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Lung Ultrasound for the Diagnosis of Neonatal Respiratory Distress Syndrome

A Meta-analysis

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Abstract: Chest radiography is the primary imaging modality used for the assessment of neonatal respiratory distress syndrome (NRDS) in newborns. However, excessively exposing a growing neonate to harmful ionizing radiation may have long-term consequences. Some studies have shown that lung ultrasound (LUS) is helpful in the diagnosis of NRDS. A comprehensive search was carried out using PubMed, Embase, and the Cochrane Library to identify studies in which newborns with clinically suspected NRDS were assessed by LUS. Two investigators independently screened the literature and extracted the data. Any discrepancies were resolved via discussion with the senior author. Study quality was assessed by the Quality Assessment of Diagnostic Accuracy Studies 2 tool, and pooled sensitivity and specificity of various LUS findings for diagnosing NRDS were determined. Summary receiver operating characteristic curve was used to assess the overall performance of LUS. Ten studies with a total of 887 neonates were included in this meta-analysis. There was significant heterogeneity across the included studies. The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio for the diagnosis of NRDS using LUS were 0.92 (95% confidence interval [CI], 0.89–0.94), 0.95 (95% CI, 0.93–0.97), 20.23 (95% CI, 8.54–47.92), 0.07 (95% CI, 0.03–0.14), and 455.30 (95% CI, 153.01–1354.79), respectively. Furthermore, the summary receiver operating characteristic area under the curve was calculated to be 0.9888. The main LUS characteristics of NRDS include bilateral white lung, pleural line abnormalities, and lung consolidation. In summary, LUS is a highly valuable diagnostic technology that complements chest radiography in the diagnosis and follow-up monitoring of NRDS.

Key Words: neonatal respiratory distress syndrome, lung ultrasound, meta-analysis, diagnostic accuracy

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Neonatal respiratory distress syndrome (NRDS) is recognized as one of the most common etiologies of respiratory distress in newborn preterm infants in neonatal intensive care unit, which is mainly caused by pulmonary surfactant deficiency at birth.[1] Pulmonary insufficiency commences in newborns with NRDS after birth and is increasingly severe in the first 2 days of life.[2] It is more frequently seen in newborn preterm infants.[3,4] Infants with NRDS account for 92% of infants born at 24 to 25 weeks gestation, 88% at 26 to 27 weeks, 76% at 28 to 29 weeks, and 57% at 30 to 31 weeks.[2]

At about 24 weeks, type 2 pneumocytes secrete pulmonary surfactant, which reaches a level that supports breathing after birth by 36 weeks gestation.[5]

Because of surfactant deficiency in premature infants with NRDS, alveoli are more likely to collapse at the end of expiration.[6,7] Clinical manifestation of NRDS shows respiratory distress including cyanosis, tachypnea, substernal and intercostal retraction, and grunting from expiratory air colliding with a partially closed glottis at or shortly after birth.[8] Newborns affected by NRDS generally require exogenous surfactants and mechanical ventilation to maintain alveolar expansion.[9] Neonatal respiratory distress syndrome with the characters of severe illness, rapid progress, and poor prognosis is the main cause of neonatal death, and therefore, early diagnosis and early treatment are exceedingly significant for preterm newborns to improve the prognosis.[10,11] Usually, the diagnosis of NRDS is based on clinical manifestations, findings of chest x-ray (CXR), and arterial blood gas results.[8,12] However, excessively exposing a growing neonate in early part of life to harmful ionizing radiation may have long-term consequences. Persons exposed early in life have especially high relative risks for many cancers, and radiation-related risk of solid cancers appears to persist throughout life.[13] There is a need for identifying an alternative diagnostic test without ionizing radiation. Ultrasound is a noninvasive, nonradioactive and cost-effective technique that has become an important tool for diagnosis in cranial and abdominal abnormalities in neonatal intensive care units.[14,15] Lung ultrasound (LUS) has been successfully applied to the diagnosis of infant lung diseases such as pneumonia, transient tachypnea of the newborn (TTN), and NRDS in recent years.[16,17] Ultrasound findings of pulmonary diseases such as TTN, NRDS, and pneumonia include bilateral white lung, pleural line abnormalities, lung consolidation, and pleural effusion.

For the moment, a few of studies with small patient populations have demonstrated promising results with LUS for the diagnosis of NRDS. To comprehensively address this issue, we performed a systemic meta-analysis to determine the diagnostic performance of LUS in newborns with NRDS and provided evidence-based medicine for clinical evidence.

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MATERIALS AND METHODS

Protocol and Registration

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Diagnostic Test Accuracy guidelines, http://links.lww.com/RUQ/A204, which include 27 items and provide specific guidance for reporting of systematic reviews.[18] We registered our protocol with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42020149412).

Search Strategy

Pubmed, EMBASE, and the Cochrane Library were comprehensively screened to identify potentially eligible studies from inception to July 2019. The search terms included and captured the concepts of *ultraso**, *sonog**, *respiratory distress*, *hyaline membrane disease*, and *surfactant deficiency disorder*. Details of the search strategy are included in Appendix 1, http://links.lww.com/RUQ/A203. The reference lists of all retrieved articles were manually screened to expand the number of included studies. Only studies in English, which satisfied the inclusion criteria, were enrolled.

Study Eligibility

Two investigators (J.W. and Y.W.) independently screened the search results for potentially eligible studies. Before identifying the literature, inclusion and exclusion criteria were defined to increase validity and reproducibility. Any discrepancies were resolved via discussion with the senior author (Z.W.). The authors are all ultrasound diagnosticians with more than 10 years of experience.

The inclusion criteria were as follows: (1) randomized control trials and cohort or case-control studies were included; (2) studies involving neonates in a clinical condition with signs and symptoms of NRDS within 48 hours of birth were included in this meta-analysis; (3) the accuracy of LUS in the diagnosis of NRDS was evaluated; and (4) a reference standard was adopted to confirm NRDS, including clinical manifestations, clinical follow-up, CXR, and/or laboratory blood gas analysis.

The exclusion criteria were as follows: (1) case reports, case series, letters, editorials, comments, and unpublished articles; (2) studies that contained the same sample; and (3) studies without enough information to construct diagnostic 2×2 contingency tables.

Data Extraction

Two investigators (J.W. and Y.W.) independently extracted the relevant data from the included studies using a predesigned data collection form. Any discrepancies were resolved via discussion with the senior author (Z.W.). For eligible studies, the following items were extracted: last name of the first author, year of publication, country, study type, study population size, blinding, mean gestational age of the study newborns, method of NRDS diagnosis, LUS operator specialty, LUS diagnostic technique, time between CXR and LUS, LUS diagnostic criteria, true positives, and true negatives, as well as false positives and false negatives of LUS in the diagnosis of NRDS.

Study Quality

The risk of bias and methodological quality was evaluated by 2 investigators (J.W. and Y.W.) independently by using the Quality Assessment of Diagnostic Accuracy Studies 2 tool,[19] which was a revised quality assessment application developed definitely for a meta-analysis of diagnostic accuracy studies. Any discrepancies were resolved by consensus. The quality of each included study was evaluated by an appraisal of the risk of bias of 4 domains and clinical applicability of 3 domains of the study characteristics. Four domains consisted of patient selection, index test, reference standard, and flow and timing. Each domain was evaluated for risk of bias, and the first 3 domains were evaluated for applicability. The processing of the quality assessment was performed using RevMan 5.3 software (Nordic Cochrane Centre, Copenhagen, Denmark).

Statistical Analysis

The present meta-analysis was conducted by Meta-Disc Version 1.4 (Unit of Clinical Biostatistics Team of the Ramony Cajal Hospital, Madrid, Spain) and STATA 12.0 (Stata Corporation, College Station, TX). The summary estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with corresponding 95% confidence intervals (CIs) were calculated using a bivariate meta-analysis model in the present analysis, which indicated the accuracy of LUS in the diagnosis of NRDS. Meanwhile, the summary receiver operating characteristics (SROC) curve, which assessed the overall performance of LUS, was constructed, and the area under the curve (AUC) was calculated. An AUC close to 0.5 shows a poor test, whereas an AUC of 1.0 demonstrates an excellent diagnostic test.[20] The χ^2 and the inconsistency index (I^2) were used to assess the heterogeneity among different studies with $I^2 > 50\%$ suggesting significant heterogeneity. Then, we would use a random-effect model to continue our analysis.[21] The Deeks funnel plot asymmetry test was applied to assess publication bias,[22] through a P value of >0.05 denoting no significant publication bias.

RESULTS

Search Results

The electronic search for studies, which assessed the diagnostic accuracy of LUS for NRDS, provided a number of 1173 articles, of which 872 relevant studies remained after exclusion of 301 duplicate citations. Of these, after scanning the abstracts and titles, 856 studies were omitted because it was obvious from the title or abstract that they were not relevant to the present meta-analysis. Full text of the remaining studies was reviewed, and another 6 references were excluded. Therefore, 10 studies were ultimately included in the present meta-analysis.[23–32] Manual searching of the reference cited in these 10 studies did not yield any additional relevant studies. A flow chart depicting the literature search is presented in Figure 1.

Characteristics of the Included Studies

As indicated in Table 1, the 10 included studies with a total of 887 neonates were published between 1990 and 2019 and written in English. Among the studies, 7 were prospective cohort studies,[23,24,26,28,30–32] and 3 were case-control studies.[25,27,29] The mean number of neonates per study was 88.7 (range, 40–146). Six studies were conducted in Europe,[23–25,28,30,32] and 4 studies in Asia.[26,27,29,31] Eight studies[24,26–32] reported sex ratios: 58.7%

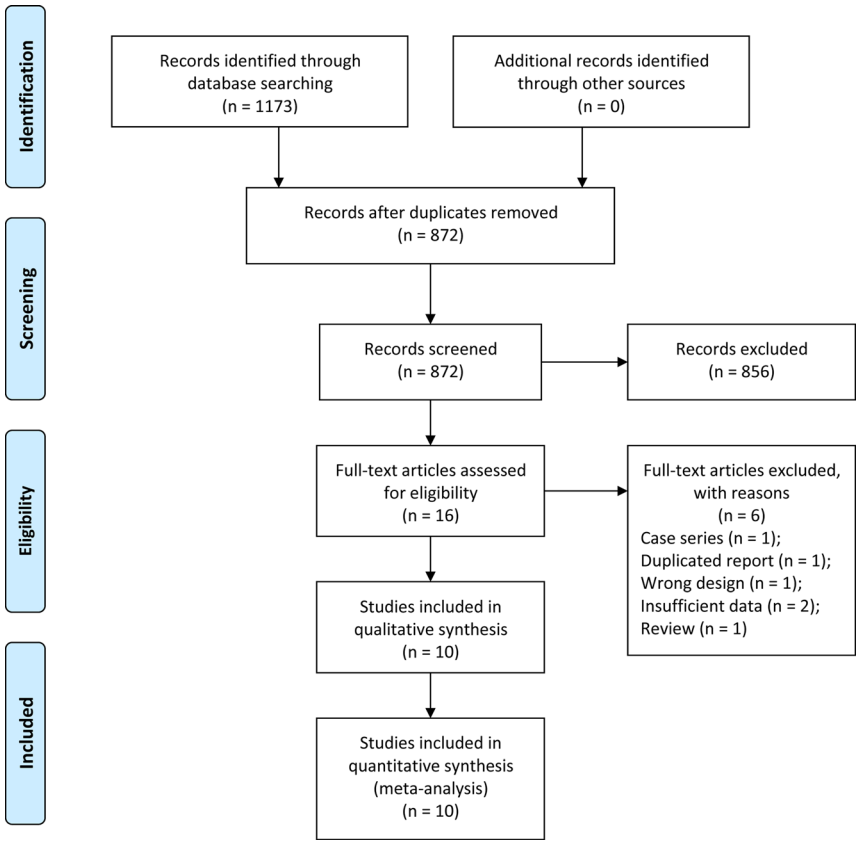

FIGURE 1. PRISMA flow diagram.

of neonates were male, and 41.3% were female. The mean gestational age of neonates was depicted in 9 of 10 studies (range, 27.2 ± 2.7–35.9 ± 2.7 weeks). Table 2 epitomized the general characteristics of the included studies.

Quality Assessment

The quality assessment results of the risk of bias and applicability concerns of the selected studies were presented

TABLE 1. Primary Data Extracted From Included Studies for Meta-analysis

Author, Year	Country	Study type	Sampling Method	Cases, n	Gestational Age, Mean ± SD, wk	TP	FP	FN	TN
Avni et al, 1990[23]	Belgium	Prospective	Consecutive	40	NR	24	0	0	16
Bober and Świetliński, 2006[24]	Poland	Prospective	Consecutive	131	32 ± 4.4	101	8	0	22
Copetti et al, 2008[25]	Italy	Case-control	Unclear	55	NRDS group, 27.2 ± 2.7; control group, 30.4 ± 3.4	40	0	0	15
Ahuja et al, 2012[26]	India	Prospective	Consecutive	88	29.9 d ± 11 d	32	6	6	44
Liu et al, 2014[27]	China	Case-control	Unclear	100	Cases group, 34.9 ± 2.7; control group, 35.1 ± 2.8	50	0	0	50
Vergine et al, 2014[28]	Italy	Prospective	Unclear	59	33 ± 4	22	2	1	34
Rachuri et al, 2017[29]	India	Case-control	Unclear	94	Cases group, 34.5 ± 3.2; control group, 35.9 ± 2.7	29	1	0	64
Corsini et al, 2018[30]	Italy	Prospective	Consecutive	124	33 ± 5	58	2	2	72
Pang et al (1),* 2019[31]	China	Prospective	Consecutive	146	NRDS group, 29.0 ± 3.4; TTN group, 35.1 ± 2.9	77	0	19	50
Pang et al (2),* 2019[31]	China	Prospective	Consecutive	146	NRDS group, 29.0 ± 3.4; TTN group, 35.1 ± 2.9	79	0	17	50
Jagła et al, 2019[32]	Poland	Prospective	Consecutive	50	33.2 (23–41)	21	2	2	25

*There were different diagnostic criteria mentioned in the studies showing different sensitivity or specificity.

NR, not reported; TP, true positive; FP, false positive; FN, false negative; TN, true negative.

TABLE 2. Characteristics of the Included Studies

Author, Year	Blinded Method	Diagnostic Method	LUS Operator	LUS technique	Time Between CXR and LUS	LUS Diagnostic Criteria	LUS Equipment
Avni et al, 1990[23]	NR	CXR and clinical diagnosis	NR	Transabdominal	<24 h	Retrohepatic hyperechogenicity	A commercially available high-resolution sector 5 MHz transducer
Bober and Świetliński, 2006[24]	Double blinded	CXR + blood results	Physician	Transabdominal	<24 h	Retrophrenic hyperechogenicity with B lines diverging radially	Siemens SI 450 equipped with a sector 5-MHz transducer
Copetti et al, 2008[25]	Single blinded	CXR and clinical diagnosis	Pediatrician and cardiologist	Transthoracic	<24 h	Bilateral white lung, absence of spared areas, thickened and irregular pleural line, lung consolidation	Megas CVX Esaote, Medical Systems, Florence, Italy (10 MHz Linear Probe)
Ahuja et al, 2012[26]	Single blinded	Gastric aspirate test + clinical diagnosis + CXR	Radiologist	Transabdominal	<24 h	Diffuse retrodiaphragmatic hyperechogenicity completely replacing the normal diaphragm complex	HDI 3500 (Advanced Technologies Laboratories [ATL] Ultrasound, Bothell, WA), a curvilinear probe (5–12 MHz)
Liu et al, 2014[27]	Double blinded	CXR + clinical diagnosis + blood results	An expert	Transthoracic	Immediately	Lung consolidation, pleural line abnormalities, pleural effusion, bilateral white lung	A high-resolution line probe (11–12 MHz) (GE Voluson i or E6, USA)
Vergine et al, 2014[28]	Double blinded	CXR + clinical diagnosis	A trained neonatologist	Transthoracic	<24 h	Bilateral white without spared areas, a thickened and irregular pleural line	Vivid-i (GE Medical Systems, Milan, Italy) using a high-resolution 10–12 MHz linear probe
Rachuri et al, 2017[29]	Single blinded	CXR + clinical diagnosis	Neonatologist	Transabdominal and transthoracic	<1 h	Transthoracic view: bilateral white lung, a thickened and irregular pleural line; transabdominal view: diffuse retrodiaphragmatic hyperechogenicity	Philips machine using a linear probe of frequency 10–12 MHz or intracavitary probe of frequency 4–8 MHz
Corsini et al, 2018[30]	Double blinded	CXR	Neonatologist	Transabdominal and transthoracic	<24 h	Bilateral sign of abnormalities of the pleural line, white lung image, and absence of spared area in all lung fields	A Philips CX50 ultrasound machine using a high-frequency (10–12 MHz) linear
Pang et al (1),* 2019[31]	Double blinded	CXR + clinical diagnosis + blood results	Radiologist	Transthoracic	<24 h	LUS score with cutoff of 21.5	A high-resolution linear probe (Voluson S8; GE Healthcare, Waukesha, WI) with a frequency of >7.5 MHz (generally 10 MHz)
Pang et al (2),* 2019[31]	Double blinded	CXR + clinical diagnosis + blood results	Radiologist	Transthoracic	<24 h	Consolidation areas with cutoff of 0.5	A high-resolution linear probe (Voluson S8, GE Healthcare, Waukesha, WI) with a frequency of >7.5 MHz (generally 10 MHz)
Jagła et al, 2019[32]	Single blinded	CXR + clinical diagnosis + a capillary blood gas analysis	Neonatologist	Transthoracic	<2 h	Bilateral white lung without spared areas, thickened and irregular pleural line with disseminated subpleural consolidations with fluid alveologram	A portable US scanner equipped with a broadband linear L 5 to 12 MHz probe (Sonoscape S2, China)

*There were different diagnostic criteria mentioned in the studies showing different sensitivity or specificity.

NR, not reported.

graphically in Figure 2. With respect to the patient selection domain, 5 studies[25,27–30] did not clearly describe consecutive patients; 3 studies were considered as having high bias because of adopting a case-control design.[25,27,29] Concerning the index test domain, 1 study[23] was considered as *unknown* because the blinded status was not explicitly reported; 4 studies were labeled as having high bias because the researchers were not blinded to the reference standard at the time of interpretation of LUS.[25,26,29,32]

Regarding the reference standard domain, 1 study[23] was considered as unknown because the blinded status was not explicitly reported. With regard to the flow and timing domain, 7 studies were considered as unknown because they reported the interval between LUS and CXR as less than 24 hours but failed to supply more accurate timing.[23–26,28,30,31]

Regarding applicability, 2 studies[25,27] were considered high risk for the patient selection domain, because only normal neonates and newborns with NRDS were included. For the index test and reference standard domains, all studies were considered to have low concerns.

Data Synthesis

The pooled sensitivity, specificity, PLR, NLR, and DOR of LUS in the diagnosis of NRDS were 0.92 (95% CI, 0.89–0.94), 0.95 (95% CI, 0.93–0.97), 20.23 (95% CI, 8.54–47.92), 0.07 (95% CI, 0.03–0.14), and 455.30 (95% CI, 153.01–1354.79), respectively (Figs. 3A–E). Significant heterogeneity was found for the sensitivity (I^2 = 85.4%), specificity (I^2 = 75.6%), PLR (I^2 = 73.8%), NLR (I^2 = 77.1%), and DOR (I^2 = 48.9%), respectively. Because of significant heterogeneity, a random-effect model was used. The AUC under the SROC curve for the value of LUS in the diagnosis of NRDS was 0.9888 (Fig. 4).

The Spearman correlation coefficient between the log of sensitivity and the log of 1 – specificity was determined to be 0.220 (P = 0.515), which indicated no significant threshold effect among the individual studies. The Deeks funnel plot asymmetry test demonstrated that the studies were distributed symmetrically with a P value of 1.00 (Fig. 5), which indicated that there was no significant publication bias in present meta-analysis.

Meta-regression and Subgroup Analyses

Because of the significant heterogeneity among studies, meta-regression analysis was then conducted to explore other potential sources of heterogeneity. The covariates included year published (1990–2012 vs 2014–2019), location (Asia vs Europe), study design (prospective vs case control), number of cases (≤100 vs > 100), and sampling method (consecutive vs unclear). As shown in Table 3, meta-regression demonstrated that none of the covariates assessed explained the heterogeneity observed.

Subgroup analysis of 5 studies[25,27,28,31,32] using a transthoracic technique showed pooled sensitivity of 0.88 (95% CI, 0.84–0.91) and specificity of 0.98 (95% CI, 0.96–1.00), respectively, with the SROC AUC of 0.9893; in comparison, 3 studies[23,24,26] using a transabdominal scanning technique revealed pooled sensitivity of 0.96 (95% CI, 0.92–0.99) and specificity of 0.85 (95% CI, 0.77–0.92), respectively, with the SROC AUC of 0.9463.

DISCUSSION

This meta-analysis, which evaluated the diagnostic value of LUS in the diagnosis of NRDS, provided a pooled sensitivity of 0.92 (95% CI, 0.89–0.94), specificity of 0.95 (95% CI, 0.93–0.97), and DOR of 455.30 (95% CI, 153.01–1354.79), respectively, with an SROC AUC of 0.9888. The findings of this

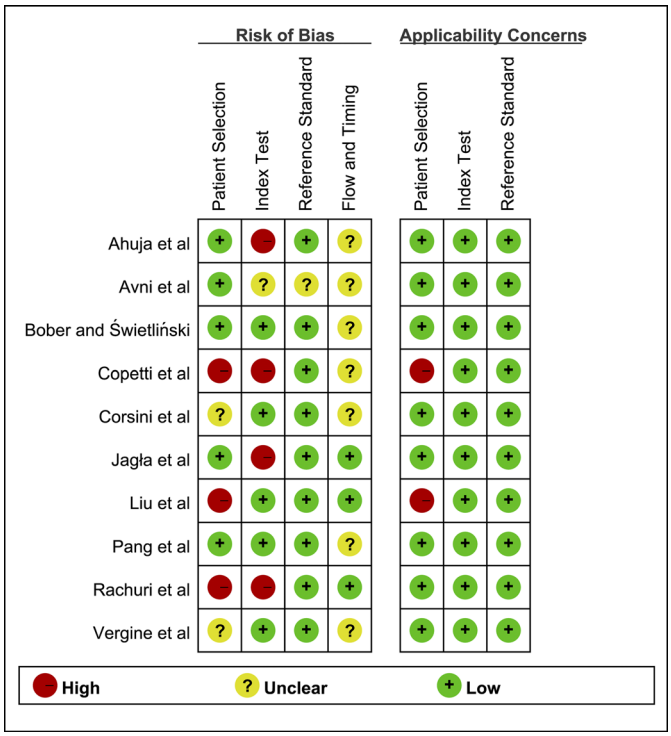

FIGURE 2. Quality assessment of the included studies using Quality Assessment of Diagnostic Accuracy Studies 2 tool.

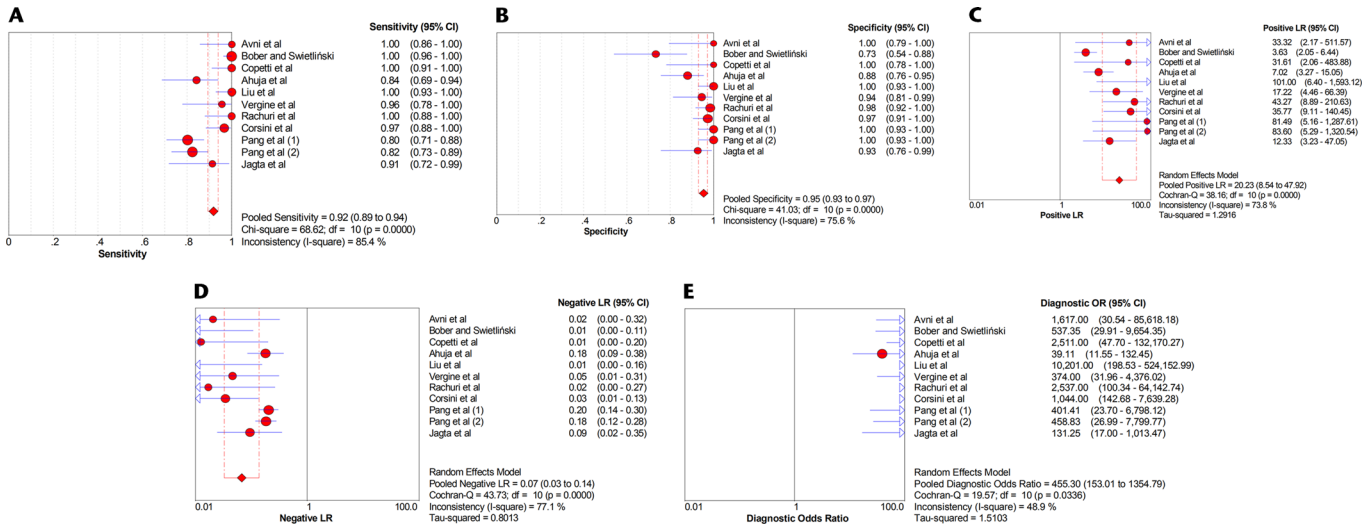

FIGURE 3. A–E, Forest diagrams of LUS in the diagnosis of NRDS, showing sensitivity, specificity, PLR, NLR, and DOR.

meta-analysis demonstrate that LUS has high diagnostic value for NRDS. In addition, this meta-analysis shows a high PLR of 20.23 (95% CI, 8.54–47.92) and a low NLR of 0.07 (95% CI, 0.03–0.14), suggesting that the diagnostic test performs well in correctly identifying the true disease conditions in newborns.

Our comparison between transthoracic scanning technique and transabdominal scanning technique for the diagnosis of NRDS demonstrates that transthoracic scanning technique has higher accuracy (sensitivity, 0.88 vs 0.96; specificity, 0.98 vs 0.85; Youden index, 0.86 vs 0.81; SROC AUC, 0.9893 vs 0.9463). It reveals that transthoracic scanning technique is superior to transabdominal scanning technique in the diagnostic accuracy of NRDS. However, with respect to clinical application, more multicenter studies are required to affirm the

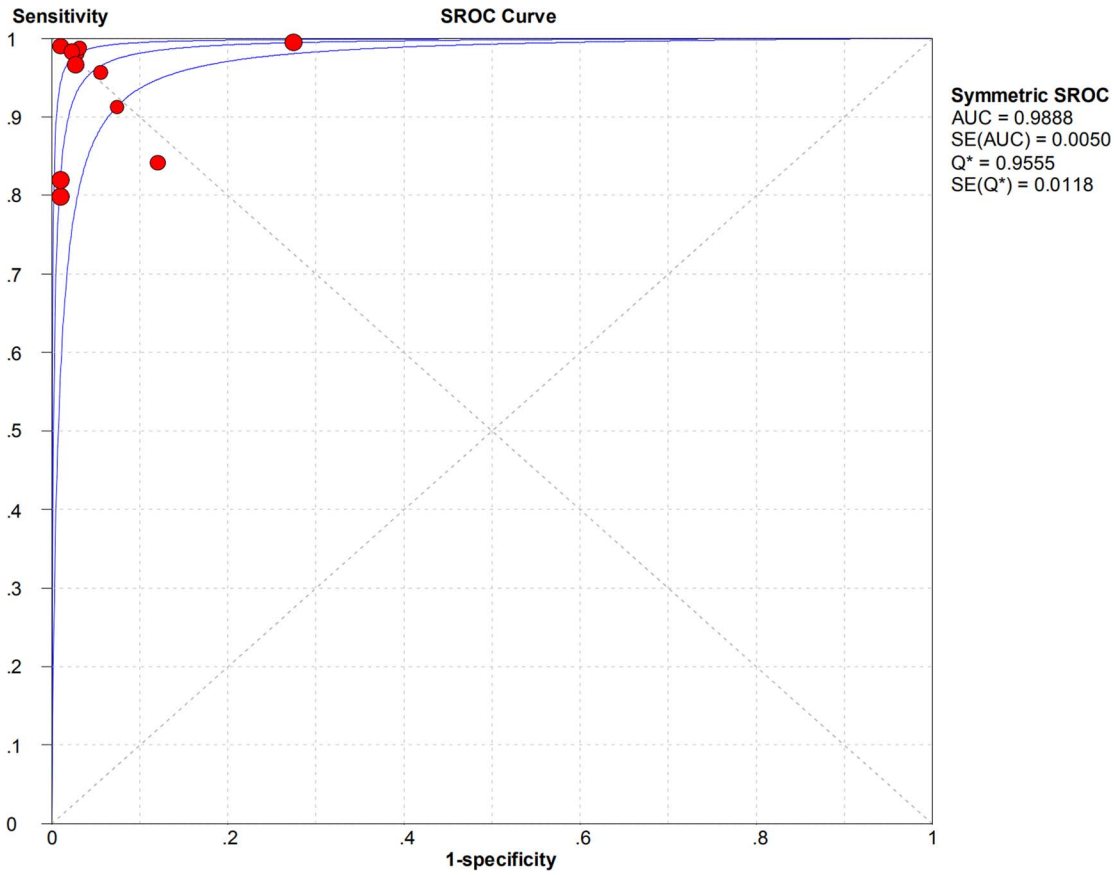

FIGURE 4. Summary receiver operating characteristics curve of LUS for NRDS.

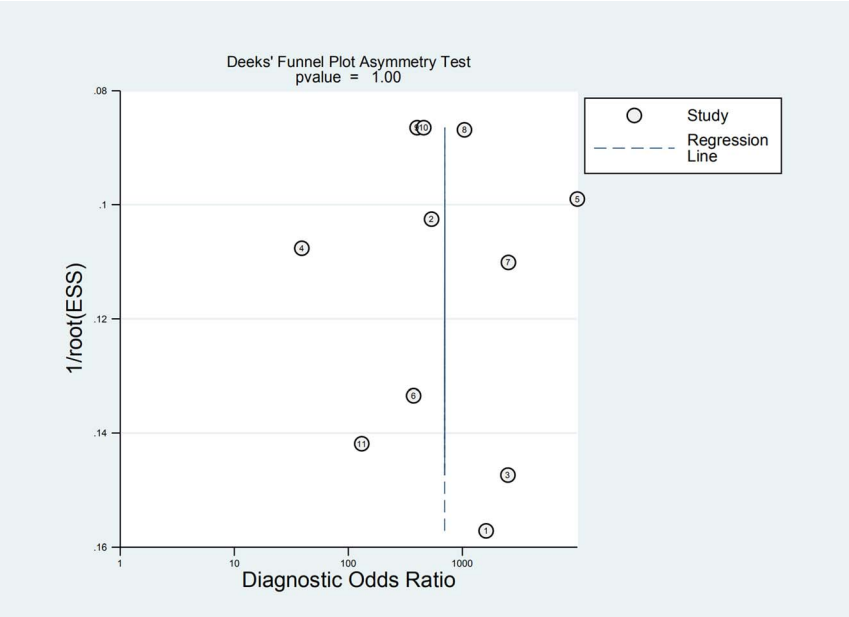

FIGURE 5. Funnel plot of LUS for NRDS.

superiority of transthoracic scanning technique over transabdominal scanning technique in the diagnosis of NRDS.

A previous systematic review,[8] which comprised a total of 480 newborns, depicted 6 studies evaluating the accuracy of LUS in the diagnosis of NRDS. The pooled estimates of sensitivity and specificity for the diagnosis of NRDS were 0.97 (95% CI, 0.94–0.99) and 91% (95% CI, 0.86–0.95), respectively. Compared with the previous systematic review, our meta-analysis comprising a total of 887 newborns reported 10 studies evaluating the accuracy of LUS in the diagnosis of NRDS. Furthermore, the included studies of the previous systematic review were published between 2006 and 2014, whereas the included studies of this meta-analysis were published between 1990 and 2019. Although our results are similar to the previous study, our meta-analysis adds additional objective studies to support clinical practice of LUS for the diagnosis of NRDS.

According to the eligible studies, the main LUS diagnostic criteria of NRDS include bilateral white lung, pleural line abnormalities, and lung consolidation. Except for lung consolidation, the other abnormalities can also be identified in TTN neonates.[31] Liu et al[27] found that the simultaneous coexistence of lung consolidation, pleural line abnormalities, and bilateral white lung or disappearance of lung consolidation, pleural line abnormalities, and A-lines disappearance occurs with a sensitivity and specificity of 100% for predicting NRDS. Consequently, the most important and specific feature of NRDS is lung consolidation.

There was significant heterogeneity observed in this study, but meta-regression analysis demonstrated that the source of year published, study design, number of cases, sampling method, and location did not explain the source of heterogeneity. However, There were several factors that might involve the significant heterogeneity. First, the factor that could interpret part of the significant heterogeneity might be the different LUS diagnostic criteria used among the included studies for diagnosing NRDS by LUS. Second, the included studies involved a large variety of ultrasonic operators of different specialties such as physician, radiologist, pediatrician, cardiologist, and neonatologist, with different experience levels, and this might account for part of the heterogeneity identified in present meta-analysis. Finally, other factors such as the different equipments used in different studies and observers' experience might also play an important role in heterogeneity among studies.

Although LUS has high diagnostic performance for detecting NRDS, it is also important to consider several limitations in relation to the use of LUS. First, as with lots of ultrasonic applications, this modality is notoriously operator dependant.[33] Therefore, it is considerable to ensure that operators acquire sufficient training and practice with this modality. Second, the exposure levels used in diagnostic LUS, the long-term biological effects of ultrasound on neonatal lung tissue are unknown.[34] Importantly, modest tissue damage may occur in certain identifiable applications, so it is considerable to ensure that prudent clinical use of LUS is required to minimize the possible damage. Finally, the accuracy diagnosis of smaller pneumothorax,

TABLE 3. Meta-regression Analysis of the Possible Sources of Heterogeneity

Study Characteristics	*P*	RDOR	95% CI
Year published (1990–2012 vs 2014–2019)	0.1219	0.16	0.01–1.85
Location (Asia vs Europe)	0.8422	0.76	0.03–17.51
Study design (prospective vs case-control)	0.0852	14.31	0.63–325.53
No. cases (≤ 100 vs > 100)	0.6567	0.59	0.04–8.50
Sampling method (consecutive vs unclear)	0.1612	0.16	0.01–2.47

$P < 0.05$ indicated significant relationship between the characteristics of studies and the diagnostic OR.

RDOR, relative diagnostic odds ratio.

pneumomediastinum, and pneumopericardium by LUS remains an enormous challenge, and therefore, CXR is required to rule out them for neonates with suspected NRDS.[35–37] However, the use of CXR can be reduced during monitoring and follow-up of NRDS by LUS.

Scoring systems of the LUS scores and the number of lung consolidation areas have also been applied for the diagnosis of NRDS. Pang et al[31] generated scoring systems to discriminate NRDS from TTN, based on the main LUS characteristics of NRDS including lung consolidation, the number of B-lines, the presence of pleural effusion, and pleural line abnormalities. The receiver operating curve analysis of the LUS score showed that a cutoff of 21.5 was defined, with scores >21.5 suggesting NRDS; the receiver operating curve analysis of the number of lung consolidation areas demonstrated that a cutoff of 0.5 was defined, with scores >0.5 suggesting NRDS. There was no difference in diagnostic value of the 2 scores. Utility of scoring systems in the diagnosis of NRDS could reduce the influence of subjective judgment by sonographers.

It is important to consider several limitations with respect to the present meta-analysis. First, the included studies were limited by language, as the literature search merely included those written in English. Furthermore, significant heterogeneity had been observed across the included studies, but we could not identify the factors that could actually explain this heterogeneity. Moreover, most of the included studies failed to depict the precise duration between CXR and subsequent LUS except 3 of them.[27,29,32] It is considerable when comparing LUS with the reference standard that both are carried out within a narrow time frame to reduce performance bias.[19] In addition, only 1 study[30] reported interobserver variability and acquired a well concordance rate ($k = 0.88$). Thus, more studies are needed to evaluate interobserver variability. Moreover, with the exception of 2 studies,[26,29] the majority of the included studies did not address whether newborns were treated before LUS examination. If neonates had been treated before LUS examination, this might bias the results. Finally, most of the eligible studies had methodological limitations, especially in domains such as patient selection, the index test, and flow and timing, and therefore, improvements in the future study design are required to accurately address the issue under investigation.

In summary, LUS is a very valuable diagnostic modality that complements CXR in the diagnosis and follow-up monitoring of NRDS. Of vital importance, this technique of LUS is a nonradiative imaging modality.[38] The present meta-analysis shows that the sensitivity and specificity of LUS for detecting NRDS are excellent. However, the conclusion of our study based solely on a small number of studies that met our specific inclusion criteria should be interpreted with caution. Large prospective international multicenter studies are still required to identify the present conclusion and to further develop the diagnostic application of LUS in NRDS.

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