RESEARCH ARTICLE

WILEY

Clinical value of serum miR-92 and miR-122 expression level combined with pulmonary ultrasound score in the prognosis of neonatal acute respiratory distress syndrome

Haiyan Hong[1] | Binbin Fu[2] | Renyuan Wang[3]

[1]Department of Ultrasound, Sanya Central Hospital, Sanya, China

[2]Department of Clinical Laboratory, Haikou Maternal and Child Health Care Hospital, Haikou, China

[3]Department of Pediatrics, Hainan Women and Children's Medical Center, Haikou, China

Correspondence
Renyuan Wang, Department of Gynecology, Hainan Women and Children's Medical Center, 75 Longkunnan Road, 570100 Haikou, China.
Email: wangrenyuan202110@163.com

Abstract

Purpose: To explore the value of the expression of serum miR-92 and miR-122 combined with lung ultrasound score (LUS) in the prognosis of neonatal acute respiratory distress syndrome (ARDS).

Patients and methods: This study involved 148 neonatal ARDS cases from January 2018 to October 2021, of which 77 children were discharged from hospital and 31 died. The children with ARDS were classified according to disease severity based on X-ray examination as mild ($n = 69$ cases) and severe ($n = 39$ cases). The expression of serum miR-92 and miR-122 was detected by real-time fluorescence quantitative PCR and the LUS score was recorded. The data were subjected to ROC curve analysis and Pearson correlation analysis.

Results: The expression of serum miR-92, miR-122, and LUS score in the patients that died were significantly higher than in those who survived ($p < 0.05$). These indicators were also significantly higher in the severe disease group compared to the mild disease group ($p < 0.05$). ROC curve showed that serum miR-92 and miR-122 combined with the LUS score had the largest area under the curve (0.920, 95% CI: 0.860–0.977) for predicting death, with a sensitivity and specificity of 92.0% and 87.0%, respectively. Pearson correlation analysis showed that the expression levels of serum miR-92 and miR-122 were positively correlated with the LUS score (all $p < 0.01$).

Conclusions: The increased expression of serum miR-92 and miR-122 is related to the severity and prognosis of children with ARDS, combined with the LUS score are of value to predict the prognosis of children with ARDS.

KEYWORDS
acute respiratory distress syndrome, miR-122, miR-92, prognostic evaluation, pulmonary ultrasound score

Haiyan Hong and Binbin Fu contributed equally to this work.

1 | INTRODUCTION

Neonatal acute respiratory distress syndrome (ARDS) is a respiratory disease caused by primary or secondary reduction of alveolar surfactant, with rapid progression and high mortality that seriously threatens the life of newborns. ARDS is a respiratory critical disease that seriously threatens the life of newborns. Its main manifestations are hypoxemia of varying degrees, diffuse decreased light transmittance, inflammatory exudation, and decreased lung compliance. The incidence of ARDS in China can be as high as 11%, and the mortality is about 20%. In 2017, neonatal ARDS was separated from adult ARDS and child ARDS for the first time in the world, and a separate diagnostic criterion (Montreux diagnostic criterion) was developed. The diagnostic criterion emphasizes the pathogenic factors of lung injury of neonatal ARDS. At present, there is still a lack of specific treatment for neonatal ARDS. In clinical practice, respiratory support, PS replacement therapy, extracorporeal pulmonary oxygenation, nutritional support, and fluid management are the main treatment methods for neonatal ARDS. MicroRNA (miRNA), as a new class of gene regulatory molecules, can regulate inflammatory pathways and immune responses by affecting the expression of target genes[1–10] and play an important role in the pathogenesis of respiratory distress syndrome.[11] Recent studies reported that miR-92 and miR-122 are expressed in inflammatory lung diseases, participating in multiple signaling pathways and various immune inflammatory reactions, and play an important regulatory role in the occurrence and development of respiratory distress syndrome.[12,13] The Lung Ultrasound Score (LUS) can evaluate the changes in lung ventilation to determine the severity and prognosis of ARDS[14]; however, the mechanism of action and prognostic value of miR-92 and miR-122 in children with ARDS have not been clarified. This study evaluated the prognostic value of the combination of the expression of serum miR-92 and miR-122 and LUS score in children with ARDS to provide a reference for the treatment of children with ARDS.

2 | MATERIALS AND METHODS

2.1 | Research subjects

Children with ARDS admitted to our hospital from January 2018 to October 2019 were included in this study if they met the following criteria: (1) diagnosed according to the Montreux definition of neonatal ARDS (2017 edition),[15] (2) chest X-ray showed diffuse shadows in both lungs with pulmonary edema and echocardiography showed (no left atrial hypertension), and (3) the duration of mechanical ventilation in the intensive care unit was ≥72 h for acute onset. The exclusion criteria were: (1) the presence of primary alveolar surfactant deficiency, hereditary congenital heart disease, congenital metabolic disorders, and congenital malformation of lung and chest wall, (2) ARDS occurred after admission, and (3) they were unwilling to participate in the study. This study was approved by the hospital ethics committee, and the children's families provided informed consent.

2.2 | Research methods

This prospective study involved children diagnosed with neonatal ARDS who were discharged from hospital after recovery ($n = 77$) or died ($n = 31$). The X-ray images were graded as follows: grade I – the brightness of the two lung fields decreased significantly, with uniformly scattered fine particles and reticular shadows; grade II –in addition to grade I, there were signs of bronchial inflation extending to the outer lung field; grade III –the lesions were aggravated, with decreased brightness of the lung field and blurred heart margin and diaphragmatic surface; grade IV –the whole lung field was white, with more obvious bronchial air signs like the branches of bald leaves. The cases were classified according to disease severity: mild (grade I and II, $n = 69$) and severe (grade III and IV, $n = 39$). Sonography was used for lung ultrasound examination of all children and the LUS score was recorded. The LUS score ranged from 0 to 36, and the higher the score, the more serious the disease. Venous blood (5 ml) was collected on the day of diagnosis and the serum was separated by centrifugation for analysis of the expression of miR-92 and miR-122 by real-time PCR as previously described.[16]

2.3 | Statistical methods

SPSS20.0 statistical software was used for analysis. All continuous variables were tested for normality, and normally distributed data were expressed as mean ± standard deviation (x±S), and t-tests were used for comparison between groups. The $\chi 2$ test was used to compare the data groups. The value of serum miR-92 and miR-122 expression levels and LUS score in predicting the death of ARDS children was analyzed by drawing ROC curves, with Pearson correlations applied for correlation analysis. A p-value < 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Clinicopathological patient characteristics

This study involved 108 neonatal ARDS patients (68 males and 40 females), with a gestational age of 34–39 weeks (average gestational age =37.20 ± 1.15 weeks). There were no significant differences in gender, gestational age, birth weight, etiology, maternal age, twin, cesarean section, or abnormal amniotic fluid between the patients who died and those who survived (Table 1).

3.2 | Detection of miR-92, miR-122, and LUS score

The expression of serum miR-92 and miR-122 and the LUS score in the patients who died were significantly higher than in the patients who survived (Figure 1). Also, these indicators were significantly higher in the severe group than in the mild group (Figure 2).

TABLE 1 Comparison of baseline clinical data between survival group and death group in ARDS children

Parameters	Survival group (n = 77)	Death group (n = 31)	p
Gender [male, example (%)]	46(59.7)	22(71.0)	0.274
Gestational age (weeks)	37.30 ± 1.20	37.15 ± 1.08	0.647
Birth weight (g)	2842 ± 204	2837 ± 210	0.582
Etiology [cases (%)]			
Choking	30(38.9)	14(45.2)	0.716
Meconium aspiration syndrome	21(27.3)	9(29.0)	
Pneumonia	15(19.5)	6(19.4)	
Sepsis	11(14.3)	2(6.4)	
Age of mother (age)	29.40 ± 4.15	29.82 ± 4.60	0.372
Twin twins [cases (%)]	4(5.2)	3(9.7)	0.392
Cesarean section [cases (%)]	48(62.3)	20(64.5)	0.832
Abnormal amniotic fluid [cases (%)]	7(9.1)	4(12.9)	0.553

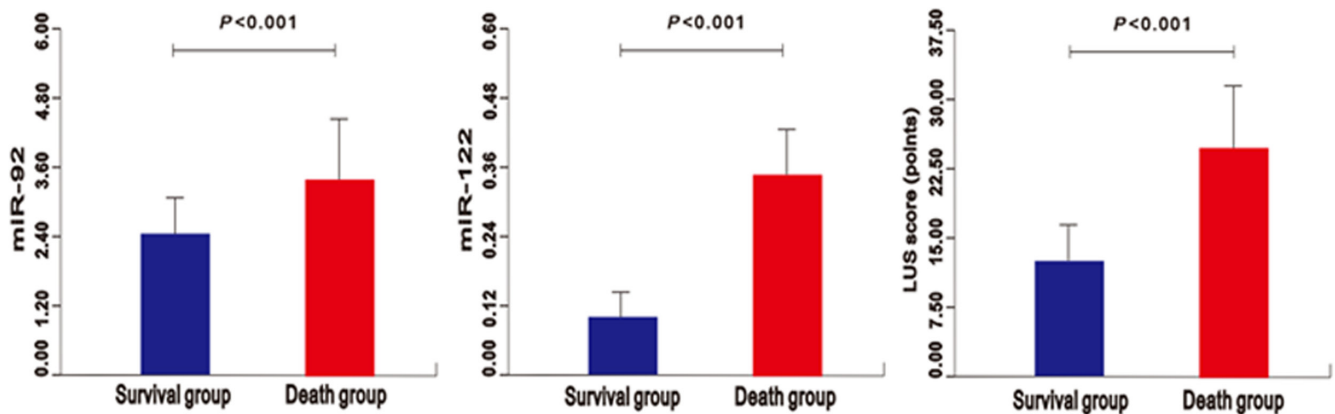Abbreviation: ARDS, acute respiratory distress syndrome.

FIGURE 1 Expression levels of miR-92, miR-122, and LUS in both death group and survival group. LUS, lung ultrasound score
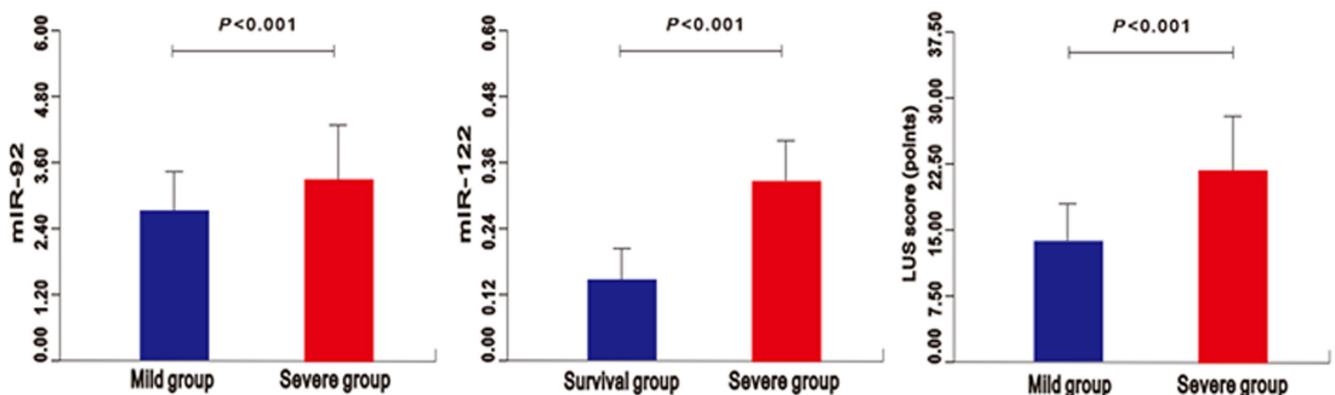

FIGURE 2 Expression levels of miR-92, miR-122, and LUS in both mild group and severe group. LUS, lung ultrasound score

3.3 | Predictive value of serum miR-92 and miR-122 and LUS score

The optimal cut-off values of serum miR-92 and miR-122 expression levels and LUS score in predicting death in children with ARDS were 2.93, 0.21, and 16.30 points, respectively. The AUC (95% CI) of the combination in predicting death in children with ARDS was 0.920 (0.860–0.977), which was significantly higher than miR-92 (0.794 [0.740–0.856]), miR-122 (0.840 [0.782–0.897]), and LUS score (0.783 [0.724–0.841]) alone. The difference was statistically significant ($p < 0.05$), and the sensitivity and specificity were 92.0% and 87.0%, respectively (Figure 3).

3.4 | Correlation analysis

Pearson correlation analysis showed that serum miR-92 and miR-122 expression positively correlated with LUS score in the patients who died ($r = 0.775$, $p < 0.01$ and $r = 0.802$, $p < 0.01$, respectively) (Figure 4).

4 | DISCUSSION

Acute respiratory distress syndrome is the most common critical neonatal disease, and its main clinical manifestations are varying degrees of hypoxemia, diffuse decreased light transmittance of both lungs, inflammatory exudation, and decreased lung compliance. It is an important cause of neonatal respiratory failure and death. At present, the treatment of children with ARDS is based on symptomatic and comprehensive treatment such as respiratory support, pulmonary surfactant replacement, extracorporeal membrane oxygenation, nutritional support, and fluid management. However, neonatal ARDS is difficult to treat and still has a high mortality rate; therefore,

a timely and accurate prognosis of ARDS children is important for the targeted treatment to improve their outcomes.

There is accumulating evidence that miRNA, a class of small non-coding RNAs, participate in the post-transcriptional regulation of target genes through miRNA shearing and protein translation inhibition, thereby playing an important role in cell differentiation, proliferation, apoptosis, angiogenesis, and the inflammatory immune response.[17,18] MiRNA is involved in the occurrence and development of ARDS, regulating the inflammatory response and apoptosis, thus is a potential novel biomarker and therapeutic target for ARDS.[19]

Lung ultrasound score is a method based on ultrasound signs, which can not only better display the lung apex and focal lesions in the lung, but also further evaluate the severity of the lung injury; therefore, it is important for predicting the ARDS prognosis and guiding clinical treatment.[20] At present, most studies are based on the clinical application of miRNA in adult ARDS, while there are no relevant studies on the prognostic value of miR-92 and miR-122 in children with ARDS.

As far as we know, this is the first study which investigates serum miR-92 and miR-122 and LUS score in neonatal ARDS. This study showed that the expression of serum miR-92 and miR-122 and LUS score in neonates who died were significantly higher than in those that survived. Furthermore, the expression of serum miR-92 and miR-122 and LUS score in the severe disease group were significantly higher than those in the mild disease group. These results indicate that the high expression levels of serum miR-92 and miR-122 and LUS score are related to disease severity in children with ARDS. Children with ARDS with a high expression of miR-92 and miR-122 have a poor prognosis and a higher risk of death. It has been suggested that serum miRNA expression level is significantly increased in children with ARDS, which is closely related to the severity and prognosis of ARDS in children.[21] To further explore the prognostic value of miR-92 and miR-122 in children with ARDS, ROC curve analysis was performed showing that the optimal cut-off values of serum miR-92 and miR-122 expression and LUS score to predict the death of ARDS children were 2.93, 0.21, and 16.30 points, respectively. The area under the curve of miR-92 and miR-122 combined with the LUS score to predict the death of ARDS children was the largest, with good sensitivity and specificity. In addition, the expression of serum miR-92 and miR-122 in this group
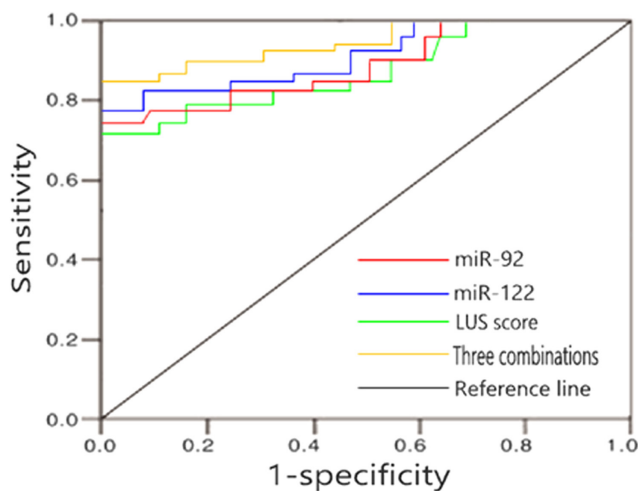

FIGURE 3 ROC curve for predicting sensitivity and specificity by the combination of three methods in ALI patients. ROC, receiver operator characteristic
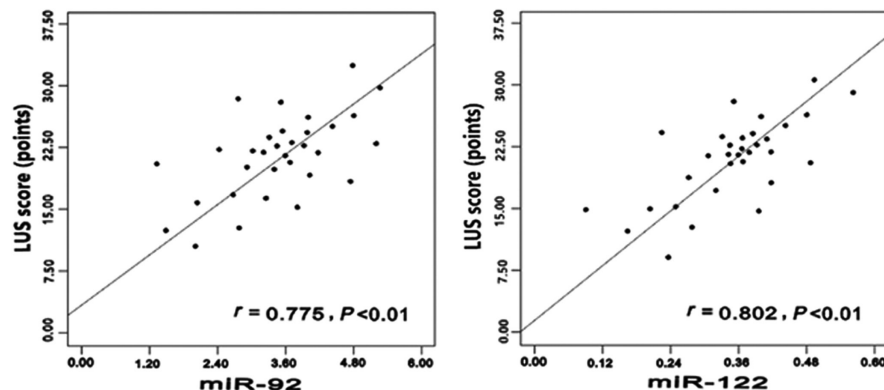

FIGURE 4 Correlation of serum miR-92 and miR-122 levels with LUS. LUS, lung ultrasound score

positively correlated with the LUS score, further demonstrating that the combination of the three measures was of value in predicting the prognosis of ARDS children. Bioinformatics is an emerging discipline that emerged with the launch of the Human Genome Project (HGP), which integrates mathematics, computer science, and biology to elucidate the biological significance of various types of data. Currently, bioinformatics plays a pivotal role in the development of medicine.[22-25] In the future study, we would like to explore the current topic in bioinformatics.

5 | CONCLUSION

In conclusion, the increased expression of serum miR-92 and miR-122 correlated with the severity and prognosis of ARDS children, with the combination of LUS score and miR-92 and miR-122 expression levels of value in predicting the prognosis of ARDS children.

AUTHOR CONTRIBUTION
Renyuan Wang conceived study design; Renyuan Wang conceived the content concept; Haiyan Hong and Binbin Fu performed the data collection and extraction and analyzed the data. Haiyan Hong interpreted and reviewed the data and drafts. Renyuan Wang reviewed the final draft. All authors were involved in literature search, writing the paper, and had final approval of the submitted and published versions.

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT
All data generated or analyzed during this study are included in this published article.

ORCID
Renyuan Wang https://orcid.org/0000-0001-6192-167X

REFERENCES
1. Guo C, Yao Y, Li Q, Gao Y, Cao H. Expression and clinical value of miR-185 and miR-424 in patients with acute ischemic stroke. *Int J Gen Med*. 2022;15:71-78.
2. Lin L, Lu B, Yu J, Liu W, Zhou A. Serum miR-224 as a biomarker for detection of hepatocellular carcinoma at early stage. *Clin Res Hepatol Gastroenterol*. 2016;40(4):397-404.
3. Ning S, Liu H, Gao B. miR-155, miR-96 and miR-99a as potential diagnostic and prognostic tools for the clinical management of hepatocellular carcinoma. *Oncol Lett*. 2019;18(3):3381-3387.
4. Mamdouh S, Khorshed F, Aboushousha T. Evaluation of Mir-224, Mir-215 and Mir-143 as serum biomarkers for HCV associated hepatocellular carcinoma. *Asian Pac J Cancer Prev*. 2017;18(11):3167-3171.
5. Dai M, Li L, Qin X. Clinical value of miRNA-122 in the diagnosis and prognosis of various types of cancer. *Oncol Lett*. 2019;17(4):3919-3929.
6. Liao WW, Zhang C, Liu FR, Wang WJ. Effects of miR-155 on proliferation and apoptosis by regulating FoxO3a/BIM in liver cancer cell line HCCLM3. *Eur Rev Med Pharmacol Sci*. 2020;24(13):7196.
7. Sadri Nahand J, Bokharaei-Salim F, Salmaninejad A. microRNAs: key players in virus-associated hepatocellular carcinoma. *J Cell Physiol*. 2019;234(8):12188-12225.
8. Weis A, Marquart L, Calvopina DA. Serum MicroRNAs as biomarkers in hepatitis C: preliminary evidence of a MicroRNA panel for the diagnosis of hepatocellular carcinoma. *Int J Mol Sci*. 2019;20(4):864.
9. Liu X, Duan B, Dong Y. MicroRNA-139-3p indicates a poor prognosis of colon cancer. *Int J Clin Exp Pathol*. 2014;7(11):8046-8052.
10. Feng Y, Dong YW, Song YN. MicroRNA449a is a potential predictor of colitisassociated colorectal cancer progression. *Oncol Rep*. 2018;40(3):1684-1694.
11. Wang Q, Feng Q, Zhang Y, Zhou S, Chen H. Decreased microRNA 103 and microRNA 107 predict increased risks of acute respiratory distress syndrome and 28-day mortality in sepsis patients. *Medicine (Baltimore)*. 2020;99(25):e20729.
12. Fu L, Zhu P, Qi S, Li C, Zhao K. MicroRNA-92a antagonism attenuates lipopolysaccharide (LPS)-induced pulmonary inflammation and injury in mice through suppressing the PTEN/AKT/NF-kappaB signaling pathway. *Biomed Pharmacother*. 2018;107:703-711.
13. Rahmel T, Rump K, Adamzik M, Peters J, Frey UH. Increased circulating microRNA-122 is associated with mortality and acute liver injury in the acute respiratory distress syndrome. *BMC Anesthesiol*. 2018;18(1):75.
14. Lv W, Wang S, Wang L. G994T polymorphism in exon 9 of plasma platelet-activating factor acetylhydrolase gene and lung ultrasound score as prognostic markers in evaluating the outcome of acute respiratory distress syndrome. *Exp Ther Med*. 2019;17(4):3174-3180.
15. De Luca D, van Kaam AH, Tingay DG. The Montreux definition of neonatal ARDS: biological and clinical background behind the description of a new entity. *Lancet Respir Med*. 2017;5(8):657-666.
16. Chen X, Su X, Lin M. Expression of miR-192-5p in colon cancer serum and its relationship with clinicopathologic features. *Am J Transl Res*. 2021;13(8):9371-9376.
17. Chen X, Yang T, Wang W. Circular RNAs in immune responses and immune diseases. *Theranostics*. 2019;9(2):588-607.
18. Dua K, Chellappan DK, Singhvi G. Targeting microRNAs using nanotechnology in pulmonary diseases. *Panminerva Med*. 2018;60(4):230-231.
19. Zheng Y, Liu SQ, Sun Q. Plasma microRNAs levels are different between pulmonary and extrapulmonary ARDS patients: a clinical observational study. *Ann Intensive Care*. 2018;8(1):23.
20. See KC, Ong V, Tan YL, Sahagun J, Taculod J. Chest radiography versus lung ultrasound for identification of acute respiratory distress syndrome: a retrospective observational study. *Crit Care*. 2018;22(1):203.
21. Zhang FY, Yang N, Rao YF. Profiling of miRNAs in neonatal cloned bovines with collapsed lungs and respiratory distress. *Reprod Domest Anim*. 2018;53(2):550-555.
22. Xie J, Li H, Chen L. A novel pyroptosis-related lncRNA signature for predicting the prognosis of skin cutaneous melanoma. *Int J Gen Med*. 2021;14:6517-6527.
23. Qiu Y, Li H, Xie J, Qiao X, Wu J. Identification of ABCC5 among ATP-binding cassette transporter family as a new biomarker for

hepatocellular carcinoma based on bioinformatics analysis. *Int J Gen Med*. 2021;14:7235-7246.

24. Qiu Y, Li H, Zhang Q, Qiao X, Wu J. Ferroptosis-related long non-coding RNAs as prognostic marker for colon adenocarcinoma. *Appl Bionics Biomech*. 2022;2022:5220368.

25. Xie J, Chen L, Sun Q. An immune subtype-related prognostic signature of hepatocellular carcinoma based on single-cell sequencing analysis. *Aging (Albany NY)*. 2022;14(7):3276-3292.