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Can lung ultrasound score accurately predict surfactant replacement? A systematic review and meta-analysis of diagnostic test studies

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Abstract

Background: Clinical and radiographic criteria are traditionally used to determine the need for surfactant therapy in preterm infants. Lung ultrasound is a bedside test that offers a rapid, radiation-free, alternative to this approach.

Objective: To conduct a systematic review and meta-analysis to determine the accuracy of a lung ultrasound score (LUS) in identifying infants who would receive at least one surfactant dose. Secondary aims were to evaluate the predictive accuracy for ≥2 doses and the accuracy of a different image classification system based on three lung ultrasound profiles.

Methods: PubMed, SCOPUS, Biomed Central, and the Cochrane library between January 2011 and December 2021 were searched. Full articles enrolling preterm neonates who underwent lung ultrasound to predict surfactant administration were assessed and analyzed following Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and QUADAS-2 guidelines.

Results: Seven prospective studies recruiting 697 infants met the inclusion criteria. Risk of bias was generally low. Oxygen requirement, clinical and radiographic signs of respiratory distress syndrome were used as reference standards for surfactant replacement. The summary receiver operator characteristic (sROC) curve for LUS predicting first surfactant dose showed an area under the curve (AUC) = 0.88 (95% confidence interval [CI]: 0.82–0.91); optimal specificity and sensitivity (Youden index) were 0.83 and 0.81 respectively. Pooled estimates of sensitivity, specificity, diagnostic odds ratio, negative predictive value, and positive predictive value for LUS predicting the first surfactant dose were 0.89 (0.82–0.95), 0.86 (0.78–0.95), 3.78

Abbreviations: AUC, area under the curve; DOR, diagnostic odds ratio; GA, gestational age; LUS, lung ultrasound score; NPV, negative predictive value; PPV, positive predictive value; RDS, respiratory distress syndrome; S/F ratio, oxygen saturation over inspired oxygen ratio; SGA, small for gestational age; sROC, summary receiver operating characteristic.

(3.05–4.50), 0.92 (0.87–0.97), 0.79 (0.65–0.92). The sROC curve for the accuracy of Type 1 lung profile in predicting first surfactant dose showed an AUC of 0.88; optimal specificity and sensitivity were both 0.86. Two studies addressing the predictive accuracy of LUS for ≥2 surfactant doses had high heterogeneity and were unsuitable to combine in a meta-analysis.

Discussion: Despite current significant variation in LUS thresholds, lung ultrasound is highly predictive of the need for early surfactant replacement. This evidence was derived from studies with homogeneous patient characteristics and low risk of bias.

KEYWORDS

lung ultrasound, meta-analysis, preterm neonate, respiratory distress syndrome, surfactant

1 | INTRODUCTION

Primary surfactant deficiency leads to respiratory distress syndrome (RDS) which is a leading cause of morbidity and mortality in preterm infants. Surfactant replacement has greatly improved short- and long-term prognosis of RDS, especially when administered in the first 3 h of life.[1] Not all preterm babies require surfactant and criteria for administration vary between units, countries, and scientific societies. Current European guidelines recommend surfactant therapy when an infant's oxygen requirement remains above 30% ($FiO_2 > 0.30$) despite continuous positive airway pressure (CPAP) treatment.[2] Rather than being a true index of surfactant deficiency, the oxygen requirement threshold is a proxy that varies according to the level of positive pressure provided, the saturation target, and other factors.[3] Furthermore, a recent prospective study showed modest accuracy (sensitivity 57%) of the $FiO_2 > 0.30$ in predicting the need for surfactant in preterm neonates in the first 3 h of life.[4] A recent, multicenter, pragmatic study demonstrated that this policy may result in delayed surfactant treatment.[5]

Lung ultrasound is a noninvasive bedside tool, which provides reliable estimates of parenchymal aeration.[6] In 2012, Raimondi et al. studied a cohort of 154 infants and noted three typical ultrasound appearances or profiles present in the first 2 h of life. These profiles were applied to describe postnatal lung fluid clearance[7] and were shown to be predictive of failure of noninvasive respiratory support.[8] In 2015, Brat et al.[9] adapted to neonatal respiratory medicine a classification system validated in adults. A progressive numerical score was assigned to a lung images series showing less aeration. This lung ultrasound score (LUS) was inversely correlated to patient oxygenation and reliably predicted the need for surfactant replacement.

Since a previous review of evidence by Razak et al. in 2018,[10] several groups have evaluated the reliability of LUS as a predictor of failure of noninvasive respiratory support.[11–13] As results may depend on study populations, score thresholds, and scoring systems, the need for replication and standardization arises. The aim of this systematic review and metanalysis was to evaluate in preterm neonates in first hours of life, the accuracy of the LUS versus the reference standard (expressed as oxygen requirement, radiographic and clinical signs of neonatal RDS) to predict the need for surfactant therapy.

2 | METHODS

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.[14] Before starting the project, we agreed on a systematic review protocol, including the choice of databases to be searched, search terms, eligibility criteria, and data to be extracted. Methods to aggregate data and to solve any dispute were also decided. The protocol was registered in PROSPERO database (registration number: CRD42021247888).[15] PRISMA-P abstract and study checklists are provided as Supporting Information: materials. IRB approval is not required for this study type.

Studies were selected according to the following criteria.

2.1 | Eligibility criteria

Articles were included if they were diagnostic accuracy studies published in English as full papers and enrolled preterm neonates ≤34 weeks undergoing lung ultrasound to predict surfactant administration according to one of the following scoring systems:

(1) LUS calculated during the first hours of life on three areas for each lung including[9,16]: Score = 0 indicating normal lung imaging (A lines and pleural sliding present); Score = 1 indicating alveolar interstitial pattern (B lines not coalescent); Score = 2 indicating severe alveolar interstitial pattern (multiple and or coalescent B lines with or without consolidations limited to subpleural space); Score = 3 indicating more extensive consolidation in addition to the pattern seen in Score = 2.
(2) Qualitative lung ultrasound performed with an image classification system based on three lung ultrasound profiles (LP) with the following characteristics[7,8]: Type 1 for coalescent B lines without

significant consolidations in the subpleural space (white lung image); Type 2 for partial alveolar interstitial pattern (B lines not coalescent); Type 3 for normal lung imaging (A lines and pleural sliding present).

Preterm neonatal lung ultrasounds of infants who received surfactant treatment were compared with those who did not receive surfactant.

The following relevant clinical variables were also compared between the same group: gestational age (GA); oxygen saturation over inspired oxygen fraction (S/F); small for gestational age (SGA); gender and prenatal steroid administration.

We excluded "grey" literature, unpublished, or nonpeer-reviewed reports.

Information Sources and search strategy.

The databases PubMed, SCOPUS, Biomed Central, and Cochrane library were searched between January 2011 and December 2021.

The 10-year interval provides a comprehensive search of the topic as Brat and coworkers reported the numerical score for the first time in 2015.[9]

The above databases were searched using keywords: Lung ultrasound and surfactant and neonate. Reference lists of included articles were scanned for any additional eligible studies.

2.2 | Data management

Literature search results were shared among all authors to approve the eligibility of selected studies according to the eligibility criteria. Duplicate publications and multiple reports of the same study were identified and excluded.

2.3 | Selection process

Two reviewers (Letizia Capasso and Francesco Raimondi) independently selected eligible abstracts and verified the acceptability of the full studies. Two authors (Letizia Capasso and Daniela Pacella) extracted data. Two independent authors assessed of bias in each individual study and assessed risk of publication bias (Letizia Capasso and Daniela Pacella). Results were compared and discussed among all the authors and controversies were resolved by discussion.

2.4 | Data collection process and items

Data were extracted using a standardized form derived from the Cochrane data collection template and reported in a Microsoft Excel (Microsoft, 2013) spreadsheet. The following data were extracted from the studies: author, year of publication, number of neonates included, number of areas scored, LUS or lung ultrasound profile predictive for surfactant treatment, and area under the curve (AUC); reported (or derived) raw true negative, false negative, true positive, and false positive were extracted to compute sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios, diagnostic odds ratio (DOR).

The following clinical characteristics of surfactant treated, and nontreated infants were recorded: GA in weeks (median); oxygen saturation over inspired oxygen ratio (S/F ratio); sex (percentage of male infants), SGA, and use of prenatal steroids. Additionally, we planned to report the need for mechanical ventilation, pneumothorax, bronchopulmonary dysplasia, and death for both surfactant treated and nontreated infants.

2.5 | Outcomes and prioritization

Our primary outcome was to test the accuracy of the LUS score performed on preterm neonates within the first hours of life to predict treatment with surfactant.

Secondary outcomes included the accuracy of LUS to predict the need for two or more doses of surfactant. Finally, we analyzed LP classification by images (Types 1–3) to predict the need for surfactant.

2.6 | Risk of bias in included studies

Quality and risk of bias for the systematic review and meta-analysis were assessed using QUADAS-2.[17] The four domains assessed for risk of bias included: patient selection, index test, reference standard, and flow and timing. Applicability concerns were assessed in the first three domains. In each domain, we answered the signaling questions with "Yes," "No," or "Unclear" and for each domain judged the risk of bias as "Low," "High," or "Unclear" risk.

All eligible studies were considered for the meta-analysis, regardless of their quality, and assessed for risk of bias. However, a sensitivity analysis was planned excluding studies with high risk of bias.

2.7 | Summary measures and data synthesis

The accuracy of the LUS score and Type 1/2 LP in predicting the first and subsequent surfactant doses were expressed as pooled estimates of sensitivity, specificity, DOR (or log DOR, as appropriate), NPV, and PPV. Pooled standardized mean difference was reported for the variables GA and S/F ratio. Where mean and standard deviation were not available or reported, the Hozo method of converting median (interquartile range) to mean (standard deviation) was used. Pooled risk ratio was reported for the categorical variables (expressed in proportion) sex, SGA, and prenatal steroid administration. Considering the meta-analysis included studies with different LUS thresholds due to the lack of standardization, high heterogeneity was expected. Heterogeneity was assessed using both I^2 statistic and Kendall's T. For high heterogeneity studies (i.e., I^2 test $p < 0.05$), or for studies,

which involved populations with different baseline clinical and demographic characteristics, subgroup analysis was planned. Additionally, summary receiver operator characteristic (sROC) curves were computed with their corresponding AUC.

2.8 | Assessment of study quality and publication bias

Authors assessed each study sampling strategy, representativeness, comparability of the samples, and use of comparable instruments. Along with risk of bias in individual studies, biases in the meta-analysis were assessed as follows:

- Risk of publication bias assessed with visual inspection of funnel plots and of computed sROCs;
- Strategies to handle studies at high risk of selective reporting bias included;
- If applicable, authors could be contacted to clarify unclear or missing observations, data, or outcomes;
- Studies could be excluded from the pooled analyses.

Confidence in cumulative evidence

The strength of the body of evidence was assessed as follows:

- For the interpretation of the study contribution to the findings, reference was made to the prior assessment of the included studies' methodological quality;
- Consistency and inconsistency across findings were assessed and any incoherent or contradictory evidence was highlighted and discussed;
- GRADE or CERQual approaches were employed for standardized assessment of cumulative evidence quality.

3 | RESULTS

The results of search strategy and study selection process are detailed in Figure 1. The initial search strategy identified 664 publications. Sixteen full-text articles were reviewed for eligibility. Nine were excluded for the following reasons: five studies reported a classification using LP[4,7,8,18,19]; Szymansky et al.[20] used a different LUS grading system which was not comparable with others; Perri et al.[21] studied LUS after surfactant replacement; Raschetti et al. and Rodriguez Fanjul et al. investigated LUS without performing a diagnostic accuracy study (alternatively used a quality improvement, before-and-after uncontrolled and a randomized controlled design, respectively).[22,23]

Finally, seven studies were included in qualitative and quantitative analysis.[5,9,11,24–27] Main characteristics of the included studies are reported in Tables 1 and 2.

All included studies enrolled infants ≤34 weeks of GA who had LUS assigned in the first 2 h of life before surfactant treatment. Gregorio-Hernández et al.[25] describe a lung ultrasound performed in the first 12 h (median 2.5 h) of life.

All preterm neonates included in the studies were supported with CPAP after birth.

All studies used $FiO_2 \pm$ CXR and clinical signs of RDS as the reference standard to determine the need for surfactant treatment as detailed below.

For all neonates studied, the criteria to treat infants with first surfactant dose was $FiO_2 > 0.3$ except Vardar et al.[26] who used $FiO_2 \geq 0.3$.

Aldecoa et al.[27] and Raimondi et al.[5] used CXR diagnosis of RDS and signs of respiratory distress other than $FiO_2 > 0.3$ as indicators for surfactant therapy.

Gregorio-Hernández administered surfactant when the infant required an $FiO_2 > 0.3$ after 1 h of noninvasive respiratory support of any kind.[25] In all other studies surfactant was replaced according to the European guidelines.[2]

The lung ultrasound scan assessed three segments of each lung for all studies and the scoring systems were compatible with those specified in our inclusion criteria. Some authors[9,11,24–26] studied upper anterior, lower anterior, and lateral regions of each lung. Other authors[5,27] studied each lung in the midclavicular, anterior axillary, and posterior axillary line as detailed in Table 1.

Not all enrolled studies used the same LUS cut-off for accuracy analysis as detailed in Table 2; however, three studies[5,11,27] totaling 467 of 697 included infants, used an LUS cut-off > 8. All studies had a maximum score of 18.

Four studies declared no funding source, two studies declared no conflict of interest, and one study received funding from the Spanish Neonatology Society.

True positive, false positive, false negative, true negative, sensitivity, specificity of included studies for LUS cut-off predicting the need for first dose of surfactant are reported in Table 2. For De Martino et al., two values of LUS cut-off were presented by the authors and were therefore considered separately in this analysis; in the main manuscript, an LUS cut-off = 8 was used, while in a supplementary file the analysis shows an LUS cut-off = 6.

Using the QUADAS-2 tool, the overall methodological quality of included studies was good and the risk of bias was low (Figure 2).

In particular, the participant selection domain had a low risk of bias as on the whole studies avoided inappropriate exclusions, none used a case-control design and the participants were consecutively enrolled.

Regarding the index test domain, the conduct or interpretation of the index test (i.e., LUS) showed an unclear risk of bias in three out of seven publications where we were unable to determine whether LUS results were interpreted without knowledge of the patients' FiO_2.[5,25,27] On the other hand, all authors used a prespecified LUS score.

The evaluation of reference standard domain also showed a low risk as clinicians who administered surfactant according to the reference standard were blinded to LUS results. Similarly, a low risk

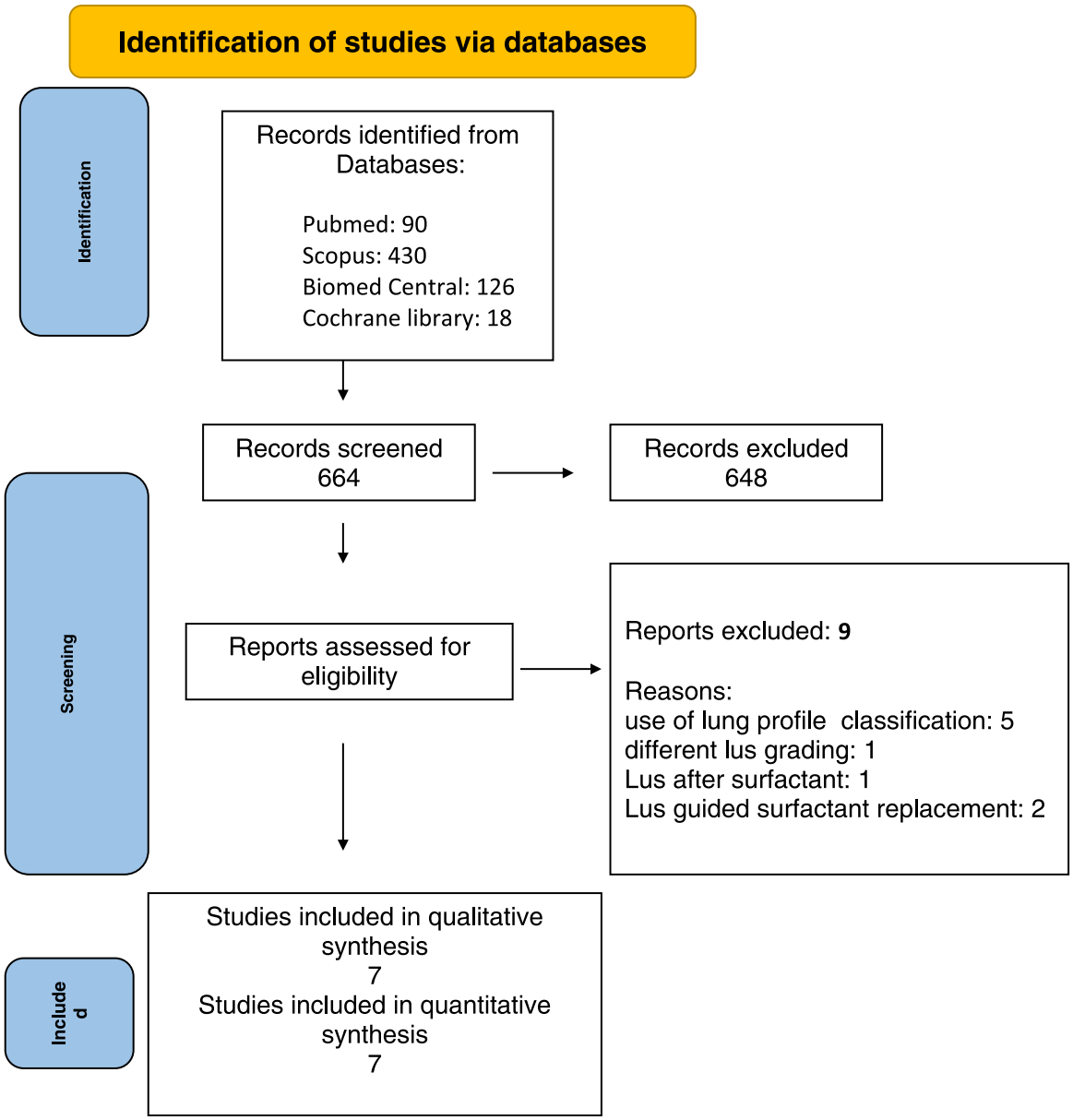

FIGURE 1 Flow diagram of search results.

of bias was assigned to the flow and timing domain as LUS was attributed in the first hours of life before surfactant treatment and all patients were managed using a similar reference standard.

No concerns regarding applicability were found in all domains.

To investigate our primary outcome regarding the accuracy of LUS performed in the first day of life to predict the first surfactant treatment in preterm neonates, we constructed an sROC curve. Using all LUS thresholds, the AUC was 0.88 (95% CI 0.82–0.91) with De Martino cut-off at 8 and optimal specificity and sensitivity derived from the sROC curve (Youden index) were 0.83 and 0.81 (Figure 3).

With De Martino cut-off at 6, the AUC was 0.87 (95% CI 0.82–0.92) and Youden Index 0.8 and 0.83 (Supporting Information: Figure 1).

Pooled estimates of sensitivity, specificity, DOR, NPV, and PPV for LUS predicting first surfactant dose are reported in Figure 4 and Supporting Information: Figure 2.

The findings of each individual are represented both in the sROC curves and in the Forest plots.

Data regarding the assessment of the accuracy of using LUS to predict the need for ≥2 surfactant doses were reported in four studies[5,11,24,26] but were extracted only from the first two papers. These studies had high heterogeneity and were unsuitable to combine in a meta-analysis. Concerning the excluded studies, one[24] studied LUS after surfactant replacement and the other[26] had insufficient data for analysis.

Five studies using an LP classification (i.e., Types 1–3 grading)[4,7,8,18,19] were excluded from our primary analysis.

TABLE 1 Characteristics of included studied for the LUS predicting surfactant replacement (first dose).

Studies	*n*[a] neonates	GA (week)	Inclusion criteria	Exclusion criteria	Surfactant administration criteria	Time of US	LUS scoring areas	Areas[a]
Brat 2015	65	<34	RDS NCPAP supported before surfactant; GA < 34 week[b]	Chromosomal abnormalities or complex congenital malformations and lung diseases; severe sepsis/septic shock; MAS; surfactant in delivery room	$FiO_2 > 0.3$	As soon as possible before surfactant	Upper anterior, lower anterior and lateral regions each lung	3
De Martino 2018	133	≤30	All neonates ≤30 week; NCPAP supported before surfactant	Chromosomal abnormalities or complex congenital malformations and lung diseases; severe sepsis/septic shock; surgery need in first week; surfactant in delivery room	$FiO_2 > 0.3$	After NICU admission and before surfactant	Upper anterior, lower anterior and lateral regions each lung	3
De Martino 2018	[c]	[c]	[c]	[c]	[c]	[c]	[c]	3
Perri 2018	56	31 (± 3)	RDS NCPAP supported before surfactant; any GA within 2 h of life	Chromosomal abnormalities or complex congenital malformations and lung diseases; severe sepsis; MAS; delivery room intubation	$FiO_2 > 0.3$	Within 2 h from CPAP started, before surfactant	Upper anterior, lower anterior and lateral regions each lung	3
Gregorio-Hernández 2020	64	<35	RDS NCPAP supported before surfactant; GA < 35 weeks	Lack of informed consent; meconium-stained amniotic fluid; Chromosomal abnormalities or congenital malformations; mechanical ventilation or endotracheal surfactant prior of US	$FiO_2 > 0.3$ after 1 h of non invasive ventilation	First 12 h of life median 2.5 h (1.5–4.8 h) before surfactant	Upper anterior, lower anterior and lateral regions each lung	3
Vardar 2020	45	<34	RDS NCPAP supported before surfactant; GA < 34 weeks	Respiratory failure other than RDS as congenital diaphragmatic hernia, congenital anomalies and meconium aspiration syndrome; surfactant in delivery room	$FiO_2 \geq 0.3$	First hours of life median 50 min (42–60 min) before surfactant	Upper anterior, lower anterior and lateral regions each lung	3
Aldecoa 2021	94	23–31	RDS CPAP supported before surfactant; GA 23–31 weeks	Refusing to participate in the study; resolution of RDS; gone off respiratory support and surfactant administration before performing the LUS	$FiO_2 > 0.3$ and radiological and clinical sign of RDS	60–120 min of life before surfactant	Midclavicular, anterior axillary and posterior axillary line each lung	3
Raimondi 2021	240	25–33	RDS NCPAP supported before surfactant; GA 25–33 week within 2 h from birth	Major congenital malformations	$FiO_2 > 0.3$ and radiological and clinical sign of RDS	First hours of life before surfactant	Midclavicular, anterior axillary and posterior axillary line each lung	3
Total *n*[a] neonates	697							

Abbreviations: GA, gestational age; LUS, lung ultrasound score; MAS, meconium aspiration syndrome; NCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; US, ultrasound.

[a]Number of areas studied each lung.

[b]Brat 2015 study considered also a population ≥34 weeks that has been excluded in this analysis.[7]

[c]Already computed above.

TABLE 2 True positive (TP), false positive (FP), false negative (FN), true negative (TR), sensitivity, specificity of included studied for the LUS cut-off predicting surfactant replacement (first dose).

Studies	LUS cut-off	TP	FP	FN	TN	Sensitivity	Specificity
Brat 2015	4	16	19	0	30	1	0.61
De Martino 2018	>6	61	13	7	52	0.9	0.8
De Martino 2018	>8	56	5	12	60	0.82	0,92
Perri 2018	≥5	19	4	3	30	0.86	0.88
Gregorio-Hernández 2020	>12	15	3	1	45	0.93	0.93
Vardar 2020	>4	24	0	1	20	0.96	1
Aldecoa 2021	>8	20	12	3	59	0.87	0.83
Raimondi 2021	≥9	85	22	23	108	0.79	0.83

Abbreviation: LUS, lung ultrasound score.

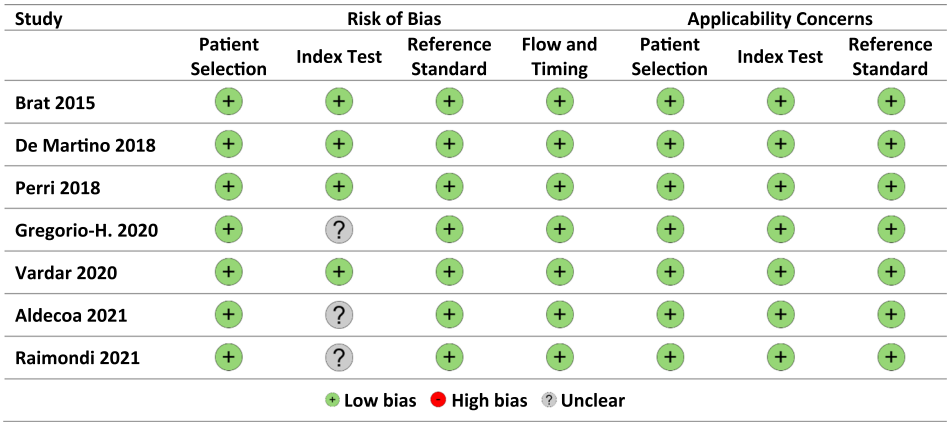

FIGURE 2 Risk of bias and applicability concerns summary: review authors judgements about each domain for each included study.

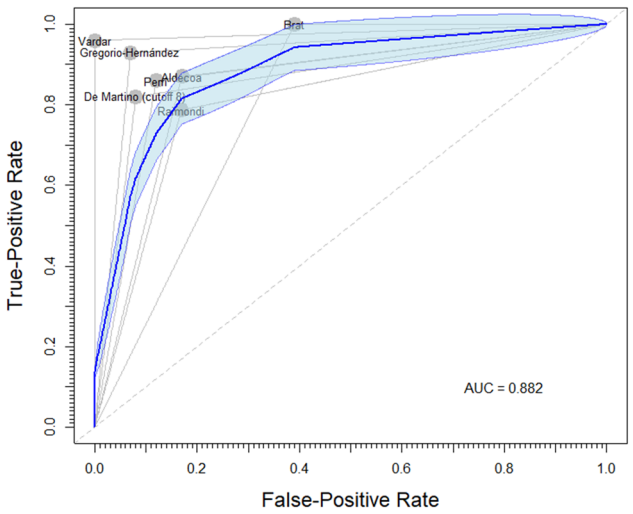

FIGURE 3 Summary ROC curve for LUS predicting the first surfactant dose with De Martino 2018[9] cut-off 8. AUC was 0.882 (95% CI: 0.826–0.917). The optimal specificity and sensitivity derived from the summary ROC curve (Youden Index) were 0.83 and 0.816. AUC, area under the curve; CI, confidence interval; LUS, lung ultrasound score; ROC, receiver operator characteristic.

Three of them used an LP classification within first 3 h of life to predict need for surfactant[4,8,18] and were analyzed for secondary outcomes[4,8,18]; characteristics of studies are reported in Supporting Information: Table 1. All three studies enrolled preterm neonates (≤34 weeks of GA). Lung ultrasound scan was performed in two areas for each lung for Raimondi (anterior and lateral chest wall) and Kayki (upper and lower anterior chest wall); while an axillary approach for each lung was used by Badurdeen. The AUC of the sROC curve constructed to evaluate the accuracy of Type 1 LP in predicting need for first surfactant dose was 0.88 (95% CI: 0.81–0.95). The optimal specificity and sensitivity (Youden Index) were both 0.86 (Supporting Information: Figure 3). Pooled estimates of sensitivity, specificity, DOR, PPV, and NPV for LP Type 1 predicting first surfactant dose is reported, and no significant heterogeneity between studies was found (Supporting Information: Figure 4).

With regard to supplementary analysis, the pooled effect size of relevant clinical variables showed a significant association between GA and S/F ratio with later treatment using surfactant. However, the relationship was not significant for SGA, male gender, and prenatal steroid administration (Supporting Information: Figure 5).

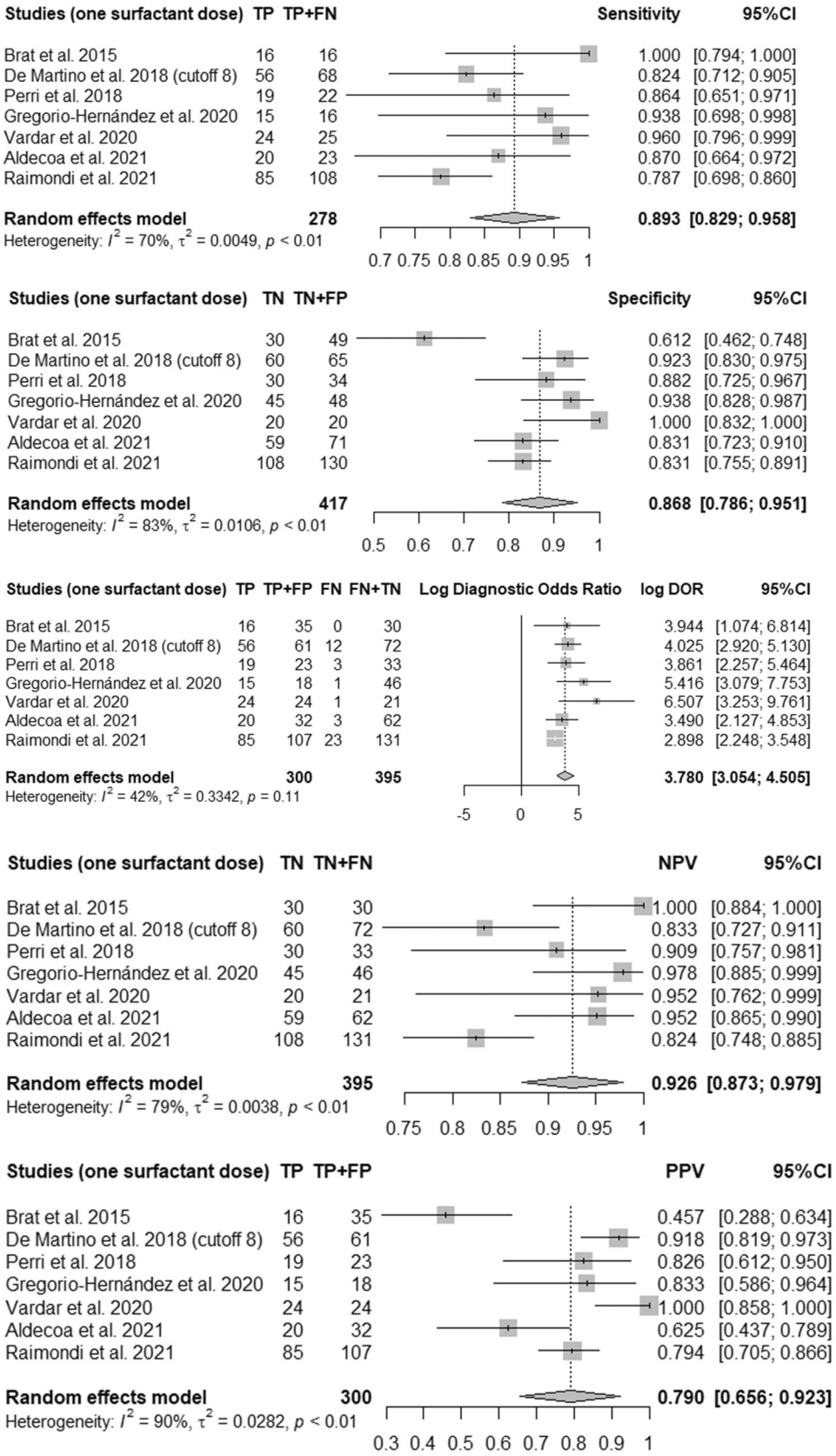

FIGURE 4 Pooled estimates of sensitivity, specificity, DOR, NPV, and PPV for LUS predicting the first surfactant dose with De Martino 2018[9] cut-off 8. Each study is represented by a square whose size is proportional to the study weight. Horizontal lines indicate 95% confidence intervals. Only for NPV and PPV the square size is proportional to the estimate precision. CI, confidence interval; DOR, diagnostic odds ratio; FN, false negative; FP, false positive; LUS, lung ultrasound score; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

There were no retrievable data on need for mechanical ventilation, occurrence of pneumothorax, bronchopulmonary dysplasia, and deaths among infants treated and untreated with surfactant.

4 | DISCUSSION

This review demonstrates that lung ultrasound accurately predicts the need for the first dose of surfactant. Similar results were reported in a pooled analysis of 189 infants from two studies evaluating lung ultrasound in 2018.[10] This paper expands the analysis to almost seven hundred infants recruited in seven studies, and it focuses specifically on the first surfactant administration.

The publications included in this review were of high quality and low risk of bias. Only minor differences in LUS thresholds and operational protocols between studies were found. According to previous literature, the interpretation of basic lung ultrasound semiology (i.e., the signs composing both profiles and score) can be effectively provided using probes of different frequencies and footprints regardless of the operators' expertize.[28]

An early lung ultrasound represents an important advance in the delivery of personalized care to preterm infants with RDS. The technique may be integrated with the oxygen threshold recommended in the current European guidelines to improve the timely administration of the first surfactant dose. The latter criterion was supported by a single retrospective study conducted in two Australian neonatal intensive care units where a large nasal CPAP range (up to 8 H_2O cm) was allowed and no definite time limit was given for surfactant replacement[29]; whereas Raimondi et al.[5] demonstrated in a multicenter cohort that the median age at the first surfactant dose is 2 (2–3) h of life for 25–27 weeks GA and increases to 3 (5.7–2.25) h of life for 28–30 weeks GA and 8 h (27–3.5) for 31–33 weeks' GA. The Cochrane review of the topic suggests that surfactant replacement, especially in the first 3 h of life, improves the short- and long-term outcomes of preterm infants with RDS.[1]

Studies comparing outcomes of babies managed with alternative strategies are therefore justified. A small ($n = 56$) RCT by Rodriguez Fanjul et al. showed that preterm babies who received surfactant based on LUS had a significantly shorter oxygen exposure than those treated using an $FiO_2 > 0.3$ criterion.[23] Raschetti et al.,[22] in a quality improvement project, compared a 3-year period following publication of the European guideline to a subsequent era when LUS was added. They reported that the adoption of LUS was associated with less oxygen exposure, earlier surfactant administration, and more ventilation-free days. The lung ultrasound scans in the seven studies included in this review facilitated early surfactant administration which is associated with a lower rate of bronchopulmonary dysplasia.[1]

A recent multicenter, prospective study showed that $FiO_2 = 0.29$ in the second hour of life was the best predictor of early CPAP failure and need of surfactant with sensitivity = 0.73, specificity = 0.57.[30] Translating our results into practice, we may conclude that LUS would be more accurate than this FiO_2 threshold by correctly identifying 16% more babies who need surfactant and 36% more infants who do not need it.

Furthermore, the most recent studies demonstrate that the association of LUS and Sat/FiO_2 performs better than the individual parameters as predictors of early surfactant requirement.[5,27]

The high heterogeneity apparent in the two studies evaluating the accuracy of LUS in predicting the need for ≥2 doses of surfactant precluded conclusions from being drawn.

It is worth highlighting the similar performance of the two image classification systems. The score scale essentially differs from the profile strategy in adding an additional consolidation category (score = 3). However, consolidation is seldom detected on ultrasound in the early stages of RDS. The homogeneous nature of primary surfactant deficiency within the neonatal lung may explain why a consistent white lung image (i.e., a Type 1 profile, that is, the equivalent of a score = 2) is a reliable marker of poor aeration and need for surfactant replacement. A rapid scan is therefore sufficient to guide surfactant administration.

However, we acknowledge that the current evidence on lung ultrasound profiles (based on 177 cases) is somewhat less robust than that of LUS (697 cases).

A possible drawback of this paper is the lack of a formal search for papers published in languages other than English. However, one of the authors (FR) monitored the literature in Italian, Spanish, and French with no significant addition to the main search results.

Another limitation emerges from our study. Although similar results were retrieved from the studies included in the present analysis, minor differences in scanning protocols (e.g., in the ultrasound views) generated different LUS cut-off values. These methodological differences may introduce a bias when evaluating the prognostic performance. Thus, there is an urgent need for the development of standardized scoring procedures.

To facilitate the wider use of LUS, we recommend a standardization process similar to that proposed for adult critical care.[31] In this we are supported by the recent American Academy of Pediatrics clinical report suggesting that LUS should be used to ensure early surfactant administration in preterm infants.[32]

In conclusion, lung ultrasound is a powerful and noninvasive technique to customize the first dose of surfactant in infants with RDS.

AUTHOR CONTRIBUTIONS

Raimondi and Capasso conceived and supervised the project, conducted the literature search, managed data, and wrote the manuscript. Pacella wrote the manuscript managed and analyzed the data. Migliaro, Salomè, Grasso, and Corsini contributed to data collection and with the writing of the manuscript. De Luca and Davis critically reviewed the manuscript with important intellectual contributions. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data will be shared upon request to corresponding author.

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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