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Lung ultrasound score as early predictor of bronchopulmonary dysplasia in very low birth weight infants

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Abstract

Background: Lung ultrasound (LU) has been widely used to diagnose and monitor acute lung diseases in neonates, but its role in chronic diseases has not been elucidated.

Objective: We aim to describe the evolution of a lung ultrasound score (LU score) in very low birth weight infants (VLBWI) with and without bronchopulmonary dysplasia (BPD).

Methods: We prospectively included 59 VLBWI and performed LU in the first 24 and 72 hours of life, and then weekly until 36 weeks´ postmenstrual age (PMA). We calculated the LU score as a semiquantitative score representing the aeration (0-3) in three different areas of each lung.

Results: The non-BPD group (n = 38) had lower LU score at 1, 2, 3, 4, and 36 weeks' PMA than the BPD group: median score of 1 (0-4) vs 7 (3-10), $P < .001$; 0 (0-1) vs 7 (4-9), $P < .001$; 0 (0-1) vs 8 (7-11), $P < .001$; 0 (0-2) vs 9 (4-12), $P < .001$; 0 (0-0) vs 3 (0-6), $P < .001$. A LU score of 5 or above at 1 week of life predicted BPD with a sensitivity (Se) of 71%, specificity (Sp) 80%, area under the ROC curve (AUC) 0.8, and at 2 weeks of life with Se 74%, Sp 100%, and AUC 0.93. An LU score of 4 or above at 4 weeks predicted moderate-severe BPD (Se 100%, Sp 80%, and AUC 0.89).

Conclusion: In VLBWI without BPD, LU score increases during the first week of life and decreases thereafter, whereas among subjects with BPD, the LU score remains high until 36 weeks´ PMA. LU score can predict the diagnosis of BPD at 1 week and 2 weeks of life, and may predict moderate-severe BPD at 4 weeks of life.

KEYWORDS

bronchopulmonary dysplasia, lung/diagnostic imaging, neonatal intensive care unit, ultrasonography, very low birth weight infants

1 | INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the primary complications of prematurity affecting the psychomotor development of preterm-born children at age 5,[1] alongside brain injury and severe retinopathy of prematurity. Detecting early signs of this lung disease is challenging, and in the absence of a reliable marker for this evolving disorder, a window of opportunity to provide specific treatment or further adapt respiratory

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support is often missed. Cytokines and various proteins in blood or tracheal aspirate,[2,3] as well as thoracic X-rays[4] have been studied as potential biomarkers for BPD, but none has been proven sufficiently robust to be utilized in clinical practice.

Lung ultrasound (LU) has gained importance in the management of patients in the Neonatal Intensive Care Unit (NICU) as a safe and effective test to diagnose respiratory disease in newborns.[5-7] It can be used to predict the need for respiratory support in the first hours of life[8] or the need for surfactant administration in preterm infants.[9,10] LU is reproducible[11] and reduces the number of thoracic X-rays performed in the NICU.[12] It is increasingly recognized as a useful tool in very low birth weight infants (VLBWI) with BPD. Two studies have shown that persistent retrodiaphragmatic hyperechogenicity in the subcostal view after 9[13] or 18 days of life (DOL)[14] predicted the development of BPD in VLBWI. A semiquantiative lung ultrasound score (LU score), adapted from adult studies, has been proposed as a predictor of BPD from 2 to 8 weeks of life in VLBWI.[15] While promising, research regarding LU in BPD is otherwise scarce. In this study we aim to describe LU score evolution in VLBWI with and without BPD and assess whether it is useful as a BPD predictor.

2 | MATERIAL AND METHODS

From November 2017 to December 2018, every VLBWI (with a birth weight ≤ 1500 g and/or gestational age ≤ 32 weeks) admitted to the NICU at Hospital Puerta del Mar in Cádiz, Spain (inborn or transferred from another hospital in the first 24 hours of life) was included after parental consent. Infants with chromosomal abnormalities, major malformations or those who died before 36 weeks' postmenstrual age (PMA) were excluded. The local Ethics Committee approved the study protocol.

In accordance with the European guidelines for respiratory support in VLBWI,[16] we provide face-mask ventilation to unresponsive patients at birth with a T-Piece device to control target peak inspiratory pressure and deliver constant positive end expiratory pressure. Those unresponsive are intubated in the delivery room and receive early surfactant administration. Those who respond adequately at birth are transferred to NICU on nasal CPAP (nCPAP) if they are born before 30 weeks of gestation. Infants on nCPAP can be moved to nasal intermittent positive pressure ventilation (NIPPV) in case of progressive respiratory distress or respiratory acidosis. Less invasive surfactant administration (LISA) is performed if needed.

Participants were subsequently divided into two groups, BPD and non-BPD, using the previously published definition of BPD[17]:

- Mild BPD: oxygen requirement for the first 28 days but in room air at 36 weeks' PMA.
- Moderate BPD: oxygen requirement for the first 28 days and oxygen < 30% at 36 weeks' PMA. A room-air challenge was performed in these infants and only those that failed the reduction (oxygen saturation 80% to 87% for 5 minutes, or < 80% for 1 minute) were diagnosed as moderate BPD.
- Severe BPD: oxygen requirement for the first 28 days and oxygen > 30% and continuous positive airway pressure or mechanical ventilation at 36 weeks' PMA.

2.1 | Lung ultrasound

Bedside LU was performed using a high-frequency linear 8 to 15 MHz probe (Sonoscape Medical Corp., Shenzhen, China) with the probe held perpendicular to the ribs. All LUs were performed by the attending physician and were recorded anonymously. A neonatologist with LU experience, blinded to the status of the patient, reviewed all LUs and calculated the LU score. We performed LU on the first and third DOLs, then weekly until 28 DOL, and later in patients who were still on respiratory support. After 28 DOL, if the patient was not on respiratory support, we would perform a LU every 2 weeks. We calculated the LU score as previously described by Brat et al[9] by adding the score (0-3) obtained in three areas of the thorax defined by the anterior axillary line, the posterior axillary line, and the mammary line (upper anterior, lower anterior, and lateral) with a total score range of 0 to 18.

2.2 | Statistical analysis

We calculated median and interquartile range (IQR), or absolute numbers and percentages to describe the variables measured. To compare variables between groups, we used Student *t* test or the Wilcoxon rank sum test depending on the distribution of the variables, with Bonferroni correction for multiple comparisons. The first 20 images were used to calculate the intra-observer agreement for image interpretation with kappa score. We calculated the power of the study to detect a minimum difference of three points in the LU score between BPD and non-BPD patients, using a standard deviation of 2 and an α-risk of 5%.

To estimate a predictive model of LU score evolution in VLBWI with and without BPD we used linear multilevel mixed-effects regression to adjust for repeated measurements.[18-20]

We calculated sensitivity (Se), specificity (Sp), area under the receiver operating characteristic (ROC) curve (AUC), positive and negative likelihood ratio (LR+ and LR−) and positive and negative predictive values (PPV and NPV) for LU score at different time points to predict any BPD, and moderate-severe BPD. At each time point, optimal cutoff points were selected for maximum efficiency of the test, but also trying to maximize Sp due to the importance of the BPD diagnosis.

All tests were considered statistically significant if $P < .05$. We used STATA v.14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

TABLE 1 Descriptive statistics of patients included: values are represented as mean (95% confidence interval) or absolute number (percentage)

	Non-BPD patients (n = 38)	BPD patients (n = 21)
GA at birth (wk)	29.5 (27-32)	27.4 (23-31)
Birth weight (g)	1241 (837-1440)	914 (461-1367)
Male	18 (51%)	16 (76%)
Length of admission (d)	47 (22-72)	89 (32-146)
Bronchopulmonary dysplasia	0	Mild: 13 (62%) Moderate: 2 (9%) Severe 6 (29%)
Complete course of antenatal steroids	31 (82%)	15 (71%)
CRIB-II	7 (3-10)	12 (7-17)
SNAPPE-II	13 (0-26)	24 (0-54)
Cesarean delivery	30 (79%)	18 (86%)
Hyaline membrane disease	13 (35%)	11 (52%)
Severe intraventricular hemorrhage	4 (10%)	3 (15%)
Patent arterial duct treated	2 (5.3%)	2 (9.5%)
Cystic white matter disease	0 (0%)	2 (10%)
Severe retinopathy of prematurity	0 (0%)	1 (5%)
Severe necrotizing enterocolitis	0 (0%)	0 (0%)
Pulmonary hemorrhage	1 (2.6%)	1 (5%)
Surfactant administration	21 (55%)	15 (72%)
Infants on mechanical ventilation on day 7	7 (18.4%)	13 (62%)
Pneumothorax	0 (0%)	1 (4.8%)
Mechanical ventilation (d)	2 (0-5)	8 (0-17)
Respiratory support (d)	15 (4-26)	52 (21-83)
Postnatal steroids use	1 (2.6%)	2 (9.5%)
Oxygen at discharge	0 (0%)	5 (24%)

Abbreviations: BPD, bronchopulmonary dysplasia; GA, gestational age.

3 | RESULTS

We recruited 64 VLBWI; five died before 36 weeks' PMA and were excluded, leaving 59 subjects who were later classified into BPD and non-BPD groups. The perinatal variables of the included patients are described in Table 1: 21 subjects (36%) developed BPD and eight (14% of the total sample) had moderate-severe BPD. We performed 284 LUs, with a median number of 5 (IQR 3-6) in the non-BPD group and 7 (IQR 6-8) in the BPD group. Intra-observer agreement for image interpretation was high ($\kappa = 0.87$, 95% CI, 0.63-1).

The LU score (median and IQR) in BPD and non-BPD patients is shown in Figure 1. There is a significant difference in LU score between BPD and non-BPD patients after the first week of life until

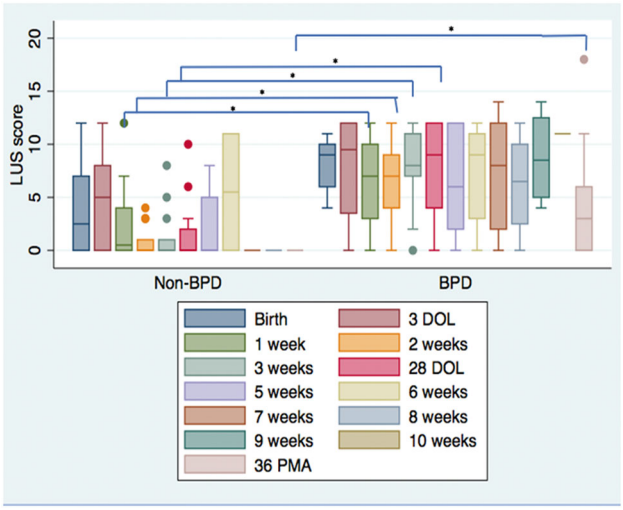

FIGURE 1 Lung ultrasound score (LUS) as median (interquartile rank) at different points of time. BPD, bronchopulmonary dysplasia; DOL, days of life; PMA, postmenstrual age *P < .05 [Color figure can be viewed at wileyonlinelibrary.com]

28 DOL, and then at 36 weeks' PMA. The calculated power of the study to compare LU score between the two groups is 100% (β risk 0%).

The linear multilevel mixed-effects regression model was calculated with splines: according to the apparent evolution of LU score described in Figure 1, we created three knot points (s1 = from birth until 3 DOL, s2 = from 3 DOL until 1 week, and s3 = from 1 week until 36 weeks' PMA), and used the variable BPD as an independent and modifier variable. In this way, the final equations were: non-BPD patients LU score = 2.4 + 3.1s1−2s2 + 0.02s3 and BPD patients LU score = 8.3−1.8s1 + 0.7s2−0.24s3. Regression coefficients and a summary of statistics from the model are shown in Table 2. When tested, it was accepted as a better model compared

FIGURE 2 Predicted lung ultrasound score by mixed-effects multilevel lineal regression in BPD (bronchopulmonary dysplasia) and non-BPD patients [Color figure can be viewed at wileyonlinelibrary.com]

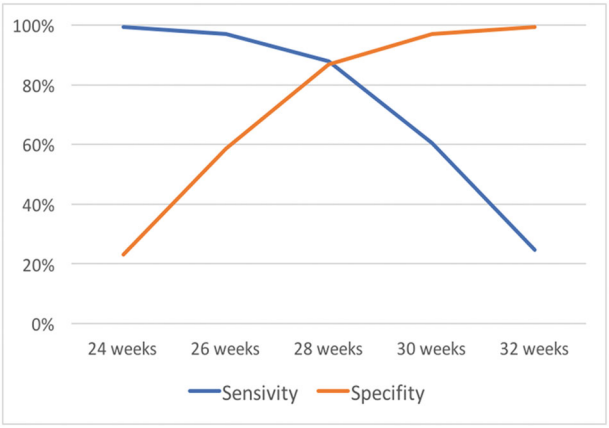

FIGURE 3 Predictive values of lung ultrasound score cutoff of 5 for any degree of bronchopulmonary dysplasia at two weeks of age, according to gestational age at birth [Color figure can be viewed at wileyonlinelibrary.com]

with mixed-effects model without splines and without interactions ($P < .05$). The calculated distribution of predicted LU score in both groups according to the equation selected by multilevel mixed-effects regression is represented in Figure 2.

The estimated Se, Sp, AUC, LR+ and LR−, PPV, and NPV for any degree of BPD and for moderate-severe BPD at different points of time are shown in Table 3. The optimal times to predict any degree of BPD are at 1 week of age, with a cutoff point of 5 (Se 71%, Sp 79%, AUC 0.8 [95% CI, 0.7-0.9]) and at 2 weeks of age, with a cutoff point of 5 (Se 74%, Sp 100%, AUC 0.93 [95% CI, 0.8-1]), and to predict moderate-severe BPD is at 4 weeks of age, with a cutoff point of 4 (Se 100%, Sp 78%, AUC 0.89 [95% CI, 0.8-1]). ROC curves for LU score at 1 week and 2 weeks of life as predictors of any BPD, and ROC curve for LU score at 4 weeks of age as predictor of moderate-severe BPD are shown in Supplementary material. Se and Sp of LUS score cutoff of 5 at 2 weeks according to gestational age (GA) at birth are shown in Figure 3: Se decreases if GA at birth increases, while SP increases inversely.

4 | DISCUSSION

We found that LU is a useful tool to predict BPD in VLBWI as early as 1 week of life. Among VLBWI, the LU score evolves differently in those who later develop BPD. While non-BPD infants experience a sharp decline in LU score at 1 week of life, after a slight increase at 3 DOL, infants who develop BPD maintain a high LU score from 3 DOL until 36 weeks' PMA. The LU score can predict BPD at 1 week (with Se 71% and Sp 79%) and at 2 weeks of life (Se 74% and Sp 100%). These findings suggest that the LU score may be useful as an early marker of BPD with the advantages of being safe and easy to perform, noninvasive, not painful and not involving ionizing radiation.

The calculated values vary with GA at birth: in the most immature patients, LU score displays a higher Se and lower Sp. These findings

TABLE 2 Statistics of the mixed-effect multilevel linear regression model for lung ultrasound score evolution in very low birth weight infants

	Coefficient	Standard error	*Z*	*P*
Constant	2.39	0.993	2.41	.016
s1	3.07	1.47	2.09	.036
s2	−2.0	0.60	−3.33	.001
s3	0.02	0.13	0.12	.903
BPD	5.86	1.89	3.09	.002
s1xBPD	−4.87	2.52	−1.93	.054
s2xBPD	2.67	0.93	2.86	.004
s3xBPD	−0.26	0.18	−1.46	.144

Abbreviation: BPD, bronchopulmonary dysplasia7.

suggest that younger patients may present higher LU score more persistently over time, regardless of whether they later develop BPD. We might therefore need to develop different LU score criteria based on GA to optimize the predictive capacity of LU score. The need for oxygen at 36 weeks PMA can be better predicted at 4 weeks of age, with a Se of 100% and a Sp of 78%.

Using thoracic X-ray, Kim et al reported that the existence of an interstitial infiltrate at 7 DOL predicts the later development of BPD in VLBWI.[4] This interstitial infiltrate in the thoracic X-ray correlates well with the existence of multiple B-lines in LU.[21,22] This is consistent with our findings, with diffuse interstitial infiltrate corresponding to a LU score of 6 or higher and at 1 week of age this value would be related to the later development of BPD.

Previous studies evaluating early signs in LU related to BPD, include Pieper et al[13] and Avni et al[14] who measured retro-diaphragmatic hyperechogenicity duration in LU in the subcostal view. Both agreed that patients in whom this sign disappeared before 9 or 18 DOL, respectively, did not develop BPD. Our study included this area of assessment, as well as the whole lung, and we demonstrate that a small increase in the number of B-lines (LU score lower than 5) can be found in these infants with no subsequent development of BPD.

More recently, Abdelmawla et al retrospectively examined 27 patients born before 30 weeks' GA, with 64 LUs and measured the LU score weekly, finding that a score higher than 5 between two and 8 weeks of life can predict moderate-severe BPD.[15] The discrepancy with our findings regarding the optimal values and timing for prediction, may be due to their inclusion of more immature infants (median GA at birth 26 weeks), possibly necessitating higher values to predict BPD. The study by Abdelmawla et al also aimed to predict BPD at any time point from 1 to 9 weeks of life. Our study includes a larger sample size, is prospective and we evaluate LU score as a predictor of BPD at specific time points separately using multilevel mixed-effects regression, reinforcing our findings. Notably, the higher prevalence of moderate-severe BPD reported by Abdelmawla et al, 50% vs 14% in ours, might be responsible for a higher PPV and lower NPV reported by them.

TABLE 3 Predictive capacity of LUS for bronchopulmonary dysplasia (BPD) at different points of time

	OCP	Sensitivity	Specificity	LR+	LR−	AUC	PPV (%)	NPV (%)
Any form of BPD								
1 d	6	80% (37.6-96.4%)	71.4% (45.4-88.3%)	2.8	0.28	0.79 (0.54-0.94)	50	90.9
3 DOL	5	75% (46.8-91.1%)	47.1% (26.2-69%)	1.4	0.5	0.69 (0.49-0.85)	50	72.7
1 wk	5	70.6% (46.9-86.7%)	79.2% (59.5-86.7%)	3.4	0.37	0.8 (0.65-0.91)	70.6	79.2
2 wk	5	73.7% (51.2%- 88.2%)	100% (82.4-100%)	>100	0.26	0.93 (0.8-0.99)	100	78.3
3 wk	6	85.7% (60.1-96%)	93.8% (71.7-98.9%)	13.7	0.15	0.92 (0.75-0.99)	92.3	88.2
Moderate-severe BPD								
1 d	9	50% (9.5-90.5%)	70.6% (46.9-86.7%)	1.7	0.71	0.63 (0.38-0.84)	16.7	92.3
3 DOL	10	75% (30.1-95.4%)	76% (56.6-88.5%)	3.13	0.33	0.78 (0.59-0.91)	33.3	95
1 wk	8	42.9% (15.8-75%)	85.3% (69.9-93.6%)	2.91	0.67	0.65 (0.49-0.79)	37.5	87.9
2 wk	8	42.9% (15.8-75%)	83.3% (66.4-92.7%)	2.57	0.69	0.69 (0.51-0.83)	37.5	86.2
3 wk	6	100% (51-100%)	65.4% (46.2-80.6%)	2.89	0	0.71 (0.51-0.86)	30.8	100
4 wk	4	100% (64.6-100%)	78.1% (61.2-89%)	4.57	0	0.89 (0.75-0.97)	50	100
5 wk	5	80% (37.6-96.4%)	53.3% (30.1-75.2%)	1.71	0.37	0.64 (0.4-0.84)	36.4	88.9
6 wk	12	60% (23.1-88.2%)	100% (74.1-100%)	>100	0.4	0.74 (0.46-0.92)	100	84.6

Abbreviations: AUC, area under the curve; DOL, days of life; LR+, positive likelihood ratio; LR−, negative likelihood ratio; LUS, lung ultrasound score; OCP, optimal cuttoff point; PPN, negative predictive value; PPV, positive predictive value.

The limitations of this study include the lack of an external validity test for the LU score, which may be different depending on operator experience. Our results may be more difficult to apply at NICUs with less experience in LU. Other limitations of our study include a small sample size and a low number of moderate-severe patients with BPD.

Further research in this area is warranted, focusing on the usefulness of LU score in BPD prediction based on GA at birth, as well as its role in combination with other early biomarkers being studied in the prediction of BPD.

5 | CONCLUSIONS

In VLBWI infants, early LU score among those who do not subsequently develop BPD increases during the first week of life, with a later decline, while in patients with BPD it remains high until 36 weeks' PMA. LU score cutoff of 5 at 1 week of age and at 2 weeks of age are predictors of BPD. LU score cutoff of 4 at 4 weeks of life predicts moderate-severe BPD. The Se and Sp of these values vary according to GA at birth.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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