


# Predictive Value of Lung Ultrasound Scores Combined with Serum ANGPTL4 Levels on Severity and Prognosis of Neonatal Respiratory Distress Syndrome

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**Objective:** Respiratory distress syndrome threatens neonates' life. This study probed the predictive value of lung ultrasound scores combined with serum angiopoietin-like protein 4 (ANGPTL4) levels on neonatal respiratory distress syndrome (NRDS) severity and prognosis.

**Methods:** The NRDS group (n = 115) and control group (n = 30) were established. In both groups, lung ultrasound scores and serum ANGPTL4 levels, lung ultrasound scores and serum ANGPTL4 levels of newborns with NRDS of different severity, the risk factors affecting the poor prognosis of NRDS neonates, and the value of serum ANGPTL4 levels combined with lung ultrasound scores in determining the severity and prognosis of newborns with NRDS were analyzed.

**Results:** The NRDS groups had higher lung ultrasound scores and serum ANGPTL4 levels, and lower Apgar scores than the control group; lung ultrasound scores and serum ANGPTL4 levels were higher in the moderate and severe groups than in the mild group, and those were higher in the severe group than in the moderate group (all  $p < 0.05$ ). The logistic regression analysis showed that high lung ultrasound scores, and high serum ANGPTL4 levels were risk factors for NRDS poor prognosis ( $OR > 1, p < 0.05$ ), and high Apgar scores are the protective factor for poor prognosis in NRDS neonates ( $OR < 1, p < 0.05$ ). The area under the curve of lung ultrasound scores combined with serum ANGPTL4 levels to assess the severity and prognosis of NRDS neonates exhibited a higher assessed value than the single test.

**Conclusion:** Lung ultrasound scores and serum ANGPTL4 levels are closely related to the severity and prognosis of NRDS neonates, and the combination of the two improves the assessed value of the severity and prognosis of NRDS neonates. The study provided a reference for the disease severity assessment of NRDS and the prediction of its prognosis.

**Keywords:** neonatal respiratory distress syndrome, lung ultrasound scores, angiopoietin-like protein 4, severity, prognosis

## Introduction

Respiratory distress syndrome is regarded as the most common respiratory disease in premature infants. The pathogenesis of neonatal respiratory distress syndrome (NRDS) is based on the rapid formation of the oxygen-reactive species, surpassing the detoxification capacity of the anti-oxidative defense system.<sup>1</sup> NRDS, a disorder unique to newborn infants, results from deficient pulmonary surfactant, which is usually ready to be activated around the perinatal period.<sup>2</sup> Pulmonary surfactant is a lipoprotein complex lining the surface of alveoli that reduce surface tension and promotes inspiration.<sup>3</sup> However, the proportion of term newborns with morbidity due to lack of surfactant may vary according to a number of factors, including genetic, environmental, and maternal conditions. Large-scale prospective studies with

detailed clinical data collection and statistical analysis are needed to obtain accurate incidence rates. Based on current medical knowledge and clinical experience, it is known that term newborns who do not produce surfactant constitute a certain percentage of patients with NRDS. In one study, the results display a prevalence of NRDS of 47.5% in the 703 neonates studied.<sup>4</sup> NRDS develops most often within the first few hours of life, and most commonly in the immediate postpartum period. Respiratory distress syndrome mainly affects preterm newborns and, less frequently, term infants, and its incidence is inversely proportional to the infant's gestational age, with smaller and more preterm newborns being more severely affected.<sup>5</sup> In order to gain a more comprehensive understanding of the differences and commonalities in NRDS among neonates of different gestational ages, the neonates included in this study included both preterm and term infants. NRDS is a frequent reason for neonatal mortality particularly in preterm infants,<sup>6</sup> therefore, early identification of risk factors for the development of NRDS and early treatment of its causes is a major challenge.

Lung ultrasound, a radiological method, enables the diagnosis of respiratory distress syndrome in premature neonates.<sup>7</sup> As a promising method, lung ultrasound is easily carried out, inexpensive, non-ionizing and repeatable and can be conducted at the bedside. More and more evidence has been reported that lung ultrasound may be a reliable diagnostic tool for NRDS.<sup>8</sup> Lung ultrasound might be implemented as an initial screening tool, which can accurately diagnose and reliably differentiate transient tachypnea of newborn infants and respiratory distress syndrome in preterm neonates.<sup>9</sup> It has been described in a previous study that lung ultrasound scores possess utility in the early stages of NRDS. Moreover, lung ultrasound scores are considered as a useful, bedside, noninvasive tool that can monitor the respiratory status.<sup>10</sup> However, lung ultrasound alone may not be sufficient to fully assess the severity and prognosis of NRDS, so it is particularly important to explore the combined use of other biomarkers. In this area, angiotensin-like protein 4 (ANGPTL4) has gradually attracted attention. ANGPTL4, first discovered in 2000,<sup>11</sup> is a crucial factor in the modulation of lipid and glucose metabolism in metabolic disorders.<sup>12</sup> ANGPTL4 belongs to the angiotensin-like protein family and can mediate the suppression of lipoprotein lipase activity. Emerging evidence has demonstrated that ANGPTL4 possesses pleiotropic functions with pro- and anti-inflammatory properties.<sup>13</sup> In a previous study, it is demonstrated that ANGPTL4 deficiency can increase respiration.<sup>14</sup> It is also reported that ANGPTL4 is involved in acute respiratory distress syndrome (ARDS).<sup>15</sup> However, the combined role of lung ultrasound scores and serum ANGPTL4 levels in NRDS has not been explored. Consequently, this research was aimed at investigating the predictive value of lung ultrasound scores combined with serum ANGPTL4 expression levels on the severity and prognosis of NRDS, and providing a reference for the disease severity assessment of NRDS and the prediction of its prognosis.

## Materials and Methods

### Ethics Statement

This research was under the approval of the Ethics Committee of Shenyang Fourth People's Hospital. All informants supplied written informed consent before participation. The study complied with the Declaration of Helsinki.

### Study Subjects

This was a retrospective cohort study. A total of 115 neonates with respiratory distress syndrome admitted to Second People's Hospital of Changzhou Affiliated to Nanjing Medical University from March 2020 to March 2023 were selected. Inclusion criteria: (1) NRDS children met the diagnostic criteria for respiratory distress syndrome;<sup>16</sup> (2) NRDS children's families signed the written informed consent; (3) NRDS children without serious extrapulmonary infections; (4) those with complete medical records. Exclusion criteria: (1) NRDS children with congenital diseases or genetic defects such as diaphragmatic hernia, surfactant, or pulmonary adenomatoid malformation; (2) those combined with hematopoietic or immune system damage or malignant tumors; (3) those combined with damage to other organs such as the kidneys, heart, and liver; (4) those with contraindications to ultrasonography; and (5) those with incomplete clinical information. Another 30 cases of healthy newborns in the same period were selected as the control group. According to "Montreux definition of neonatal acute respiratory distress syndrome (ARDS)" and oxygenation index (OI) at the time of the neonate's first mechanical ventilation, the neonates were divided into the mild group (OI:  $4 \sim < 8$ ;  $n =$

46), the moderate group (OI:  $8 \sim < 16$ ;  $n = 38$ ), and the severe group (OI:  $\geq 16$ ;  $n = 31$ ), with OI = inhaled oxygen concentration  $\times$  mean airway pressure  $\times$  100/partial pressure of oxygen.

## Lung Ultrasound

Upon admission, the neonates were subjected to lung ultrasound evaluation by two trained physicians. A portable diagnostic color Doppler ultrasound machine was selected for lung ultrasound evaluation, and a phased array convex probe was utilized. After frequency adjustment, the lungs were scanned on both sides in the supine position of the neonates, with a total of 12 lung regions. Lung ultrasound was scored as follows:<sup>17</sup> score 0: normal lung ventilation area and lung sliding sign with A lines or 1 separate B line; score 1: moderate lung ventilation reduction area and multiple and typical B lines; score 2: severe lung ventilation reduction area and multiple fused B lines; score 3: lung consolidation area and typical air bronchogram. The most severe manifestation of each region was selected for scoring, and the sum of the scores of each component was the total score.

## Detection of Serum ANGPTL4 Levels

A total of 3 mL of fasting venous blood was drawn from all newborns in the early morning of the next day of hospitalization, and the supernatant was centrifuged. Then the serum was separated, and ANGPTL4 levels in the serum were tested by enzyme-linked immunosorbent assay (ELISA). The kit was purchased from Wuhan Elabscience Biotechnology Co., Ltd. (Wuhan, China).

## Clinical Data Collection

Based on the information from the neonatal electronic medical record system, the general data about all neonates were collected, including gender, day old, birth weight, cesarean section or not, preterm or not, duration of mechanical ventilation, OI, Apgar scores, lung ultrasound scores, and serum ANGPTL4 levels.

## Prognosis

All children received mechanical ventilation and respiratory support, nutritional support and fluid management. Survival was tracked at discharge from the neonatal intensive care unit. Newborns with NRDS were categorized into the survival group ( $n = 79$ ) and the death group ( $n = 36$ ) according to clinical outcomes at discharge. Neonates in the survival group were those who were discharged from the hospital with stable vital signs after treatment, with obviously reduced or disappeared respiratory symptoms and signs, and essentially normal chest radiographs, and were taken off ventilator support and oxygen therapy. The death group included newborns who did not respond well to treatment, had unstable vital signs, were unable to be weaned off oxygen or ventilator support, and had severe complications; in some cases, the families of these newborns requested to discontinue treatment and discharge them from the hospital due to economic constraints or poor prognosis, while in others, the newborns exhibited disappeared vital signs and were declared clinically dead.

## Outcomes

The primary outcome of this study was to analyze the value of lung ultrasound score and serum ANGPTL4 level in predicting the severity of disease and prognosis of children with NRDS by adopting the receiver-operating characteristic (ROC) curve, and to analyze the factors affecting the prognosis of children with NRDS by the logistic regression. The secondary outcome was to compare the lung ultrasound scores, serum ANGPTL4 levels, and the correlation between lung ultrasound scores, serum ANGPTL4 levels and the oxygen index among children with NRDS of different severity and different prognosis.

## Statistics

SPSS 24.0 software (IBM Corp, Armonk, N.Y., USA) and GraphPad Prism 6.01 software (GraphPad Inc., La Jolla, CA, USA) were employed for data analysis. Measurement data were depicted as mean  $\pm$  standard deviation, and the *t*-test or ANOVA (analysis of variance) was utilized for comparisons among groups. Enumeration data were expressed as rates

(%) and the  $\chi^2$  test was implemented for comparisons among groups. Correlation analysis was performed using the Pearson test. Multivariate logistic regression was employed to analyze the factors affecting the prognosis of children with NRDS. The value of lung ultrasound scores and serum ANGPTL4 levels in predicting the severity and prognosis of NRDS was analyzed utilizing the ROC curve.  $p < 0.05$  indicated a statistically significant difference.

## Results

### Lung Ultrasound Scores and Serum ANGPTL4 Levels in the Groups with Different Severity

Comparison of lung ultrasound scores, serum ANGPTL4 levels and Apgar scores between the control and NRDS group displayed that lung ultrasound scores ( $p < 0.001$ ) and serum ANGPTL4 levels ( $p < 0.001$ ) were elevated and Apgar scores ( $p < 0.001$ ) were decreased in the NRDS group neonates compared to the control group (Table 1). Then the lung ultrasound scores and serum ANGPTL4 levels were analyzed among the NRDS newborns with different severity, and the results uncovered that the lung ultrasound scores ( $p < 0.001$ ,  $p < 0.001$ ) and serum ANGPTL4 levels ( $p = 0.002$ ,  $p < 0.001$ ) were elevated in the moderate and severe groups compared to in the mild group; lung ultrasound scores ( $p = 0.028$ ) and serum ANGPTL4 levels ( $p = 0.001$ ) were elevated in the severe group compared to in the moderate group (Table 2). The results unearthed that compared with healthy newborns, NRDS possessed higher lung ultrasound scores and serum ANGPTL4 expression levels, and the more severe the NRDS was, the higher the lung ultrasound scores and the serum ANGPTL4 expression levels were.

### Correlation of Lung Ultrasound Scores and Serum ANGPTL4 Levels with OI

Pearson's correlation coefficient analysis unearthed that lung ultrasound scores and serum ANGPTL4 levels of NRDS were positively correlated with OI ( $r = 0.660$ ,  $r = 0.618$ ,  $p < 0.001$ ) (Figure 1). These results revealed that higher lung ultrasound scores and serum ANGPTL4 levels of NRDS reflected higher OI and severe NRDS.

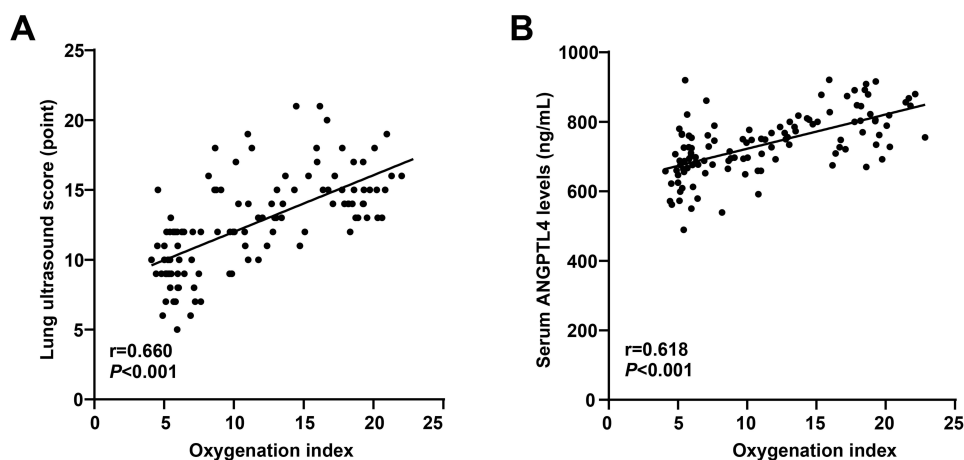
**Table 1** Clinical Data Between the Control Group and the NRDS Group

Items	Control Group (n = 30)	NRDS Group (n = 115)	$\chi^2/t$ value	p value
Gender			0.561	0.454
Male	19 (63.33%)	81 (70.43%)		
Female	11 (36.67%)	34 (29.57%)		
Day old (days)	9.13 ± 1.04	9.60 ± 1.94	1.270	0.206
Birth weight (kg)	2.62 ± 0.24	2.46 ± 0.43	1.937	0.055
Cesarean section			0.307	0.580
Yes	15 (50.00%)	64 (55.65%)		
No	15 (50.00%)	51 (44.35%)		
Preterm			0.274	0.601
Yes	17 (56.67%)	59 (51.30%)		
No	13 (43.33%)	56 (48.70%)		
Apgar scores (scores)	9.23 ± 0.77	8.21 ± 1.19	4.475	< 0.001
Lung ultrasound scores (scores)	4.27 ± 0.78	12.53 ± 3.43	13.068	< 0.001
Serum ANGPTL4 (ng/mL)	90.53 ± 9.77	735.52 ± 89.03	39.518	< 0.001

**Table 2** Lung Ultrasound Scores and Serum ANGPTL4 Levels in Groups with Different Condition

Items	Mild Group (n = 46)	Moderate Group (n = 38)	Severe Group (n = 31)	F value	p value
Lung ultrasound scores (scores)	9.59 ± 2.15	13.87 ± 2.84*	15.26 ± 2.16*#	60.493	< 0.001
Serum ANGPTL4 (ng/mL)	686.65 ± 82.38	741.16 ± 73.09*	801.13 ± 72.12*#	20.774	< 0.001

Note: \* $p < 0.05$  vs the mild group; #  $p < 0.05$  vs the moderate group.



**Figure 1** Correlation of lung ultrasound scores and serum ANGPTL4 levels with OI in NRDS children. **(A)** Correlation between lung ultrasound scores and OI in NRDS children (n = 115); **(B)** Correlation between serum ANGPTL4 levels and OI in NRDS children (n = 115).

## Lung Ultrasound Scores Combined with Serum ANGPTL4 Levels Predict the Severity of NRDS

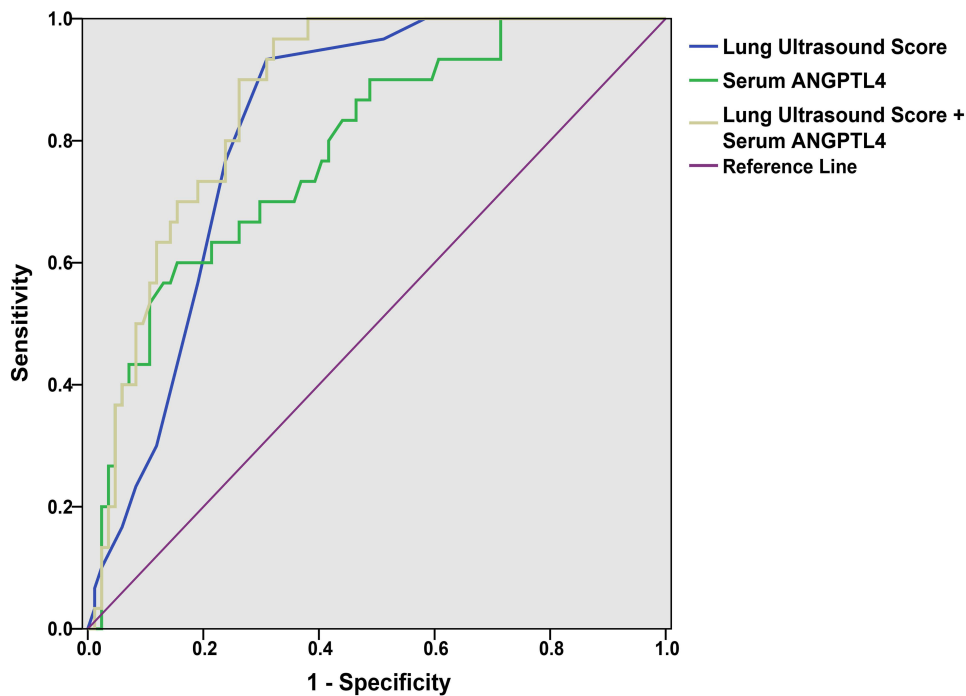
The predictive value of lung ultrasound scores and serum ANGPTL4 levels in mild, moderate and severe NRDS was analyzed by the ROC curve. The results unearthed that lung ultrasound scores predicted the severity of NRDS with an area under the curve (AUC) of 0.823, and when the Youden index was 0.623, the sensitivity was 93.3%, and the specificity was 69.0%; serum ANGPTL4 levels predicted the severity of NRDS with an AUC of 0.785, and when the Youden index was 0.445, the sensitivity was 60.0% and the specificity was 84.5%. The AUC predicted by lung ultrasound scores combined with serum ANGPTL4 levels was higher versus that predicted alone, which was 0.870, and when the Youden index was 0.646, the sensitivity was 96.7% and the specificity was 67.9% (Table 3 and Figure 2). These results indicated that lung ultrasound scores in combination with serum ANGPTL4 levels possessed a good predictive value for the severity of NRDS.

## Univariate Analysis for the Factors Affecting the Prognosis of NRDS

The mechanical ventilation time, OI, lung ultrasound scores, and serum ANGPTL4 levels were higher and the Apgar scores were lower in the death group versus those in the survival group (all  $p < 0.001$ ). While the differences were not statistically significant when comparing the gender, day age, birth weight cesarean section or not, and preterm or not in the two groups (all  $p > 0.05$ ) (Table 4). The results unraveled that the mechanical ventilation time, OI, Apgar scores, lung ultrasound scores, and serum ANGPTL4 levels were linked to the prognosis of NRDS.

**Table 3** Lung Ultrasound Scores Combined with Serum ANGPTL4 Levels Predict NRDS Severity

Variants	AUC	Asymptotic 95% Confidence Interval		Standard Error	Progressive Sig.	Sensitivity (%)	Specificity (%)	Youden Index
		Lower Limit	Upper Limit					
Lung ultrasound scores	0.823	0.748	0.898	0.038	0.000	93.3	69.0	0.623
Serum ANGPTL4	0.785	0.693	0.878	0.047	0.000	60.0	84.5	0.445
The two combination	0.870	0.806	0.933	0.032	0.000	96.7	67.9	0.646



**Figure 2** ROC curves of lung ultrasound scores combined with serum ANGPTL4 levels for assessing disease severity in newborns with NRDS.

### Multivariable Analysis for the Factors Affecting the Prognosis of NRDS

A logistic regression model was established with prognosis (survival = 0, death = 1) as the dependent variable and the mechanical ventilation time, OI, Apgar scores, lung ultrasound scores, and serum ANGPTL4 levels as the independent variables. The results revealed that high lung ultrasound scores (OR, 1.717; 95% CI, 1.034–2.852,  $p = 0.037$ ) and high serum ANGPTL4 levels (OR, 1.026; 95% CI, 1.006–1.047,  $p = 0.010$ ) were risk factors for poor prognosis of NRDS, and high Apgar scores (OR, 0.039; 95% CI, 0.004–0.392,  $p = 0.006$ ) were the protective factor against poor prognosis in NRDS neonates. The results indicated that lower Apgar scores, higher lung ultrasound scores and serum ANGPTL4 levels reflected a worse prognosis of NRDS (Table 5).

**Table 4** Univariate Analysis for the Factors Affecting the Prognosis of NRDS

Items	Survival Group (n = 79)	Death Group (n = 36)	$\chi^2/t$ value	$p$ value
Gender			0.025	0.875
Male	56 (70.89%)	25 (69.44%)		
Female	23 (29.11%)	11 (30.56%)		
Day old (days)	9.57 ± 1.87	9.67 ± 2.11	0.248	0.805
Birth weight (kg)	2.49 ± 0.42	2.39 ± 0.45	1.147	0.250
Cesarean section			0.153	0.696
Yes	43 (54.43%)	21 (58.33%)		
No	36 (45.57%)	15 (41.67%)		
Preterm			0.379	0.538
Yes	39 (49.37%)	20 (55.56%)		
No	40 (50.63%)	16 (44.44%)		
Mechanical ventilation time (days)	7.30 ± 0.98	8.94 ± 1.09	8.032	< 0.001
OI	9.08 ± 4.63	16.20 ± 4.23	7.850	< 0.001
Apgar scores (scores)	8.73 ± 0.87	7.06 ± 0.95	9.287	< 0.001
Lung ultrasound scores (scores)	11.08 ± 2.89	15.72 ± 2.13	8.637	< 0.001
Serum ANGPTL4 (ng/mL)	705.42 ± 77.44	801.58 ± 76.93	6.188	< 0.001

**Table 5** Multivariate Analysis for the Factors Affecting the Prognosis of NRDS

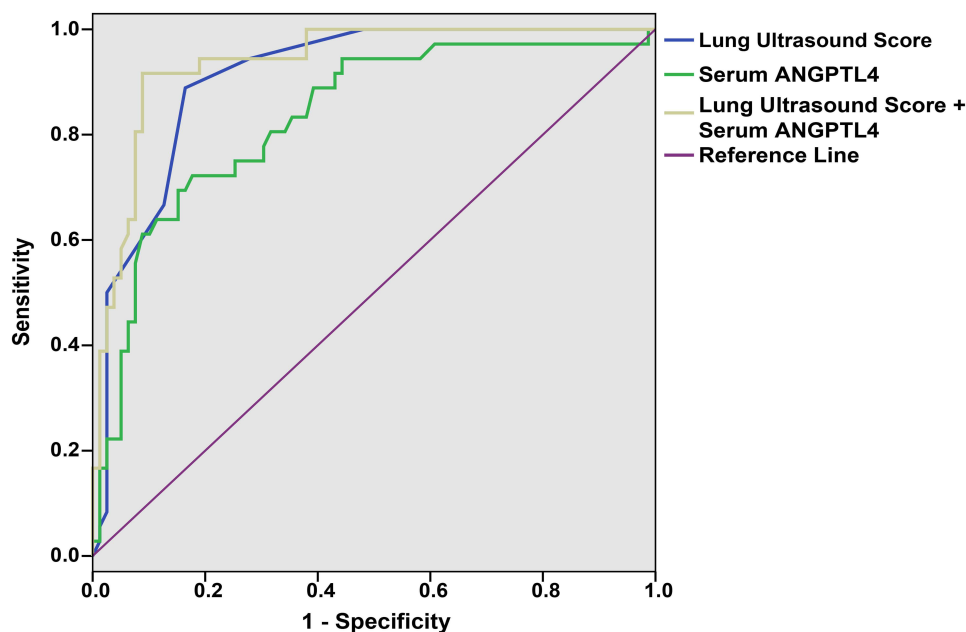
Items	$\beta$	SE	Wald $\chi^2$	p value	OR value	95% CI
Mechanical ventilation time	1.139	0.686	2.759	0.097	3.125	0.815–11.989
OI	0.098	0.118	0.690	0.406	1.103	0.875–1.390
Apgar scores	-3.247	1.179	7.590	0.006	0.039	0.004–0.392
Lung ultrasound scores	0.540	0.259	4.357	0.037	1.717	1.034–2.852
Serum ANGPTL4	0.026	0.010	6.703	0.010	1.026	1.006–1.047

**Table 6** Lung Ultrasound Scores Combined with Serum ANGPTL4 Levels Predict NRDS Prognosis

Variants	AUC	Asymptotic 95% Confidence Interval		Standard Error	Progressive Sig.	Sensitivity (%)	Specificity (%)	Youden Index
		Lower Limit	Upper Limit					
Lung ultrasound scores	0.910	0.857	0.963	0.027	0.000	88.9	83.5	0.724
Serum ANGPTL4	0.832	0.751	0.914	0.042	0.000	72.2	82.3	0.545
The two combination	0.938	0.895	0.981	0.022	0.000	91.7	91.1	0.828

## Lung Ultrasound Scores Combined with Serum ANGPTL4 Levels Predict NRDS Prognosis

The predictive value of lung ultrasound scores and serum ANGPTL4 levels in NRDS prognosis was analyzed by the ROC curve. The results unraveled that lung ultrasound scores predicted the prognosis of NRDS with an AUC of 0.910, and when the Youden index was 0.724, the sensitivity was 88.9%, and the specificity was 83.5%; serum ANGPTL4 levels predicted the prognosis of NRDS with an AUC of 0.832, and when the Youden index was 0.545, the sensitivity was 72.2% and the specificity was 82.3%. The AUC predicted by lung ultrasound scores combined with serum ANGPTL4 levels was higher versus that predicted alone, which was 0.938, and when the Youden index was 0.828, the sensitivity was 91.7% and the specificity was 91.1%. These results demonstrated that lung ultrasound scores combined with serum ANGPTL4 levels had a good predictive value for the prognosis of NRDS (Table 6 and Figure 3).

**Figure 3** ROC curves of lung ultrasound scores combined with serum ANGPTL4 levels for assessing prognosis in newborns with NRDS.



## Discussion

Respiratory distress is a prevalent problem in newborn infants,<sup>18</sup> which results in significant morbidity and mortality.<sup>19</sup> This study focused on the predictive value of lung ultrasound scores combined with serum ANGPTL4 levels in the severity and prognosis of NRDS.

In this study, while exploring lung ultrasound scores and serum ANGPTL4 levels in different severity groups, it was found that lung ultrasound scores and serum ANGPTL4 levels were elevated, and Apgar scores were decreased in neonates in the NRDS group as compared to the control group. Among the different severity groups, lung ultrasound scores and serum ANGPTL4 levels were raised in the moderate and severe groups when comparing the mild group, and those were elevated in the severe group when comparing the moderate group. This suggested that lung ultrasound scores and serum ANGPTL4 levels were higher in NRDS compared to healthy neonates, and the more severe the NRDS, the higher the lung ultrasound scores and serum ANGPTL4 levels. Additionally, the results of this study also unveiled that lung ultrasound score and serum ANGPTL4 levels in NRDS were positively correlated with OI.

Lung ultrasonography is a practical, cost-effective, and simple method of diagnosing respiratory distress syndrome in neonates. As previously reported, lung ultrasonography has become a crucial tool in the diagnosis and follow-up of lung diseases in the newborn period. Lung diseases such as transient neonatal dyspnea and respiratory distress syndrome can be diagnosed by lung ultrasonography.<sup>20</sup> Lung ultrasound appears to be a very promising method for the future clinical management of newborns in both acute and chronic phases of pulmonary pathology associated with prematurity.<sup>21</sup> ANGPTL4 is a hypoxia-induced gene. It is reported that ANGPTL4 is highly expressed in most lung cancer cell lines than in normal cell lines.<sup>22</sup> As previously reported, ANGPTL4 might act as a novel prognostic biomarker in ARDS. Moreover, ANGPTL4 levels are elevated in ARDS patients and linked to disease severity and mortality.<sup>15</sup> Furthermore, higher concentrations of ANGPTL4 are correlated with higher proportions of ARDS.<sup>23</sup> Median lung ultrasound scores in the surfactant group are higher than those in the no surfactant group. Early high lung ultrasound scores correlate with surfactant necessity in preterm infants with respiratory distress at birth.<sup>24</sup> Lung ultrasound and lung ultrasound scores are highly reliable and efficient in newborns with NRDS. It has been found that lung ultrasound scores are gradually increased ranging from non-NRDS, mild-NRDS, to severe-NRDS groups.<sup>25</sup> This was consistent with our results. We also observed in this study that lung ultrasound scores combined with serum ANGPTL4 levels could predict the severity of NRDS, and the combination of the two had a higher predictive value for the severity of NRDS than a single test.

A previous study has reported that there is a significant correlation between lung ultrasound scores and the ratio of oxygen saturation to inspired oxygen throughout the admission.<sup>10</sup> Emerging evidence indicated that the oxidative stress linked to the physio-pathology of NRDS is especially associated with oxygen supplementation, mechanical ventilation, and inflammation/infection.<sup>1</sup> In our study, the findings disclosed that mechanical ventilation time, OI, Apgar scores, lung ultrasound scores, and serum ANGPTL4 expression levels were associated with the prognosis of NRDS. The early and right diagnosis is the key to improving respiratory distress syndrome prognosis. Ultrasound is accurate and reliable in the diagnosis and differential diagnosis of respiratory distress syndrome;<sup>26</sup> in acute respiratory distress syndrome, ANGPTL4 levels are elevated and obviously correlated with disease severity and mortality, and ANGPTL4 may be a novel prognostic biomarker for acute respiratory distress syndrome.<sup>15</sup> This study uncovered that high lung ultrasound scores and high serum ANGPTL4 levels were risk factors for poor prognosis of NRDS. Moreover, lower Apgar scores, higher lung ultrasound scores and serum ANGPTL4 levels reflected a poorer prognosis of NRDS. Meanwhile, the combination of lung ultrasound score and serum ANGPTL4 level could predict the prognosis of NRDS, and the combination of the two exhibited a higher predictive value for the prognosis of NRDS than a single test.

Previously, lung ultrasound scores have often been adopted alone to predict NRDS, such as in data showing that in preterm neonates affected by respiratory distress syndrome, the trajectory of respiratory distress syndrome is related to gestational age, markedly correlates with oxygenation status, and predicts bronchopulmonary dysplasia. In this population, lung ultrasound is a useful bedside noninvasive tool for monitoring respiratory status.<sup>10</sup> However, ANGPTL4 has been applied to predict NRDS in fewer studies. As reported previously, ANGPTL4 may be a novel prognostic biomarker for acute respiratory distress syndrome: serum ANGPTL4 is concerned with the severity of multiple organ dysfunction syndrome based on Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation II



(APACHE II) scores; compared with APACHE II scores or arterial pressure of oxygen/inspiratory fraction of oxygen ratios, serum ANGPTL4 is more predictive of 28-day acute respiratory distress syndrome-related mortality; serum ANGPTL4 is identified as an independent risk factor for mortality in a univariate Cox regression model.<sup>15</sup> In contrast with previous studies utilizing lung ultrasound scores alone to predict NRDS or serum ANGPTL4 to predict associated respiratory distress syndrome, this study combined the two for the first time and achieved better predictive results. This suggests that the combined use of multiple assessment tools can compensate for the shortcomings of a single method and improve the accuracy of prediction. Nevertheless, sample size calculation was not performed, which is a limitation of this study. In the future, the specific mechanism of ANGPTL4 in NRDS needs to be further ascertained to provide a deeper theoretical basis for treatment.

## Conclusion

To sum up, this study demonstrates that lung ultrasound score and serum ANGPTL4 level are closely related to NRDS, and lung ultrasound score combined with serum ANGPTL4 level can effectively predict the severity and prognosis of NRDS. This finding not only enriches the prediction of NRDS, but also provides clinicians with a more comprehensive and accurate assessment tool. The novelty of this study is that it is the first time to combine the lung ultrasound score with the serum ANGPTL4 level, which provides a new way of thinking for the early identification, disease monitoring and prognosis assessment of NRDS. The results of this study have important clinical significance: by combining lung ultrasound score and serum ANGPTL4 level, clinicians can identify children with high-risk NRDS earlier, so as to take more aggressive treatment measures and improve the prognosis of the children.

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## Disclosure

The authors declare no conflicts of interest directly related to the contents of this article.

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