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INTEGRATED STUDY MASTER´S THESIS

Impact of Lung Ultrasound Implementation in Preterm Neonates

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2. Abbreviations

- AAP – American Academy of Paediatrics
- AUC – Area Under the Curve
- BPD – Bronchopulmonary Dysplasia
- CI – Confidence Interval
- CPAP – Continuous Positive Airway Pressure
- CXR – Chest X-Ray
- ET – Endotracheal Tube
- FiO_2 – Fraction of Inspired Oxygen
- FRC – Functional Residual Capacity
- GA – Gestational Age
- IN-SUR-E – Intubation Surfactant Extubation strategy
- IQR – Interquartile Range
- IVH – Intraventricular Haemorrhage
- LISA – Less Invasive Surfactant Administration
- LUS – Lung Ultrasound
- LUS score – Lung Ultrasound Score
- MV – Mechanical Ventilation
- NICU – Neonatal Intensive Care Unit
- NIPPV – Nasal Intermittent Positive Pressure Ventilation
- NIV – Non-Invasive Ventilation
- NRS – Non-Invasive Respiratory Support
- NPV – Negative Predictive Value
- PB – Preterm Birth
- PEEP – Positive End-Expiratory Pressure
- POCUS – Point-of-Care Ultrasound
- PPV – Positive Predictive Value
- PPROM – Preterm Premature Rupture of Membranes
- RDS – Respiratory Distress Syndrome
- ROP – Retinopathy of Prematurity
- SD – Standard Deviation
- TTN – Tachypnoea of the Newborn
- OR – Odds Ratio
- IRR – Incidence Rate Ratio
- ROC – Receiver Operating Characteristic

3. Summary

Background

Lung ultrasound (LUS) is an increasingly used bedside diagnostic tool in neonatal intensive care units (NICUs) for assessing respiratory disorders in preterm neonates and supporting the choice of respiratory treatment. Although the lung ultrasound score (LUS score) is well described in international literature, data on the standardised use of this tool in clinical practice in Lithuania are lacking. This is the first study in Lithuania evaluating the impact of standardised LUS protocol implementation on the choice of respiratory therapy.

Aim

The aim of this study was to evaluate the impact of lung ultrasound implementation on the choice of respiratory therapy in preterm neonates and to assess the safety of this diagnostic tool by comparing short-term clinical outcome rates.

Objectives

- To compare surfactant use and administration rates before and after lung ultrasound implementation.
- To assess the association between lung ultrasound implementation and the choice of respiratory support modality.
- To compare short-term clinical outcome rates before and after the implementation of a standardised lung ultrasound protocol.

Results

The study included 172 preterm neonates: 84 before and 88 after LUS protocol implementation. Baseline neonatal characteristics were generally similar between the two eras, although some maternal and pregnancy-related factors differed. After LUS protocol implementation, the need for mechanical ventilation (MV) after birth decreased, while the initiation rate of continuous positive airway pressure (CPAP) remained similar. However, the duration of both MV and CPAP was longer after LUS implementation. Surfactant administration frequency and instillation technique did not differ significantly between eras. The predictive value of the fraction of inspired oxygen (FiO_2) for surfactant administration improved after LUS implementation. In the post-LUS cohort, the LUS score was an independent predictor of surfactant administration, whereas the FiO_2 threshold alone was not statistically significant in the adjusted model. Regarding safety, the rates of common prematurity-related complications, including intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) and sepsis did not differ significantly between the pre-LUS and post-LUS eras.

Conclusions

In this single-centre retrospective cohort study, the implementation of a standardised LUS protocol was associated with changes in the choice of respiratory therapy, including a reduced need for MV initiation. We demonstrated that LUS is a safe diagnostic tool, and its implementation was not associated with increased complication rates. After protocol implementation, LUS score-based lung assessment also provided clinically useful information for surfactant decision-making. Further prospective multicentre studies are needed to confirm these findings.

Keywords

Lung ultrasound; lung ultrasound score; preterm neonate; neonatal intensive care unit; respiratory distress syndrome; surfactant; mechanical ventilation.

4. Santrauka

Pagrindimas

Plaučių ultragarsinis tyrimas (LUS) – tai diagnostinis prie paciento lovos naudojamas įrankis, kuris vis dažniau taikomas naujagimių intensyviosios terapijos skyriuose (NITS) neišnešiotų naujagimių kvėpavimo sutrikimams vertinti ir gydymo metodui pasirinkti. Nors plaučių ultragarsinis tyrimas LUS yra plačiai aprašytas tarptautinėje literatūroje, duomenų apie šio įrankio standartizuotą naudojimą klinikinėje praktikoje Lietuvoje nėra. Tai pirmas tyrimas Lietuvoje vertinantis standartizuoto LUS protokolo įdiegimo poveikį kvėpuojamosios terapijos pasirinkimui.

Tikslas

Šio tyrimo tikslas – įvertinti plaučių ultragarsinio tyrimo įdiegimo poveikį neišnešiotų naujagimių kvėpavimo terapijos psirinkimui ir šio diagnostinio įrankio saugumą, palyginant trumpalaikių klinikinių baigčių dažnius.

Uždaviniai

- Palyginti surfaktanto vartojimą ir jo skyrimo dažnį prieš plaučių ultragarsinio tyrimo įdiegimą ir po jo.
- Įvertinti ryšį tarp plaučių ultragarso taikymo ir kvėpavimo palaikymo metodo pasirinkimo.
- Palyginti trumpalaikių klinikinių baigčių dažnius prieš ir po plaučių ultragarsinio tyrimo standartizuoto protokolo įdiegimą.

Rezultatai

Į tyrimą įtraukti 172 neišnešioti naujagimiai: 84 – prieš LUS protokolo įdiegimą ir 88 – po jo įdiegimo. Pradinės naujagimių charakteristikos tarp laikotarpių iš esmės buvo panašios, tačiau kai

kurie motinos ir nėštumo veiksniai skyrėsi. Įdiegus LUS protokolą, mechaninės ventiliacijos (MV) poreikis po gimimo sumažėjo, o nuolatinio teigiamo slėgio kvėpavimo takuose terapijos (CPAP) taikymo pradžios dažnis išliko panašus. Vis dėlto tiek MV, tiek CPAP trukmės po LUS įdiegimo buvo ilgesnės. Surfaktanto skyrimo dažnis ir instiliacijos metodas tarp laikotarpių reikšmingai nesiskyrė. Tačiau įkvėpiamo deguonies frakcijos (FiO_2) prognostinė vertė surfaktanto skyrimui po LUS įdiegimo pagerėjo. Po LUS įdiegimo tirtoje kohortoje LUS balas buvo nepriklausomas surfaktanto skyrimo prediktorius, o vien FiO_2 slenkstinė vertė koreguotame modelyje nebuvo statistiškai reikšminga. Vertinant saugumą, dažnų su neišnešiotumu susijusių komplikacijų – intraventrikulinės hemoragijos (IVH), neišnešiotų naujagimių retinopatijos (ROP), bronchopulmoninės displazijos (BPD) ir sepsio – dažniai tarp laikotarpių prieš LUS įdiegimą ir po jo reikšmingai nesiskyrė.

Išvados

Šiame vieno centro retrospektyviniame kohortos tyrime standartizuoto LUS protokolo įdiegimas buvo susijęs su kvėpavimo terapijos pasirinkimo pokyčiais, įskaitant sumažėjusį MV inicijavimo poreikį. Mes pademonstravom, kad LUS yra saugus diagnostinis įrankis, ir jo įdiegimas nėra susijęs su komplikacijų dažniu. Po protokolo įdiegimo LUS balu pagrįstas plaučių vertinimas taip pat suteikė kliniškai naudingos informacijos priimant sprendimus dėl surfaktanto skyrimo. Reikalingi tolesni prospektyvūs daugiacentriai tyrimai, siekiant patvirtinti šiuos rezultatus.

Reikšminiai žodžiai

Plaučių ultragarsinis tyrimas; plaučių ultragarsinis balas; neišnešiotas naujagimis; naujagimių intensyviosios terapijos skyrius; respiracinio distreso sindromas; surfaktantas; mechaninė ventiliacija.

5. Introduction

Extremely preterm infants often need respiratory support to assist the cardiopulmonary adaptation that takes place during the first hours after birth [1]. Newly updated resuscitation guidelines focus on supporting the postnatal transition, with the establishment of lung aeration, effective breathing or ventilation, and optimising pulmonary blood flow [2]. Respiratory distress is the most frequent indication for admission to the NICU. Rapid recognition of the underlying cause and initiation of appropriate treatment are important for improving both short- and long-term outcomes [3,4].

MV is a cornerstone of therapy in modern NICUs [5]. However, MV can lead to severe complications, including barotrauma, volumetric injury, ventilator-associated pneumonia, air leak syndrome, hyperventilation, and BPD [6–8]. Neonatologists must be able to select and manage both invasive and non-invasive respiratory support (NRS) appropriately to treat a wide spectrum of pulmonary diseases. Current NICU practice favours the use of NRS in preference to MV whenever clinically

feasible [9]. An important challenge for NICU clinicians is determining which neonates are suitable candidates for non-invasive ventilation (NIV) and which require MV [4,10].

Several studies have demonstrated that implementing LUS in the NICU can aid in these decisions. LUS can characterise different causes of infant respiratory distress dynamically [11–13]. LUS is widely available, can be performed directly at the bedside without the need for NICU transfer, and does not expose infants to ionising radiation [14]. Furthermore, it can be used to assess the efficacy of MV, thereby guiding ventilation settings [15].

Overall, LUS allows more frequent monitoring of treatment response and helps clinicians detect improvement or progression of pulmonary pathology. It also enables real-time assessment of lung status and supports the day-to-day management of neonates with respiratory failure [16].

Despite growing evidence supporting the value of LUS in neonatal respiratory assessment, its impact on real-world clinical decision-making in the NICU remains unclear. Data evaluating how the implementation of LUS influences respiratory management decisions and short-term clinical outcomes in preterm neonates are limited. Assessing these effects in a real-world NICU setting is therefore clinically relevant.

6. Literature Review

6.1 Background

The World Health Organisation defines prematurity as any infant born alive before 37 completed weeks of gestation, categorising prematurity as moderate to late preterm (32 to < 37 weeks), very preterm (28 to <32 weeks), or extremely preterm (<28 weeks) [17].

Table 1. Newborn Terminology. Adapted from [17,18].

Description		**Weeks of gestation**
Early term infant	Extremely preterm	Less than 28+0
	Very preterm	28+0 to 31+6 weeks of gestation
	Moderate to late preterm	32+0 to 36+6 weeks of gestation
Full term infant		39+0 to 40+6 weeks of gestation
Late term infant		41+0 to 41+6 weeks of gestation
Post term infant		42+0 week of gestation and beyond

6.2 Lung Development and Maturation

Understanding lung development and maturation is central in caring for preterm infants, because lung function is one of the main determinants of early survival and later respiratory morbidity. Early observations of surface-active material in pulmonary foam and lung extracts set the stage for the

surfactant concept, and a major milestone came in 1959 when Avery and Mead linked respiratory failure in infants with respiratory distress syndrome (RDS) to reduced surfactant levels in lung extracts [19].

Once the relationship between atelectasis, hyaline membranes, and surfactant deficiency was recognised, international research accelerated, leading to clinically useful ways to assess lung maturity before birth: Gluck and colleagues introduced the lecithin-sphingomyelin ratio in 1971, and phosphatidylglycerol was later identified as an additional marker of lung maturity testing [20].

In parallel, applying respiratory physiology improved outcomes, for example, when Gregory and colleagues introduced CPAP to help maintain functional residual capacity (FRC) in infants with RDS; antenatal corticosteroids were another breakthrough, with Liggins and Howie reporting a reduced incidence of RDS after maternal corticosteroid treatment in 1972 [21]. In this context, LUS may be regarded as a more recent development in the same trajectory of physiology-based neonatal respiratory care [22].

Embryogenesis of the Respiratory Tract

From a structural development perspective, the lung begins very early as a ventral bud from the foregut just below the laryngotracheal sulcus, and early branching and morphogenesis are tightly controlled by epithelial-mesenchymal interactions [23]. Differentiation of endodermal cells into airway epithelial lineages requires coordinated expression of transcription factors and developmental gene families [24]. Early development is also dependent on multiple growth and differentiation pathways, and disruption of these regulators can lead to severe abnormalities ranging from altered branching to lung hypoplasia or even aplasia, while normal airway branching progresses in a timed sequence with lobar and segmental airway formation over the first weeks of fetal life. During this phase, pulmonary vascular development also proceeds in parallel, branching from the sixth aortic arch and forming a vascular plexus within the mesenchyme [25].

During the pseudoglandular stage (Figure 1), approximately the fifth to the eighteenth week, the conducting airway tree undergoes extensive branching, and cellular differentiation begins in a proximal-to-distal pattern, with multiple signalling pathways regulating morphogenesis and regional growth [26].

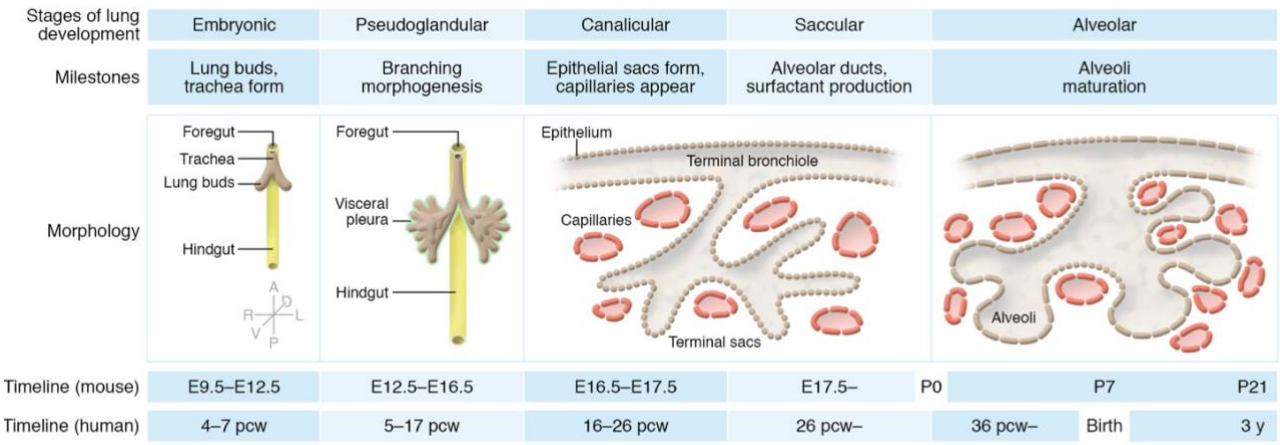

Figure 1. Timeline of five stages of lung development in mice and humans. Adapted from [27].

The canalicular stage (Figure 1), roughly 16 to 25 weeks, is especially relevant for viability because it represents the transition from a pre-viable lung to a potentially viable lung capable of gas exchange [28]. Key events in this phase include formation of the acinus, epithelial differentiation with development of the future air-blood barrier, and the beginning of surfactant synthesis in recognisable type II cells [25]. The surrounding mesenchyme becomes progressively more vascular and closely opposed to the airway epithelium, and the capillary network remodels toward a single capillary layer; failure of this fusion process can result in severe hypoxemia due to alveolar-capillary dysplasia. During this stage, many epithelial cells are still intermediate — meaning they are not fully developed as type I or type II cells [29].

The saccular stage (Figure 1) spans the potentially viable period from about 24 weeks to term, and this is the developmental window that overlaps directly with extreme prematurity; terminal saccules elongate and widen, and alveolarization begins around 32 weeks in the fetal human lung [23]. Alveolar numbers then increase rapidly from around 32 weeks to term, reaching tens of millions of alveoli by term (with wide physiologic variability), creating the anatomical potential for effective gas exchange and, therefore, fetal viability [30]. Notably, viable gas exchange can sometimes be supported even at 22-23 weeks if structural maturation is sufficiently advanced, and antenatal corticosteroids improve survival at these very early gestational ages (GA), indicating that maturation of gas exchange capacity can be induced earlier than previously assumed [31].

LUS findings can be linked to the developmental physiology outlined in this chapter. In very preterm infants born during the saccular stage, LUS performed within the first hour of life may show features of severe RDS, such as coalescent B-lines and air bronchograms, reflecting diffuse atelectasis due to surfactant deficiency [32]. By contrast, in late preterm and term neonates, separated B-lines are more consistent with delayed fetal lung fluid clearance as seen in tachypnoea of the newborn (TTN), rather than surfactant deficiency [33]. Repeated LUS examinations may also demonstrate the physiological

transition from a fluid-filled fetal lung to an increasingly aerated lung, corresponding to the sodium channel-mediated fluid clearance mechanisms discussed below [34].

Clinical Relevance of the Development of the Lung

Alveolarization continues rapidly into early postnatal life. Older assumptions that alveolar development ends in early childhood have been challenged by newer evidence showing ongoing alveolar formation well into later life. Animal 3-D imaging studies suggest continued alveolar formation into adulthood [23], and hyperpolarised helium MRI data indicate alveolar formation continues at least until young adulthood in humans [35]. This regenerative potential helps explain why some preterm infants with impaired early lung development may still achieve relatively good lung function later in life, although the long- term trajectory depends on the severity of injury and subsequent exposures. Alveolarization can be supported or hindered by multiple factors.

Chronic MV, even at modest tidal volumes and low oxygen concentrations, can disturb both alveolar and vascular development [36], leading to an arrested pattern characterised by fewer, larger alveoli and abnormal elastin deposition [37]. Similar findings have been reported in preterm infants who died after prolonged ventilation or after developing BPD, including reduced alveolar numbers and attenuated microvasculature, with a different injury pattern than historically described [38].

Inflammatory exposures also matter: antenatal inflammation associated with chorioamnionitis can delay alveolar and microvascular development, and although later lung growth is substantial, structural consequences may persist after severe BPD, whereas milder disease can show near-normal alveolar numbers on imaging in adolescence [39]. In this context, early postnatal LUS may provide prognostic information. In a multicentre prospective cohort of 147 extremely preterm infants born at ≤30 weeks of gestation, Loi et al. performed serial LUS assessments during the first four weeks of life and showed that GA-adjusted LUS scores predict BPD at 36 weeks of postmenstrual age, with good diagnostic accuracy from day 7 onward. These findings suggest that early sonographic aeration patterns may reflect not only acute respiratory status, but also evolving lung injury and later risk of impaired alveolar development [14].

Fetal Lung Fluid

Finally, fetal lung fluid is an important piece of early respiratory physiology because the airways are fluid-filled until birth, and effective clearance is essential for postnatal transition. Near term, fetal lungs contain enough fluid to maintain airway fluid volumes that can exceed the later FRC once air breathing begins [40]. The composition and regulation of fetal lung fluid differ across species, but key principles include active transepithelial chloride secretion that supports fluid production, and the

fact that normal fluid volumes support lung development while clearance after birth is required for normal respiratory adaptation [41].

During labour and delivery, the volume of fetal lung fluid decreases. A substantial portion must still be absorbed after birth, with most fluid moving into the interstitial space and then into the pulmonary circulation. Postnatal clearance depends on active sodium transport through epithelial sodium channels. Failure of this mechanism can be fatal in animal models. Glucocorticoids upregulate epithelial sodium channel expression in fetal human lung, supporting the clinical observation that delayed fluid clearance can contribute to transient respiratory difficulties in newborns and further highlighting the influence of maturation processes and perinatal exposures on early respiratory outcomes [25]. LUS can provide a direct bedside assessment of this fluid-clearance process. In healthy term neonates, the sonographic pattern changes from B-line-predominant images, consistent with residual fetal lung fluid, to A-line predominant findings once aeration is completed — usually within the first hour of life [34]. Persistence of a diffuse B-line pattern beyond this early transition period may indicate delayed aeration and has been associated with a higher likelihood of respiratory support [42].

Surfactant

Surfactant is a lipoprotein mixture in the alveoli that consists mainly of phospholipids (roughly 70-80%). It contains a smaller fraction of proteins and neutral lipids such as cholesterol, and its key surface-active component is saturated phosphatidylcholine. In the immature lung, surfactant composition and overall function are often qualitatively inferior to those of the mature lung. This contributes to why preterm infants can deteriorate quickly despite apparently similar clinical presentations [25]. Surfactant is produced and handled primarily by type II cells, which package it into lamellar bodies and release it into the airspaces. Secretion can be stimulated by catecholamines and by mechanical stretch when the lung distends [43].

Clinically, a low effective surfactant pool size is one reason why some infants fail non-invasive support [44]. Surfactant improves alveolar stability by lowering surface tension, helping prevent collapse and limiting fluid entry into alveoli and small airways, which supports more uniform lung inflation [45]. In surfactant-deficient lungs, positive pressure tends to overexpand the better units, while other regions remain collapsed.

Despite the scientific progress, a major ongoing challenge remains the prevention of BPD in very preterm infants, which is closely linked to interrupted lung development and the exposures that accompany intensive respiratory care [25].

6.3 The Basics of Neonatal Lung Ultrasound

History and Introduction to Neonatal Lung Ultrasound

Lung ultrasound is a portable, radiation-free imaging method that can be performed by the treating clinician to evaluate neonatal respiratory conditions [22,46]. Its clinical use has grown substantially during the last two decades, supported by the increasing availability of compact, affordable and user-friendly ultrasound devices [47]. Initially established mainly in adult emergency and critical care settings, LUS is now increasingly integrated into NICU practice for diagnostic assessment and procedural support.

The learning curve is generally considered favourable: there is extensive educational literature, and structured training pathways exist in many countries, with competence improving through focused hands-on teaching [48–51]. At the same time, LUS is not an automated technique. It is operator-dependent, meaning the exam's quality depends on both image acquisition and correct interpretation [48]. The American Academy of Paediatrics (AAP) technical report highlights that safe use requires an institutional framework, including structured training, quality assurance, and credentialing, and raises patient-safety concerns when adoption outpaces training and oversight [48]. Practical barriers to broader implementation include equipment costs, the need for ongoing quality control, and medico-legal issues related to documentation, credentialing, and supervision [52].

In neonates, bedside point-of-care ultrasound (POCUS) has expanded beyond lung assessment and is now used across multiple systems, including cardiac, abdominal, cranial, and vascular assessments [53].

Preparing for a Lung Ultrasound Examination

Preparing for a LUS examination in the NICU requires careful planning to optimize diagnostic quality while minimizing any negative impact on the neonate. The examination should be performed efficiently and with attention to patient safety, comfort, and environmental stability. Particular care should be taken to avoid hypothermia by keeping the study as brief as possible and minimizing unnecessary handling or changes in position [54]. In addition, strict infection control is essential: both the equipment and the hands of all involved staff must be thoroughly sanitized, and transducers and leads should be disinfected before and after patient contact [54].

Basic Physical Principles of Lung Ultrasound

Ultrasound is an imaging technique that uses very high-frequency sound waves to visualise internal structures and organs. These sound waves are produced by piezoelectric crystals within a transducer encased in the probe, which also detects the returning echoes. The strength of the echo depends on the properties of the tissue, and stronger echoes appear brighter on the image. The further a structure

is from the probe, the longer the echo takes to return, and this determines where it is displayed on the screen [55].

LUS differs from ultrasound of solid organs because normal lung contains air, so image interpretation relies heavily on artifacts at the pleural surface rather than direct visualization of lung tissue; therefore, understanding these artifacts is fundamental to interpreting neonatal LUS [56]. In the healthy aerated lung, the pleural surface reflects the ultrasound beam because it marks the interface between the fluid-rich chest wall and the air-containing lung. This generates a hyperechoic pleural line with posterior acoustic shadowing. The parietal and visceral pleura are not distinguishable individually and are therefore seen as a single echogenic line. As a result, structures visualized below the pleural line in the normal lung are artifacts rather than true anatomical images [57,58].

The key patterns are relatively straightforward: A-lines are horizontal reverberation artifacts appearing as parallel lines below the pleural line, consistent with normal aeration. These are created by sound waves bouncing back and forth between the pleural line and the ultrasound probe [48,56,59]. B-lines are vertical artifacts that extend from the pleural line to the bottom of the ultrasound screen, representing thickened interlobular septa caused by interstitial or alveolar fluid accumulation and represents nonaerated lung, often with an abnormal pleural line and air bronchograms [53]. Interpreting the pattern and distribution of these findings helps differentiate conditions that can clinically appear similar and allows clinicians to track changes over time with treatment [48].

Standard Scanning Protocol and Technique

Technically, neonatal LUS is typically performed with a high-frequency linear probe, often with the infant in a supine position [60]. It could also be performed in the prone position, but this body position needs to be maintained for at least 1 hour to allow lung fluids to settle with gravity [61]. With adjusted image depth and gain to show clear air-fluid interface patterns any probe could be used. A recent study found no significant differences in the interpretation of artifacts between different probes in newborns [33].

To obtain high-quality images during LUS, several machine settings should be optimized, particularly gain, depth, and focal zones. Gain should be adjusted so that rib shadows appear black (hypoechoic), the pleural line appears bright white (hyperechoic), and the superficial tissues are displayed in shades of grey [57]. Although no universally recommended depth has been established for newborns, a setting of approximately 3-4 cm is generally adequate [54].

LUS is primarily performed in two-dimensional mode (2D), also known as B-mode, which represents the standard imaging mode for lung assessment. This technique generates cross-sectional images by transmitting and receiving sound waves through the transducer, allowing visualization of structures

in terms of width and depth. In addition, motion mode (M-mode) can be used to assess the movement of the pleural layers during respiration, particularly to evaluate lung sliding [54,63].

Lung Ultrasound Examination

A systematic LUS examination evaluates the anterior, lateral, and posterior lung fields bilaterally. As shown in Figure 2, each hemithorax is divided into three regions: the anterior region between the sternum and the anterior axillary line, the lateral region between the anterior and posterior axillary lines, and the posterior region between the posterior axillary line and the spine. For LUS scoring in neonates, the anterior and lateral regions are commonly subdivided into upper and lower parts using the nipple line as a landmark, resulting in six scorable zones: right upper anterior (R1), right lower anterior (R2), right lateral (R3), left upper anterior (L1), left lower anterior (L2), and left lateral (L3) [54,60,64].

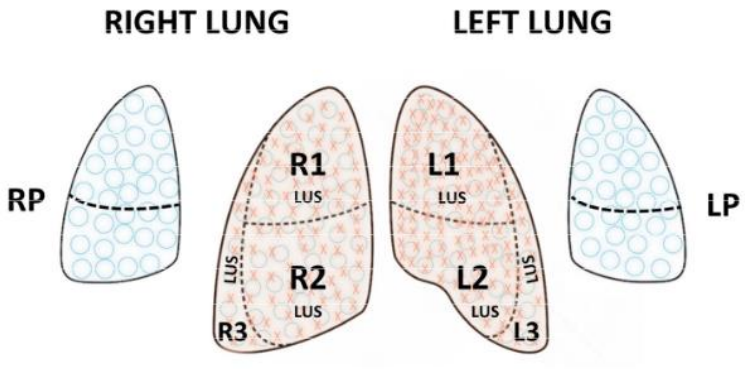

Figure 2. Lung regions for systematic LUS examination and scoring in neonates. R1-R3 and L1-L3 represent the anterior and lateral scoring regions, while RP and LP indicate the posterior regions. Adapted from [54].

LUS can be performed in two planes: a vertical longitudinal scan (Figure 3.A) and a horizontal transcostal scan (Figure 3.B). The vertical longitudinal view is the primary and most used scanning mode for lung evaluation in neonates, while the horizontal transcostal view serves as a complementary approach that may help avoid rib shadowing and provide additional information on the extent or depth of pathological findings. For accurate imaging, the transducer should be positioned perpendicular to the lung [54].

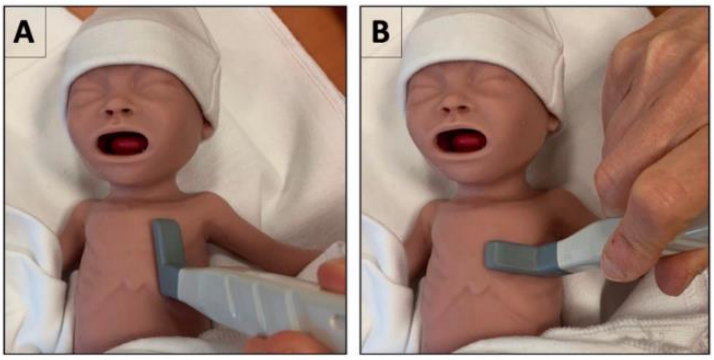

Figure 3. Probe position for neonatal lung ultrasound. Panel A shows the vertical longitudinal scan, and Panel B shows the horizontal transcostal scan. Adapted from [54].

Lung Ultrasound Scoring System

The most commonly used scoring system is the LUS score originally described by Brat et al [65]. In this system, each lung is divided into three regions-upper anterior, lower anterior, and lateral — resulting in a total of six regions across both lungs (Figure 2). Each region is assigned a score from 0 to 3 according to the degree of aeration, with 0 indicating best aeration and 3 indicating worst pathology. The zone scores are summed to produce a global score reflecting overall lung aeration and the regional scores are then summed to obtain the total LUS score [53]. A score of 0 indicates a normally aerated lung with A-lines (Figure 4.1), consistent with preserved alveolar aeration at end-expiration [48,65]. A score of 1 indicates the presence of multiple separated B-lines (Figure 4.2), representing mild loss of aeration or increased interstitial fluid, a pattern more typical of retained fetal lung fluid, as seen in TTN, than of marked surfactant deficiency [48,65,66]. A score of 2 indicates confluent B-lines with disappearance of A-lines (Figure 4.3), corresponding to more pronounced aeration loss, which in RDS may reflect alveolar collapse related to surfactant deficiency and increased surface tension [48,65,67]. A score of 3 indicating severe aeration loss with consolidative changes, typically including subpleural consolidation and/or air bronchograms as shown in Figure 4.4 [48,65]. This pattern may reflect severe regional loss of aeration, where non-aerated lung tissue surrounds air-filled bronchi, making air bronchogram visible sonographically [48,65]. A recent multicentre prospective study confirmed that LUS aeration score correlates with direct measures of surfactant deficiency (stable microbubble rating) and with chest X-ray (CXR) severity, supporting the interpretation that the score reflects the underlying pathophysiology rather than just a sonographic pattern [68].

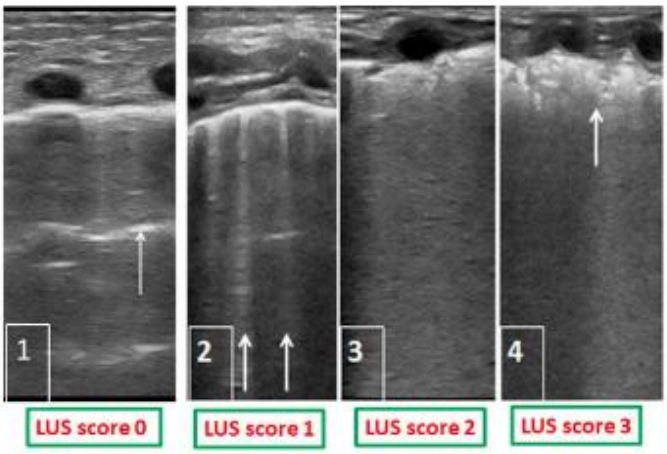

Figure 4. Four typical LUS patterns and their corresponding severity scores. In pattern 1, the arrow indicates the A-line artifact. In pattern 2, the arrows indicate separated B-lines. In pattern 4, the arrow indicates a subpleural air bronchogram. Adapted from [48].

The total LUS score increases as lung aeration decreases. In preterm infants born before 30 weeks of gestation, values above 8 have been reported to predict the need for surfactant therapy [69]. Nevertheless, the optimal cut-off is not universal and depends on the scoring system applied. A multicentre study comparing the three most commonly used scoring systems – Brat, Raimondi and Rodriguez-Fanjul – showed that each system predicted surfactant requirement with good diagnostic performance (AUC 0.79-0.85), but with different cut-off values: 8 for Brat and Raimondi and 10 or higher for Rodriguez-Fanjul [70]. Therefore, LUS cut-off should be interpreted according to the scoring system used and centres should apply one scoring approach consistently.

In preterm infants with RDS, the highest clinical relevance of this score lies in its ability to identify the sonographic pattern of surfactant-deficient lung disease before deterioration is expressed only by rising oxygen demand [54,71]. Higher scores reflect diffuse and bilateral loss of aeration, a pattern that is consistent with more severe surfactant deficiency and increasing alveolar decruitment [54,72]. This is especially important for the cohort investigated in the present study, where LUS was used in preterm infants with respiratory distress to support early respiratory decision-making.

A further advantage of the score is that it transforms qualitative sonographic findings into a semi-quantitative bedside parameter that can be followed over time. In this way, LUS does not only describe lung morphology but also supports functional assessment of disease severity and treatment response. This is one reason why neonatal LUS is increasingly discussed not only as a diagnostic tool but also as a decision support tool for interventions such as surfactant therapy [46,48].

The clinical urgency of early LUS assessment is rooted in the time-sensitivity of surfactant therapy. In RDS, surfactant deficiency is most pronounced immediately after birth, while endogenous production increases gradually over the following days. Exogenous surfactant is most effective when

administered early – ideally within the first 2-3 hours of life – before significant alveolar injury and surfactant inactivation have developed [73]. An umbrella review of high-certainty evidence confirmed that early selective surfactant administration, compared with delayed therapy, is associated with a lower risk of BPD or mortality (RR 0.83; 95% CI 0.75-0.91) [74]. However, FiO_2-based thresholds may only be reached after this optimal window has passed, because impaired oxygen is a late consequence in the pathophysiology cascade [75]. By contrast, LUS can identify sonographic patterns consistent with surfactant-deficient lung disease before management depends solely on rising oxygen demand, thereby supporting surfactant treatment within the optimal time window [76]. The updated 2025 European Consensus Guidelines on the management of RDS recognise LUS as a tool that may support early surfactant decision-making alongside conventional criteria [77].

Clinical Context and Neonatal Transition

During the neonatal transition period, there is significant interplay between the heart and the lungs. LUS plays a crucial role in this context, as it helps differentiate between various conditions, their underlying causes and severity. Recent evidence shows that LUS is increasingly used even in the delivery room to assess respiratory transition and guide early respiratory management, with normal postnatal adaption characterised by rapid progression from fluid-rich to aerated lung patterns [78].

Over the last decade, its uptake has been driven by evidence suggesting high diagnostic accuracy for several neonatal lung conditions and by the practical advantage of avoiding repeated chest radiographs in very preterm infants [2]. The AAP supports the use of LUS in the diagnosis and management of neonatal respiratory disease, including RDS, TTN, pneumothorax and lung consolidation [48].

In preterm infants with evolving RDS, early LUS findings are valuable because clinical signs may initially be non-specific despite progressive loss of lung aeration [79]. Timely sonographic assessment can support earlier differential diagnosis and may help avoid both delayed treatment and unnecessary intervention [70,71,80]. This is especially relevant for surfactant decision-making, where LUS adds information beyond clinical assessment and FiO_2 requirement alone [71,77].

In summary, LUS provides NICU clinicians with a practical tool that complements clinical assessment and traditional imaging. It is particularly suitable for neonatal care because it is fast, repeatable, and enables dynamic real-time assessment of respiratory pathologies — an important advantage in preterm infants, in whom similar symptoms may arise from different underlying mechanisms [52].

6.4 Neonatal Respiratory Distress Syndrome

Neonatal RDS, also referred to as surfactant deficiency disorder, is a pulmonary condition in infants caused by insufficient pulmonary surfactant [81]. It is one of the core diagnoses and a leading cause of morbidity in neonatology because it is common, time-sensitive, and directly linked to prematurity-related lung immaturity [25]. Classic risk factors that increase the likelihood or severity include prematurity itself, male sex, multiple gestation, and maternal diabetes [82].

Pathophysiology

Preterm lungs are not fully ready to stay open after birth. The main problem is surfactant deficiency combined with structural and functional immaturity of the developing lung. This is why RDS is seen predominantly in preterm infants and why the incidence rises the lower the GA, particularly in infants born before 32 weeks [82]. The immaturity of type II pneumocytes leads to inadequate surfactant production. This triggers a cascade of responses leading to decreased alveolar distensibility, capillary leak oedema, noncompliant lungs, and respiratory distress [25].

Pathophysiologically, the lack of surfactant increases alveolar surface tension, promoting alveolar collapse at end-expiration. Once alveoli repeatedly collapse, the lungs become stiffer (reduced compliance), the infant must generate higher pressures to ventilate, and effective gas exchange becomes harder. This leads to ventilation-perfusion mismatch, progressive hypoxaemia, and rising work of breathing. If the disease progresses, the infant can deteriorate quickly [82].

Clinical Presentation

Clinically, RDS usually becomes apparent within minutes to hours after birth and often worsens during the first day or two. Typical signs are tachypnoea, grunting, nasal flaring, retractions, and, in more severe cases, cyanosis. On auscultation, breath sounds may be reduced, and fine crackles may be present. However, clinical findings alone are not specific.

Diagnosis

In practice, diagnosis is based on the clinical picture, GA, increasing oxygen requirements, and supportive imaging. Chest radiography classically shows a diffuse, symmetrical ground-glass or reticulogranular pattern with air bronchograms (Figure 5), reflecting reduced aeration and widespread atelectasis. Because many neonatal conditions present with respiratory distress as the first sign, it is important to consider differentials, especially early after birth.

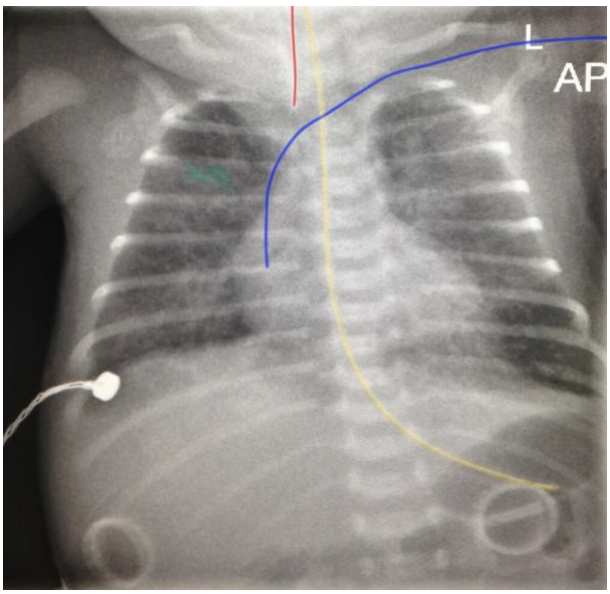

Figure 5. RDS. X-ray chest (AP view). Lungs show a diffuse granular pattern with low volumes. Air bronchogram (green overlay) can be seen. Endotracheal (red) and nasogastric (yellow) tubes are present. There is also a left central line (blue). Adapted from: [83].

Typical LUS findings are preserved lung sliding, an irregular and thickened pleural line, subpleural consolidations, and numerous confluent B-lines, producing a bilateral homogeneous "white lung" appearance (Figure 6). In severe RDS requiring surfactant replacement therapy, spared areas are typically absent, meaning that normal regions with a regular pleural line and A-lines are not seen [54,84].

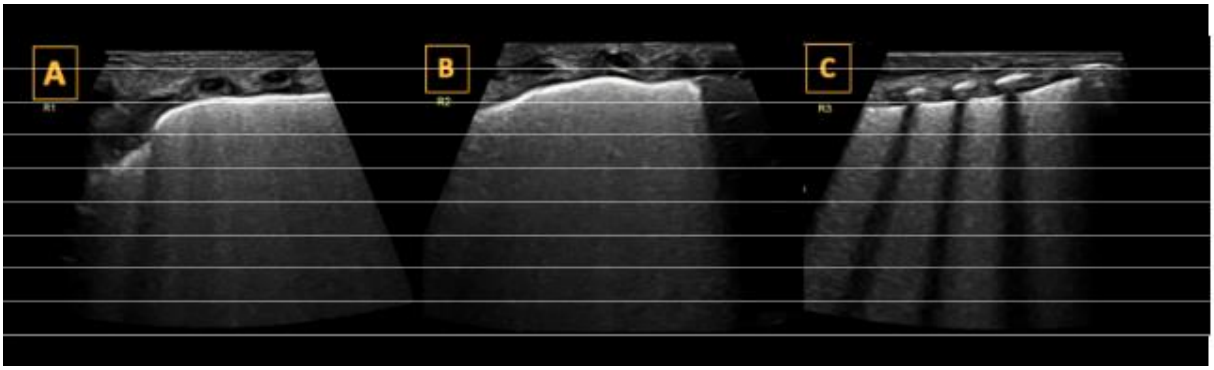

Figure 6. LUS appearance of RDS. Panels (A-C) present longitudinal views of the right anterior upper (R1), right anterior lower (R2), and right lateral lung regions of a preterm infant with RDS. The pleural line appears thickened, and all examined lung fields demonstrate a diffuse "white lung" pattern without visible A-lines, consistent with marked loss of aeration in RDS. On LUS scoring, each right-sided region is graded 2, resulting in a right lung score of 6. The left lung was likewise scored 6, giving a total LUS of 12/18. Adapted from [54].

Differential Diagnosis

Conditions that can symptomatically mimic RDS or overlap with it include TTN due to delayed lung fluid clearance, meconium aspiration, pneumonia, neonatal sepsis, pneumothorax or other air leaks. Also, non-pulmonary causes such as congenital heart disease or congenital diaphragmatic hernia. Clinically, these can look similar at the bedside, yet the underlying mechanism and, therefore, the best management can differ significantly. This is one of the reasons why bedside tools that help distinguish pathology early are so useful in neonatal care [82].

Prognosis

Outcomes for infants with RDS have improved substantially over time due to advances in perinatal care, particularly antenatal corticosteroids and surfactant therapy. However, RDS is still clinically important because it sits on a pathway that can lead to complications. Severe or prolonged respiratory disease and escalation to invasive ventilation increase the risk of BPD and can be associated with broader prematurity-related morbidity, including adverse neurodevelopmental outcomes - especially in extremely preterm infants. In that sense, RDS is not only a short-term respiratory issue; it can influence the entire NICU course and long-term health [82].

Prevention

Prevention is therefore a major theme in neonatology. Antenatal care, especially the use of antenatal corticosteroids in mothers at risk of preterm delivery, reduces both the incidence and severity of RDS. It remains a key strategy in modern perinatal management [85].

6.5 Management of Respiratory Distress Syndrome

Due to medical innovations, the survival of preterm infants continues to improve. There is a growing trend to offer life support to neonates born at lower levels of viability [86]. With increasing numbers of younger preterm infants, the challenges also increase [87]. Management of RDS is generally based on early stabilisation and respiratory support, with a preference for non-invasive approaches when possible and for surfactant replacement when indicated. Clinical practice aims to maintain adequate oxygenation and ventilation while minimising lung injury, because prolonged or aggressive MV is a major contributor to ventilator-induced lung injury and later BPD [77,88].

Prenatal Care

Lack of antenatal care is associated with a higher risk of death or severe morbidity [89]. In the context of RDS, management begins before birth. A key priority is the early identification of pregnancies at high risk of preterm delivery so that mothers can be transferred in utero to tertiary perinatal centres, particularly when birth before 28-30 weeks of gestation is expected, where appropriate expertise for the management of severe prematurity and RDS is available [77].

Among prenatal interventions, antenatal corticosteroids are one of the most important evidence-based measures. A single course administered to women with anticipated preterm birth before 34 weeks of gestation has been shown to improve neonatal survival and reduce the risk of RDS, necrotising enterocolitis, and IVH, without relevant short-term maternal or fetal adverse effects [90]. The greatest benefit is achieved when steroids are given at least 24 hours before birth. In selected cases of persistent threatened preterm birth before 32 weeks, a single repeat course may be considered if the initial course was given 1-2 weeks earlier [77,82].

Delivery Room Stabilisation

Delivery room management is a critical part of RDS care, as the first minutes after birth may strongly influence subsequent respiratory outcome. Staff members attending births must be able to rapidly identify infants who need immediate airway support and lung inflation in order to establish effective gas exchange and support cardiopulmonary transition [88]. European resuscitation guidance particularly emphasises early recognition of infants born in poor condition and prompt intervention focused on airway opening and lung aeration [2]. Each of the delivery room interventions discussed below, represent a modifiable factor that, if not optimised, can independently compound the underlying surfactant deficiency and worsen the severity and course of RDS [77,91].

An important aspect of early stabilisation is umbilical cord management. Current evidence suggests that immediate cord clamping should be avoided whenever possible, as delayed clamping is associated with lower in-hospital mortality and a reduced combined risk of death or disability at 2 years [92]. Longer delay may provide additional benefit, with deferral beyond 2 minutes being associated with the lowest mortality risk [93]. In this context, physiologically based cord clamping has been proposed as an alternative to a strictly time-based approach, meaning that the cord is clamped only after respiratory stability has been achieved [94].

For spontaneously breathing infants, early CPAP is the preferred initial support, as it is associated with less lung injury and a lower risk of BPD than intubation [95].

Body temperature should be maintained between 36.5 and 37.5°C, and preterm infants ≤32 weeks should be protected from heat loss using plastic wrapping and preheated radiant warmers [96]. Oxygen supplementation should be titrated with an air-oxygen blender, as preterm infants may require higher oxygen concentrations than term infants during transition, while avoiding excessive oxygen exposure [97]. Monitoring during this period focuses mainly on heart rate and oxygen saturation, with S_pO_2 expected to rise progressively during the first 10 minutes after birth [77].

Although LUS is most often performed after NICU admission, emerging evidence suggests that it may also be useful during delivery room stabilisation. A systematic review of delivery room LUS

applications found that neonatologists-performed scanning during resuscitation is feasible and clinically informative, with several scoring systems showing good discriminative performance for predicting the need for respiratory support shortly after birth [98]. In very and extremely preterm infants, LUS performed as early as 5-10 minutes after birth predicted surfactant need with an AUC of 0.78, outperforming FiO_2 at the same point. Predictive accuracy increased further at 1-3 hours of life (AUC 0.86) [99]. These findings suggest that early LUS may complement the clinical assessment tools described above even before NICU transfer, although delivery room scanning introduces logistical challenges and requires trained personnel.

Surfactant Therapy

The feasibility of surfactant replacement was first demonstrated in animal models in the 1970s and then successfully translated to clinical use in humans in 1980, ultimately establishing antenatal corticosteroids and postnatal surfactant as two of the most effective therapies in neonatology for RDS related to immaturity [100].

Surfactant therapy improves survival and reduces oxygen exposure, ventilator requirement, and pneumothorax, which makes it one of the most important treatments for surfactant-deficient lung disease in preterm infants [87,88]. In contemporary care, surfactant is no longer viewed as routine prophylaxis for all preterm infants, but as an early and targeted therapy for infants with clinically significant RDS [101]. After administration, oxygenation often improves rapidly, whereas improvement in lung compliance and carbon dioxide clearance may occur more gradually [103].

In earlier trials, surfactant was usually delivered as a bolus through an endotracheal tube (ET), often followed by positive- pressure ventilation and a period of ventilator weaning. This traditional method allows reliable delivery of a full dose directly into the trachea but requires airway expertise and may contribute to lung injury if ventilation is not carefully controlled. To reduce the disadvantages of prolonged intubation, the IN-SUR-E approach represented an important step toward limiting ventilation time and reducing lung injury, in which surfactant is given through an ET followed by brief manual ventilation and rapid extubation back to CPAP [104,105].

Current evidence, however, supports thin-catheter administration during spontaneous breathing on CPAP, commonly referred to as less invasive surfactant administration (LISA), as the preferred technique in suitable infants [101,106–108]. This method avoids routine bagging, reduces the need for MV, and has been associated with lower rates of death or BPD and less IVH compared with IN-SUR-E at similar treatment thresholds [106]. Cohort data and clinical experience from Europe also suggest overall better outcomes with this method [109,110], and early rescue LISA may additionally reduce oxygen exposure, air leaks, ventilation need, and treatment costs [77]. Nevertheless, LISA still requires laryngoscopy, which may be uncomfortable and destabilising in very small infants, while

sedation may decrease discomfort but increase apnoea and the later need for positive- pressure ventilation [111]. For more mature infants, laryngeal mask administration may be an alternative, whereas nebulised surfactant remains investigational and has not yet shown convincing benefit in the smallest infants [109,112].

A major challenge in surfactant therapy is deciding when treatment should be given. If intubation is required during stabilisation, especially in infants between 24 and 30 weeks of gestation, surfactant should be administered immediately in order to improve lung compliance and support early extubation [79]. Infants at 22-23 weeks of gestation form a special group in whom planned intubation and very early surfactant treatment are often considered necessary. At the same time, many preterm infants can initially be managed on CPAP, and surfactant is therefore generally used as time-sensitive rescue therapy once RDS becomes clinically apparent [112]. In routine practice, treatment decisions are still mainly guided by pragmatic FiO_2 and CPAP thresholds [109,112]. The decision is further complicated by variability in clinical guidelines. Uncertainty remains regarding optimal thresholds in routine practice and across settings. Clinical and radiological criteria for surfactant need are limited in sensitivity and specificity since extremely preterm infants may require different strategies than those born at a later GA.

LUS scoring has been proposed as a useful approach to address this challenge: a meta-analysis of ten studies (1162 neonates) found that LUS performed within 1-3 hours after birth predicted the need for surfactant with a pooled sensitivity of 86% and a specificity of 82% [76]. A multicentre pragmatic study also showed that LUS predicted the first surfactant dose reliably across GA, with even stronger predictive performance when combined with S_pO_2/FiO_2 ratio (AUC 0.93) [113]. In addition, the ULTRASURF randomised trial reported that LUS-guided surfactant administration resulted in earlier administration (1 vs. 6 hours of life) and improved oxygenation after therapy compared with criteria based on FiO_2 alone [114]. However, evidence that LUS-guided surfactant strategies improve major clinical outcomes such as BPD or mortality is still lacking. The ongoing international LUNG-Study (NCT05198375) is specifically designed to test whether LUS-guided surfactant decision can reduce BPD or death in 668 infants born at 25-29 weeks of gestation [70].

CPAP

Continuous positive airway pressure is a mode of spontaneous breathing support in which a constant positive end-expiratory pressure (PEEP) is maintained throughout both inspiration and expiration, functionally comparable to continuous PEEP. By preventing end-expiratory alveolar collapse, CPAP increases functional residual capacity, improves oxygenation, reduces the work of breathing, and may also decrease the frequency of apnoeic episodes [25,115]. In preterm infants with RDS, CPAP is therefore used to stabilise lung aeration early and to avoid intubation whenever possible.

In neonatal practice, CPAP is usually delivered non-invasively via nasal prongs or nasal masks using heated and humidified gas, generally at pressures in the range of about 5-10 cmH_20 [115]. Current resuscitation guidance recommends early CPAP support for spontaneously breathing preterm infants, with a starting PEEP level of around 6 cmH_20 [2]. Higher pressures may further improve oxygenation, but they also increase the risk of complications such as air leaks or gastric distension, so the pressure level must be adjusted according to the individual infant's respiratory condition [116].

From a technical perspective, the principle of CPAP is the generation of a continuous distending pressure in the airways. Historically, this could also be achieved in intubated, spontaneously breathing patients using a T-piece system with continuous fresh-gas flow, a PEEP valve, a reservoir bag, and a manometer [117]. In modern neonatal intensive care, however, CPAP is typically provided by dedicated ventilator modes or neonatal CPAP systems, making separate classical devices no longer necessary [117]. Within the broader concept of NRS, CPAP remains one of the main first-line strategies for infants at risk of RDS who do not require immediate intubation [25].

LUS may also support the assessment of the response to CPAP and decisions about when CPAP can safely be discontinued. In a prospective physiological study, stepwise increase in CPAP from 4 to 8 cmH_2O was associated with improved LUS-assessed lung aeration and oxygenation, although the additional benefit appeared limited above 6 cmH_20, particularly in infants with RDS [118]. In addition, a multi-outcome study reported that LUS performed before CPAP withdrawal predicted successful discontinuation with excellent accuracy (AUC 0.86) [119].

Mechanical Ventilation Strategies

Mechanical ventilation is required in preterm infants with RDS when NRS is insufficient, particularly in infants who remain apnoeic or bradycardic and therefore require intubation for stabilisation [120]. Although avoidance of ventilation is associated with better outcomes overall, this is not always feasible, especially in extremely preterm infants at the margins of viability, in whom primary intubation may sometimes be the safest approach [110,121,122]. Even with modern non- invasive strategies and prophylactic surfactant, a substantial proportion of extremely preterm infants still require MV during their clinical course [110].

The purpose of MV is to maintain adequate gas exchange by applying positive pressure while minimising ventilator-induced lung injury. This requires an "open lung" strategy that avoids both overdistension and repeated collapse of unstable alveoli. Excessive inflation may lead to air leaks and pulmonary interstitial emphysema, whereas insufficient distending pressure promotes cyclical opening and closing of atelectatic lung units, thereby contributing to injury and inflammation [123]. For this reason, the duration of MV should be kept as short as possible, and lung-protective ventilation strategies should be preferred whenever invasive support is necessary [120]. In particular, volume-

targeted ventilation is considered preferable to pressure-limited modes in infants with RDS who require MV [77].

Adjunctive pharmacological support also plays an important role during invasive respiratory care. Caffeine citrate, usually given as a 20 mg/kg loading dose followed by 5-10 mg/kg maintenance, is used to facilitate weaning from MV and to reduce the risk of bronchopulmonary dysplasia. Prophylactic caffeine in standard doses is recommended for infants born before 32 weeks of gestation [77].

LUS may also contribute to decisions around MV. An early LUS score >7, assessed within 0-6 hours of life, predicted the need for MV within 72 hours with 89% sensitivity (AUC 0.80)[119]. Among neonates already on NIV, a LUS higher than 7 also helped to distinguish infants who later required escalation to invasive ventilation with an AUC of 0.82 [124]. Furthermore, LUS has shown potential for predicting extubation failure, with reported 95% sensitivity, 85% specificity, and an AUC of 0.95 [125]. Additional evidence supports the use of LUS for predicting extubation outcomes across different GA groups. In preterm infants born before 34 weeks of gestation, a pre-extubation LUS cut-off higher than 7 predicted 80% sensitivity and standardised 96% specificity (AUC of 0.97) [126]. A systematic review also identified LUS as a promising tool for assessing extubation failure, although the included studies used different scoring systems and cut-off values, meaning that further validation is still needed [127].

6.6 Conventional Decision-making Tools and Their Limitations

A central dilemma in contemporary neonatal respiratory care is determining the optimal timing of surfactant administration. In infants who develop RDS, surfactant deficiency is greatest shortly after birth, while endogenous surfactant production increases gradually over the following 3-5 days [128,129]. Exogenous surfactant has the greatest effect when given before substantial lung injury and impaired gas exchange have developed; its efficacy may be reduced once RDS is fully established, with alveolar and airway injury and increasing surfactant inactivation [79]. In current NICU practice, RDS severity is therefore usually assessed indirectly using bedside clinical signs, FiO_2 requirement, and imaging-based evaluation of lung aeration, traditionally by CXR [77,130]. Although this approach remains clinically useful, each of these parameters can be influenced by ongoing respiratory support, particularly CPAP, making early treatment decisions challenging [108]. Early recognition is therefore important, because respiratory support and surfactant therapy should ideally be initiated before further deterioration occurs [77,79].

Fraction of Inspired Oxygen

FiO_2 describes the fraction of oxygen in the inspired gas mixture delivered to the infant, typically through CPAP or nasal intermittent positive pressure ventilation (NIPPV). It is always interpreted in the context of the infant's overall clinical status and the level of respiratory support. A rising FiO_2 requirement generally indicates the infant needs more oxygen to maintain adequate saturation, often suggesting worsening oxygenation (hypoxaemia) and more severe respiratory disease. Many international guidelines use FiO_2 thresholds around 0.30 on CPAP as a trigger for rescue surfactant in preterm infants with RDS. Particularly when the increase is sustained above baseline and accompanied by ongoing clinical signs of distress [88].

FiO_2 alone is an imperfect marker and sometimes delayed [71,112] for guiding decisions on respiratory support and surfactant administration in preterm infants with RDS because it does not capture the multifactorial nature of respiratory failure in this population. FiO_2 requirements can be affected by factors beyond surfactant deficiency, such as atelectasis, infection, haemodynamic instability or differences in lung compliance. In addition, an increased FiO_2 requirement may also reflect ventilation-perfusion mismatch rather than surfactant deficiency itself. This is clinically relevant because impaired oxygenation can therefore occur even in the absence of true RDS progression. It does not directly measure the underlying pathophysiology [70,117]. There is also a substantial variability between infants: the same FiO_2 may reflect very different degrees of lung disease depending on GA and the effectiveness of NIV in recruiting and stabilising the lung [25]. In that situation, relying too heavily on FiO_2 may lead to polar errors: delaying surfactant in an infant whose RDS is progressing quickly or giving surfactant to an infant whose oxygen needs are transient and driven by something else. For these reasons, FiO_2 is most useful when interpreted together with the clinical examination and trends over time, and, when available, with additional information such as blood gas results and imaging [130]. Overall, good decision-making requires integrating FiO_2 into the broader clinical context rather than treating it as a single trigger [112].

Chest X-Ray

Chest X-ray has traditionally been the main imaging tool used in the NICU to support the diagnosis of neonatal respiratory disease, assess severity, and identify complications such as air leaks or ET malposition [131]. Its widespread use is largely explained by broad availability and familiarity among clinicians [132]. However, chest radiography also has significant disadvantages. In very preterm infants, repeated imaging during long NICU stays results in cumulative radiation exposure [133]. Beyond radiation, CXR also has a practical limitation: it provides only a static snapshot. It does not reflect rapid changes in lung aeration and recruitment, which are exactly what clinicians are trying to understand in the acute phase of respiratory distress [134]. Radiographic findings may also not fully match early clinical severity [135]. The interpretation can be influenced by practical issues such as

positioning and the technical quality of the image in fragile infants. Supine views and patient rotation can introduce artefacts that complicate interpretation and may lead to uncertainty or misclassification. These limitations have increased interest in bedside, repeatable, radiation-free tools such as LUS [134].

Taken together, clinical assessment, FiO_2 trends, and CXR all provide useful information, but none alone reliably captures lung aeration and disease evolution in real time. [131]. An ideal bedside tool would be rapid, repeatable, feasible during NIV, and would not add radiation burden. LUS meets many of these requirements and has therefore gained increasing attention in neonatal intensive care units.

6.7 Lung Ultrasound in Neonatal Respiratory Decision Making

In neonatal intensive care, LUS has become increasingly relevant as a bedside adjunct that can support respiratory decision making in a way that complements, rather than replaces, conventional assessment. The AAP describes POCUS as an extension of the physical examination that can provide rapid bedside information to support immediate clinical decisions, while not substituting for formal radiology imaging when a more comprehensive diagnostic assessment is required [19]. This is particularly important in the NICU, where respiratory status may change quickly and repeated reassessment is often necessary. Because LUS is radiation-free, portable, and suitable for serial examinations at the bedside [53], it offers practical advantages over CXR [46] in unstable preterm infants and fits well into routine NICU workflow [19,111]. In this context, LUS is increasingly regarded as a useful adjunct to CXR, preserving the strengths of bedside imaging such as speed, repeatability, and absence of radiation, while still requiring a structured and standardised approach to ensure consistent quality [136].

The clinical value of LUS lies not only in diagnosis but in its ability to support earlier and more individualised therapeutic decisions. In preterm infants with evolving RDS, respiratory symptoms shortly after birth may still be non-specific even though the underlying pathology is already progressing [79]. Early sonographic assessment can therefore help differentiate between transient TTN, evolving RDS, pneumothorax, or consolidation, and may reduce both delayed treatment and unnecessary intervention [70,71,80]. This is especially relevant for surfactant decision making, because LUS links bedside imaging more directly to the pathophysiological severity of lung disease rather than waiting for later clinical deterioration alone [71,77]. Contemporary surfactant care still relies largely on pragmatic FiO_2 and CPAP thresholds [11,112]. More recent work has therefore increasingly separated the question of when surfactant should be given from how it is administered, focusing on whether bedside tools such as LUS can refine treatment selection while the delivery technique itself may still depend on the infant's stability [69,70].

LUS Score

A major advantage of LUS is that it can be applied in a structured and repeatable [53] manner through semi-quantitative scoring. Rather than offering only a binary bedside impression, LUS scores provide an additional layer of functional information [137] that can support serial monitoring and more standardised decision making. In preterm neonates with RDS, several studies have shown that semi-quantitative LUS scores can help identify infants who are more likely to require surfactant, thereby supporting earlier and more targeted treatment [65,72,138,139].

A recent meta-analysis suggested that LUS is generally very good at identifying infants who will need surfactant early, particularly for ruling out those unlikely to require treatment, although its ability to positively predict treatment need was somewhat less strong [72]. This is clinically meaningful because surfactant tends to be most effective when administered early, ideally within the first 2-3 hours after birth, yet FiO_2-based criteria may only be met later in the course of disease [71,79,138]. Accordingly, LUS-guided surfactant replacement strategies, including echography-guided surfactant therapy (ESTHER), have been associated with a higher proportion of infants treated within the optimal time window, lower oxygen exposure before treatment, and improved oxygenation after surfactant administration, without increasing overall surfactant use [25,37,39]. A practical example of how the LUS score can complement FiO_2-based decisions comes from the ESTHER quality improvement project, where surfactant was administered when either FiO_2 exceeded a local cut-off or the LUS score exceeded a defined cut-off (e.g. >8), whichever occurred first. This approach improved the timeliness of surfactant replacement and reduced the maximal FiO_2 reached before treatment [71]. Overall, the key idea is that the LUS score adds an additional layer of information that can support earlier and more individualised respiratory decisions, rather than waiting for oxygen requirements alone to declare failure.

Reflecting the growing importance of this concept, ongoing multicentre trials are now evaluating whether combining FiO_2 criteria with LUS score thresholds results in better clinically meaningful outcomes than conventional threshold-based management alone [70]. Despite these advantages, several limitations of LUS in respiratory decision-making should be acknowledged. As discussed in Chapter 6.3, LUS is operator dependent and requires structured training and institutional oversight. A scoping review comparing LUS with CXR reported generally excellent interobserver agreement for LUS scoring (Cohen's $\kappa \geq 0.83$), but emphasised that reliability depends on standardised scanning protocols and consistent training [134]. Furthermore, LUS scoring systems use different cut-off values, which are not interchangeable across studies [70]. Therefore, the same scoring approach should be applied consistently within a given unit. To reduce training-related variability, the ESPNIC has recently published an expert consensus framework outlining a standardised pathway for neonatal

LUS competency assessment [140]. Finally, although LUS-guided strategies have shown benefits in process outcomes, such as earlier surfactant administration and reduced MV initiation, evidence from large, randomised trials demonstrating improvement in major clinical outcomes such as BPD or mortality, is still awaited.

6.8 Summary and Evidence gap

In the delivery room and early NICU period, respiratory management of very preterm infants is a constant balance between two goals that can pull in different directions: on the one hand, stabilising gas exchange quickly enough to prevent hypoxaemia and deterioration. On the other hand, avoiding unnecessary intubation and MV is important because ventilator-induced lung injury can contribute to downstream complications such as BPD [2].

In practice, clinicians start with clinical assessment and oxygenation targets and then escalate support stepwise, usually beginning with NIV and reserving intubation for infants who do not stabilise. This overall approach is well established. The difficult part is the key decisions: when to escalate and when to give surfactant. These decisions often must be made early, sometimes while the infant is still evolving clinically. A specific dilemma for neonatologists is the timing of surfactant administration [88]. That uncertainty is exactly where clinicians can feel stuck, either waiting too long, risking deterioration, or treating too early, risking overtreatment and potentially avoidable escalation steps.

This is why LUS has gained so much attention in neonatal care. LUS scoring allows moving from "how much oxygen does the baby need?" to "what is happening in the lung right now?", which is closer to the clinical decision neonatologists are trying to make.

Evidence supporting LUS score-guided respiratory decisions is growing. Semi-quantitative LUS scoring has been shown to correlate with oxygenation and to predict the need for surfactant in neonates supported with CPAP [65]. Predictive value has also been demonstrated in extremely preterm populations [139]. On top of that, implementation and quality improvement projects suggest that adding LUS scores into the decision process can improve the timeliness of surfactant therapy when used alongside conventional FiO_2-based criteria [71]. Together, these studies support the concept that LUS scoring can refine decision-making, particularly around early treatment and escalation.

However, there are still important evidence gaps that matter for real-world NICU practice. Much of the published evidence comes from selected cohorts, single-centre protocols or quality improvement interventions. Results may depend heavily on factors such as operator training, standardisation of scanning and reporting, local thresholds, and the specific case-mix in a given unit [48]. In addition, guideline evidence for delivery-room recommendations is more limited at the threshold of viability,

which increases uncertainty precisely among infants at highest risk and those in whom decisions are most time-sensitive [2]. Finally, while neonatal imaging literature suggests LUS scoring can be reliable across several indications and offers clear practical advantages over CXR, the key question for many centres is not only whether LUS works diagnostically, but whether implementing it as part of routine care actually leads to meaningful changes in respiratory management and short-term outcomes at the population level [134].

This is the rationale for the current work. By analysing outcomes before and after LUS implementation in a preterm NICU cohort, this retrospective study addresses a very practical question: when LUS moves from a promising tool in the literature for standardised use in an actual unit, does it measurably change respiratory management and short-term clinical outcomes in everyday practice? This evidence gap is directly relevant to neonatologists considering implementation, because it connects diagnostic performance with what ultimately matters in the NICU-treatment decisions, escalation patterns, and patient outcomes [134].

7. Methods

The methodological framework follows the department´s established protocol and the analysis plan used by the research team in the associated ongoing publication project.

7.1 Study Design and Population

This retrospective cohort study was conducted in the Neonatal Department of Vilnius University Hospital Santaros Klinikos (VUHSK) after approval by the regional bioethics committee (KMP Nr. 00007840). Clinical information was retrieved from electronic medical records, anonymised and organised into a structured dataset for analysis.

The cohort comprised premature neonates born between 01. January 2021 and 30 June 2024, with a GA of 23 – 32 weeks, who were admitted to the NICU. Infants meeting the predefined exclusion criteria of early neonatal death were not included. To assess changes associated with the introduction of a standardised LUS approach, two time periods were defined: a pre-LUS era (before the LUS implementation) and a post-LUS era (after routine standardised LUS use).

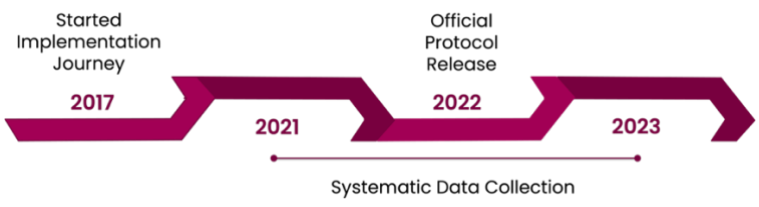

Figure 7. Protocol Timeline.

7.2 Lung Ultrasound Implementation and Protocol

In the post-LUS era, LUS examinations were performed at the bedside by trained attending neonatologists using a hospital-approved standardised protocol. Documentation included the interpreted findings and a conclusion adapted to GA, clinical condition and the course of disease. Repeated examinations were carried out when clinically indicated. As part of quality assurance, examinations and documentation were reviewed in accordance with departmental practice, including an independent review by experienced neonatologists with ultrasound expertise [141].

7.3 Lung Ultrasound Scoring and Criteria for Surfactant Guidance

In cases of severe RDS, a semi-quantitative LUS assessment was used to support surfactant decisions. Under the protocol, scoring was performed within the first hour after birth for all infants born at < 28 weeks' gestation, and for infants >29 weeks who had clinical signs of RDS and/or required >30% supplemental oxygen. Lung aeration was assessed in three regions per lung (anterior superior, anterior inferior and lateral). Each region was assigned a score of 0-3 according to the BRAT scoring system, based on ultrasound pattern and B-line appearance. A total LUS score ≥ 8 was considered indicative of severe RDS and supported the decision to administer surfactant [64].

7.4 Surfactant Policy Across Gestational Ages and Eras

In the delivery room, surfactant was given prophylactically to infants ≤ 26 weeks' gestation, based on departmental consensus. Infants >26 weeks´ gestation, surfactant administration was determined by combined clinical assessment in the pre-LUS era and by clinical assessment supplemented by LUS in the post-LUS era. In practice, treatment was indicated in infants with respiratory distress when FiO_2 exceeded approximately 0.30-0.35 early in the course, or after LUS implementation when the LUS score was ≥ 8 [64].

7.5 Outcomes and Definitions

Primary outcomes included the need for and duration of invasive and NRS, as well as surfactant use. To evaluate safety, common prematurity-related complications were compared between eras, including sepsis, IVH, BPD, and ROP.

BPD was defined based on persistent need for supplemental oxygen and/or respiratory support at 28 days of life, at 36 weeks postmenstrual age or at hospital discharge. Sepsis was defined according to institutional early- and late-onset protocols, based on clinical and/or laboratory evidence, with or without positive blood cultures. IVH was diagnosed using cranial ultrasound and graded using adapted Papile and Volpe classifications. ROP was diagnosed according to the International Classification of Retinopathy of Prematurity and the hospital screening protocol [64].

7.6 Statistical Analysis

All analyses were performed in R (version 4.4.2). Normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed variables are reported ± standard deviation (SD) and compared using independent sample t-tests. Non-normally distributed variables are reported as median (IQR) and compared using the Mann-Whitney U test. Categorical variables are presented as counts and percentages and compared using x^2 tests for Fisher´s exact test where appropriate.

Regression methods were selected based on outcome type. Binary endpoints were analysed using logistic regression. Over-dispersed count outcomes were analysed with negative binomial regression. Right-skewed continuous variables were log-transformed and modelled using linear regression. Results are presented as odds ratios (OR), incidence rate ratios (IRR), or ß coefficients with 95% confidence intervals (CI) and p-values.

Forest plots were created to visualise regression estimates. Receiver operating characteristic curve (ROC) analysis was applied to identify optimal cut-offs for continuous predictors (FiO_2 and LUS) using Youden´s index, with analyses performed for the overall cohort and separately for the pre-LUS and post-LUS eras. Statistical significance was set at $p < 0.05$.

8. Research results

8.1 Baseline Characteristics

The final cohort included 172 preterm neonates admitted to the NICU, with 84 infants in the pre-LUS period and 88 infants in the post-LUS period. Across the two eras, neonatal baseline characteristics were largely comparable, including sex distribution, birth weight, and GA. Differences were mainly seen on the maternal/pregnancy side: pregnancy complications were reported more frequently in the post-LUS era, and premature prelabour rupture of membranes (PPROM) was more common post-LUS, whereas spontaneous preterm birth was more frequent pre-LUS. Baseline characteristics are presented in Table 2.

Table 2. Baseline Characteristics:

Characteristics		**Pre-LUS n = 84 (49%)**	**Post-LUS n = 88 (51%)**	**p-value**
Neonatal	Sex female, n (%)	37 (44)	41 (47)	0.738 [1]
	Birth weight, g, mean (±SD)	1422.80 (±472.40)	1481.14 (±498.74)	0.433 [4]
	Gestational age, weeks, median (IQR)	30 (3)	31 (3.25)	0.111 [2]
	wGA ≥ 28, n (%)	65 (77)	70 (80)	0.730 [1]
	Latency period >18 hours, n (%)	13 (16)	30 (36)	0.003 [1]

	Congenital anomalies, n (%)	5 (6)	12 (14)	0.091 [3]
	Antenatal steroids, n (%)	67 (80)	60 (71)	0.168 [1]
	Resuscitation after birth, n (%)	10 (12)	13 (15)	0.581 [1]
Maternal	Mothers age, years, mean (±SD)	32.06 (±4.57)	32.25 (±5.22)	0.812 [4]
	Gravidity, median (IQR)	2 (1.25)	2 (2)	0.398 [2]
	Pregnancy complications, n (%)	26 (31)	53 (61)	<0.001[1]
	Caesarian section, n (%)	51(61)	45 (53)	0.308 [1]
	Causes of PB			
	PPROM, n (%)	20 (24)	31 (35)	0.040 [1]
	Spontaneous PB, n (%)	26 (31)	17 (19)	0.040 [1]
	Other, n (%)	38 (45)	40 (46)	1.0 [1]

IQR – interquartile range; PB- preterm birth; PPROM – preterm premature rupture of membranes; pre-LUS – before lung ultrasound protocol adoption; post-LUS – after lung ultrasound protocol adoption; SD – standard deviation; wGA – weeks of gestational age; Statistical tests used: [1]Pearson's Chi-squared test; [2]Mann-Whitney U test; [3]Fisher's Exact Test; [4]Two Sample t-test.

8.2 Respiratory Support Strategies

Overall, the data suggest that respiratory support practice changed after the introduction of the LUS protocol (Table 3). Most importantly, the proportion of infants who were started on invasive MV dropped markedly after implementation: MV initiation decreased by 25% ($p < 0.001$). In contrast, starting non-invasive support with CPAP did not change significantly between eras. This finding appears counterintuitive, as fewer infants were intubated initially, but the time spent on respiratory support increased in the post-LUS era. Median MV duration increased from 72 hours to 132 hours ($p = 0.002$), and median CPAP duration increased from 31 hours to 48 hours ($p = 0.007$).

Table 3. Comparison of respiratory support strategies before and after LUS protocol implementation.

	Pre-LUS	**Post-LUS**	**p-value**
CPAP initiated, n (%)	79 (94)	84 (96)	0.742
CPAP duration, hours, median (IQR)	31 (33)	48 (72)	0.007
MV initiated, n (%)	30 (36)	9 (10)	<0.001
MV duration, hours, median (IQR)	72 (84)	132 (144)	0.002

CPAP – continuous positive airway pressure; IQR – interquartile range; MV – mechanical ventilation; pre-LUS – before lung ultrasound protocol implementation; post-LUS – after lung ultrasound protocol implementation.

These differences persisted after accounting for GA. In the GA-adjusted model, infants in the post-LUS era had much lower odds of MV after birth: LUS implementation was associated with an 85% reduction in MV odds (OR 0.15; 95% CI: 0.05-0.38, $p < 0.001$) compared to the pre-LUS era. GA was also strongly associated with MV requirement: each additional week was linked to lower MV odds (OR 0.63; 95% CI: 0.52-0.75, $p < 0.001$), corresponding to a 37% reduction per additional gestational week. Because duration outcomes were right-skewed, we analysed CPAP and MV duration using linear regression on log-transformed durations.

For CPAP duration, being in the post-LUS era was associated with a 56.5% longer CPAP duration on average (B = 0.45; 95% CI: 0.14-0.75; $p < 0.01$), while GA was not associated with CPAP duration (B = -0.01; 95% CI: - 0.07-0.05; $p = 0.793$). For MV duration, post-LUS infants had an 84% longer MV duration on average compared with pre-LUS infants (B = 0.61; 95% CI: 0.22-0.99; $p < 0.01$). At the same time, each additional gestational week was associated with a 12.6% shorter MV duration (B = -0.13; 95% CI: -0.20-0.05; $p < 0.01$).

Finally, we explored whether antenatal steroids affected MV or CPAP duration, but the linear regression showed no association. For this reason, antenatal steroids were not included in the multivariable logistic regression models.

8.3 Surfactant Administration

To assess whether surfactant practice changed after LUS was introduced, we compared surfactant administration between the pre-LUS and post-LUS eras (Table 3). Overall, there was no statistically significant difference in the frequency of surfactant administration between the two periods ($p = 0.374$). Likewise, the method of surfactant instillation did not differ significantly between eras ($p = 0.108$) (Table 4). Even so, across both time periods, the LISA technique was used more often than ET administration, which aligns with the general shift in neonatology toward less invasive approaches.

Table 4. Comparison of surfactant administration and instillation techniques before and after LUS protocol implementation.

	Pre-LUS	**Post-LUS**	**p-value**
Surfactant administration n (%)	49 (59)	46 (52)	0.374
Instillation technique			0.108
LISA, n (%)	27 (55)	33 (72)	
via ET, n (%)	21(43)	7 (15)	
Unspecified, n (%)	1 (2)	6 (13)	

ET – endotracheal tube; LISA – less invasive surfactant administration; pre-LUS – before lung ultrasound protocol implementation; post-LUS – after lung ultrasound protocol implementation.

Because surfactant decisions are usually tied to oxygen requirement, we also evaluated how well FiO_2 predicts surfactant administration before vs after LUS implementation. We plotted Receiver operating

characteristic (ROC) curves and calculated areas under the curves (AUCs) to assess FiO_2 performance (Figure 8, Table 5). After LUS implementation, FiO_2 performed better as a predictor, showing higher specificity, accuracy (Table 5), and AUC than in the pre-LUS era. In the pre-LUS era specifically, an FiO_2 cut-off of 0.325 had a negative predictive value (NPV) of 92%, meaning that infants needing <32.5% FiO_2 were very unlikely to receive surfactant (Table 5).

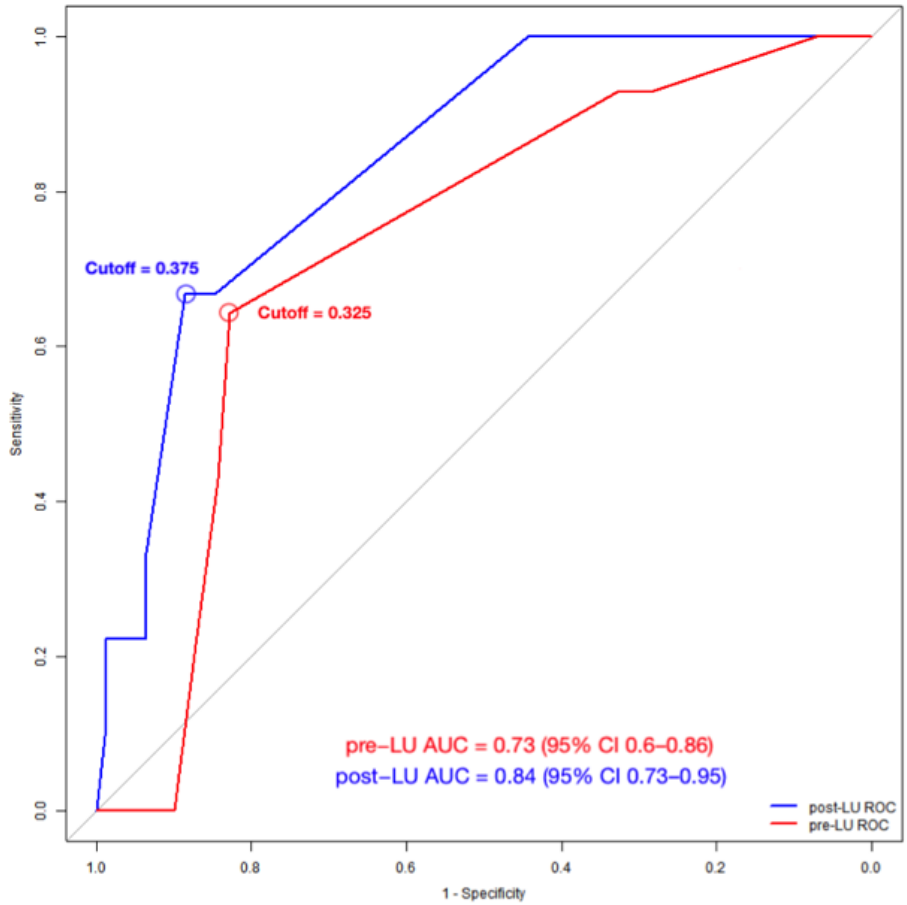

Figure 8. Receiver operating characteristic curves for FiO_2 as a predictor of early surfactant administration before and after protocol implementation.

AUC – area under the curve; CI – confidence interval; FiO_2 – fraction of inspired oxygen; pre-LUS – before lung ultrasound protocol implementation; post-LUS – after lung ultrasound protocol implementation; ROC – receiver operating characteristics.

ROC curves (Figure 8) showing how well FiO_2 predicts early surfactant administration before and after LUS protocol implementation. In the pre-LUS era (red curve), FiO_2 showed moderate discrimination (AUC 0.73; 95% CI 0.60-0.86), with an optimal cut-off of 0.325. In the post-LUS era (blue curve), FiO_2 performed better overall, with an AUC of 0.84 (95% CI 0.73-0.95) and a higher cut-off of 0.375, suggesting improved predictive accuracy during the LUS protocol period.

Table 5. Diagnostic performance of FiO_2 as a predictor of surfactant administration in the pre-LUS and post-LUS eras.

Era	FiO_2 Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
Pre-LUS	32.5%	64	83	43	92	0.73 (0.60 – 0.86)
Post-LUS	37.5%	67	89	40	96	0.84 (0.73 – 0.95)

AUC – Area Under the Curve; CI – Confidence Interval; FiO_2 – Fraction of Inspired Oxygen; NPV – Negative Predictive Value; PPV – Positive Predictive Value; pre-LUS – before lung ultrasound protocol implementation; post-LUS- after lung ultrasound protocol implementation.

Next, within the post-LUS era, we used logistic regression to test whether LUS findings add predictive value beyond an FiO_2 threshold, while also controlling for GA (Figure 9). In this model, LUS remained a statistically significant positive predictor of surfactant administration even after adjustment for FiO_2 (>37.5%) and wGA. Quantitatively, each 1-point increase in LUS was associated with about a 40% increase in the odds of receiving surfactant. In contrast, each additional week of GA was associated with a 36% reduction in the odds of early surfactant administration. Although $FiO_2 \geq 0.375$ tended to increase the estimated odds of surfactant use, this did not reach statistical significance, and the confidence interval was wide. Overall, this analysis supports LUS as a stronger independent predictor of surfactant instillation than FiO_2 alone.

Logistic regression model (post-LUS era) assessing predictors of surfactant administration, as shown in Figure 9. In this model, the LUS severity score was the strongest independent predictor: each 1-point increase in LUS score was associated with higher odds of receiving surfactant (OR 1.4; 95% CI 1.2-1.8; $p < 0.001$). GA showed the opposite effect: more mature infants were less likely to receive surfactant (OR 0.51; 95% CI 0.32-0.71; $p < 0.001$). In contrast, using $FiO_2 \geq 37.5\%$ as a binary threshold did not predict surfactant use in this adjusted model (OR 0.52; 95% CI 0.052-6.4; $p = 0.587$), and the confidence interval was wide.

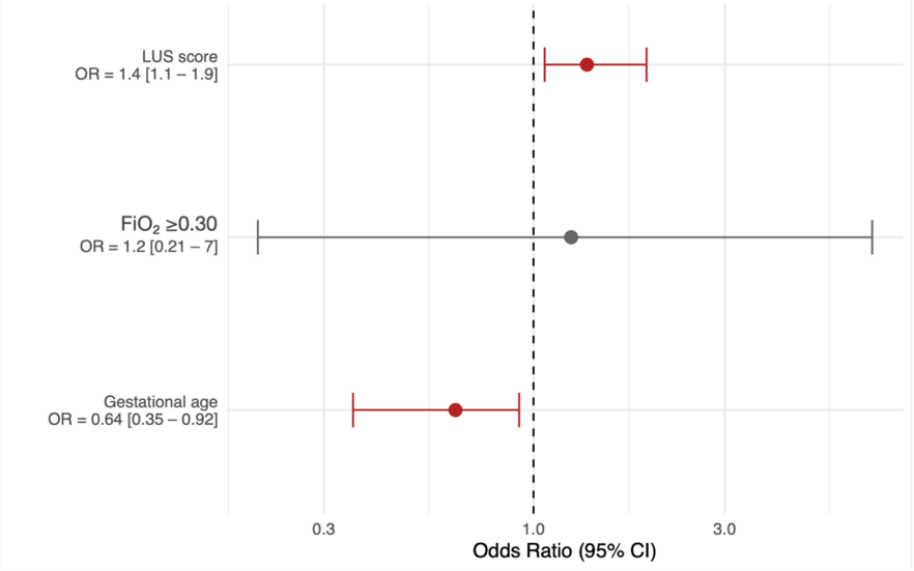

Figure 9. Post-LUS logistic regression for predicting early surfactant (<3 hours) use based on LUS and FiO_2, cutoff of 0.3: CI – confidence interval; FiO_2 – fraction of inspired oxygen; LUS score – lung ultrasound score; OR – odds ratio.

Finally, we sought a practical LUS score cut-off to predict surfactant administration. A threshold of 7.5 performed well overall, with 64% sensitivity, 94% specificity, 94% PPV, and 64% NPV. Overall discrimination was good, with an AUC of 0.83 (95% CI 0.69-0.96). In our cohort, 62% of infants had an LUS score < 7.5, and 38% had an LUS score ≥ 7.5, and this split remained similar when comparing the 7.5 versus 8.0 cut-offs.

8.4 Adverse Neonatal Outcomes

To assess safety after introducing the LUS protocol, we compared the frequency of common prematurity-related complications between the pre-LUS and post-LUS eras: IVH, ROP, BPD, and sepsis (Table 6). Across all four outcomes, none of the differences between eras reached statistical significance. In other words, within this cohort, introducing LUS into routine practice was not associated with higher rates of adverse neonatal outcomes, suggesting that the protocol implementation did not appear to cause measurable clinical harm.

Table 6. Comparison of common prematurity-related factors before and after the standardised implementation of LUS.

Complications	Pre-LUS	Post-LUS	p-value
IVH, n (%)	25 (30)	26 (30)	0.975
ROP, n (%)	24(29)	22(25)	0.564
BPD, n (%)	7(8)	11(13)	0.387
Sepsis, n (%)	7(8)	12 (14)	0.267

BPD – bronchopulmonary dysplasia; IVH – intraventricular haemorrhage; pre-LUS – before lung ultrasound protocol implementation; post-LUS – after lung ultrasound protocol implementation; ROP – retinopathy of prematurity.

9. Discussion

9.1 Interpretation of the Main Respiratory Findings

Following the implementation of the LUS protocol, the initial respiratory support decisions in this NICU changed significantly: the number of infants intubated and placed on MV decreased, while CPAP use remained largely unchanged. This trend supports the neonatology goal of keeping infants on non-invasive support whenever possible and reducing ventilator-associated lung injuries. This decrease in MV remained even after accounting for GA. Overall, it emphasises the importance of minimising invasive support to prevent lung injuries in newborns. The persistent reduction in MV after accounting for GA is significant because GA is usually the strongest predictor of a preterm infant's need for respiratory support. Even with GA included in the analysis, the post-implementation

period was independently linked to lower MV use, while GA behaved as expected. The finding that MV was initiated less often, yet MV and CPAP durations were longer, requires nuanced interpretation. One straightforward explanation is a "case selection" effect: if fewer borderline infants are intubated early, the smaller group that still ends up ventilated may simply represent the sicker infants, and longer ventilation in that subgroup would be expected. A similar logic applies to CPAP. Keeping more infants non-invasively supported can also mean CPAP is continued for longer as part of a cautious step-down strategy rather than indicating worse disease.

This is also in line with how bedside POCUS is described in the NICU: as an extension of clinical assessment that supports repeated reassessment and more structured decisions when respiratory status changes quickly [48].

The duration regression models provide additional context. Post-implementation status was associated with longer CPAP duration on the log scale ($B = 0.45$; $p < 0.01$), whereas GA was not ($p = 0.793$). For MV duration, post-implementation status was associated with longer MV duration ($B = 0.61$; $p < 0.01$), while each additional gestational week was associated with shorter MV duration ($ß = -0.13$; $p < 0.01$). These patterns suggest that CPAP duration may be influenced more by unit practice and weaning behaviour than by GA alone, whereas MV duration retains a stronger relationship with maturity.

Antenatal steroids were not associated with MV or CPAP duration in the linear regression models and were therefore not included in the multivariable logistic models. This finding should be interpreted cautiously, as no association was detected in this dataset, rather than as evidence against the known respiratory benefits of antenatal steroids described in neonatal literature [25].

9.2 Confounding Considerations

A critical limitation of a pre/post-implementation design is that baseline differences across eras can influence outcomes independently of the protocol. In this cohort, neonatal baseline variables were broadly similar, but several maternal/pregnancy characteristics differed between eras (for example, pregnancy complications were more frequent post-implementation, and PPROM and latency were higher). These differences may affect early respiratory course and oxygen requirement through mechanisms beyond pure surfactant deficiency, such as inflammatory exposure or infection risk, which could partly contribute to longer respiratory support duration even if MV initiation decreases [88]. For this reason, the most defensible interpretation is that LUS protocol implementation was associated with a change in management patterns; it cannot fully establish causality without a prospective design or more extensive confounder adjustment.

9.3 Surfactant Administration and Decision Metrics

Surfactant exposure and instillation technique distribution did not differ significantly between eras. This is clinically relevant because the aim of LUS protocol implementation is not necessarily to change total surfactant exposure, but to improve confidence in targeting and timing in infants where conventional markers are imperfect. Current European guidance still relies on FiO_2 thresholds on CPAP as pragmatic triggers for early rescue surfactant and recognises that bedside tools may refine decision-making in practice [88].

The ROC analysis adds nuance to the FiO_2-based approach. In the pre-implementation era, FiO_2 showed moderate discrimination for early surfactant administration (AUC 0.73; cut-off 0.325), and the cut-off had a high negative predictive value (NPV 92%), suggesting that low oxygen requirement performed well as a rule-out marker. In the post-implementation era, FiO_2 showed better overall discrimination (AUC 0.84; cut-off 0.375). This improvement may reflect more standardised respiratory assessment and documentation after LUS protocol implementation, but it also highlights that FiO_2 remains an indirect surrogate and may be influenced by recruitment, interface effectiveness, and mixed pathology in very preterm infants [130].

From a clinical decision-making perspective, AUC values are helpful but do not directly answer the bedside question "what happens if this threshold is used?" The key message from the FiO_2 cut-offs in this cohort is that the negative predictive value was high, supporting FiO_2 as a useful rule-out marker, whereas the positive predictive value remained lower, suggesting that an FiO_2 threshold alone is less reliable as a stand-alone rule-in tool. This is consistent with the broader literature showing that surfactant decision thresholds vary across settings and that FiO_2 alone cannot fully capture the heterogeneity of respiratory failure in very preterm infants on CPAP [130].

The post-implementation regression model supports an additional role for LUS scoring. After adjusting for GA and a binary FiO_2 threshold ($\geq$37.5%), the LUS score remained an independent predictor of surfactant administration, whereas the binary FiO_2 threshold was not significant and had wide confidence intervals. This pattern supports the interpretation that the LUS score captures clinically relevant information about aeration severity that is not fully represented by oxygen requirement alone. Evidence from prior studies indicates that semi-quantitative LUS scoring correlates with oxygenation and predicts the need for surfactant in CPAP-treated neonates, including extremely preterm infants [65,139].

The practical cut-off analysis provides a clinically usable interpretation of the score. A threshold of 7.5 yielded a rule-in profile with high specificity and PPV (both 94%) and good overall discrimination (AUC 0.83). The cohort's score distribution (62% < 7.5 and 38% $\geq$ 7.5) suggests that a minority of infants would be classified as high risk using this threshold, which is plausible in a NICU population

where surfactant use is common. The close alignment with previously described thresholds around 8 supports the conclusion that the identified cut-off lies within the expected range of prior protocols [139].

9.4 Comparison with Implementation Literature

The findings are consistent with implementation-focused work, such as the ESTHER quality improvement project, in which surfactant was administered when either FiO_2 crossed a local threshold or the LUS score exceeded a cut-off, whichever occurred first, with the explicit aim of improving timeliness rather than increasing overall surfactant exposure [71].

The present cohort showed stable overall surfactant rates but stronger structure in surfactant decision metrics during the post-implementation era, supporting a similar interpretation: LUS scoring may enable earlier, more confident identification of infants likely to benefit from surfactant without necessarily increasing total surfactant exposure.

9.5 Imaging Context and Workflow Relevance

Beyond surfactant decision-making, LUS fits neonatal workflows because it can be repeated at the bedside without ionising radiation. Radiation burden is a relevant concern in very preterm infants who may undergo repeated chest radiographs during prolonged NICU admissions [131]. Evidence from the neonatal imaging literature suggests that LUS and CXR are similarly reliable across several neonatal indications, while ultrasound offers practical advantages, such as portability and the ability to perform serial reassessment without radiation [134]. LUS is operator-dependent, and safe, consistent clinical use requires training, standardised scanning, unified documentation, and quality assurance [48].

9.6 Safety Outcomes

A key concern in implementation studies is whether a new diagnostic pathway leads to unintended harm through delayed escalation, misclassification, or inconsistent treatment. In this cohort, rates of IVH, ROP, BPD, and sepsis did not differ significantly between eras. While lack of statistical significance does not prove equivalence, these findings are reassuring and do not suggest that routine LUS protocol implementation was associated with increased prematurity-related complications during the study period.

It is also important to interpret these safety findings with appropriate caution. Several of these complications are multifactorial and influenced by GA, infection/inflammation, haemodynamic stability, and broader NICU practices, so small differences may not be detectable in a single-centre cohort. Therefore, the safest conclusion is that no increase was detected in this dataset, while larger prospective studies would be needed to confirm equivalence and explore longer-term outcomes [59].

9.7 Strengths

A major strength of this study is that it is the first study in Lithuania to evaluate the implementation of a standardised LUS protocol into routine neonatal clinical practice. In addition, LUS was not tested as a "research add-on“ but was introduced as part of routine care in a tertiary-level NICU. This makes the findings more representative of real clinical practice. After the protocol was implemented, all neonatologists in the department received LUS training, and documentation was standardised, likely improving consistency and reducing variation in how findings were recorded.

The cohort included 172 preterm neonates, which is a realistic sample size for a single tertiary centre. Even though the total sample size was limited by the centre's capacity, the G*Power calculations indicated that the main statistical tests had high power (>95%), supporting the analyses' adequacy for the study's primary comparisons. In addition, LUS was performed using a validated scoring approach, and the use of structured electronic medical records enabled us to comprehensively evaluate not only respiratory but also safety outcomes.

9.8 Limitations

At the same time, there are important limitations. First, this was a retrospective analysis, meaning we had limited control over how LUS images were acquired and interpreted at the bedside at the time, and we depended on documentation quality. Some cases were also excluded because the medical records were incomplete, which introduces a risk of selection bias.

Second, this study was conducted in a single NICU in Lithuania, so the results may not be generalised to other hospitals with different patient populations, staffing structures, respiratory management strategies, or LUS experience.

Finally, the sample size was inherently limited by the number of very preterm births in the centre: the perinatology centre accounts for roughly 10-11% of ~3000 annual deliveries, which is why an observational period of about 1.5 years was needed to reach the final cohort. While the sample size appeared sufficient for the primary analyses, the next step would be larger multicentre prospective studies to confirm whether these practice changes and outcomes are reproducible across different NICUs [141].

10. Conclusion

Surfactant administration did not change significantly after the introduction of the LUS protocol. The proportion of infants receiving surfactant was comparable between eras (59% pre-LU vs 52% post-LUS; $p = 0.374$), and the distribution of instillation techniques also showed no statistically significant shift ($p = 0.108$), although LISA was the most used approach in both periods. In the implementation

era, decision metrics improved: FiO_2 showed better predictive performance for early surfactant administration after LUS implementation (AUC 0.84 vs 0.73), and within the post-LUS cohort the LUS score was an independent predictor of surfactant administration (OR 1.4 per point; 95% CI 1.2-1.8; $p < 0.001$), whereas the binary FiO_2 threshold (≥37.5%) was not significant in the adjusted model ($p = 0.587$). A practical LUS cut-off of 7.5 demonstrated high specificity and PPV (both 94%) with an AUC of 0.83, supporting its usefulness as a "rule-in" threshold for identifying infants likely to require surfactant.

Implementation of the LUS protocol was associated with a substantial reduction in initiation of MV after birth. MV initiation decreased from 36% in the pre-LUS era to 10% post-LUS ($p < 0.001$), while CPAP initiation remained high and statistically unchanged (94% vs 96%; $p = 0.742$). After adjustment for GA, the post-LUS era remained strongly associated with lower odds of MV after birth (OR 0.15; 95% CI 0.05-0.38; $p < 0.001$), and increasing GA was also associated with reduced MV odds (OR 0.63 per week; $p < 0.001$). Although fewer infants were ventilated invasively, the duration of both MV and CPAP was longer in the post-LUS era, suggesting that respiratory support strategies may have shifted toward more individualised and cautious management over time rather than simply becoming less intensive.

No statistically significant differences were found in rates of IVH, ROP, BPD, or sepsis between the pre-LUS and post-LUS eras. Within the limitations of a retrospective single-centre design, these findings are reassuring and support that routine LUS implementation in this NICU was not associated with a detectable increase in common prematurity-related complications during the study period.

In this tertiary NICU cohort, routine implementation of a standardised LUS protocol was associated with a measurable shift in respiratory management – most notably MV – while maintaining stable surfactant use rates and without evidence of increased short-term complications. LUS scoring also provided clinically relevant information for surfactant decision-making during the implementation era.

11. Practical Recommendations

1. Maintain LUS as a standard bedside assessment tool in preterm respiratory care. Given the association with reduced MV initiation and the absence of a signal toward increased short-term complications, routine LUS use appears suitable for continued integration into daily NICU practice in this setting.
2. Prioritise training and standardised documentation during implementation. Because LUS is operator-dependent, consistent benefit requires structured training, supervision, and unified

documentation. Ongoing competency maintenance (refresher training and internal review of scans) should be prioritised to preserve reproducibility.

3. Use LUS scoring as an adjunct to clinical assessment and FiO_2 trends when surfactant decisions are uncertain. In the post-LUS cohort, LUS was a stronger independent predictor of surfactant administration than a binary FiO_2 threshold. In practice, this supports combining LUS scoring with clinical assessment rather than relying solely on oxygen requirements, particularly in borderline cases on CPAP/NIV.
4. If a local cut-off is used, a LUS threshold around 7.5-8 can be considered as a "rule-in" indicator. A LUS cut-off of 7.5 showed high specificity and PPV in this cohort, which is clinically useful when the aim is to avoid missing infants likely to require surfactant. Any cut-off should still be applied within the full clinical context and aligned with unit workflow.
5. Future research should confirm generalisability in prospective and multi-centre settings. To better separate implementation effects from changes in case-mix and practice over time, future studies should ideally be prospective and multi-centre. Priority endpoints include MV initiation and duration, surfactant timing (not only frequency), and clinically meaningful outcomes such as BPD severity and longer-term respiratory follow-up.

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13. Annexes

1. Poster from Abstract Presentation at SIGNEC 2025 and Neonatal QI & Innovation Conference. 22.-23.05.2025

Impact of Lung Ultrasound Implementation in Preterm Neonates: A Neonatal Quality Improvement Study

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Vilnius University

01 Introduction

- Lung ultrasound (LU) is a non-invasive tool increasingly used in NICUs.
- In 2022, LU was implemented as standard care in Santaros NICU.

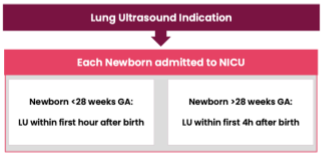
02 Aim

To assess the clinical impact of LU on neonatal respiratory support and outcomes.

03 Methodology

- **Design**: Retrospective cohort study (2021–2023)
- **Population**: 139 neonates
- **Groups**: Pre-LU (n=73) vs Post-LU (n=66)
- **Outcomes**: MV need, Surfactant use, NICU stay, BPD, IVH, ROP, Sepsis
- **Analysis**: Non-parametric tests and logistic/quantile regression

04 Protocol Information

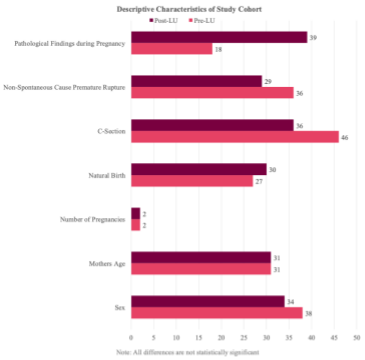


Hospital
Perinatology Centre
(3,000 births/year)

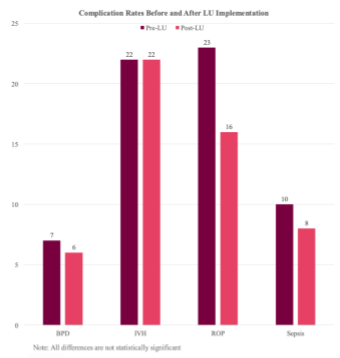
Ethics Approval
No: 2024/11-1618-1074

05 Results/Findings

Participant Profile



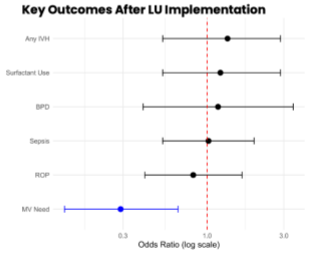
Complication Rates Comparison



Primary Clinical Outcomes

Outcome	Pre-LU	Post-LU	p-value
MV use	47.9%	18.2%	0.001
Surfactant received (outside of delivery room)	70.2%	61.5%	0.39
NICU stay (days)	9 (median)	6 (median)	0.28

Key Outcomes After LU Implementation



06 Conclusion

- LU implementation significantly reduced mechanical ventilation use.
- NICU stay was shorter but not independently associated after GA adjustment.
- LU is a safe, effective bedside tool that supports individualized and timely care.
- Further prospective studies are needed to confirm long-term effects.

07 Acknowledgements

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