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Neonatal respiratory distress syndrome - Chest X-Ray or lung ultrasound? A systematic review

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Abstract

Background and aim. Neonatal respiratory distress syndrome (NRDS) is a leading cause of morbidity in preterm new-born babies (< 37 weeks gestation age [GA]). The current diagnostic reference standard includes clinical testing and chest radiography (CXR) with associated exposure to ionising radiation. The aim of this review was to compare the diagnostic accuracy of lung ultrasound (LUS) against the reference standard in symptomatic neonates of $\leq$ 42 weeks GA.

Methods. A systematic search of literature published between 1990 and 2016 identified 803 potentially relevant studies. Six studies met the review inclusion criteria and were retrieved for analysis. Quality assessment was performed before data extraction and meta-analysis.

Results. Four prospective cohort studies and two case control studies included 480 neonates. All studies were of moderate methodological quality although heterogeneity was evident across the studies. The pooled sensitivity and specificity of LUS were 97% (95% confidence interval [CI] 94%-99%) and 91% (CI: 86%-95%) respectively. False positive diagnoses were made in sixteen cases due to pneumonia (n=8), transient tachypnoea (n=3), pneumothorax (n=1) and meconium aspiration syndrome (n=1); the diagnoses of the remaining three false positive results were not specified. False negatives diagnoses occurred in nine cases, only two were specified as air-leak syndromes.

Conclusions. LUS was highly sensitive for the detection of NRDS although there is potential to miss co-morbid air-leak syndromes (ALS). Further research into LUS

diagnostic accuracy for neonatal ALS and economic modelling for service integration is required before LUS can replace CXR as the imaging component of the reference standard.

Key words. Neonatal respiratory distress syndrome, lung ultrasound, chest X-ray, diagnosis.

Introduction

Neonatal respiratory distress syndrome (NRDS) is a breathing disorder arising at, or shortly after birth (<24 hours); it increases in severity during the first 48 hours of life.[1] Although full term new-borns with a gestational age [GA] between 37- 42 weeks can be affected, approximately four out of five cases occur in those born prematurely (< 37 weeks).[2,3] Severity and incidence of NRDS are inversely related to GA with 92% of neonates born at 24-25 weeks affected, 88% at 26-27 weeks, 76% at 28-29 weeks and 57% at 30-31weeks.[4,5]

NRDS is caused by physiological and structural pulmonary immaturity - insufficient levels of pulmonary surfactant compromise alveolar integrity, impeding normal gas exchange due to deregulation of acinar surface tension.[6,7] Resulting atelectasis causes decreased lung compliance through an increase of collapsed alveoli in the terminal airways.[8] NRDS progresses through hypoventilation, hypoxemia and respiratory acidosis.[6,7,8] It is a leading cause of morbidity in premature new-borns and is a common reason for admission to the neonatal intensive care unit (NICU).[9,10]

NRDS is diagnosed by a combination of clinical signs and symptoms, laboratory analysis and chest radiography (CXR).[1,6] Early diagnosis is important so that interventional therapy, respiratory support and surfactant replacement, can be instigated.[7,8] Follow up imaging is required to monitor therapeutic effect and reduce broncho-pulmonary dysplasia as a result of unnecessary mechanical ventilation.[11]

Clinical signs and symptoms

Clinical presentations of NRDS include non-specific tachypnoea, nasal flaring, cyanosis, substernal and intercostal retraction and grunting from expiratory air colliding with a partially closed glottis.[8] The 'Clinical Risk Index for Babies' (CRIB) is a risk assessment tool scoring birth weight, gestational age, maximum and minimum fraction of inspired oxygen, maximum base excess during the first 12 hours of life and presence of congenital malformations.[12] In suspected NRDS the CRIB can be used to estimate severity of NRDS and trigger administration of assisted ventilation.[12]

Laboratory tests

Arterial partial oxygen pressure (PaO_2) levels below 50 mmHg with cyanosis in room air, or the need for supplementary oxygen to maintain PaO_2 > 50 mmHg, is indicative of NRDS.[6] A blood sample can determine levels of metabolic and respiratory acidosis which indicate anaerobic metabolism and atelectasis respectively.[13]

Swallowed lung fluid is a significant constituent of neonatal gastric aspirate. The gastric aspirate shake test (GAST) identifies the presence or a lack of surfactant.[14] GAST is reported to have 100% sensitivity and 92% specificity for NRDS. [15]

Chest radiography

In a study of 59 neonates with clinically suspected NRDS, Vergine et al.[16] found CXR to have sensitivity and specificity of 91% and 84% respectively when radiologists where blinded to clinical test results. Morris[17] suggests radiological appearances correlate well with clinical disease severity, atelectasis being represented by a bi-lateral fine granular or "ground glass" appearance such that extent of disease

corresponds to level of lung opacity. Reduced lung expansion, dilated bronchioles and air bronchograms are also visible depending on disease stage.[7]

Further to diagnostic use, CXR is used to confirm endotracheal tube (ETT) position; premature new-borns with severe NRDS frequently receive continuous positive airways pressure (CPAP) in order to improve ventilation and oxygenation as well as facilitating intratracheal administration of surfactant.[1,6] Confirmation of the ETT position minimises lung damage caused by malpositioning[1].

Chest radiography involves exposure to ionising radiation. Neonates, due to their small size and the close proximity of radiosensitive tissues and organs, are at greater risk from latent effects of CXR in comparison to other age groups.[18] Although the actual risk of adverse latent effects from neonatal radiation exposure has not been quantified,[19,20] the theoretical risk can be predicted using the linear no-threshold (LNT) model with relative risk increasing as absorbed dose increases.[20] With neonates undergoing multiple CXR examinations during their stay on the NICU, efforts have been made to identify an alternative diagnostic test.[21,22]

Lung ultrasound

In the past, ultrasound has not been widely used for neonatal chest imaging due to the obscuring artefact generated by normal air-filled lung.[21]

Ultrasound does not involve ionising radiation but is associated with potential risks due to mechanical (inertial cavitation) and thermal tissue damage.[23] The risk of these adverse bio-effects is low in routine clinical practice, but proportional to duration of ultrasound examination, dependent on the specific tissues under examination and

the output of the ultrasound transducer. Risk is quantified in terms of mechanical and thermal indices, MI and TI respectively and displayed during scanning.[24] The “as low as reasonably practicable” (ALARP) principle, along with acoustic safety guidelines are implemented to minimise risk.[25]

Lung ultrasound (LUS) has recently emerged as a promising diagnostic tool with studies reporting accurate results in the diagnosis of NRDS [4,9,11,13,26,27,28] and other neonatal pulmonary diseases.[22,29] The presence of artefact has been recognised as a useful clinical marker to demonstrate normality, its absence being indicative of disease (Table 1 and Figure 1a,1b & 1c) [21] .Raised fluid levels in diseased lung and the absence of the normal air-filled gap between the pleura and pulmonary interstitium provide a propagation medium for ultrasound transmission and demonstration of lung tissue.[4,9]

Ultrasonic verification of ETT position in neonates has also shown potential. Studies have reported close correlation between ultrasound and CXR measurements and is comparatively much faster [30,31]. Due to a lack of high quality supporting evidence CXR remains the gold standard.[32]

Aim

The aim of this review was to compare the diagnostic accuracy of LUS against the reference standard clinical test and CXR in symptomatic neonates of ≤ 42 weeks gestational age.

Method

Search strategy

Studies were identified during August 2016 using the following databases: OVID Embase 1996-2016, OVID Medline (R) 1996-2016, PUBMED 1996-2016, Science Direct 1995-2016, Leeds University Library's Journals/Books@OVID (full-text), CINAHL 1990-2016, The Cochrane Library 2005-2016 and Google Scholar.

Initial search terms were identified from a preliminary literature search and accepted by unanimous agreement amongst review team members. Medical Subject Headings (MeSH) were used to generate additional search terms for ultrasound, neonates, X-ray and NRDS (Table 2). The Boolean operators (AND) and (OR) were used to minimise irrelevant literature and maximise the breadth of the search.[33] Truncation was used to increase the yield of studies that used alternate endings to the search terms.[34]

Inclusion and exclusion criteria were designed in accordance with the Population, Intervention, Comparator, Outcome (PICO) framework to correlate with the research question. To increase validity and reproducibility they were defined *a priori*. Studies were included if they were randomized control trials (RCTs), cohort or case-control studies, recruited neonates ≤ 42wks GA in a clinical setting with signs and symptoms of NRDS within 48 hours of birth, and had NRDS diagnosed using a combination of clinical indicators (presentation, vital signs and auscultation), CXR, and/or laboratory blood gas analysis. Limited resources restricted inclusion to studies published in English. Although this may introduce language bias[33] there is little evidence to suggest that systematic bias occurs with such an approach.[35] Articles were not excluded on the basis of geographical location or publication date to limit bias and maximise retrieval of relevant material.[33,34]

Studies were excluded where it was not possible to extract sufficient data to populate 2x2 contingency tables, obtain them through the local institutional or British Library, where requisite permission from parents and ethical committees had not been obtained or where studies collected non-human or cadaveric data.

After removing duplicate results, study titles, abstracts or full-papers were reviewed to determine inclusion in the review. Differences of opinion were resolved by discussion. The reference lists of included studies were examined to identify further relevant studies that had not been retrieved by the database search; forward citation tracking was performed in Google Scholar. The rigorous search and selection process limited selection bias and reduced the chance of random error.[33,34]

Quality assessment

Since the inclusion of studies other than RCTs can increase selection and reporting bias,[33] quality assessment was performed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool.[36] Risk of bias and applicability were assessed in four key areas relevant to the research question: patient selection, index test, reference standard and test flow and timing. Three team members individually scored each study awarding one point for each criterion where risk of bias was considered to be low.[36]

Patient selection was considered to have low risk of bias if there was a consecutive sample of neonates, they were suspected to have NRDS within 48 hours of birth, and subjects had not been excluded inappropriately. Applicability concerns were considered low if neonates with congenital heart and chest disease had been

excluded, studies were conducted in an appropriate clinical setting and there was no evidence of recruitment according to disease severity.

Index test bias criteria required LUS practitioners to be blinded to the results of the CXR and applicability concerns related to appropriateness of probe frequency and age and capability of equipment. Conversely for the reference standard, clinicians would ideally be blinded to the results of the LUS examination (low bias) and the clinical test had to be appropriate (applicability).

In terms of flow and timing of the reference and index tests, risk of bias was deemed low if all neonates received the same clinical test and a CXR, the interval between LUS and CXR was ≤ 5 hours and all recruits where included in 2x2 contingency table analysis.

Data extraction and analysis

Data extraction was carried out independently by MH and CW. The following data were extracted: sample size, age range, study design, blinding, method of NRDS diagnosis, LUS operator skill level, LUS diagnostic technique, time between CXR and LUS, LUS diagnostic criteria and the number of true positives, true negatives, false positives and false negatives.

Contingency tables were created to calculate test sensitivity and specificity and the DerSimonian and Laird random effects model[37] was fitted to the data to account for the heterogeneity across the studies. Use of a random-effects model is recommended in systematic reviews of diagnostic studies due to heterogeneity.[33] 95% Confidence intervals (CIs) were calculated for individual and pooled data. The chi-squared test

(χ^2) was applied to assess risk of heterogeneity ($p<0.10$).[31] The Inconsistency (I^2) test was used to quantify heterogeneity (significance greater than 50%).[33] Statistical analysis was undertaken using Meta-DiSc ® version 1.4 software.[38]

Results

Identification of studies

The search returned 803 studies of which 10 full texts were assessed for eligibility against the inclusion/exclusion criteria. Six of these studies were omitted because they had insufficient detail to produce 2x2 contingency tables (n=4)[9,24,39,40], reported LUS results for lung zones instead of individual neonates (n=1)[41] or assessed LUS for predicting the need for mechanical ventilation rather than diagnosing NRDS (n=1).[11] Two further quantitative studies identified through forward and backward searching[16,42] were included in the analysis (Figure 2).

Study characteristics

Table 3 details the six studies included for analysis.[4,10,13,14,16,42] Four were prospective cohort studies[4,13,14,16] and two prospective case-control studies.[10,42] A total of 480 neonates were studied, mean age 31.3 (SD ± 1.1) weeks. Four studies (378 neonates) reported gender ratios: 62% of participants were male, 38% female. Five studies enrolled participants from single centre NICUs, the other was a two-centre study.[10] Two studies used a transabdominal scanning technique,[13,14] three adopted a transthoracic approach[10,16,42] and one study performed both techniques on all enrolled neonates.[4] Table 4 summarises the general characteristics of the studies.

Quality assessment

The quality of the studies included in the review was 'moderate' with an overall score 32 out of 42 (Table 5). The reference standard, care settings and level of LUS expertise were consistently acceptable across all studies. Double blinding between the reference and index tests occurred in three (50%) of the six studies[10,13,16] with single blinding of the CXR to LUS results occurring in the remaining 50% [4,14,42] . All studies conducted CXR first followed by LUS. Four studies stated the interval between LUS and CXR as less than 24 hours but failed to provide more precise timing[13,14,16,42] .Two studies reported LUS and CXR examinations were performed within 5 hours of each other [4,10.] All studies used a combination of ultrasound findings to formulate the diagnostic threshold. The four studies using transthoracic scanning diagnosed NRDS on detection of consolidation, pleural line abnormalities and bilateral white lung.[4,10,16,42] The two studies adopting a transabdominal approach defined the presence of retro-diaphragmatic hyper-echogenicity with >3 B-lines as indicative of NRDS.[13,14]

Meta-analysis

Across the six studies, pooled sensitivity and specificity for the diagnosis of NRDS was 0.97 (CI: 0.94-0.99) and 0.91 (CI: 0.86-0.95) respectively (Figures 3a and 3b). The χ^2 values were statistically significant ($p<0.10$) indicating heterogeneity amongst the studies due to chance; χ^2 22.92 ($p=0.0003$) and χ^2 21.60 ($p=0.0006$). The I^2 statistic values were 78.2% and 76.9%. Since these values were >50% this was considered to be significant heterogeneity based on recommendations from the Cochrane handbook (2008)[33]

Subgroup analysis of the four prospective cohort studies[4,13,14,16] showed pooled sensitivity of 96% (CI: 92%-98%) and specificity 86% (CI: 79%-92%). For the four

studies using transthoracic scanning,[4,10,16,42] LUS sensitivity was 99% (CI: 95%-100%) and specificity 98% (CI: 93%-100%); in comparison the pooled sensitivity of the two studies using transabdominal scanning[13,14] was 96% (CI: 91-98%) and the specificity 83% (CI: 72%-98%).

Discussion

Diagnostic accuracy of LUS

Meta-analysis of six studies which compared LUS to CXR and clinical information showed high sensitivity (97%) and specificity (91%) for detecting and excluding NRDS respectively. Subgroup analysis of the four prospective cohort studies showed markedly lower specificity. Although the healthy controls underwent the same index and reference tests as the disease group in the two case-control studies, the absence of a random or a consecutive sample of participants may have resulted in over-estimation of diagnostic accuracy in this subgroup.[36] As such we feel the subgroup analysis of prospective cohort studies provides the most accurate reflection of test accuracy (sensitivity 96%, specificity 86%).

The transthoracic technique appeared to be superior to the transabdominal approach for diagnosing NRDS because subgroup analysis demonstrated it to have marginally better sensitivity (99%, 97% respectively) and better specificity (98%, 82% respectively). The increased specificity of the transthoracic technique would reduce the number of false positive diagnoses and have the clinical benefit of reducing unnecessary additional testing or intervention.

Vergine et al.[16] measured the diagnostic accuracy of CXR without the addition of clinical information and found a sensitivity of 91% and a specificity of 84%. Based on these values, LUS appears to be a comparable test.

Timing of test performance

During the acute phase of NRDS the clinical picture can vary significantly over time.[6,7] Such changes are influenced by naturally increasing disease severity and the impact of any treatment provided. It is important when comparing a proposed new test with an existing 'reference' test that both are carried out within a narrow time frame to reduce performance bias.[36] Two studies[4,10] specified that both tests were conducted within 5 hours. The remaining four studies[13,14,16,42] completed LUS and CXR within 24 hours. This increases the risk of bias due to the possibility that changes occurred as a result of advancing disease severity or conversely, due to treatment response (Table 5). [34]

Limitations of imaging

The long term biological effects of ultrasound on neonatal lung tissue are unknown.[25] Through prudent clinical use and the avoidance of ionising radiation, LUS is a safer alternative to CXR theoretically.[21] Despite an established pattern of radiological appearances in NRDS findings often overlap with other respiratory pathologies that are common among premature neonates.[11,21] The static, planar nature of the CXR can make differential diagnosis difficult and a degree of inter-observer disagreement is inevitable, especially in less advanced disease.[21]

LUS has its own characteristic signs associated with NRDS, [9,10,11,21] the identification of which are aided by real-time visualisation of lung parenchyma and the performance of numerous multi-planar sweeps across the lung fields.[10, 13] Ultrasound is notoriously operator dependant, an inherent source of potential error, [25] although utilisation of a standard approach helps to limit operator dependency and can improve diagnostic accuracy.[21]

If LUS is to be used as a first line investigation for NRDS it must be carried out soon after birth in order to maximise positive health outcomes. This presents economic and administrative challenges as LUS would require neonatal clinicians to spend time learning a new skill or alternatively, a LUS practitioner would be required to service the NICU twenty four hours a week.

Consequences of diagnostic error

The relatively low (91%) pooled specificity for LUS implied a tendency for over-diagnosis of NRDS. Sixteen false positives cases were described across the studies due to pneumonia (n=8), transient tachypnoea (n=3), pneumothorax (n-1) and meconium aspiration syndrome (n=1); in three cases no alternate diagnosis was given.

Pneumonia occurs frequently in new-borns and shares many of the same sonographic and radiographic appearances of NRDS. Consolidation with air bronchograms, pleural line abnormality, and alveolar interstitial syndrome (presence of >3 b-lines) are all associated with the disease.[43] Consolidation in severe cases of pneumonia is often large with irregular margins; in less severe cases multi-focal areas of consolidation can be mistaken for NRDS.[44]In many cases the diagnosis of pneumonia requires bacteriologic culture to identify the presence of infection.[7]

Transient tachypnoea of the new-born (TTN) occurs in approximately 1% of all new-borns due to insufficient clearance of foetal lung fluid.[16] The resulting respiratory distress is accompanied by similar clinico-radiological features to those seen in NRDS. Copetti and Cattarossi[45] described 'the double lung point' sign in TTN which improves the accuracy of LUS for diagnosis (sensitivity 93%, specificity 97%). The

'double lung point' sign features a normal pleural line with sliding lung, difference in echogenicity of lower and upper lung areas, and comet tail artefacts in the inferior lung but largely absent in the superior lung.[45] All three false positives with TTN were from the same study[14] which utilised a transabdominal technique. Copetti et al.[42] suggests it is not possible to examine either the superior lung field or the pleural line using this approach, which may explain the failures to correctly diagnose the condition.

Of the nine false negative cases identified seven were insufficiently reported and the eventual diagnosis is unknown. The remaining two were diagnosed by CXR as partial pneumothorax. This can be a complication of NRDS along with other associated air-leak syndromes such as interstitial emphysema,[21] pneumomediastinum and pneumopericardium.[7,10,] Air leaks may occur spontaneously, but more commonly occur through inadequate mechanical ventilation pressure causing alveolar rupture and subsequent escape of air beyond the terminal airways.[8] Neonates with NRDS have an increased risk of air-leaks due to the delicate nature of the surfactant-deficient lung and their frequent oxygen therapy requirement.[46] Lichtenstein et al[47] defined a pattern of LUS features that can be used to diagnose pneumothorax, normal lung sliding and b-lines originating from the visceral pleura are obliterated at the site of pneumothorax. The point at which normal findings diminish is 'the lung point' which demarcates the presence of air in the pleural cavity (pneumothorax) and is associated with 79% sensitivity, 100%specificity.[47] Both instances of false negative pneumothorax were diagnosed by CXR in the study by Lovrenski,[4] the author maintaining that despite a well-defined pattern, smaller pneumothoraces remain diagnostically challenging. Bober and Swietliński[13] support this idea and

suggest that an ultrasound beam can propagate through a small pneumothorax into the lung field, rendering production of the lung point sign impossible.

Pneumothoraces are also frequently encountered in cases of meconium aspiration syndrome which may explain the isolated false positive case identified in this review. Air is unable to escape upon exhalation due to airway constriction around aspirated meconium which increases the resistance of expiratory airflow. This 'ball valve' effect creates a volume of trapped gas causing hyperinflation and possible alveolar rupture (air-leak).[48]

The use of LUS for the detection of pneumomediastinum and pneumopericardium is yet more contentious with arguments for[49,50] and against.[10,16] There is little high quality evidence to support or deny a role for LUS in this area. This is important, as a chief concern with suspected NRDS is the presence of leaking air due to its deleterious consequences (tension causing compression of vessels and airways).[46] with this in mind, CXR appears requisite to rule out air-leak syndromes for neonates with suspected NRDS.

Summary

This review has shown that LUS compares well with this current reference standard for the diagnosis of NRDS. With appropriate technique and knowledge of standardised findings and potential pitfalls, e.g. TTN, pneumothorax, the diagnostic accuracy of LUS could be further improved. LUS has superior diagnostic accuracy for alveolar consolidation - a major component of the NRDS pattern (90% sensitivity, 98% specificity). Reduced CXR sensitivity (68% sensitivity 95% specificity) occurs when the radiograph is acquired in the supine position – a necessity in neonates.[44]

Less intra-observer variation occurs in LUS identification of small pneumonias and air bronchograms - a problematic source of error in CXR reading.[51] This may be due to real- time visualisation of lung behaviour in synchronisation with the respiratory cycle and the ability to access multiple cross sections of the lung fields.[13] Reduced lung volume, smaller thorax diameter and a thin thoracic wall in neonates may also improve image quality.[5,13,52]

Review limitations.

A degree of heterogeneity across studies was expected and this was confirmed statistically by I^2 values greater than 50% across both forest plots (Figures 3a and 3b). In addition to the differences in study design and scanning technique addressed in the subgroup analysis, three other sources of heterogeneity were identified.

LUS operators were not blinded to clinico-radiologic information in 50% of the studies (Table 4). As prior knowledge can influence the interpretation of the forthcoming examination this could have biased diagnostic accuracy favourably.

With the exception of two studies,[4,10] the duration between CXR and subsequent LUS was variable. This could have inflated LUS sensitivity due to disease progression leading to increased detection of pathology in the second test. Conversely, LUS sensitivity for NRDS may have appeared diminished due to the effects of surfactant replacement therapy between tests. No study reported instigation of treatment during the test interval so the effect of this bias remains unknown.

All studies used signs and symptoms in the clinical diagnosis; only three studies included a supplementary blood test.[4,10,13] Additional CRIB and GAST tests were

used in only two studies.[13,14] Differences in the clinical tests used across the studies could have introduced bias leading to their varying diagnostic accuracy and applicability (Table 4).[34,36]

The six studies included 480 participants. This sample may not reflect the full spectrum of NRDS, or diseases that mimic the appearance of NRDS, which a larger sample size might. In cases of non-advanced disease a differential diagnosis with LUS becomes harder to define, although this is a problem that is shared with CXR.

Although used as the reference standard the absolute diagnostic accuracy of 'CXR and clinical tests' has not been verified in neonates.[47]

Recommendations

Owing to the frequency of NRDS admissions to NICU's and the number of CXRs performed on neonates, LUS adheres to the ALARP principle by reducing ionising radiation burden. The following recommendations are suggested:

- CXR is required in suspected NRDS to assess for air-leak syndromes.
- The combination of consolidation, pleural line abnormalities and bilateral white lung detected via the transthoracic technique offers the most reliable diagnostic criteria (sensitivity 99%, specificity 98%).
- Future research is required to understand LUS effectiveness as;
    a. An initial screening tool for NRDS and comorbid ALS.
    b. ETT assessment to compare LUS and CXR at four hours of postnatal age.
    c. Follow up imaging tool for informing surfactant and ventilatory therapy in NRDS patients.

d. Comparison of neonatologist vs. ultrasound practitioner vs. neonatal nurse practitioner in acquiring and interpreting LUS.
e. Economic modelling to determine the feasibility of either current neonatal staff learning a new skill, spend time practicing it and interpreting the results; number of neonatologists or nurse practitioners or ultrasound practitioners to carry out LUS.
f. Impact on neonatal service delivery 24/7 review.

Conclusion

The diagnostic accuracy of LUS appears to be comparable with the reference standard of CXR and clinical tests. However the presence of heterogeneity among studies, which have small sample sizes, and no independently validated comparator mean the results must be treated cautiously.[33] LUS may potentially miss ALS (pneumothorax, pneumomediastinum and pneumopericardium), and therefore CXR remains necessary for suspected NRDS. It is a promising technique although currently in its infancy with a limited body of experimental studies to support its use. High quality RCT studies are required to quantify the diagnostic accuracy of LUS for NRDS and comorbid ALS, and to assess LUS effectiveness in follow up imaging. A significant role of CXR in NRDS is verification of ETT position for neonates receiving invasive ventilation.[32] Further study into the effectiveness of ultrasound ETT confirmation is required if the absorbed dose of IR is to be reduced. Future research should address ways to integrate LUS practice into NICUs in terms of personnel to perform the examination and its economic feasibility.

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Table 1. LUS appearances of the normal and NRDS affected lung[21]

LUS Finding	Normal Lung	Abnormal Lung
Pleural line (lung sliding)	Smooth echogenic appearance <0.5mm thick. Visceral and parietal pleura visualised 'sliding' with respiration.	Absence or disruption of the line, >0.5mm thickness, no 'sliding'.
A-lines (Figure 1a)	Equidistant echogenic lines beneath and parallel to the pleural line. Reverberation artefact caused by large change in acoustic impedance at the lung-pleura interface.	Absent.
B-lines (Figure 1b)	Usually absent, <3 B-lines occasionally demonstrated due to watery nature of the neonatal lung, but disappear within 24 hours of life.	>3 Hyper echoic artifactual lines extending vertically from the pleural line into the lung field. These lines erase A-lines and move with respiration. Delineates increased fluid in the interlobular septae between the alveoli.
B3-lines (Figure 1c)	Absent	B-lines closely merged (within 3mm) create a 'white lung' appearance through increased oedema indicative of alveolar interstitial syndrome (AIS).
Consolidation	Absent	Areas of de-arieted lung parenchyma mimicking the appearance of the liver (hepatatization), and/or presence of air or fluid bronchograms delineated by hyper echoic punctate specs and branching lines. Indicative of atelectasis.
Pleural- effusion	Absent	Anechoic fluid delineated by the pleural line, the diaphragm and the lungs visceral surface.

Table 2. Search terms

Neonate (≤42wk)	Ultrasound	Chest X- Ray	Neonatal Respiratory Distress Syndrome
neonat*, infant*, pediatric* newborn*, preterm, premature, babies, baby.	ultraso*, sonog*, lung ultrasound,	X-Ray, radiograph*, conventional radiograph*, plain film, radiolog*, computed radiography, digital radiography, radiogram, roentgenogram.	neonatal respiratory distress syndrome, infantile respiratory distress syndrome, hyaline membrane disease, respiratory distress syndrome, Pulmonary surfactant, lung disease, respiratory disease, surfactant deficiency disorder.

** Indicates truncation command*

Table 3. Primary data extracted from retrieved studies for meta-analysis

Study	Year	Origin	Study type	Sample size	Gestational age (mean ± SD weeks)	Male/ female, *n*	True positive *n*	False positive *n*	True negative *n*	False negative *n*
Ahuja et al[14]	2012	India	Prospective	88	29+6d ± 11d	50/38	32	6	44	6
Bober & Świetliński[13]	2006	Poland	Prospective	131	32 ± 4.4	86/45	101	8	22	0
Copetti et al[42]	2008	Italy	Case - control	55	27.2 ± 2.7	unknown	40	0	15	0
Liu et al[10]	2014	China	Case-control	100	34.9 ± 2.7	62/38	50	0	50	0
Lovrenski[4]	2012	Serbia	prospective	47	30.9 ± 3.16	unknown	43	0	2	2
Vergine et al[16]	2014	Italy	prospective	59	33 ± 4	36/23	22	2	34	1

Table 4. General study characteristics

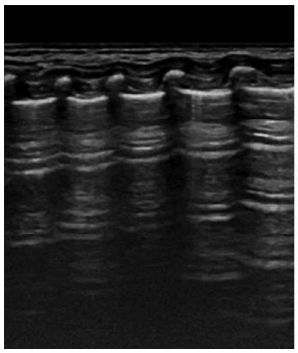
Study + QUDAS-2 Score (0-7)	Diagnostic Method	LUS Operator	LUS Technique	US Equipment	LUS Diagnostic Criteria	Time Between CXR & LUS	Blinding
Ahuja et al[14] **(5)**	Gastric aspirate test + clinical diagnosis + CXR	Radiologist	Transabdominal	HDI 3500 [Advanced Technologies Laboratories (ATL) Ultrasound, Bothell, WA, USA] (5-12 MHz) curvilinear probe	Diffuse retrodiaphragmatic hyperechogenicity completely replacing the normal diaphragm	<20Hrs	Not blinded
Bober & Świetliński[13] **(6)**	CRIB score + CXR + blood results	Physician	Transabdominal	Siemens SI 450, unknown origin, equipped with a sector 5-MHz transducer	Retrophrenic hyperechogenicity with B lines diverging radially	<24Hrs	Blinded
Copetti et al[42] **(4)**	Clinical diagnosis + CXR	Paediatrician + Cardiologist	Transthoracic	Megas CVX Esaote, Medical Systems, Florence, Italy (10MHz Linear Probe)	Bi-lateral white lung, absence of spared areas, thickened and irregular pleural line	<24Hrs	Not blinded
Liu et al[10] **(6)**	Clinical diagnosis + CXR + blood results	1 'expert'	Transthoracic	High resolution line probe (11-12 MHz) (GE Voluson i or E6, USA)	Consolidation, Pleural line Abnormalities and Bilateral White Lung	Immediate	Blinded
Lovrenski[4] **(5)**	Clinical Diagnosis + CXR + blood results	Paediatric Radiologist	Transthoracic + Transabdominal	7.5 MHz linear probe (Sonoline Adara, Siemens, Erlangen, Germany)	Consolidation; air bronchograms and B-Lines	3.24–4.96 hours	Not blinded
Vergine et al.[16] **(6)**	Clinical diagnosis + CXR	Neonatologist	Transthoracic	Vivid-I Ge Medical Systems, Milan, Italy using a high res 10-12MHz linear probe	Bi-lateral white lung, coalescent B-lines & thickened and irregular pleural line	<24Hrs	Blinded

Table 5. QUADAS-2 Risk of bias and applicability assessment.

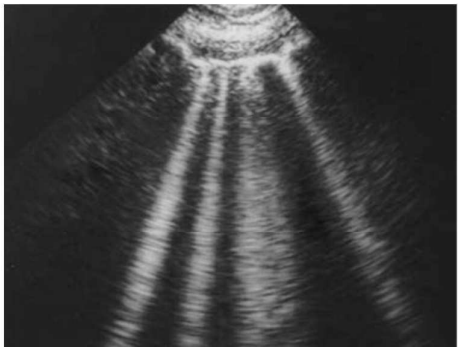
Study	Risk of Bias				Applicability Concerns			Score
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard	(0-7)
Ahuja et al[14]	☺	☹	☺	☹	☺	☺	☺	5
Bober & Świetliński[13]	☺	☺	☺	☹	☺	☺	☺	6
Copetti et al[42]	☹	☹	☺	☹	☺	☺	☺	4
Liu et al[10]	☹	☺	☺	☺	☺	☺	☺	6
Lovrenski[4]	☺	☹	☺	☹	☺	☺	☺	5
Vergine et al[16]	☺	☺	☺	☹	☺	☺	☺	6

☺ = *Low* ☹ = *High*

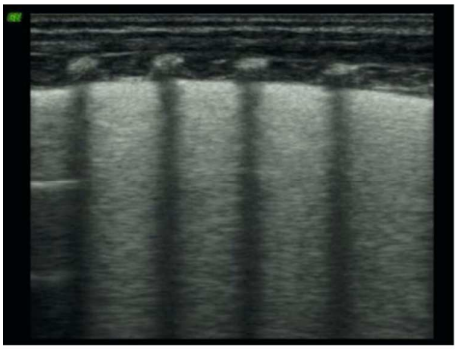
Figures 1a,1b and 1c. Normal and abnormal transthoracic LUS appearances of NRDS.



1a. Normal; A-lines.

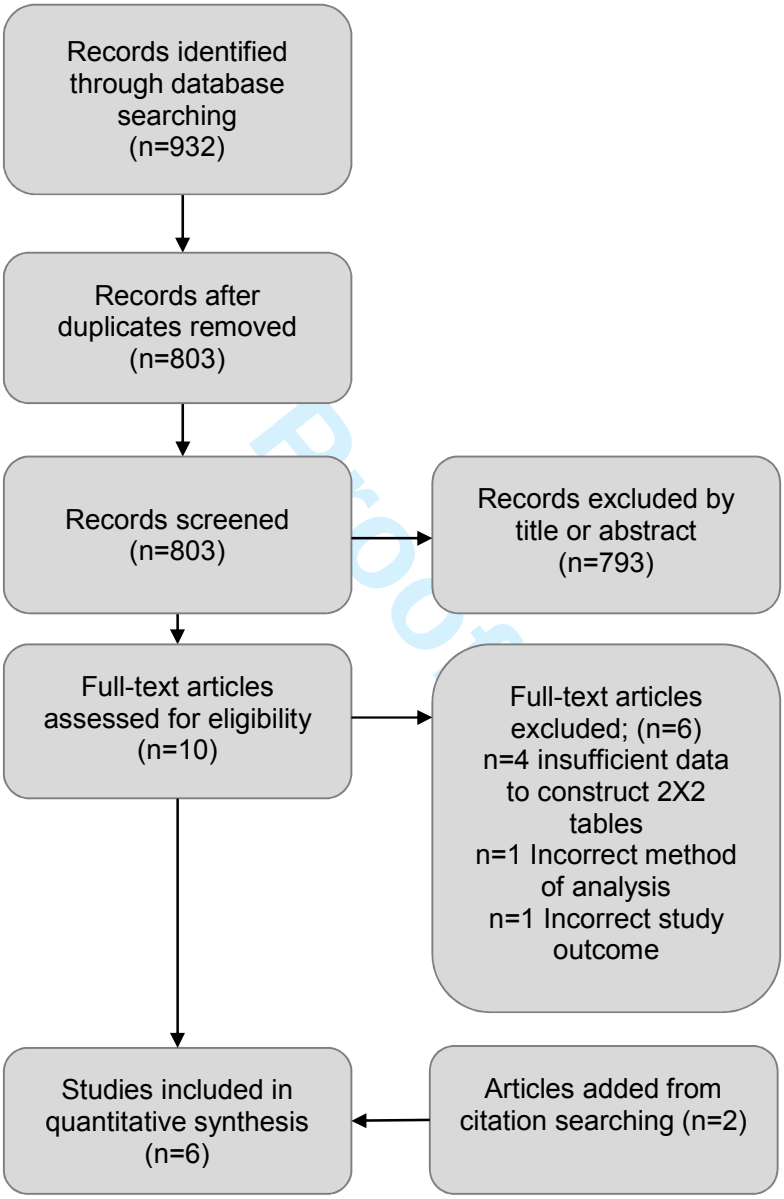


1b. Abnormal; >3 B-lines.

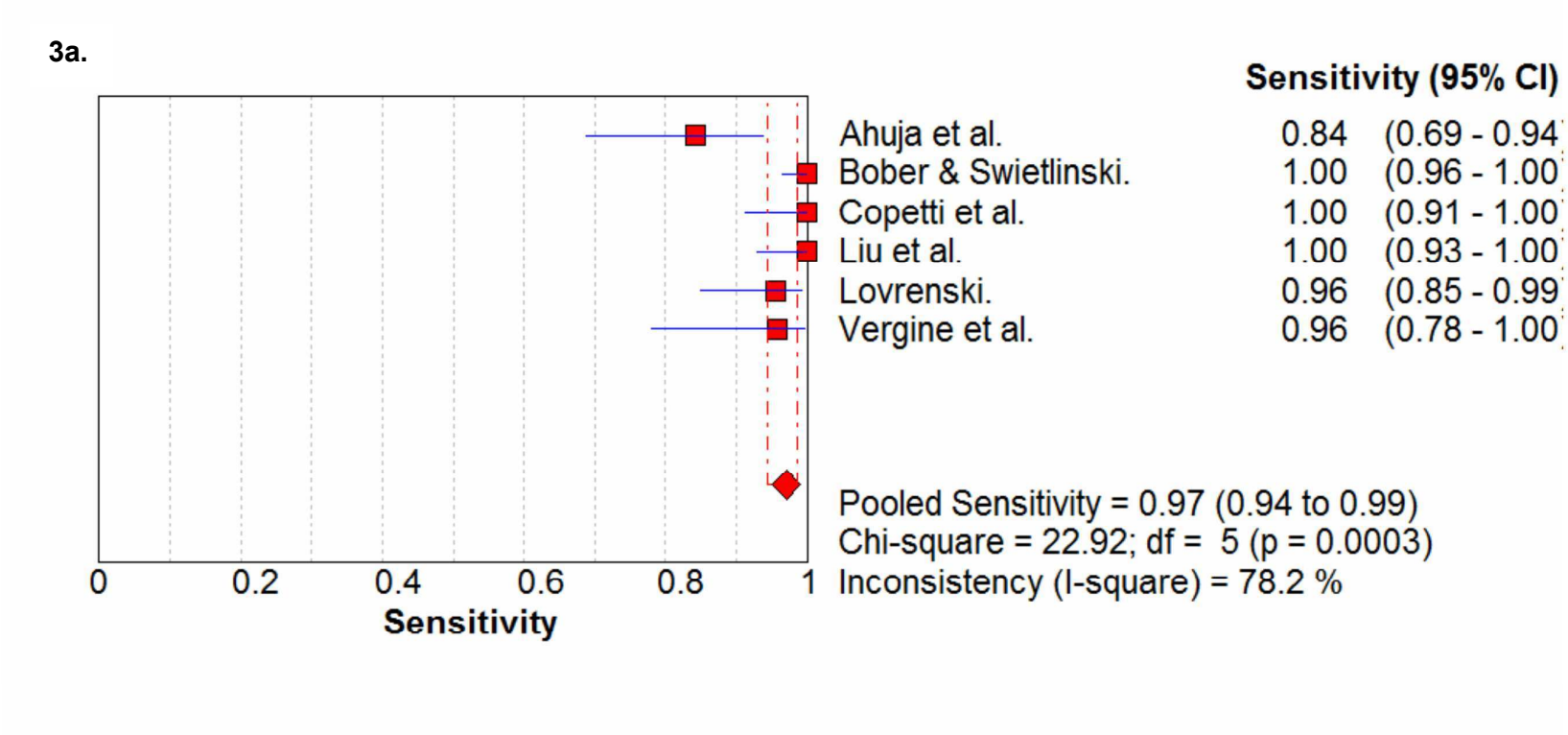


1c. Abnormal; 'White-out'.

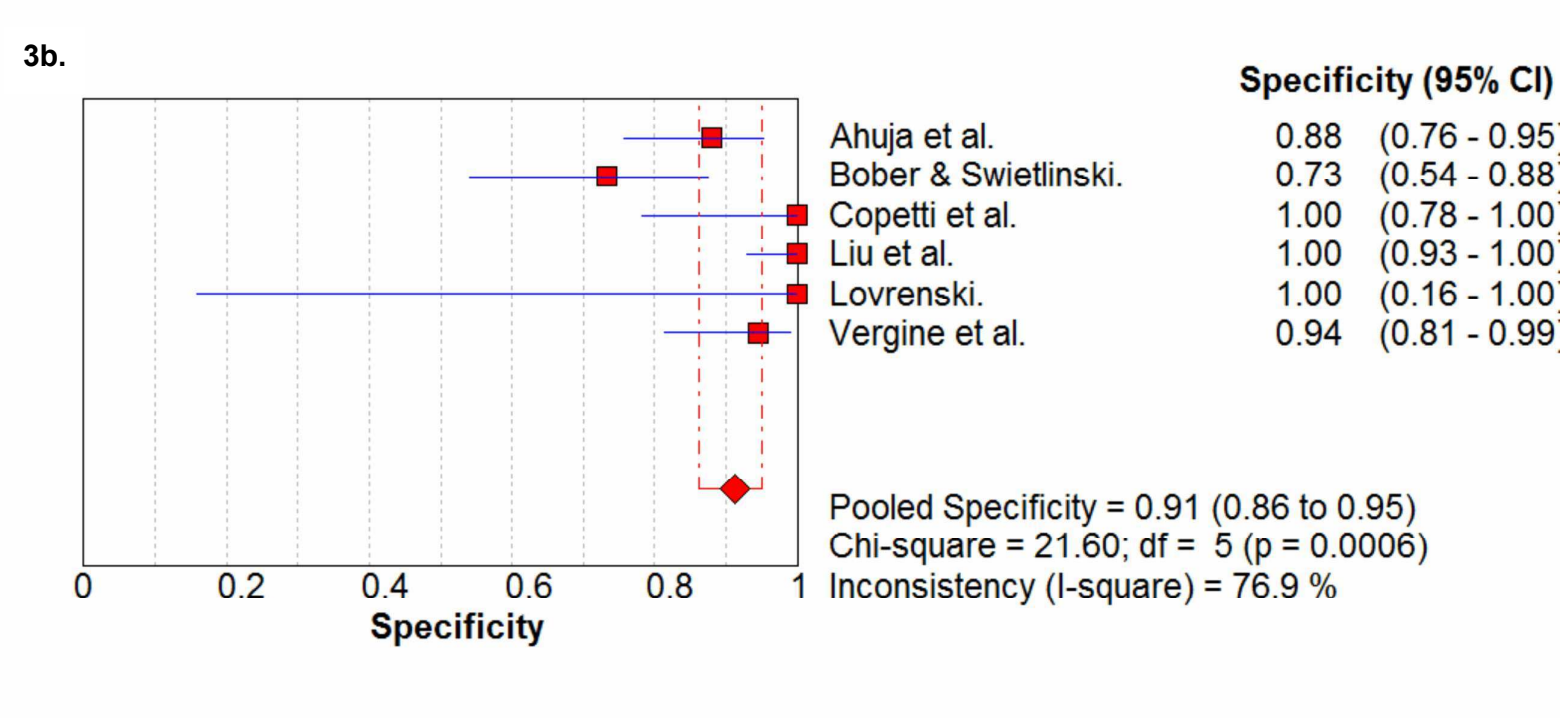
Figure 2. PRISMA flow diagram of search process.



Figures 3a and 3b. Forest plots describing the sensitivity (2a) and specificity (2b) of LUS for the diagnosis of NRDS.



3b.


Specificity (95% CI)
Ahuja et al. 0.88 (0.76 - 0.95
Bober & Swietlinski. 0.73 (0.54 - 0.88
Copetti et al. 1.00 (0.78 - 1.00
Liu et al. 1.00 (0.93 - 1.00
Lovrenski. 1.00 (0.16 - 1.00
Vergine et al. 0.94 (0.81 - 0.99
Pooled Specificity = 0.91 (0.86 to 0.95)
Chi-square = 21.60; df = 5 (p = 0.0006)
Inconsistency (I-square) = 76.9 %
0
0.2
0.4
0.6
0.8
1
Specificity