Original Article

Lung ultrasound in diagnosing neonatal respiratory distress syndrome: a meta-analysis

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Abstract

Background Neonatal respiratory distress syndrome (NRDS) is commonly diagnosed by clinical sign and symptoms, blood gas analysis, and chest x-ray. In the past, lung ultrasound (LUS) was not standard for NRDS examination. Many studies show that ultrasound diagnostic tool for NRDS is accurate, reliable, low cost, easy to use, and safe because due to no ionizing radiation.

Objective To determine the sensitivity and specificity of LUS in diagnosing NRDS.

Methods This meta-analysis study was conducted LUS as a diagnostic tool for NRDS. Inclusion criteria were all studies from PubMed, Embase, and The Cochrane Library, without any limitation on published journals, as well as using keywords or search terms of ultrasound, neonatal, and respiratory distress syndrome. Statistical analysis was undertaken using *MedCalc®* version 18.2 software.

Results Seven studies with a total of 580 patients met the inclusion criteria. Proportional meta-analysis obtained random effects models, with total sensitivity of LUS was 97.2% (95% CI for I2 74.24 to 92.88; P<0.0001) and specificity of LUS was 94.8% (95% CI for I2 88.60 to 98.03; P<0.00001).

Conclusion Lung ultrasound should be considered as a diagnostic tool for NRDS because it is high in sensitivity and specificity, inexpensive, safe, as well as limited radiation exposure. **[Paediatr Indones. 2019;59:340-8; doi: http://dx.doi.org/10.14238/ pi59.6.2019.340-8]**.

Keywords: *neonatal respiratory distress syndrome; lung ultrasound*

The capability of newborn babies to adapt to life outside the uterus is important for their survival.[1] After birth, almost all body function are switched from fetal to newborn. Respiratory system, in particular, has a new important role in infant survival.[2] Some lung disorders do not affect fetus inside uterus because all nutrition and oxygen from the mother through a placenta.[3] Neonatal respiratory distress syndrome (NRDS) is a primary cause of morbidity and mortality in preterm newborn because of breathing disorders involving a lack of surfactant in the lung and structural pulmonary immaturity.[4,5]

Neonatal respiratory distress syndrome is a common reason for admission to the neonatal intensive care unit (NICU), with newborns exhibiting tachypnea, poor feeding, nasal flaring, grunting,

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cyanosis, intercostal retraction, and reduction of respiratory sounds upon lung auscultation. In under developed countries, the mortality rate of NRDS is ten times higher than that of in developing countries, reaching about 60%.[6,7]

A study reported that gestational age, intrauterine distress, and gestational diabetes could increase the risk of NRDS.[8] Full term newborns have a lower risk than preterm newborns. Neonatal respiratory distress syndrome is considered as a neonatal emergency, with reported prevalence of around 47.5% in Cameroon,[9] 23% in Karachi,[10] 26.2% in Nigeria,[11] 12% in USA,[12] and 9-14% in Indonesia.[13]

Neonatal respiratory distress syndrome is generally diagnosed by clinical signs and symptoms, blood gas analysis, and chest x-ray (CXR). Chest x-ray is a routine examination to evaluate lung and other chest anomalies in neonates. It may be required more than once. A study using thermoluminescence dosimetry showed that the total risk of radiation to the baby was low for one time CXR.[14] In addition, another study found that neonates, including preterm newborns were exposed to 65-67 microGy in evaluations using entrance skin dose (ESD) measurements.[15] Although CXR is deemed safe, previous studies showed that cancer risk is inversely proportional with age, suggesting that neonatal radiosensitivity is higher than that of children or adults, especially in neonates who are exposed to more than 70 microGy.[16]

The latest studies have shown that lung ultrasound has high sensitivity and specificity as a diagnostic tool for NRDS.[17] In the past, lung ultrasound was not a standard examination tools for NRDS examination. However, many studies showed that ultrasound is a useful diagnostic tool due to its good accuracy, reliability, low cost, ease of use, and safety because it has no ionizing radiation.[18,19] As such, we conducted this study to determine the sensitivity and specificity of lung ultrasound in neonatal respiratory distress syndrome.

Methods

This proportional meta-analysis study was performed by collecting data from the latest studies about sensitivity and specificity of lung ultrasound as a diagnostic tool for NRDS. Studies were collected and identified in August 2018 using databases of PubMed 2000-2018, Embase 2000-2018, and The Cochrane Library 2008-2018. Search terms were neonates, lung, ultrasound, and respiratory distress syndrome.

The study subjects were the total number of fulfilling the inclusion criteria namely randomized control trials, case-control studies, or prospective studies; neonates of ≤ 42 weeks gestational age; newborns aged 0-28 days; neonates suffering from respiratory distress syndrome diagnosed with using clinical signs and chest x-ray; and full text manuscript. The exclusion criteria consisted of in silico, in vitro, in vivo, or ex vivo experimental animal studies; lung ultrasound used as diagnostic tool for diagnosing other than NRDS; lung ultrasound used as a diagnostic tool for NRDS in children other than neonates; neonates congenital heart disease; studies lacking of sensitivity and specificity data; studies lacking of full text manuscripts; studies found more than once in other websites or databases; and meta-analysis studies.

Studies were assessed for selecting and reporting bias. Quality was assessed using the *Quality Assessment of Diagnostic Accuracy Studies 2* tool. It was accessed in *Review Manager 5.3* software which has four domains for risk of bias and applicability concerns: patient selection, index test, reference standard, and test flow and timing. Five team members individually scored each study for all domains.

Patient selection was rated to be low risk if neonates were suspected for having respiratory distress syndrome. Applicability concerns were rated to be low risk if neonatal congenital heart disease had been excluded. The index test was rated to have low risk if sonographers were blinded to the chest x-ray results. Applicability concerns were about specification and capability of ultrasonography machine. The reference standard was rated to be low risk if the clinicians were blinded to the lung ultrasound results. Applicability concerns were about good clinical signs and tests. Flow and timing test was rated low if neonates underwent the same clinical examinations and chest x-ray, with interval time between chest x-ray and lung ultrasound was less than 24 hours. Differences in opinion among team members were resolved by discussion.

In our study, a 95% confidence interval indicates a 95% probability that the sample is representative mean of real population. The inconsistency (I^2)

test was used to quantify heterogeneity, and it was considered to be significant when greater than 50%. Sensitivity is a true positive rate which measures the proportion of real positives. Specificity is a true negative rate which measures the proportion of real negatives.

We performed statistical analyses using *MedCalc®* version 18 software, with a proportional meta-analysis. We assessed statistical heterogeneity using the I2 statistic, indicating significance if the I2 was greater than 50%. We reported the 95% confidence interval (CI) on all estimates and used a random-effects model for meta-analysis due to heterogeneity.

Results

Database search in August 2018 with keywords such as 'lung ultrasound,' 'neonatal,' and 'respiratory distress syndrome' yielded 649 PubMed studies, 97 Embase studies, and 1 Cochrane Library study (**Figure 1**). Of these, 7 studies with a total of 580 patients met our inclusion criteria. Those studies were fulfilled to analyze (**Table 1**).

Most studies were from PubMed, as it is a database connected to many libraries, scientific studies, and articles from all over the world. Some of studies from Embase and The Cochrane Library were also found in PubMed. The oldest article included was published in 2006 by Bober *et al.*[19] The most recent study was written by El-Malah *et al.*[20] and published in 2015. The largest sample size was found in Bober *et al.*[19] (131 subjects) and the smallest sample size was found in Lovrenski[21] study (47 subjects). Two studies were done in Italy while 5 others were conducted in India, Poland, China, Serbia, and Egypt. Those 7 studies comprised of 5 prospective studies and 2 case-control studies (**Table 1**).

The studies evaluated diagnostic methods, in terms of lung ultrasound operator, technique, equipment, and diagnostic criteria, as seen in **Table 2**. The proportional metaanalysis revealed a total LUS sensitivity of 97.2% (95% CI for I2 74.2 to 92.8; P<0.0001) and LUS specificity of 94.8% (95%CI for I2 88.6 to 98.0 ; P<0.0001).
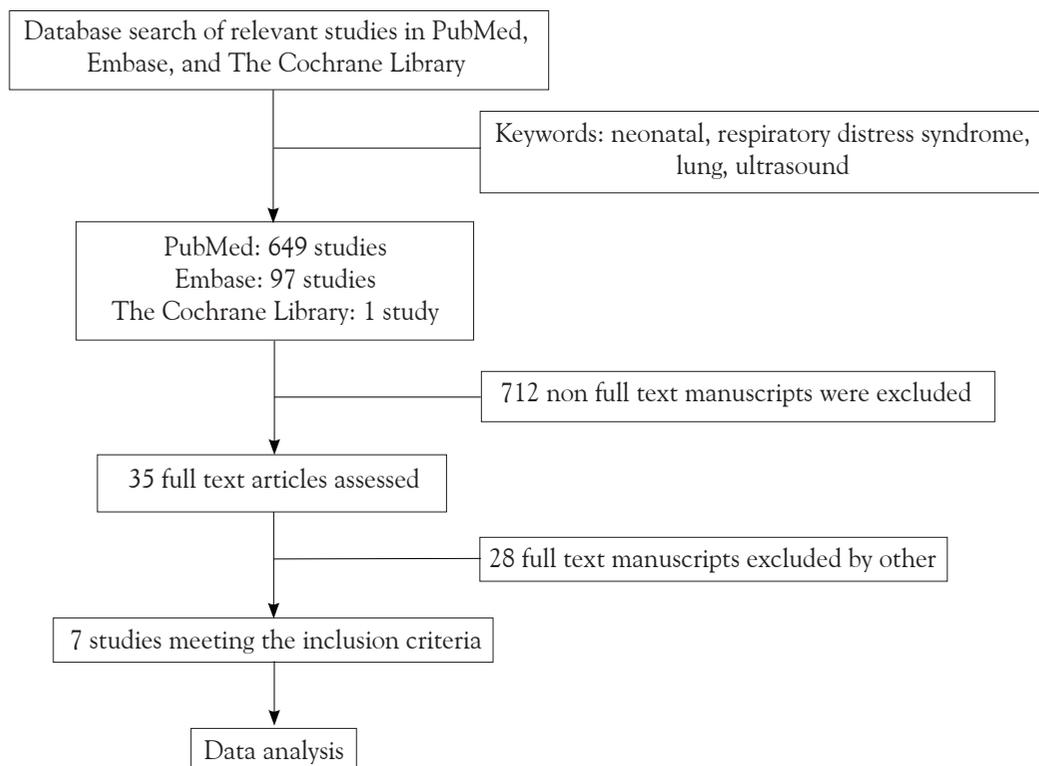
Figure 1. Flow chart study inclusion

Table 1. Primary data extracted from meta-analysis studies

Study	Year	Origin	Study type	Sample size	Gestational age, weeks	Male:female ratio	LUS Sensitivity (%)	LUS Specificity (%)
Bober *et al.*[19]	2006	Poland	Prospective	131	24-42	86/45	100	73
Copetti *et al.*[22]	2008	Italy	Case control	55	23-34	Unknown	100	100
Ahuja *et al.*[18]	2012	India	Prospective	88	25-32	50/38	84.2	88
Lovrenski J[21]	2012	Serbia	Prospective	47	23-36	Unknown	95	100
Liu *et al.*[23]	2014	China	Case control	100	27-41	62/38	100	100
Vergine *et al.*[25]	2014	Italy	Prospective	59	24-35	35/23	95.6	94
El-Malah *et al.*[20]	2015	Egypt	Prospective	100	36-42	66/44	98	92

Table 2. General characteristics of the studies

Study	Diagnostic methods	LUS operator	LUS technique	LUS equipment	LUS diagnostic criteria
Ahuja *et al.*[18]	Gastric aspirate test + clinical diagnosis + CXR	Radiologist	Transabdominal	HDI 3500 [advanced technologies laboratories (ATL) ultrasound, Bothell, WA, USA] (5-12MHz) curvalinier probe	Diffuse retrodiaphragmatic hyperechogenicity completely replacing the normal diaphragm
Bober *et al.*[19]	CRIB score + CXR + blood results	Physician	Transabdominal	Siemens SI 450, equipped with a sector 5MHz transducer	Retrophrenic hyperechogenicity with B-lines diverging radially
Copetti *et al.*[22]	Clinical diagnosis + CXR	Pediatrician + cardiologist	Transthoracic	Megas CVX Esaote, Medical system, Florence, Italy (10MHz linear probe)	Bi-lateral white lung, absence of spared areas, thickened and irregular pleural line
Liu *et al.*[23]	Clinical diagnosis + CXR + blood results	Expert physician	Transthoracic	High resolution line probe (11-12MHz) (GE voluson I or E6, USA)	Consolidation, pleural line abnormalities and bilateral white lung
Lovrenski[21]	Clinical diagnosis + CXR + blood results	Pediatric radiologist	Transthoracic + transabdominal	7.5MHz linear probe (Sonoline Adara, Siemens, Erlangen, Germany)	Consolidation; air bronchogram and B-lines
Vergine *et al.*[25]	Clinical diagnosis + CXR	Neonatologist	Transthoracic	Vivid-I Ge Medical Systems, Milan, Italy using a high res 10-12 MHz linear probe	Bi-lateral white lung, coalescent B-lines and thickened and irregular pleural line
El-Malah, *et al.*[20]	Clinical diagnosis + CXR	Radiologist	Transthoracic + transabdominal	Sonoline, Adara, Siemens, Erlangen, Germany using a 7.5MHz linear probe and 5MHz convex probe	B-lines, complete disappearance of white lung

CXR=chest X-ray

The sensitivity of lung ultrasound in diagnosing NRDS was figured in forest plot (**Figure 2**). The diamond sign is not across vertical lines (1.0) which means those studies has significant results. The I^2 of sensitivity obtained 86.5% then we took random effects models. It resolved heterogeneity in meta-analysis. **Table 3** explained the sensitivity proportion and the 95% CI for I^2 of each study. The proportion of Ahuja *et al.*,[18] Bober *et al.*,[19] El-Malah *et al.*,[20] Lovrenski,[21] Copetti *et al.*,[22] Liu *et al.*,[23] and Vergine *et al.*,[24] and were 84.2%, 100%, 95.6%, 100%, 100%, 98%, 95%, respectively. Then, it can be concluded that the total proportion of sensitivity revealed 97.2%.

The specificity of lung ultrasound in diagnosing NRDS was figured in forest plot (**Figure 3**). The diamond sign is not across vertical lines (1.0) which
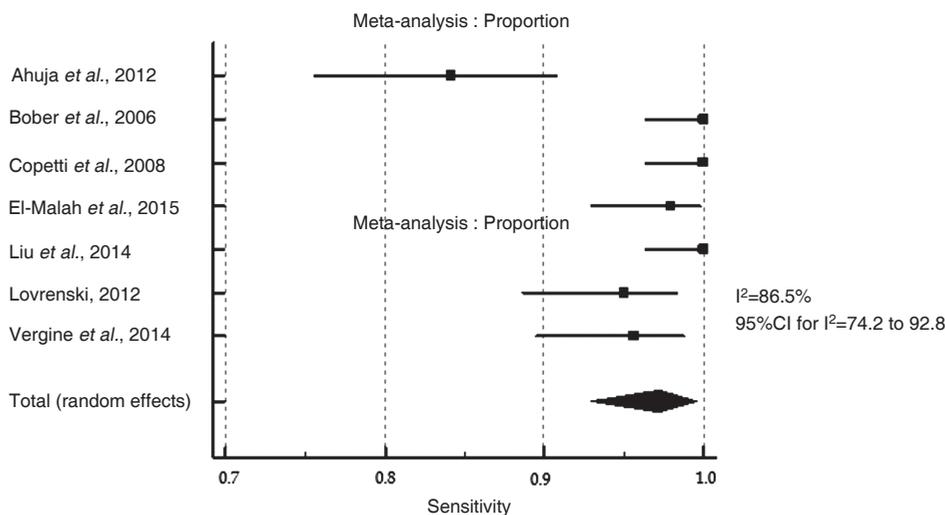
Figure 2. Forest plot: the sensitivity of lung ultrasound in diagnosis of NRDS

Table 3. Proportional meta-analysis: the sensitivity of lung ultrasound in diagnosis of NRDS

Study	Sample size	Proportion, %	95%CI	Weight, % [random effects]
Ahuja *et al.*[18]	100	84.2	75.5 to 90.7	14.3
Bober *et al.*[19]	100	100	96.3 to 100	14.3
Copetti *et al.*[22]	100	100	96.3 to 100	14.3
Liu *et al.*[23]	100	98	92.9 to 99.8	14.3
Lovrenski[21]	100	100	96.3 to 100	14.3
Vergine *et al.*[25]	100	95	88.7 tp 98.4	14.3
El-Malah, *et al.*[20]	100	95.6	89.5 to 98.7	14.3
Total (random effects)	700	97.2	92.9 to 99.5	100

Notes: Q=44.3, DF=6, significance level P<0.0001, I² (inconsistency)=86.5%, 95%CI for I²=74.2 to 92.8
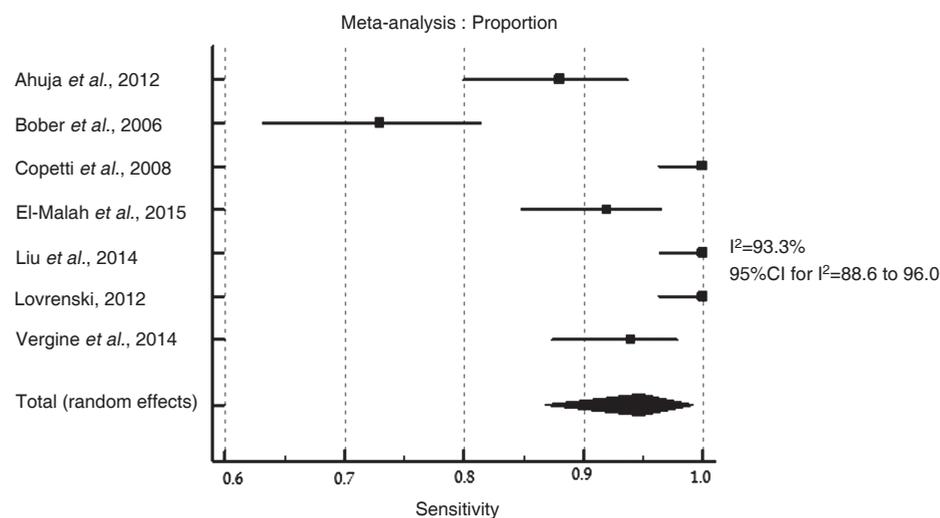

Figure 3. Forest plot: the specificity of lung ultrasound in diagnosis of NRDS

means those studies has significant results. The I^2 of sensitivity obtained 93.3% then we took random effects models. It resolved heterogeneity in meta-analysis. **Table 4** explained the specificity proportion and the 95% CI for I^2 of each study. The proportion of Ahuja et al.,[18] Bober et al.,[19] El-Malah et al.,[20] Lovrenski,[21] Copetti et al.,[22] Liu et al.,[23] and Vergine et al.,[24] and were 88%, 73%, 94%, 100%, 100%, 92%, 100%, respectively. Then, it can be concluded that the total proportion of specivicity revealed 94.8%.

The I^2 test results were greater than 50% across both forest plots (**Figure 2** and **Figure 3**). It confirmed a degree of heterogeneity among studies. Each subgroup was analyzed by Quadas-2 tool. The

quality of the studies had an overall score of 30 out of 42 as shown in **Figure 4**.

Discussion

Neonatal respiratory distress syndrome is a common reason for NICU admission. It is the main cause of morbidity in preterm newborns with gestational age <37 weeks.[25] The standard diagnostic tools for diagnosing NRDS is a combination of clinical signs and symptoms as well as chest x-ray.[25,26] However, neonates may be vulnerable to excessive radiation of x-ray.[26] The radiation side effects lead to cataract

Table 4. Proportional meta-analysis: the specificity of lung ultrasound in diagnosis of NRDS

Study	Sample size	Proportion, %	95%CI	Weight, % [random effects]
Ahuja et al.[18]	100	88	79.9 to 93.6	14.3
Bober et al.[19]	100	73	63.2 to 81.4	14.3
Copetti et al.[22]	100	100	96.3 to 100	14.3
Liu et al.[23]	100	92	84.8 to 96.4	14.3
Lovrenski[21]	100	100	96.3 to 100	14.3
Vergine et al.[25]	100	100	96.3 to 100	14.3
El-Malah, et al.[20]	100	94	87.4 to 97.8	14.3
Total (random effects)	700	94.8	86.8 to 99.2	100

Notes: Q=89.2, DF=6, significance level P<0.0001, I^2 (inconsistency)=93.3%, 95%CI for I^2=88.6 to 96.0
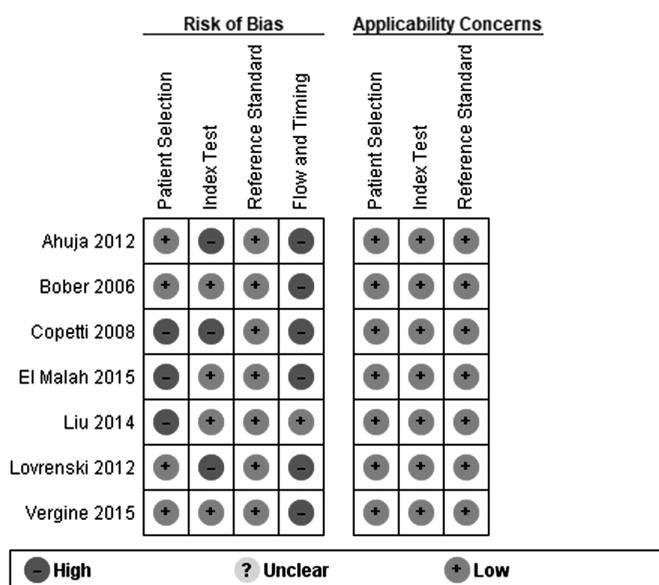
Figure 4. QUADAS-2: risk of bias and applicability concerns

and skin injury, as well as higher risk of hematology malignancy and cancer.[26,27] Infants of younger ages are more sensitive to radiation exposure.[27] Some studies using electrostatic discharge (ESD) showed that radiation exposure below 70 microGy can be tolerated by neonates.[27,28]

Chest x-ray (CXR) examination of NRDS reveals a ground glass appearance and air bronchogram.[29] Some experts say decreased pulmonary lucency as well as widespread net and grain high density shadows were not pathognomonic.[30,31] Hence, respiratory disorders in newborns could be diagnosed with others examinations.[32]

A previous study reported that CXR had sensitivity and specificity (35% and 82%, respectively), high sensitivity and specificity for diaphragmatic hernia and pneumothorax (100%). However it had 0% sensitivity and 98% specificity for congenital heart diseases and 0% sensitivity and 100% specificity for transient tachypnea.[33]

Lung ultrasound is an imaging examination with high accuracy, low cost, and no radiation side effects. Thus, some experts have suggested to use it as a diagnostic tool. It can be done on bedside and does not require sedation.[30,31] Lung ultrasound examination is considered to be superior by experts because it uses a transducer to emit radiofrequency waves, which reflect back to the transducer when encountering organ tissue. When air inside the alveoli is decreased as in NRDS, the transducer would receives a typical image which helps in diagnostic determination.

The seven studies included 580 neonates who may have had not only NRDS, but also any differential diagnoses with clinical signs similar to respiratory distress syndrome. The differences of study design could also have influenced subject inclusion. More than half of the sonographers in the seven studies were not blinded to clinical signs and chest x-ray examinations. This knowledge and the sonographers' skills could have influenced the final interpretation for diagnosis of NRDS, which could bias the diagnostic accuracy of the LUS.

The seven studies used clinical signs and symptoms and CXR to diagnose NRDS. Additional gastric aspiration test, clinical risk index for babies (CRIB) score, and blood gas analysis were used in four studies. These differences in clinical tests could also have led to bias in diagnostic accuracy of LUS. The NRDS reference standard still used clinical signs and symptoms as well as CXR in all studies.

The time duration between CXR and lung ultrasound varied among the studies, which could have biased the results due to the progressive severity of the disease. In addition, therapy or medication during the test could also lead to bias.

Our meta-analysis revealed >94% specificity and >97% sensitivity of lung ultrasonography as a diagnostic tool for NRDS. These high sensitivity and specificity values were closest to studies by Copetti *et al.* and Lovrenski that was omitted 100% numbers,[22,23] and in accordance with the most recent study by Al Kayat *et al.*[29] who reported 100% sensitivity and also found an 81% specificity of LUS for NRDS.

In conclusion, in diagnosing NRDS, lung ultrasound is superior to chest x ray as it has high sensitivity and specificity compared to those of chest x ray. Therefore, lung ultrasound can be considered as an alternative diagnostic tool for NRDS. Moreover, it is inexpesive, safe, and free radiation side effects.

Conflict of interest

None declared.

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