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miR-221-3p, arterial blood gas, and lung ultrasound: a multimodal approach for predicting neonatal respiratory distress syndrome outcomes

Meixin Liang[1†], Tao Pan[2†], Yanan Hou[3], Zhihua Liu[3], Zhiqiang Liu[3], Jing Mo[4], Yang Zhang[3*] and Jinfeng Wen[5*]

Abstract

Background Neonatal respiratory distress syndrome (NRDS) is one of the critical illnesses causing early death in infants due to alveolar surface-active substance deficiency, and the prognosis may show varying degrees of sequelae. Some miRNAs are valuable in the prognosis of NRDS infants. The objective of this research was to assess the predictive value of combining the three factors on the prognosis of NRDS infants by analyzing miR-221-3p levels, arterial blood gas analysis parameters and lung ultrasound (LUS) scores in NRDS infants with good and poor prognosis.

Methods Serum miR-221-3p levels were measured by qRT-PCR. Effect of miR-221-3p expression in prognosis of NRDS infants using Kaplan-Meier curve and COX analyses. Arterial blood gas parameters were analyzed, as well as LUS score was recorded for NRDS infants. Role of miR-221-3p combined with arterial blood gas parameters and LUS score in prognosis of NRDS infants was assessed by ROC curves. Pearson correlation was applied to assess the association of miR-221-3p with arterial blood gas analysis parameters and LUS score.

Results Serum miR-221-3p was notably greater in NRDS infants than in healthy newborns. High miR-221-3p level was related to poor prognosis for NRDS infants. pH and PaO_2 were lower and $PaCO_2$ was higher in arterial blood gas analysis parameters in poor prognosis. Furthermore, LUS score was greater on poor prognosis as opposed to good prognosis. miR-221-3p combined with arterial blood gas parameters and LUS score has a high accuracy in predicting prognosis in NRDS infants. Moreover, miR-221-3p was associated negatively with pH and PaO_2 and positively with $PaCO_2$ and LUS score.

Conclusions Elevated miR-221-3p may be related to poor survival outcomes in NRDS infants. miR-221-3p in combination with arterial blood gas parameters and LUS score has a high accuracy in determining the survival outcome of NRDS infants and may be a useful tool for clinical NRDS prognosis.

†Meixin Liang and Tao Pan are joint first author.

*Correspondence:
Yang Zhang
Zhangyangslchos@163.com
Jinfeng Wen
Wenjinfenghg@163.com

Full list of author information is available at the end of the article

Keywords miR-221-3p, NRDS, Arterial blood gas analysis, LUS score, Prognosis

Background

Neonatal respiratory distress syndrome (NRDS), otherwise called neonatal pulmonary hyaline membrane disease, is a disease attributed to alveolar atrophy due to structural immaturity of the lungs and insufficient production of lung surface-active substances [1]. The primary clinical symptoms are dyspnea, shortness of breath, cyanosis, nasal instigation, and even respiratory failure in severe cases, endangering the lives of infants [2]. Especially in preterm infants, the occurrence of NRDS is higher and the disease progresses more rapidly, which is one of the major factors of death in preterm infants, as well as an acute and critical condition in neonatology [3]. Therefore, early detection and therapy of NRDS is critical to neonatal lives.

The determination of diagnosis and post-treatment observation of NRDS in current clinical work is based on clinical manifestations, blood gas analysis, X-ray and lung ultrasound (LUS) score [4, 5]. Infants are primarily managed clinically with pulmonary surface-active substances and ventilation support, but the prognosis of some infants with standardized treatment is still poor and death occurs [6, 7]. Hence, we considered searching for effective prognostic factors for NRDS infants at the molecular level, to enhance resuscitation success rate and to improve prognosis.

Abnormal expression of microRNAs (miRNAs) under different pathological conditions is an essential indicator of disease progression and prognosis [8]. The function of MiRNAs in the diagnosis and prognosis concerning respiratory distress continues to be discovered [9]. Previous work identified abnormal miR-221-3p expression for lung disease, with upregulated expression in acute pulmonary embolism combined with pulmonary hypertension, non-small cell lung cancer, and lung adenocarcinoma [10–12]. Notably, miR-221-3p was identified in blood exosomes from patients with acute respiratory distress syndrome that exhibited an upregulation trend [13]. Nonetheless, the value of miR-221-3p on NRDS remains unexplored.

Accordingly, the research question we posed was what role does miR-221-3p combined with arterial blood gas analysis and LUS score play in NRDS? The aim of the research was to evaluate prognostic value of combining the three elements on NRDS infants by analyzing the relationship of miR-221-3p expression level with arterial blood gas parameters and LUS score in infants with good and poor prognosis. We analyzed the variability and correlation of miR-221-3p levels, arterial blood gas parameter levels and LUS score in NRDS infants with different prognostic outcomes. Moreover, the prognostic value of miR-221-3p combined with arterial blood gas parameters and LUS score for NRDS infants was investigated. In order to contribute to the prognostic assessment of NRDS infants in the clinic.

Methods

General information collection of research objects

The study was endorsed by the Ethics Committee of Shengli Oilfield Central Hospital and guardians of neonates voluntarily signed an informed consent.

Sample size calculations based on G-power 3.1.9.7, the necessary sample size of each group was estimated to be more than 88 in the case of an alpha error probability of 0.05 and p power (1-beta) of 0.95. Therefore, a total of 122 infants with NRDS hospitalized in Shengli Oilfield Central Hospital from 2018 to 2023 and 99 healthy infants born during the same period were admitted to this research using a case-control study method. The diagnosis of NRDS is essentially in accordance with clinical symptoms and imaging phenomena, which are manifested by a respiratory rate of > 60 breaths/min, dyspnea, tachypnoea, cyanosis, intercostal or subcostal or suprasternal retraction, bronchial congestion, and frothy mouth. Additionally, chest X-ray findings revealed typical manifestations such as decreased transparency of both lungs, blurring of the cardiac and diaphragmatic margins, ground-glass changes, bronchial gas signs, and white lungs. The inclusion criteria for NRDS infants were that all parameters were premature infants with a gestational age of 28–37 weeks, the children met the diagnostic criteria for NRDS, and the clinical history was complete. Exclusion criteria were primary alveolar surface-active substance deficiency, diseases such as congenital heart failure, dyspnea with infectious pneumonia or diaphragmatic hernia. Inclusion criteria for the healthy group were neonates with a gestational age of 28–37 weeks, no other postnatal infections, and exclusion of confounding factors such as congenital developmental anomalies, inherited metabolic and chromosomal disorders.

General information about the subjects of the study was gathered, including gender, gestational age, birth weight, height and delivery mode.

Arterial blood gas analysis

After delivery of the neonate and cutting of the umbilical cord, 2 mL of umbilical artery blood was withdrawn by syringe under aseptic conditions, and the tip of the needle was sealed with a rubber stopper and sent for examination immediately. Neonatal umbilical artery blood gases were measured by a fully automated blood gas analyzer (Werfen, USA) for Pondus Hydrogenii (pH), partial

pressure of arterial oxygen (PaO_2) and partial pressure of arterial carbon dioxide ($PaCO_2$). The measuring period is controlled within 30 min to ensure that the samples are not exposed to air for too long or mixed with air to cause errors.

Pulmonary ultrasonography

LUS was performed in infants within 6 h after birth. In the supine, lateral or prone position, each side of lung was classified as 6 regions: anterior superior, anterior inferior, supra-axillary, sub-axillary, posterior superior and posterior inferior by connecting the parasternal, anterior axillary, posterior axillary, posterior median, and biparietal nipple lines. From top to bottom and from left to right, ultrasound was performed and registered in the 12 regions of both lungs. The scoring methodology is referenced from previous studies, with each region scoring 4 points on a scale of 0–48, with higher scores representing more severe conditions [14, 15].

RNA extraction and qRT-PCR

Venous blood was obtained in neonates within 3 h of delivery, and serum was gained by low-temperature centrifugation. Total RNA was acquired from serum by TRIzol reagent (Invitrogen, USA). RNA concentrations and OD260/280 were established by NanoDrop 2000 (Invitrogen, USA) with DEPC water (Invitrogen, USA) as a control. Extracted RNA was reverse transcribed to cDNA using PrimeScript RT Reagent Kit (TaKaRa, Japan). The qRT-PCR reaction was undertaken following the instructions of the SYBR Green I Master Mix kit (Invitrogen, USA). The relative miR-221-3p level is estimated based on U6 as an internal reference gene.

Prognostic record

The NRDS infants enrolled in the study were categorized as good and poor prognosis groups according to their recovery after 28 days of treatment. In good prognosis group, infants had stable vital signs, significantly lower or totally resolved respiratory disturbances, and essentially normal chest radiographs. In poor prognosis group, the neonates had unstable vital signs, required mechanical ventilation support, suffered from serious complications such as patent ductus arteriosus, pulmonary hypertension, intracranial hemorrhage, or even die, or had family members who requested treatment to be abandoned.

Table 1 General information on neonates included in the study

Parameters	Healthy ($n=99$)	NRDS ($n=122$)	*P* value
Gender (male/female)	54/45	68/54	0.588
Gestational age (weeks)	32.82 ± 1.64	32.13 ± 1.92	0.068
Birth weight (g)	1903.43 ± 303.81	1841.30 ± 341.67	0.159
Birth height(cm)	45.73 ± 2.75	44.45 ± 2.94	0.065
Delivery mode (eutocia/Cesarean section)	59/40	63/59	0.239
pH	7.37 ± 0.20	7.19 ± 0.23	< 0.001
PaO_2 (mmHg)	74.25 ± 6.15	51.19 ± 5.90	< 0.001
$PaCO_2$ (mmHg)	40.17 ± 2.87	49.66 ± 5.22	< 0.001
LUS score	23.95 ± 2.95	38.28 ± 3.08	< 0.001

Notes: NRDS, neonatal respiratory distress syndrome, pH, Pondus Hydrogenii; LUS, Lung ultrasound. All data were presented as mean ± standard deviation or n

Statistical analysis

Data were characterized using SPSS 27.0 and GraphPad Prism 9. Normally distributed data were reported as mean ± standard deviation (SD), and independent samples t-test were used for comparisons between groups. The impact of miR-221-3p expression on prognosis to NRDS infants using Kaplan-Meier curve and COX analyses. The predictive value of miR-221-3p combined with arterial blood gas parameters and LUS score for mortality in NRDS children was assessed by plotting ROC curves. Correlation analysis was applied using Pearson analysis. $P<0.05$ was set as a level of significance test.

Results

Clinical features of newborns

This study included 122 NRDS and 99 healthy infants, and their general information was shown in Table 1. The healthy infants included 54 males and 45 females, with a gestational age of 32.82 ± 1.64 weeks, a birth weight of 1903.43 ± 303.81 g, 59 eutocia and 40 caesarean section. There were 68 males and 54 females among the NRDS infants with gestational age of 32.13 ± 1.92 weeks, birth weight of 1841.30 ± 341.67 g, 63 eutocia and 59 caesarean section. The analysis demonstrated that NRDS did not differ markedly from healthy infants in gender, gestational age, birth weight, height, and delivery mode ($P>0.05$). Compared with healthy infants, NRDS infants had significantly lower pH and PaO_2, and higher $PaCO_2$ and LUS score ($P<0.001$).

Effect of miR-221-3p on the prognosis of NRDS infants

Serum miR-221-3p levels were markedly raised in NRDS infants compared to healthy ($P<0.001$, Fig. 1A). All neonates entered the research were categorized into high and low expression groups depending on the median miR-221-3p value, and the Kaplan-Meier curve suggested that miR-221-3p high expression group had a poor prognosis (Fig. 1B). Multivariate Cox analysis revealed miR-221-3p was markedly linked to prognosis of NRDS infants ($P=0.015$), besides pH and LUS score were also related to the prognosis ($P=0.049$, $P=0.029$, Table 2).

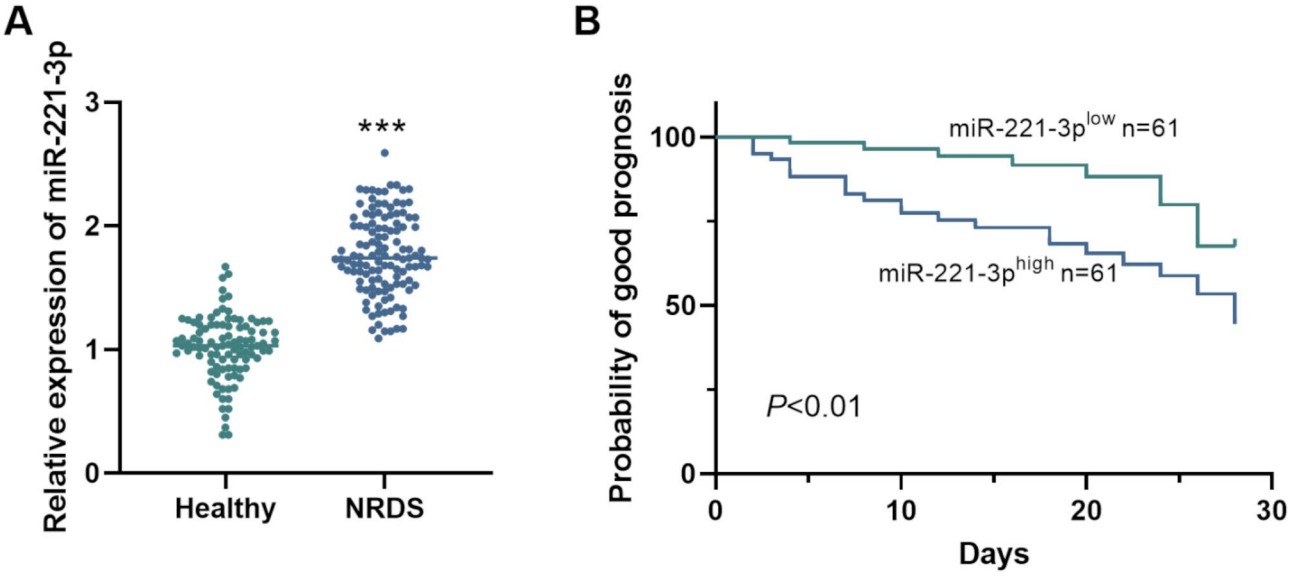

Fig. 1 Impact of miR-221-3p on the prognosis of NRDS infants. (**A**) miR-221-3p expression in healthy and NRDS infants. (**B**) Impact of miR-221-3p differential expression on prognosis of NRDS infants. ***$P < 0.001$

Table 2 Multivariate Cox analysis of detection factors and prognosis of NRDS infants

Factors	HR	95%CI	*P*
miR-221-3p	4.835	1.353–17.278	0.015
pH	0.281	0.080–0.994	0.049
PaO_2 (mmHg)	0.586	0.179–1.920	0.378
$PaCO_2$ (mmHg)	1.414	0.424–4.714	0.572
LUS score	3.917	1.152–13.322	0.029

Notes: HR, Hazard ratio; 95%CI, 95% Confidence interval; pH, Pondus Hydrogenii; LUS, Lung ultrasound

Detection of miR-221-3p, pH, PaO_2, $PaCO_2$ and LUS score for prognosis in NRDS infants

Serum miR-221-3p levels were checked in NRDS infants in the good and poor prognosis groups, and miR-221-3p was markedly overexpressed in poor prognosis compared with the good prognosis ($P < 0.001$, Fig. 2A). Arterial blood gas parameters analysis demonstrated lower pH and PaO_2 levels in poor prognosis group, and the discrepancy was notable ($P < 0.001$, Fig. 2B and C). In contrast, $PaCO_2$ was considerably higher in poor prognosis group ($P < 0.001$, Fig. 2D). The lung 12-region LUS score was performed on the NRDS neonates and revealed that the total score was considerably greater in poor prognosis as compared to good prognosis ($P < 0.001$, Fig. 2E).

Predictive value of miR-221-3p combined pH, PaO_2, $PaCO_2$, and LUS score

ROC analysis was employed to evaluate the prognostic value of miR-221-3p combined with arterial blood gas parameters and LUS score in NRDS infants. The ROC curve result revealed that miR-221-3p predicted survival in NRDS infants with an AUC of 0.866. The AUC in arterial blood gas parameters pH, PaO_2 and $PaCO_2$ to forecast survival in NRDS infants were 0.835, 0.832 and 0.839, respectively. The AUC for LUS score to predict survival in NRDS infants was 0.848. In addition, the combined analysis suggested that miR-221-3p in combination with each arterial blood gas parameter and LUS score showed a greater value in predicting survival outcomes in NRDS infants, with an AUC of 0.987 (Fig. 3; Table 3).

Correlation of miR-221-3p with pH, PaO_2, $PaCO_2$ and LUS score

Pearson correlation analysis was adopted to explore the relationship between miR-221-3p levels and arterial blood gas parameters and LUS score in NRDS infants. The findings revealed that miR-221-3p levels exhibited a negative link to pH and PaO_2 (Fig. 4A and B). Conversely, there was a positive effect between miR-221-3p levels and $PaCO_2$ and LUS score (Fig. 4C and D).

Discussion

NRDS is a condition of progressive dyspnea and respiratory failure that occurs soon after delivery, and its pathogenesis is mainly related to insufficient neonatal lung surface-active substances [16]. The disease is most severe 24 to 48 h after the birth of a neonate and has a high mortality rate [17]. The NRDS care pathway develops slowly, and those who can survive neonates for more than 3 days have increased lung maturity and may gradually recover [18]. However, many infants suffer from complications of lung infections, which re-exacerbate the condition and may lead to death in severe cases. Therefore, it is essential to develop an accurate prognosis for NRDS infants and

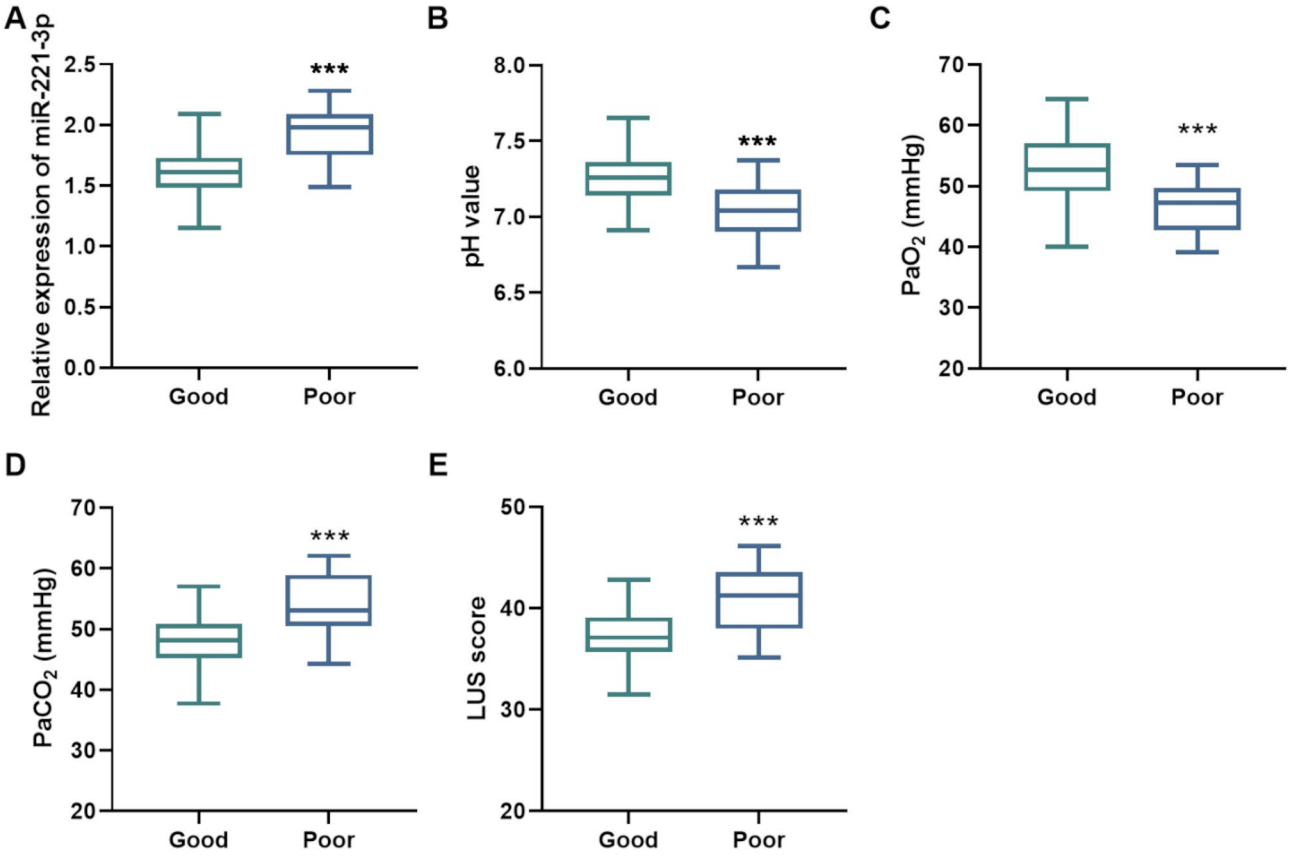

Fig. 2 Comparison of test indicators between the good and poor prognosis groups. (**A**) miR-221-3p expression in different prognosis groups. (**B**) pH in different prognosis groups. (**C**) PaO_2 in different prognosis groups. (**D**) $PaCO_2$ in different prognosis groups. (**E**) LUS score in different prognosis groups. ***$P < 0.001$

to provide effective treatment in a timely and targeted manner.

Research on miRNAs in disease has been a hot point of interest recently. Several studies have identified the value of miRNAs in the diagnosis and prognosis of NRDS. For example, miR-338-3p is correlated with the severity of NRDS and is a biomarker for diagnosing NRDS infants [19]. miR-375 is associated with adverse survival outcomes in NRDS [20]. miR-221-3p is engaged in multiple lung diseases and tumors modulation [21, 22]. Furthermore, in vivo study indicated that miR-221-3p is highly expressed and exerts a regulatory function of NRDS [23]. The results of this experiment revealed that miR-221-3p level in NRDS infants was greater compared to healthy infants, as well as the miR-221-3p level was notably raise of the infants of poor prognosis group, which was in line with the previous related reports [13]. Clinical detection of NRDS infants is currently done by arterial blood gas analysis and X-rays. However, NRDS has similarities with wet lungs and aspiration pneumonia and requires careful judgement by doctors from a variety of sources [24]. miR-221-3p may accurately and rapidly identify NRDS infants at the molecular level, contributing to improved diagnostic efficiency.

Arterial blood gas analysis is a confident indicator of the presence of an imbalance in the acid-base balance of the organism, as well as hypoxia and the degree of hypoxia, and it is the most tested method for the diagnosis of NRDS [25]. Study indicates that blood gas analysis can identify neonates at high risk for NRDS early and provide better and more accurate care for them [26]. The lower pH, PaO_2 or higher $PaCO_2$ levels imply a greater risk of asphyxia in the infant [27]. In our research, pH, PaO_2 level were lower and $PaCO_2$ level was higher remarkably in poor prognosis group. This suggested that there is a correlation between lower pH, PaO_2 or higher $PaCO_2$ levels in arterial blood gas analysis parameters and poorer survival outcomes in NRDS infants.

With the development of ultrasound technology, LUS has been widely applied in neonatal intensive care units due to its advantages of being bedside, radiation-free, and capable of dynamic multiple assessments [28]. Recently, some domestic and international studies have found that the LUS score has a predictive value in the prognostic evaluation of NRDS infants. For example, Szymanski et

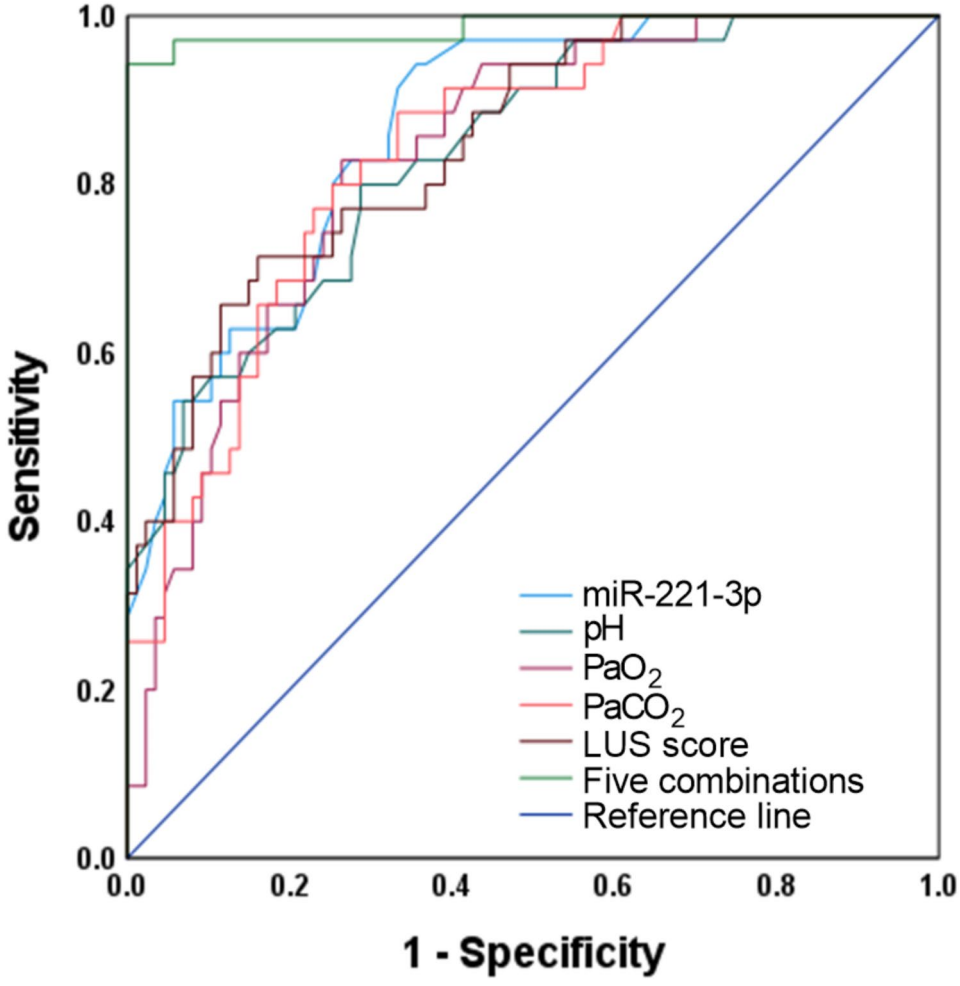

Fig. 3 ROC curve of miR-221-3p combined with arterial blood gas parameters and LUS score for forecasting survival outcomes in NRDS infants

Table 3 ROC curve analysis of miR-221-3p level combined with arterial blood gas analysis and LUS score to evaluate the prognosis of NRDS infants

Factors	AUC	95%CI	Sensitivity	Specificity	*P*
miR-221-3p	0.866	0.801–0.931	0.800	0.759	< 0.001
pH	0.835	0.759–0.912	0.743	0.701	< 0.001
PaO_2 (mmHg)	0.832	0.758–0.906	0.800	0.736	< 0.001
$PaCO_2$ (mmHg)	0.839	0.767–0.912	0.800	0.736	< 0.001
LUS score	0.848	0.776–0.921	0.714	0.839	< 0.001
Combinations	0.987	0.963-1.000	0.943	0.977	< 0.001

Notes: AUC, area under curve; 95%CI, 95% Confidence interval; pH, Pondus Hydrogenii; LUS, Lung ultrasound

al. discovered that a modified LUS score predicted ventilation requirements in NRDS infants [29]. In addition, it has been reported that higher LUS scores represent a worse prognosis for NRDS infants [30]. The LUS score of poor prognosis group was significantly lower than that of good prognosis group in the study, confirming the conjecture that LUS score is associated with prognosis in NRDS infants.

In addition, arterial blood gas parameters combined with LUS score to forecast survival outcomes of patients with lung disease have been reported [31]. However, miR-221-3p combined with arterial blood gas parameters and LUS score to predict survival outcomes in NRDS infants has rarely been reported. To examine the accuracy of miR-221-3p with arterial blood gas parameters and LUS score for forecasting survival outcomes in NRDS infants, we performed a ROC analysis. The results showed that miR-221-3p combined with arterial blood gas analysis parameters and LUS score had a high AUC compared to single indicators. This suggested that this combined analysis had greater accuracy in predicting survival outcomes in NRDS infants.

To further discuss the association of high miR-221-3p expression with survival outcomes in NRDS infants. We performed a correlation study of miR-221-3p with arterial blood gas analysis parameters and LUS score. As expected, there was a negative correlation between miR-221-3p level and pH and PaO_2, and a positive correlation with $PaCO_2$ and LUS score. This indicated that

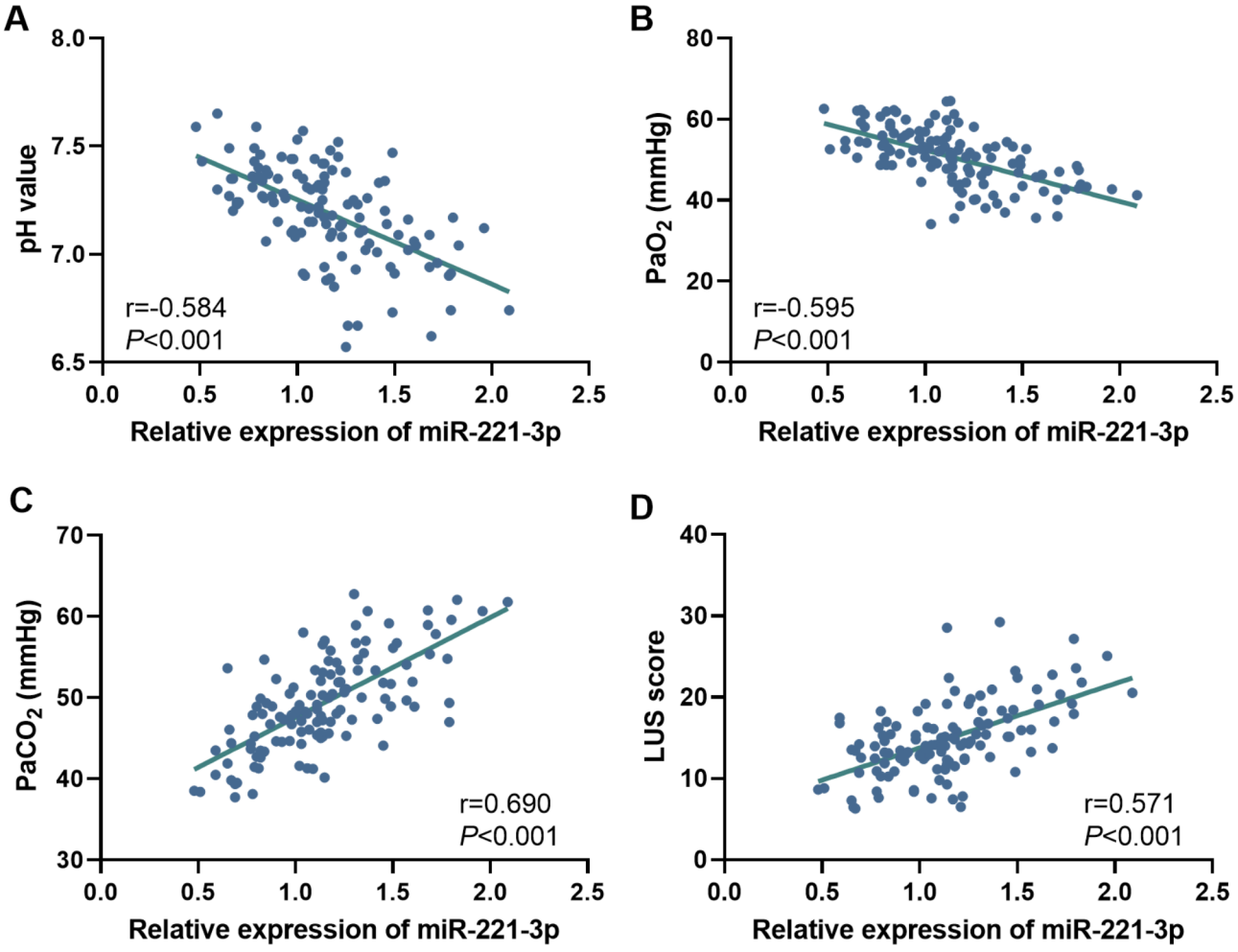

Fig. 4 Correlation of miR-221-3p levels with arterial blood gas parameters and LUS score in NRDS infants. (**A-C)** Correlation of miR-221-3p levels with arterial blood gas parameters of pH, PaO_2 or $PaCO_2$. (**D)** Correlation of miR-221-3p levels with LUS score

miR-221-3p has a potential to predict survival outcomes in NRDS infants and may serve as a biomarker for NRDS prognosis.

We made efforts for possible bias in the study. Firstly, the research objects were allocated by randomization to ensure that the two groups were similar in general information. Secondly, we established standardized operating procedures to ensure that all operations during the study followed uniform standards and to reduce inter-operator variation. Thirdly, strict procedures for collecting, recording, and storing were established to ensure the accuracy and completeness of the data. Finally, at the data analysis stage, appropriate statistical methods were used to reduce bias.

Even though, there are still some limitations of this research. We only investigated the prognostic value of miR-221-3p in combination with arterial blood gas analysis and LUS score in NRDS, without exploring its specific mechanism in NRDS. Besides, the number of subjects included in our research was small, and their numbers and characteristics may affect the results. Therefore, we will continue to expand the sample size and deeply investigate the mechanism of miR-221-3p in NRDS to explore its functional role.

Conclusions

In this study, we focused on discussing the ability of serum miR-221-3p combined with arterial blood gas analysis parameters and LUS score in NRDS. Taken together, upregulated miR-221-3p predicted poorer survival outcomes in NRDS infants, suggesting that miR-221-3p may be a prognostic marker for NRDS. Furthermore, miR-221-3p combined with arterial blood gas parameters and LUS score had high accuracy in predicting survival outcomes in NRDS infants and may be a useful tool for clinical NRDS prognosis.

Abbreviations

NRDS	Neonatal respiratory distress syndrome
miRNAs	MicroRNAs
SD	Standard deviation

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None.

Author contributions
Yanan Hou, Zhihua Liu, Zhiqiang Liu, Meixin Liang, Tao Pan, Jinfeng Wen and Jing Mo made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, and draft of the manuscript. Yang Zhang, Meixin Liang, Tao Pan and Jinfeng Wen revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was endorsed by the Ethics Committee of Shengli Oilfield Central Hospital and guardians of neonates voluntarily signed an informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Ultrasonography Medicine, Qinzhou Maternal and Child Health Care Hospital, Qinzhou, Guangxi, China
[2]Department of Ultrasound, Seventh Medical Center of Chinese PLA General Hospital, Beijing 100700, China
[3]Shengli Oilfield Central Hospital, Paediatric Ward 1, No.31, Jinan Road, Dongying District, Dongying 257000, Shandong, China
[4]Outpatient Department, Shengli Oilfield Central Hospital, Dongying, Shandong, China
[5]Department of Ultrasound Medicine, Huanggang Central Hospital, No.126, Qi'an Avenue, Huanggang City 438000, Hubei Province, China

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