A Modified Lung Ultrasound Score for Assessing Oxygenation Status and Predicting the Need for Invasive Ventilation in Preterm Neonates with RDS

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Research article

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Abstract

Purpose

We propose a modified lung ultrasound score (LUS) in neonates with respiratory distress syndrome (RDS), which includes posterior instead of lateral lung fields, and a 5-grade rating scale instead of a 4-grade rating scale. The LUS was evaluated for validity, interrater agreement and prognostic power in relation to the need for respiratory support on day of life (DOL) 3. The hypothesis of the dominant weight of posterior scans in the LUS was also verified.

Materials and methods

A total of 647 serial lung scans were performed in 70 preterm infants <32 weeks gestation and birth weight <1500 g. Assessments were performed within 24 hours of birth (LUS₀) and on days 2, 3, 5, 7, 10, 14, 21 and 28. LUS was correlated to oxygen saturation over fraction of inspired oxygen (SpO₂/FiO₂) and mode of respiratory support. Probabilities of the need for respiratory support on DOL 3 were assessed with ordinal logistic regression.

Results

The LUS correlated significantly with SpO₂/FiO₂ (Spearman rho = -0.635; p<0.0001) and had excellent interrater agreement (Cronbach's alpha = 0.99). Posterior fields had dominant weight over the anterior fields (ls mean [confidence level]) 4.0 [3.8–4.1] vs 2.2 [2.0–2.4]; p<0.0001. Significant predictors of ventilation requirements on DOL 3 were LUS₀ (p<0.016) and birth weight (BW) (p<0.0001); invasive ventilation was the most likely option with LUS₀ ≥7 (BW 900 g), ≥10 (BW 1050 g) and ≥15 (BW 1280 g).

Conclusion

Postbirth LUS predicts the need for mechanical ventilation on DOL 3. Posterior fields play a dominant role in sonographic assessment of lungs in neonatal RDS.

Introduction

An increasing number of reports have recently been published on the usefulness of the lung ultrasound score (LUS) to assess lung function in premature infants with respiratory distress syndrome (RDS) [1–7]. In all reports concerning LUS in neonatal RDS, sonograms were limited to the early post-birth period, typically the first 24 hours of life [1–6]. This early post-birth LUS proved to be well correlated with the gas exchange indices [1, 6]. In some studies, LUS also had a significant prognostic value relative to the short-term endpoint, e.g., the need for exogenous surfactant [1, 2, 5, 6].

The scoring scheme as described initially by the group of DeLuca [6] was based on evaluation of anterior and lateral pulmonary fields. Anterior fields were additionally divided into upper-anterior and lower-anterior. The four-grade scale to assess each lung field was 0 to 3, where border scores corresponded to
the normal lung ("0") and solid pulmonary consolidations ("3"). The sum of all lung field scores was the overall LUS.

Clinical observations, however, show that most of the pulmonary pathologies in premature neonates are found in the posterior lung fields. This is consistent with the gravitational effect, which affects the lowest parts of the lungs in the supine position. This gravitational impact on the lungs is not seen during intrauterine life and is also not seen immediately after birth. However, it becomes relevant in the subsequent hours and days of life. Ultrasound images of the lung in neonatal RDS typically differ much more in the anteroposterior gradient than in the upper-lower gradient. Posterior scans, therefore, provide valuable information that should not be overlooked. In turn, anterior scans present a largely homogenous picture with respect to upper-anterior vs lower-anterior fields, especially in the first hours of life.

Thus, we propose an alternative approach to lung ultrasound assessment that relies, in short, on (1) scanning posterior rather than lateral fields, (2) evaluating anterior fields as a whole, without division into upper and lower parts and (3) introducing an additional grade to the current scoring scheme.

The aim of this study was to confirm the correlation of the proposed LUS with the indices of arterial blood oxygenation and to verify the hypothesis that posterior lung fields have dominant weight in the overall LUS score in the first 28 days of life. Additionally, we assessed the capability of early post-birth (< 24 hours after birth) LUS to predict the degree of respiratory support on the third day of life (DOL 3).

Materials And Methods

Patients and study design

Serial lung ultrasound scans were performed in 70 premature newborns admitted to the neonatal intensive care unit (NICU) of the Children's University Hospital in Cracow. The study center is an academic, tertiary-referral 30-bed NICU, with approximately 450 admissions per year. The hospital does not have a maternity ward, and all study patients were outborn. Infants were considered for the study if they were ≤32 weeks of gestation, had a birth weight ≤1500 g and were admitted within the first 24 hours of life. The presence of severe birth defects was an exclusion criterion. All parents or legal guardians provided written informed consent, and the study protocol was approved by the Bioethical Committee of Jagiellonian University, Cracow.

Ultrasound examinations

Newborns meeting the enrollment criteria were subjected to an initial lung ultrasound scan within the first 24 hours of life (LUS₀) and subsequent scans on days 2, 3, 5, 7, 10, 14, 21 and 28. Examinations were performed by two expert-level neonatal sonographers using a Phillips HD 11 scanner with a linear probe of 12 – 5 MHz. Four lung areas were assessed: anterior (left), anterior (right), posterior (left) and posterior (right), using both transversal and longitudinal scans. Newborns were placed in a prone or lateral position to examine the posterior areas. Each lung field was graded according to the five-grade scale shown in
Fig. 1, where “0” corresponded to normal lung and “4” indicated the presence of pulmonary consolidations. The sum of all four area scores was the total LUS, which could therefore range from 0 to 16. Compared to the previously described grades for pulmonary scans, we introduced an additional grade of “white lung with fluid alveologram” (score “3”). All scans were recorded and stored as uncompressed video files on an external storage device for subsequent evaluation of interrater agreement.

**Study measures**

For each lung scan, the corresponding fraction of inspired oxygen (FiO\textsubscript{2}) and blood oxygen saturation (SpO\textsubscript{2}) was recorded. The SpO\textsubscript{2}/FiO\textsubscript{2} ratio served as an oxygenation measure against which correlation with the LUS was assessed. An appropriate correlation coefficient served as the LUS quality measure.

Respiratory support modes were assigned to the corresponding LUS scores. The support modes included the following interventions (in escalating order): oxygen delivery via nasal cannula, continuous positive airway pressure (CPAP), intermittent positive pressure ventilation (IPPV) and high frequency oscillatory ventilation (HFOV). The latter was used as rescue therapy in cases where no stabilization of respiratory function could be achieved with IPPV.

LUS obtained in the first 24 hours of life (LUS\textsubscript{0}) was tested for prognostic capability with regard to ventilatory modes on DOL 3.

**Statistics**

LUS association with SpO\textsubscript{2}/FiO\textsubscript{2} was evaluated using the correlation coefficient of Spearman ranks. To assess the weight of the posterior area scores in the total LUS, we used linear mixed effects regression. In this analysis, patients were set as a random factor, while the anteroposterior gradient of the LUS and the postnatal day of examination were fixed effects. Probabilities for the need for particular modes of respiratory support on DOL 3 were assessed with ordinal logistic regression. To check for interrater agreement of the LUS, Cronbach’s alpha was calculated. For all analyses, p values less than 0.05 were regarded as significant.

**Results**

The study cohort consisted of 70 premature newborns (31 [47%] males), with a median gestational age of 28 weeks (IQR, 26–29) and a mean birth weight of 1037 ± 270 g. Of those 70 babies, 8 (11.4%) died before discharge, and 6 (8.5%) were transferred to another hospital and were lost to follow-up.

A total of 647 lung sonograms were performed, including 625 *per protocol* scans and 22 additional scans carried out beyond the day of life 28. In 6 of 647 (0.9%) examinations, LUS was not calculated because scans revealed pneumothorax (n = 5) or hydrothorax (n = 1). Baseline sonograms were performed at an average postnatal age of 10.7 (7.5–15.5) hours (median, IQR).
The distribution of the LUS and the corresponding SpO$_2$/FiO$_2$ ratio is presented in Fig. 2. LUS correlated significantly with SpO$_2$/FiO$_2$ (Spearman rho = −0.635; p < 0.0001).

The LUS score showed excellent interrater agreement (Cronbach’s alpha = 0.99).

In the mixed effects linear model, posterior pulmonary field scores dominated over anterior fields in the total LUS. Based on all scans performed, the posterior fields had an average score (ls mean, confidence level) of 4.0 (3.8–4.1), while anterior pulmonary fields had an average score of 2.2 (2.0–2.4). The difference was statistically significant (1.8; p < 0.0001).

LUS presented linear growth depending on the requirement for respiratory support. Infants who breathed spontaneously and did not need oxygen supplementation had a median (IQR) LUS of 2 (0–4). Escalation of therapy from oxygen supplementation to CPAP and further to invasive ventilation (IPPV) and HFOV as the ultimate option involved a linear increase in LUS; the respective medians (IQR) were 3 (2-4.5) for O$_2$ cannula, 6 (4–8) for CPAP, 10 (7–12) for IPPV and 14 (12.5–15.5) for HFOV (Fig. 3).

In the ordinal logistic regression model, the need for invasive ventilation on DOL 3 was predicted by the lung scan performed in the first 24 hours of life (LUS$_0$; p = 0.016) and by birth weight (p < 0.0001) but not by gestational age. Depending on the birth weight, invasive ventilation was the most likely option of respiratory support on DOL 3 if the following thresholds of LUS$_0$ were reached: ≥7 (for BW 900 g), ≥10 (for BW 1050 g) and ≥15 (for BW 1280 g) (Fig. 4).

**Discussion**

To date, several studies have been published assessing the clinical usefulness of lung ultrasound in newborns with respiratory disorders [1–14]. These works focused mainly on preterm infants with RDS and transient tachypnea of the newborn (TTN); in both cases, LUS was performed primarily on the first day of life. [1–11, 13, 14].

Our research provides an additional body of evidence as it was based on post-birth lung sonograms complemented by sequential scans performed over a period of 28 days. As a result, the correlation of LUS with the severity of respiratory failure as expressed by oxygenation indices and the need for respiratory support was demonstrated beyond the first day of life.

Additionally, our study covered a diverse spectrum of patients, both before and after administration of surfactant, infants with significant posttreatment improvement and those who deteriorated in the follow-up examinations, patients with developing pneumonia and those with bronchopulmonary dysplasia (BPD). Sonograms reflected all sorts of respiratory statuses, ranging from spontaneous breathing ambient air through nasal CPAP to invasive ventilation. Thus, a close correlation between the LUS and the indices of respiratory failure was demonstrated in much more diverse clinical conditions. This allows the LUS to be treated as a more universal measure of pulmonary pathology and is not limited to the typical changes observed in neonates with RDS on the first day of life.
In studies where lung ultrasound images were quantified, four-grade scales were mainly used (a score of 0-1-2-3) [1, 3, 5, 6, 8–11]. In our work, we proposed a five-grade scale (a score of 0-1-2-3-4), defining an additional category of “white lung with fluid alveologram”. This sonographic pattern is sometimes referred to in the literature as shallow consolidations and should be distinguished from true consolidations. True consolidations are hypoechoic triangular-shaped changes with visible air bronchogram, while fluid alveologram is a subpleural accumulation of exudative fluid, which mixed with air, fulfills the alveoli. Fluid alveologram can be observed in severe RDS [10] and, as a rule, is not seen in the first day of life but rather in the following days. Since the study covered the entire first month of life of premature babies, it seems appropriate to classify this type of change separately.

We abandoned the division of pulmonary fields into upper and lower sections. Previously, Pang et al. [10] expanded the assessment scales by including posterior pulmonary fields, dividing each of the studied lung areas into the upper and lower parts while maintaining a four-grade scale. This type of division used also by Raimondi et al. [11] is adopted from adult studies, where due to the chest size, it seems expedient.

In our modification of the lung ultrasound examination, we propose assessment of posterior and not lateral pulmonary fields. In almost all available works, ultrasound examination was limited to the anterior and lateral parts of the lungs. Very few studies have reported assessments of posterior pulmonary fields [4, 10, 11]. The “anterior-lateral” approach leads to deviation from the significant advantage of lung ultrasound over standard anteroposterior X-ray, namely, the possibility of distinguishing between changes in the anterior and posterior parts of the lungs. Additionally, it is known from daily clinical practice that most pulmonary pathologies tend to have gravitational positioning. Our study confirmed this observation, as posterior scores had significantly higher weight in the total LUS score compared to anterior scores (Is means 4.0 vs 2.2; p < 0.0001).

In the analysis, we did not focus on the prognostic value of LUS in relation to the need for surfactant treatment, which has been previously reported [5]. Because LUS is closely correlated with oxygenation indices and surfactant administration is based on the level of inspired oxygen fraction, such a relationship seems expected. However, we demonstrated significant predictive ability of the postnatal (performed within 24 hours from birth) LUS to prognose the need for mechanical ventilation on subsequent days – an aspect that has not been investigated before. Depending on the birth weight, specific LUS cut-off levels indicate infants in whom invasive ventilation is the most likely mode of respiratory support on DOL 3. The need for invasive ventilation on DOL 3 is a widely recognized endpoint in neonatal RDS and is strongly correlated with subsequent adverse outcomes. Thus, our findings may have significant practical implications. Modified LUS allows for early identification of the most vulnerable infants and may lead to earlier decisions, e.g., administration of exogenous surfactant or more aggressive respiratory support.

The analysis also provides an important observation regarding the association of oxygen requirements and the severity of lung changes. As shown in Fig. 2, the increasing severity of pulmonary changes is not accompanied by a parallel increase in oxygen demand until the LUS reaches 5–6 points, which
corresponds to approximately 1/3 of the LUS maximum possible score. Simply put, this means that only when approximately one-third of the lung parenchyma is involved in the pathological process does an increased demand for oxygen appear. This observation is not surprising from a pathophysiological point of view, as for most organs (kidney, liver), the pathological process must cover a certain area of the organ to cause clinical symptoms.

However, this fact sheds new light on the applied criteria for surfactant treatment. According to the current therapeutic guidelines, the decision of surfactant administration is based on the required level of inspired oxygen [15]. With the current approach, if there is no increased oxygen requirement, surfactant is not applied. In light of our findings, this means that treatment is not administered until the severity of lung changes as measured by LUS reach at least 1/3 of its maximum possible level. The current treatment paradigm requires verification in properly designed clinical trials where surfactant would be LUS-guided, and the primary efficacy endpoint would not be the failure of CPAP, as it is at present, but the development of bronchopulmonary dysplasia.

In our study, LUS assessments had a very high interrater agreement, as reflected by Cronbach's alpha equal to 0.99. Although all scans were assessed by two neonatologists with expert-level skills, lung ultrasound is known to be a diagnostic procedure that is easy to master and has a steep learning curve. Daily observations outside the scope of this study show that lung ultrasound examination can be easily learned during two-day courses and 1–2 months of supervised practice. It is therefore likely that the reproducibility of the LUS assessments carried out by ultrasound experts would be replicated by less experienced sonographers.

The current situation of using different scales for assessing the severity of changes in lung ultrasound in newborns is summarized in a meta-analysis published by Razak et al. [16]. In their conclusions, the authors emphasize the close correlation of ultrasound assessment to clinical parameters, which proves the usefulness of this tool.

In summary, we proposed a modified LUS, which is characterized by a high correlation with oxygenation parameters and respiratory support modes and a very high consistency of assessments between performers. We also confirmed the need to examine the lungs as a whole, including the posterior fields, taking into account the impact of gravity on the location of the lesions. The study showed that LUS is a tool that can be used for the early postnatal identification of infants at risk of invasive ventilation in the subsequent days of life. Finally, the modified LUS is suitable not only in newborns during the first days of life and remaining on noninvasive respiratory support but also in mechanically ventilated infants with various respiratory disorders during the first month of life.

Declarations

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 carried out 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 Bioethical Committee of Jagiellonian University, Cracow (ref. no. KBET/209/B/2012).

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**Competing interests**

RH, who drafted the manuscript collaboratively with PK, is an employee of Chiesi Poland, the company which provided financial support for the publication of this article. The study presented was neither funded by Chiesi nor was the company involved in its design, data collection and the decision to publish.

**Authors' contributions**

PS and PK co-designed the study and were equally involved in collecting the data. PW was responsible for the database design and data entry. RH wrote the manuscript in consultation with PK and PS. PS, PK and RH were involved in interpretation of findings. All authors discussed the results and approved the final draft.

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Not applicable

**Availability of data and materials**

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

**References**

1. Perri A, Tana M, Riccardi R, et al. Neonatal lung ultrasonography score after surfactant in preterm infants: a prospective observational study. Pediatr Pulmonol. 2020;55:116–21.
2. Gregorio-Hernández R, Arriaga-Redondo M, Pérez-Pérez A, et al. Lung ultrasound in preterm infants with respiratory distress: experience in a neonatal intensive care unit. Eur J Pediatr. 2020;179:81–9.

3. Louis D, Belen K, Farooqui M, et al. Prone versus supine position for lung ultrasound in neonates with respiratory distress. Am J Perinatol. 2019. doi:10.1055/s-0039-1695776.

4. Oktem A, Yigit S, Oğuz B, et al. Accuracy of lung ultrasonography in the diagnosis of respiratory distress syndrome in newborns. J Matern Fetal Neonatal Med 2019: 1–6. doi:10.1080/14767058.2019.1605350.

5. De Martino L, Yousef N, Ben-Ammar R, et al. Lung ultrasound score predicts surfactant need in extremely preterm neonates. Pediatrics. 2018;142:e20180463.

6. Brat R, Yousef N, Klifa R, et al. Lung ultrasonography score to evaluate oxygenation and surfactant need in neonates treated with continuous positive airway pressure. JAMA Pediatr. 2015;169:e151797.

7. Liu J, Cao HY, Wang HW, et al. The role of lung ultrasound in diagnosis of respiratory distress syndrome in newborn infants. Iran J Pediatr. 2015;25:e323.

8. Raschetti R, Yousef N, Vigo G, et al. Echography-guided surfactant therapy to improve timeliness of surfactant replacement: a quality improvement project. J Pediatr. 2019;212:137–43.e1.

9. Mongodi S, Bouhemad B, Orlando A, et al. Modified lung ultrasound score for assessing and monitoring pulmonary aeration. Ultraschall Med. 2017;38:530–7.

10. Pang H, Zhang B, Shi J, et al. Diagnostic value of lung ultrasound in evaluating the severity of neonatal respiratory distress syndrome. Eur J Radiol. 2019;116:186–91.

11. Raimondi F, Yousef N, Rodriguez Fanjul J, et al. A multicenter lung ultrasound study on transient tachypnea of the neonate. Neonatology. 2019;115:263–8.

12. Liu J, Wang Y, Fu W, et al. Diagnosis of neonatal transient tachypnea and its differentiation from respiratory distress syndrome using lung ultrasound. Medicine. 2014;93:e197.

13. Ibrahim M, Omran A, AbdAllah NB, et al. Lung ultrasound in early diagnosis of neonatal transient tachypnea and its differentiation from other causes of neonatal respiratory distress. J Neonatal Perinatal Med. 2018;11:281–7.

14. Copetti R, Cattarossi L. The 'double lung point': an ultrasound sign diagnostic of transient tachypnea of the newborn. Neonatology. 2007;91:203–9.

15. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome — 2019 update. Neonatology. 2019;115:432–50.

16. Razak A, Faden M. Neonatal lung ultrasonography to evaluate need for surfactant or mechanical ventilation: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2020;105:164–71.

Figures
**Figure 1**

The grading system for the evaluation of pulmonary areas, based on the pleural ultrasound artifacts.

| Score | Description                                      |
|-------|--------------------------------------------------|
| 0     | Normal lung (A-profile)                          |
| 1     | B lines (B-profile)                              |
| 2     | "White lung"                                    |
| 3     | "White lung" and fluid alveologram              |
| 4     | "White lung" and consolidations                  |

![Image of grading system](image-url)
Figure 2

Distribution of LUS and the corresponding SpO\textsubscript{2}/FiO\textsubscript{2}. Horizontal lines depict median SpO\textsubscript{2}/FiO\textsubscript{2} values.
Figure 3

Lung ultrasound score vs mode of respiratory support. Horizontal lines are medians, boxes denote interquartile range and whiskers are 10th and 90th percentile. Outlying scores are marked with crosses.
Figure 4

Probability of the need for respiratory support on the 3rd day of life, depending on the LUS performed within 24 hours from birth (LUS0). Probabilities calculated for the median birth weight (middle graph), 25th percentile (left graph) and 75th percentile (right graph). No infants in the study cohort were using O2 cannula or HFOV on DOL 3.