Study protocol

Neonatologist-performed lung ultrasound during immediate transition after birth to predict the need for respiratory support persisting more than 1 hour – a pilot study

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1. Introduction

Lung ultrasound is an emerging clinical tool to assess the lung in a dynamic way. Recently, the focus has been on establishing lung ultrasound in the neonatal intensive care unit (NICU) as a point-of care application. As a result, the corresponding guidelines have been issued by the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) in 2020. (Kurepa *et al.*, 2018; Singh *et al.*, 2020)

Neonatologist-performed lung ultrasound (NPLUS) has proven to be a safe, accessible, and reliable diagnostic tool in neonatal intensive care. Compared to X-ray examination, NPLUS is a highly specific and sensitive approach which is not relying on ionizing radiation (Aichhorn *et al.*, 2021; Singh *et al.*, 2021; Renz *et al.*, 2022).

Diagnostic applications for NPLUS include the evaluation and serial monitoring of respiratory conditions such as respiratory distress syndrome (RDS), transient tachypnoea of the newborn (TTN), pneumonia, pleural effusion, atelectasis, lung oedema, meconium aspiration syndrome (MAS) and pneumothorax. By applying the lung ultrasound score, a semi-quantitative method to assess the neonatal lung, neonatologists are able to identify infants in need for surfactant or infants at risk of bronchopulmonary dysplasia. (Rodriguez-Fanjul *et al.*, 2020; Aichhorn *et al.*, 2021; Küng *et al.*, 2022; Schmidt and Ramamoorthy, 2022)

2. Background

Lung ultrasound is based on the interpretation of ultrasound artefacts (A- and B- lines), analysis of the pleura, and the visualization of consolidations and pleural effusions enhancing the differential diagnosis of acute respiratory distress in newborns. The impairment of lung aeration can be quantified based on the number and type of visualized artefacts. (Raimondi *et al.*, 2021; Ollier *et al.*, 2022)

There is emerging evidence that NPLUS is a reliable tool to differentiate between the different causes leading to RDS in neonates. By today, different scoring systems have been developed in different clinical contexts. (Brat *et al.*, 2015; Mongodi *et al.*, 2021; Rodriguez-Gonzalez *et al.*, 2022) These scores aim at giving a comprehensive look on the lung's condition by screening the lung fields.

Despite the growing body of evidence, studies on NPLUS during stabilization and resuscitation immediately after birth are still scarce. In the study performed by Blank et al., they found that in healthy term and late preterm infants within the first 20 min after birth, the lung ultrasound score for neonates requiring respiratory support at the NICU was highly predictive. (Blank *et al.*, 2017) In the ULTRASURF study, a randomized controlled trial from Rodriguez-Fanjul *et al.* in 2020, NPLUS was performed within 1 hour after birth in preterm neonates (≤ 32 weeks of gestation) with RDS. In the study protocol, three scans of the anterior, lateral, and posterior chest walls were performed on each side. A 0- to 3-point score was given for each scanned area with a total score ranging from 0 to 18. One randomized group received surfactant based on this lung ultrasound score ≥ 8 and FiO2 thresholds, in the other group surfactant was administered solely based on FiO2 thresholds. In the group, in which the diagnosis was based on the lung ultrasound score, neonates received earlier surfactant without increasing the number of patients requiring surfactant treatment. (Rodriguez-Fanjul *et al.*, 2020)

Neonates born by a Caesarean section are particularly prone to have an altered adaption to extrauterine life. Especially in the first hours after birth, TTN may occur due to delayed lung fluid clearance after birth. (Riskin *et al.*, 2005; Poerio *et al.*, 2021) While acute RDS in the first hours after

birth may be a self-limiting disorder and therefore a benign condition, it remains difficult to identify infants in need for further respiratory support at the NICU. Admission to the NICU not only causes parental stress but also contributes to additional healthcare costs. (Pierro *et al.*, 2023). Using the lung ultrasound score for the early identification of neonates in need of respiratory support persisting more than 1 hour would be highly advantageous. Neonates requiring further treatment could benefit from early admission at the NICU, whilst the others could be prevented from an 'unnecessary' transfer to the NICU which would in turn reduce the burden of transport, workload, and healthcare costs.

3. Objectives

The objective of this study is to evaluate the role of NPLUS during the immediate transition after birth of late preterm and full-term neonates using the lung ultrasound score to predict the need for respiratory support persisting more than 1 hour. NPLUS will be conducted at specific time points after birth (at 5, 15, 30 and 60 minutes) by a trained medical doctor who will complement as an additional member of the medical team.

- **Hypothesis I:**
  We hypothesize that there is a cut-off value of the lung ultrasound score performed 5, 15, 30 and 60 minutes after birth that is reliable to predict the need for respiratory support persisting > 1 hour in late preterm and full-term neonates.

- **Hypothesis II:**
  We hypothesize that there is a cut-off value of the lung ultrasound score performed 5, 15, 30 and 60 minutes after birth that is reliable to predict the need for admission to the NICU in late preterm and full-term neonates.

- **Hypothesis III:**
  We hypothesize that neonates in need of respiratory support persisting > 1 hour have significantly higher lung ultrasound scores even when assessed already in 5, 15, 30 and 60 minutes after birth, compared to neonates requiring respiratory support < 1 hour after birth.

- **Hypothesis IV:**
  We hypothesize that there is a correlation between the lung ultrasound score performed at 5, 15, 30, and 60 minutes after birth, the length of respiratory support and the required mode of ventilation.

- **Hypothesis V:**

  We hypothesize that the lung ultrasound score assessed by NPLUS decreases between 5 and 60 minutes after birth.

4. Design, setting and participants

The present **study design** is conceived as an observational prospective pilot study.

Study procedures: In this study NPLUS is performed to quantify the lung ultrasound score 5, 15, 30 and 60 minutes after birth in late preterm and full-term neonates. The lung ultrasound examination of the anterior and lateral chest walls is conducted in supine position of the neonate, the examination of the posterior chest walls requires turning the neonate into lateral position for a couple of seconds. After 60 minutes after birth, the study patients do not require any additional examination. Furthermore, we ensure that the clinical routine care is not affected by NPLUS.

Routine care: Immediately after cord clamping, the neonate is placed under an overhead heater on the resuscitation cot ('CosyCot', Fisher&Paykel Healthcare; New Zealand) in supine position by the midwife. If obstructions of the upper airways are obvious, immediate suction of the oropharynx is performed. If necessary, respiratory support is applied by using a 'Neopuff Infant T- Piece Resuscitator' (Perivent, Fisher& Paykel Healthcare; New Zealand) and a face mask of appropriate size (PVC face mask no. 0 or 1, VBM; Germany). For infants with RDS, NPLUS is an optional diagnostic approach to evaluate lung aeration during neonatal transition and to rule out morbidities such as a pneumothorax.

NPLUS is frequently performed in daily routine within the first 30 minutes after birth for an early examination of the lungs and/ or following the initial treatment after one to two hours after birth when the neonate is admitted to the NICU.

Lung ultrasound score: Although the score of Brat et. al. is currently the most used one, we intend to use the score introduced by Rodriguez-Fanjul *et al.* in the ULTRASURF study. (Brat *et al.*, 2015; Rodriguez-Fanjul *et al.*, 2020) This score was developed to assess the neonate's lung within the first hour after birth, focusing not only on the anterior and lateral parts of the hemithorax but it also considers the posterior chest walls. Since our study is particularly aimed at neonates born by a Caesarean section, for which TTN is likely to occur, it is advantageous to include the posterior chest walls in the lung ultrasound score. (Riskin *et al.*, 2005; Blank *et al.*, 2017) Moreover, a congenital pneumonia is detected the best in a comprehensive examination of the lung.

NPLUS is conducted with a 12-15 MHz linear transducer preferably using the presets "lung" or "small parts". Sequences of 3-5 seconds are saved and scored. To minimize interference with the routine care, NPLUS will be performed by an independent trained medical doctor and clinical findings will not be passed on to the medical team in charge. The only exception to communicate the obtained NPLUS findings would be a pneumothorax. In this situation the diagnosis will be communicated to the medical team, and the neonate will be excluded from the study.

To ensure **inter-observer reliability** the anonymous video sequences are then blinded and rated by two independent neonatologists.

Inclusion criteria:

- Late preterm neonates (born between 34 0/7 and 36 6/7 weeks of gestation) and full-term neonates (born later than 36 6/7 weeks of gestation) delivered by Caesarean section at the Department of Obstetrics and Gynaecology, Medical University of Graz
- Presence of any sign of respiratory distress (defined as tachypnoea/ dyspnoea, grunting, flaring of the nostrils or chest retractions)
- Written informed consent obtained from the parents prior to birth.

Exclusion criteria:

- Presence of cardiopulmonary malformations
- Patients with pneumothorax diagnosed by NPLUS

Sample size: Statistical analysis for cut-off determination will be performed with a sample-size of 40 individuals, excluding patients with pneumothorax diagnosed by NPLUS. Hence, we aim at comparing 20 neonates who are transferred to the NICU with 20 neonates who initially need respiratory support but then do not require any 60 minutes after birth.

Sample size calculations cannot be performed beforehand, since no data from previous studies are available. Hence, this pilot study is conducted to generate data for the sample size calculation of the consecutive main study (Thabane *et al.*, 2010).

5. Statistical analysis

Demographic information, clinical characteristics, and lung ultrasound features will be summarized. First, the Kolmogorov–Smirnov test will be applied to test the data significance, which will then be represented as the mean (standard deviation, SD) or median (interquartile range, IQR). The predictive performance of the lung ultrasound score for the need for respiratory support persisting more than 1 hour after birth and for admission to the NICU will be analysed by plotting the receiver operating characteristic (ROC) curve, and areas under the ROC curves (AUCs) determining cut-off values. Group differences in primary and secondary outcome parameters between patients who are transferred to the NICU in need for respiratory support for more than 60 minutes and patients who do not need any respiratory support after 60 minutes after birth are calculated using χ^2 and Fisher's exact tests for discrete variables, and t-test or Mann-Whitney U test for continuous variables. Additionally, the correlations between the lung ultrasound score, length of respiratory support and the mode of ventilation will be analysed using either the Spearman's rank correlation coefficient or the Pearson's correlation depending on which one is more appropriate. The correlation analyses are considered in an explorative sense; therefore, no multiple testing corrections will be performed. SPSS23.0 (IBM Corporation, New York, NY, USA) is used for statistical analysis.

6. Outcome measures

Primary

- Determination of the lung ultrasound score according to Rodriguez-Fanjul *et al.* 2020 at 5, 15, 30 and 60 minutes after birth
- Need for respiratory support persisting more than 1 hour
- Admission to the NICU

Secondary

- Length of respiratory support (in minutes)
- Mode of respiratory support (non-invasive versus invasive ventilation)
- Routinely obtained capillary blood gas analysis of the newborn
- Routinely obtained monitoring parameters including arterial oxygen saturation (SpO2), heart rate (either by pulse oximetry or electrocardiography), and cerebral oxygen saturation (near-infrared spectroscopy)
- SpO2/FiO2 ratio (S/F ratio)
- pH of the umbilical artery
- Apgar score
- Pregnancy risk factors including intra-amniotic infection, and premature rupture of the membranes
- Prenatal corticosteroids

7. Research plan and time table

The study will start in spring 2024.
The study is designed for an approximate running time of three years.

8. References

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