

Lung ultrasound (LUS) in pre-term neonates with respiratory distress: A prospective observational study

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ABSTRACT

Aim: To find out the diagnostic use of lung ultrasound (LUS) in respiratory distress in neonates by taking clinico-radiological (clinical plus X-ray) diagnosis as the gold standard. Secondary objectives were to find out if modified LUS score can predict the need for surfactant therapy. **Methods:** A prospective observational study was done in a tertiary care neonatal intensive care unit over a period of 1 year (January–December 2018). All pre-term infants with respiratory distress were screened with LUS and CXR within 2 h of admission and modified LUS score was calculated to find out the lung water content and its correlation with the severity of respiratory distress syndrome (RDS). **Results:** In total, 92 neonates were screened during the study period, and 61 were finally diagnosed as RDS. The Kappa statistic between the clinico-radiological diagnosis and LUS diagnosis was 0.639. LUS diagnosis and CXR diagnosis had a Kappa correlation value of 0.786 (95% CI: 0.678–0.983). The most common LUS feature in RDS was pleural line thickening (100%), followed by whiteout lungs (75.4%). The modified LUS score was higher in babies who needed surfactant therapy (median (IQR): 49 (44, 53.5) vs. 29.5 (21, 46)) ($P < 0.0001$). **Conclusion:** Our study shows that LUS in neonatal RDS can predict the severity of the disease, need for surfactant therapy and has good agreement with clinical and Xray diagnosis.

KEY WORDS: Chest X-ray, LUS (Lung ultrasound), neonates, Respiratory distress syndrome (RDS)

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INTRODUCTION

Respiratory distress is one of the most common causes of neonatal intensive care unit (NICU) admission. Significant respiratory morbidity is documented in 29% of pre-term infants admitted to the NICU.^[1] A variety of cardiovascular, respiratory and metabolic diseases present with respiratory distress. Early diagnosis and quick treatment are very important for successful management. Traditionally, the diagnosis of pulmonary disease mainly relied on clinical features along with chest radiography (CXR).

Lung ultrasound (LUS) is low cost, simple and devoid of radiation exposure, making bedside use both feasible and convenient in NICU.^[2] Different studies have shown variable sensitivity of LUS from 85% to 100% in cases of respiratory distress syndrome (RDS) and other lung pathology presenting with respiratory distress in neonates, but its use to grade severity of RDS and treatment was limited.^[3-6] Whether LUS can replace CXR as the primary

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investigation of choice for RDS in NICU is still not answered. Only a few studies have compared the diagnostic correlation between LUS and CXR in neonates.^[6,7] The use of LUS in NICU is limited; thus, we planned a study.

AIM

To find out the diagnostic use of LUS in respiratory distress in neonates by taking clinico-radiological (clinical plus X-ray) diagnosis as the gold standard. Secondary objectives are to find out if LUS can predict the need for surfactant therapy.

METHODOLOGY

A prospective observational study was done in a tertiary care NICU over a period of 1 year (January–December 2018). All pre-term (<37 weeks gestational age) neonates (<24 h of life) admitted to NICU (both inborn and outborn) during the study period with features of respiratory distress on admission (presence of one or more of respiratory rate (RR) >60/min (tachypnoea), presence of retractions (intercostal and/or subcostal), cyanosis, grunting, nasal flaring) were included in the study.^[8] All eligible neonates were screened with LUS and chest X-ray within 2 h of admission. Neonates with major congenital anomalies or with non-pulmonary causes of respiratory distress were excluded from the study. LUS and X-ray were performed within 2 h and before delivery of surfactant to avoid mismatch due to effect of disease course or treatment given. During admission, a detailed antenatal history, maternal risk factors, antenatal corticosteroid coverage and delivery details were documented. LUS was performed by a designated neonatologist who was trained for LUS prior to the start of this study. All the LUS findings were recorded and stored, and doubtful images were confirmed by a radiologist who was unaware of the patient's condition. Reading of X-ray for immediate management was done by the treating neonatologist, but the final X-ray reporting was done by a radiologist unaware of the patient's condition for the study purpose. The final/gold standard diagnosis is the diagnosis set by the treating consultant depending on the X-ray picture and clinical course of the neonate (clinico-radiological diagnosis).

Pre-term babies were treated with CPAP/mechanical ventilation/surfactant as per existing NICU policy. Surfactant was given using the Intubation, Surfactant, Extubation to CPAP (INSURE) technique for neonates on CPAP if neonates met the treatment criteria of oxygen requirement >30% in ≤26 weeks gestation and >40% for other pre-term babies.^[9] In total, eight zones were examined, consisting of scanning four chest areas [Figure 1]: the upper anterior (R1, L1), lower anterior chest (R2, L2), the upper lateral (R3, L3) and basal area of lateral chest (R4, L4). In addition, posterolateral alveolar and/or pleural syndrome (PLAPS), a basic term used in the BLUE protocol, points on both sides were scanned.^[10]

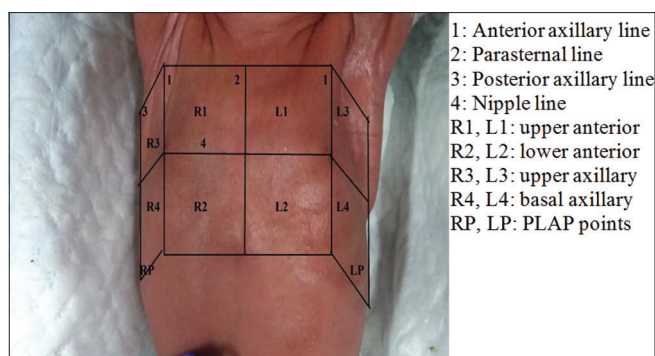


Figure 1: Lung ultrasound zones

Lung ultrasound diagnosis

LUS was done with a Sonosite M-Turbo portable ultrasound machine with a sectoral P10X probe, which has a frequency range of 8–4 MHz (FUJIFILM Sonosite, Inc. WA, USA). In LUS, the pleura appears as a smooth regular echogenic line known as the pleural line. Pleural line thickness of more than 0.5 mm is evidence of small subpleural consolidation and is considered thickened pleura.^[3] 'A lines' are equidistant lines parallel to pleural lines and are reverberation artefacts, whereas B-lines are vertically projected artefacts from the pleural line because of interaction between ultrasound ray and the alveolar gas–liquid interface. Three or more B-lines between two ribs are called lung rockets. Interstitial syndrome is defined as the presence of more than three B-lines or the presence of lung rockets in every examined area.^[3] Bilateral white lung is the presence of compact B-line producing a white lung field in all areas without horizontal reverberation.^[3] The sharp distinction in echogenicity between the upper and lower lung fields with a longitudinal scan is known as a 'double lung point' (DLP).^[11] The presence of confluent B-lines with an echographic white lung appearance, the presence of a thickened and irregular pleural line and multiple subpleural lung consolidations indicating alveolar collapse are features of RDS.^[3] LUS picture with the presence of a normal, well-defined and regular pleural line in bilateral lungs and DLP were diagnosed as transient tachypnoea of neonate (TTN).^[11] The ultrasonographic findings of lung consolidation with irregular margins surrounded by multiple B-lines, with the absence of lung sliding and presence of Shred sign are specific for pneumonia.^[12] Modified LUS score was calculated, as described by Enghard *et al.*^[13] Each lung zone is scored between 1 and 8 depending on the number of B-lines or percentage of whiteout area in a scan. Total LUS Score is calculated by adding B-line score of all eight zones.

X-ray features suggestive of RDS included diffuse atelectasis, 'ground glass' appearance of the lung fields, low volume lung and air bronchograms. X-ray findings of hyperinflation, prominent fissure and perihilar cuffing are features of TTN.

Statistical analysis

Data were expressed as mean (standard deviation) for normally distributed parameters and as

median (inter-quartile range) for skewed distribution. The Cohen κ coefficient was calculated to find agreement between clinico-radiological, CXR and LUS diagnosis. Receiver operating characteristic (ROC) analysis was used to evaluate the ability of the LUS score to predict surfactant administration: Areas under the curves (AUCs) and cut-off values showing the best sensitivity and specificity were reported. $P < 0.05$ is considered to be statistically significant. Assuming a κ coefficient of correlation of 0.97 between final diagnosis and LUS diagnoses, a sample size of 52 patients was calculated to obtain a statistical power of 80% with an alpha error of 5%, margin of error of 5% and 15% inflation.^[7] The entire data were statistically analysed using Statistical Package for Social Sciences (SPSS ver 21.0, IBM Corporation; NY, USA) for MS Windows. This study was approved by the institutional ethics committee.

RESULTS

Out of the total 460 admissions with respiratory distress, 92 pre-term neonates were screened during the study period [Figure 2]. Sixty-one neonates were finally diagnosed as RDS (clinico-radiological diagnosis), and 45 neonates required surfactant (40 needed one dose and five needed two doses). The mean (\pm SD) gestational age (GA) of the study population was 30.6 (\pm 3.05) weeks, and the majority (87%) were <34 weeks. The baseline characteristic of the study population and neonates with the final diagnosis of RDS is shown in Table 1.

LUS diagnosis of RDS was made in 51 neonates, TTN in 32 neonates and congenital pneumonia in four neonates. Chest radiograph diagnosis of respiratory distress was TTN in 31 neonates, RDS in 44 neonates and pneumonia in six neonates. In five neonates, LUS features were of normal lung, and in 11 neonates, X-ray was reported to be normal and not helpful in diagnosis. However, these neonates clinically had respiratory distress and the final diagnosis was different. Out of the total 61 cases with the final diagnosis of RDS, CXR diagnosis of RDS was present only in 43 (70.5%) cases, which is less than the cases

detected by LUS (49 cases, 80.3%). In cases of RDS, LUS has a sensitivity of 80%, a specificity of 93.5%, a positive predictive value of 96% and a negative predictive value of 70.7% [Table 2]. Though for diagnosis of RDS, X-ray has a higher specificity than LUS, it was less sensitive as a screening tool. (sensitivity: 70.49%, specificity: 96.77% [Table 3] LUS was able to diagnose 43 (95.6%) out of these 45 neonates who required surfactant therapy.

In the agreement between LUS diagnosis and CXR diagnosis for causes of respiratory distress, we found a Kappa correlation value of 0.786 (95% CI: 0.678–0.983) [Table 4]. Similarly, the Kappa statistic between the final diagnosis (clinico-radiological diagnosis) and LUS diagnosis was 0.639 [Table 5].

On analysing the LUS characteristics [Table 6], we found thickened pleura (100%) and whiteout lung (75%) [Figure 3] as the common LUS feature in RDS, followed

Table 1: Baseline characteristic of the study population

Variable	[Total number of neonates: 92]	[Total number of neonates with RDS: 61] n (%)
Gestational Age; Mean (SD)	30.6 (3.05)	29.9 (2.82)
Birth weight; Median (IQR)	1240 (947, 1548)	1190 (898, 1325)
Sex		
Male n (%)	54 (63)	37 (60.7)
Female; n (%)	34 (37)	24 (39.3)
Mode of delivery		
LSCS; n (%)	66 (71.7)	43 (70.5)
No resuscitation required; n (%)	50 (54.3)	30 (49.2)
Delivery room CPAP; n (%)	67 (72.8)	48 (78.7)
SA Score of >4 on admission; n (%)	80 (87)	58 (95.1)
Maternal Characteristics	N=92	N=61
PPROM; n (%)	26 (28.3)	19 (31.1)
PIH; n (%)	33 (35.9)	24 (39.3)
GDM; n (%)	5 (5.4)	4 (6.6)
Hypothyroidism; n (%)	11 (12)	7 (11.5)
Antenatal steroid; n (%)	77 (83.7)	54 (88.5)

*SA Score - Silverman-Anderson Score, PPRM - Pre-term Premature Rupture of Membranes, PIH- Pregnancy-Induced Hypertension, GDM - Gestational Diabetes Mellitus

Table 2: Comparison of LUS diagnosis and final diagnosis

Final diagnosis\LUS diagnosis	RDS	NO RDS	TOTAL
RDS	49	2	51
NO RDS	12	29	41
TOTAL	61	31	92

Sensitivity: 80.32%, Specificity: 93.54%, PPV: 96.07%, NPV: 70.73%

Table 3: Comparison of X-ray diagnosis and final diagnosis

Final diagnosis\CXR diagnosis	RDS	NO RDS	TOTAL
RDS	43	1	44
NO RDS	18	30	48
TOTAL	61	31	92

Sensitivity: 70.49%, Specificity: 96.77%

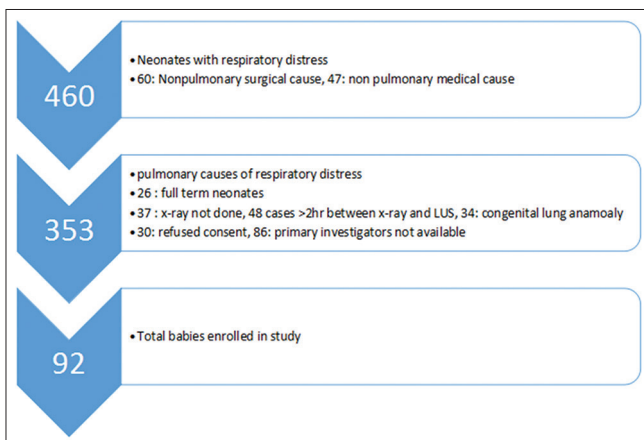


Figure 2: Study flow diagram

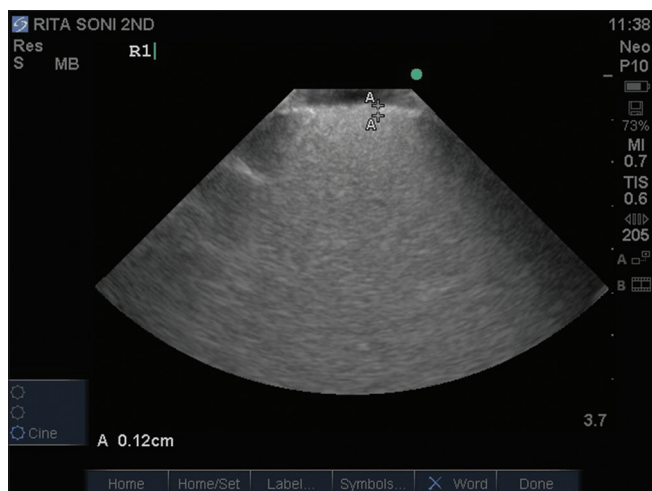


Figure 3: White lung in RDS



Figure 4: Lung rockets in TTN

Table 4: Association between CXR and LUS diagnosis

CXR diagnosis	Normal	TTN	RDS	Pneumonia	Total (%)
LUS diagnosis					
NORMAL	4	1	0	0	5 (5.4)
TTN	3	28	0	1	32 (34.8)
RDS	4	2	44	1	51 (55.4)
PNEUMONIA	0	0	0	4	4 (4.4)
Total (%)	11 (11.9)	31 (33.7)	44 (47.8)	6 (6.5)	92 (100)

Kappa value: 0.786 with 95% CI: 0.678-0.983. TTN: Transient tachypnoea of newborn, RDS: Respiratory distress syndrome

Table 5: Association between clinico-radiological diagnosis and LUS diagnosis

Clinico-radiological diagnosis	TTN	RDS	Pneumonia	Total (%)
LUS diagnosis				
NORMAL	1	2	2	5 (5.4)
TTN	21	10	1	32 (34.8)
RDS	1	49	1	51 (55.4)
PNEUMONIA	0	0	4	4 (4.4)
Total (%)	23 (25)	61 (66.3)	8 (8.7)	92 (100)

K-agreement value: 0.639 [TTN: Transient tachypnoea of newborn, RDS: Respiratory distress syndrome]

Table 6: LUS pattern of neonates with a final diagnosis of RDS

LUS pattern	n (%) [Total neonates: 61]
Thickened Pleura	61 (100)
Interstitial Syndrome	8 (13.1)
DLP	4 (6.6)
B/L White lung	41 (67.2)
Unilateral whiteout lung	5 (8.2)
B-line score, Median (IQR)	48 (40, 52.5)
Pleural Thickness in mm, Median (IQR)	1.33 (1.2, 1.52)

DLP: Double Lung Point, B/L: Bilateral, IQR: Inter-quartile range, mm: Millimetre

by interstitial syndrome [Figure A3] in 13.3% cases and DLP in 6.7%. The median (IQR) of modified LUS score was 48 (40, 52.5) in neonates with RDS, suggestive of increased extravascular lung water content and improper clearance of foetal lung water. The LUS score was higher in cases where surfactant was needed when

compared to cases where only respiratory support was needed (median (IQR): 49 (44, 53.5) vs. 29.5 (21, 46)). The difference was statistically significant ($P < 0.0001$). On computing the ROC by using pleural thickness and LUS score, we found that the LUS score has an area under curve (AUC) of 0.825, and a LUS score of 40 or above alone has a sensitivity of 74% and specificity of 90% for the diagnosis of RDS [Figure 5].

DISCUSSION

In our study, we found that LUS has a sensitivity of 80% and a specificity of 93.5%. A study from Egypt, comparing LUS with chest X-ray, reported LUS had sensitivity and specificity of 98% and 92% respectively in detection of pulmonary manifestations of RDS.^[14] A meta-analysis of six studies that compared LUS to CXR and clinical information showed high sensitivity (97%) and specificity (91%) of LUS for detecting and excluding RDS.^[15] The drop in sensitivity could be because of screening at a single point of time. A good agreement was found between LUS diagnosis and CXR for different causes of respiratory distress with a kappa value of 0.78; a similar correlation was found by Iuri Corsini *et al.*^[6] with a κ statistic of 0.88 (95% CI: 0.81–0.94). Lifetime risk associated with high radiation exposure during neonatal period is unknown and ELBW neonates are at increased risk of radiation exposure during NICU stay, use of LUS can help in decreasing the number of X-ray exposure.^[16] LUS features such as pleural thickening were found in 100% of cases and whiteout lung in 75%, which was similar to the results observed by Copetti *et al.*^[3] and Liu *et al.*^[4] DLP, which was considered a diagnostic sign in cases of TTN earlier, can also be found in cases of RDS because of gradual clearance of lung fluid. DLP was found in 6.7% of cases in our study; Liu *et al.*^[17] also found DLP in 7.5% of cases during the recovery phase. Increasing the extravascular lung water (EVLW) increases the LUS score. Thus, the LUS score can be used to predict the severity of RDS and use of surfactants. In our study,

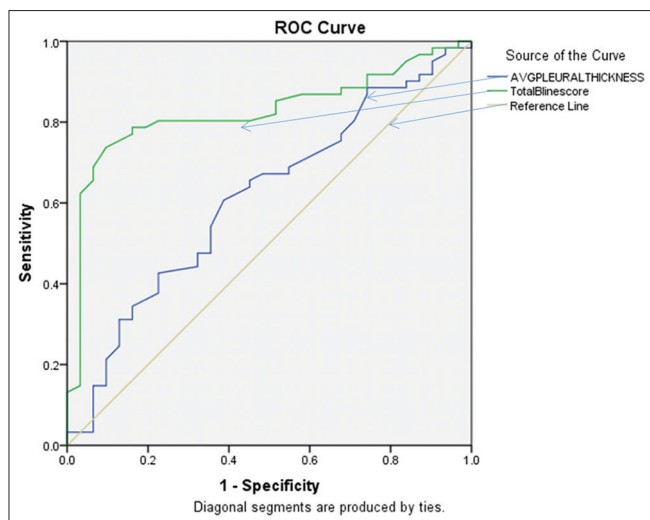


Figure 5: ROC curve (total B-line score and average pleural thickness)

the LUS score was significantly higher in cases of RDS and more so in neonates requiring surfactant. Roselyne Brat *et al.*^[18] used a modified score for lung water and found that the LUS score significantly correlated with all indices of oxygenation, independent of gestational age, and predicted the need for surfactant better in pre-term babies. We found that a LUS score of 40 or above has a sensitivity of 74% and a specificity of 90% for the diagnosis of RDS. Similarly, a recent meta-analysis of six studies found that LUS score has a pooled sensitivity of 88% (95% CI: 80–93) and a specificity of 82% (95% CI: 74–89).^[19]

The major strength of our study is the enrolment of pre-term and VLBW neonates. To avoid observation bias, LUS was performed by only one neonatologist and the results were not disclosed to the treating consultant. Management of respiratory distress was done as per the standard protocol of the unit. Use of B-line score for assessment of EVLW and RDS along with a qualitative description of LUS feature can be effectively used to diagnose and predict severity of RDS. This has the potential to significantly reduce radiation exposure from X-rays. At the same time, we acknowledge some study limitations. Ultrasonography is generally thought to be operator dependent, though studies have shown a short training was sufficient for LUS.^[20] This study was done at a tertiary care centre with bed-side ultrasonography machine, which may not be possible at a peripheral centre.

CONCLUSION

Our study shows that LUS had good sensitivity and PPV in cases of neonatal RDS. LUS score can predict the severity of neonatal RDS and the need for surfactant therapy. Neonatologist-performed LUS can reduce

radiation exposure and has the potential to improve overall outcomes of neonatal RDS.

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Conflicts of interest

There are no conflicts of interest.

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