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"Use of Lung Ultrasound to Evaluate Response to Early Surfactant Therapy and Predict Need for Second Dose in Premature Neonates in Suez Canal District"

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Abstract:

Background

Ratio of neonatal intensive care unit (NICU) admission by respiratory distress syndrome (RDS) as a part of total NICU admission is increasing yearly with the highest increase in RDS incidence in extreme preterm neonates. Lung ultrasound (LUS) can be used in diagnosis of RDS complication with better detection, compared to Chest X-ray, of consolidation and sub-pleural atelectasis. It can be used also in follow up and early assessment of the response to surfactant replacement therapy.

Aim

Assess the response to early selective replacement therapy in premature neonates using lung ultrasonography and predict need for second dose of surfactant replacement therapy using lung ultrasonography.

Patients /Methods

Neonates ≤ 34 weeks (60 neonates) was enrolled in this study and treated with early continuous positive airway pressure (CPAP). LUS was performed in the first 2 hours of postnatal life. 16 neonates treated with surfactant replacement therapy according to European consensus guidelines 2019 update. LUS was repeated after surfactant administration within 2 hours. 7 neonates needed second dose of surfactant if the oxygen requirements remained high ≥10 hours (the expected half-life of surfactant) after first dose administration.

Results

Our study shows that LUS score pre surfactant at a cut off value of ≥ 10 has a sensitivity of 85.7 % and specificity of 77.8 % for prediction of surfactant retreatment. LUS score post surfactant at a cut off value of ≥ 6 has a sensitivity of 85.7 % and specificity of 88.9 %.

Conclusion

Lung ultrasound score is useful in assessment of the response to early selective surfactant therapy in preterm neonate and predict need for second dose of surfactant therapy.

Key words: Lung ultrasound, premature neonates, surfactant.

Introduction :

Ratio of neonatal intensive care unit (NICU) admission by respiratory distress syndrome (RDS) as a part of total NICU admission is increasing yearly with the highest increase in RDS incidence in extreme preterm neonates. Many risk factors contribute to this increase such as old maternal age, planned caesarean sections and increased incidence of premature delivery especially after in vitro fertilization and other assistive reproductive techniques [1–3].

Currently, using early continuous positive airway pressure (CPAP) in the management of preterm neonates since birth together with early selective administration of surfactant, for those with signs of ongoing RDS, is an alternative to prophylactic surfactant administration [4]. On the other hand, surfactant prophylaxis is no longer indicated for preterm neonates stabilized by non-invasive respiratory support [5].

New methods in diagnosis for assessment of endogenous surfactant and lung maturity as lamellar bodies count present in gastric aspirate are now available to help in detecting preterm neonates need early surfactant administration [6]. However these methods can’t be widely adopted because of technical difficulties, and there is an increasing need for a simple bedside test that can be done within the NICU [5]. Lung ultrasound (LUS) may be a helpful tool [7].

Lung ultrasound (LUS), as a simple and non-invasive diagnostic technique with no exposure to ionizing radiation, can be used as a reliable diagnostic tool for causes of neonatal respiratory distress with good sensitivity and specificity, as reported in a literature review [8]. LUS can be a useful tool in diagnosis of RDS with good sensitivity and specificity, as reported in a previous study, about 97% and 91% respectively [9]. Detection of abnormalities of pleural line, lung consolidation and either bilateral white lung or A-line disappearance can detect RDS with 100% sensitivity and specificity [10]. It can also predict need for surfactant administration [11–13].

In this study we assessed the applicability of lung ultrasonography to assess response to surfactant replacement therapy and need for second dose of surfactant.

Methods:

This study is cross sectional analytic study on premature neonates ≤34 week admitted to Neonatal Intensive Care Unit (NICU) and treated on positive continuous airway pressure (CPAP) according to European guidelines 2019 update. Exclusion criteria includes congenital pneumonia, complex congenital malformations or chromosomal aberrations, meconium aspiration syndrome, congenital lung diseases, severe neonatal sepsis and septic shock and surfactant administration in delivery room as per European guidelines 2019 update [7]. We used convenience sampling. Sixty neonates admitted to the NICU in AL Salam Port said hospital and suez canal university hospital eligible for the study`s criteria between October 2020 and April 2022 were chosen.

In details, according to European consensus guidelines 2019 update, premature neonates who require intubation in delivery room received surfactant and excluded from the study. Spontaneously breathing premature neonates were treated with CPAP of 6 cm H_2O. LUS was performed in the first two hours of life. Surfactant was given when Fio_2 (fraction of inspired oxygen) required exceeds 0.30 by INSURE technique [intubate-surfactant-extubate] [7].

We used a high-resolution linear transducer with 9 MHz frequency in this study. We obtained The images using GE LOGIQ e with linear probe 9L. LUS was done by a single performer (trained neonatologist on neonatal LUS with 3 months of hands-on performance under supervision) before surfactant administration within the first 2 hours after admission. While in a quiet state, prematures are positioned in a supine and lateral position, we divided each lung into 3 areas (anterior, lateral, posterior). When using the LUS approach, the anterior lung area was examined between the sternum and the anterior axillary line, the lateral lung area was examined between the anterior and posterior axillary lines, and the posterior lung area was examined between the posterior axillary line and the spine. In the supine position, the anterior and lateral lung areas were assessed, and the posterior lung areas were examined in the lateral decubitus positions. (0-3) point score was given for each lung area (total score ranging from (0-18) in both lungs).

Lung ultrasound results were masked to clinicians in charge decided whether to give surfactant or not, also the LUS performer wasn't involved in any decision in treating the preterm neonates. In the prematures received surfactant replacement therapy, another LUS assessment was performed within two hours after surfactant administration.

The LUS score was edited from a score done for adult patients [14]. It was tested in a previous study on preterm neonates to evaluate surfactant need, it includes full spectrum of possible conditions; normal lung aeration, interstitial pattern, alveolar pattern and consolidation [15–17].

In details, LUS is designed as follows:

- 0 score for A-pattern (indicates presence of A lines only).
- 1 score for B-pattern (indicates presence of ≥ 3 well-spaced B-lines).
- 2 score for severe B-pattern (indicates presence of overcrowded and coalesced B-lines with or without subpleural consolidations).
- 3 score for extended consolidations.

the chest x-ray score (0-8 points), which was adapted from [18] (0 = normal radiolucent lung fields with sharp cardiac and diaphragmatic margins; 1 = slightly reduced radiolucency with still sharp cardiac and diaphragmatic margins; 2 = noticeably reduced radiolucency with retained cardiac and diaphragmatic margins; 3 = significantly reduced radiolucency with air bronchogram and blurred cardiac and diaphragmatic margins; 4 = nearly completely white lung fields with or without air bronchogram. [15,18]

The Statistical Package for Social Science (SPSS) for Windows version 25 was used for the statistical analysis. The computer statistical package was used to enter the collected, coded data.

Approval from the research ethics committee in faculty of medicine Port said university was obtained in May 2020. Administrative permissions were requested from the hospitals in which the study was performed. Informed consent was obtained from the parents.

Results :

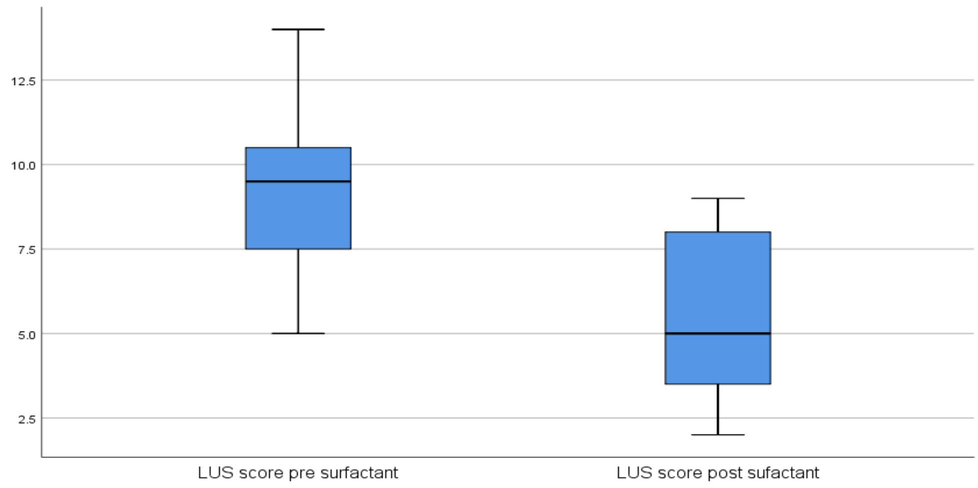
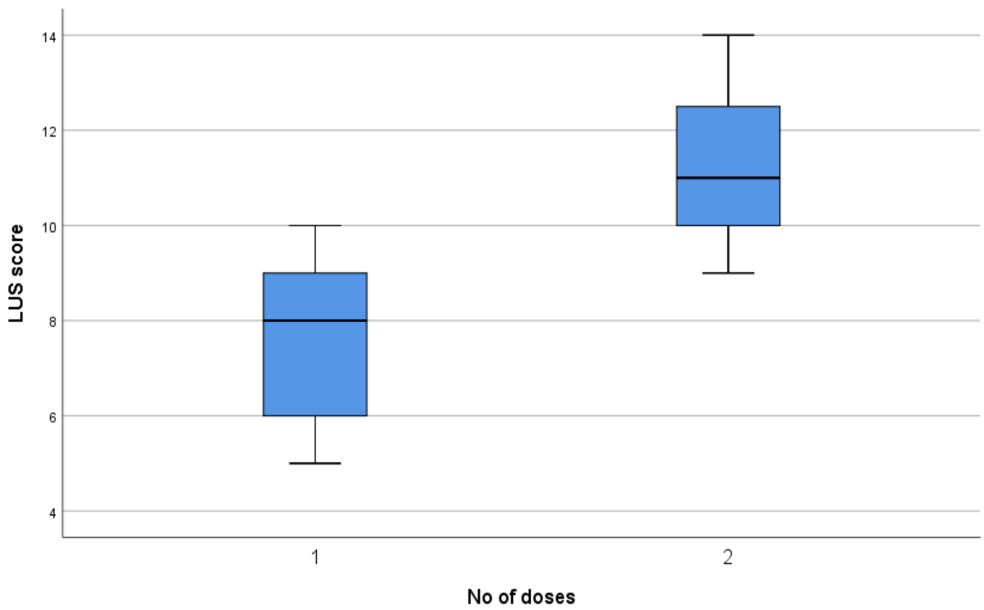


Figure 1: shows the median value, 25th percentile, 75th percentile, upper and lower limit of LUS score pre and post surfactant treatment.

In the group received surfactant the mean LUS score (± SD) was 9 ± 2 pre surfactant treatment and became 5 ± 2 after surfactant treatment. The median LUS score pre surfactant was 10. 7 and 11, respectively, were the 25th and 75th percentiles. The median LUS score was 5 post-



surfactant, but the 25th and 75th percentiles were 3 and 8, respectively.

Figure 2: shows the median value, 25th percentile, 75th percentile, upper and lower limit of LUS score in the different groups received single and two doses of surfactant.

In the group received one dose of surfactant the median LUS score was 8. 6 and 9, respectively, were the 25th and 75th percentiles. While the median LUS score was 11, the 25th and 75th percentiles were 10 and 13, respectively, in the group that received two doses of surfactant.

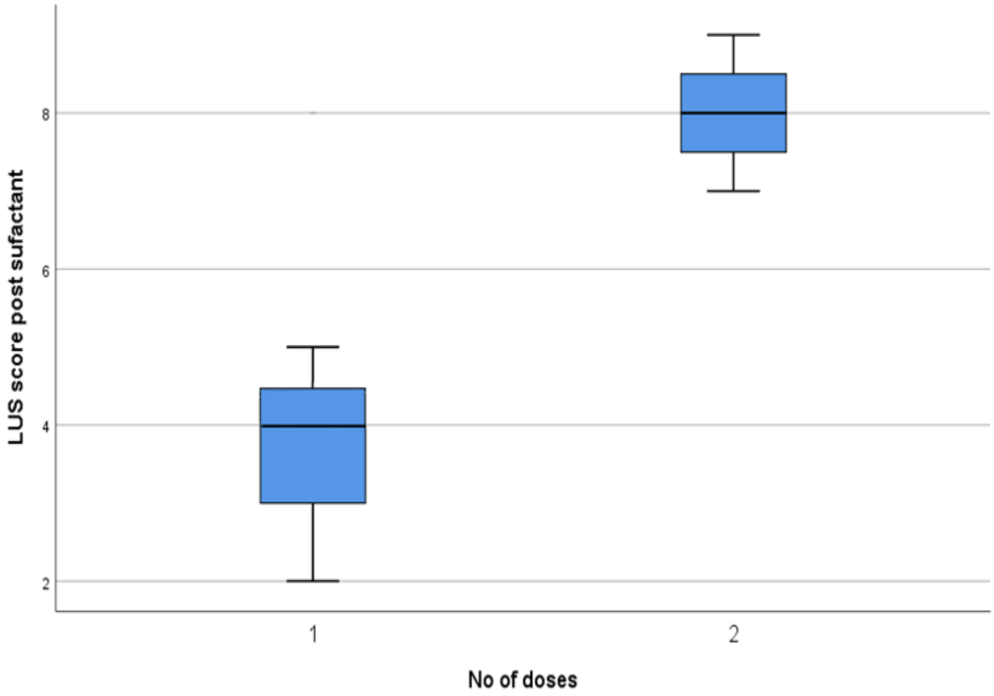


Figure 3: shows the median value, 25th percentile, 75th percentile, upper and lower limit of LUS score, post first dose, in the different groups received single and two doses of surfactant.

In the group received one dose of surfactant the median LUS score post surfactant was 4. 3 and 5, respectively, represented the 25th and 75th percentiles. While the median LUS score was 8, the 25th and 75th percentiles were 7 and 9, respectively, in the group that received two doses of surfactant.

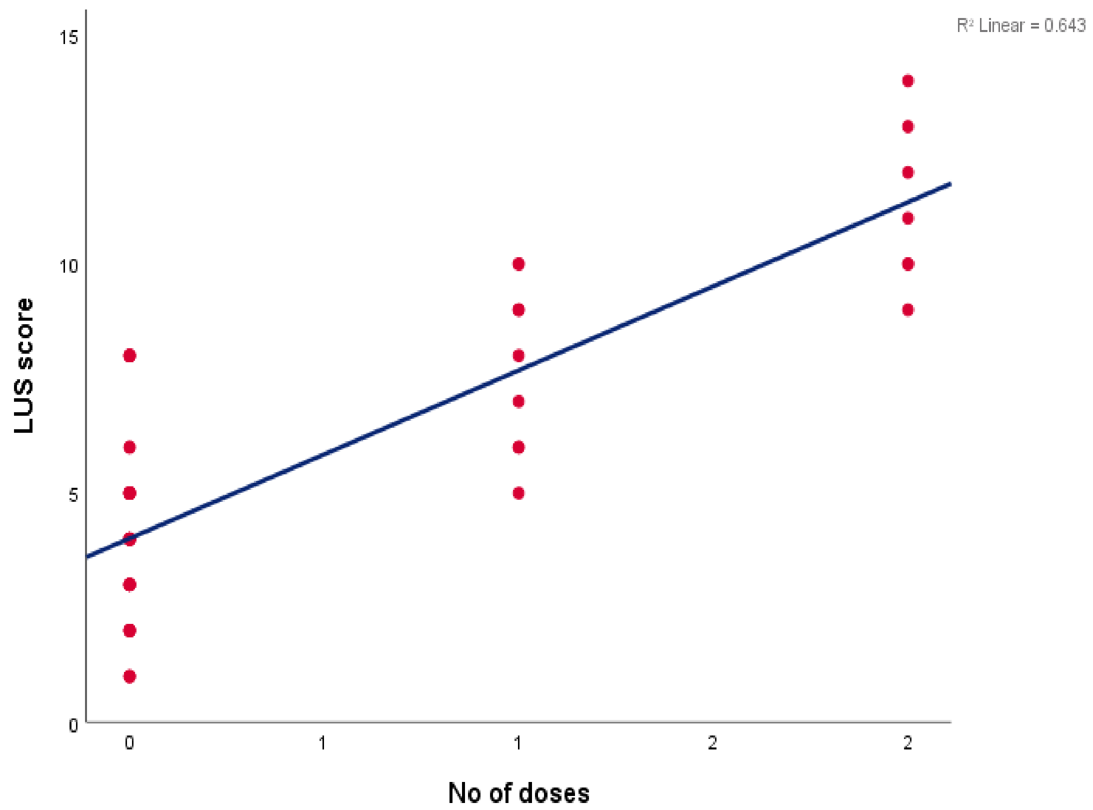


Figure 4: Scatter plot shows correlation between No of surfactant doses and LUS score.

This figure shows the strong positive Correlation (r = 0.802) between No of surfactant doses and LUS score. correlation is significant statistically ($P \leq 0.001$).

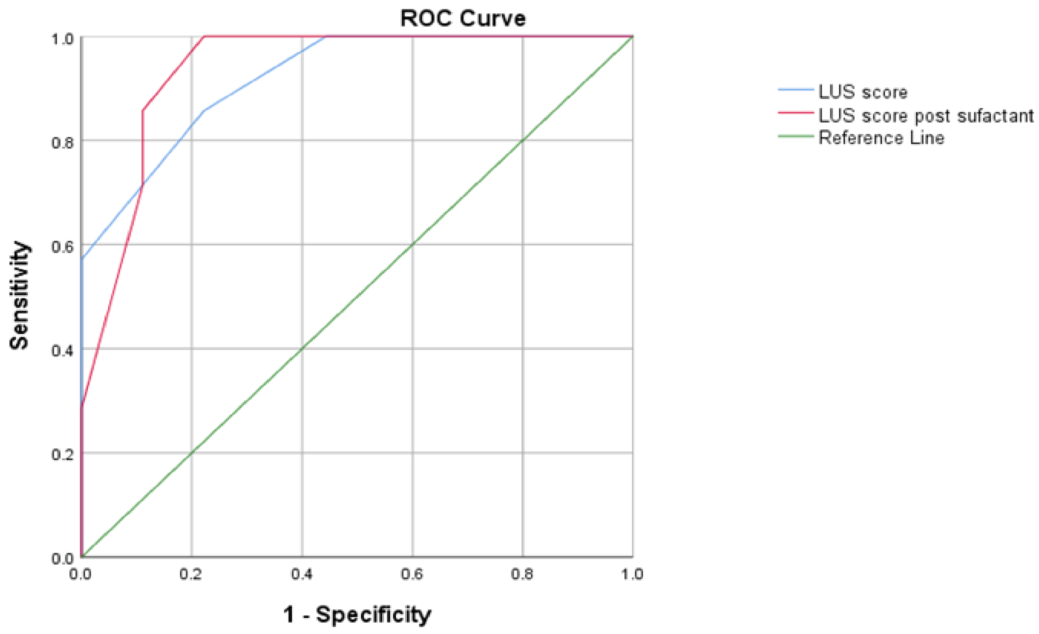


Figure 5: ROC analysis for the prediction of surfactant retreatment using LUS score pre and post surfactant.

	AUC	P value	95% confidence interval		Best cut off value
			Lower Bound	Upper Bound	
LUS score pre surfactant	0.921	<0.001*	0.858	0.984	≥ 10
LUS score post surfactant	0.908	<0.001*	0.844	0.972	≥ 6

* Statistically significant at p<0.05

ROC analysis for the prediction of surfactant retreatment using LUS score pre and post surfactant shows an area under curve (AUC) of 0.921 for LUS score pre surfactant treatment and AUC of 0.908 for LUS score post surfactant treatment. Both are statistically significant (p=<0.001).

Table 1: Reliability of LUS score pre and post surfactant for prediction of surfactant retreatment.

	Best cut off value	Sensitivity	Specificity	+ve predictive	-ve predictive
LUS score pre surfactant	≥ 10	85.7 %	77.8 %	75 %	87.5 %
LUS score post surfactant	≥ 6	85.7 %	88.9 %	85.7 %	88.9 %

This table displays the accuracy of the LUS score before and after the surfactant for predicting the retreatment of the surfactant. At a cutoff value of 10, the LUS score pre surfactant has an 85.7% sensitivity and a 77.8% specificity. The LUS score post surfactant has a sensitivity of 85.7% and a specificity of 88.9% at a cutoff value of 6.

Discussion:

Respiratory distress syndrome (RDS) represents a crucial problem for premature neonates despite the new advancement in management [19]. Nowadays, management of RDS is through using early continuous positive airway pressure (CPAP) in management of premature neonates since birth and early selective administration of surfactant [4]. On the other hand, surfactant prophylaxis isn't indicated for premature neonates treated by non-invasive respiratory support [5].

New techniques in diagnosis for assessment of surfactant and lung maturation as lamellar bodies count found in gastric aspirate are now used to help in detecting premature neonates in need for early surfactant administration [6]. However these methods can't be used widely because of technical difficulties, and there is increasing needs for simple bedside diagnostic test that can be performed within the NICU [5]. LUS may be a helpful tool [7].

LUS can be used in detection of RDS with high sensitivity and specificity, as reported in a literature review, about 97% and 91% respectively [9]. When lung consolidation, pleural line abnormalities, and either bilateral white lung or A-line disappearance are found at the same time, RDS can be diagnosed with 100% sensitivity and specificity [10].

In this study we assessed the applicability of lung ultrasonography to assess response to surfactant replacement therapy and need for second dose of surfactant.

We studied premature neonates $\leq$ 34 weeks (60 neonates) treated with early CPAP; LUS was performed in the first 2 hours of life. 16 neonates treated with surfactant therapy according to European consensus guidelines 2019 update. LUS was repeated after the surfactant within 2 hours. 7 neonates treated with second dose of surfactant if the oxygen requirements remained high $\geq$10 hours (the median half-life of surfactant) after the first administration.

In the current study, we discovered a significant strong positive correlation between the LUS score and the number of surfactant doses ($r = 0.802$). correlation is statistically significant ($P=<0.001$). This is consistent with the results found by **Vardar *et al.* 2021** [20] who showed a significant correlation between LUS score and the need for total surfactant doses.

Our study found that ROC analysis for the prediction of surfactant retreatment using LUS score pre and post surfactant showed an area under curve (AUC) of 0.921 for LUS score pre surfactant treatment and AUC of 0.908 for LUS score post surfactant treatment. Both are statistically significant ($p=<0.001$). at a cut off value equals or greater than ten, LUS score pre surfactant has a sensitivity of 85.7 % and specificity of 77.8 %. Also, At a cutoff value of 6, the LUS score post surfactant has a sensitivity of 85.7% and a specificity of 88.9%.

This is in agreement with what is published by **Perri *et al.* 2020** [12] who reported that The ROC analysis for the LUS 2h after surfactant produced an area under the curve of 0.8, and a LUS score of 7 indicated the need for surfactant retreatment with 94% sensitivity, 60% specificity, a negative predicted value of 95%, and a positive predicted value of 56%.

Also, **De Martino *et al.* 2018** [21] found that ROC analysis for the LUS score for surfactant re-treatment showed an AUC of 0.803 for the entire population and that at cut off value of 10 or greater, LUS score had a sensitivity of 84 % and specificity of 70 %.

In another literature published by **Vardar *et al.* 2021** [20] ROC curve analysis for prediction of surfactant need in preterm infants using LUS score showed AUC of 0.994 ($p \leq 0.001$) and the need for additional doses with AUC of 0.993 ($p \leq 0.001$).

A systematic review published by **Razak and Faden 2020** [13] showed that Studies using In comparison to a study that used a lower LUS score cut off value of greater than four, the study using a higher LUS score cut off value of greater than five demonstrated better diagnostic accuracy. In comparison to infants with LUS scores below five, meta-analysis revealed a significantly higher risk of surfactant therapy or mechanical ventilation in infants with LUS scores above five.

There were few limitations to our study. First, there are different protocols to perform LUS. Also, the score of LUS is operator and equipment dependent. This limits the ability to generalize of the results of our study.

Second, we used high frequency liner probe in performing LUS in this study which limits number of fields we can examine in premature neonates.

Finally, we need larger number of cases requiring retreatment with second dose and more of surfactant for more statistically informative results.

Conclusion:

In conclusion, Lung ultrasound score is helpful in determining how preterm neonates respond to early selective surfactant therapy and in identifying when a second dose of surfactant therapy is required. At a cutoff value of 10, the LUS score pre surfactant has an 85.7% sensitivity and a 77.8% specificity. At a cutoff value of 6, the LUS score post surfactant has an 85.7% sensitivity and an 88.9% specificity.

Abbreviations:

AUC: area under curve; **CPAP**: continuous positive airway pressure; **LUS**: lung ultrasound; **NEC**: necrotizing enterocolitis; **NICU**: neonatal intensive care unit; **RDS**: respiratory distress syndrome; **ROC**: receiver operating characteristics; **SPSS**: statistical package for social science.

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