Lung Ultrasound Score Progress in Neonatal Respiratory Distress Syndrome

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abstract

BACKGROUND AND OBJECTIVES: The utility of a lung ultrasound score (LUS) has been described in the early phases of neonatal respiratory distress syndrome (RDS). We investigated lung ultrasound as a tool to monitor respiratory status in preterm neonates throughout the course of RDS.

METHODS: Preterm neonates, stratified in 3 gestational age cohorts (25–27, 28–30, and 31–33 weeks), underwent lung ultrasound at weekly intervals from birth. Clinical data, respiratory support variables, and major complications (sepsis, patent ductus arteriosus, pneumothorax, and persistent pulmonary hypertension of the neonate) were also recorded.

RESULTS: We enrolled 240 infants in total. The 3 gestational age intervals had significantly different LUS patterns. There was a significant correlation between LUS and the ratio of oxygen saturation to inspired oxygen throughout the admission, increasing with gestational age (b = −0.002 [$P < .001$] at 25–27 weeks; b = −0.006 [$P < .001$] at 28–30 weeks; b = −0.012 [$P < .001$] at 31–33 weeks). Infants with complications had a higher LUS already at birth (12 interquartile range 13–8 vs 8 interquartile range 12–4 control group; $P = .001$). In infants 25 to 30 weeks' gestation, the LUS at 7 days of life predicted bronchopulmonary dysplasia with an area under the curve of 0.82 (95% confidence interval 0.71 to 93).

CONCLUSIONS: In preterm neonates affected by RDS, the LUS trajectory is gestational age dependent, significantly correlates with the oxygenation status, and predicts bronchopulmonary dysplasia. In this population, LUS is a useful, bedside, noninvasive tool to monitor the respiratory status.

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WHAT'S KNOWN ON THIS SUBJECT: Lung ultrasound is a noninvasive, bedside imaging technique used to make a differential diagnosis of respiratory distress. Early in the course of neonatal respiratory distress syndrome, a lung ultrasound score can predict the need for noninvasive respiratory support or surfactant administration.

WHAT THIS STUDY ADDS: Over the whole admission for respiratory distress syndrome, the trajectory of the lung ultrasound score is significantly correlated with gestational age, the ratio of oxygen saturation to fraction of inspired oxygen index, and the presence or absence of major postnatal complications and allows for an early bronchopulmonary dysplasia prediction.

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Neonatal lung ultrasound is an area of intense and growing clinical research, with relevant clinical implications.[1,2] This bedside, noninvasive imaging technique can be used to describe the postnatal adaptation[3] and differential diagnosis of neonatal respiratory distress[4] and to predict the need for noninvasive respiratory support[5] or mechanical ventilation.[6] Brat et al[7] have validated a lung ultrasound score (LUS) by demonstrating its significant correlation with several, mostly invasive, oxygenation indexes. These findings have led the same group to test LUS as a possible benchmark for surfactant administration.[8] Most of this pioneering work was from a single center and mainly in the early stages of the respiratory distress. Recently, a prospective international study revealed that LUS could be used as a respiratory status–monitoring tool in term and late-preterm neonates with transient tachypnea, from the onset of respiratory distress to discharge.[9] Following the same line of thought, here we investigated the LUS pattern during the entire NICU admission of a population of preterm infants with respiratory distress syndrome (RDS). To better characterize the usefulness of this possible respiratory marker, we correlated the LUS trajectory with gestational age, the ratio of peripheral oxygen saturation ($Sato_2$) to the fraction of inspired oxygen (Fio_2), and the presence or absence of major postnatal complications.

METHODS

Population

This was a prospective, multicenter, observational study in 8 level III, Italian NICUs (Università Federico II, Naples; Ospedale Careggi, Florence; Ospedale Buzzi, Milan; Università Cattolica, Rome; Università di Brescia, Brescia; Università di Ancona, Ancona; Clinica Mangiagalli, Milan; Università di Udine, Udine). It was conducted from May 2018 to May 2020. We included premature neonates with RDS, infants with a gestational age between 25^0 and 336 weeks and infants with enrollment within 72 hours from birth and/or before the administration of the first surfactant dose. Exclusion criteria were gestational age beyond 336 weeks, postnatal age beyond 72 hours and/or administered surfactant, and major congenital malformations. Written parental consent was obtained, and the study was approved by the Ethics Committee for Activities "Carlo Romano" International Office for Bioethics Research, Federico II University of Naples (protocol 1621/17). Formal approval was also obtained by the ethics committee of each participating center. The study was conducted following the Strengthening the Reporting of Observational Studies in Epidemiology statement guidelines.[10] Enrolled newborns were divided into 3 groups by gestational age, calculated from the first day of the last menstrual period: 25^0 to 276; 28^0 to 306; and 31^0 to 336 weeks.

Data Collected

At enrollment, major prenatal variables were recorded. Preterm neonates were monitored with lung ultrasound from enrollment at birth to discharge or death. Monitoring included a complete lung scan in the first 24 hours of life (shown in the figures as T0) and a weekly scan afterward. The T1 scan was then acquired at the end of the first week of life. The LUS protocol was performed by an experienced ultrasonographer using a linear or microlinear, high frequency (10–15 MHz) transducer. No harmonics were used. The gain was left to the automatic determination of the machine software, with focus placed on the pleural line and depth just below. Short clips at the emiclavear, anterior, and posterior axillary lines of both hemithoraces were recorded. LUS was assigned by each local ultrasonographer, as per Brat et al,[7] with minor modifications, and it is detailed in the Supplemental Information. The interobserver agreement was performed between the local operators and 1 of 2 investigators (F.M. and F.R.) located in the Naples reference center. Surfactant (poractant alfa [200 mg/kg for the first dose and 100 mg/kg for the following doses]; Chiesi Farmaceutici, Parma, Italy) was prescribed according to the European guidelines[11] by an attending neonatologist unaware of the study purpose. Before each examination, the local investigator recorded blood gas laboratory results, respiratory support mode if present, clinical complications that occurred after the previous ultrasound scan, and the $Sato_2/Fio_2$ ratio. $Sato_2$ was recorded at the right hand by pulse oximetry, as determined by local technology. $Sato_2$ was maintained in the 90% to 95% range by an adequate Fio_2, as indicated by local ventilators or continuous positive airway pressure devices.

Study Outcomes

The primary outcome of the study was the LUS trajectory over the course of the NICU admission and correlation between LUS and the $Sato_2/Fio_2$ ratio in a population of significantly preterm infants.

Secondary outcomes were the correlation between LUS and $Sato_2/Fio_2$ ratio in the 3 gestational subgroups, the LUS time course for $\geq$1 complication (ie, clinical- or culture-proven sepsis, patent ductus arteriosus [PDA] requiring medical or surgical treatment, pneumothorax, and persistent pulmonary hypertension [PPHN]) versus controls, and an early LUS threshold for bronchopulmonary

dysplasia (BPD) in infants who developed complications.

Definitions

BPD was defined as per Jensen et al.[12] RDS in the preterm infant was defined as the presence of intercostal and subcostal retractions with expiratory grunting shortly after birth in the presence of compatible radiographic features.[13]

Sepsis was defined as the sudden onset of apnea, mottled skin, temperature instability, feeding intolerance, significant abdominal distension, respiratory distress, and hemodynamic instability together with laboratory criteria. The latter were elevated C-reactive protein (cutoff = 1 mg/dL), abnormal leukocyte count (cutoff < 5000/mL or >20 000/mL), and immature to total neutrophil ratio (cutoff > 0.2) with or without positive blood culture results; PDA was considered clinically significant when treated medically and/or surgically as per the individual NICU protocol; and pneumothorax and PPHN were confirmed by chest radiogram and echocardiogram, respectively.

Statistics

Quantitative variables were presented as mean (± SD) or median (interquartile range), as appropriate, whereas categorical variables were presented as frequencies (percentage). Cohen's κ coefficient was also provided to assess the interobserver variability. Our cohort was divided by gestational age; Student's *t* test or Mann–Whitney *U* test, as appropriate, were performed for comparison between infants developing clinical complications and those in the control group, with respect to quantitative variables, whereas χ^2 test was used for categorical variables.

Mixed-effect models were used for the longitudinal analysis of LUS and $Sato_2/Fio_2$ ratio and to study their relationship over time. Moreover, gestational age was included as a main fixed effect, and an interaction term between gestational age and time was also considered. As a random effect, we considered both the intercept and the slope for the effect of time in all the models. Autocorrelation among within-subject errors, common in observations collected over time, were specified in the models fitting a continuous first-order autoregressive process in the errors.

A logistic regression analysis was performed to investigate the prognostic values of LUS (taken separately at different times) for BPD, including medical complications, gestational age, and birth weight as covariates. These variables were chosen for their clinical relevance. The R^2 and the Hosmer and Lemeshow test were used to test the goodness of fit of the logistic regression. A receiver operating characteristic curve was constructed and the area under the curve (AUC) was computed to evaluate to predictive accuracy of LUS for BPD. Comparisons between AUCs were performed by using the DeLong method.

All tests were 2-sided and performed at a significance level of α = .05. The R 3.6.0 statistical software was used for all statistical analyses. The lme function implemented in the nlme R package was used for the mixed-effect models.

TABLE 1 General Characteristics of the Study Population

	25–27 wk (*n* = 65)	28–30 wk (*n* = 76)	31–33 wk (*n* = 99)
Gestational age, d, mean (± SD)	186 ± 6	206 ± 6	227 ± 6
Birth wt, g, mean (± SD)	865 ± 165	1140 ± 284	1682 ± 373
SVD, *n* (%)	20 (30.7)	10 (13.1)	23 (23.2)
Maternal complications, *n* (%)			
Chorioamnionitis	6 (9.2)	4 (5.2)	4 (4)
Maternal hypertension	10 (15.4)	20 (26.3)	22 (22.2)
PROM	10 (15.4)	11 (14.4)	9 (9)
IUGR	6 (9.2)	24 (31.5)	21 (21)
Apgar score at 5 min ≤5, *n* (%)	0	1 (1.3)	0
Steroid use, *n* (%)			
No antenatal steroids	2 (3)	0	6 (6)
1 dose antenatal steroids	11 (16.9)	10 (13.1)	14 (14.1)
2 doses antenatal steroids	52 (80)	66 (86.8)	79 (79.8)
Surfactant, *n* (%)	46 (71)	39 (51)	23 (23)
1 dose	27 (41.5)	29 (38.1)	20 (20.2)
2 doses	8 (12.3)	7 (9.2)	3 (3)
>2 doses	11 (16.9)	3 (3.9)	0
Received PPV in DR, *n* (%)	8 (12.3)	7 (9.2)	6 (6)
Received CPAP in DR, *n* (%)	53 (81.5)	69 (90.7)	55 (55.5)
Major complications, infant, *n* (%)			
Sepsis	25 (38.4)	20 (26.3)	11 (11.1)
PDA	21 (32.3)	13 (17.1)	3 (3)
Pneumothorax	2 (3)	0	0
PPHN	1 (1.5)	0	0
BPD	12 (18.4)	11 (14.4)	0
No. LUSs, median	11	8	6

CPAP, continuous positive airway pressure; DR, delivery room; IUGR, intrauterine growth retardation; PPV, positive pressure ventilation; PROM, premature rapture of membrane; SVD, spontaneous vaginal delivery.

Sample Size Calculation

The $Sato_2/Fio_2$ ratio has been revealed to be a reliable surrogate for the Pao_2/Fio_2 ratio in a variety of clinical settings, including pulmonary dysfunction during sepsis, anesthesia, and surfactant administration in preterm infants.[14] Previous observations on a cohort of 75

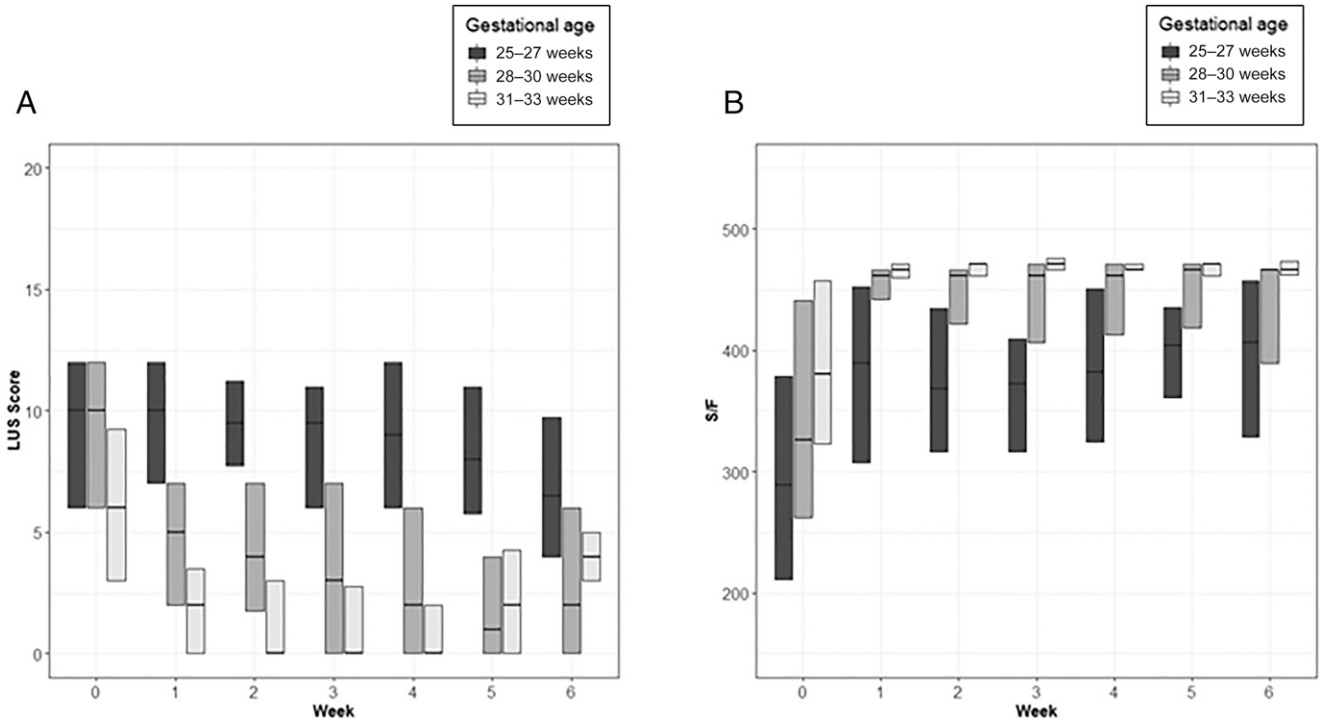

FIGURE 1

Time course of LUS and $Sato_2/Fio_2$ ratio (S/F) in the 3 gestational age patient subgroups. A, LUS patterns are both gestational age and time dependent. B, Patterns of S/F are gestational age dependent. The only significant difference over time is between the first and the third group ($P = .007$).

neonates revealed that LUS correlated significantly with the Pao_2/Fio_2 ratio ($r = -0.55$; 95% confidence interval [CI] = −0.68 to −0.35; $P < .0001$) and the alveolar arterial gradient ($r = 0.59$; 95% CI = 0.41 to 0.69; $P < .0001$).[15] We calculated that, taking into account the lowest correlation coefficient from the previous data (−0.35 for the Pao_2/Fio_2 ratio), each cohort should enumerate at least 61 patients (effect size $|\rho| = 0.35$; $\alpha = .05$;

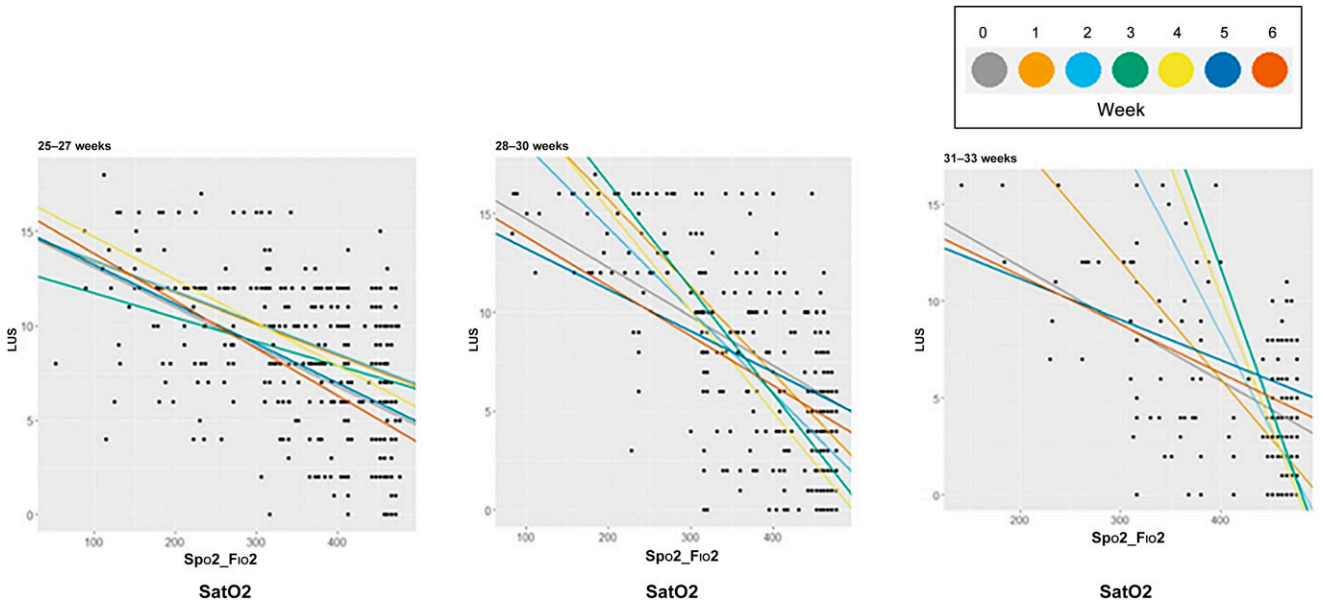

FIGURE 2

LUS and $Sato_2$ to Fio_2 relation according to time and gestational age. There is a significant inverse relation between LUS and $Sato_2/Fio_2$ ratio for all gestational age groups (b = −0.002 [$P < .001$] at 25–27 weeks' PMA; b = −0.006 [$P < .001$] at 28–30 weeks' PMA; b = −0.012 [$P < .001$] at 31–33 weeks' PMA).

power = 0.8) for a total of 183 neonates to be enrolled.

RESULTS

We enrolled 240 patients and divided them into 3 gestational age cohorts: 65 infants in the more immature cohort (25–27 weeks), 76 in the 28 to 30 weeks' group, and 99 in the 31 to 33 weeks' group. Their general characteristics are reported in Table 1. We collected 1871 complete scans, which were reviewed by 2 experts in neonatal lung ultrasound (F.M. and F.R.) to calculate LUS interobserver variation. Cohen's κ coefficient was 0.91.

LUS and $Sato_2/FIo_2$ Ratio Time Courses

We calculated the LUS and the trajectories of the $Sato_2/FIo_2$ ratio for the whole study population, in which the variables reveal, respectively, a significant negative and positive trend ($P < .001$) (Supplemental Information). Because of NICU discharges of healed patients, the relative weight of each determination decreases with time after T6. In Fig 1, we report the course of LUS (Fig 1A) and $Sato_2/FIo_2$ ratio (Fig 1B) in the 3 gestational age groups during the NICU admission. The former reveals a significant negative trend ($P < .001$) with a relevant interaction with gestational age. In particular, there is a significant difference between the LUS patterns of the least mature infants and each of the other 2 ($P < .001$ in both comparisons), with a widening difference over time. More mature infants in the 2 other cohorts also have a significant difference between them that changes over time ($P = .024$). The $Sato_2/FIo_2$ ratio describes a positive pattern that is significantly different among the gestational age groups ($P < .001$). This difference, however, is not time dependent except for the comparison between the least and the most mature neonates ($P = .007$).

TABLE 2 Antenatal and Postnatal Characteristics of the 25–30 Weeks' Cohort Based on Clinical Complications

	Complications (n = 72)	No Complications (n = 69)	P
Gestational age, d, mean (± SD)	191 ± 11	203 ± 9.7	<.001
Birth wt, g, mean (± SD)	913 ± 236	1111 ± 270	<.001
SVD, n (%)	17 (23.6)	11 (15.9)	.35
Maternal complications, n (%)			
Chorioamnionitis	8 (1.5)	6 (8.6)	.63
Maternal hypertension	14 (19.4)	16 (23.2)	.73
PROM	15 (21)	9 (13)	.31
IUGR	16 (22.2)	14 (14.4)	.94
Steroid use, n (%)			
No antenatal steroids	1 (1.4)	1 (1.4)	.98
1 dose antenatal steroids	14 (19.4)	10 (14.4)	.31
2 doses antenatal steroids	57 (79.1)	58 (84)	.28
Surfactant, n (%)	58 (80.5)	27 (39.1)	<.001
1 dose	49 (68)	25 (36.2)	<.001
2 doses	8 (11.1)	2 (2.8)	.057
>2 doses	1 (1.4)	0	.98
Intubated in DR, n (%)	11 (15.3)	6 (8.7)	.23
Received mask PPV in DR, n (%)	61 (84.7)	62 (89.8)	.61
Major complications, infant, n (%)			
Sepsis, ≥1 episode	45 (62.5)	0	.001
PDA	37 (51.4)	0	.001
Pneumothorax	2 (2.7)	0	.001
PPHN	2 (2.7)	0	.001
BPD	17 (25)	6 (8.5)	.017

DR, delivery room; IUGR, intrauterine growth retardation; PPV, positive pressure ventilation; PROM, premature rapture of membrane; SVD, spontaneous vaginal delivery.

LUS and $Sato_2$ to FIo_2 Relation

At the initial scan (ie, T0), we report a significant correlation between the 2 variables ($r = -0.51$ for infants 25–27 weeks' gestation; $r = -0.55$ for infants 28–30 weeks' gestation; and $r = -0.54$ for the most mature neonates; $P < .001$ for the 3 groups).

Figure 2 shows the significant inverse relation between LUS and $Sato_2/FIo_2$ ratio for all gestational age groups over time (b = −0.002 [$P < .001$] at 25–27 weeks; b = −0.006 [$P < .001$]; at 28–30 weeks; b = −0.012 [$P < .001$] at 31–33 weeks). The interaction between gestational age and $Sato_2/FIo_2$ ratio is statistically significant ($P < .001$), which in particular suggests that the strength of the relation between LUS and $Sato_2/FIo_2$ ratio increases with gestational age.

LUS and Postnatal Complications

The vast majority of infants 31 to 33 weeks' gestational age did not suffer from major complications (ie, clinical- and/or culture-proven sepsis, PDA deserving medical and/or surgical treatment, pneumothorax, and PPHN). When complication data were aggregated for neonates between 25 and 30 weeks' gestation, two distinct LUS patterns emerged since birth (Supplemental Information), and they did not merge until T8, when the relative weight of the sickest infants became dominant. The analysis of major antenatal variables did not result in significant differences between infants with complications and infants in the control group (Table 2). When BPD was considered as an additional variable, 3 trajectories emerged, as shown in Fig 3. Infants with complications and BPD (n = 18 at T0) had a significantly higher score than infants with complications but no BPD (n = 51 at T0) ($P = .017$). Both groups had higher scores compared to neonates without complications (n = 74 at T =

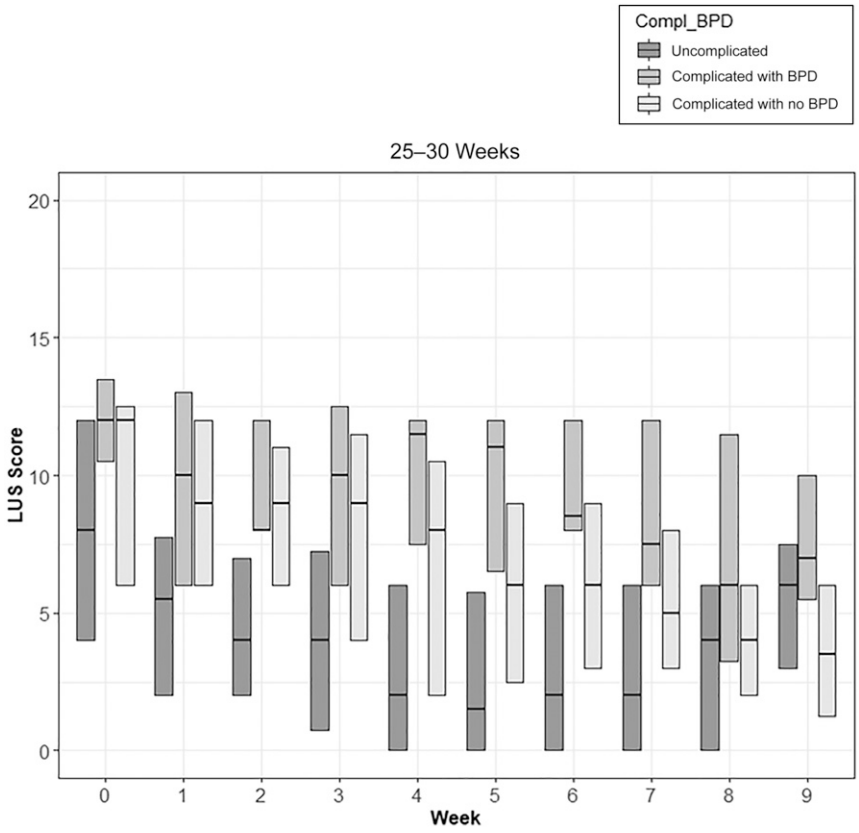

FIGURE 3

LUS time course in infants who developed complications and in those in the control group. Infants 25 to 30 weeks' gestation with major complications, with and without BPD, had a significantly higher LUS since birth compared with those in the control group. This difference does not change significantly over time. Compl_BPD, major neonatal complications and BPD.

0) ($P < .01$). These differences did not significantly change over time.

LUS and BPD

Our multicenter database reveals that although no infant in the 31 to 33 weeks' group developed BPD according to the most updated definition,[12] this was the case for 23 infants in the 25 to 30 weeks' gestational age cohort. Infants suffering from major complications had a significantly higher incidence of BPD (see Table 2). A logistic regression model was built, keeping gestational age, birth weight, and the presence of medical complications as confounders. We found that LUS was an independent predictor of BPD already at 7 days after birth (Fig 4A) with an odds ratio of 1.19 ($P = .006$), whereas the odds ratio was 1.34 ($P = .6253$) for complications, 0.76 ($P = .5724$) for gestational age, and 0.99 ($P = .0785$) for birth weight ($R^2 = 0.31$; Hosmer and Lemeshow test: X2 = 11.9, degrees of freedom = 8; $P = .156$).

The corresponding receiver operating characteristic curves results revealed that LUS predicted BPD, with an AUC of 0.82 (95% CI 0.71 to 93); cutoff of 10; sensitivity of 0.68; specificity of 0.82; predictive positive value of 0.28; negative positive value of 0.98; and likelihood ratio of 3.77, considering the whole 25 to 30 weeks' gestational age cohort. The 25 to 27 weeks' group had an AUC of 0.5, whereas the 28 to 30 weeks' group had an AUC of 0.89, cutoff of 10, sensitivity of 0.78, specificity of 0.87, predictive positive value of 0.43, negative positive value of 0.97, and likelihood ratio of 5.88. The difference between $AUC_{25–27}$ and $AUC_{28–30}$ reached statistical significance ($P < .001$). The related graphs are added to the Supplemental Information.

These latter results suggested an interaction between LUS and gestational age. Consequently, we added in the logistic regression model for this interaction term, which was found to be statistically significant ($P = .023$), and the goodness of fit of the model improved ($R^2 = 0.36$; Hosmer and Lemeshow test: X2 = 4.7, degrees of freedom = 8; $P = .789$). Moreover, a new model was tested considering only patients in the 25 to 27 weeks and the 28 to 30 weeks' groups and adding again the interaction terms between LUS and gestational age. Figure 4B shows the prediction of BPD as a function of LUS separately for the 25 to 27 weeks and the 28 to 30 weeks' groups. In this model both LUS and gestational age were statistically significant ($P = .022$ and $P < .001$, respectively), as was their interaction term ($P < .001$).

DISCUSSION

A neonatal LUS is a significant noninvasive correlate of oxygenation status and lung injury,[16] with relevant clinical implications. In our pragmatic study, we expand previous single-center observations[17] providing the first multicenter reference values on LUS in a cohort of premature infants stratified by narrow gestational age intervals over the entire duration of their hospital admission. We showed that LUS has a significant correlation with gestational age, with the presence or absence of major complications, and with $Sato_2/Fio_2$ ratio. LUS is also an early predictor of BPD.

Earlier work by Brat et al[7] had revealed that when a gestational age cutoff was set at 34 weeks, the median LUS at the admission in the NICU was 5 and not dependent on gestational age. When the same investigators set the cutoff at 28

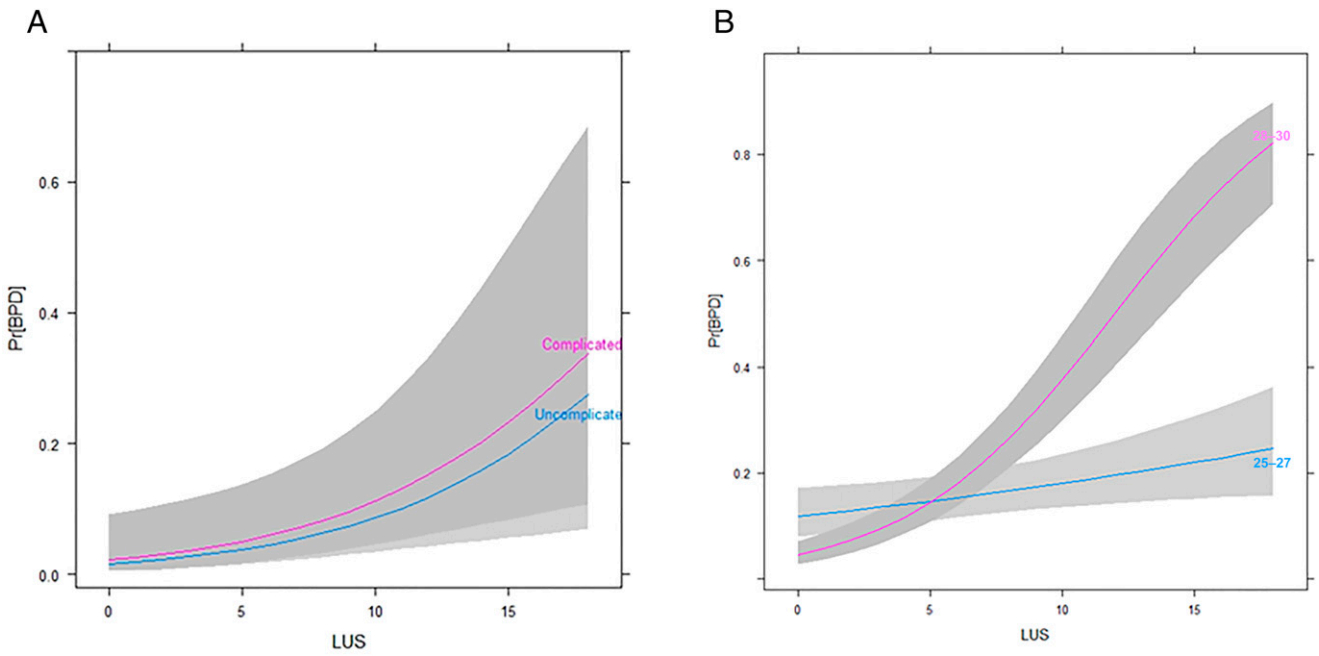

FIGURE 4

LUS and BPD prediction (Pr[BPD]) in a cohort of infants 25 to 30 weeks' gestation and its gestational age subgroups. A, Predictions of BPD obtained through multiple logistic regression, as a function of LUS and complications, while keeping constant gestational age and birth weight. B, Relation between LUS and gestational age in predicting BPD at 7 days of age.

weeks, the initial LUS was significantly higher (median LUS = 10) in less mature infants and close to our initial estimate in similar infants.[8] Besides using a similar yet not identical scoring system, the differences may also be attributable to the scanning protocol. Compared to those earlier articles, we concentrated less on the anterior regions and gave a fuller representation of the lateral and lateroposterior zones of the lung. Besides the starting value, the entire trajectory of the LUS depends on gestational age, with higher values for less mature infants. Clinicians have to keep this variable in mind if LUS has to be used as an imaging tool to monitor lung status. Such a strategy is possible because LUS is a noninvasive technique with a significant link to the oxygenation status. This had already been revealed by previous investigators in the early stages of RDS using both invasive and noninvasive markers.[6,7] We provide evidence that the correlation between LUS and $Sato_2/Fio_2$ ratio persists during the infant's NICU stay and is directly related to gestational age. We acknowledge that $Sato_2/Fio_2$ ratio is an imperfect marker of the infant oxygenation status because it may be less reliable than the Pao_2/Fio_2 ratio in circumstances of hemodynamic instability and poor perfusion.[18] However, we felt that more invasive measurements were unethical, especially on the infants of our population who were rapidly turning healthier. Indeed, when the initial general health status of our 25 to 30 weeks cohort was evaluated, we found that higher LUS early identified a subgroup of infants developing significant clinical complications and that these infants retained a different LUS pattern over time compared to those in the control group. Given the link between LUS and oxygen need, our observations are in keeping with the work of Laughon et al[19] and Nobile et al[20] who were able to identify early patterns of neonatal respiratory disease on the sole basis of oxygen requirement. In future studies, LUS may reveal its superiority as a descriptor of pulmonary status, being less dependent from pressure support than oxygen need. The LUS relation to pulmonary status is also implied by our logistic regression model that found LUS to be an independent predictor of BPD when calculated already at 7 days of life. In this respect, we confirm previous findings from Canada and Spain on the ability of LUS to predict BPD. Abdelmawla et al[21] described a small retrospective cohort in which a LUS of 6 had a remarkable performance (sensitivity = 78%; specificity = 97%; PPV = 95%; NPV = 82%) in predicting BPD. This predictive power, however, was spread over a wide interval of postnatal age (median age at 5-week ultrasound 5, with interquartile range 2–8). In a cohort of 59 very low birth weight infants (median postmenstrual age [PMA] = 29 weeks), Alonso-Ojembarrena et al[17] showed that a LUS score of 5 at 2 weeks postnatal age (ie, PMA = 31 weeks) predicted BPD with an AUC = 0.93. Similar results were recently published also by Oulego-Erroz et al[22]

and Gao et al[23]. Differences in the LUS predictive power between ours and other investigations may be attributable to the study design and population, LUS protocol, sample size, and BPD definition. In this respect, both the Canadian and the Spanish colleagues used the classic oxygen dependence at 36 weeks' PMA. Later, a new classification that focused on the infant's dependence on flow and/or pressure support at the same PMA became available.[12] We adopted it because it comes from a data-driven approach rather than expert consensus and best predicts late death or severe respiratory morbidity. Our model also reveals that the early prediction power of LUS for BPD increases significantly with gestational age, and we speculate that the PMA-dependent relation between LUS and $Sato_2/Fio_2$ ratio might play a role. In future studies, researchers may evaluate the role of LUS and chest radiograph in neonatal respiratory medicine. Despite its wide use, the latter has a poor correlation with lung function,[24] and when a direct comparison has been attempted, chest radiography was often found to perform worse than ultrasound.[4,25,26]

CONCLUSIONS

LUS is an imaging marker inversely correlated to both the $Sato_2/Fio_2$ ratio and gestational age. LUS allows an early BPD prediction in the 28 to 30 weeks' PMA. Our data and LUS intrinsic handiness suggest that LUS may become a valuable tool in everyday neonatal respiratory care.

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ABBREVIATIONS

AUC: area under the curve
BPD: bronchopulmonary dysplasia
CI: confidence interval
Fio2: fraction of inspired oxygen
LUS: lung ultrasound score
PDA: patent ductus arteriosus
PMA: postmenstrual age
PPHN: persistent pulmonary hypertension of the neonate
RDS: respiratory distress syndrome
$Sato_2$: oxygen saturation

Drs Raimondi, Migliaro, Pierri, Lista, and Dolce conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript; Drs Corsini, Meneghin, Perri, Nobile, Savoia, Varano, Gatto, Lama, Aversa, and Leonardi designed the data collection instruments, collected data, conducted the initial analyses, and reviewed and revised the manuscript; Drs Dani, Carnielli, Mosca, Capasso, and Vento conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; and all authors agree to be accountable for all aspects of the work and approved the final manuscript as submitted.

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