# Prediction of Lung Ultrasound Score for Surfactant Requirement in Neonates Less than 30 Weeks of Gestational Age with Respiratory Distress Syndrome

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**Abstract:** ***The study was conducted to evaluate the efficacy of lung ultrasound in predicting the surfactant need in neonates less <30 weeks of gestation with RDS. Forty preterm neonates with GA <30 weeks were included in the study of which 24(60%) were males and 16(40%) were females. The mean GA was 29±1.3weeks and the mean birth weight was 1300±350grams. Patients were clinically assessed using Downe's score (DS) and those with DS>4 were put on CPAP. Neonates requiring FIO2 >0.3 and not maintaining saturation of >91% were considered for receiving surfactant. Lung ultrasound was done within 2 hours of life before the decision about surfactant administration was made. The median lung ultrasound score in the subjects was 8 (IQR of 2-16) with mean of 8.65±4.05. A LUS score >7 increased the probability with surfactant treatment with sensitivity of 95.2%, specificity of 100% with positive predictive value of 100% and negative predictive value of 95% with diagnostic accuracy of 97.5%. We concluded that LUS in preterm neonates less than 30 weeks of gestation when done early after birth can predict the need for surfactant replacement therapy and can be used as an adjunct if not alternative to FIO2 and CPAP requirements used previously.***

**Keywords:** neonate; preterm; respiratory distress syndrome; lung ultrasound; lung ultrasound score

## 1. Introduction

Respiratory distress syndrome (RDS) or hyaline membrane disease (HMD), is a major cause of neonatal mortality especially in developing countries. Literature shows the incidence rate to be 80% in infants born at less than 28 weeks' gestation, 60% at 29 weeks, 15-30% at 32-34 weeks, and 5% at 35-36 weeks. Accordingly, the incidence rate is estimated to be 80% for infants weighing <750g at birth and 55% for infants weighing 750-1000g.[1] In another study, the incidence was found to be 98% at 24 weeks, 5% at 34 weeks, and less than 1% at 37 weeks.[2] The prevalence and the severity of RDS decrease as the gestational age increases, hence, mostly affected are preterm infants.[3][4][5] Deficiency of pulmonary surfactant (a phospholipid mixture produced by type II pneumocytes) has been implicated to be a major factor in the pathogenesis of RDS. Surfactant reduces the surface tension within the alveoli and prevent their collapse during breathing. Immature alveolar cells produce less surfactant causing collapse of alveoli, the result being poor gas exchange manifesting as respiratory distress shortly after birth.

Besides low gestational age, low birth weight is another important risk factor for RDS. Other known risk factors include male gender, caesarean delivery, previous baby with RDS, perinatal asphyxia, perinatal infection, multiple births, infants of diabetic mothers, etc.

The clinical signs usually develop immediately or within six hours of birth, worsening over the next 48-72 hours and may include tachypnoea, decreased breath sounds, diminished peripheral pulses and/or cyanosis with signs of increased work of breathing like nasal flaring, subcostal/ intercostal/ suprasternal retractions, grunting, and use of accessory muscles of respiration. These may progress to respiratory failure, lethargy, apnea and death.[11]

The diagnosis of RDS is mostly made on clinical grounds together with blood gas analysis and radiological features. Clinical scoring such as 'Downe's score' is often used to grade the severity of respiratory distress.

The most important treatment options include continuous positive airway pressure (CPAP)/positive end-expiratory pressure (PEEP), and surfactant replacement therapy. Antenatal glucocorticoids are also used for prevention of RDS in high risk cases. Besides, supportive care in the form of nutritional support, thermoregulation, fluid and electrolyte management, optimal antibiotic coverage can also significantly decrease the severity of RDS and the complications associated with it.[6][7]

Targeted surfactant replacement therapy has been shown to have a remarkable effect on the disease outcome and is commonly administered using INSURE technique (Intubation-SURfactant-Extubation).

Pulmonary surfactant production begins at around 24 weeks of gestation by type II pneumocytes and spreads as a thin layer over the air-fluid barrier of alveoli. The primary components are phospholipids (phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine) which contribute to approximately 90% with the rest 10% formed by proteins (proteins A-D). The surface characteristics of surfactant are caused by the organization of surfactant protein B and C (SP-B, SP-C) into tubular myelin, which is crucial for lowering surface tension.

These include paucity or absence of A-lines, dense B-lines with a white lung appearance representing alveolar-intersititial syndrome, presence of a thickened and irregular pleural line, and multiple sub-pleural consolidations.[8] These findings aid in assessing the severity of RDS semi-quantitatively by employing some established scoring methods, the commonest one introduced by Brat et al.[9]

Some studies have shown LUS to be helpful in predicting the need for exogenous surfactant therapy in neonates.[10] However due to previous lack of expertise and paucity of literature regarding its role especially in a region like Kashmir, we decided to take on this study in neonates born before 30 weeks of gestation at our Institute.

## 2. Methods

This study was a prospective longitudinal study carried in the department of paediatrics and neonatology, Sher-i-Kashmir Institute of Medical Sciences Soura, an Institute in north India, over a period of two years. The study was conducted to evaluate the efficacy of lung ultrasound in predicting the surfactant need in preterm neonates with gestational age <30 weeks with respiratory distress syndrome admitted in our department.

**Inclusion criteria**

- All neonates of gestational age less the 30 weeks admitted in neonatal ICU with respiratory distress syndrome.

**Exclusion criteria**

- All neonates of gestational age greater than 30 weeks.
- Neonates with congenital heart/lung disease.
- Neonates having early onset sepsis or septic shock.

A complete history was taken and examination carried at time of admission. Clinical assessment was done immediately after getting admitted to NICU and severity of respiratory distress was graded using Downe's scoring (DS). All patients with moderate to severe distress (DS >4) were put on CPAP with FIO2 0.3 and PEEP of 6mm of H20. Neonates requiring FIO2 >0.3 and not maintaining saturation of >91% were considered for receiving surfactant via INSURE technique. A trans-thoracic lung ultrasound was done in all neonates <30 weeks of gestational age having respiratory distress admitted in NICU within 2 hours of life while they were on CPAP and before the decision about surfactant administration has been made. All LUS examinations were performed with Sonosite (FUJIFILM, Inc. Bothell WA 98021 USA) using a linear high frequency probe (6-13 MHz). A lung ultrasound score was assigned based on scoring method used by Brat which used a 0-18 point score based on assessment of 6 portions of chest (3 on each side) giving a score of 0-3 to each portion depending upon the severity of findings, the highest score indicating worst aeration.[9] The decision about the administration of surfactant was solely made on patients' fraction of inspired oxygen (FIO2). The association of lung ultrasound was done with surfactant requirement by using independent t Test and univariate logistic regression analysis. We also calculated the risk factors for surfactant requirement by using univariate and multivariate logistic regression analysis.

**Statistical Analysis**:-

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means±SD and as median with 25th and 75th percentiles (interquartile range). Sensitivity, specificity, positive predictive value and negative predictive value was calculated for LUS findings for predicting RDS. Univariate and multivariate logistic regression was used to find out significant risk factors of Respiratory distress syndrome.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0.

For statistical significance, p value of less than 0.05 was considered statistically significant.

## 3. Results

Fifty two neonates less than 30 weeks of gestational age were admitted during the study period out of which 12 patients were excluded from the study as they didn't meet the inclusion criteria. Rest of 40 patients were included in the study.

Table 1 shows demographic and clinical characteristics of study subjects.

The mean Downe's score recorded was 5.48±1.27 with median of 5 (IQR: 4-6). All neonates with moderate to severe respiratory distress syndrome (DS>4) were initially treated with CPAP. Of 40 neonates, 32 were put on CPAP and 8 patients on $O_2$ hood. Among these 32 patients, only 10 required FIO2 <30% while 22 patients required FIO2>30% (mean of 36±12.1 and median of 40 (IQR:25-49)).

Among 32 patients who were on CPAP and received surfactant via INSURE technique and put back on CPAP, 7 among them developed CPAP failure requiring FIO2 >60% for maintaining saturation above 91%.

Patients requiring FIO2>30% and PEEP of 6mm of H2O were considered for surfactant requirement via INSURE technique.

A total of 21/40 (52.5%) patients received surfactant while as 19/40 (47.5%) patients didn't require surfactant therapy.

The study group was followed till the discharge or death of the patient. Among 40 patients, 24 (60%) were discharged while 16 (40%) died, and 12(75%) patients who died were from the surfactant group.

The mean lung ultrasound score of the study population was 8.65±4.05 with median of 8(IQR:5.75-12) and range of 2-16.

Receiver operating characteristic (ROC) curve analysis was used to predict the need for surfactant requirement which revealed an area under ROC curve of 0.98 (95% Confidence Interval or CI) with p value of 0.0001 which is statistically significant. A LUS >7 increased the probability with surfactant treatment with sensitivity of 95.2 %and specificity of 100% with positive predictive value of 100% (83.2-100%) and negative predictive value of 95% (75.1-99.9) with diagnostic accuracy of 97.5%.

Patients who required surfactant (n=21) had mean LUS of 11.9±2.49 with median of 12 (IQR:10-14) in range of (6-16) and patients who didn't require surfactant (n=19) treatment had mean LUS of 5±1.61SD with median of 5(IQR:4-6) in the range if (2-7) with p value of <0.001 which showed statistical significance of patients requiring surfactant treatment with higher LUS. Using univariate logistic regression analysis, positive association was found between higher LUS and the need for surfactant therapy with p value of 0.004 (Table 2).

On multivariate logistic regression analysis no association were found in patients with low gestational age and surfactant requirement with p value of 0.702 but positive association was found between high LUS and surfactant requirement with p value of 0.005. (Table 3)

## 4. Discussion

In our study 60% neonates were males (24/60) and 40% (16/40) were females. 65% (26/40) patients were delivered by LSCS and 35% (14/40) were born by NVD with their mean age of gestation 29±1.3 weeks. The mean weight of subjects was 1300±350g with a median of 1300g. Similar study was done by Lucia de martino et. al which included 133 neonates with RDS.[10] Among them 50% were male babies and 50% were female babies. 47.3% were delivered by LSCS and 52.6% were NVD born with mean gestational age of 28±2 weeks and mean birth weight of 1043g. Roselyne Brat et.al did a similar study in 130 neonates out of which 32(24.6%) were LSCS born and 98(75.3%) were NVD born with mean gestation age 33±3 weeks and mean birth weight of 2067±852g.[9] Shiraz Badurdeen et al conducted similar study in 52 patients 28(54%) males and 24(46%) females with mean gestational age 26-28 weeks and median weight of 922g.[11]

In our study, only 10/40 (25%) patients had received two doses of steroids while 25/40 (62.5%) patients had received only one dose of steroid and 5/40 (12.5%) patients did not receive any dose. In the study by Lucia de martino, 76 (57%) subjects received full dose of steroids.[10] In the study by Shiraz Badurdeen et al, among 52 patients, 32 (62%) received full dose of steroids.[11]

The median lung ultrasound score for predicting surfactant therapy in our study subjects was 8 (IQR of 2-16) with mean of 8.65±4.05 similar to the study done by Lucia de martino et al where the median score was 8 (IQR:4-12).[10] In the study by Roselyne Brat, the median lung ultrasound score was 5(IQR:3-10).[9] G Vardar had median lung ultrasound score of 10(IQR:9-12).[12]

The cut-off value for surfactant replacement therapy in our study was LUS>7 while as study done by Lucia de Martino et al, the cut-off was >8. [10] Tanima Roy et al in a similar study found a LUS cut-off of ≥9 for surfactant replacement therapy while Shiraz Badurdeen had taken a cut-off >7 which also correlates with our study.[11][13]

ROC analysis used in our study to predict the reliability of LUS for surfactant need showed AUC of 0.984 (95%CI:0.883-1.000) with p value of <0.0001. ROC analysis used by Lucia de martino showed AUC of 0.94(95%CI:0.90-0.98) with P value <0.001.[10] Similar results were found by Tanima Roy and Badurdeen et al. [11][13]

We found a positive association between LUS and need for surfactant requirement by using independent t test and univariate logistic regression analysis with p value of < 0.001 and 0.004 respectively which correlates with study done by Lucia de Martino and Roselyne Brat et al.[9][10]

In our study, the sensitivity of LUS in predicting surfactant requirement in neonates less than 30 weeks was 95.2% while the specificity was 100% with positive predictive value of 100% and negative predictive value of 95%. The diagnostic accuracy was 97.50%. Lucia de martino et al in their study found LUS to have 90 % sensitivity and 80% specificity.[10] Tanima Roy et al had sensitivity of 70.9% and specificity 68.75%.[13]

We also studied the association of various risk factors for surfactant requirement by using multiple logistic regression analysis which showed a positive association between LUS and surfactant requirement with p value of 0.005.which indicates higher the LUS more the requirement for surfactant replacement therapy.

## 5. Conclusion and Future Scope

LUS is a readily available bed-side tool when used by expert hands has a potential to be used as an adjunct or in selected cases as an alternative to FIO2 and CPAP to predict and determine the need for exogenous surfactant replacement therapy in preterm neonates less than 30 weeks of gestation with RDS.

## Tables

**Table 1:** Demographic and clinical characteristics of study subjects

| | Frequency | Percentage |
|---|---|---|
| **Gender** | | |
| Female | 16 | 40% |
| Male | 24 | 60% |
| Mode of delivery | | |
| NVD | 14 | 35% |
| LSCS | 26 | 65% |
| **Gestational age at birth(weeks)** | | |
| Mean ± SD | 29 ± 1.3 | |
| Median (25th-75th percentile) | 29.6 (28.14-30) | |
| Range | 25-30 | |
| **Weight(g)** | | |
| Mean ± SD | 1300 ± 350 | |
| Median(25th-75th percentile) | 1300 (1000g-1525) | |
| Range | 700-1960g | |
| **Antenatal steroids** | | |
| Two doses given | 10(25%) | |
| One dose given | 25(62.5%) | |
| No dose given | 5(12.5%) | |
| **Maternal obstetric and medical disease** | | |
| a) PIH | 15(37.5%) | |
| b) PPROM | 13(32.5%) | |
| c) APH | 5(12.5%) | |
| d) GDM | 5(12.5%) | |
| e) Twin pregnancy | 2(5%) | |

NVD: Normal vaginal delivery; LSCS: Lower segment caesarean section; SD: Standard deviation; PIH: Pregnancy induced hypertension; PPROM: Preterm premature rupture of membranes; APH: Antepartum hemorhhage; GDM: Gestational diabetes mellitus

**Table 2:** Univariate logistic regression to find out association of LUS with surfactant requirement

| Variable | Beta coefficient | Standard error | P value | Odds ratio | Odds ratio Lower bound (95%) | Odds ratio Upper bound (95%) |
|---|---|---|---|---|---|---|
| Gestational age | -0.780 | 0.376 | 0.038 | 0.458 | 0.219 | 0.958 |
| Lung ultrasound score | 1.245 | 0.437 | 0.004 | 3.474 | 1.474 | 8.184 |
| Gender | | | | | | |
| Female | | | | 1.000 | | |
| Male | 0.160 | 0.646 | 0.804 | 1.173 | 0.331 | 4.165 |

**Table 3:** Multivariate forward conditional logistic regression to find out independent risk factors of surfactant requirement

| Variable | Beta coefficient | Standard error | P value | Odds ratio | Odds ratio Lower bound (95%) | Odds ratio Upper bound (95%) |
|---|---|---|---|---|---|---|
| Gestational age | 0.328 | 0.858 | 0.702 | 1.389 | 0.258 | 7.464 |
| Lung ultrasound score | 1.124 | 0.402 | 0.005 | 3.076 | 1.398 | 6.770 |

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