     | ↑ NF-κB signaling pathway | Downregulation of MALAT1 decreased the number of TNF-α and iNOS positive cells. | (10)      |
| MALAT1   | †                  | 196 patients with sepsis and 196 HCs, | H9c2                | ↓ miR-150-5p, ↑ NF-κB signaling pathway | - | Downregulation of MALAT1 increased inflammatory responses, neutrophil migration, skeletal muscle cell apoptosis, and AKT-1 phosphorylation. | (11)      |
| MALAT1   | †                  | sepsis mice                      | U937                | ↓ BRCA1, Ezh2         | -                 | Downregulation of MALAT1 reduced inflammatory response and downregulated NF-κB signaling pathway. | (12)      |
| MALAT1   | †                  | male SD rats                     | CMVECs              | ↑ Ezh2               | -                 | MALAT1 significantly inhibited levels of Ezh2 target genes, DAB2IP and Brachyury. Up-regulation of CRNDE increased permeability and apoptosis. | (13)      |
| MALAT1   | †                  | 196 patients with sepsis and 196 HCs, | -                   | ↓ miR-125a            | -                 | MALAT1 expression was positively correlated with APACHE II score, SOFA score, serum creatinine, CRP, TNF-α, IL-1β, IL-6, 28-day deaths, and negatively with albumin. | (14)      |
| MALAT1   | †                  | sepsis mice                      | -                   | ↓ miR-23a, ↑ MCEMP1    | -                 | Downregulation of MALAT1 suppressed expression of MPO, IL-6, IL-10, TNF-α, and IL-1β, and reduced inflammation. | (20)      |
| MALAT1   | †                  | male C57 mice                    | -                   | ↑ p38 MAPK / pS6 NF-κB signaling pathway | - | Downregulation of MALAT1 reduced MPO and inflammatory responses. | (21)      |
| MALAT1   | †                  | a lung injury inflammatory cell model | -                   | ↑ p38 MAPK / pS6 NF-κB signaling pathway | ↑ NF-κB pathway | Downregulation of MALAT1 reduced the levels of MyD88, TNF-α, IL-1β, and IL-6, and prevented the NF-κB pathway. | (22)      |
| MALAT1   | †                  | CLP-induced septic mice           | HUVECs, PAECs       | ↓ miR-149, ↑ MyD88    | ↑ NF-κB pathway | Downregulation of MALAT1 reduced apoptosis, ER stress and inflammation. | (23)      |
| MALAT1   | † in ARDS group    | 152 patients with sepsis (41 ARDS and 111 Non-ARDS patients) | -                   | ↑ IL-6, ↑ TNF-α, ↑ SAA3 | - | MALAT1 expression was association with APACHE II score, SOFA score, inflammatory factors levels, and high mortality. | (24)      |
| MALAT1   | †                  | GEO dataset (GSE3140), male CS7BL/6 mice | HL-1                | ↑ IL-6, ↑ TFN-α, ↑ SAA3 | - | Downregulation of MALAT1 Protected Cardiomyocytes from LPS-induced Apoptosis. | (25)      |
| MALAT1   | †                  | 190 patients with sepsis and 190 HCs | -                   | ↓ miR-125b            | -                 | MALAT1 expression was associated with Scr, WBC, CRP, PCT, TNF-α, IL-8, IL-17, APACHE II score, SOFA score, and 28-day deaths. Expression of MALAT1 was found to be an independent risk factor for sepsis, poor prognosis and septic shock. | (26)      |
| MALAT1   | †                  | 120 patients with sepsis and 60 HCs | -                   | -                     | -                 | Downregulation of MALAT1 attenuated the burn injury and post-burn sepsis-induced inflammatory reaction. | (27)      |
| MALAT1   | †                  | female CS7BL/6 mice               | THP-1               | ↓ miR-214, ↑ TLR5     | -                 | Down-regulation of MALAT1 attenuated sepsis-induced myocardial injury. | (28)      |
| KCNQ1OT1 | ↓                  | male SD rats                      | H9c2                | ↑ miR-192-5p, ↓ XIAP  | -                 | Up-regulation of KCNQ1OT1 ameliorated proliferation and impeded apoptosis in sepsis-induced myocardial injury. | (29)      |
| IncRNA     | Expression Pattern | Clinical Samples/ Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|------------|--------------------|--------------------------------|---------------------|----------------------|--------------------|-----------------------------------------------------------------------------|-----------|
| CYTOR      | ↓                  | male SD rats                  | H9c2                | ↑ miR-24, ↓ XIAP     |                   | Up-regulation of CYTOR ameliorated viability and inhibited apoptosis in sepsis-induced myocardial injury. (30) |
| IncRNA-5657| ↑                  | 15 patients with sepsis-induced ARDS and 15 non-septic and non-ARDS patients, SD rats | NR8383             | ↑ Spns2              |                   | Downregulation of IncRNA-5657 prevented sepsis-induced lung injury and LPS-induced inflammation. (31) |
| RMRP       | ↓                  | male C57BL/6 mice             | HL-1                | ↑ miR-1-5p, ↓ HSPA4  | ↑ NF-κB Pathway    | Up-regulation of RMRP reduced LPS-induced damage, apoptosis and mitochondrial damage and LPS-induced sepsis. (32) |
| NEAT1      | ↑                  | 15 patients with sepsis-induced liver injury and 15 HCs | Kupffer, Raw264.7   | ↓ Let-7a, ↑ TLR4     |                   | Downregulation of NEAT1 reduced expression of inflammatory factors in sepsis-induced liver injury. (15) |
| NEAT1      | ↑                  | 25 Sepsis patients and 25 HCs | RAW 264.7           | ↑ miR-370-3p, ↑ TSP-1 |                   | Downregulation of NEAT1 prevented LPS-mediated inflammation and apoptosis and ameliorated proliferation. (16) |
| NEAT1      | ↑                  | male pathogen-free C57BL/6 mice | -                  | ↓ miR-125, ↑ MOEMP1  |                   | Downregulation of NEAT1 suppressed inflammation and T lymphocyte apoptosis. (18) |
| NEAT1      | ↑                  | 68 patients with sepsis and 32 HCs | THP-1 macrophages   | ↓ miR-17-5p, ↑ TLR4  |                   | Downregulation of NEAT1 prevented LPS-induced inflammatory responses in macrophages. (17) |
| NEAT1      | ↑                  | mouse with sepsis-induced lung injury | -                  | ↓ miR-16-5p, ↑ BRD4  |                   | Downregulation of NEAT1 inhibited inflammation, apoptosis, pulmonary edema, MPO activity, pathological changes, promoted viability. (33) |
| NEAT1      | ↑                  | male C57 mice                 | -                   | ↑ TLR2/ NF-κB signaling pathway | ↑ HMGB1/RAGE signaling pathway | Downregulation of NEAT1 increased viability attenuated LPS-induced apoptosis and suppressed inflammation. (35) |
| NEAT1      | ↑                  | male C57BL/6 mice             | A549                | -                   | ↑ TLR2/ NF-κB signaling pathway | Downregulation of NEAT1 increased proliferation and inhibited apoptosis and inflammation. (36) |
| NEAT1      | ↑                  | 30 patients with sepsis and 30 HCs | HK-2                | ↓ let-7b-5p, ↑ TRAF6 |                   | Downregulation of NEAT1 decreased inflammation by promoting macrophage M2 polarization. (37) |
| NEAT1      | ↑                  | -                              | RAW264.7            | ↓ miR-125a-5p, ↑ TRAF6, ↑ P-TAK1 |                   | Downregulation of NEAT1 inhibited apoptosis, inflammation and oxidative stress. (38) |
| NEAT1      | ↑                  | patients with sepsis           | HK2                 | ↓ miR-95-5p, ↑ TNF, ↑ P-TAK1 |                   | Downregulation of NEAT1 ameliorated viability, prevented apoptosis and the expression of inflammatory cytokines. (39) |
| NEAT1      | ↑                  | sepsis tissues and ANCTs       | AW 264.7 and HL-1   | ↓ miR-370-3p, ↑ Irak2 |                   | Downregulation of NEAT1 ameliorated viability, prevented apoptosis and inflammatory response in LPS-induced myocardial cell injury. (40) |
| NEAT1      | ↑                  | -                              | HL-1                | ↓ miR-144-3p, ↑ NF-κB signaling pathway |                   | Up-regulation of NEAT1 was positively associated with Acute Physiology and Chronic Health Evaluation II score, inflammatory responses, while negatively associated with IL-10. (41) |
| NEAT1      | ↑                  | 152 patients with sepsis and 150 | -                   | -                   | -                   | Downregulation of NEAT1 inhibited inflammatory responses and apoptosis. Overexpression of TRIM37 rescued influence of downregulation of NEAT1 on cell's. (42) |
| NEAT1      | ↑                  | C57BL/6 mice                  | WI-38               | ↓ miR-944, ↑ TRIM37  |                   | Downregulation of NEAT1 inhibited inflammatory responses and apoptosis. Overexpression of TRIM37 rescued influence of downregulation of NEAT1 on cell's. (42) |
| NEAT1      | ↑                  | 59 patients with sepsis, 52 patients with noninfectious SIRS, and 56 HCs | PBMCs              | -                   | -                   | Levels of NEAT1 could be considered as a good predictor for the diagnosis of sepsis. (43) |
| NEAT1      | ↑                  | 127 patients with sepsis and 50 HCs | -                   | ↑ Th1, ↑ Th17       | -                   | Overexpression of NEAT1 was associated with chronic health evaluation II score, CRP level, acute physiology, and SOFA score. (44) |

(Continued)
### TABLE 1 | Continued

| IncRNA   | Expression Pattern | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|----------|--------------------|-------------------------------|---------------------|----------------------|--------------------|------------------------------------------------------------------------------|-----------|
| NEAT1    | †                  | male C57BL/6 mice             | RAW264.7            | ↓ miR-22-3p          | ↑ NF-xB pathway      | Overexpression of NEAT1 was associated with inflammatory responses.          | (45)      |
| NEAT1    | †                  | 102 patients with sepsis and 100 HCs | –                   | ↓ miR-125a          | –                   | High levels of NEAT1 was associated with SOFA score, APACHE II score, 28-day deaths, and high ARDS risk. | (46)      |
| NEAT1    | †                  | Septic Mice                   | –                   | ↑ NF-xB             | –                   | Downregulation of NEAT1 increased activity of nerve cells and reduced apoptosis. | (47)      |
| NEAT1    | †                  | 82 patients with sepsis and 82 HCs | –                   | ↓ miR-124           | –                   | NEAT1 showed a good predictive value for increased sepsis risk. NEAT1 expression was positively associated with disease severity, CRP, PCT, TNF-α, and IL-1β, 28-day deaths. | (48)      |
| NEAT1    | †                  | 18 patients with sepsis-induced AKI and 18 HCs | HK-2               | ↓ miR-31-5p         | –                   | Downregulation of NEAT1 reduced levels of autophagy factors and inflammatory responses. | (49)      |
| NEAT1    | †                  | 22 patients with sepsis and 22 HCs | H9c2                | ↓ miR-590-3p        | NF-xB signaling pathway | Downregulation of NEAT1 reduced apoptosis and inflammatory responses in LPS-induced sepsis. | (50)      |
| H19      | †                  | 69 patients with sepsis and HCs, male BALB/c mice | –                   | ↑ miR-874, ↓ AQP1   | –                   | Downregulation of H19 contributed to inflammatory responses. Up-regulation of H19 ameliorated the impairment of sepsis companied myocardial dysfunction. | (51)      |
| H19      | †                  | 104 patients with sepsis, and 92 HCs rats | HSAECs             | ↑ miR-93-5p         | –                   | Up-regulation of H19 suppressed inflammatory responses in sepsis-induced myocardial injury. | (52)      |
| CASC9    | †                  | 60 patients with sepsis and 60 HCs | HCAECs             | ↑ miR-195-5p, ↓ PDK4 | –                   | Expression of H19 was negatively associated with 28-day deaths and inflammatory response markers. | (53)      |
| LUADT1   | †                  | 66 patients with sepsis and 66 HCs | HBEpCs             | ↓ miR-19a           | –                   | Up-regulation of LUADT1 reduced inflammatory responses.                      | (54)      |
| MiAT     | †                  | male SD rats                  | NRK-52E            | ↓ miR-29a           | –                   | Up-regulation of MiAT promoted apoptosis in sepsis-related kidney injury.     | (55)      |
| MiAT     | †                  | male BALB/c mice              | HL-1               | ↑ miR-330-5p        | ↑ NF-xB signaling | Downregulation of MiAT restrained inflammation and oxidative stress in Sepsis-Induced Cardiac Injury. | (56)      |
| THRIL    | †                  | 66 patients with sepsis and 66 HCs | MPVECs             | ↓ miR-155-5p        | –                   | Up-regulation of THRIL promoted apoptosis.                                  | (57)      |
| THRIL    | †                  | male C57BL/6 mice             | Kupffer             | ↑ BRD4              | –                   | Downregulation of XIST reduced inflammation, oxidative stress, and apoptosis in sepsis-induced acute liver injury. | (58)      |

(Continued)
### TABLE 1 | Continued

| IncRNA     | Expression Pattern | Clinical Samples/ Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|------------|--------------------|--------------------------------|--------------------|----------------------|--------------------|-----------------------------------------------------------------------------|-----------|
| XIST       | ↑                  | GEO database: GSE94717 (6 patients with sepsis-induced AKI and 6 HCs) | MPC5               | ↓ miR-15a-5p, ↑ CUL3 | -                  | Up-regulation of XIST enhanced apoptosis in sepsis-induced AKI.             | (65)      |
| xist       | ↑                  | -                              | -                  | -                    | -                  | Downregulation of xist inhibited apoptosis and induced proliferation.       | (66)      |
| GASS       | ↓                  | 60 patients with sepsis and 60 HCs | AC16               | ↓ miR-214            | -                  | Downregulation of GASS restrained apoptosis of cardiomyocytes induced by LPS. GASS could regulate miR-214 through methylation pathway. | (67)      |
| CRNDE      | ↓                  | male specific-pathogen-free Wistar rats | -                  | ↑ miR-29a, ↓ SIRT1, ↑ NF-xB/ PARP1 signaling | -                  | Up-regulation of CRNDE reduced apoptosis, oxidative stress and inflammatory response. | (68)      |
| CRNDE      | ↑                  | 136 patients with sepsis and 151 HCs | TBP-1              | ↓ miR-181a-5p, ↑ TLPA4 | -                  | Up-regulation of CRNDE was correlated with poorer OS and was a significant predictor in patients with sepsis. Downregulation of CRNDE reduced sepsis-related inflammatory pathogenesis. | (69)      |
| CRNDE      | ↑                  | male C57 mice                   | -                  | ↑ p65                | ↑ TLPA4/ NF-xB pathway signaling | Downregulation of CRNDE reduced edema, necrosis and apoptosis in sepsis-induced AKI. | (70)      |
| CRNDE      | ↑                  | HK-2                            | -                  | ↑ miR-146a           | ↑ TLPA4/ NF-xB signaling pathway | Up-regulation of CRNDE enhanced cell injuries, inflammatory responses and apoptosis in sepsis-induced AKI. | (71)      |
| CRNDE      | ↓                  | rats                            | HK-2, HEP293       | ↑ miR-181a-5p, ↓ PPARγ | -                  | Downregulation of CRNDE increased the urea nitrogen and serum creatinine, and reduced proliferation and promoted apoptosis. | (72)      |
| CRNDE      | ↓                  | male SD rats                    | L02                | ↑ miR-126-5p, ↓ BCL2L2 | -                  | Downregulation of CRNDE increased viability and repressed apoptosis in sepsis-induced liver injury. | (73)      |
| HOTAIR     | ↓                  | male SD rats                    | HK-2               | ↑ miR-34a           | -                  | Up-regulation of HOTAIR reduced apoptosis in sepsis-induced AKI.            | (74)      |
| HULC       | ↑                  | 110 patients with sepsis and 100 HCs | HMEC-1, CRL-3243 | ↓ miR-128-3p, ↑ RAC1 | -                  | Downregulation of HULC restrained apoptosis and inflammation, and protected HMEC-1 cells from LPS-induced injury. | (75)      |
| HULC       | ↑                  | 174 patients with sepsis and 100 HCs | -                  | -                    | -                  | Expression of HULC was correlated with APACHE II, SOFA score, and 28-day deaths. It was also positively associated with Scr, WBC, and CRP, but negatively correlated with albumin. | (76)      |
| HULC       | ↑                  | 56 patients with sepsis and 56 HCs | HUVECs             | ↓ miR-204-5p, ↑ TRPM7 | -                  | Downregulation of HULC promoted viability and reduced apoptosis, inflammatory responses and oxidative stress. | (77)      |
| HULC       | ↑                  | C57BL/6 mice                    | HMECs             | ↑ IL6, ↑ ICAM1, ↑ VCAM1 | -                  | Downregulation of HULC reduced levels of pro-inflammatory factors.        | (78)      |
| TapSAKI    | ↑                  | SD rats                         | HK-2               | ↓ miR-22            | ↑ TLPA4/ NF-xB pathway | Downregulation of TapSAKI decreased inflammatory factors and renal function indicators, so decreased kidney injury. | (79)      |
| ITS1N1-2   | ↑                  | 309 patients with intensive care unit (ICU)-treated sepsis and 300 HCs | -                  | -                    | -                  | High levels of ITS1N1-2 were correlated with elevated disease severity, inflammation, and poor prognosis in sepsis patients. | (80)      |
| LncRNA-p21 | ↑                  | sepsis-induced ALI rat model     | BEAS-2B c          | -                    | -                  | Downregulation of LncRNA-p21 restrained apoptosis, inflammatory responses and oxidative stress in sepsis-induced ALI. | (81)      |
| TCONS_00016233 | ↑ | 15 patients with septic AKI and non-AKI, and 15 HCs, C57BL/6j mice | HK-2               | miR-22-3p, ↑ AIM1    | TLPA4/ p38MAPK axis | Downregulation of TCONS_00016233 restrained LPS-induced apoptosis. Up-regulation of TCONS_00016233 induced LPS-induced apoptosis and inflammatory responses. | (82)      |
| UCA1       | ↑                  | C57BL/6 mice                    | HMECs             | ↑ IL6, ↑ ICAM1, ↑ VCAM1 | -                  | Downregulation of UCA1 reduced inflammatory responses.                      | (83)      |

(Continued)
### TABLE 1  | Continued

| IncRNA  | Expression Pattern | Clinical Samples/ Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description | Reference |
|---------|--------------------|-------------------------------|---------------------|----------------------|-------------------|-------------|-----------|
| NR024118 | ↓                  | 82 patients with sepsis without MD, 35 patients with sepsis and MD and 82 HCs | AC16               | ↑ IL-6               | NF-κB signaling pathway | Up-regulation of NR024118 reduced the secretion of IL-6 and apoptosis, and improved LPS-induced myocardial APD duration and cell injury. | (83) |
| MIR155HG | ↑                  | 28 patients with sepsis and 28 without sepsis | HL-1, RAW 264.7   | ↓ miR-194-5p, ↑ MEF2A |                  | Downregulation of MIR155HG increased viability and decreased apoptosis and inflammatory responses. | (84) |
| LUCAT1   | ↑                  | GEO dataset: GSE101639       | H9c2               | ↓ miR-642a, ↑ ROCK1   |                  | Downregulation of LUCAT1 decreased inflammatory responses. | (85) |
| SOX2OT   | ↑                  | male C57B6/L mice            | H9c2               | ↑ SOX2               |                  | Downregulation of SOX2OT reduced mitochondrial dysfunction in septic cardiomyopathy. | (86) |
| MEG3     | ↑                  | male C57BL/6 mice            | TECs               | ↓ miR-18a-3P         |                  | Downexpression of MEG3 expression was positively correlated with cardiomyopathy, APACHE II score, SOFA score, Scr, TNF-α, IL-1β, IL-6, and IL-17, 28-day deaths, while negatively correlated with albumin. | (87) |
| MEG3     | ↑                  | 82 patients with sepsis and 54 HCs | Human primary renal mixed epithelial cells , AC16 |                  |                  | Downregulation of MEG3 reduced mitochondrial dysfunction in septic cardiomyopathy and expression of GSDMD in LPS-induced AKI. | (88) |
| MEG3     | ↑                  | 112 patients with sepsis and 100 HCs | —                 | —                   |                  | High levels of MEG3 were associated with 28-day deaths and it was found to be a predictor of higher ARDS risk. | (89) |
| MEG3     | ↑                  | 219 patients with sepsis and 219 HCs, male C57BL/6 J mice | —                 | ↓ miR-21             |                  | Lnc-MEG3 expression was positively correlated with cardiomyopathy, APACHE II score, SOFA score, Scr, TNF-α, IL-1β, IL-6, and IL-17, 28-day deaths, while negatively correlated with albumin. | (90) |
| MEG3     | ↓                  | male C57/BL mice             | Caco2              | ↑ miR-129-5p, ↓ SP-D |                  | Overexpression of MEG3 reduced villus length and apoptosis, inhibited intestinal injury and enhanced proliferation. | (91) |
| GASS     | ↓                  | —                             | conditional immortalized podocyte line THLE-3 | ↓ PTEN             | ↑ PI3K/ AKT pathway | Downregulation of GASS elevated the Podocyte Injury. | (92) |
| LINC00472| ↑                  | male SD rats                 | —                  | —                   |                  | Downregulation of LINC00472 enhanced viability and suppressed apoptosis. | (93) |
| HOTAIR   | ↑                  | male C57B6/L mice            | HL-1               | ↑ p-p65, ↑ NF-κB     | NF-κB pathway      | Downregulation of HOTAIR restrained LPS-induced myocardial dysfunction in septic mic. HOTAIR was involved in p65 phosphorylation and NF-κB activation, leading to 15 TNF-α production. | (94) |
| HOTAIR   | ↑                  | male SD rats                 | HK-2               | ↓ miR-22, ↑ HMGB1    |                  | Downregulation of HOTAIR reduced renal function indicators (blood urea nitrogen and serum creatinine). | (95) |
| Hotairm1  | ↑                  | male C57BL/6 mice            | MDSCs              | ↑ S100A9 localization |                  | Downregulation of Hotairm1 restrained the suppressive functions of late sepsis Gr1+CD11b+ MDSCs. Hotairm1 Was involved in shutting S100A9 protein to the nucleus. | (96) |
| NKILA    | ↑                  | —                             | HK2                | ↓ miR-140-5p, ↑ CLDN2 |                  | Downregulation of NKILA restrained apoptosis, autophagy and inflammation and promoted viability in sepsis-induced AKI. | (97) |
| HOXA-AS2  | ↓                  | 44 patients with sepsis and 44 HCs, adults clean Kunming mice | HK-2               | ↑ Wnt/β-catenin and NF-κB pathways |                  | Up-regulation of HOXA-AS2 increased viability and repressed apoptosis and protect cells to resist LPS-induced damage in sepsis-induced AKI. | (98) |
| SNHG14   | ↑                  | —                             | HK-2               | miR-93, IL-6, ↑ TLR4/NF-κB pathway, ↑ NF-κB pathway |                  | Up-regulation of SNHG14 promoted oxidative stress, inflammation, and apoptosis. TLR4/NF-κB pathway induced upregulation of SNHG14. | (99) |

(Continued)
| IncRNA | Expression Pattern | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description | Reference |
|--------|-------------------|-------------------------------|---------------------|----------------------|-------------------|-------------|----------|
| IncRNA-CCL2 | ↑ | male C57BL/6 mice | _ | ↓ SIRT1 | _ | Expression of IncRNA-CCL2 was inhibited by SIRT1 through maintaining a more repressive chromatin state in IncRNA-CCL2 locus. Downregulation of SIRT1 induced inflammatory response. | (100) |
| DLX6-AS1 | ↑ | patients with septic AKI | HK-2 | ↓ miR-223-3p, ↑ NLRP3 | _ | Downregulation of DLX6-AS1 suppressed LPS-induced cytotoxicity and pyroptosis. Expression of DLX6-AS1 was positively correlated with levels of creatinine in the serum of patients. | (101) |
| CASC2 | ↓ | patients with sepsis and HCs | HK-2 | ↑ miR-155 | ↑ NF-κB signaling pathway | The levels of CASC2 were negatively correlated with the severity of AKI. CASC2 expression induced cell viability and inhibited inflammatory response, apoptosis and oxidative stress. | (102) |
| CASC2 | ↓ | patients with sepsis and HCs | HPAEpiC | ↑ miR-152-3p, ↓ PDK4 | _ | Up-regulation of CASC2 increased viability and restrained apoptosis, inflammatory and oxidative damages. | (103) |
| ZFAS1 | ↓ | 202 patients with sepsis and 200 HCs | _ | _ | _ | Expression of ZFAS1 was negatively associated with APACHE II, level of CRP, TNF-α, IL-6 and positively with IL-10. | (104) |
| ZFAS1 | ↓ | male SD rats | H9C2 | ↑ miR-34b-5p, ↓ SIRT1 | _ | Up-regulation of ZFAS1 decreased inflammatory responses and apoptosis. | (105) |
| ZFAS1 | ↑ | male C57BL/6 mice | _ | ↓ miR-590-3p, SP1 | AMPK/mTOR signaling pathway | Downregulation of ZFAS1 reduced LPS-induced pyroptosis and enhanced LPS-suppressed autophagy in sepsis-induced cardiac dysfunction. | (106) |
| ZFAS1 | ↓ | 22 patients with SIMI and 24 HCs, rats treated by LPS | H9C2 | ↑ miR-138-5p, ↓ SESN2 | _ | Up-regulation of ZFAS1 attenuated myocardial injury and inflammatory response. | (107) |
| Mirt2 | ↓ | male SD rats | _ | ↑ MiR-101 | ↓ PI3K/AKT Signaling Pathway | Up-regulation of Mirt2 inhibited inflammatory responses and improved cardiac function. | (108) |
| Mirt2 | ↓ | 40 patients with sepsis, 40 patients with sepsis-AI, 40 HCs | HBEpCs | ↓ miR-1246 | _ | Up-regulation of Mirt2 inhibited LPS-induced inflammatory response, apoptosis, and promoted miR-1246 expression but reduced its gene methylation. | (109) |
| TCONS_00016406 | ↓ | male C57BL/6 mice | PTEC | ↑ miR-687, ↓ PTEN | _ | Up-regulation of IncRNA 6406 inhibited inflammatory responses, apoptosis and oxidative stress in LPS-induced AKI. | (110) |
| NORAD | ↑ in NS patients | 88 patients with late-onset NS and 86 patients with pneumonia neonates | RAW264.7 | ↓ miR-410-3p | _ | Expression of NORAD was closely correlated with WBC, PCT, IL-6, IL-8, and TNF-α. | (111) |
| GAS5 | ↑ | _ | THP-1 | ↓ miR-23a-3p, ↑ TLR4 | _ | Downregulation of GAS5 inhibited inflammation and apoptosis. | (112) |
| Inc-ANRIL | ↑ | 126 patients with sepsis and 125 HCs | _ | ↓ miR-125a | _ | Inc-ANRIL showed good predictive values for sepsis risk. Inc-ANRIL was positively associated with CRP and PCT levels, disease severity scale scores, and pro-inflammatory cytokine levels, 28-day deaths in sepsis patients, | (113) |
| PVT1 | ↑ | 109 patients with sepsis and 100 HCs | _ | _ | _ | PVT1 was found to be an independent risk factor for sepsis ARDS. And PVT1 expression positively associated with disease severity and 28-day deaths. | (114) |
| PVT1 | ↑ | _ | THP-1 | _ | ↑ p38 MAPK signaling pathway | Downregulation of PVT1 reduced levels of IL-1β and TNF-α mRNA and inhibited the p38 MAPK signaling pathway, | (115) |
In general, the pathophysiology of sepsis is considered as an initial hyperinflammatory phase ("cytokine storm") followed by a protracted immunosuppressive phase. Since no data is available about the differential expression of non-coding RNAs during these two distinct phases, future studies are needed to evaluate expression patterns of non-coding RNAs in these two phases. It is possible that some of the non-coding RNAs that suppress the immune response could be used as biomarkers to indicate the immunoparalysis in sepsis.

From a therapeutic point of view, several studies have shown that up-regulation/silencing of circRNAs, circRNAs and miRNAs in the context of sepsis. These transcripts, particularly miRNAs can be used as diagnostic or prognostic markers in sepsis. Expression levels of these regulatory transcripts might be used for diagnosis of organ specific damages during the course of sepsis.

In general, the pathophysiology of sepsis is considered as an initial hyperinflammatory phase ("cytokine storm") followed by a protracted immunosuppressive phase. Since no data is available about the differential expression of non-coding RNAs during these two distinct phases, future studies are needed to evaluate expression patterns of non-coding RNAs in these two phases. It is possible that some of the non-coding RNAs that suppress the immune response could be used as biomarkers to indicate the immunoparalysis in sepsis.

From a therapeutic point of view, several in vitro and in vivo studies have shown that up-regulation/silencing of circRNAs,
### TABLE 2 | Lists the function of miRNAs in the course of sepsis.

| miRNA Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description | Reference |
|-----------------------------|------------------------------|---------------------|----------------------|--------------------|-------------|-----------|
| miR-125a-5p                 | GEO database: GSE94717 (6 patients with sepsis-induced AKI and 6 HCs) | MPC8 | ↓ XIST, ↓ CUL3 | - | Downregulation of miR-15a-5p reduced apoptosis in sepsis-induced AKI. | (65) |
| miR-494-3p                  | Patients with sepsis and HCs | RAW264.7 | ↑ TLR6 | - | Upregulation of microRNA-494-3p reduced inflammation, TNF-α level, and prevented nuclear translocation of NF-κB p65. | (132) |
| miR-218                     | 53 Patients with sepsis and 20 HCs, septic mouse model | PBMCs | ↑ VOPP1↑ JAK/STAT pathway | | Upregulation of microRNA-494-3p reduced inflammation. | (133) |
| miR-122                     | male S SD rats | RAW264.7 | ↑ RUNX2 | | Up-regulation of miR-218 inhibited inflammatory response. | (141) |
| miR-208a-5p                 | septic mouse model | - | ↓ SOCS2↑ NF-κB/ HIF-1α pathway | | miR-122 showed higher AUC in comparison with CRP and TLC which had 66.6% sensitivity, 50% specificity, and 56.6% accuracy as a prognostic biomarker for sepsis. | (134) |
| miR-328                     | 110 Patients with sepsis and 89 HCs, male SD rats | - | - | | miR-328 expression was positively associated with Scr, WBC, CRP, PTC, APACHE II score, and SOFA score. miR-328 was found to be a good diagnostic value for sepsis. Downregulation of miR-328 reduced inflammatory response. | (139) |
| miR-452                     | 47 sepsis patients with AKI, 50 patients without AKI, and 10 HCs | BUMPT | NF-KB | - | Serum and urinary miR-452 could be a potential biomarker for early detection of septic AKI. It was upregulated in sepsis patients with AKI compared with without AKI, miR-452 had high diagnostic value for AKI. | (140) |
| miR-21                      | 219 Patients with sepsis and 219 HCs | - | - | | miR-21 was found to be a good value in predicting sepsis risk. miR-21 expression was negatively correlated with APACHE II, SOFA score, and 28-day mortality risk. | (142) |
| miR-126                     | 208 Patients with sepsis and 210 HCs | - | - | | miR-126 expression was positively correlated with APACHE II, serum creatinine, CRP, TNF, IL-6, IL-8, mortality rate, but negatively with IL-10. | (143) |
| mir-103                     | 196 Patients with sepsis and 196 HCs | - | - | | mir-103 predicted high ARDS risk. Mir-103 and was negatively associated with APACHE II score, SOFA score, serum creatinine, CRP, TNF, IL-1β, IL-6, IL-8, 28-day deaths, but positively correlated with albumin. mir-107 predicted high ARDS risk, mir-107 and was negatively associated with APACHE II score, SOFA score, serum creatinine, CRP, TNF, IL-1β, IL-6, IL-8, 28-day deaths, but positively correlated with albumin. | (144) |
| mir-107                     | 196 Patients with sepsis and 196 HCs | - | - | | mir-107 predicted high ARDS risk. Mir-103 and was negatively associated with APACHE II score, SOFA score, serum creatinine, CRP, TNF, IL-1β, IL-6, IL-8, 28-day deaths, but positively correlated with albumin. mir-107 and was negatively associated with APACHE II score, SOFA score, serum creatinine, CRP, TNF, IL-1β, IL-6, IL-8, 28-day deaths, but positively correlated with albumin. | (144) |
| miR-92a                     | in sepsis-induced ARDS | HPMEC, A549 | - | ↑ Akt/mTOR signaling pathway | Downregulation of mir-92a reduced apoptosis and inflammatory response, and enhanced migration | (145) |
| mir-98                      | male C57BL/6 mice | - | ↑ HMG2A↑ NF-κB pathway | | Upregulation of miR-98 prevented HMG2A, NF-κB, TNF-α, IL-6, IL-8, Bcl-2 and augmented IL-10, Cleaved caspase-3 and Bax expression, it reduced LVEDP, CTR-I, BNP, ALT, AST, TBIL, LDH, and PaCO2 but elevated +dp/dt max, −dp/dt max, pH and PaO2. | (146) |
| miR-125a                    | 150 Patients with sepsis and 150 HCs | - | - | | miR-125a expression was positively associated with Scr, APACHE II score, SOFA score. | (147) |
| miR-125b                    | 150 Patients with sepsis and 150 HCs | - | - | | miR-125b was correlated with Scr, CRP, APACHE II score, SOFA score, and chronic obstructive pulmonary disease , and 28-days death. | (147) |
| mir-199a                    | male C57BL/6 mice | - | ↓ SIRT1 | - | Downregulation of mir-199a reduced apoptosis and inflammatory response. | (148) |
| mir-496                     | 105 Patients with sepsis and 100 HCs, rats | - | - | | miR-496 was negatively correlated with Scr, WBC, CRP, PCT, APACHE II score and SOFA score. CLP rats showed worse LVSP, LVEDP, ±dp/dtmax, and exhibited an increase in serum CTR-I, CK-MB, TNF-α, IL-6 and IL-1β. | (149) |
| mir-106a                    | 50 patients with sepsis and 30 HCs, clean Kunming mice | TCMK-1 | ↓ THBS2 | - | Downregulation of mir-106a reduced apoptosis and inflammatory response. | (150) |

(Continued)
miR-21 was decreased in septic mice and improved their survival rate through IL-1β stimulation resulted in packaging miR-146a into exosomes. The exosomal miR-146a was transferred to macrophages, yielded to M2 polarization, and finally led to high survival in septic mice.

Upregulation of miR-574 increased viability, inhibited apoptosis, and reduced sepsis-induced ERS.

MicroRNA-195 could promote cardiac remodeling by up-regulating the nanobiotics signaling pathway in sepsis rats.

Downregulation of miR-133a prevented inflammatory response, sepsis-induced lung, liver and kidney injuries.

Upregulation of miR-191-5p prevented inflammatory response and apoptosis in sepsis.

MI-146a was of good value in predicting high sepsis risk and 28-day mortality risk. MI-146b was positively associated with biochemical indices, inflammatory cytokines, overall disease severity.

miR-146b was of good value in predicting high sepsis risk and 28-day mortality risk. MI-146a was positively associated with biochemical indices, inflammatory cytokines, overall disease severity.

miR-126 was negatively associated with the levels of caspase-3, APACHE II score, and positively with 28-day cumulative survival rate. AUC for predicting the prognosis by miR-126 was 0.823.

Upregulation of mir-223 impelled M2 macrophage through lower activity of glycolysis Pathway, the implementation of miR-223 over-expressed macrophages with IL-4 preconditioning alleviated sepsis severity.

Treatment with hucMSC-Ex improved survival in mice with sepsis by reducing levels of IRAK1, increasing of miR-126, and inhibition of NF-κB activity.

miR-1-3p decreased proliferation, and increased apoptosis, and permeability and HUVECs membrane injury.

Levels of miR-25 was associated with the severity of sepsis, SOFA score, CRP and PCT level, 28-day deaths, and levels of oxidative stress indicators.

miR-370-3p was associated with TNF-α and increased brain apoptosis in SAE mice.

miR-21 inhibition alleviated renal disease by exosomes. The exosomal miR-21 was transported from ischemic limbs to the kidneys by exosomes.

miR-21 decreased inflammatory and apoptosis.

miR-21 levels so reduced inflammatory responses and increased viability. IfMSCs-derived exosomes reduced symptoms in septic mice and improved their survival rate through miR-21 upregulation.

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TABLE 2 | Continued

| miRNA     | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|-----------|-----------------------|-------------------------------|---------------------|----------------------|--------------------|-------------------------------------------------------------------------------|-----------|
| miR-21    | ↑                     | septic C57BL/6J mice          | PTEN                | ↓ PGE2, ↓ IL-10      |                    | Downregulation of miR-21 reduced bacterial growth, systemic inflammation, organ damage, macrophage glycolysis, and increased animal survival. | (165)     |
| miR-21-3p | ↑                     | SD rats                       | TECs                | ↓ AKT, ↓ CDK2, ↑ FOXO1|                    | miR-21-3p regulated lipid metabolism and increased cell cycle arrest and apoptosis. | (166)     |
| miR-34    | ↑                     | male C57BL/6 mice (15 control group and 15 sepsis model group) |                    |                      | ↓ KLF4             | Plasma miR-34a was positively associated with SCR and BUN.                    | (167)     |
| miR-483-5p| ↑                     | CLP-treated mice              | PMVECs              | ↓ PIAS1              |                    | Downregulation of miR-483-5p reduced inflammation and apoptosis and improved lung injury in mice with sepsis-induced ALI. | (168)     |
| miR-125a  | ↓                     | CLP-treated mice              |                     | ↑ HMGB1              |                    | Upregulation of miR-181-5p reduced inflammatory response, and sepsis-induced renal and hepatic dysfunction. | (169)     |
| miR-20a   | ↑                     | SD rats                       |                     |                      |                    | miR-20a could deteriorated AKI via activating autophagy in sepsis rats.       | (170)     |
| hsa-miR-92a-3p | ↓ in sepsis-induced coagulopathy group | 116 patients with sepsis |                     |                      |                    | AUC of hsa-miR-92a-3p was 0.660. Levels of plasma hsa-miR-92a-3p were related to plasma lipocalin-2 level, activated partial thromboplastin time, and prothrombin activity. | (171)     |
| miR-93-5p | ↓                     | septic mouse model            | HK2                 | ↑ KDM6B, ↓ H3K27me3 |                    | Extracellular vesicles containing miR-93-5p reduced inflammation, apoptosis, multiple organ injury, and vascular leakage in septic mice. | (172)     |
| miR-223   | ↓                     | 143 patients with sepsis and 44 HCs |                     |                      |                    | Expression of miR-223 was negatively correlated with SOFA scores and positively with survival rate. Upregulation of miR-223 decreased apoptosis and increased proliferation and G1/S transition. | (173)     |
| miR-34a   | ↑                     | male C57BL/6 mice             | ↓ SIRT1, ↓ ATG4B    |                      |                    | Downregulation of miR-34a reduced inflammatory response and pyroptosis, apoptosis and enhanced autophagy. | (174)     |
| miR-30a   | ↑                     | septic rats                   |                     | ↓ SOCS-1 ↑ JAK/STAT signaling pathway |                    | Upr egulation of miR-30a promoted apoptosis and inhibited proliferation. | (175)     |
| miR-150-5p| ↓                     | rat septic shock model        | H9C2                | ↑ Akt2               |                    | Upregulation of miR-150-5p inhibited apoptosis.                               | (176)     |
| miR-140   | ↓                     | SPF male BALB/c mice          |                     | ↑ WNT signaling pathway |                    | Upregulation of miR-140 inhibited apoptosis and inflammation, skeletal muscle glycolysis and atrophy. | (177)     |
| miR-22-3p | ↓                     | male SD rats                  | HK-2                | ↑ HMGB1 ↑ PTEN       |                    | Upregulation of miR-22-3p inhibited apoptosis and inflammatory response Down regulation of miR-205-5b increased HMGB1 expression in LPS-induced sepsis. Upr egulation of miR-526b increased viability by inhibiting autophagy. | (178)     |
| miR-205-5b| ↑                     | BALB/c mice                   | RAW264.7            |                     |                    | Upregulation of miR-205-5b increased viability by inhibiting autophagy.       | (179)     |
| miR-526b  | ↓                     | BALB/c mice                   | HK2                 | ↑ ATG7               |                    | Upregulation of miR-526b reduced levels of proinflammatory cytokines.       | (180)     |
| miR-145a  | ↓                     | septic mouse model            |                     | ↑ Fl-1               | ↑ NF-kB signaling   | AUC of miR-125a: 0.749 miR-125a was positively correlated with APACHE II score and SOFA score. AUC of miR-125b: 0.839 miR-125b was positively correlated with APACHE II score, SOFA score CPR, TNF-α, IL-6, IL-17, IL-23, and 28-day mortality risk. Upregulation of miR-135a exacerbated inflammation and myocardial dysfunction. | (181)     |
| miR-125a  | ↑                     | 150 patients with sepsis and 150 HCs |                     |                      |                    | AUC of miR-125a: 0.749 miR-125a was positively correlated with APACHE II score and SOFA score. AUC of miR-125b: 0.839 miR-125b was positively correlated with APACHE II score, SOFA score CPR, TNF-α, IL-6, IL-17, IL-23, and 28-day mortality risk. Upregulation of miR-135a exacerbated inflammation and myocardial dysfunction. | (182)     |
| miR-125b  | ↑                     | 150 patients with sepsis and 150 HCs |                     |                      |                    | AUC of miR-125a: 0.749 miR-125a was positively correlated with APACHE II score and SOFA score. AUC of miR-125b: 0.839 miR-125b was positively correlated with APACHE II score, SOFA score CPR, TNF-α, IL-6, IL-17, IL-23, and 28-day mortality risk. Upregulation of miR-135a exacerbated inflammation and myocardial dysfunction. | (183)     |
| miR-122  | ↑                     | 108 patients with sepsis and 20 patients with infections without sepsis as controls |                     |                      |                    | AUC of miR-122: 0.760 miR-122 was found as independent prognostic factor for 30-day mortality. Upregulation of miR-135a exacerbated inflammation and myocardial dysfunction. | (184)     |
| miR-135a  | ↑                     | patients with sepsis and HCs, BALB/c mice |                     |                      | ↑ p38 MAPK/NF-kB pathway ↑ NF-kB pathway | Upr egulation of miR-135a exacerbated inflammation and myocardial dysfunction. | (185)     |
| miR-133a  | ↓                     | TCMK-1                        | ↑ BNIP3L            |                    |                    | Upregulation of miR-133a reduced inflammation and apoptosis.               | (186)     |
### TABLE 2 | Continued

| miRNA   | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|---------|-----------------------|-------------------------------|---------------------|----------------------|-------------------|-----------------------------------------------------------------------------|----------|
| miR-223 | †                     | male C57BL/6 mice             |                     |                      |                   | In multiple models of experimental sepsis, miR-223 showed the complex role in the pathogenesis of septic kidney injury. (186) |         |
| miR-155 | †                     | 44 patients with severe sepsis, 102 patients with sepsis, and 19 HCs | †                   | †                    | †                 | AUC of miR-155: 0.782 (for predicting 30-day mortality in ALI) (187)          |         |
| miR-146 | †                     | 44 patients with severe sepsis, 102 patients with sepsis, and 19 HCs | †                   | †                    | †                 | AUC of miR-146a: 0.733 (for predicting 30-day mortality in ALI). CC genotype of rs2910164 in miR-146a was correlated with worse treatment result. (188) |         |
| miR-194 | †                     | H9c2                          | † Stc7a5            | †                    | † Wnt/β-catenin pathway | Upregulation of miR-194 increased apoptosis. (189)                          |         |
| miR-30a | †                     | male C57BL/6 mice             | RAW 264.7           | † ADAR1, † SOCS3     | †                 | Upregulation of ADAR1 (a target of miR-30a) reduced inflammation and organ damage. (190) |         |
| miR-27b | †                     | male C57BL/6 mice             | BMSCs               | † JMJD3              | † NF-κB signaling pathway | Upregulation of miR-27b MSC-derived exosomes reduced pro-inflammatory cytokines. (191) |         |
| miR-155 | †                     | BALB/c mice                   |                     | † SOCS1              | † JAK/STAT signaling pathway | Downregulation of miR-155 alleviated LPS-induced mortality and liver injury (192) |         |
| miR-155 | †                     | C57BL/6 mice                  |                     | † Ar rb2             | † JNK signaling pathway | Upregulation of miR-155 ameliorated late sepsis survival and its cardiac dysfunction, and reduced pro-inflammatory responses. (193) |         |
| miR-155 | †                     | patients with sepsis and HCs, mouse septic shock model |                     | † CD47               |                   | Downregulation of microRNA-155 reduced sepsis-associated cardiovascular dysfunction and mortality. (194) |         |
| miR-155 | †                     | 60 patients with sepsis and 20 HCs |                     | † Foxp3              |                   | Expression of miR-155 was correlated with APACHE II score, it was significantly higher in non-survival group. (195) |         |
| miR-155 | †                     | 156 patients with sepsis (41 with ALI and 32 with ARDS) |                     |                   |                   | AUC of miR-155: 0.87, miR-155 was positively associated with IL-1β, TNF-α levels, and ALI/ARDS score, but negatively with PaO2/FIO2. (196) |         |
| miR-29c-3p | †                  | 86 patients with sepsis and 65 HCs, male SD rats |                     |                   |                   | AUC of miR-29c-3p: 0.872 miR-29c-3p expression was positively correlated with APACHE II score, SOFA score, levels of CRP and PCT. miR-29c-3p was found to be an independent factor in the occurrence of cardiac dysfunction. PTEN increased miR125 production through associating with the nuclear localization of Drosha-Dgcr8. Downregulation of PTEN resulted in cytokine production, MyD88 abundance and mortality. (197) |         |
| miR-125b | †                     | 40 patients with sepsis and HCs, female and male C57BL/6 mice |                     | † PTEN, † MyD88     |                   | PTEN increased miR125 production through associating with the nuclear localization of Drosha- Dgcr8, Downregulation of PTEN resulted in cytokine production, MyD88 abundance and mortality. (198) |         |
| miR-203b | †                     | 40 patients with sepsis and HCs, female and male C57BL/6 mice |                     | † PTEN, † MyD88     |                   | PTEN increased miR203b production through associating with the nuclear localization of Drosha-Dgcr8, Downregulation of PTEN resulted in cytokine production, MyD88 abundance and mortality. (199) |         |
| miR-146 | †                     | EA. hy926                     |                     | † NF-κB signaling pathway |                   | Upregulation of reduced levels inflammatory cytokines. (200)               |         |
| miR-140-5p | †                 | male SPF rats                 | MLE-12              | † TLR4, † MyD88     | † NF-κB signaling pathway | Shikonin could alleviated sepsis-induced ALI by increasing the levels of miR-A-140-5p and decreasing the levels of TLR4. (201) |         |
| miR-125b | †                     | male C57BL/6 mice             | HUVECs              | † ICAM-1, † VCAM-1, † TRAF6 | † NF-κB signaling pathway | Upregulation of miR-125b alleviated sepsis-induced cardiac dysfunction and ameliorated survival. (202) |         |
| miR-494 | †                     | ARDS rat models               |                     |                     | † Nrf2 signaling pathway | Upregulation of miR-494 increased inflammatory response, oxidative stress and ALI. (203) |         |

(Continued)
### TABLE 2 | Continued

| miRNA     | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|-----------|-----------------------|-------------------------------|--------------------|----------------------|-------------------|----------------------------------------------------------------------------|----------|
| miR-146a  | ↓                     | male C57BL/6 mice             | HiCa2, J774        | ↑ IRAK, ↑ TRAF6       | ↑ NF-κB signaling pathway | Upregulation of miR-146 reduced levels of inflammatory cytokines and sepsis-induced cardiac dysfunction | (202)    |
| miR-223   |                       | 221 patients with sepsis and 75 HCs, male C57BL/6 mice |                     |                      |                   | Levels of serum miR-223 did not differ between critically ill patients and HCs, but ICU patients with APACHE-II score had moderately decreased circulating miR-223, | (203)    |
| miR-300   | ↓                     | septic mouse model            |                    | ↑ NAMPT              | ↓ AMPK/mTOR signaling pathway | Upregulation of miR-300 increased autophagy, cell cycle entry and reduced apoptosis and inflammatory response. | (204)    |
| miR-126   | ↓                     | male C57BL/6 mice             |                    | ↓ HSPA12B            |                   | Upregulation of HSPA12B increased levels of miR-126, upregulation of miR-126 reduced levels of adhesion molecules and improved sepsis-induced cardiac dysfunction, | (205)    |
| miR-10a   | ↓                     | 62 patients with sepsis and 20 HCs |                     | ↑ MAP3K7             | ↑ NF-κB signaling pathway | miR-10a expression was negatively associated with disease severity scores, levels of c-reactive protein, procalcitonin, and 28-day death. | (206)    |
| miR-146a  | ↓                     | mice                          |                    | ↑ Notch1             | ↑ NF-κB signaling pathway | Upregulation of miR-146a reduced inflammatory responses of macrophages and protected mice from organ damage | (207)    |
| miR-19a   | ↓                     | CLP mice                      | RAW 264.7           | ↑ Fn14               |                   | Upregulation of miR-19a reduced LPS-Induced Tubular Damage, it was found to protected mice from sepsis-induced AKI. | (208)    |
| miR-214   |                       | male Kunming mice             |                    |                      |                   | Upregulation of miR-214 reduced apoptosis, inflammatory response, myocardial injury, and improved cardiac function in SMI. | (209)    |
| miR-539-5p| ↓                     | male C57BL/6 mice             | MPVECs             | ↑ ROCK1              |                   | Upregulation of miR-539-5p reduced apoptosis, inflammatory response, sepsis-induced pulmonary injury. | (210)    |
| miR-155   | ↑                     | 60 patients with sepsis and 30 HCs |                    |                      |                   | miR-155 was positively correlated with a higher SOFA score and a greater severity. AUC of miR-155 for 28-day survival was 0.763, miR-155 derived immunosuppression through CD39(+) Tregs. | (211)    |
| miR-146a  | ↑ in sepsis group compared to shame group | male BALB/C mice |                     |                      |                   | Up-regulation of miR-146a reduced levels of inflammatory cytokine TNF-α and mitigated inflammatory reaction and lung tissue injury in sepsis-induced ALI. | (212)    |
| miR-7110-5p| ↑                    | 52 patients with pneumonia, 44 patients with sepsis and 21 HCs |                     |                      |                   | The sensitivity and specificity of miR-7110-5p were 84.2 and 90.5% respectively. (sepsis vs HCs) | (213)    |
| miR-223-3p| ↑                    | 52 patients with pneumonia, 44 patients with sepsis and 21 HCs |                     |                      |                   | The sensitivity and specificity of miR-223-3p were 82.9 and 100% respectively. (sepsis vs HCs) | (214)    |
| miR-19a   | ↑                    | patients with sepsis          | B cells from patients with sepsis | CD22                |                   | Expression of CD22 initially increased but subsequently reduced. Upregulation of miR-19a resulted in an increased BCR signaling, while overexpression of CD22 reduced the effect of miR-19a and promoted its expression. miR-206 was positively associated with SOFA score and APACHE-II score. It was observed an activated partial thromboplastin time and notably longer prothrombin time. | (215)    |
| miR-206   | ↑                    | 63 patients with sepsis, 30 patients with septic shock and HCs |                     |                      |                   | Up-regulation of miR-146a reduced apoptosis, inflammatory response, and weakened organ injury in splenic macrophages. | (216)    |
| miR-146a  | ↓                    | male C57BL/6 mice             | RAW264.7            | ↑ NF-κB signaling     |                   | Up-regulation of miR-146a reduced apoptosis, inflammatory response, and weakened organ injury in splenic macrophages. | (217)    |
| miR-19b-3p| ↓                    | 103 patients with sepsis and 98 HCs | HUVECs             |                      |                   | Up-regulation of miR-19b-3p reduced inflammatory response. miR-19b-3p was found to be an independent prognostic factor for 28-day survival. Up-regulation of miR-129-5p reduced apoptosis, inflammatory response, lung wet/dry weight ratio, and myeloperoxidase activity. | (218)    |
| miR-129-5p| ↓                    | CLP mice                      | MLE-12             | ↑ HMGB1              |                   | Up-regulation of miR-129-5p reduced apoptosis, inflammatory response, lung wet/dry weight ratio, and myeloperoxidase activity. | (219)    |
### TABLE 2 | Continued

| miRNA   | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|---------|-----------------------|-------------------------------|---------------------|-----------------------|-------------------|------------------------------------------------------------------------------|-----------|
| miR-23b | ↓                     | 30 patients with sepsis and 30 HCs | THP-1               | ↑ ADAM10              |                   | Up-regulation of miR-23b reduced apoptosis and inflammatory response.        | (219)     |
| miR-150 | ↓                     | 140 patients multiple trauma and 10 HCs | MDSCs               | ↑ ARG31               |                   | Up-regulation of miR-150 reduced IL-6, TGF-β and IL-10.                       | (220)     |
| miR-375 | ↓                     | patients with sepsis, septic mice | MDSCs               | ↑ miR-21             | ↑ JAK2/STAT3 pathway | Up-regulation of miR-375 reduced the number of sepsis Gr1+CD11b+ MDSCs in mice. | (221)     |
| miR-31 | ↑                     | male SD rats                  | Caco-2              | ↓ HMOX1              | ↑ NF-κB/HIF-1α pathway | Downregulation of miR-31 reduced intestinal barrier function, intestinal mucosal permeability, oxidative damage and inflammation level. | (222)     |
| miR-21 and 181b | ↑ (in early sepsis), sustained (in late sepsis) | male BALB/c mice | MDSCs               | ↑ NFI-A              |                   | Down regulation of miR-21 and miR-181b decreased, immunosuppression, reprogramming myeloid cell, late-sepsis mortality, and improved bacterial clearance. | (223)     |
| miR-150 | ↓ slightly            | 223 critically ill patients (including 138 fulfilled sepsis criteria) and 76 HCs | –                  | –                    | –                 | Serum levels of miR-150 were associated with hepatic or renal dysfunction. Low levels were correlated with an unfavorable prognosis of patients. Serum levels of miR-150 were not suitable for predicting of sepsis. | (224)     |
| miR-10a | ↑                     | SD rats                       | –                  | –                    | ↑ TGF-β1/Smad pathway | Up-regulation of miR-10a increased ROS, TNF-α, IL-6, and MPO, and downregulation reduced sepsis-induced liver injury. | (225)     |
| miR-145 | ↓                     | septic mice                   | HUVECs              | ↑ TGFB2, ↑ SMAD2, ↑ DNMT1 |                   | Up-regulation of miR-145 reduced LPS-Induced sepsis and improved the overall survival of septic mice. | (226)     |
| miR-150 | ↓                     | 17 patients with sepsis and 32 HCs | –                  | –                    | –                 | Levels of miR-150 were negatively correlated with the level of disease severity, TNF-α, IL-10, and IL-18. | (227)     |
| miR-103a-3p | ↑                     | 30 patients with sepsis and 30 HCs, male C57 BL/6 mice | AML12, LO2          | ↓ FBXW7              |                   | Downregulation of miR-103a-3p reduced apoptosis, and inflammatory response. | (228)     |
| miR-143 | ↑                     | 103 patients with sepsis, 95 patients with SIRS and 16 HCs | –                  | –                    | –                 | miR-143 was positively correlated with SOFA score and APACHE II score in patients with sepsis. For distinguishing between sepsis and SIRS, miR-143 showed a sensitivity of 78.6% and specificity of 91.6%. | (229)     |
| miR-145 | ↓                     | 33 patients with sepsis and 22 HCs, septic mice | BEAS-2B             | ↑ TGFB2              |                   | Up-regulation of miR-145 reduced inflammatory response and improved the overall survival of septic mice. | (230)     |
| miR-150 | ↓                     | C57Blk/6J mice                 | HPAECs              | ↑ Ang2               |                   | Downregulation of miR-150 damaged adherens junctions reannealing after injury, which caused an irreversible increase in vascular permeability. Up-regulation of miR-150 reduced vascular injury and mortality. | (231)     |
| miR-34b-3p | ↓                     | CLP mice                       | RMCs                | ↑ UBL4A              | ↑ NF-κB signaling | Up-regulation of MIR-34b-3p reduced inflammatory response and AKI in sepsis mice. | (232)     |
| miR-21-3p | ↑                     | patients with sepsis, C57BL/6 mice | –                  | ↓ SORBS2            |                   | Downregulation of miR-21-3p induced mitochondrial ultrastructural damage and autophagy in LPS-treated mice. Levels of miR-21-3p increased in patients with cardiac dysfunction than without cardiac dysfunction. | (233)     |
| miR-199a-5p | ↑                     | C57BL/6 mice                   | HEK-293T            | ↓ SP-D              | ↑ NF-κB signaling | Down regulation of miR-199a-5p reduced D-lactic acid, DAO, FD-40, oxidative damage and inflammation. | (234)     |
| miR-17 | ↓                     | mice                           | BMSCs, RAW264.7     | ↑ BDR4, ↑ EZH2, ↑ TRAIL |                   | MIR-17 carried by BMSC-EVs reduced inflammation and apoptosis. | (235)     |
| miR-125b | ↑                     | 120 patients with sepsis and 120 HCs | –                  | –                    | –                 | AUC of miR-125b: 0.658. MiR-125b was positively associated with APACHE II score, SOFA score, Scr, CRP, PCT, TNF-α, and IL-6 levels. MiR-125b was found to be an independent risk factor for mortality risk. | (236)     |

(Continued)
Continued

| miRNA     | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|-----------|-----------------------|-------------------------------|--------------------|----------------------|-------------------|-------------------------------------------------------------------------------|-----------|
| miR-30e   | ↓                     | septic rats                   |                    | ↑ FOSL2              | ↑ JAK/STAT signaling | Up-regulation of miR-30e increased proliferation and reduced apoptosis.       | (237)     |
| miR-20b-5p| ↑                     | SD rats                       | HEK-293T           | ↓ circDMNT3B         |                   | Downregulation of miR-20b-5p reduced level of d-lactic acid, FD-40, MDA, diamine oxidase, IL-10, IL-6, oxidative damage and inflammatory factors level. | (238)     |
| miR-146b  | ↓                     | CLP mice                      |                    | ↑ Notch1             |                   | Up-regulation of miR-146b reduced apoptosis and inflammatory response.        | (239)     |
| miR-27a   | ↓                     | SD rats                       | Hi9C2              | ↑ PTEN, ↑ TLR4       | ↑ NF-κB signaling  | Up-regulation of miR-25 reduced apoptosis and enhanced survival rate.         | (240)     |
| miR-96-5p | ↑                     | septic mice                   | MDSCs, GR-1 +CD11b + cells | ↑ C/EBPβ, ↑ Stat3    |                   | Stat3 and C/EBPβ increased miR-21 and miR-181b expression by binding to their promoters during sepsis. | (241)     |
| miR-128-3p| ↓                     | septic mice                   | LPS-induced macrophages, HBMECs | ↑ TLR4              |                   | Sch B increased miR-17-5p expression and reduced inflammation.               | (242)     |
| miR-200a-3p| ↑                    | male C57BL/6J mice            |                    | ↑ NLRP3, ↑ Keep1, ↓ Nrf2, ↓ HO-1 |                   | Up-regulation of miR-200a-3p induced inflammatory response in sepsis-induced brain injury. | (243)     |
| miR-26b   | ↓                     | 14 patients with sepsis and 7 patients with septic shock and 21 HCs | MEG-01             | ↑ SELP, ↓ Dicer1     |                   | Low levels of miR-26b was correlated with the severity and mortality of sepsis. | (244)     |
| miR-96-5p | ↓                     | RAW264.7                      | ↑ NAMPT            | ↑ NF-κB pathway     |                   | Up-regulation of miR-96-5p reduced inflammatory response.                     | (245)     |
| miR-27a   | ↑                     | septic mice                   |                    | ↑ NLRP3, ↑ NF-κB pathway |                   | Downregulation of miR-27a reduced inflammatory response and promoted survival of septic mice. | (246)     |
| miR-21a-3p| ↑                    | specific pathogen-free SD rats | NRP52E             | ↑ Ago2, ↑ Nrp-1      |                   | miR-21a-3p was found to be internalized by TECs via Nrp-1 and Ago2.            | (247)     |
| miR-574-5p| ↑                    | 118 patients with sepsis      |                    |                   |                   | miR-574-5p was associated with the death of sepsis patients.                  | (248)     |
| miR-181b  | ↓                     | 26 patients with sepsis, 36 patients with sepsis plus sepsis/ARDS and 16 HCs, male C57BL/6 mice | TPH-1, HLVECs      | ↑ importin-α3       | ↑ NF-κB signaling pathway | Up-regulation of miR-181b reduced mortality rate, inflammation response, LPS-induced EC activation, leukocyte accumulation. | (249)     |
| miR-182-5p| ↑                    | male C57BL/6 mice             | endothelial cells  | ↓ BCL-2, ↓ Sirt1, ↓ Pim-1 |                   | Downregulation of miR-182-5p reduced apoptosis, inflammation response and promoted viability and proliferation. | (250)     |
| miR-195   | ↑                    | female C57BL/6 mice           |                    |                   |                   | Downregulation of miR-182-5p reduced apoptosis, and improved survival.        | (251)     |
| miR-205   | ↓                     | male SD rats                  |                    | ↑ HMGB1-PTEN signaling pathway |                   | Up-regulation of miR-205 reduced apoptosis and renal injury.                   | (252)     |
| miR-21-3p | ↑ in AKI group       | 49 patients with sepsis-induced AKI and 93 sepsis patients with non-AKI |                    | ↑ Scr, ↑ Cys-C, ↑ KIM-1 |                   | Levels of miR-21-3p was positively associated with Scr, Cys-C, and KIM-1 in the AKI group. | (253)     |
| miR-181a-2-3p| ↓                  | GSE46955 data set, CLP mouse model | TCMK-1             | ↑ GJB2              |                   | Up-regulation of miR-181a-2-3p reduced apoptosis and inflammatory response.   | (254)     |
| miR-21    | ↓                     | female Wistar rats            | HK-2               | ↑ PTEN, ↑ PI3K, ↑ AKT |                   | Up-regulation of miR-21 suppressed apoptosis and kidney injury.              | (255)     |
| miR-146a  | ↓                     | female ICR mice               | Raw264.7           | ↑ JMJ D3, ↑ NF-κB p65 |                   | GSKJ4 reduced inflammatory response by increasing miR-146a levels.            | (256)     |
| miR-294   | ↓                     | RAW264.7                      | TREM-1             |                   |                   | Transcription of miR-146a was negatively regulated by JMJ D3 through epigenetic mechanism. | (257)     |
| miR-128-3p| ↑                    | CLP mouse model               | TCMK-1             | ↓ NRP1             |                   | miR-294 reduced TNF-κB and IL-6 secretion.                                    | (258)     |

(Continued)
### TABLE 2 | Continued

| miRNA   | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|---------|-----------------------|-------------------------------|---------------------|----------------------|-------------------|------------------------------------------------------------------------------|-----------|
| miR-146a | ↓                     |                               | HiC2                | ErbB4, ↑TRAFl, ↑IRAK1|                   | Up-regulation of miR-146a reduced apoptosis and inflammatory response and promoted viability. | (259)     |
| miR-511  | ↑ in S mice           | C57BL/6J (S) mice, SFRET/ Ei (S) mice, | BUMPT               | NF-kB, NFkBZ          |                   | miR-511 was induced by glucocorticoids. miR-511 inhibited endotoxemia and experimental hepatitis. | (260)     |
| miR-376b | ↓ in sepsis with AKI group | 20 Patients with sepsis with AKI, 20 patients with sepsis without AKI and 10 HCs, male C57BL/6 mice | BUMPT               |                   |                   | miR-376b inhibited NF-kB inhibitor ↓[NFkBZ] expression and NF-kB inhibited miR-376b expression so they created a negative feedback loop. | (261)     |
| miR-101-3p | ↑                    | clean grade Kunming mice      | HEK-293T            | ↑ VNN1                | ↓ AKT signaling pathway | Up-regulation of miR-203 reduced apoptosis, inflammatory response, MDA, ALT, and AST in lung tissues, PMN and PAM levels in BALF and increased SOD activity. | (264)     |
| miR-34a  | ↑                     | CLP-induced suckling rats     | U937                | ↑ STAT3 pathway       |                   | Up-regulation of miR-34a reduced apoptotic pathway. miR-34a inhibited C-reactive protein, pro-calcitonin, IL-6 and TNF-α. | (265)     |
| miR-146a | ↓                     | patients with sepsis and HCs | Human primary T cells | ↑ PPKCε              |                   | Reduced levels of miR-146a contributes to the pathogenesis of sepsis. | (266)     |
| miR-223  | ↑                     | 187 patients with sepsis and 186 HCs | HEK-293T            | ↑ VNN1                |                   | Up-regulation of miR-203 reduced apoptosis, inflammatory response, MDA, ALT, and AST in lung tissues, PMN and PAM levels in BALF and increased SOD activity. | (267)     |
| miR-214  | ↓                     | male Kunming mice             | PTEN                | ↑ AKT pathway         |                   | Up-regulation of miR-214 reduced oxidative stress and autophagy, so ameliorated CLP-induced AKI. | (268)     |
| miR-27a  | ↑                     | LPS induced sepsis mice model | HiC2                | ↓ rhTNFR: Fc, ↓Nrf2   |                   | rhTNFR:Fc elevated viability and reduced apoptosis by increasing Nrf2 levels and reducing miR-27a levels. | (269)     |
| miR-150  | ↓ in non-survival group | 48 patients with septic shock (23 survival patients and 25 non-survival patients) | RAW264.7            | ↑ PTEN                |                   | MiR-150 level was positively associated with cardiac index and negatively with EVLWI and PVI. | (270)     |
| miR-148a-3p | ↑                   | male adult wild-type mice and myeloid-specific RBP-J-deficient mice | RAW264.7            | ↑ Notch signaling and NF-kB pathway                               |                   | Up-regulation of miR-148a-3p increased proinflammatory cytokines and decreased protective effect of EVs in LPS induced sepsis. | (271)     |
| miR-218-5p | ↑                    | male ICR mice                 | GMCs                | ↓ HO-1                |                   | miR-218-5p was reduced in honokiol-treated septic mice, so the survival rate was increased. Up-regulation of miR-218-5p reduced inflammatory response and sepsis-related liver damage. | (272)     |
| miR-425-5p | ↑                    | C57BL/6 mice                  | hepatocytes         | ↑ Rip1                |                   | Serum levels of miR-122 were associated with APTT ratios, FIB and antithrombin III levels. Downregulation of reduced apoptosis and inflammatory response. | (273)     |
| miR-101-3p | ↑                    | 168 patients with sepsis (CA group and CN group) | RAW264.7            | ↑ MAPK p38 and NF-kB pathways                                     |                   | Up-regulation of miR-148a-3p increased proinflammatory cytokines and decreased protective effect of EVs in LPS induced sepsis. | (274)     |
| miR-122  | ↑ in CA group        | 168 patients with sepsis (CA group and CN group) | RAW264.7            | ↑ MAPK p38 and NF-kB pathways                                     |                   | Up-regulation of miR-148a-3p increased proinflammatory cytokines and decreased protective effect of EVs in LPS induced sepsis. | (275)     |
| miR-101-3p | ↑                    | RAW264.7|                   |                   |                   | (Continued)                                                                 |           |
| miRNA   | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways                  | Description                                                                 | Reference |
|---------|-----------------------|-------------------------------|---------------------|----------------------|-------------------------------------|-------------------------------------------------------------------------------|-----------|
| miR-124 | ↓                     | mouse model of ALI            | _                   | ↑ MAPK14              | ↑ MAPK signaling pathway            | Up-regulation of miR-124 reduced apoptosis and inflammatory response and promoted proliferation. | (277)    |
| miR-942-5p | ↓                   | _                             | HK-2                | ↑ FOXO3              | _                                   | Up-regulation of miR-942-5p reduced apoptosis and inflammatory response and promoted viability. | (278)    |
| miR-23a-5p | ↑                   | SD rats                       | NR8383              | _                    | _                                   | _                                                                             | (279)    |
| miR-124 | ↑                     | _                             | BEAS-2B             | ↓ SOCS6,             | ↑ STAT3                             | Up-regulation of miR-124-5p induced cell permeability and inflammatory response and reduced proliferation. | (280)    |
| miR-942-5p | ↓                   | male C57BL/6 mice             | MPC5                | ↑ CCL-2              | _                                   | Propofol increased levels of miR-290-5p and decreased CCL-2 and inflammatory response. | (281)    |
| miR-124 | ↑ in AKI group       | 155 patients with sepsis (68 AKI and 87 non-AKI) and 57 patients with non-infectious SIRS | _                   | _                    | _                                   | _                                                                             | (282)    |
| miR-124 | ↑                     | Rat model of SAK0             | _                   | _                    | _                                   | _                                                                             | (283)    |
| miR-29a | ↑ in AKI group       | 74 patients with AKI and 41 without AKI | _                   | _                    | _                                   | AUC for miR-29a: 0.82                                                         | (284)    |
| miR-10a-5p | ↑ in AKI group      | 74 patients with AKI and 41 without AKI | _                   | _                    | _                                   | AUC for miR-10a-5p: 0.75                                                      | (285)    |
| miR-155 | ↑                     | septic mice                   | NCM460              | _                    | ↑ NF-κB signaling                  | Up-regulation of miR-155 increased hyperpermeability to FITC-dextran, TNF-α and IL-6 levels, and decreased ZO-1 and Occludin expression. | (286)    |
| miR-155 | ↑                     | male C57BL/6 mice             | Raw264.7,           | _                    | ↑ PI3K/AKT signaling pathways       | Curcumin inhibited inflammatory responses and miR-155 expression.             | (287)    |
| miR-497 | ↑ in myocardial injury group | 148 patients with sepsis (58 myocardial injury group and 90 non-myocardial injury group) | BEAS-2B             | ↓ IL2RB               | _                                   | Plasma miRNA-497 was correlated with cTnI in patients with myocardial injury. | (288)    |
| miR-497-5p | ↑                   | GEO database, male C57BL/6 mice | _                   | _                    | _                                   | Downregulation of miR-497-5p reduced apoptosis and inflammatory responses. | (289)    |
| miR-30a | ↓                     | _                             | monocytes           | ↑ STAT1, ↑ MD-2      | _                                   | _                                                                             | (290)    |
| miR-150 | ↓                     | C57BL/6 mice                  | HLVECs              | ↑ NF-κB1             | _                                   | _                                                                             | (291)    |
| miR-146a | _                   | _                             | THP-1               | RBM4, Ago2, p38      | _                                   | _                                                                             | (292)    |
| miR-146b | _                   | C57BL/6 mice                  | HEK293TN, J774.1    | _                    | _                                   | _                                                                             | (293)    |
| miR-27a | ↓                     | septic mice                   | _                   | ↑ TAB3               | ↑ NF-κB signaling pathway           | Up-regulation of miR-146b reduced mortality and increased Ago2-RBM4 protein interaction, so reduced inflammatory responses. | (294)    |
| miR-146a | ↓ in septic patients than SIRS and HCs groups | 50 patients with sepsis, 30 patients with SIRS and 20 HCs | _                   | _                    | _                                   | Up-regulation of miR-146a reduced morphine mediated hyper-inflammation.     | (295)    |
| miR-146a | _                   | _                             | _                   | _                    | _                                   | _                                                                             | (296)    |

(Continued)
### TABLE 2 | Continued

| miRNA   | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description | Reference |
|---------|-----------------------|------------------------------|---------------------|----------------------|--------------------|-------------|-----------|
| miR-223 | ↓ in septic patients than SIRS and HCs groups | 50 patients with sepsis, 30 patients with SIRS and 20 HCs | _ _ _ | _ _ _ | _ _ _ | AUC for miR-223: 0.804 | (298) |
| miR-339-5p | ↓ in septic mice | RAW264.7 | ↑ HMGB1, ↑ IKK-β | _ _ _ | _ _ _ | Paeonol could reduce inflammatory responses by upregulating miR-339-5p expression. | (299) |
| miR-99b | ↑ in male C57BL/6 J mice | RAW264.7 | ↓ MFG-E8 | _ _ _ | _ _ _ | Spherical nucleic acid increased migration by inhibiting miR-99b. | (300) |
| miR-215-5p | ↓ in H9c2 | Hi5c2 | ↑ LLRFIP1, ↑ IFL3 | _ _ _ | _ _ _ | miR-215-5p reduced inflammatory responses. | (301) |
| miR-15a | ↑ in sepsis and SIRS than HCs | 166 patients with sepsis, 32 patients with SIRS, and 24 HCs | _ _ _ | _ _ _ | _ _ _ | miR-15a could distinguish sepsis/SIRS from HCs. | (302) |
| miR-16 | ↑ in sepsis and SIRS than HCs | 166 patients with sepsis, 32 patients with SIRS, and 24 HCs | _ _ _ | _ _ _ | _ _ _ | miR-16 could distinguish sepsis/SIRS from HCs. | (303) |

miRNAs and Sepsis. AKI, Acute kidney injury; HCs, healthy controls; AUC, significant higher area under curve; CRP, C-reactive protein; TLC, total leucocytes count; SD, Sprague-Dawley; SOFA, sequential organ failure assessment; Scr, serum creatinine; WBC, white blood cell; PCT, procalcitonin; APACHE, physiology and chronic health evaluation; CLP, cecal ligation and puncture; ERS, endoplasmic reticulum stress; AUC, area under the ROC curve; SAE, sepsis-associated encephalopathy; BUN, blood urea nitrogen; rIPC, remote ischemic preconditioning; SPF, specific pathogen-free; GEO, Gene Expression Omnibus; SIMI, sepsis-induced myocardial injury; Tregs, regulatory T-cells; Sch B, Schisandrin B; DXM, dexamethasone; MDA, malondialdehyde; ALT, aminotransferase; AST, aspartate aminotransferase; PAM, pulmonary alveolar macrophages; PMN, polymorphonuclear neutrophils; BALF, bronchoalveolar lavage fluid; SOD, superoxide dismutase; CA, coagulation abnormal; CN, coagulation normal; APTT, serum activated partial thromboplastin time; FIB, fibrinogen; SIC, sepsis-induced cardiomyopathy; SIRS, systemic inflammatory response syndrome; DEX, dexamethasone; SAKI, sepsis-induced acute kidney injury.

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**FIGURE 3** | Down-regulated miRNAs in sepsis.
TABLE 3 | CircRNAs and Sepsis.

| circRNA          | Pattern of Expression | Clinical Samples/Animal Model | Assessed Cell Lines | Targets / Regulators | Signaling Pathways | Description                                                                 | Reference |
|------------------|-----------------------|-------------------------------|---------------------|----------------------|--------------------|------------------------------------------------------------------------------|-----------|
| circVMA21        | ↓                     | CLP rats                      | HK-2, WI-38         | miR-9-39, ↓          | SMG1                | CircVMA21 reduced apoptosis, inflammatory responses and oxidative stress.    | (306)     |
| hsa_circRNA_104484 | ↑                     | 25 patients with sepsis and 22 HCs | MPVECs              | miR-545              |                    | Low levels of circ-PRKCI were correlated with sepsis risk, clinical disease severity and 28-day mortality risk. | (308)     |
| hsa_circRNA_104670 | ↑                     | 25 patients with sepsis and 22 HCs | Caco2               | miR-20b-5p, ↓        | SOD                | Downregulation of circDNMT3B decreased cell survival and increased apoptosis, inflammatory responses and oxidative damage. | (328)     |
| circ_0114428     | ↑                     | HK2                           | ↓                    | miR-495-3p, ↑        | CRBN               | Downregulation of circ_0114428 decreased apoptosis, inflammatory responses, oxidative stress, and ER stress. | (307)     |
| circ_0001105     | ↓                     | septic rats                   | ↑                    | YAP1                 |                    | Up-regulation of circ_0001105 decreased apoptosis, inflammatory responses and oxidative damage. | (309)     |
| circ_Fryl        | ↑                     | septic mice                   | HK2                 | miR-545, ↓           | ZEB2               | Up-regulation of circPRKCI reduced LPS-induced cell injury and inflammatory responses. | (311)     |
| hsa_circ_0003420 | ↑                     | CLP rats                      | HK2                 | miR-183a, ↑          | Rcan2              | Up-regulation of circPRKCI reduced LPS-induced cell injury and oxidative damage. | (312)     |
| circ_Ttc3        | ↓                     | CLP rats                      | ↑                    | miR-148a, ↓          |                    | Up-regulation of circPRKCI reduced LPS-induced cell injury and oxidative damage. | (313)     |
| circPRKCI        | ↓                     | patients with sepsis and HCs  | HK2                 | miR-545, ↓           | 2EB2               | Up-regulation of circPRKCI reduced LPS-induced cell injury and inflammatory responses. | (314)     |
| circ_0091702     | ↓                     | septic mice                   | HK2                 | miR-182, ↑           | PDE7A              | Up-regulation of circ_0091702 reduced LPS-induced cell injury.               | (315)     |
| circVMA21        | ↓                     | ADSCs, LPS-induced AEC damage model | ↑                    | SIRT3 in ADSC exosomes | SIRT3/AMPK signaling | Up-regulation of circVMA21 reduced LPS-induced cell injury and inflammatory responses. | (316)     |
| circTLK1         | ↑                     | HEBEpCs                       | ↑                    | mature miR-15a-5p    |                    | Downregulation of circTLK1 reduced apoptosis, inflammatory responses and oxidative stress. | (317)     |
| circFADS2        | ↑                     | 50 patients with sepsis and 50 HCs | ↑                    | miR-545-3p, ↑        | THBS2              | Up-regulation of circ_0091702 reduced LPS-induced cell injury.               | (318)     |
| circ_0091702     | ↓                     | septic mice                   | HK2                 | miR-545-3p, ↑        | THBS2              | Up-regulation of circ_0091702 reduced LPS-induced cell injury.               | (319)     |
| hsa_circ_0068,888 | ↓                     | C57BL/6 mice                  | ↑                    | miR-21-5p, ↑         |                    | Up-regulation of hsa_circ_0068,888 reduced inflammatory response and oxidative stress and increased viability. | (305)     |
| circPTK2         | ↓                     | septic mice                   | B2V microglia       | miR-181c-5p, ↑       |                    | Downregulation of circPTK2 reduced apoptosis, inflammatory responses.       | (320)     |
| circ-FANCA       | ↑                     | 19 patients with sepsis and 19 HCs | HK2                 | miR-93-5p, ↑         | OXSR1              | Downregulation of circ-FANCA reduced apoptosis, inflammatory responses and oxidative stress and increased proliferation. | (321)     |
| circANKRD36      | ↑                     | 60 patients with sepsis-induced ARDS | RAW264.7            | miR-330, ↑           | ROCK1              | Downregulation of circANKRD36 reduced viability and migration alleviated inflammatory responses. | (322)     |
| circPRKCI        | ↓                     | HK2                           | ↑                    | miR-106b-5p, ↑       | GAB1               | Up-regulation of circPRKCI reduced apoptosis, inflammatory responses and oxidative stress and increased viability. | (323)     |

HCs, healthy controls; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome.
IncRNAs and miRNAs can ameliorate the pathologic events in the target organs, particularly heart and kidney during sepsis. Yet, this field is still in its infancy needing verification in additional animal models and cell lines. Moreover, since sepsis is an emergency situation, any therapeutic option should be verified in terms of bioavailability, efficiency and instant amelioration of pathological events.

Since the pathoetiology of sepsis-related complications is not completely understood, high throughput sequencing strategies focusing on different classes of non-coding as well coding RNAs are necessary to find the complicated networks between these transcripts in the context of sepsis.

AUTHOR CONTRIBUTIONS

SG-F wrote the draft and revised it. MT designed and supervised the study. NA, BH, and TK collected the data and designed the figures and tables. All authors contributed to the article and approved the submitted version.
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