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Prognostic Relevance of the Lung Ultrasound Score: A Multioutcome Study in Infants with Respiratory Distress Syndrome

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Abstract

Objective There is growing evidence for the usefulness of the lung ultrasound score (LUS) in neonatal intensive care. We evaluated whether the LUS is predictive of outcomes in infants with respiratory distress syndrome (RDS).

Study Design Neonates less than 34 weeks of gestational age were eligible for this prospective, multicenter cohort study. The outcomes of interest were the need for mechanical ventilation (MV) at <72 hours of life, the need for surfactant (SF), successful weaning from continuous positive airway pressure (CPAP), extubation readiness, and bronchopulmonary dysplasia. Lung scans were taken at 0 to 6 hours of life (Day 1), on Days 2, 3, and 7, and before CPAP withdrawal or extubation. Sonograms were scored (range 0–16) by a blinded expert sonographer. The area under the receiver operating characteristic curve (AUC) was used to estimate the prediction accuracy of the LUS.

Results A total of 647 scans were obtained from 155 newborns with a median gestational age of 32 weeks. On Day 1, a cutoff LUS of 6 had a sensitivity (Se) of 88% and a specificity (Sp) of 79% to predict the need for SF (AUC = 0.86), while a cutoff LUS of 7 predicted the need for MV at <72 hours of life (Se = 89%, Sp = 65%, AUC = 0.80). LUS

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acquired prior to weaning off CPAP was an excellent predictor of successful CPAP withdrawal, with a cutoff level of 1 (Se = 67%, Sp = 100%, AUC = 0.86).
Conclusion The LUS has significant predictive ability for important outcomes in neonatal RDS.

Key Points

- Lung ultrasound has significant prognostic abilities in neonatal RDS.
- Early sonograms (0–6 h of life) accurately predict the requirement for SF and ventilation.
- Weaning off CPAP is effective when the LUS (range 0–16) is less than or equal to 1.

Lung ultrasonography is rapidly gaining popularity and has the potential to become the first-choice lung imaging technique in the management of neonatal respiratory distress syndrome (RDS). Many neonatologists who treat RDS are currently moving away from schematic treatment and toward individualized therapeutic measures. Such an approach, called "personalized medicine," requires the accurate identification of pathophysiological problems in a specific patient. Because ultrasonography is a nonhazardous bedside technique that is suitable for repeated examinations, it can provide quick insights into the dynamics of changes in the lungs. However, the question is whether quick and repeatable imaging with quantification of lung lesions can assist neonatologists in addressing the following dilemmas when seeking to implement a tailored strategy for an RDS patient: (1.) When should the newborn be given surfactant (SF)? (2.) Will the infant require mechanical ventilation (MV)? (3.) When is it safe to discontinue respiratory support? (4.) What is the risk of developing bronchopulmonary dysplasia (BPD)? A reliable response to these questions can aid in the selection of the best treatment options.

Current evidence with lung ultrasound is limited but growing. In previous research, the lung ultrasound score (LUS) was shown to reliably predict, for example, the need for SF,[1] the development of BPD,[2–5] extubation readiness,[6,7] or the need for neonatal intensive care unit (NICU) admission.[8] An early LUS was also demonstrated to be a significant noninvasive predictor of the requirement for continuous positive airway pressure (CPAP) and SF in infants born at >33 weeks gestation.[9]

We chose to investigate multiple clinical endpoints rather than just one to better match the LUS with the real practice scenario, where several outcomes are considered. In this exploratory study, we tested repeated postnatal lung scans for their prognostic value in relation to the need for SF, the need for early (within 72 h from birth) MV, successful discontinuation of CPAP/MV, and the development of moderate to severe BPD. We hypothesized that repeated lung scans in the first week of life might predict more than one of the endpoints that characterize the course of respiratory failure in RDS patients.

Materials and Methods

Study Design and Participants

Patients for this prospective cohort study were recruited from May 2021 to April 2022 from five tertiary-referral neonatal centers. Infants who were <34 weeks of gestational age were eligible, had confirmed RDS or were at risk of developing RDS, and required noninvasive respiratory support after birth. The exclusion criterion was primary intubation with subsequent MV.

The outcomes of interest were the need for MV at <72 hours of life, the need for SF, successful weaning from CPAP, extubation readiness, and the development of moderate to severe BPD.

The SF administration criteria were in accordance with European RDS Guidelines[10] and included impairment of respiratory function when FiO_2 was greater than 0.30 on a CPAP pressure of at least 6 cm H_2O.

The criteria for intubation and MV were a fraction of inspired oxygen (FiO_2) level $\geq$ 0.45 to maintain an oxygen saturation of 92%, a pH of 7.25 with a $PaCO_2 > 8.5$ kPa, severe apnea with desaturation, and bradycardia.

The decision to discontinue CPAP was based on a clinical evaluation of breathing effort, oxygen demand, and blood gases.

The index date for BPD diagnosis was 36 weeks postmenstrual age (very preterm infants) or Day 56 of life (moderately preterm infants). The diagnostic criteria for BPD were ≥28 days of oxygen supplementation and breathing at the index date or discharge, whichever came first: ambient air (mild BPD), oxygen < 30% (moderate BPD), oxygen > 30%/CPAP (severe BPD).[11]

The Bioethical Committee of Warsaw Medical University approved the study protocol (ref. no. KB/47/2021), and all parents provided written informed consent.

The Scanning Protocol

Baseline scans were taken at 0 to 6 hours after birth, and subsequent scans were taken on Days 2, 3, and 7 of life, directly before weaning from CPAP and before extubation. For infants requiring SF, all baseline scans were taken before SF administration. The infant's position had not been changed for at least 1 hour before the lung assessment.

Lung scans were performed with a linear probe with a single focus set on the pleural line. Persistence, ultrasound crossbeam, postprocessing image amplifiers and harmonics were disabled. For each pulmonary field, 8- to 10-second video clips were taken using transverse and longitudinal sections.

The assessment began with the anterior fields in neonates lying supine, and with the posterior fields in babies resting in prone position. This was consistent with our usual approach of alternating pronation and supination in newborns with respiratory failure. The midaxillary line marked the border between the anterior and posterior lung areas. Immediately after the assessment of nondependent (anterior in supine and posterior in prone body position) areas, the baby was turned sideways or 180 degrees, and the alternate lung fields were examined.

All lung assessments were performed in-line with the standard safety protocols which included transducer cleaning and low-level disinfection after each use and applying warmed gel. The average examination time did not exceed 2 minutes.

A blinded expert sonographer graded all scans using the scale described by Szymański et al.[12] This technique evaluates anterior and posterior lung fields and includes a grade of "white lung with fluid alveologram" added to the four-grade scale provided by Brat et al.[13] The total score ranges from 0 to 16 (►Fig. 1).

The investigators (point-of-care sonographers) were neonatologists who were not actively involved in patient care. The majority of them had completed dedicated training on lung ultrasound. Both the investigators and the blinded rater remained separate from the clinical decision-making process. The lung ultrasound findings were not known to the attending physician.

Data Analysis

The prognostic accuracy of the LUS was evaluated with receiver operating characteristic (ROC) curves. An area under the ROC curve (AUC) between 0.7 and 0.8 suggests acceptable, 0.8 and 0.9 suggests excellent, and >0.9 suggests outstanding prognostic accuracy.[14] The Youden index method was used to calculate optimal cutoff values.[15]

ROC analyses included the following endpoints and patients: the need for SF—155 patients (58 positive for the outcome); need for early MV—142 patients (9 positive for the outcome); BPD—136 patients (18 positive for the outcome); and effective weaning from CPAP—73 patients (67 positive for the outcome).

The prognostic properties of the LUS were additionally confirmed in multivariate logistic regression models using maximum likelihood estimation. In those analyses, LUS and baseline characteristic parameters were included as the explanatory variables, and study outcomes were the response variable. Analysis of weaning from CPAP included oxygen saturation over the fraction of inspired oxygen (SpO_2/FiO_2).

A backward stepwise technique based on the Akaike information criterion was used to obtain the final logistic regression model.

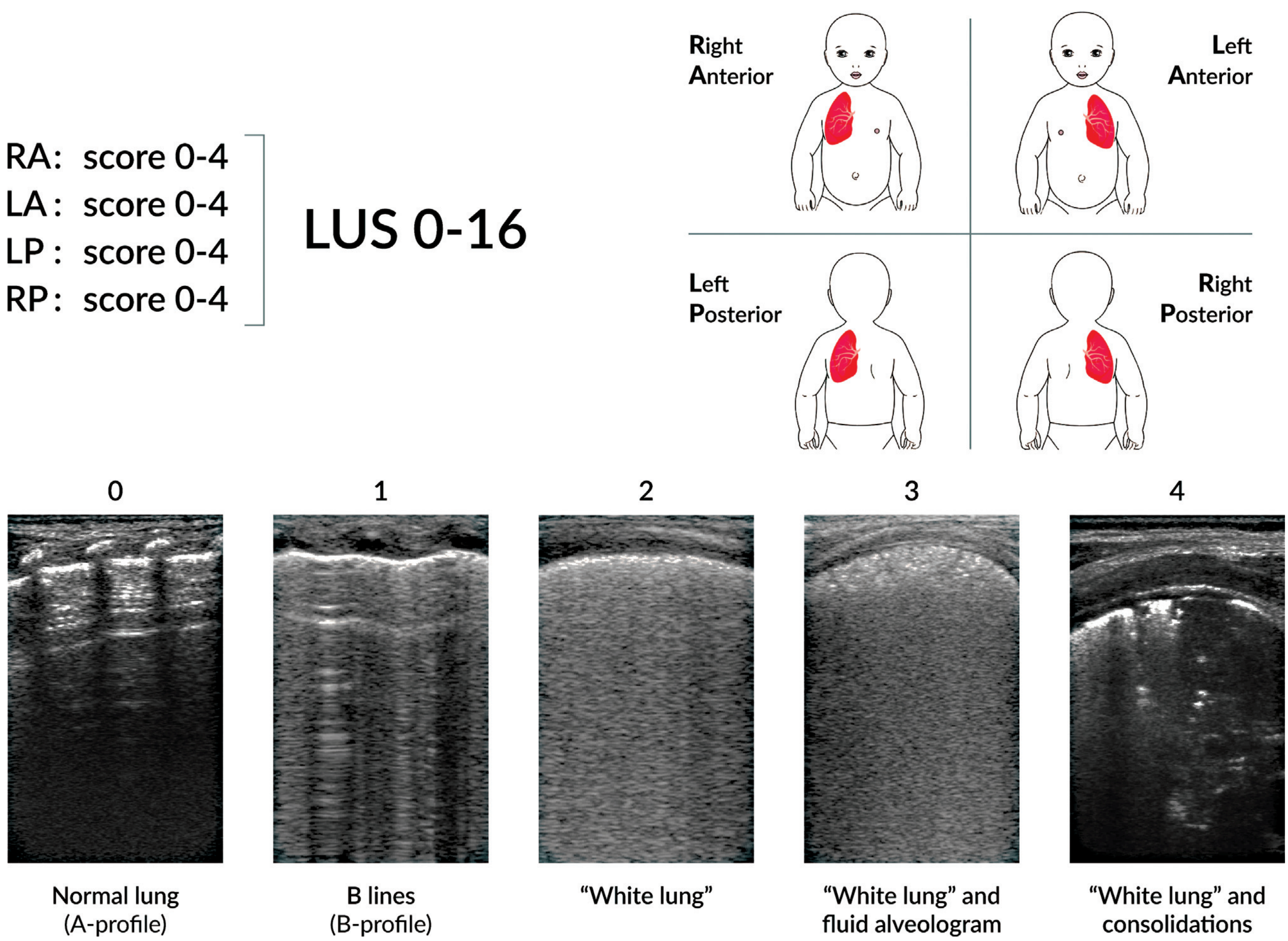

Fig. 1 The grading scale used for lung scan evaluation. LUS, lung ultrasound score.

All demographic and clinical parameters were subjected to descriptive statistics. For all analyses, p-values less than 0.05 were deemed significant.

Results

The study enrolled 155 newborns with a median (interquartile range [IQR]) gestational age of 32 (30–33) weeks.

Detailed clinical characteristics of the study cohort are presented in ►Table 1.

A total of 647 lung scans were taken, including on day 1 ($n=155$), day 2 ($n=152$), day 3 ($n=147$), day 7 ($n=144$), and on other days ($n=49$). ►Supplementary Table S1 (available in the online version) summarizes the indicators of systemic

Table 1 Descriptive statistics of the study cohort

	N **= 155**
Gestational age (wk), median (IQR)	32 (30–33)
Gestational age categories, *n* (%)	
24–28 weeks	22 (14)
29–32 weeks	78 (50)
33–34 weeks	55 (36)
Birth weight (g), mean ± SD	1,660 ± 495
Male, *n* (%)	93 (60)
Cesarean section, *n* (%)	123 (79)
Antenatal steroids, *n* (%)	113 (73)
LUS, median (IQR)	
0 to 6 hours from birth	5 (2–8)
Day 2	1 (0–6)
Day 3	1 (0–5)
Day 7	0 (0–2)
Treatment with surfactant, *n* (%)	58 (37)
Time from birth to surfactant treatment (h), median (IQR)	2.6 (1.6–6.7)
Mechanical ventilation, *n* (%)	19 (13)
Including MV at <72 hours of life, *n* (%)	11 (7.3)
Duration of mechanical ventilation (days)	3 (2–4.5)
Bronchopulmonary dysplasia, *n* (%)	
Mild	12 (8.3)
Moderate	6 (4.2)
Severe	1 (0.6)
Bronchopulmonary dysplasia[a], *n* (%)	
24–28 weeks' GA	13/18 (72)
29–32 weeks' GA	6/74 (8.1)
33–34 weeks' GA	0/52 (0)
In-hospital mortality	6 (3.9)

Abbreviations: BPD, bronchopulmonary dysplasia; GA, gestational age; IQR, interquartile range; LUS, lung ultrasound score; MV, mechanical ventilation.

[a]Data on BPD were missing for the following GA ranges: 24–28 weeks, 4 neonates; 29–32 weeks, 4 neonates; and 33–34 weeks, 3 neonates.

Table 2 Summary of the predictive accuracy of the lung ultrasound score based on receiver operating characteristic analysis

Outcome	Time of lung scan	LUS cut-off	Sensitivity	Specificity	PPV	NPV	LR+	LR−	AUC
MV at <72 hours of life	0 to 6 hours of life	7	89% (67–100%)	65% (56–73%)	15% (11–19%)	99% (97–100%)	2.54 (1.52–3.70)	0.17 (0.00–0.59)	0.80 (0.64–0.96)
Need for surfactant	0 to 6 hours of life	6	88% (79–97%)	79% (71–88%)	72% (64–81%)	92% (86–97%)	4.19 (2.72–8.08)	0.15 (0.03–0.30)	0.86 (0.80–0.92)
Moderate/severe BPD	Day 7	5	71% (29–100%)	93% (88–97%)	36% (19–58%)	98% (96–100%)	10.14 (2.42–33.33)	0.31 (0.00–0.81)	0.89 (0.79–1.00)
Successful weaning from CPAP	Directly before weaning	1	67% (55–77%)	100% (100–100%)	100% (100–100%)	21% (17–29%)	–[a]	0.33 (0.23–0.45)	0.86 (0.76–0.96)

Abbreviations: AUC, area under the receiver operating characteristic curve; BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; LR −, negative likelihood ratio; LR +, positive likelihood ratio; LUS, lung ultrasound score; MV, mechanical ventilation; NPV, negative predictive value; PPV, positive predictive value.

Note: Values in brackets represent 95% confidence intervals.

[a]Not available due to zero width of the 95% confidence interval for specificity.

oxygenation and types of respiratory support at the study time points.

Surfactant and Mechanical Ventilation at <72 Hours of Life

Baseline scans (LUS_0) were performed 1.6 (0.8–3.3) hours after birth (median, IQR), with 57% of babies having scans during the first 2 hours of life.

In ROC analysis, LUS_0 demonstrated excellent prognostic accuracy as an indicator of the need for SF (AUC = 0.86). A score of 6 was the best predictive cutoff value (sensitivity [(Se)] = 88%, specificity [Sp] = 79%).

LUS_0 exhibited acceptable predictive ability to indicate the need for MV at <72 hours of life (AUC = 0.80). A cutoff value of 7 was optimal for prognosis (Se = 89%, Sp = 65%; ►Table 2).

In the multivariate regression model, LUS_0 (odds ratio [OR] = 1.09, 95% confidence interval [CI] = 1.07–1.11) and gestational age (OR = 0.96, 95% CI = 0.93–0.98) were the only variables significantly associated with the need for SF administration.

The need for MV at <72 hours of life was significantly affected by the LUS_0 (OR = 1.01, 95% CI = 1.00–1.02) and by gestational age (OR = 0.98, 95% CI = 0.97–1.00).

Successful Weaning from Noninvasive Ventilation

The LUS obtained prior to weaning from CPAP was an excellent (AUC = 0.86) predictor of successful withdrawal. The score ≤ 1 prior to weaning indicated successful withdrawal (►Table 2).

In the multivariate model, the LUS before weaning was the only significant factor influencing weaning success (OR 0.93, 95% CI = 0.90–0.97).

Successful Extubation

Among the 19 infants who needed MV, 11 (58%) had a successful first extubation attempt.

However, only 7 of the 19 patients had a lung scan before extubation.

The LUS prior to extubation showed no significant effect on the extubation outcome.

Moderate to Severe Bronchopulmonary Dysplasia

Significant factors affecting the occurrence of moderate to severe BPD included the LUS on Day 7 (OR = 1.02, 95% CI = 1.00–1.04, p = 0.028), gestational age (OR = 0.97, 95% CI = 0.95–0.98, p < 0.001), and MV duration (OR = 1.02, 95% CI = 1.00–1.04, p = 0.018).

Within the subset of neonates not needing SF, infants who eventually developed BPD (n = 6) had numerically higher LUS values in the first days of life than those who did not (n = 87; ►Fig. 2).

Post Hoc Power Analysis

The sample size of the study (n = 155) was based on a "convenience sample." A post hoc power analysis using the bootstrap method revealed that with α = 0.05, the study was adequately powered to detect a significant impact of the LUS in predicting the need for MV at <72 hours of life (power 86%), the need for SF, successful weaning from CPAP, and BPD development (power > 95% for the above variables).

Discussion

In the last 3 years, there has been a substantial increase in interest in the predictive potential of the LUS. Most studies have focused solely on the occurrence of BPD.[3,4,16–21]

We looked at a variety of outcomes, and the most striking finding was the LUS's predictive value for CPAP cessation. This finding is particularly important because there are no well-established criteria for discontinuing noninvasive respiratory support. LUS appeared to be a high-specificity predictor for successful CPAP termination, which may have practical relevance in everyday practice or, at the very least, encourages more research to further assess this association. CPAP cessation has received relatively little attention in ultrasonography studies thus far, and the feasibility of utilizing the LUS to determine CPAP withdrawal readiness was

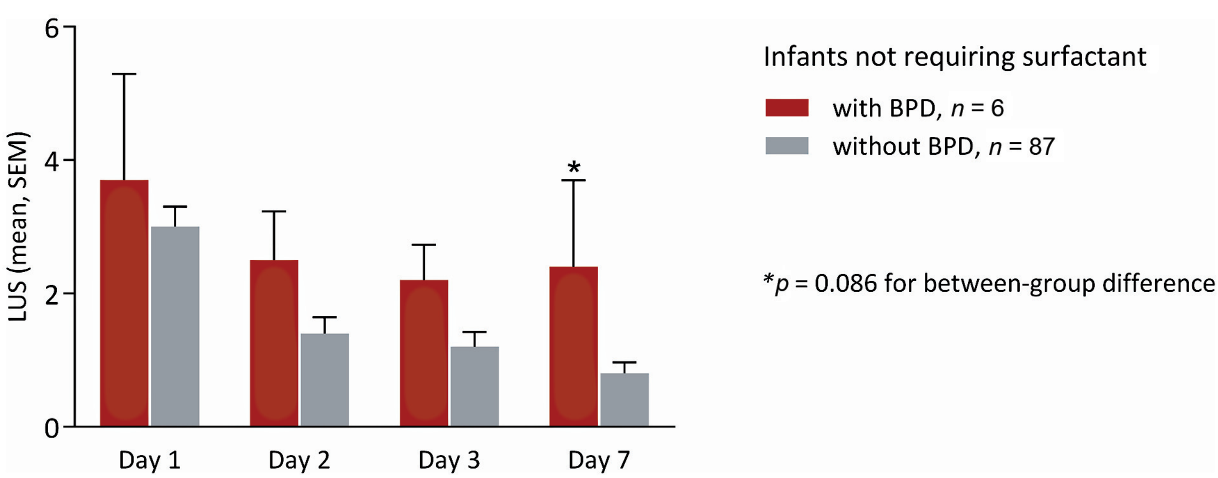

Fig. 2 Lung ultrasound scores in a subset of infants who did not require surfactant administration. LUS, lung ultrasound score; SEM, standard error of mean.

highlighted in a paper published only in 2022.[22] Our results showed similar prediction accuracy (AUC = 0.86 vs. 0.87 from Abdelmawla et al[22]). Surprisingly, in our regression model, weaning readiness was strongly associated with the LUS but not with SpO_2/FiO_2. This demonstrates that assessing systemic oxygenation alone is insufficient for deciding whether to discontinue CPAP, and patient evaluation should include lung scans.

Another noteworthy finding is the high accuracy in predicting the requirement for SF (AUC = 0.86). This might considerably speed up the administration of SF because baseline scans were performed, on average, 1.6 hours after birth, but SF was given only 2.6 hours after birth, guided by the increasing oxygen requirements. Early postnatal lung ultrasonography may be a better trigger for the use of SF, ultimately resulting in improved treatment outcomes. There is already some evidence in support of this assumption. In a quality improvement project, ultrasound-guided SF treatment resulted in an increased proportion of babies who received therapy earlier. This led to an increase in ventilator-free days and a significantly shorter duration of ventilation.[23]

Currently, some argue that the LUS, rather than oxygen demand, should be the primary criterion for SF treatment.[24] A somewhat similar viewpoint is articulated in the most recent European Guidelines on RDS Management,[25] which propose deciding on SF treatment using FiO_2 or appropriate lung ultrasonography. Given that the recommendations contain no particular guidance other than "if lung ultrasonography suggests SF need," it is all the more important that the results of our study provide neonatologists with a practical indication to the ultrasound threshold for SF.

A special focus and additional research are required for the subset of neonates who have an oxygen demand of <30% and hence do not fulfill the criteria for SF yet develop BPD. We only had six infants meeting these conditions, and our study was underpowered to evaluate whether serial LUSs may be used as discriminating tests to identify newborns at risk of BPD. Based on a post hoc power calculation, a sample of 30 newborns with BPD would be required to offer 80% power for finding significant LUS differences between the groups, at a 0.05 significance level. This is an intriguing topic for future study, and if the relevance of the LUS in this aspect is demonstrated, it will be crucial to determine whether these neonates could benefit from SF treatment.

The technique of lung imaging we adopted, which encompassed posterior lung fields, could have affected our results. Other studies[16,19] have also noted the importance of assessing the posterior lung fields. In the study by Alonso-Ojembarrena et al, the examination of the posterior lung fields increased the accuracy of predicting BPD compared with the evaluation of the anterolateral fields alone, but only on Day 14 of life.[16] In another BPD study by Oulego-Erroz et al,[19] assessment of posterior lung fields significantly improved prognostic accuracy, although the authors investigated the LUS only on Day 7 of life (AUC = 0.94). The higher diagnostic accuracy with the examination of the posterior lung zones was not confirmed in the meta-analysis of Pezza et al.[26] The work of Loi et al.[4] showed similar BPD prediction reliability of the LUS using grading schemes that either included or excluded the posterior lung zones.

We believe that investigating the posterior lung fields has a strong pathophysiological rationale, which arises from, among other factors, the posterior fields' substantially larger area, reaching the 11th rib, as opposed to the anterior fields which end at the 5th rib line. Additionally, the LUS reflects the amount of interstitial water in lung tissue. Because the fluid distribution in many lung disorders (including RDS) is gravitational, its assessment is more thorough when scans are performed along the gradient (front–back). Although the lungs present a homogenous picture shortly after birth in neonatal RDS, our study evaluated infants at up to 7 days' postnatal age. At this age, even in patients initially exhibiting RDS, the lung image is clearly gravitationally dependent, as we demonstrated in our previous study.[12] Only concerns about the newborn's destabilization upon shifting position warrant limiting the examination to the anterior and lateral areas. For this reason, many studies have not investigated the posterior pulmonary fields. Some sonographers avoid changing the position of a child during scanning for fear of causing harm. Our clinical observations do not support such a concern. A recent publication from the DeLuca group also showed that the prone position increased gas exchange and lung aeration in a cohort that included preterm babies born at <32 weeks gestation with RDS and a postnatal age of ≤5 days.[27] Pronation had no clinically significant hemodynamic effects. A Canadian group published a study in which the lung ultrasonography procedure involved altering the patient's position (supine to prone and prone to supine) in neonates ≥29 weeks of gestational age.[28] The study confirmed the feasibility of the prone position for lung ultrasound assessment.

Our project's strengths are that it was prospective, all scans were evaluated by a single rater with extensive experience in lung ultrasound, and standardized image settings were used to optimize the ability to quantify the B-line densities. Finally, we evaluated posterior pulmonary fields.

The main drawback of our study was the failure to perform preextubation examinations in most patients (12 out of 19) who received MV. This made evaluating the prognostic properties of the LUS for extubation success impossible. Nonetheless, the LUS predicts successful extubation in mechanically ventilated infants.[29,30]

The BPD analysis is associated with the greatest number of constraints. First, our study excluded infants who were primarily intubated, i.e., those who were most prone to develop BPD. Second, we employed the BPD definition from the National Institute of Child Health published in 2001,[11] which is not easily comparable with newer definitions of BPD.[31,32] This makes it difficult to compare the study's findings to those of other studies.

Additionally, the study cohort was strongly skewed toward more mature newborns. This limited the number of infants with moderate to severe BPD. As a result, despite their statistical significance, prognostic calculations for the occurrence of moderate to severe BPD should be regarded cautiously—as a warning measure rather than definitive prediction numbers. The predominance of the more mature infants in our study, together with the small proportion of babies with relevant outcomes, makes the study results also less generalizable to the population of very preterm and extremely preterm babies.

Finally, the lung scoring system that we used has not been used by other teams. This may generate issues with the cross-interpretation of the results. There are many modifications of the original Brat's scale, with changes in both the pulmonary areas studied and the definitions of the individual point values.[33] Our grading system is one of the few used in neonatology.[34] However, for all the grading scales that are in use, a correlation in the same direction between the total score and the systemic oxygenation indicators was consistently demonstrated.[33] The drawback is that the use of different scoring methods make it challenging to determine cutoff values in meta-analyses.

Conclusion

In conclusion, our results showed significant predictive value of the LUS in the first week of life with regard to critical outcomes in neonatal RDS. The predictive value is not related to a single endpoint but rather to the entire set of endpoints that characterize the course of respiratory failure. This indicates the usefulness of the LUS in clinical practice.

Ethics Approval and Consent to Participate

Detailed information about the aim and course of the study was given to all parents or legal guardians of the participating infants, and written informed consent was obtained. All procedures were performed in compliance with the ethical principles laid forth in the Helsinki Declaration of 1964 and its subsequent amendments. The study protocol was approved by the Ethics Committee of Warsaw Medical University (ref. no. KB/47/2021), in accordance with the principal investigator's affiliation.

Authors' Contributions

P.S., R.H., R.B., P.K., I.S-K., and W.B. were involved in planning and supervision of the study. R.H., P.K., M.S., and I.S-K. drafted the manuscript with input from all authors. R.H. designed the figures. P.K. compiled the literature sources and provided critical feedback. R.B., J. P-G., U.M., A.T., M.K-M., N.S-W., and P.S. performed ultrasound examinations. All authors discussed the results and approved the version to be published.

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Conflict of Interest

P.S., M.S., W.B., I.S-K., P.K., and R.B. received honoraria from Chiesi Poland for lecturing and participation on advisory boards. R.H. is employed by Chiesi Poland, the sponsor of the study. The remaining authors report no conflict of interest.

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