ORIGINAL ARTICLE

Early Lung Ultrasound Scores in Neonates With Respiratory Distress - A Cross-Sectional Study From South India

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ABSTRACT

Objective: To estimate the lung ultrasound (LUS) scores within 6 hours of birth in neonates with respiratory distress (RD) and assess its ability to predict the severity of RD.

Methods: This single-center cross-sectional study included all neonates admitted with RD during the study period for whom a LUS was performed within 6h of birth. LUS scoring was done by dividing the lung fields into 3 fields on either side and a score from 0 to 3 per field (maximum score 18). We excluded neonates with congenital heart disease, congenital anomalies of chest/lung, chromosomal anomalies and if the operator for LUS was not available. ROC curves were constructed for estimating the cut-off LUS score for the severity of RD in terms of the following six outcomes: fraction of inspired oxygen (FiO2) requirement > 50% during first 3 days of life, need for invasive ventilation on day 3 of life, Silverman-Anderson score ≥ 7, surfactant requirement, radiological grades of respiratory distress syndrome (RDS), and death.

Results: The median (IQR) LUS scores were significantly higher in neonates with greater severity of RD in terms of FiO2 requirement >50% during first 3 days of life [12.0, (5.0, 14.0)], need for invasive ventilation on day 3 of life [12.0 (7.5, 12.5)], Silverman-Anderson score ≥ 7 in preterm [9.5, (6.0, 12.0)], surfactant requirement [11.5, (4.0, 12.5)], radiological grades of RDS [10.0, (4.0, 12.0)], and death [12.0, (7.0, 15.0)]. In logistic regression analysis, with continuous LUS_0 scores as covariates, the odds ratio significantly increased for every unit increase in LUS_0 score.

Conclusion: Early LUS scores can predict the prognosis and severity of neonatal RD.

Keywords: *Lung disease, Neonatal Mortality, Prematurity, Surfactant, Ventilation, Silverman-Anderson score*

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INTRODUCTION

Respiratory distress (RD) in neonates is commonly caused by respiratory distress syndrome (RDS), transient tachypnea of newborn (TTN), meconium aspiration syndrome (MAS), pneumothorax, and pneumonia [1]. Though the clinical outcomes of neonates with RD have improved with advances in treatment, RD continues to be an important cause of neonatal morbidity and mortality warranting early diagnosis and treatment [2]. Due to the unreliability of chest *X*-rays in the early diagnosis of RD, lung ultrasound (LUS) is being increasingly used [3].

Point-of-care ultrasonography (POCUS) is being increasingly used in many Neonatal intensive care units (NICUs) [4,5]. Neonates and children are ideal candidates for LUS because of their thin chest walls and the small size of their lungs [6]. Scoring systems have been developed based on the detection of A or B lines or consolidation using LUS [7-9]. A significant correlation has been reported between LUS scores and the diagnosis of RDS [8]. However, the potential of early LUS to predict the severity and prognosis of neonates with RD has not been explored.

The objective of the study was to estimate the LUS in neonates with RD within 6 hours of birth (LUS_0) and to correlate these scores with the severity and prognosis of RD. The secondary objective of the study was to estimate the cut-off LUS_0 score for predicting the need for fraction of inspired oxygen (FiO2) requirement of > 50% in ventilated neonates during the first 3 days of life, invasive ventilatory requirement on day 3 of life, Silverman-Anderson score ≥7 in preterm at birth, need for surfactant administration, radiological grades of RDS, and death.

METHODS

This single-center cross-sectional study was conducted in a tertiary hospital in South India between February 2023 and May 2023. We included all neonates admitted with RD

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in the first 6 hours of life. Neonates with heart disease or congenital anomalies of the chest/lung, chromosomal anomalies, or those admitted during the period of non-availability of the operator to perform LUS were excluded. For all the neonates, basic demographic data, details of birth, and maternal antenatal steroid administration were collected. The outcome of the neonate was labeled as discharge or death. Prior approval for the study was obtained from the institutional ethics committee. Informed consent was taken from the parents.

For this study, a physician (SG) who had undergone formal training in POCUS and had more than 3 years of experience in performing neonatal LUS was designated as the operator to perform LUS (Philips Ultrasound Inc, Bothel, Washington, USA – Model: 3300G) with a high-frequency (12 MHz) linear probe. The LUS was performed after initial stabilization and within 6 hours of life. The LUS is performed by dividing the lung into 3 fields on either side – anterior superior, anterior inferior, and lateral fields [8]. For each lung field, a point score from 0 to 3 was given (total score ranging from 0 to 18) as follows: Only A lines: 0, B-pattern (presence of ≥3 well-spaced B lines): 1, severe B-pattern (presence of crowded and coalescent B lines with and without subpleural consolidation): 2, and extensive consolidation: 3 (**Web Fig. 1**).

Radiological grading of RDS (grade I to IV) was based upon the findings of the operator [9]. Surfactant administration, oxygen therapy, and ventilation were done as per the clinical practice guidelines, of the National Neonatology Forum of India [10]. The diagnosis of RDS and TTN was based on the clinical and radiological features. Silverman-Anderson scoring in preterm and Downe's scoring for term neonates were used to assess the severity of RD and the scoring was done by one of the investigators on admission [11].

Based on the study by De Martino et al where in, the median (IQR) LUS score in neonates with RD was 8 [4,12], hence, with 95% CI and 15% relative precision and assuming to estimate the average LUS score, assuming the expected population standard deviation to be 5.92 (estimated using the formula SD=IQR/1.35) a sample size of 93 neonates with RD was needed [12].

Statistical analysis: Data were analyzed using R software version 4.1.1. All categorical data were presented using frequency and percentage and all continuous measurements were summarized using mean (SD) or median (IQR) after assessing the normality assumption using the Shapiro-Wilk test. The LUS_0 score across different baselines and clinical outcomes was compared using the Mann-Whitney U test for two levels and the Kruskal Wallis test for more than two levels of variables. For the categories with significant P values in the Kruskal Wallis test, a Two-sample Wilcoxon rank-sum test (Mann-Whitney) was performed to compare the LUS_0 scores in a variable against other variables in that category. Logistic regression analysis was done on the six outcome measures separately with continuous LUS_0 score measurement as covariate and an odds ratio (95% CI) was estimated for each outcome for one unit increase in LUS_0 score. Receiver Operating Characteristic (ROC) analysis was carried out to estimate the best cut-off point of the LUS_0 score in predicting the clinical outcomes and area under curves (AUC) was computed with sensitivity and specificity. *P* value was considered significant at a 5% level of significance.

RESULTS

During the study period, 168 neonates were admitted with RD; 67 neonates were excluded for reasons like admission after 6 hours of life ($n = 12$), congenital anomalies ($n = 1$), and non-availability of the operator ($n = 54$). LUS_0 was done within 6 hours of life for 101 neonates who were included in the study (**Table I**). About 15.84% were term neonates, 60.4% were born by cesarean section, and 16.83% were extramural deliveries. About 18.8% of term and 24.7% of preterm neonates required invasive ventilation. The mean birth weight (SD) and gestational age (SD) were 1,861.58 (140.54) grams and 32.50 (0.69) weeks respectively. About 35.64% of neonates were administered surfactant. About 12.5% of term neonates and 18.83% of preterm neonates had severe RD as per Downe and Silverman Anderson scoring respectively. Among neonates with RDS ($n = 50$), 78% had radiological features of the disease. Double lung point, which is a sharp line of demarcation between normally aerated lungs with A-lines and fluid-filled lungs with B lines, was seen in 22 (51.16%) neonates with TTN (**Web Fig. 1**). Lung sliding was absent, and the bar code sign was present in both cases of pneumothorax. 23 (22.8%) neonates died; primary respiratory disease was the cause of death in 11 (47.82%) and 12 (52.17%) died due to comorbidities.

The median (IQR) LUS_0 score in RDS was significantly higher than those with TTN. The median LUS_0 scores were significantly higher in the preterm and in low-born weight categories. On application of the two-sample Wilcoxon rank sum test, significantly higher LUS_0 scores were observed in neonates with gestational age ≤ 27 weeks compared to those with gestational age ≥ 37 weeks, 33-36 weeks and 28-32 weeks ($P < 0.001$). Likewise, those with birth weight ≤ 1000 g had significantly higher LUS_0 scores compared to those weighing 1000-1500 g, 1500-2500 g and those ≥ 2500 g ($P < 0.001$). LUS_0 scores were

significantly higher in RDS compared to neonates with TTN ($P < 0.001$). However, rest of the comparisons of LUS_0 scores were not significantly different. LUS_0 scores were not associated with gender or maternal antenatal steroid administration. See **Table I**. The median LUS_0 scores were significantly higher in neonates with RD in terms of the six outcome measures studied (**Table II**).

For estimating the cut-off LUS_0 score for predicting the severity of RD in terms of the six outcome measures studied, ROC curves were constructed and sensitivity and specificity for LUS_0 scores arrived (**Fig. 1**). Cut-off LUS_0 scores for the outcome measures and their sensitivity and specificity values were shown in **Table III**. On logistic regression analysis, with continuous LUS_0 scores as the covariate, the odds ratio was significantly higher for all six outcome measures studied, which implies that higher LUS_0 was associated with poor outcomes (**Table IV**).

Table I Clinical profile and LUS_0 scores (n = 101)

Factor	*n (%)*	*LUS_0 score Median (IQR)*	*P value*
Gender[a]			
Female	53 (52.47%)	2.5 (0.0, 12.0)	0.210
Male	48 (47.53%)	1.0 (0.0, 5.0)	
Gestational age (wks)[b]			
≥ 37	16 (15.84%)	0.0 (0.0, 2.0)	< 0.001
33-36	29 (28.71%)	0.0 (0.0, 4.0)	
28-32	45 (44.55%)	1.0 (0.0, 6.0)	
≤ 27[c]	11 (10.89%)	13.0 (12.0, 15.0)	
Birthweight (g)[b]			
≤ 1000[c]	14 (13.86%)	12.0 (9.0, 15.0)	< 0.001
1001-1500	23 (22.77%)	2.0 (0.0, 7.0)	
1501-2500	43 (42.57%)	0.0 (0.0, 4.0)	
≥ 2500	21 (20.79%)	0.0 (0.0, 2.0)	
Maternal antenatal steroid administration[b]			
Received 4 doses	21 (24.70%)	1.0 (0.0, 4.0)	0.822
Received 1-3 doses	34 (40.00%)	3.0 (0.0, 11.0)	
Not received	30 (35.30%)	1.5 (0.0, 8.0)	
Final diagnosis[b]			
Meconium Aspiration Syndrome	3 (2.97%)	2.0 (0.0, 12.0)	<0.001
Pneumonia	3 (2.97%)	6.0 (0.0, 9.0)	
Pneumothorax	2 (1.98%)	0.0 (0.0, 0.0)	
Respiratory distress syndrome[c]	50 (49.50%)	7.0 (2.0, 12.0)	
Transient tachypnea of newborn	43 (42.57%)	0.0 (0.0, 0.0)	

[a]Mann Whitney U test, [b]Kruskal Wallis test, [c]P <0.001; Two-sample Wilcoxon rank sum test

Table II LUS_0 scores in Relation to Severity of Respiratory Distress

Factors	*n (%)*	*LUS_0 score Median (IQR)*	*P value*
Ventilatory requirement on day 3 of life[a]			
Invasive ventilation	24 (23.76%)	12.0 (7.5, 12.5)	< 0.001
NIV/Spontaneous	77 (76.24%)	0.0 (0.0, 4.0)	
Fraction of inspired oxygen (FiO_2) requirement during the first 3 days of life in ventilated neonates[b]			
Up to 50%	67 (75.3%)	0.0 (0.0, 6.0)	< 0.001
51%-75%	10 (11.2%)	8.5 (2.0, 12.0)	
>75%	12 (13.5%)	12.5 (10.5, 15.0)	
Silverman-Anderson score in preterm at birth[a]			
<7	69 (81.17%)	0.0 (0.0, 6.0)	0.002
≥ 7	16 (18.83%)	9.5 (6.0, 12.0)	
Respiratory Distress Syndrome grade in chest *X*-ray[a]			
Grades I-IV	39 (78%)	10.0 (4.0, 12.0)	< 0.001
Normal	11 (22%)	0.0 (0.0, 2.0)	
Surfactant requirement[a]			
Yes	36 (35.64%)	11.5 (4.0 12.5)	< 0.001
No	65 (64.36%)	0.0 (0.0, 2.0)	
Outcome[a]			
Death	23 (22.77%)	12.0 (7.0, 15.0)	< 0.001
Graduated	78 (77.23%)	0.0 (0.0, 4.0)	

[a]Mann Whitney U test, [b]Kruskal Wallis test

DISCUSSION

In the present study, we observed a higher median LUS_0 score in RDS than in TTN. The ability of LUS to differentiate RDS from TTN has been extensively studied and many studies have demonstrated qualitative differences between them [13,14]. Srinivasan et al reported that the findings of pulmonary edema manifesting as an alveolar-interstitial syndrome, double lung point sign, and white-out lungs without consolidation are diagnostic of TTN [13]. This study also observed these qualitative changes in RDS and TTN, which have been assessed quantitatively as LUS scores. The ability of early LUS to differentiate TTN quantitatively and qualitatively from RDS will be of much clinical significance to the treating physicians, especially in late preterm neonates.

In the present study, significantly higher LUS_0 scores were noted in preterm, and LBW neonates. Previously, LUS scores have been shown to be inversely proportional to lung maturity, and hence higher scores are expected in preterm and LBW neonates [8]. We did not demonstrate a significant correlation between LUS_0 scores and antenatal

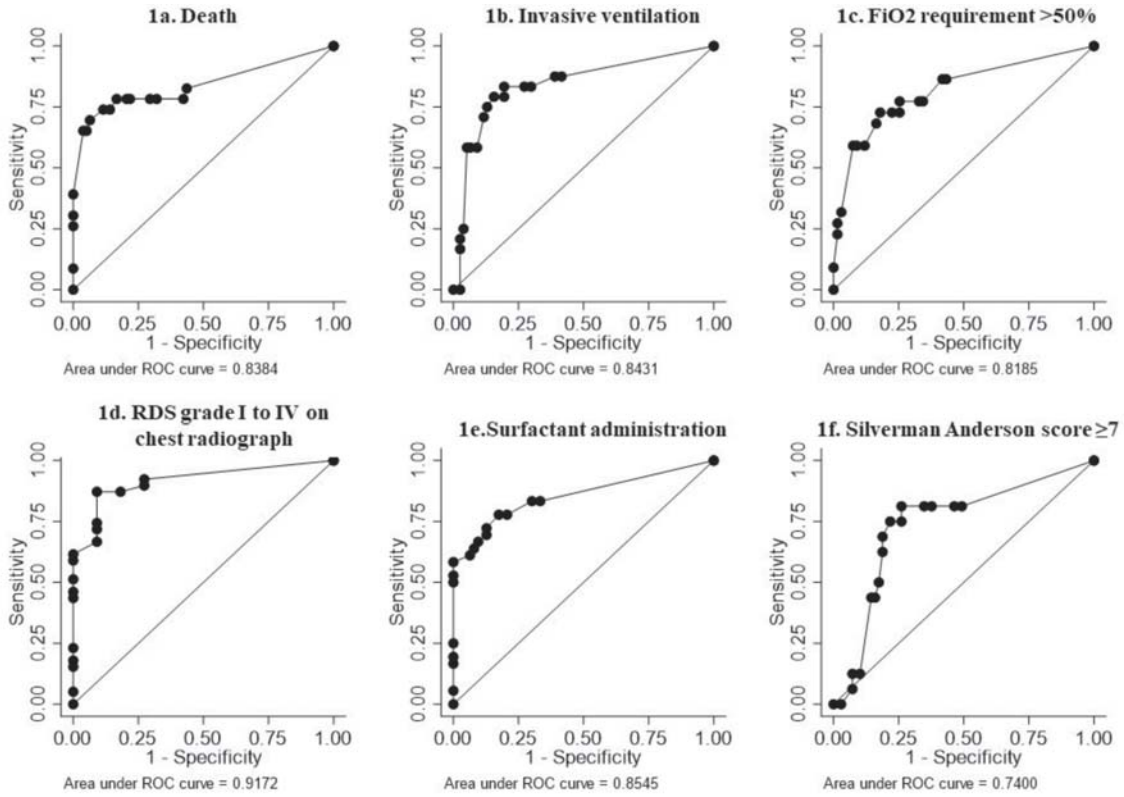

Fig. 1: Receiver Operating Characteristic (ROC) curves for the determining cut-off LUS_0 scores for predicting (a) Death, (b) Need for invasive ventilation, (c) Need for FiO2 > 50%, (d) RDS grade I to IV on chest radiograph, (e) Need for surfactant administration, (f) Siverman Anderson score ≥ 7

Table III Sensitivity, Specificity, and Cut-off LUS_0 Scores for Various outcomes

Outcome measure	*Best cut-off LUS_0 score*	*Sensitivity*	*Specificity*	*AUC*
Silverman-Anderson score ≥ 7 in preterms at birth	≥ 5	81.25%	73.91%	0.740
Respiratory Distress Syndrome (*X*-ray Grade I – IV)	≥ 4	87.18%	90.91%	0.917
Surfactant administration	≥ 4	77.80%	82.54%	0.854
Fio2 requirement >50% in ventilated neonates during the first 3 days of life	≥ 8	72.73%	82.09%	0.818
Invasive ventilation on day 3 of life	≥ 7	79.17%	84.42%	0.843
Death	≥ 7	78.26%	83.33%	0.838

AUC Area Under Curve

Table IV Risk for increased respiratory distress as measured in terms of the six outcome measures for every unit increase in LUS_0 Score

Outcome measure	*Odds Ratio (95% C.I)*	*P value*
Silverman-Anderson score ≥7 in preterm at birth	1.17 (1.06, 1.29)	0.002
Respiratory Distress Syndrome *X*-ray Grade I-IV	1.69 (1.19, 2.39)	0.003
Surfactant requirement	1.4 (1.24, 1.59)	< 0.001
Fio2 requirement >50% in ventilated neonates during the first 3 days of life	1.27 (1.14, 1.41)	< 0.001
Invasive Ventilation on day 3 of life	1.3 (1.17, 1.45)	< 0.001
Death	1.35 (1.2, 1.51)	< 0.001

WHAT THIS STUDY ADDS?

- Early neonatal lung ultrasound also holds the potential to predict the severity and outcome in neonates with respiratory distress.

steroid administration. This may be because ours is a referral hospital and caters more to emergency deliveries and only a small proportion of mothers receive complete courses of steroids before delivery. Our study has demonstrated that neonates who required invasive ventilation had a higher median (IQR) LUS score of 12 (7.5,12.5) before 6 hours of life and a cut-off score of ≥ 7 can predict the need for invasive ventilation on the third day of life with 79.17% sensitivity and 84.42% sensitivity (AUC = 0.843). A few studies have demonstrated the ability of the LUS score as a tool to predict the need for invasive ventilation. Szymanski et al employed a 4-lung zone and 5-scale scoring system and reported that LUS done on the first day of life had high reliability in predicting invasive ventilation on the third day of life [15]. A score of ≥ 7 (in infants with birth weight [BW] 900 g), ≥ 10 (in infants with BW 1050 g), and ≥15 (in infants with BW 1280 g) before 24 hours of life predicted the need for invasive ventilation on day 3 of life. However, in this study, we did not propose differential cut-offs based on birth weight.

In this study, a cut-off LUS_0 score of 5 correlated with a Silverman-Anderson Score of ≥ 7 at birth with 81.25% sensitivity and 73.91% specificity (AUC = 0.740). A study by Raimondi et al also demonstrated a significant correlation between Silverman score and LUS scores [16].

In the present study, a cut-off LUS_0 score of 4 was able to predict the requirement of surfactant with 77.80% sensitivity and 82.54% specificity (AUC=0.854). In the study by Brat et al, LUS score > 2 in preterm neonates >34 weeks of gestational age or LUS score > 4 in preterm neonates <34 weeks of gestational age predicted the need for surfactant administration [8]. De Martino et al recommended a cut-off LUS score between 6 and 8 for surfactant administration, although gestational age was not accounted for [12]. Perri et al demonstrated a higher efficacy for LUS scores compared to *X*-ray scores in predicting the need for surfactant administration in RDS in terms of AUC [17].

The correlation between the radiological grades in RDS and LUS scores has been extensively studied [18,19]. This study reported a median LUS_0 score of 10.0 (4.0, 12.0) and a cut-off value of ≥4 which correlates well with the radiological abnormalities of RDS. There were no studies that utilized a similar 6-field LUS scoring system and correlated LUS scores with radiological grades in RDS. A study by Kartikeswar et al who employed a 4-zone and 9-scale scoring system found that the LUS diagnosis and CXR diagnosis had a Kappa correlation value of 0.786 (95% CI: 0.678–0.983) [20]. However, the question of whether LUS can replace *X*-rays to diagnose RDS remains unanswered.

The present study has reported a median LUS_0 score of 12.0 (7.0, 15.0) in the neonates who died. A cut-off LUS_0 score of ≥ 7 (sensitivity 78.26% and specificity 83.33%, AUC 0.838) was derived for death in neonates with RD. The association between early LUS scores and death has not been studied so far. The confounding factors in the analysis of death in these neonates are sepsis, perinatal hypoxia, or other comorbidities associated with prematurity. The major limiting factor in the study is that only one operator was employed, and the repeatability of the LUS scores was not studied. The other limiting factors were longitudinal scoring was not done, and gestational age-specific scoring was not studied for the 6 variables.

In this study, we have analyzed the usefulness of early LUS scores in the prediction of severity and prognosis in neonates with RD using a simple 6-field LUS scoring system. Despite several scoring systems that are used for grading the severity of neonatal RD, a consensus has not been arrived at yet [21]. We observed that a simple 6-field LUS scoring system is easy to use for quantitatively assessing neonates with RD. The early LUS scores hold the potential to predict the severity and outcome in neonates with RD and can complement the clinical assessment with adequate training of personnel.

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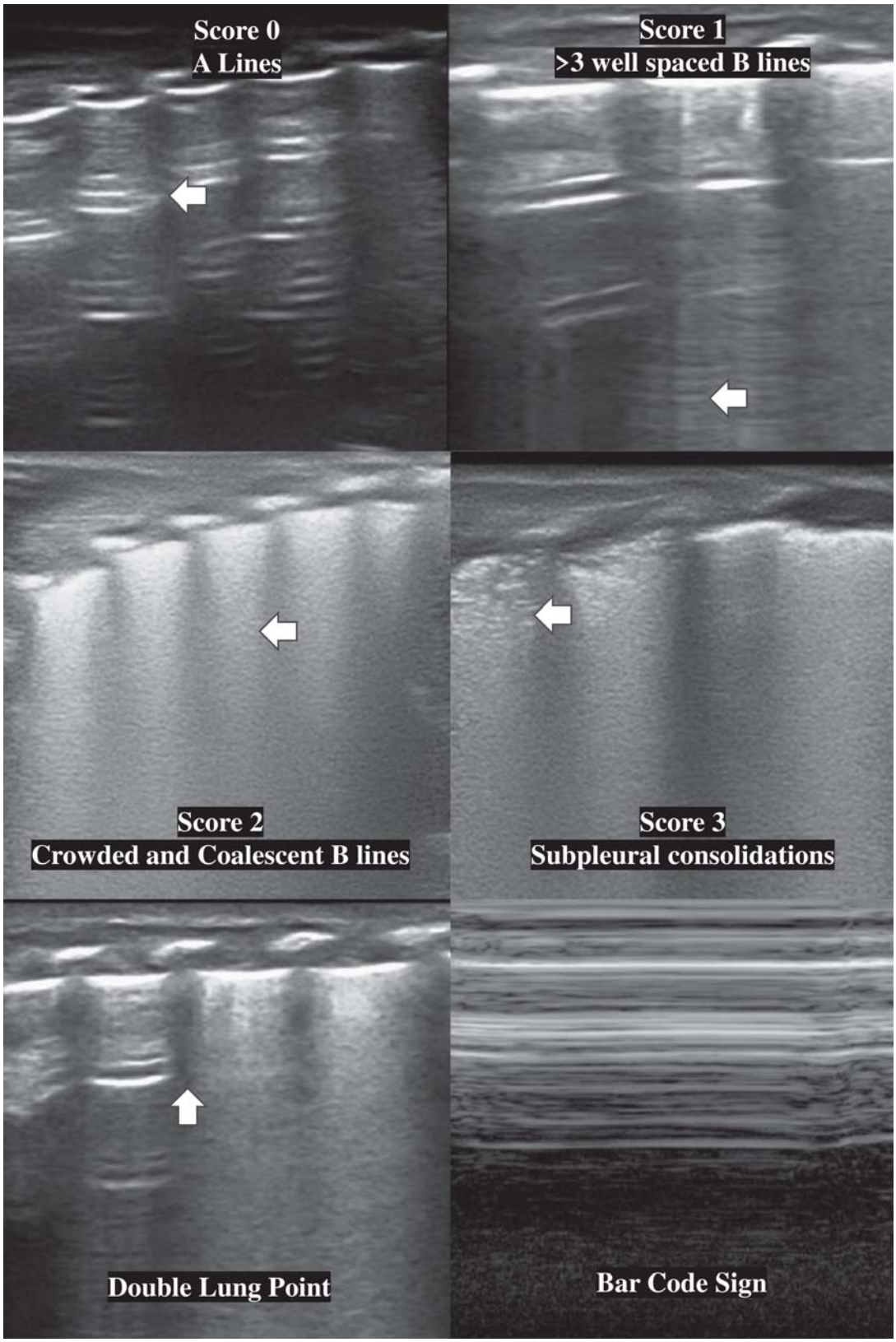

Web Fig. 1 Lung Ultrasound images from the study depicting scores 0 to 3, double lung point and bar code signs