Lung ultrasound immediately after birth predicts the need for surfactant therapy in very- and extremely preterm infants, the DOLFIN Jr Study

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Abstract

Background

Early identification of infants requiring surfactant therapy improves outcomes. We evaluated the accuracy of delivery room lung ultrasound (LUS) to predict surfactant therapy in very- and extremely preterm infants.

Methods

Infants born at <$32^{0/7}$ weeks were prospectively enrolled with parental consent at 2 centres. LUS videos of both sides of the chest were obtained 5-10 minutes, 11-20 minutes, and 1-3 hours after birth. Clinicians were masked to the results of the LUS assessment and surfactant therapy was provided according to local guidelines. LUS videos were graded blinded to clinical data. Presence of unilateral type 1 ('whiteout') LUS or worse was considered test positive. Receiver Operating Characteristic (ROC) analysis compared the accuracy of LUS and an FiO_2 threshold of 0.3 to predict subsequent surfactant therapy.

Results

Fifty-two infants with a median age of $27^{6/7}$ weeks (IQR $26^{0/7}$ to $28^{6/7}$) were studied. Thirty infants (58%) received surfactant. Area under the ROC curve (AUC) for LUS at 5-10 minutes, 11-20 minutes and 1-3 hours was 0.78 (95% CI, 0.66–0.90), 0.76 (95% CI, 0.65-0.88) and 0.86 (95% CI, 0.75-0.97) respectively, outperforming FiO_2 at the 5-10 minute timepoint (AUC 0.45, 95% CI 0.29-0.62, p=0.001). At 11-20 minutes, LUS had a specificity of 95% (95% CI 77-100%) and sensitivity of 59% (95% CI, 39-77%) to predict surfactant therapy. All infants born at 23-$27^{6/7}$ weeks with LUS test positive received surfactant. Twenty-six infants (50%) had worsening of LUS grades on serial assessment.

Conclusions

LUS in the delivery room is feasible and accurately predicts surfactant therapy in infants <$32^{0/7}$ weeks.

Study registration: ACTRN12617001256369

Background

Non-invasive respiratory support has replaced routine mechanical ventilation and surfactant therapy as the initial respiratory strategy for extremely premature infants with respiratory distress syndrome (RDS) [1]. However, over 50% of infants eventually require surfactant and early surfactant decreases the risk of death and significant pulmonary injury in infants with RDS compared to delayed treatment [1–4]. Infants with RDS often have oxygen requirements that increase gradually until a predetermined threshold is reached for surfactant [5]. Thus, identifying infants in the delivery room who will eventually require exogenous surfactant may be beneficial.

Animal studies have shown that immediately after birth, surfactant therapy increases both the uniformity and degree of lung aeration, which increases the surface area for gas exchange [6, 7]. At birth, the surface area for gas exchange is initially low but increases exponentially as the lung aerates [8]. Increasing the fraction of inspired oxygen (FiO_2) increases the partial pressure gradient for oxygen diffusion and counteracts the effect of a low surface area on oxygen exchange of the partially liquid-filled lung. Thus, a higher FiO_2 in the delivery room likely indicates poor lung aeration, whereas surfactant therapy can increase the degree of lung aeration and thereby reduce the oxygen requirement.

Lung ultrasound (LUS) has shown promise as a diagnostic tool for evaluation of newborns with respiratory distress [9–24]. LUS can be performed at the bedside in real time, may be easily repeated in response to clinical changes, and avoids exposure to ionizing radiation [25, 26]. In healthy term infants, serial LUSs show the quick transition from a liquid-filled lung to an aerated lung capable of adequate gas exchange [27–32]. In preterm infants, observational studies have shown that LUS reliably predicts the need for surfactant therapy after admission to the neonatal unit, typically 1–2 hours after birth and that it may be beneficial to guide treatment using LUS [10, 33–36]. The characteristic LUS signs may be identifiable immediately after birth, giving clinicians more time to individualize respiratory management and surfactant therapy. This may include the use of minimally invasive surfactant therapy (MIST) rather than endotracheal intubation in the early stages of RDS [37].

We aimed to characterize changes in LUS images immediately after birth for infants born at < $32^{0/7}$ weeks gestation and evaluate the diagnostic accuracy of LUS in predicting the need for surfactant therapy.

Methods

We performed a prospective, observational study of infants born at < $32^{0/7}$ weeks gestational age between January 2018 and December 2019. Study sites were two perinatal hospitals, Monash Medical Centre (MMC) and the Royal Women's Hospital (RWH), in Melbourne, Australia, together averaging more than 300 very and extremely preterm births per year. This study is reported in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines [38, 39].

Study Design

Infants born at < $32^{0/7}$ weeks without an antenatal diagnosis of significant cardiopulmonary pathology (e.g. diaphragmatic hernia or cyanotic congenital heart malformation) were eligible for participation if a researcher was available to perform LUS scans. Antenatal parental consent was sought if time permitted at both hospitals. At MMC, infants were eligible for written, retrospective parental consent if there was insufficient time to discuss the study prior to birth. The study was approved by the human research ethics committees at both institutions and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001256369).

At both institutions, infants were initially managed with CPAP, using pressures of 5-8cmH_2O and FiO_2 0.3, titrated to maintain SpO_2 91–95%. Infants requiring more support to maintain SpO_2 in this range were considered for intubation and surfactant therapy or minimally invasive surfactant therapy (MIST) [37, 40]. Indications for intubation while on CPAP included frequent apneas requiring stimulation, regardless of FiO2 requirement. Intubation-surfactant-extubation (INSURE) was not practiced at either institution [41]. At the RWH, high flow nasal cannula could be used for primary respiratory support following admission in infants ≥ 30 weeks with an FiO_2 requirement ≤ 0.3 [42]. Nasal intermittent positive pressure ventilation was not used as a primary treatment strategy [43].

Data Collection

We obtained serial LUS video recordings using a GE Venue 50 ultrasound machine (GE Healthcare, Chicago, USA) and a "hockey-stick," L8-18i linear transducer with a depth of 2 cm and a gain of 60. LUS was performed at 5–10 minutes, 11–20 minutes, 1–3 hours, then every 24 hours in the first 72 hours after birth.

The LUS transducer was placed in the infant's axillae with the notch pointed towards the infant's head. The transducer was 3.5 cm long, typically capturing images from 2–3 intercostal spaces. During the first three timepoints, the infants were assessed in a supine position. At subsequent timepoints, the infants could be assessed in either prone or supine positions, thereby minimizing handling. The transducer was adjusted until a "bat sign" was achieved and the image was optimized for the sharpest pleural line, most aeration, and least fluid retention [16, 44, 45]. Interpretation of LUS findings were not provided to the clinical team unless the researcher detected additional pulmonary pathology (e.g. pneumothorax, effusion, congenital defect). Mode of respiratory support, CPAP level or mean airway pressure, and FiO_2 were collected by the researcher at the time of each LUS. We also collected clinical and demographic information until discharge from hospital.

Lung Ultrasound Grading

LUS videos were scored at the end of study recruitment by 2 assessors blinded to all clinical data (SB and DB) using a previously validated system that grades each side of the chest on a scale of type 0–3 (Fig. 1) [9–11, 28, 29, 46]. Along this scale, type 1 (whiteout) is characterized by coalescence of "B-lines" representing retention of lung liquid/atelectasis, and type 3 is characterized by a lack of B-lines and the presence of "A-lines", representing full lung aeration. In instances of score disagreement, a third blinded assessor acted as an arbiter (OK). Unilateral type 1 or worse was considered test positive.

Analysis

In the absence of data allowing formal sample size calculation, we pre-specified a convenience sample of 50 participants for this observational study. Means and standard deviations with Student's t-test for comparisons are reported for normally distributed continuous variables. Medians with interquartile ranges with Mann Whitney U test for continuous variables or Wilcoxon signed rank test for ordinal

variables, are reported when the distribution was skewed. The scores of the right and left side of the chest of each infant at each timepoint were summed and analyzed using a Friedman's test to determine changes in LUS over time. Three investigators, blinded to the infant's clinical condition, independently assigned LUS scores for 100 images. Interobserver agreement was tested using Kendall's W coefficient of concordance. We used Receiver Operating Characteristic (ROC) analysis to determine and compare the accuracy of LUS performed on infants receiving non-invasive ventilation at 5–10 minutes, 11–20 minutes, and 1–3 hours, and of FiO_2 at the time of each LUS, to predict ST using the DeLong method [47]. We used Youden's method to determine the optimum cut-off score for LUS and threshold for FiO_2 [48]. For the selected cut-off values, we report test characteristics in terms of sensitivity, specificity, positive predictive and negative predictive values with corresponding 95% confidence intervals (CIs).

We used the pROC package in *R* version 3.6.2 (R Foundation, Vienna, Austria) and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium) for analysis [49]. Other statistical analyses were performed using IBM SPSS Statistics 21.0 (SPSS, Inc, Chicago, USA). Statistical significance was defined as $p < 0.05$.

Results

Fifty-two infants < $32^{0/7}$ weeks postmenstrual age were enrolled. Demographic and clinical details are shown in Table 1. We included 463 video recordings for analysis with no exclusions due to image quality. There were no pneumothoraces, pleural effusions, or congenital lung malformations. Infants were stable throughout all studies with no significant changes in temperature or oxygen requirement immediately following LUS assessments. Kendall's W coefficient of concordance confirmed excellent inter-rater reliability between three assessors ($W = 0.96$, $p < 0.001$), which was consistent with previous studies [28, 29].

Table 1
Demographic and clinical information based on gestational age at birth.

	Total	23–27 weeks	28–31 weeks
N	52	28	24
GA Weeks ^{days}	$27^{6/7}$ (26–$28^{6/7}$)	26 ($25^{6/7}$-$27^{2/7}$)	29 ($28^{3/7}$-$30^{3/7}$)
Weight (g)	922 (744–1166)	775 (653–925)	1161 (926–1480)
Sex, male (%)	28 (54%)	17 (61%)	11 (46%)
Fetal growth restriction	14 (27%)	6 (21%)	8 (33%)
Two or more doses of antenatal steroids	32 (62%)	21 (75%)	11 (46%)
Antenatal magnesium sulfate	47 (90%)	25 (89%)	22 (92%)
Vaginal birth	16 (31%)	11 (39%)	5 (21%)
Rupture of membranes (hours)	0 (0–6)	0 (0–1)	0 (0–7)
Apgar 1 minute	6 (5–8)	6 (4–7)	8 (6–8)
Apgar 5 minute	8 (7–9)	8 (6–8)	9 (8–9)
Intubation in the delivery room	8 (15%)	7 (25%)	1 (4%)
Surfactant therapy	30 (58%)	22 (79%)	8 (33%)
Intubation (< 72 hours)	20 (38%)	18 (63%)	2 (8%)
Days invasive ventilation	0 (0–8)	8 (0–24)	0 (0–0)
Days invasive and non-invasive ventilation	57 (20–82)	79 (59–95)	19 (5–47)
Chronic lung disease	23 (44%)	17 (61%)	6 (25%)
Death	1 (2%)	1 (4%)	0 (0%)

No LUS images were obtained for 2 infants at the 5–10 minute timepoint due to the absence of an investigator (Fig. 2). Twenty-two infants were managed with non-invasive respiratory support and did not receive surfactant therapy. Ten additional infants did not require intubation but received surfactant therapy via MIST. Twenty infants were intubated by 72 hours after birth, all received surfactant.

Lung ultrasound versus fraction of inspired oxygen to predict surfactant

Diagnostic accuracy evaluation was performed independently for each study timepoint for all infants until they were intubated, upon which subsequent assessments did not contribute to the diagnostic evaluation (Fig. 2). The optimal thresholds for predicting ST across timepoints were type 1 on at least one side of the chest (type 1/2) for LUS, and FiO_2 of 0.3. Using ROC analysis of diagnostic ability (Fig. 3), we found that LUS had an area under the curve (AUC) at 5–10 minutes, 11–20 minutes, and 1–3 hours of 0.78 (95% CI 0.66–0.90), 0.76 (95% CI 0.65–0.88) and 0.86 (95% CI 0.75–0.97) respectively. FiO_2 produced lower AUCs of 0.45 (95% CI 0.29–0.62), 0.60 (95% CI 0.44–0.76) and 0.81 (95% CI 0.68–0.95) at the same three points after birth respectively. There was a statistically significant difference in AUC for LUS compared to FiO_2 at the first (5–10 minute) timepoint ($p = 0.001$), but not at the 11–20 minute ($p = 0.088$) or 1–3 hour timepoints ($p = 0.473$).

Table 2

shows the test characteristics to predict surfactant therapy for type 1/2, type 1/1, and $FiO_2 > 0.3$. Further test characteristics by gestational age subgroup are given in the additional file [see Additional file 1]. Type 1/2 LUS had a specificity of 95% (95% CI 77–100%) and sensitivity of 59% (95% CI 39–77%) at 11–20 minutes to predict surfactant therapy. Type 1/1 LUS had 95% specificity (95% CI 77–100%) at both 5–10 minutes and at 11–20 minutes after birth for predicting surfactant therapy. Type 1/1 LUS reflects more severe lung atelectasis and impaired liquid clearance, thus improving specificity at the cost of sensitivity, which may be desirable in clinical practice.

Surfactant therapy						
Time from birth	Sensitivity			Specificity		
	LUS 1/2	LUS 1/1	$FiO_2 > 0.3$	LUS 1/2	LUS 1/1	$FiO_2 > 0.3$
5–10 min, N = 48	64% (44–81%)	54% (34–72%)	46% (28–66%)	85% (62–97%)	95% (75–100%)	50% (27–73%)
11–20 min, N = 49	59% (39–78%)	44% (25–65%)	30% (14–50%)	95% (77–100%)	95% (77–100%)	77% (55–92%)
1–3 hr, N = 43	86% (64–97%)	81% (58–95%)	57% (34–78%)	73% (50–89%)	86% (65–97%)	95% (77–100%)
Time from birth	Negative predictive value			Positive predictive value		
	LUS 1/2	LUS 1/1	$FiO_2 > 0.3$	LUS 1/2	LUS 1/1	$FiO_2 > 0.3$
5–10 min, N = 48	63% (50–74%)	59% (49–69%)	40% (28–54%)	86% (67–95%)	94% (68–99%)	57% (42–70%)
11–20 min, N = 49	66% (55–75%)	58% (50–67%)	47% (39–56%)	94% (70–99%)	92% (63–99%)	62% (38–81%)
1–3 hr, N = 43	84% (64–94%)	83% (66–92%)	70% (59–79%)	75% (60–86%)	85% (66–94%)	92% (63–99%)

Table 2: Test characteristics at each study timepoint to independently predict surfactant therapy. Test positive for lung ultrasound (LUS) 1/2 is type 1 grade or worse (i.e. grade 0 or 0.5) on either side of the chest. Test positive for LUS 1/1 is type 1 or worse on both sides of the chest. Results are presented as

test characteristics with 95% confidence intervals. Min = minutes, hr = hours, FiO_2 = fraction of inspired oxygen.

False positives and false negatives to predict surfactant: LUS and FiO_2

Eleven infants with an FiO_2 requirement > 0.3 in the delivery room did not receive surfactant therapy and were considered false positives for FiO_2 requirement. Ten of the 11 (91%) infants had LUS type 2/2 or better and were correctly identified by LUS as not needing surfactant therapy. There were 20 infants with an FiO_2 requirement < 0.3 in the delivery room who eventually received surfactant therapy and were considered false negatives for FiO_2 requirement. Fourteen of the 20 (70%) infants had LUS type 1/2 or worse and were correctly identified by LUS as needing surfactant therapy.

Eighty-five and 95% of infants who did not receive ST had LUS 2/2 or better at 5–10 and 11–20 minutes respectively. Three infants with type 2/2 at the 1–3 hour assessment who received ST were 23–27 weeks (Fig. 4). Two were intubated for apneas with a low FiO_2 requirement and received surfactant after intubation. The third received ST via MIST. No infant ≥ 28 weeks with type 2/2 or better after neonatal intensive care unit (NICU) admission received ST. All infants born at $23–27^{6/7}$ weeks with type 1/2 LUS or worse received ST. There were 3 infants with type 1/2 or worse in the delivery room who did not receive ST and were considered false positives. All three infants were ≥ 30 weeks and ≥ 1400 g at birth.

Lung ultrasound over time and “backsliding”

The median LUS grade assessed across all study participants (N = 52) changed over time, with the lowest median score measured at 1–3 hours after birth ($p < 0.001$), which was significantly different from all other timepoints (5–10 min, $p = 0.009$; 11–20 min, $p = 0.005$; 12–24 hour, $p = 0.001$, 24–72 hour $p = 0.001$, Fig. 5). No differences were seen between the other timepoints.

Twenty-six infants (50%) had lower LUS grades on subsequent assessments compared to their previous LUS score, either in the delivery room (11–20 minutes, 6 infants) or on admission to the NICU (1–3 hours, 20 infants). We have termed this “backsliding” [29]. Infants with backsliding while on CPAP had a longer duration between rupture of membranes and birth ($p = 0.046$), otherwise, there were no significant predictive patient characteristics for backsliding while on CPAP (Table 3). Infants with backsliding while on CPAP were more likely to require intubation than infants on CPAP who did not have backsliding ($p = 0.01$).

Table 3
Comparisons, outcomes, and test characteristics of infants on CPAP with backsliding versus without backsliding the 1–3 hour assessment. Infants diagnosed with chronic lung disease were receiving respiratory support (positive pressure or supplemental oxygen) ≥ 36 weeks corrected gestational age.

	Backsliding on CPAP N = 21	**No backsliding N = 25**	**p-value**
GA Weeks ^{days}	$27^{6/7}$ ($26^{1/7}$-$28^{6/7}$)	$28^{2/7}$ ($27^{2/7}$-$29^{1/7}$)	0.79
Weight (g)	924 (821–1325)	1086 (910–1312)	0.96
Gender, male, n, (%)	15 (71%)	12 (46%)	0.06
Intrauterine growth restriction, n, (%)	6 (29%)	7 (27%)	0.50
Two or more doses of antenatal steroids, n, (%)	15 (65%)	15 (58%)	0.41
Vaginal birth, n, (%)	5 (24%)	9 (35%)	0.85
Rupture of membranes (hours)	0 (0–1)	1 (0–19)	**0.05**
APGAR 1 minute	6 (5–8)	6 (5–8)	0.69
APGAR 5 minute	8 (8–9)	8 (7–9)	0.58
Intubation in the delivery room n, (%)	2 (10%)	0 (0%)	0.12
Surfactant therapy, n, (%)	14 (67%)	10 (40%)	0.07
Intubation (< 72 hours), n, (%)	10 (48%)	4 (16%)	**0.02**
Doses of surfactant, n, (%)	1 (1–2)	0 (0-0.5)	**0.04**
Days invasive ventilation, n, (%)	0 (0–9)	0 (0-0.3)	0.09
Days invasive and non-invasive ventilation, n, (%)	57 (9–83)	55 (28–69)	0.80
Chronic lung disease or death, n, (%)	10 (48%	9 (36%)	0.43

Seven of the eight (88%) infants intubated in the delivery room had backsliding following intubation, prior to the administration of surfactant in the NICU. Two of these infants had backsliding twice, seen at 11–20 minutes while on CPAP and, again, after intubation, at the 1–3 hour timepoint.

There were 10 infants that had a grade of 0.5 on at least one side of the chest, at a minimum of one timepoint. All 10 infants received surfactant therapy and 9/10 were intubated. No grades of 0.5 were seen at 5–10 minutes. In 4 infants, type 0.5 was observed only after intubation including the only infant with type 0.5 at 11–20 minutes.

Response to surfactant therapy and lung ultrasound

Thirty infants received surfactant. Two infants were intubated prior to the first LUS assessment. The first dose was given at a median time of 2.5 hours (IQR 2-3.4) with median FiO_2 of 36.5% (IQR 28–49%). Adding the LUS score of both sides of the chest together, the median LUS score prior to receiving surfactant while on CPAP was 2 (IQR 2–2), which improved to 3 (IQR 2–4, p = 0.001) at a median of 2.5 hours (IQR 0.5–21) after surfactant was given. Supplemental oxygen decreased to 25% (IQR 21–28, p = 0.001) after surfactant therapy. Five out of thirty infants had backsliding after surfactant therapy was given. Two of these infants had received MIST and showed backsliding while on CPAP, backsliding was seen in the other 3 after intubation.

Discussion

This is the first delivery room study to assess the utility of LUS and report on the evolution of LUS score after birth in very- and extremely preterm infants. We found that LUS is feasible to perform, has good diagnostic accuracy for surfactant therapy using a single axillary view, and can track the progress of lung aeration over the first few hours after birth.

Previous studies have shown that LUS performed upon admission to neonatal intensive care can predict the need for surfactant therapy [10, 22, 33, 34]. A recently published trial suggests that using LUS after NICU admission to guide surfactant therapy decreased the time to receive surfactant and increased the clinical response to surfactant versus using an FiO_2 threshold in infants < 32 weeks [36]. Our study suggests that delivery room LUS may identify infants requiring surfactant therapy even sooner after birth, while also widening the diagnostic capability to include the significant proportion of infants who are intubated and/or receive surfactant therapy prior to NICU admission.

Early surfactant administration in premature infants with RDS have improved outcomes [1, 4, 37, 50–53]. Lung ultrasound changes consistent with RDS may precede clinical signs which may not appear until several hours after birth. In the delivery room, an FiO_2 threshold of 0.3 produced more false positives (11 infants) and false negatives (20 infants) than LUS. LUS correctly identified that 10/11 of the FiO_2 false positives would not need surfactant and that 14/20 of the FiO_2 false negatives would need surfactant, including 100% of the extremely preterm infants.

Furthermore, we found that surfactant therapy significantly improved the LUS grading indicating better lung aeration. This is consistent with the observation that surfactant therapy greatly increases the uniformity of lung aeration and the distribution of ventilation in preterm rabbits [6]. As such, rapid identification of poor lung aeration using LUS may facilitate targeted surfactant in the delivery room to infants likely to benefit most from the treatment.

The time related changes in LUS grading and the relatively high incidence of backsliding is particularly interesting and provides further evidence that lung aeration is not a unidirectional process. Indeed, it has

been well documented in animal studies that airways can refill with liquid, particularly in the immature lung in the absence of an end-expiratory pressure [8]. In keeping with this, duration of rupture of membranes was shorter in the group with backsliding on CPAP compared to infants with no backsliding on CPAP in a univariate comparison of risk factors. As such, the finding that a high proportion (88%) of infants displayed backsliding following intubation in the delivery room, suggests that an increase in positive end-expiratory pressure may have reversed backsliding in infants being managed with invasive ventilation [54]. Thus, further studies are warranted to determine whether LUS has utility for determining optimal PEEP levels in intubated and ventilated infants. Similarly, 21 of the 26 infants demonstrating backsliding were initially managed on CPAP, which raises the question as to whether the introduction of CPAP or higher CPAP levels may have reversed the backsliding. LUS may be able to provide critical feedback in real time to optimize respiratory management in neonates and should be the aim of future studies [54].

The finding that overall LUS grading was lowest at 1-3hours after birth, even compared with 5–10 minutes after birth, raises several very important questions. In particular, as spontaneous breathing is primarily responsible for lung aeration after birth and the clearance of liquid that re-renters the airways between breaths, backsliding at 1–3 hours after birth may indicate breathing fatigue leading to airway reflooding and/or atelectasis. Indeed, as infants with backsliding while on CPAP were more likely to be intubated, backsliding may provide an early signal that an infant's respiratory drive is unable to maintain lung aeration or that distending pressure from the CPAP was insufficient. We feel backsliding warrants consideration in future studies and validation by other investigators.

Like backsliding, LUS type 0.5 was seen most commonly in intubated infants. Type 0.5 was previously observed in term infants as they initiated breathing after birth and is theorized to represent atelectasis [28]. Atelectasis may be caused by more severe RDS, a poorly positioned endotracheal tube, or loss of functional residual capacity in infants who receive muscle relaxants prior to intubation [55, 56].

Our study has several limitations, including the observational design, a small cohort, and a clinically important variation in gestational age. Nevertheless, the fact that over 50% of infants were < 28 weeks gestation allows generalization of our findings to extremely preterm infants. A further strength was that LUS score was graded blind to the clinical course. It will be important to validate the accuracy and reliability of our findings when LUS is performed in real-time at the bedside, alongside clinical information by a wider range of clinicians.

Future studies are needed to investigate whether adjustments in respiratory support, for example increased positive end expiratory pressure and/or early targeted surfactant, change the appearance of LUS in very preterm infants with signs of poor lung aeration. LUS may be able to optimize individual patient care by enabling clinicians to improve both the timeliness and appropriate targeting of interventions. Such work would establish the basis for larger trials investigating clinically important outcomes for preterm infants managed using LUS as an auxiliary tool in the delivery room.

Conclusions

Lung ultrasound in the delivery room is a specific predictor of failure of non-invasive respiratory support, especially in extremely preterm infants. Earlier detection of infants needing an increase in CPAP pressure or surfactant may improve clinical outcomes, but larger studies are needed.

Abbreviations

AUC
Area under the receiver operating characteristics curve
CI
Confidence interval
CPAP
Continuous positive airway pressure
FiO_2
Fraction of inspired oxygen
IQR
Interquartile range
LUS
Lung ultrasound
MIST
Minimally invasive surfactant therapy
MMC
Monash Medical Centre
NICU
Neonatal intensive care unit
PEEP
Positive end expiratory pressure
ROC
Receiver Operating Characteristics
RWH
Royal Women's Hospital

Declarations

Ethics approval and consent to participate

The study was approved by the human research ethics committees at both the Royal Women's Hospital, Melbourne, Victoria (reference number 16/35), and Monash Medical Centre, Clayton, Victoria (reference number RES-18-0000-693A). At both study centres antenatal parental consent was sought prior to birth

where possible. At Monash Medical Centre, infants were eligible for written, retrospective parental consent if there was insufficient time to discuss the study prior to birth.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

Substantial contributions to the conception or design of the work: DB, PD, OK, SR, SH, GP, SK. Acquisition, analysis or interpretation of data: SB, DB. Drafting the work or revising it critically for important intellectual content: all authors. All authors read and approved the final manuscript.

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Figures

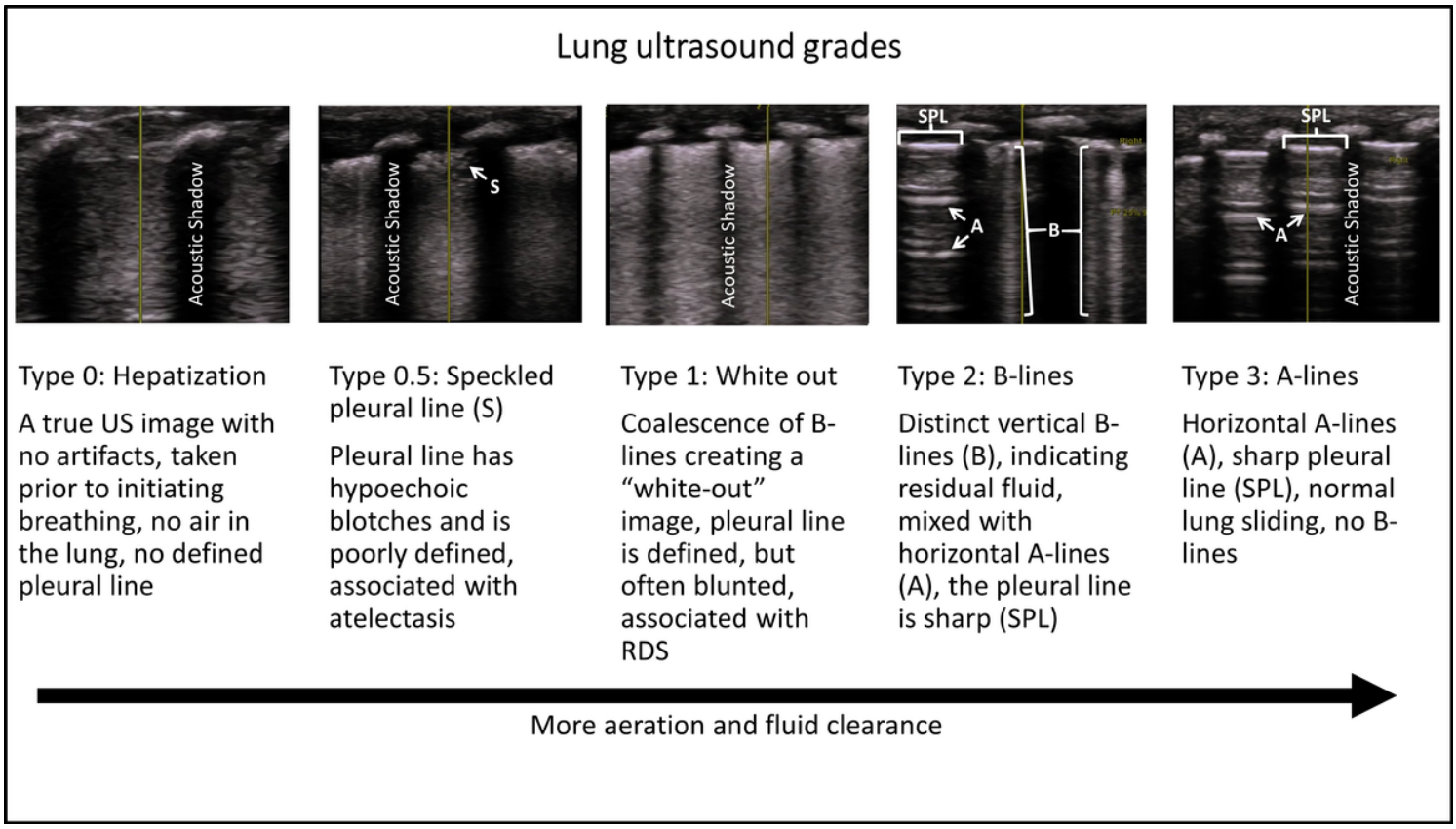

Figure 1

Grading system for lung ultrasound video recordings. Type 3 is seen in healthy lungs with a sharp pleural line, full aeration and liquid clearance, characterized by a lack of B-lines and the presence of horizontal, hyperechoic, repetitive A-lines. Normal lung motion with respirations, called lung sliding of the pleural line, should be present to distinguish type 3 lungs from an air leak syndrome. Type 2 is characterized by the discrete vertical B-lines, arising from a clearly defined pleural line, that cover A-lines. A-lines can be seen between the discrete B-lines. Type 1 images are created by the coalescence of vertical B-lines that produce a uniform, hyperechoic image called the "white-out" lung. A-lines are not visible in type 1 images. Type 1 is associated with respiratory distress syndrome. Type 0.5 and type 0 are associated with partially aerated lungs and liquid filled lungs, respectively. These images have been seen transiently as infants initiate breathing after birth, prior to establishment of the pleural line. Type 0.5 depicts the pleural line with a patchy appearance with poor definition, consisting of speckled hyperechoic areas mixed with hypoechoic lung tissue. Type 0 has been seen prior to the initiation of breathing and establishment of the pleural line. This is a true US image (no air artifacts) as the US beam passes exclusively through liquid and is described as lung hepatization.

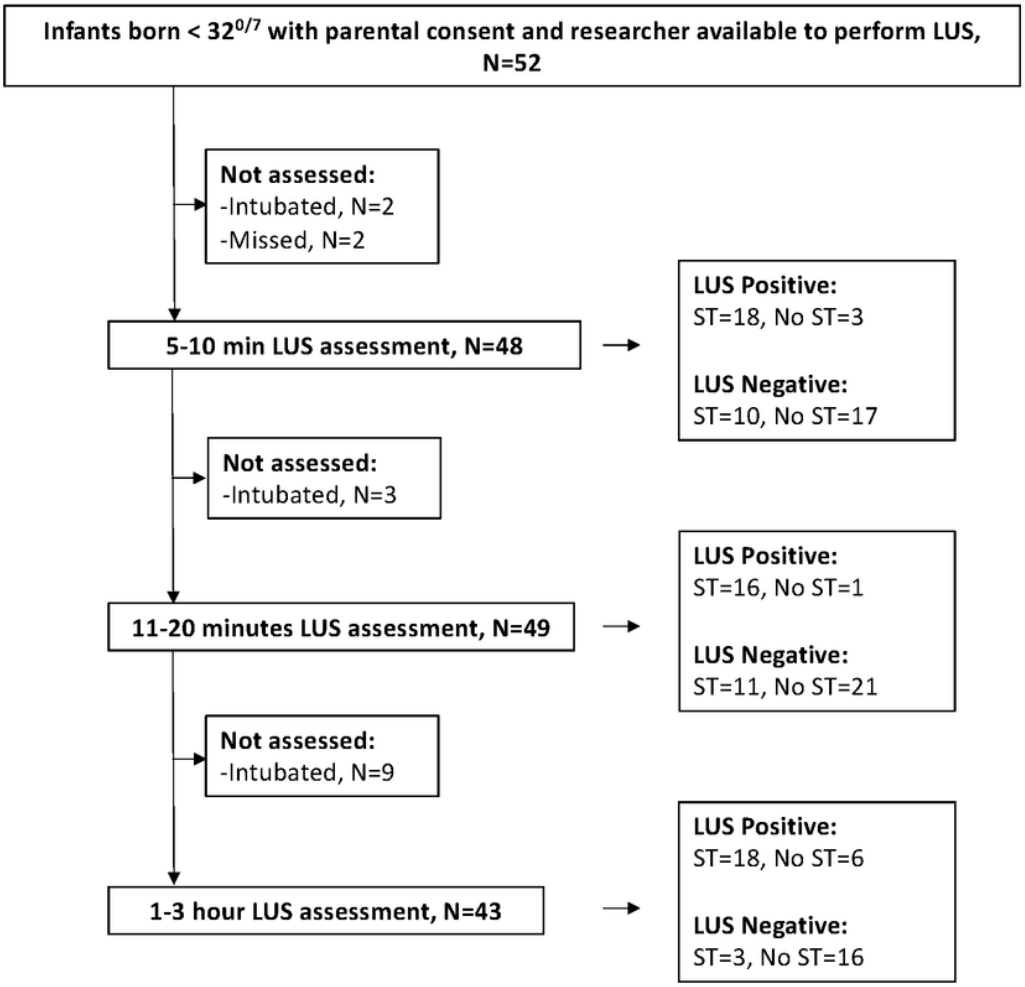

Figure 2

Participant flow diagram. Min=minutes, LUS=lung ultrasound, ST=surfactant therapy.

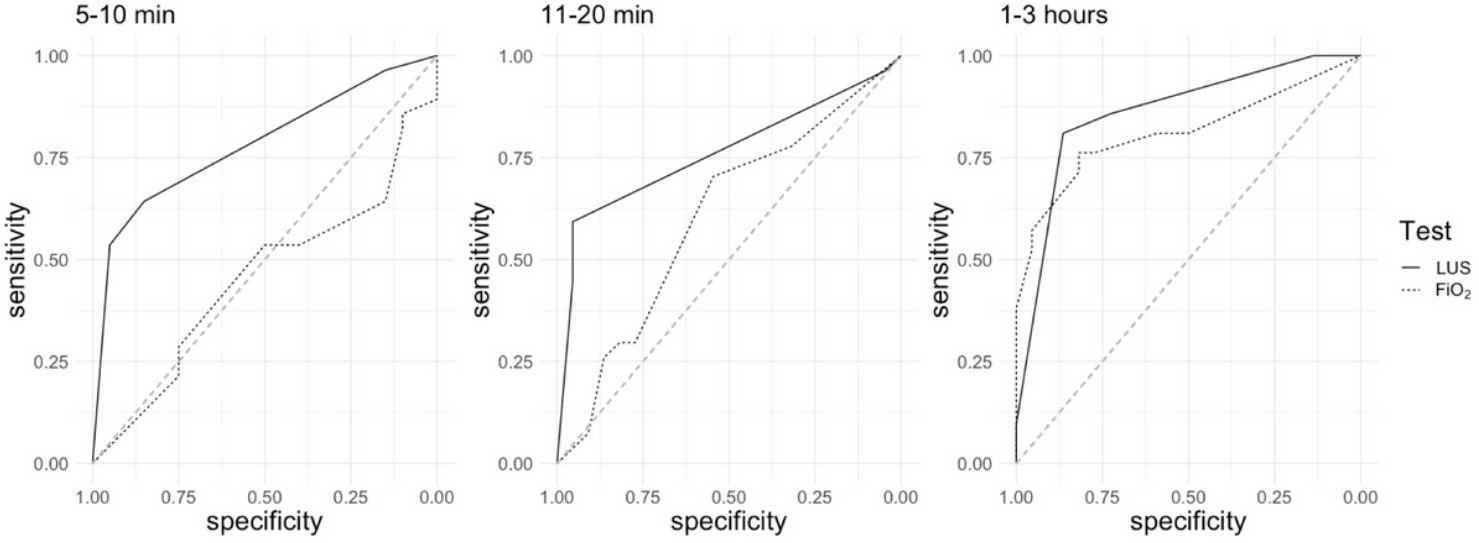

Figure 3

Receiver Operating Characteristics curves for prediction of surfactant replacement therapy by lung ultrasound score (LUS, solid line) and fraction of inspired oxygen (FiO2, interrupted line) at the 3 study timepoints (a,b and c, min=minutes). The diagonal interrupted line shows prediction by chance (Area Under the Curve=0.5).

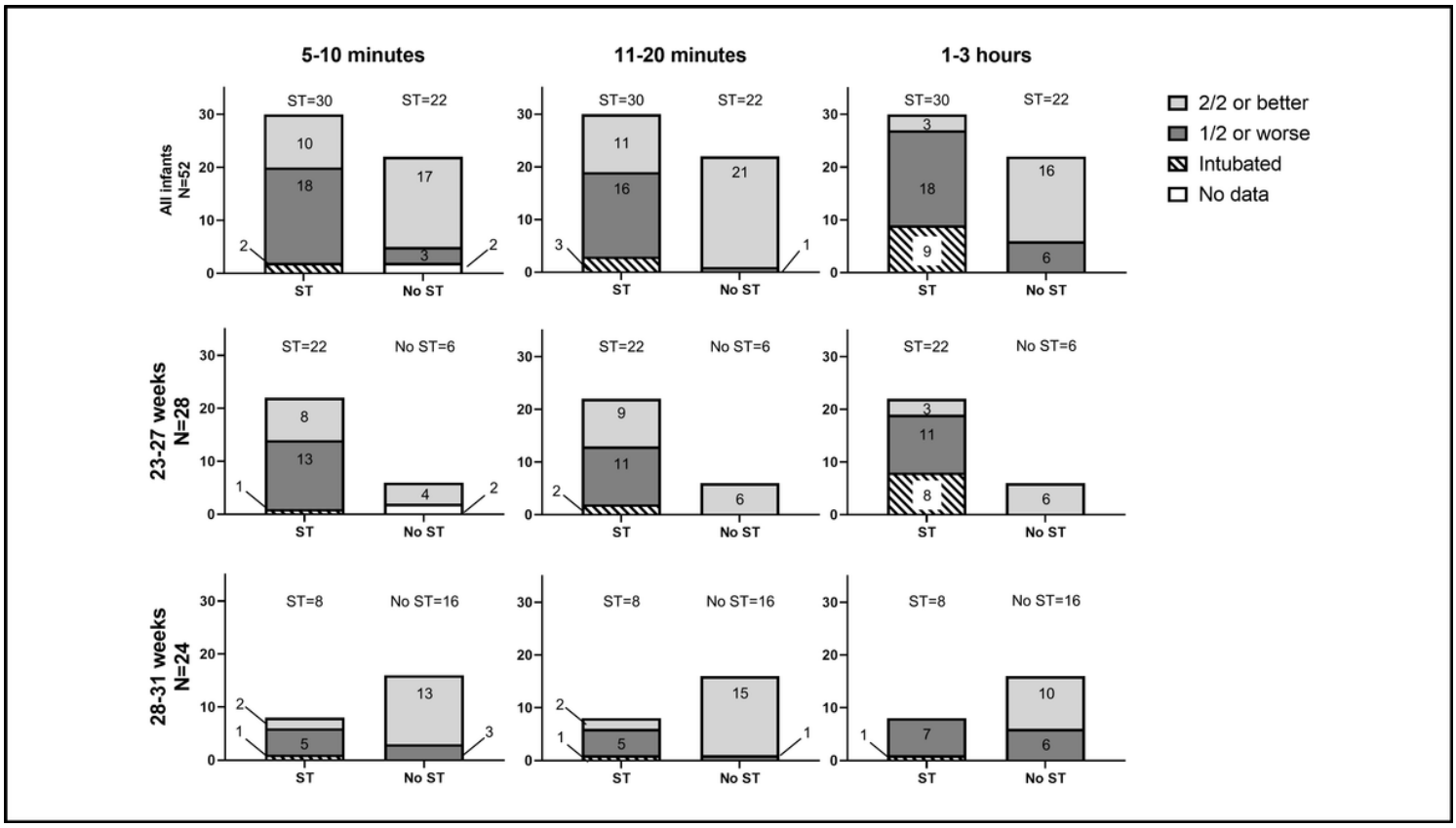

Figure 4

Distribution of lung ultrasound grades at each study timepoint for infants who did and did not subsequently receive surfactant. Top panel shows all infants, middle and lower panels show data within gestational age subgroups. In two infants, the researcher was unable to acquire LUS images at 5-10 minutes after birth. ST: surfactant replacement therapy, 1/2: type 1 or worse on at least one side of the chest, 2/2: type 2 or better on both sides of the chest.

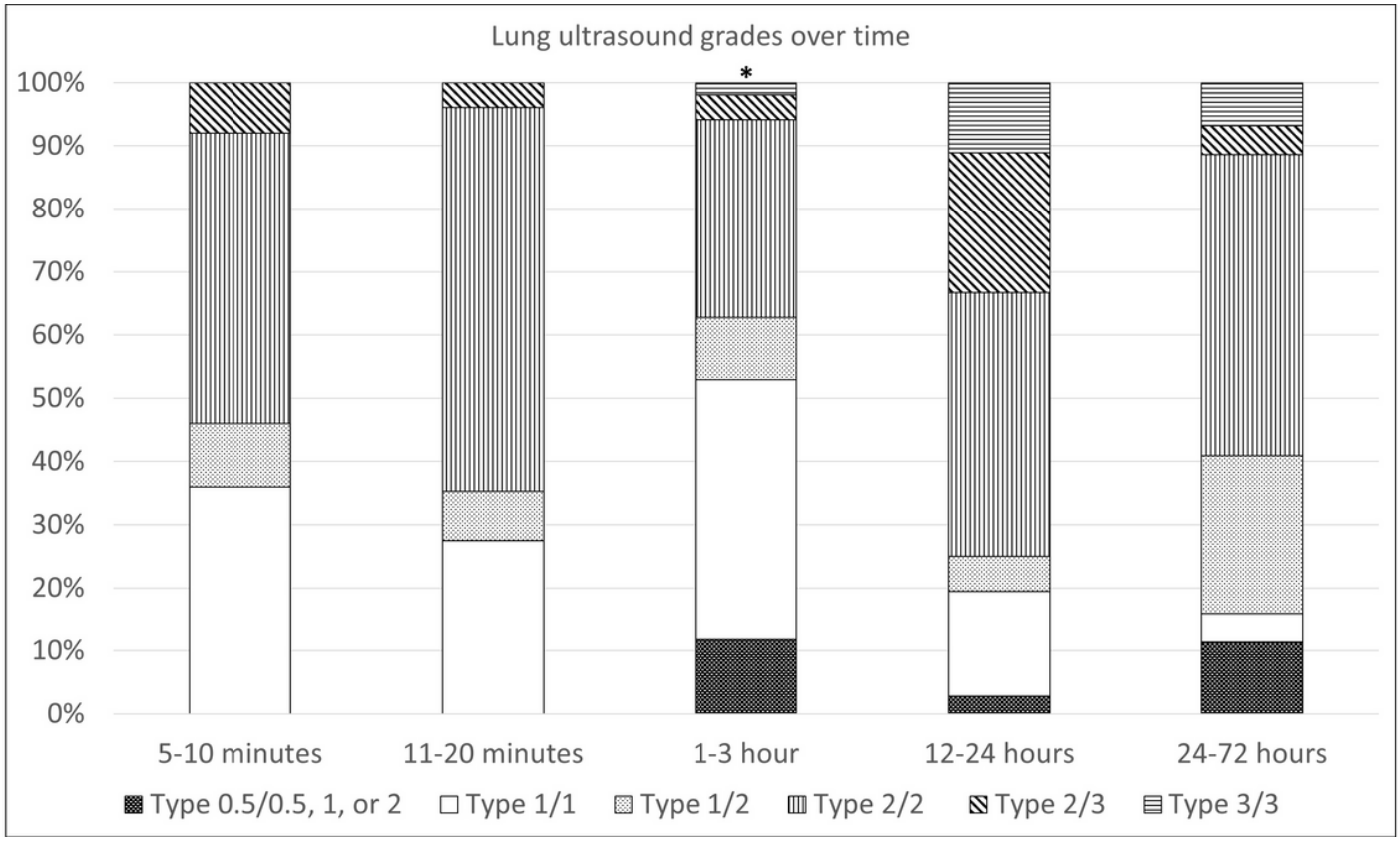

Figure 5

Changes in lung ultrasound over time determined by combining the grade for the right and left side of the chest. All infants were combined for this analysis (N=52) regardless of level of respiratory support. Lung ultrasound grades at 1-3 hours after birth were significantly lower than the other timepoints. There were no differences between the any other timepoints.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GraphAbs.pdf
- AdditionalFile1.docx