



MINI REVIEW

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Diagnostic biomarkers and miRNAs in prognosis of acute respiratory distress syndrome

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Abstract

Acute respiratory distress syndrome (ARDS) is a disease of the lung and/or extrapulmonary system characterized by acute, progressive breathing difficulty and refractory hypoxemia. After years of revision, the 2012 International Expert Conference developed a new diagnostic standard for ARDS, known as the Berlin definition, which provides good guidance on how to define and judge the disease in clinical practice. Despite the establishment of diagnostic standards and treatment improvements, ARDS mortality rate still remains high. The primary reason is that the pathophysiology has not been fully elucidated. In patients with ARDS, damage to the alveolar capillary membrane may occur, leading to increased vascular permeability and the occurrence of pulmonary edema. Therefore, exploring the pathogenesis of ARDS from the perspective of microvascular permeability and identification of effective targets may be key factors in the diagnosis and treatment of ARDS. This review presents the current literature regarding the role of miRNAs (micro ribonucleic acids) in early detection and prediction of ARDS outcome.

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Introduction

Acute respiratory distress syndrome (ARDS) is a critical condition characterized by acute and progressive difficulty in breathing and refractory hypoxemia, involving the lungs and/or extrapulmonary tissues.¹ The etiology of ARDS encompasses a wide range of diseases that can cause direct or indirect lung injury. The syndrome was first described by Ashbaugh in 1967, and its diagnosis requires a combination of clinical manifestations, oxygen status, imaging examinations, and hemodynamic criteria.²

In 2012, the International Expert Conference developed a new diagnostic standard for ARDS, known as the Berlin definition, which provides guidance on how to define and assess the disease in clinical practice,² and which classifies ARDS as mild, moderate, or severe based on the PaO₂/FiO₂ (partial pressure of oxygen in arterial blood/fraction of inspired oxygen) ratio. Over the past decade, the rapid development of the critical care profession has led to multiple advancements, necessitating the need to expand the definition of ARDS.

In 2023, 32 international critical care experts held a consensus meeting and formulated a new global definition for ARDS.³ Despite these updated diagnostic standards and treatment strategies, the mortality rate associated with ARDS remains high, ranging from 40% to 60%.⁴

The study of molecular mechanisms remains a primary research focus in the field of ARDS. In patients with ARDS, damage to the alveolar capillary membrane may occur, leading to increased vascular permeability and the occurrence of pulmonary edema.⁵ Therefore, exploring the pathogenesis of ARDS from the perspective of microvascular permeability and identifying effective targets may be crucial for the diagnosis and treatment of this complex syndrome.

This review presents the current literature regarding the molecular biological mechanisms of ARDS and summarizes recent research on the relationship between vascular endothelial cell injury and the development of ARDS.

Pathophysiology

Systemic inflammatory response syndrome (SIRS) is a critical condition characterized by uncontrolled systemic inflammatory responses triggered by various factors, often leading to multiple organ dysfunction and high mortality rates.^{6,7} ARDS represents the severe pulmonary manifestation of SIRS, with acute lung injury (ALI) triggered by severe pneumonia frequently involving multiple organs or systems.⁶

The rapid progression of ARDS poses increased danger and accelerates the associated complications.⁸ In addition to infections caused by pathogens, active defense reactions and explosive, uncontrolled systemic immune responses mediated by oversecreted cytokines play essential roles in the development of SIRS.⁹ These responses result from self-destruction due to the overactivation of immune defense mechanisms, endocrine disorders, and other contributing factors⁹ (Figure 1 and Table 1).

In patients with ARDS, the increased permeability of blood vessels due to alveolar capillary damage is a hallmark

of the disease.¹⁰ ARDS is associated with excessive anti-inflammatory reactions in response to pathogen infections and toxins.¹⁰ Cytokine-mediated inflammatory responses play crucial roles in the progression of ARDS, with a complex inflammatory network system involving proinflammatory and anti-inflammatory factors and chemokines that amplify and sustain lung injury.¹¹ The imbalance between these factors can ultimately lead to SIRS, which serves as the pathogenetic basis of ARDS.¹²

Diagnostic biomarkers for ARDS involving vascular permeability

The components responsible for maintaining and regulating the structural integrity and permeability of capillaries include the extracellular matrix, intercellular junctions, cytoskeleton, and the interaction between pinocytosis and cell substrates.¹³ ARDS can directly or indirectly injure these components, leading to altered membrane barrier permeability through various mechanisms, such as lysis of basement membrane proteins, disruption of the extracellular matrix network, and disruption of the cytoskeleton.^{14,15} Consequently, patients with ARDS may experience alveolar capillary injury and increased permeability.¹⁶

Diffuse alveolar injury, characterized by the destruction of the alveolar epithelial barrier function and damage to vascular endothelial cells, is the underlying histopathological change in ARDS, resulting in pulmonary edema.^{17,18} The pathophysiological heterogeneity of ARDS is one reason for the limited treatment success.¹⁹

Given the limitations of ARDS diagnostic criteria and predictive scoring systems, there is an increasing interest in ARDS biomarkers.²⁰ Recent studies suggest that certain biomarkers (Figure 1), such as those reflecting vascular permeability and endothelial cell injury, can identify high-risk individuals, assess clinical efficacy, predict outcomes, and optimize clinical trial objectives.¹⁰

Angiopoietin-2 (Ang-2), a protein involved in angiogenesis maturation and maintenance, has been shown to increase vascular permeability during the onset of ALI in animal experiments and clinical studies.^{21,22} Increased serum Ang-2 levels are associated with increased vascular permeability in patients with ALI and sepsis.^{22,23} The destruction of the pulmonary vascular endothelial cell barrier is essential for pulmonary edema,²⁴ and Ang-2 levels are higher in patients with ARDS than in those without ARDS.²⁵ Serum Ang-2 levels have been found to be a better predictor of ARDS than IL-6 (interleukin-6), APACHE II (Acute Physiology and Chronic Health Evaluation II) scores, and SOFA (Sequential Organ Failure Assessment) scores,^{26,27} suggesting its potential usefulness in early ARDS diagnosis and outcome prediction.

Intercellular adhesion molecule-1 (ICAM-1) is a member of the immunoglobulin superfamily of adhesion molecules and plays a crucial role in mediating adhesion reactions.²⁸ Serum and pulmonary fluid levels of ICAM-1 were significantly higher in patients with ARDS than in those with pulmonary edema,²⁹ and elevated soluble ICAM-1 levels were associated with poor clinical outcomes in patients with ARDS.³⁰ These findings suggest that serum and pulmonary edema fluid levels of ICAM-1 can predict ARDS outcomes.³⁰

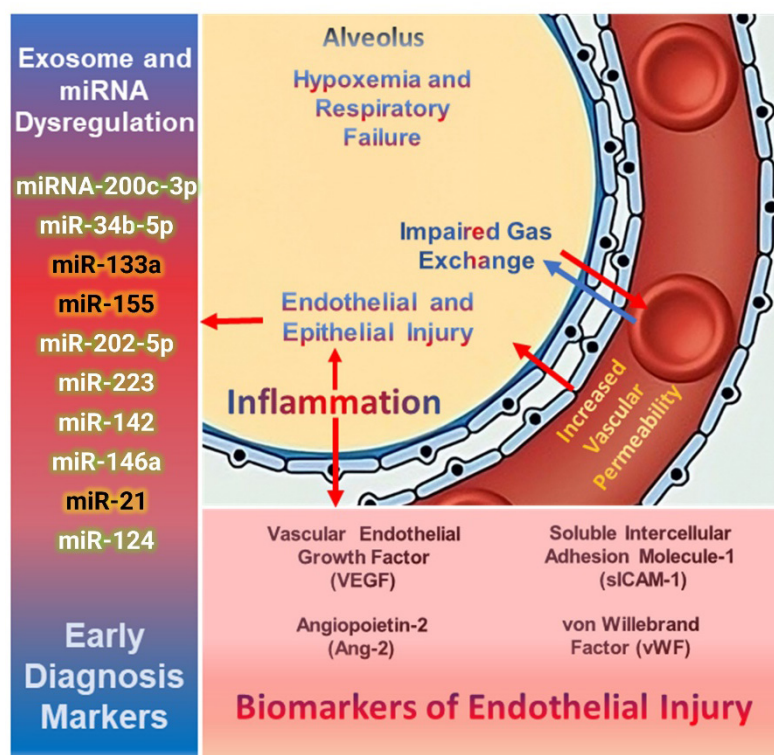


Figure 1 Early candidate diagnostic miRNAs for acute respiratory distress syndrome (ARDS) prognosis. ARDS is a severe condition resulting from an uncontrolled systemic inflammatory response, often triggered by infections, trauma, or other lung insults. This dysregulated inflammation leads to significant damage to the alveolar-capillary barrier, characterized by the overproduction of cytokines and inflammatory mediators. The heightened inflammatory state injures endothelial and alveolar epithelial cells, increasing the permeability of the alveolar-capillary barrier and causing pulmonary edema. This fluid accumulation impairs gas exchange, leading to hypoxemia and respiratory failure. Biomarkers like angiopoietin-2 (Ang-2), soluble intercellular adhesion molecule-1 (sICAM-1), vascular endothelial growth factor (VEGF), and von Willebrand factor (vWF) indicate endothelial injury and vascular permeability in ARDS. Extracellular vesicles, particularly exosomes, play a crucial role in ARDS pathogenesis by mediating intercellular communication and transferring molecular components, including miRNAs. Notably, miR-223 and miR-142 exhibit anti-inflammatory effects, while miR-146a inhibits NF- κ B signaling to reduce cytokine production. Conversely, miR-21 promotes inflammation and fibrosis and miR-124 suppresses proinflammatory cytokines by targeting STAT3.

Table 1 The list of candidate miRNAs and their possible mechanisms and roles in ARDS.

miRNA Name	Inflammatory or Anti-inflammatory	Possible Mechanism of Effect
miRNA-200c-3p	Anti-inflammatory	Helps monitor disease severity and predict outcomes by regulating gene expression in receptor cells. ⁵⁰
miR-34b-5p	Anti-inflammatory	Correlates negatively with inflammatory factors, serving as a protective factor in children with ARDS. ⁶⁴
miR-133a	Inflammatory	Elevated in sepsis patients with ARDS, serving as an independent risk factor predicting death. ⁵²
miR-155	Inflammatory	Activates and releases inflammatory factors such as IL-1 β and TNF- α , exacerbating lung injury and inflammatory reactions. ⁶⁹
miR-202-5p	Anti-inflammatory	Reduced expression in ARDS, potentially playing a role in reducing inflammation. ⁶²
miR-223	Anti-inflammatory	Reduces proinflammatory cytokine production and limits neutrophil infiltration. ⁶³
miR-142	Anti-inflammatory	Modulates macrophage polarization and reduces inflammatory responses. ⁶⁴
miR-146a	Anti-inflammatory	Inhibits NF- κ B signaling pathway, reducing the production of proinflammatory cytokines. ⁶⁵
miR-21	Inflammatory	Promotes fibrosis and inflammation by targeting anti-inflammatory pathways. ⁶⁴
miR-124	Anti-inflammatory	Suppresses the production of proinflammatory cytokines by targeting STAT3. ⁶⁶

Vascular endothelial growth factor (VEGF) is an essential regulator of fetal and adult angiogenesis, acting on endothelial cells to enhance vascular permeability, induce angiogenesis and endothelial growth, promote cell migration, and inhibit apoptosis.^{31,32} Increased serum VEGF levels correlated more strongly with patients at high risk for ARDS compared with those on mechanical ventilation and healthy controls.³³ However, decreased VEGF levels in bronchoalveolar lavage fluid (BALF) were observed in patients with ARDS and pressure pulmonary edema, suggesting that VEGF, as an endothelial cell biomarker, has limited specificity in diagnosis but may play an essential prognostic role.³⁴

Von Willebrand factor (vWF), primarily secreted by platelets and endothelial cells, plays a crucial role in mediating platelet adhesion and aggregation. Increased serum vWF levels were associated with a high risk of confirmed ARDS, with a sensitivity and specificity of 87% and 77%, respectively.³⁵ A comparative analysis of serum vWF levels on the first and third days in patients with ARDS showed that compared with survivors, patients with decreased serum vWF levels on the third day had higher levels of serum vWF and shorter durations of organ failure.³⁶ These findings suggest that vWF reflects the degree of endothelial activation and damage in patients with ARDS and are related to less favorable outcomes.³⁷

The limitation of these biomarkers is that no single biomarker can adequately predict ARDS progression or outcomes. Several lines of evidence suggest that Ang-2, soluble ICAM-1, VEGF, vWF, and other inflammatory factors can serve as inflammatory indicators of endothelial injury in ARDS; however, due to the complexity of ARDS pathogenesis, the use of these biomarkers alone is insufficient to achieve hierarchical or precise medical treatment. Moreover, current treatments targeting inflammatory factors have not yielded adequate therapeutic effects, and mortality and disabling complications associated with ARDS remain high among survivors.

Progress in molecular biology and the role of miRNAs

Intercellular communication is essential for almost all physiological and metabolic processes involving the mediation of receptor ligands, signal molecules, hormones, and extracellular vesicles (EVs) for communication and transportation.³⁸ The primary form of EVs, exosomes, secreted by pathogenic microorganisms and immune cells, plays a crucial role in initiating and regulating pathological reactions in ARDS.³⁹

Exosomes are membrane-bound bubbles with diameters ranging from 30 nm to 100 nm, released into the extracellular environment by various cells and containing a diverse array of molecules, including miRNAs (micro ribonucleic acids), m(messenger ribonucleic acids)RNAs, noncoding RNAs (ribonucleic acids), ribosomal RNAs, cytokines, proteins, lipids, and other components.⁴⁰ Exosomes also possess transmembrane proteins, such as CD(Cluster of Differentiation)9, CD63, CD81, and CD82.^{41,42} Unlike direct contact between cells and signal molecules secreted by cells, EVs represent a “third way” of intercellular communication that involves the transfer of carriers for functional

cell components such as cytoplasmic proteins, lipids, and nucleic acids between cells.⁴³ EVs mediate pulmonary immune responses and inflammatory signal transduction in ARDS animal models.⁴⁴ The RNAs of EVs comprise t(transfer)RNA, r(ribosomal)RNA, mRNA, miRNA, long-strand RNA, and others, with the potential to regulate gene transcription and expression in receptor-containing cells.⁴⁵

Several lines of evidence suggest that exosomes participate in numerous diseases and may serve as biomarkers for diagnosis.⁴⁶ Research on exosomes currently focuses on ARDS treatment by mesenchymal stem cells,⁴⁶ but studies on the pathogenesis and role of exosomes in ARDS are lacking. Specific miRNAs (Table 1), such as miRNA-200c-3p, miR-34b-5p, and miR-133a, have been identified as potential biomarkers for ARDS prognosis.^{47,48} For instance, miRNA-200c-3p levels can help monitor disease severity and predict outcomes,^{47,49} whereas miR-34b-5p levels correlate negatively with inflammatory factors and serve as a protective factor in children with ARDS.⁴⁸ Zhao et al. discovered that the serum level of miR-133a was abnormally elevated in sepsis patients with ARDS and served as an independent risk factor predicting death.^{50,51}

In ARDS, the activation and release of cytotoxic and inflammatory mediators, along with injury to alveolar epithelial cells, result in varying degrees of pulmonary tissue damage.⁵²⁻⁵⁴ Serum miR-155 is upregulated in ARDS and contributes to inflammation by activating and releasing inflammatory factors such as IL-1B (interleukin-1 beta) and TNF- α (tumor necrosis factor-alpha), thereby exacerbating lung injury and inflammatory reactions.⁵⁵⁻⁵⁸ The expression of miR-202-5p was found to be significantly reduced in the lungs of mice with ARDS. Although studies on its function have primarily focused on its role in the pathogenesis of tumors and immune diseases,⁵⁹⁻⁶¹ its mechanism of action in ARDS remains unclear and warrants further investigation, particularly regarding its impact on vascular permeability.^{58,62}

miR-223 and miR-142 are anti-inflammatory miRNAs that play crucial roles in modulating the immune response in ARDS. miR-223 reduces proinflammatory cytokine production and limits neutrophil infiltration, thereby mitigating the excessive inflammatory response characteristic of ARDS.⁶³ Similarly, miR-142 modulates macrophage polarization toward the M2 (alternatively activated macrophages) phenotype, which is associated with anti-inflammatory and tissue repair functions, thus attenuating lung injury and promoting recovery.⁶⁴ miR-146a further contributes to the anti-inflammatory milieu by inhibiting the NF- κ B (nuclear factor kappa B) signaling pathway, reducing the production of cytokines such as IL-6, IL-8, and TNF- α , and mitigating lung injury during mechanical ventilation.⁶⁵ Conversely, miR-21 is associated with proinflammatory and profibrotic roles, promoting fibrosis and inflammation by targeting anti-inflammatory pathways, which exacerbates the severity of ARDS.⁶⁴ miR-124 suppresses the production of proinflammatory cytokines by targeting the STAT3 signaling pathway, offering potential therapeutic benefits in reducing lung injury and inflammation in ARDS patients.⁶⁶ These miRNAs represent promising targets for therapeutic intervention, offering new avenues for research and treatment strategies in ARDS.

Although increasing evidence suggests that inflammatory factors such as Ang-2, sICAM-1 (soluble intercellular adhesion molecule-1), VEGF, and vWF can serve as markers

for endothelial injury in ARDS, the pathogenesis of ARDS is highly complex. Relying solely on various inflammatory factors as evaluation criteria are insufficient for achieving stratification and precision medicine. Moreover, current treatments targeting inflammatory factors have not yielded satisfactory therapeutic effects, and so the mortality rate of ARDS remains high.

Research has highlighted the crucial role of intercellular communication in nearly all physiological and metabolic processes, facilitated through receptor ligands, signaling molecules, hormones, and EVs. In recent years, it has been found that EVs, particularly exosomes, play a key role in the pathogenesis of ARDS. This perspective will further explore the pathogenesis of ARDS.

Conclusion and Perspectives

In the past decades, several clinical trials have been conducted on the epidemiology, risk factors, prevention, and treatment of ARDS.^{67,68} Despite ongoing efforts, the challenges of high morbidity, mortality, and associated healthcare costs persist, with targeted treatment options for ARDS remaining scarce.

From a future perspective, advancements in understanding the pathophysiology of ARDS will be pivotal in developing precise treatment plans and exploring new diagnostic and therapeutic targets. Notably, miRNAs and EVs hold significant potential due to their roles in immunogenic responses and activation of immune cells. Future research should prioritize identifying susceptibility mechanisms, implementing primary prevention strategies, and developing early treatment interventions. These efforts, including the exploration of miRNAs and EVs, have the potential to significantly improve success rates and reduce ARDS mortality, paving the way for more effective management of this critical condition.

Authors Contributions

X.J, M.H, J.C, contributed to the design and implementation. X. J and M.H, performed the figure and table preparations. X.J, M.H, J.C, contributed to writing and revision of manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

Authors declare no conflicts of interest.

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