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OXFORD

Feasibility of ultrasound in the diagnosis of neonatal respiratory distress syndrome in preterm infants

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ABSTRACT

Background: The aim of this study was to investigate the feasibility of lung ultrasound in the diagnosis of neonatal respiratory distress syndrome (NRDS) in preterm infants.

Methods: One hundred and nine preterm infants were prospectively recruited. Three ultrasound diagnostic criteria were developed to diagnose preterm infants with NRDS: (A) thickened or not smooth pleural line, part of the lung field shows diffuse 'B-line' sign or alveolar-interstitial syndrome (AIS); (B) thickened or not smooth pleural line, all lung fields show AIS, signifying the 'white lung' sign; (C) thickened or rough pleural line, 'white lung' sign and 'lung consolidation' sign can be observed in any lung field.

Results: The sensitivity and negative predictive value of NRDS in preterm infants with diagnostic criteria A were 100%, but the specificity and positive predictive value were 67.95 and 55.36%, respectively. The specificity and positive predictive value of diagnostic criteria B and C were 100%, while the 95% CI of diagnostic criteria B was narrower than diagnostic criteria C. The sensitivity and negative predictive value of diagnostic criteria B were higher than that of diagnostic criteria C. Of the 31 NRDS cases, 15 cases had severe NRDS and the other 16 did not have severe NRDS.

Conclusion: Thickened or rough pleural line with white lung sign is an important characteristic for the diagnosis of NRDS by lung ultrasound. White lung sign combined with the lung consolidation sign had high diagnostic efficacy when distinguishing severe NRDS from not severe NRDS.

KEYWORDS: preterm infants, NRDS, lung ultrasound, sensitivity, specificity, diagnosis

INTRODUCTION

With the annual increase in the birthrate and hospitalization rate of premature infants (gestational age of <37 weeks), neonatal respiratory distress syndrome (NRDS) has become a clinically high-risk respiratory disease, with an incidence of approximately 4.9% [1, 2]. The diagnostic criteria of NRDS mainly refer to the 2013 European NRDS Clinical Diagnostic Guidelines, that is, the blood gas analysis of newborns showing the air state partial pressure of oxygen (PaO_2) < 50 mmHg (<6.6 kPa); central purpura or oxygen uptake that can maintain PaO_2 > 50 mmHg (>6.6 kPa) with a typical chest X-ray (CXR) performance [3]. Thus, blood gas analysis and CXR are the main diagnostic criteria for NRDS diagnosis [4–6]. Given that normal lungs are filled with gas, ultrasonic waves that encounter this gas cause total reflection. Thus, the feasibility of lung ultrasound examination in NRDS has constantly been a research concern [7, 8]. With the development and maturity of ultrasound technology, lung ultrasound has been applied in the evaluation of the curative effects, especially in the field of intensive medicine. The examination of the preterm infants has been restricted due to

the low body temperature and body weight, and incubator feeding. The chest wall of newborns is thin; thus, it is highly suitable for the ultrasound examination of the lungs. Meanwhile, non-invasive, convenient and repeatable features inherent in ultrasound examination fully meet the needs of clinical examination in premature infants.

In this study, we mainly focused on the observation by lung ultrasound in premature infants with NRDS and its comparison with the existing clinical diagnostic criteria including clinical manifestations, blood gas analysis and CXR performance. The sensitivity and specificity of lung ultrasound imaging features in the diagnosis of NRDS in premature infants were evaluated. The consistency of lung ultrasound diagnostic indicators with existing clinical diagnostic indicators was also analyzed to assess the application of lung ultrasound in the diagnosis of NRDS in preterm infants. The efficacy of exogenous pulmonary surfactant (EPS), application of continuous positive airway pressure/conventional mechanical ventilation (CPAP/CMV) and the complications were also evaluated.

METHODS

Subjects

The data of premature infant patients from the neonatal intensive care unit (NICU) of our hospital from May 2021 to October 2021 were prospectively collected. All enrolled patients were premature infants with gestational ages of <37 weeks. Infants with combined hereditary diseases, congenital malformations or treated with EPS or CPAP/CMV after delivery were excluded. The infant patients underwent lung ultrasound evaluation immediately after delivery, and blood gas analysis and CXR examination were performed simultaneously.

The examination contents complied with the relevant medical ethical requirements, and the use of case data was subject to informed consent from the family. The study related to human use complied with all the relevant national regulations and institutional policies, was in accordance with the tenets of the Helsinki Declaration, and has been approved by the First Hospital of Tsinghua University institutional review board or equivalent committee. The study was approved by the Medical Ethics Committee of First Hospital of Tsinghua University.

Lung ultrasound examination

A GE LOGIQ S8 ultrasound system with a linear array ultrasound probe having a frequency of 9.0–14.0 MHz was used in this study. All patients underwent lung ultrasound examination immediately after admission (approximately 1.23 ± 0.75 h after delivery based on admission time). The patients were placed in a supine, lateral or prone position in a quiet state, with the anterior and posterior line axillaries as boundaries. The lungs were divided into the front, side and back regions. The examination was performed from the sternal line to the anterior line axillary, from the anterior line axillary to the posterior line axillary, and from the posterior line axillary to the paravertebral line. The scanning was performed sequentially from top to bottom, longitudinally (probe was perpendicular to the rib) and horizontally (probe was along the rib gap), ensuring that the entire scanning area was covered (Figure 1). All the ultrasound exams were performed by the same examiner.

Observation index

The pleural line denotes the echogenic reflection formed by the interface of the pleural–lung surface. A smooth, regular and clear linear high-level echo was observed under ultrasound. Under normal conditions, the thickness of the pleural line is ≤ 0.5 mm. The pleural line disappear, is rough and fuzzy, irregular or featured a thickness >0.5 mm, are considered abnormal [9]. The pleural line was monitored dynamically. The rising and falling movement relative to the chest wall with breathing movement is called 'lung sliding' [10]. The A-line shows the sonographic change in ultrasound generated in normal lung tissues. Sound waves pass through the pleura to produce a reverberation artifact (Figure 2A). They are expressed as a series of horizontally linear high-level echoes below the pleural line, with equal intervals. The spacing is equal to the distance between the skin and the pleural line, and the echo from the shallow-to-deep areas gradually weakens until disappearance (Figure 2B). B-line and comet-tail artifact are high-level linear echoes that originate in the pleural line and are perpendicular to the radial field and radiate deep into the lung field (Figure 2C). White lung was used to detect the diffuse dense alveolar-interstitial syndrome (AIS), which is characterized by pulmonary edema, in all lung fields (Figure 2D). Lung consolidation denotes the lung tissue with hepatization in the ultrasound examination accompanied by air or fluid bronchogram (Figure 2E).

Study design and grouping

This study sets three kinds of lung ultrasound criteria to diagnose premature infants with NRDS. Criteria A: At least one lung field of all six lung fields (frontal, lateral and posterior areas of the bilateral lungs) showed diffuse B-line changes or AIS symptoms, and an A-line

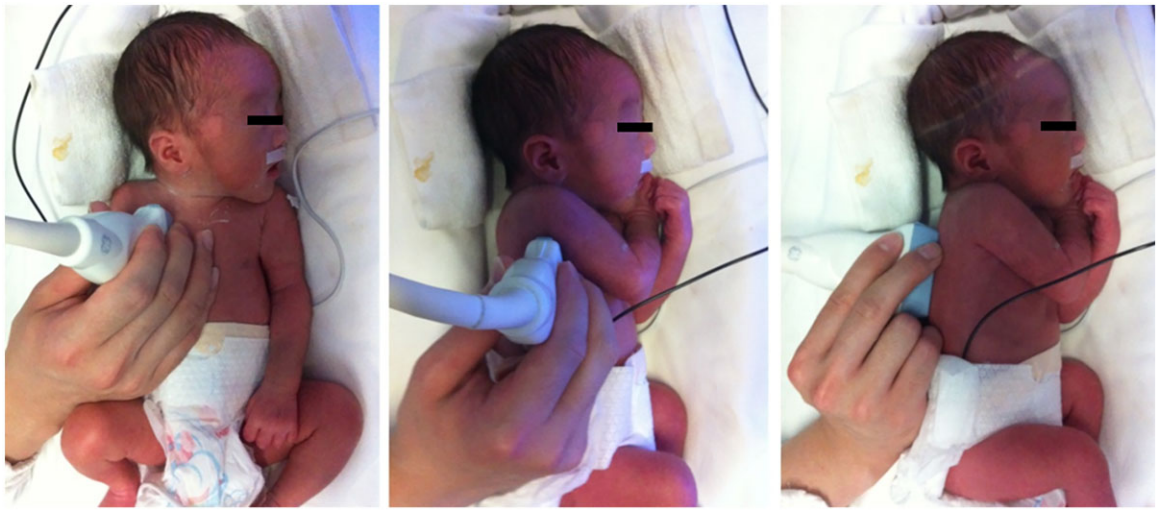

Figure 1. Lung ultrasound examination procedure in preterm infants with NRDS.

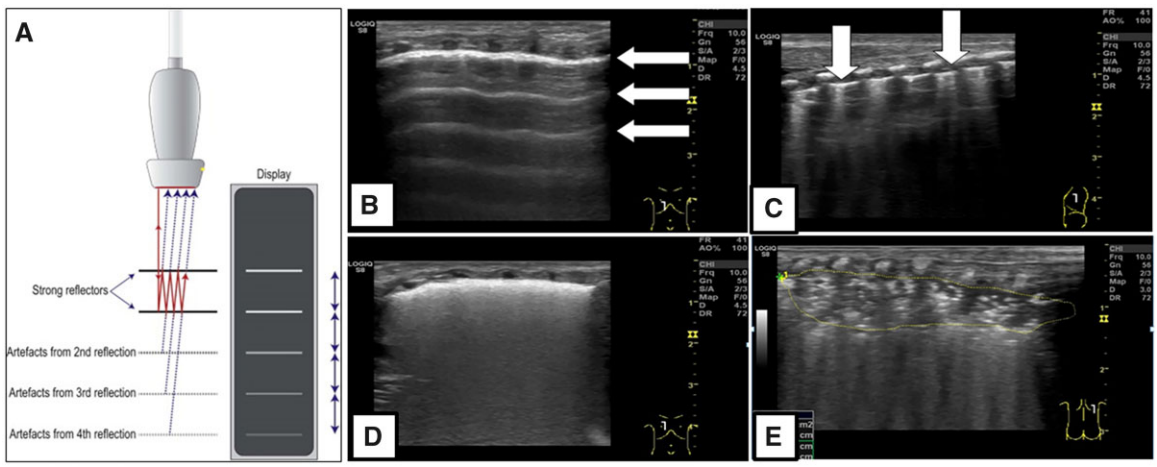

Figure 2. Relevant lung ultrasound sign in the diagnosis of NRDS. (**A**) Schematic diagram of reverberation artifacts; (**B**) A-line: the spacing is equal to the distance between the skin and pleural line, and the echo from the shallow-to-deep areas gradually weakens until disappearance; (**C**) B-line: high-level linear echoes that originate in the pleural line and are perpendicular to the radial field and radiate deep into the lung field; (**D**) White lung: the white lung is characterized by lung ultrasound to detect the diffuse dense AIS; (**E**) Lung consolidation: lung tissue with hepatization in the ultrasound examination accompanied by air or fluid bronchogram.

was observed in the remaining lung fields. Criteria B: A 'white lung' symptom indicated that the six lung fields in both lungs showed 'AIS' symptoms, all lung fields disappeared, and the pleural line was slightly thickened and rough. Criteria C: 'White lung' symptoms and any symptom of lung consolidation can be observed in any lung field.

Infants were examined by lung ultrasound based on the above diagnostic criteria, and the number of positive and negative cases determined by the three types of diagnostic criteria was recorded. The number of positive and negative cases diagnosed based on the current clinical diagnostic criteria and the number of severe cases of clinical diagnosis of NRDS (CXR diagnoses III–IV [11]) was also recorded.

Clinical diagnostic criteria

The clinical diagnostic criteria are as follows (i) gestational age <37 weeks, shortness of breath after birth at 60 times/min or more, exhalation of sputum, tri-retraction

signs when inhaling, progressively aggravated conditions, irregular breathing, apnea, bruising, breathing failure and dyspnea that cannot be relieved for 24 h; (ii) the two lungs presenting weakened breath sounds during physical examination; (iii) decreased PaO_2, increased $PaCO_2$ and a negative value of buffer excess according to blood gas analysis; (iv) CXR performance showing the significantly reduced brightness of both lungs, with alveolar collapse and bronchiole hyperinflation, bronchial aeration symptoms, cardiac borders, dim diaphragm borders and white lung; (v) lung maturity examination showing negative results for the gastric juice foam [12]. In severe NRDS, the range of lung consolidation is expanded, which is not only limited to the subpleural but also extends to the deep part of the lung with obvious bronchial inflation signs.

Statistical analysis

The statistical analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL, USA) statistical software. Diagnostic sensitivity and specificity were calculated by the equation of sensitivity = true positive/(true positive + false negative) and specificity = true negative/(true negative + false positive). The area under the receiver operating characteristic curve was used to evaluate the feasibility of ultrasound in the diagnosis of NRDS in preterm infants. Two tails $p < 0.05$ indicates a statistical difference.

RESULTS

Diagnosis of NRDS according to different diagnostic criteria

The data of 109 premature infant patients from the NICU of our hospital were prospectively collected from May 2021 to October 2021. There were 62 males and 47 females, with gestational ages of 27–36 weeks and an average gestational age of 33.22 ± 1.90 weeks. There were 22 cases with natural delivery cases and 87 cases with cesarean section delivery, with an average postoperative admission time of 1.23 ± 0.75 h and an average birth weight of 1934.72 ± 530.19 g. One hundred and nine preterm infants were included in the study, while 31 cases were NRDS and 78 cases were none-NRDS by clinical diagnostic criteria. According to diagnostic criteria A, the number of NRDS and none-NRDS were 34 and 75 (Table 1). According to diagnostic criteria B, the NRDS and none-NRDS were 10 and 99 (Table 1). For diagnostic criteria C, it was 12 and 97, respectively (Table 1).

Table 1. NRDS and none-NRDS distribution according to different diagnostic criteria

Diagnostic criteria	Clinical diagnosis		Total
	NRDS	None-NRDS	
Diagnostic criteria A			
NRDS	31	25	56
Non-NRDS	0	53	53
Total	31	78	109
Diagnostic criteria B			
NRDS	22	0	22
Non-NRDS	9	78	87
Total	31	78	109
Diagnostic criteria C			
NRDS	12	0	12
Non-NRDS	19	78	97
Total	31	78	109

Diagnostic efficacy of different diagnostic criteria

The diagnostic efficacy of different diagnostic criteria was shown in Table 2. The sensitivity and negative predictive value of NRDS in preterm infants with diagnostic criteria A were 100%, but the specificity and positive predictive value were low, which was 67.95 and 55.36%, respectively. The specificity and positive predictive value diagnostic criteria B and C were 100% while the 95% CI of diagnostic criteria B was narrower than the diagnostic criteria C. The sensitivity and negative predictive value of diagnostic criteria B were higher than the diagnostic criteria C. The sensitivity of diagnostic criteria B was significantly higher than that of diagnostic criteria C. The kappa value and AUC (area under the curve) (Az) of the three diagnostic criteria showed that the kappa value of diagnostic criteria B is 0.778 and Az is 0.855, which were higher than the diagnostic criteria A and C.

Diagnosis of severe NRDS by diagnostic criteria C

Of the 31 infants with NRDS, 15 cases had the severe disease and other 16 had no severe NRDS (Table 3). According to the diagnostic criteria C, the sensitivity, specificity, positive predictive value and negative predictive value of severe NRDS was 73.33% (44.83–91.09%), 93.75% (67.71–99.67%), 91.66% (59.75–99.56%) and 78.94% (53.90–93.02%), respectively. The kappa value and AUC were 0.676 and 0.835, respectively.

DISCUSSION

In this study, we investigated the feasibility of lung ultrasound in the diagnosis of NRDS in preterm infants. Three ultrasound diagnostic criteria were developed to

Table 2. Clinical efficacy of different diagnostic standards

Diagnostic efficacy	Diagnostic standard		
	A	B	C
Sensitivity (%) (95% CI)	100 (86.27–100)	70.96 (51.76–85.11)	38.71 (22.42–57.71)
Specificity (%) (95% CI)	67.95 (56.30–77.81)	100 (94.15–100)	100 (94.15–100)
Positive predictive value (%) (95% CI)	55.36 (41.56–68.42)	100 (81.50–100)	100 (69.87–100)
Negative predictive value (%) (95% CI)	100 (91.58–100)	89.66 (80.80–94.87)	80.41 (70.85–87.51)
Kappa value	0.547	0.778	0.475
AUC	0.840	0.855	0.694

Table 3. Severe NRDS and none-NRDS distribution according to diagnostic criteria C

Diagnostic criteria C	Clinical diagnosis		Total
	Severe NRDS	Non severe NRDS	
NRDS	11	1	12
None-NRDS	4	15	19
Total	15	16	31

diagnose preterm infants with NRDS. We found that the specificity and positive predictive value of diagnostic criteria B and C were 100%. The sensitivity and negative predictive value of diagnostic criteria B were higher than that of diagnostic criteria C. The kappa value and AUC of diagnostic criteria C were 0.676 and 0.835, respectively.

NRDS is the most common respiratory disease in preterm infants, and its incidence is related to the pulmonary maturity [13]. In 1959, Avery and Mead discovered that pulmonary surfactant (PS) deficiency primarily causes NRDS [14, 15]. PS is a phospholipid protein complex synthesized and secreted by type II alveolar epithelial cells that cover the alveoli surface to reduce its surface tension and prevent end-expiratory alveolar collapse to maintain functional residual capacity (FRC). PS develops from 18 to 20 weeks of gestation, followed by a slow rise, and a rapid increase to lung maturity level at 35–36 weeks. A low gestational age indicates a low amount of PS, leading to an increased surface tension of the alveoli and decreased FRC at the end of expiration, and alveolar collapse. Some previous studies indicated that the prevalence of preterm infants with age of <32 weeks was about 35–50% [16, 17], while other studies reported the rate of up to 80% [18]. Following the pathophysiological changes in NRDS, the clinical manifestations of patients, blood gas analysis and CXR characteristic imaging changes are the main diagnosis points for this disease, whereas EPS and CPAP/CMV application are the main treatments. After the standard EPS or CPAP treatment, the oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$) and acidosis were improved. Lung ultrasound mainly showed that 'white lung' or 'B-line' signs gradually improved, lung fields showed a normal 'A-line' sign, and the pleural line was gradually clear accompanied by the 'lung sliding' sign (Figure 3).

Animal experiments on lung ultrasound were first performed in the 1960s [19, 20]. Afterward, considering the convenience, safety, repeatability and other advantages of ultrasound examination in the ICU, the 'A-line', 'B-line' or the classic lung ultrasound signs, such as 'Comet-tail Artifact', 'Lung Sliding' and 'Lung Consolidation' have been widely investigated. This study systematically analyzed the pulmonary ultrasound signs in premature infants with NRDS and explored the ultrasound diagnosis standardization of NRDS in premature infants. Moreover, we evaluated the clinical significance of dynamic and continuous lung ultrasonography in the differential diagnosis of NRDS.

The infant patients included in the study were strictly grouped in accordance with the condition that premature infants underwent no lung examination nor EPS and CPAP/CMV treatment. The examination time commenced at the time of admission, that is, 1.23 ± 0.75 h after delivery. The setting of examination conditions was firstly based on the high incidence of NRDS in premature infants, and the pathophysiology of NRDS confirmed that alveolar epithelial necrosis and epithelial cell stripping of the basement membrane occur 0.5–1 h after delivery. Then, high amounts of cellulose, cell debris and osmosis, red blood cells, neutrophils and macrophages were exuded to form a transparent membrane. In this study, we also confirmed that all infants with final clinical diagnosis of NRDS exhibited abnormal lung ultrasound symptoms ('B-line' 'AIS' and 'lung consolidation') at a 100% positive rate,

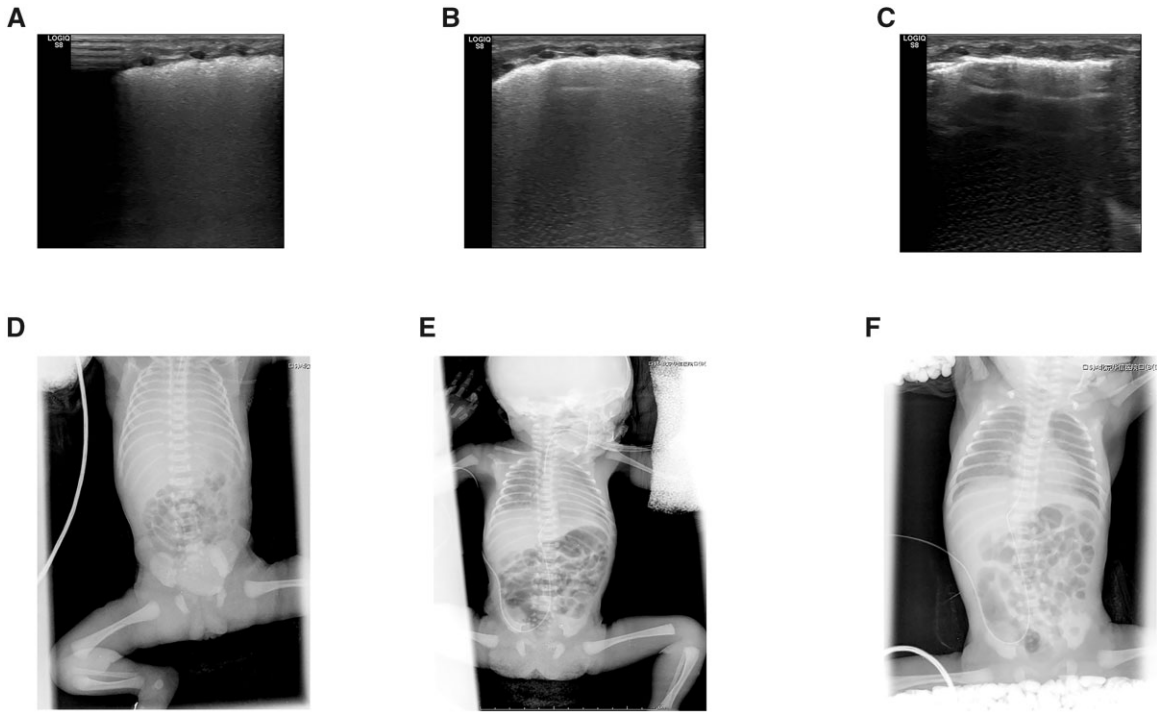

Figure 3. A female NRDS with gestational age 30+ weeks and birth weight of 1540 g. Cesarean section due to placenta previa, admission 1 h after delivery due to dyspnea. The diagnosis of NRDS was confirmed according to clinical manifestation, blood gas analysis and CXR. Lung ultrasound showed (**A**) and CXR (**D**) showed white lung in day 1. In day 2, with the improvement of symptoms, the 'A-line' was dimly seen in part of the lung field by ultrasonography (**B**), and the brightness of the lung field was improved by CXR (**E**). On the third day, the ultrasonographic findings of the lungs were normal (**C**). A-line could be seen in all the fields of the lungs. At the same time, CXR showed normal transmittance of the lungs (**F**).

thereby confirming that ultrasound diagnosis of the lungs is conducive to early diagnosis of NRDS.

Given that pathological diagnosis cannot be obtained in all patients, the clinical diagnostic criteria were assumed as the 'gold standard'. Our study revealed that the use of criteria A lung in the diagnosis of NRDS showed a low sensitivity, specificity, positive predictive value, negative predictive value and kappa value. Thus, it was not suitable for the clinical use. There was no significant difference between criteria B and C, and their specificity and positive predictive value both reached 100%. However, the sensitivity, negative predictive value and kappa value of criteria C were higher than those of criteria B. The kappa value of NRDS in severely premature infants was 0.676 when using criteria C. Therefore, we assumed that lung ultrasound signs of 'white lung' symptom and 'lung consolidation' showed high sensitivity and specificity on the diagnosis of NRDS. It is clinically useful for the diagnosis of NRDS in severe preterm infants. In the dynamic observation of the development and transformation of NRDS, lung ultrasound can provide a basis for a clinical differential diagnosis and treatment.

There were also some limitations of this study. First, the incidence of NRDS in preterm infants is affected by multiple risk factors, including gender, race, multiple pregnancies, production, history of gestational diabetes mellitus, prenatal therapy of corticoid and type B hemolytic streptococcal infection. This study neglected the influence of these confounding factors. Second, in the follow-up continuous observation of the infants, the lung ultrasound examination provided no diagnostic criteria, and there was no control. Finally, the sample size is relatively small and this study has been performed in only one center.

In conclusion, thickened or rough pleural line with white lung sign is an important characteristic for the diagnosis of NRDS by lung ultrasound. White lung sign

combined with the lung consolidation sign had high diagnostic efficacy when distinguishing severe NRDS from not severe NRDS.

FUNDING

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