Correlation between serum miR-127, miR-147a, miR-146b and the severity and prognosis of acute respiratory distress syndrome in premature infants

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ABSTRACT **Objective:** To explore the correlation between serum microRNA-127 (miR-127), miR-147a, miR-146b and the severity and prognosis of acute respiratory distress syndrome (ARDS) in premature infants.
Methods: Eighty premature infants with ARDS admitted to our hospital from October 2020 to October 2023 were regarded as the observation subjects (ARDS group). 94 healthy newborns born during the same period in our hospital were as the control group. QRT-PCR method was applied to detect the relative expression levels of miR-127, miR-147a, and miR-146b in serum. According to the oxygenation index (OI), the severity of premature infants was evaluated and the infants were separated into mild group (27 cases), moderate group (37 cases), and severe group (16 cases). Receiver operating characteristic curve (ROC) was applied to analyze the diagnostic value of serum miR-127, miR-147a, and miR-146b for death in premature infants with ARDS. The comparison of area under the curve (AUC) was conducted through Z-test. Multivariate logistic regression was applied to analyze the influencing factors of death in premature infants with ARDS.
Results: The expression level of serum miR-127 was higher in the ARDS group compared to the control group, while the expression levels of miR-147a and miR-146b were lower ($P < 0.05$). The expression level of serum miR-127 increased in the moderate and severe groups compared to the mild group, while the expression levels of miR-147a and miR-146b decreased ($P < 0.05$). The expression level of serum miR-127 increased in the severe group compared to the moderate group, while the expression levels of miR-147a and miR-146b decreased ($P < 0.05$). There was no statistically obvious difference between the survival group and the death group in terms of birth mode, gender, birth weight, assisted ventilation method, gestational age, frequency of pulmonary surfactant (PS) use, day age, hypoalbuminemia, and Apgar score ($P > 0.05$). The expression level of serum miR-127 was higher in the death group than in the survival group, while the expression levels of miR-147a and miR-146b were lower ($P < 0.05$). MiR-127 was a risk factor for death during hospitalization in premature infants with ARDS, while miR-147a and miR-146b were protective factors ($P < 0.05$). The AUC of serum miR-127, miR-147a, and miR-146b alone and in combination for diagnosing death in premature infant with ARDS was 0.825, 0.905, 0.873, and 0.977, respectively. The combined diagnostic efficacy of the three was the best ($P < 0.05$).
Conclusion: The serum miR-127 level in premature infants with ARDS increases, while the levels of miR-147a and miR-146b decrease. They are correlated with the severity of the disease and have certain diagnostic value for the prognosis.

INDEX TERMS Acute respiratory distress syndrome; Premature infants; Micro RNA-127; Micro RNA-147a; Micro RNA-146b; severity of the disease; Prognosis

I. INTRODUCTION

ACUTE respiratory distress syndrome (ARDS) is a critical illness characterized by excessive respiratory drive. Its risk factors include stretch reflex induced by alveolar collapse, hypoxemia, inflammatory stimulation, hypercapnia and so on [1]. Preterm infants lack sufficient pulmonary surfactant and have poor alveolar stability, which easily leads to alveolar collapse, pulmonary dysfunction and sub-

sequent ARDS. Neonatal ARDS is one of the major causes of mortality and disability in children [2]. Early evaluation of the severity of ARDS in preterm infants and analysis of prognostic influencing factors are of great significance for improving the survival outcomes of affected neonates. Previous studies have reported that plasma microRNA-127 (miR-127) levels are elevated in patients with acute lung injury. miR-127 acts as an independent risk factor for death in such patients and possesses predictive value for their prognosis [3]. Serum miR-147a expression is downregulated in children with pneumonia, and its level is negatively correlated with inflammatory factors while positively correlated with pulmonary function indicators, which makes it a potential therapeutic target for pneumonia [4]. As ARDS exacerbates and adverse prognosis occurs, serum miR-146b levels gradually decline. miR-146b participates in the progression of ARDS by regulating inflammatory responses, and serum miR-146b can serve as a predictive marker for poor patient prognosis [5]. The clinical value of serum miR-127, miR-147a and miR-146b in preterm infants with ARDS remains unclear. Therefore, this study mainly explores the expression of serum miR-127, miR-147a and miR-146b in preterm infants with ARDS, as well as their correlations with disease progression and prognosis. The research results are reported as follows.

II. MATERIALS AND METHODS

A. RESEARCH SUBJECTS

Preterm infants diagnosed with ARDS admitted to our hospital from October 2020 to October 2023 were selected as the ARDS group.

Inclusion criteria:

(1) Meeting the diagnostic criteria for pediatric ARDS [6];

(2) Gestational age ranging from 28 to 35 weeks, postnatal age from 1 to 7 days;

(3) Written informed consent obtained from the guardians of the children.

Exclusion criteria:

(1) Complicated with severe infection, autoimmune disorders and cardiac, hepatic or renal insufficiency;

(2) ARDS secondary to heart failure;

(3) Preterm infants with birth weight less than 1 kg.

A total of 80 preterm infants meeting the inclusion and exclusion criteria were enrolled in the ARDS group, including 46 males and 34 females, with an average gestational age of 31.05 ± 2.28 weeks and an average postnatal age of 4.62 ± 1.48 days. A total of 94 healthy newborns delivered in our hospital during the same period were selected as the control group, including 53 males and 41 females, with an average gestational age of 38.11 ± 2.34 weeks and an average postnatal age of 4.65 ± 1.43 days. This study was reviewed and approved by the Ethics Committee of our hospital.

B. EXPERIMENTAL PROCEDURES

TABLE 1. PRIMER SEQUENCES

Gene	Sequence
miR-127	F: GCGGCTCGGATCCGTCTGAGCT
	R: GTGCAGGGTCCGAGGT
miR-147a	F: ATTGGCAAGATGTTCCTTGC
	R: GTGTGTGGAAATGCTTCTGC
miR-146b	F: GCGTACTCGATGACTCCGTG
	R: ACGCTACCTGATAATGTG
U6	F: CTCGCTTCGGCAGCACA
	R: AACGCTTCACGAATTTGCGT

1) Detection of Serum miR-127, miR-147a and miR-146b Expression Levels

Peripheral venous blood was collected from all subjects, left to stand for stratification, and centrifuged to collect serum. Quantitative real-time reverse transcription-polymerase chain reaction (qRT-PCR) was adopted to detect the relative expression levels of serum miR-127, miR-147a and miR-146b. Briefly, serum samples were transferred into centrifuge tubes, and 1 mL Trizol reagent (Beyotime Biotechnology, Cat. No. R0016) was added to extract total serum RNA. The concentration and purity of RNA were determined using a Qubit 4 fluorometer (Thermo Fisher Scientific, USA, Model Q33238). A reverse transcription kit (Xinhai Gene Detection Co., Ltd., Cat. No. D0401) was used to synthesize complementary DNA (cDNA). PCR reaction system preparation: 2 μL cDNA template, 25 μL Premix Ex Taq DNA polymerase, 1 μL upstream primer and 1 μL downstream primer, supplemented with RNase-Free ddH_2O to a final volume of 50 μL. PCR amplification conditions: Pre-denaturation at 95 °C for 10 min; followed by 39 cycles of denaturation at 95 °C for 10 s and annealing & extension at 56 °C for 50 s. The relative expression levels of miR-127, miR-147a and miR-146b were analyzed by the $2^{-}\triangle\triangle$Ct method. U6 was used as the internal reference gene. All primers were synthesized by Sangon Biotech (Shanghai) Co., Ltd. The primer sequences are shown in Table 1.

2) Detection of Oxygenation Index (OI)

All neonates were placed in a supine resting position with a sensor attached to the finger. A Gasboard-3100 oxygen analyzer (Ruizhi Automatic Control) was used to measure light transmittance through tissues to calculate the OI [7]. The severity of illness in preterm infants was graded according to the Montreux criteria for neonatal acute respiratory distress syndrome (2017 edition) [6]: mild group ($4 \leq$ OI < 8, 27 cases), moderate group ($8 \leq$ OI < 16, 37 cases), severe group (OI ≥ 16, 16 cases).

3) Collection of General Clinical Data

General clinical data were extracted from the electronic medical record system, including delivery mode, gender, birth weight, assisted ventilation mode, gestational age, frequency of pulmonary surfactant (PS) administration, postnatal age, presence or absence of hypoalbuminemia, and Apgar score.

4) Prognostic Follow-up and Grouping

The in-hospital clinical outcomes of all preterm infants with ARDS were tracked throughout hospitalization. Subjects were divided into a survival group (44 cases) and a death group (36 cases) based on whether death occurred during hospitalization.

C. STATISTICAL ANALYSIS

SPSS 25.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and independent sample t-test was applied for intergroup comparison of two groups. Enumeration data were expressed as case number $\chi 2$, and Chi-square test or corrected Chi-square test was used for intergroup comparison. Receiver operating characteristic (ROC) curves were drawn to analyze the diagnostic value of serum miR-127, miR-147a and miR-146b for predicting in-hospital death in preterm infants with ARDS, and Z-test was used to compare the area under the curve (AUC). Multivariate Logistic regression analysis was performed to identify influencing factors for in-hospital death of ARDS preterm infants. $P < 0.05$ indicated statistically significant difference.

III. RESULTS

A. COMPARISON OF SERUM MIR-127, MIR-147A AND MIR-146B LEVELS BETWEEN CONTROL GROUP AND ARDS GROUP

Serum miR-127 expression was significantly higher, while miR-147a and miR-146b expression levels were significantly lower in the ARDS group compared with the control group ($P < 0.05$). See Table 2.

B. COMPARISON OF SERUM MIR-127, MIR-147A AND MIR-146B LEVELS AMONG ARDS PRETERM INFANTS WITH DIFFERENT DISEASE SEVERITY

Compared with the mild group, serum miR-127 expression was elevated, while miR-147a and miR-146b expression were decreased in the moderate and severe groups ($P < 0.05$). The severe group exhibited higher miR-127 and lower miR-147a, miR-146b levels relative to the moderate group ($P < 0.05$). See Table 3.

C. COMPARISON OF GENERAL CLINICAL DATA AND SERUM MIRNA LEVELS BETWEEN SURVIVAL GROUP AND DEATH GROUP

No statistically significant intergroup differences were observed between the survival group and death group in terms of delivery mode, gender, birth weight, assisted ventilation mode, gestational age, frequency of PS administration, postnatal age, hypoalbuminemia and Apgar score ($P > 0.05$). Serum miR-127 expression was significantly higher, whereas miR-147a and miR-146b levels were significantly lower in the death group compared with the survival group ($P < 0.05$). See Table 4.

D. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS FOR IN-HOSPITAL DEATH IN PRETERM INFANTS WITH ARDS

Taking in-hospital death of ARDS preterm infants as the dependent variable (death = 1, survival = 0), the measured expression values of miR-127, miR-147a and miR-146b were included as independent variables in the Logistic regression model. The results revealed that miR-127 was an independent risk factor for in-hospital death of ARDS preterm infants, while miR-147a and miR-146b were independent protective factors ($P < 0.05$). See Table 5.

E. DIAGNOSTIC VALUE OF SERUM MIR-127, MIR-147A AND MIR-146B FOR PREDICTING IN-HOSPITAL DEATH IN ARDS PRETERM INFANTS

ROC curves were plotted with the individual expression levels of miR-127, miR-147a, miR-146b and the combined predictive probability value as test variables, and in-hospital death status as the state variable. The results showed that the AUC values of miR-127, miR-147a, miR-146b alone and their combination for predicting in-hospital death were 0.825, 0.905, 0.873 and 0.977, respectively. The combined detection exhibited significantly superior diagnostic efficacy compared with individual indicators ($Z = 3.501, 2.530, 2.590$; $P = 0.001, 0.011, 0.010$). See Figure 1 and Table 6.

TABLE 2. COMPARISON OF SERUM MIR-127, MIR-147A AND MIR-146B LEVELS BETWEEN CONTROL GROUP AND ARDS GROUP ($\bar{x} \pm s$)

Index	Control group ($n = 94$)	ARDS group ($n = 80$)	t	P
miR-127	1.01 ± 0.14	1.24 ± 0.18	9.473	< 0.001
miR-147a	1.04 ± 0.13	0.80 ± 0.11	13.015	< 0.001
miR-146b	1.02 ± 0.13	0.77 ± 0.12	13.095	< 0.001

TABLE 3. COMPARISON OF SERUM MIR-127, MIR-147A AND MIR-146B LEVELS IN ARDS PRETERM INFANTS WITH DIFFERENT DISEASE SEVERITY ($\bar{x} \pm s$)

Index	Mild group ($n = 27$)	Moderate group ($n = 37$)	Severe group ($n = 16$)	F	P
miR-127	1.12 ± 0.16	$1.25 \pm 0.18^{*}$	$1.42 \pm 0.22^{*\#}$	13.710	< 0.001
miR-147a	0.91 ± 0.13	$0.79 \pm 0.10^{*}$	$0.62 \pm 0.09^{*\#}$	35.445	< 0.001
miR-146b	0.94 ± 0.15	$0.75 \pm 0.12^{*}$	$0.53 \pm 0.08^{*\#}$	55.105	< 0.001

NOTE: $^{*}P < 0.05$ VS MILD GROUP; $\#P < 0.05$ VS MODERATE GROUP.

TABLE 4. COMPARISON OF GENERAL CLINICAL DATA AND SERUM MIRNA LEVELS BETWEEN SURVIVAL GROUP AND DEATH GROUP[($\bar{x} \pm s$)/N(%)]

Item	Survival group ($n = 44$)	Death group ($n = 36$)	$t/\chi 2$	P
Gender n(%)			0.019	0.892
Male	25(56.82)	21(58.33)		
Female	19(43.18)	15(41.67)		
Gestational age (weeks)	31.12 ± 2.42	30.96 ± 2.07	0.314	0.755
Postnatal age (days)	4.59 ± 1.41	4.66 ± 1.53	0.213	0.832
Delivery mode n(%)			0.154	0.695
Vaginal delivery	14(31.82)	10(27.78)		
Cesarean section	30(68.18)	26(72.22)		
Birth weight (kg)	2.31 ± 0.35	2.27 ± 0.30	0.542	0.589
Apgar score (points)	7.56 ± 0.98	7.37 ± 0.96	0.871	0.387
Assisted ventilation mode n(%)			3.387	0.066
Endotracheal intubation	38(86.36)	25(69.44)		
Non-intubation ventilation	6(13.64)	11(30.56)		
Frequency of PS use n(%)			1.011	0.315
$\geq$3 times	6(13.64)	8(22.22)		
$<$3 times	38(86.36)	28(77.78)		
Hypoalbuminemia n(%)			0.822	0.365
Yes	11(25.00)	6(16.67)		
No	33(75.00)	30(83.33)		
miR-127	1.13 ± 0.13	1.37 ± 0.21	6.260	< 0.001
miR-147a	0.88 ± 0.12	0.70 ± 0.10	7.185	< 0.001
miR-146b	0.84 ± 0.11	0.68 ± 0.09	7.013	< 0.001

TABLE 5. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF PROGNOSTIC FACTORS IN ARDS PRETERM INFANTS

Influencing factor	B	SE	Wald$\chi 2$	OR	95%CI	P
miR-127	0.848	0.158	28.806	2.335	1.713~3.183	< 0.001
miR-147a	-0.764	0.251	9.254	0.466	0.285~0.762	0.002
miR-146b	-0.639	0.310	4.244	0.528	0.288~0.969	0.039

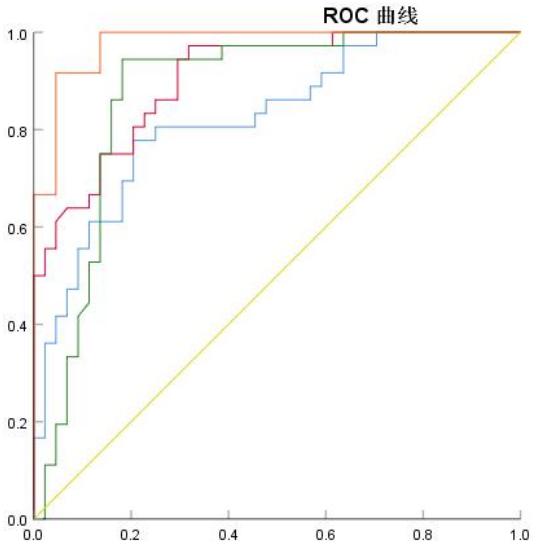

FIGURE 1. ROC CURVES OF SERUM MIR-127, MIR-147A AND MIR-146B FOR PREDICTING IN-HOSPITAL DEATH IN PRETERM INFANTS WITH ARDS

TABLE 6. DIAGNOSTIC PERFORMANCE OF SERUM MIR-127, MIR-147A AND MIR-146B FOR PREDICTING IN-HOSPITAL DEATH IN ARDS PRETERM INFANTS

Index	AUC	95%CI	Sensitivity (%)	Specificity (%)	Cut-off value
miR-127	0.825	0.724-0.901	77.78	79.55	1.21
miR-147a	0.905	0.819-0.959	97.22	68.18	0.81
miR-146b	0.873	0.779-0.937	94.44	81.82	0.79
联合	0.977	0.916-0.998	91.67	95.45	-

IV. DISCUSSION

ARDS is an acute critical respiratory disorder characterized by bilateral opacities on chest imaging and severe hypoxemia caused by non-cardiogenic pulmonary edema. The global prevalence of ARDS has surged in recent years due to pandemics such as COVID-19. It carries a high mortality rate and lacks specific therapeutic agents, and the incidence of ARDS among preterm infants and infants has increased dramatically [8], [9]. Although the pathogenic triggers of ARDS are diverse, its core pathological mechanism lies in elevated alveolar surface tension. Current clinical interventions including fluid restriction, corticosteroid administration and liquid ventilation aim to alleviate pulmonary edema and maintain adequate tissue oxygenation to buy time for disease treatment, yet the overall prognosis remains unsatisfactory, and tools for early disease evaluation and prognostic prediction still require optimization [10].

MicroRNAs (miRNAs) mature in the cytoplasm and regulate multiple biological processes including protein translation, transcript cleavage and secondary siRNA generation, and are closely involved in the progression of various diseases [11]. Previous studies have demonstrated elevated serum miR-127 levels in elderly patients with severe pneumonia, which are positively correlated with hospital stay duration. miR-127 also shows predictive performance for in-hospital mortality and can serve as a sensitive prognostic biomarker in this population [12].

Imbalanced placental redox homeostasis triggers excessive reactive oxygen species (ROS) production, which disrupts fetal immune tolerance, induces pro-inflammatory responses and leads to multiple perinatal complications and neonatal pulmonary diseases. Extracellular microvesicles act as maternal-fetal transport carriers and contain oxidation-sensitive miRNAs such as miR-127. ROS stimulation promotes massive secretion of miR-127, which amplifies systemic inflammatory responses and macrophage recruitment in preterm infants, ultimately predisposing them to ARDS [13]. Consistent with prior research, our study found that serum miR-127 was markedly upregulated in ARDS preterm infants, and its expression level increased progressively as disease severity worsened. We hypothesize that high miR-127 expression exacerbates oxidative stress and systemic inflammation, impairs fetal immune tolerance and elevates the risk of prematurity and pulmonary complications. After birth, lung injury mediated by sustained high miR-127 expression continues to progress and substantially increases the risk of adverse clinical outcomes.

miR-147a is tightly associated with respiratory diseases. Serum miR-147a levels are significantly lower in patients with severe pneumonia than those with mild pneumonia or healthy controls, suggesting that monitoring miR-147a expression facilitates early identification and prognostic assessment of severe pneumonia [14]. In vitro experiments have verified that upregulating miR-147a suppresses high

glucose-induced mesangial cell proliferation, extracellular matrix deposition, oxidative stress and inflammatory activation [15]. In lipopolysaccharide (LPS)-induced murine pneumonia models, lncRNA MIAT is overexpressed and functions as a competing endogenous RNA to sponge miR-147a. Silencing MIAT restores miR-147a expression, which further targets NKAP and inhibits NF-κB inflammatory signaling to alleviate alveolar epithelial injury [16].

In the present study, serum miR-147a was significantly downregulated in ARDS preterm infants, with expression levels declining as disease severity increased. The death group presented much lower miR-147a levels than the survival group. We infer that reduced miR-147a expression removes its inhibitory effect on NF-κB signaling, triggering excessive pulmonary inflammation and accelerating ARDS progression.

miR-146b exerts regulatory functions across multiple disease pathways. In LPS-induced acute lung injury cell models, lncRNA MINCR is upregulated while miR-146b is suppressed. Inhibiting MINCR elevates miR-146b expression, improves cell viability and reduces apoptosis to reverse pulmonary injury; silencing miR-146b abolishes the lung-protective effects of MINCR suppression [17]. Additional animal studies have confirmed that miR-146b upregulation inhibits the PI3K/AKT inflammatory pathway and alleviates ARDS in septic mice [18]. Clinical data indicate that sepsis patients complicated with ARDS have lower miR-146b levels than those without ARDS, and 28-day non-survivors exhibit significantly reduced miR-146b relative to survivors. miR-146b may act as a promising biomarker for ARDS prevention and prognostic evaluation in sepsis [19].

Our study found that serum miR-146b was decreased in ARDS preterm infants compared with healthy neonates, with expression negatively correlated with disease severity, and the lowest levels were detected in non-survivors. Low miR-146b releases the inhibition on PI3K/AKT signaling, amplifies pulmonary inflammatory cascades, damages airway and alveolar epithelia, and worsens patient prognosis.

ROC curve analysis verified that serum miR-127, miR-147a and miR-146b all possess predictive capacity for in-hospital death in ARDS preterm infants, with combined detection delivering the optimal diagnostic performance. Multivariate Logistic regression confirmed miR-127 as a mortality risk factor and miR-147a, miR-146b as protective factors. Dynamic monitoring of these three miRNAs during clinical care enables timely emergency intervention and improves survival rates of affected preterm infants.

In conclusion, serum miR-127 is upregulated while miR-147a and miR-146b are downregulated in preterm infants with ARDS. The expression levels of the three biomarkers correlate with disease severity and can be used to evaluate patient prognosis. This study has several limitations: the single-center design and limited sample size may fail to eliminate confounding bias. Multi-center, large-cohort studies will be conducted in follow-up research to further validate the accuracy of our findings.

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