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Lung ultrasound to predict the duration of respiratory support in newborn infants with respiratory distress

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List of abbreviations

AIC	Akaike Information Criterion
BE	Base excess
CART	Classification and Regression Tree (analysis)
CM	Centimeter
CONSORT	Consolidated standards of reporting trials
CPCS	Center for pediatric clinical studies
CRF	Case report form
CRP	C-reactive protein
C/S	Cesarean section
DLP	Double lung point
FiO_2	Fraction of inspired oxygen
IQR	interquartile range
ITT	Intention-to-treat
LUS	Lung ultrasound score
MAD	Mean arterial blood pressure
MAS	Meconium aspiration syndrome
MIN	Minute
MSAF	Meconium-stained amniotic fluid
NCPAP	Nasal continuous positive airway pressure
NICU	Neonatal intensive care unit
PEEP	Positive end-expiratory pressure
PL	Pleural line
ROM	Rupture of membranes
RR	Respiratory rate
SpO_2	Arterial oxygen saturation measured by pulse oximetry
SD	Standard deviation
TTN	Transient tachypnea of the newborn

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1 Introduction

1.1 Transition from intrauterine to extrauterine life

The cessation of placental perfusion during the transition from intrauterine to extrauterine life requires the newborn lung to supply oxygen on the one hand and to eliminate carbon dioxide from the organism on the other. Multiple crucial steps, partly overlapping and essentially intertwined, are required for transitioning successfully: initiation and continuation of breathing, lung aeration, lung liquid clearance, adequate surfactant activity, and circulatory changes to shift from a parallel to a serial circulation.

In utero, the fetal lung is liquid-filled due to an active chloride transport into the developing pulmonary alveoli. Facilitated by type 2 pneumocytes, said ion secretion across the pulmonary epithelium leads to a passive sodium and water influx [1, 2]. In the last trimester, the lung liquid secretion reaches about 4.1 milliliters per hour and kilogram body weight. It is crucial for lung development as it expands the lung and stimulates lung tissue growth [3, 4]. In animal models, the total lung liquid volume was determined to be 40 milliliters per kilogram 19 days before the onset of labor and between approximately 10 to 40 milliliters per kilogram at birth [5-7]. While there is agreement that lung liquid secretion and volume remain relatively constant throughout pregnancy, there is conflicting evidence as to whether they decrease before labor in preparation for birth [5, 7]. Recent studies show decreasing levels of lung liquid secretion and volume in the days even before and again accelerated after the onset of labor [7]. Causatives for switching the lung epithelium from secretion to absorption are epinephrine, steroid, and thyroid hormones mediating apical sodium absorption by increasing sodium pump activity and conductance [8].

After the onset of labor, the above endocrine-mediated pre-labor reduction of lung liquid continues as the stress hormones epinephrine and vasopressin are released in higher concentrations with increasing labor, not only inhibiting the secretion of lung liquid but, in contrast, leading to its reabsorption by activating sodium channels in the lung epithelium as stated above [9]. As part of the receptor-ligand interaction, beta-adrenergic receptor activation through beta-

adrenoceptor agonists like epinephrine partake in lung liquid clearance [9]. Following the sodium gradient, lung liquid is shifted from the alveoli to the interstitium mainly via aquaporins, then into the pulmonary circulation and the lymphatic system [10, 11]. Additionally, labor-induced contractions alter the intrauterine position of the fetus, thus leading to an outflow of lung fluid via increased pressure on the thorax and abdomen [12, 13].

The shift of lung liquid into the interstitium and the ultimate clearance from the pulmonary tissues is aided by the increased ventilation of the neonate's lung after birth, as described in more detail below [12]. Contrary to historical assumptions, the mechanical pressure exerted on the thorax during vaginal delivery plays a minor role in clearing lung liquid [12].

Following the inspiratory muscle contractions and chest wall expansion in normally breathing neonates immediately after birth, intrapleural and interstitial tissue pressure are reduced. The resulting pressure gradient forces lung liquid from the proximal into the distal airways to be further reabsorbed by the mechanisms described above [14, 15]. Particularly inspiration, in which spontaneously breathing neonates generate hydrostatic pressure gradients between 12 and 80 cmH_2O, promotes a relatively quick shift of lung liquid from the airways into the surrounding tissues and promotes establishing a functional residual capacity [15, 16]. While with each breath, more and more air enters the newborn's airways after birth, it is only partially exhaled during expiration due to a partial closure of the glottis [17]. The neonate further maintains its functional residual capacity through a distinct breathing pattern with a short inspiration and a prolonged expiration, slowing lung deflation. The resulting hydrostatic pressure during expiration also promotes lung liquid clearance from the alveoli [13].

Contrary to the quick shift from the airways to the pulmonary interstitium, lung liquid clearance via the pulmonary circulation and lymphatic system is slow. The discrepancy between the influx and elimination of lung liquid leads to a fluid overload of the interstitium, which is reflected in an increased pulmonary interstitial pressure of about 5.3 to 6.7 cmH_2O and fluid cuffs that surround pulmonary arteries corresponding to the clinical picture of pulmonary edema seen

in animal studies [18, 19]. Both interstitial pressure and perivascular fluid cuffs decrease gradually over four to six hours postnatally, reaching a maximum at around 30 to 120 minutes after birth [18, 19]. Whereas during inspiration, pressure gradients vastly surpass the increased pulmonary interstitial pressure, re-entry of lung liquid into the alveolar space occurs during expiration to a certain extent, leading to a clearing and re-entry cycle of lung liquid during in- and expiration until the pulmonary interstitial pressure decreases. The neonate's above expiratory maneuvers limit lung liquid re-entry during expiration [13].

Pulmonary surfactant from type 2 alveolar cells further helps establishing a functional residual capacity by reducing alveolar surface tension and increasing lung compliance [12, 20].

Documented in both animal models and ultrasound in healthy neonates, partial lung liquid clearance is reached within minutes and complete postnatal airway clearance in two to six and up to 24 hours, respectively [2, 21].

As for circulatory transition after birth, the parallel fetal circulation dominated by two major right-to-left shunts via the foramen ovale and the ductus arteriosus changes to a serial circulation without major shunts after a usually short transitional phase with potential bi-directional shunting. Cardiovascular adaptation is mediated by hormones on the one hand (increased levels of cortisol and thyroid hormone as well as catecholamines) and, on the other hand, by clamping of the umbilical cord. The latter removes the low vascular resistance in umbilical-placental circulation and increases systemic vascular resistance.

Pulmonary vascular resistance decreases with lung aeration, mediated crucially by endothelial nitric oxide, thus increasing blood flow through the lungs and venous return to the left atrium resulting in functional closure of the foramen ovale. Both, increased systemic vascular resistance and decreased pulmonary vascular resistance, lead to left-to-right shunting of blood through the ductus arteriosus until its functional closure on postnatal days one to four [6, 22, 23].

1.2 Failure to clear lung liquid: delayed transition and transient tachypnea of the newborn

Failure to clear lung liquid can lead to respiratory distress in newborns. In the absence of physiological hormonal influences and stress of labor as described above, less sodium and water are reabsorbed, thus leading to fetal lung liquid retention with an increased fluid load in the pulmonary interstitium, resulting in pulmonary edema impairing oxygenation and ventilation [24, 25]. Insufficient hormonal priming of the fetal lungs to prepare for extrauterine life is commonly found in near-term infants born via elective cesarean section performed before the onset of labor [26]. In addition, elective cesarean section without uterine contractions may decrease the effect of fetal postural changes on reducing intrathoracic lung liquid, leading to higher intrathoracic lung liquid volumes at birth. With higher initial lung liquid volumes, lung compliance may be reduced, and the above clearing and re-entry cycles of lung fluid are more pronounced and prolonged, resulting in an increased work of breathing [13, 27]. Since the first breaths, especially the first inspiratory volumes, are crucial for establishing a functional residual capacity and clearing lung liquid, a reduced respiratory drive postnatally, for example, in the setting of asphyxia, may result in lung liquid retention and subsequent respiratory distress [2, 6, 24, 28].

Depending on the severity of the symptoms and the clinical course, a mild manifestation of this clinical picture is referred to as “poor adaptation to extrauterine life” or “delayed transition” [24, 29-31], whereas a severe and prolonged clinical course, usually lasting longer than two hours, is called “transient tachypnea of the newborn (TTN)” [24, 30, 32]. Delayed transition and TTN are the most common causes of respiratory distress in infants born at or near term, occurring in about five to six neonates per 1,000 term births [2, 29, 30, 33]. TTN incidence increases significantly with decreasing gestational age, occurring in 5 to 11.6% of neonates born at 35 to 36 and 33 to 34 weeks of gestation, respectively [34]. In premature infants, there is an overlap with respiratory distress syndrome due to surfactant deficiency. However, both causes of respiratory distress, surfactant deficiency, and lung liquid retention can be present in premature infants [6, 35].

1.3 Risk factors for delayed transition and transient tachypnea of the newborn

Besides premature birth as well as near-term birth [29, 35, 36], other risk factors for the development of delayed transition and TTN include birth mode and timing of cesarean section [33, 35, 36], male sex [33], birth weight [33, 36], twin birth [33], perinatal asphyxia [24], maternal asthma [37], maternal obesity [38], and gestational diabetes [39].

As mentioned above, surfactant deficiency becomes more prevalent than lung liquid retention with increasing prematurity. However, both pathologies are intertwined and demonstrate a reciprocal interaction: pulmonary epithelial sodium transport is decreased in preterm infants, and term infants with TTN may show a decreased surfactant function [6, 40]. Therefore, it is plausible that late preterm infants and even term infants born via elective cesarean section benefit from antenatal corticosteroid therapy, reducing TTN incidence. Antenatal corticosteroid therapy was originally exclusively used for preterm infants below 34 weeks of gestation to reduce respiratory distress syndrome due to surfactant deficiency. However, it is also beneficial to reduce neonatal respiratory complications in infants born at 34 to 36 weeks of gestation [41, 42].

Concerning mode and timing of delivery, an elective cesarean section before 39 weeks of gestation increases the risk of TTN. The incidence of TTN is lower if there was previous labor before a cesarean section and lowest with vaginal delivery, indicating the importance of initiating lung liquid resorption by increasing fetal stress hormone levels through labor [33, 36, 43].

Being male, large or small for gestational age increases the risk for perinatal complications and respiratory distress after birth due to various risk factors, such as a higher rate of cesarean deliveries and underlying maternal conditions leading to impaired placental perfusion [44-46].

Multiple births, among others, increase the risk for preterm birth, thus the incidence of neonatal respiratory distress [47].

Maternal factors such as obesity, hypertension, and gestational diabetes increase the risk of postnatal respiratory distress due to a higher rate of cesarean deliveries and small or large for gestational age neonates in the said population [38, 39, 48]. An association between maternal asthma and TTN has been reported multiple times without fully elucidating the underlying pathophysiology, including possible genetically caused beta-adrenergic receptor hypo-responsiveness or surfactant depletion due to extensive use of beta-adrenergic receptor agonists as asthma medications [37]. Interestingly, TTN increases the risk for childhood asthma, making a possible association between TTN and beta-adrenergic receptor impairment more likely [2].

1.4 Clinical features and diagnosis of delayed transition and transient tachypnea of the newborn

Infants with delayed transition or TTN present shortly after birth with signs of respiratory distress, including tachypnea, i.e., a respiratory rate > 60 breaths per minute (/min), sometimes reaching up to > 100/min, expiratory grunting, intercostal and subcostal retractions, nasal flaring, and cyanosis. Due to an association of TTN with pulmonary hyperinflation, affected neonates may have barrel-shaped chests [2, 29, 49, 50]. Signs and symptoms of delayed transition typically cease within the first two to three hours postnatally [29], while TTN resolves within 24 to 48 hours, sometimes lasting up to one week [24, 29, 51]. Because of its short duration, chest radiographs are usually not obtained in delayed transition. However, its radiographical features are probably similar to those described in TTN: perihilar vascular markings, diffuse interstitial parenchymal infiltrates with edema of the interlobular septa, and fissures due to the retained lung liquid. Pulmonary hyperinflation may be observed [2, 52]. Lung ultrasound has become a valuable tool in diagnosing TTN and respiratory disease in neonates and will be discussed in a separate section below [2]. Other investigations in neonates presenting with delayed transition or TTN include laboratory tests to diagnose neonatal sepsis that may be present (complete blood cell count, C-reactive protein, interleukin-6, and blood cultures). A blood gas analysis should be obtained, potentially showing hypoxemia or hypercapnia due to impaired oxygenation and ventilation [24]. Typically, delayed transition and

TTN are clinical diagnoses based on the above signs in a population at risk; for example, term and near-term infants after elective cesarean section. However, since various neonatal diseases can present with early-onset respiratory distress, TTN is a diagnosis of exclusion, especially when manifesting with a prolonged course. Differential diagnoses include respiratory distress syndrome due to surfactant deficiency, pneumonia, sepsis, meconium aspiration syndrome, pneumothorax, congenital lung malformations, diaphragmatic hernia, congenital heart disease, persistent pulmonary hypertension, and inborn errors of metabolism [24].

1.5 Clinical course and management of delayed transition and transient tachypnea of the newborn

The clinical course of delayed transition and TTN is usually benign and self-limited, only requiring supportive care to a varying degree [2, 24, 29]. The infant should be placed in a comfortable position that facilitates breathing. Adequate monitoring of vital signs should be established, including continuous pulse oximetry and regular temperature checks to detect hypoxemia and provide a thermo-neutral environment to reduce each energy and oxygen consumption [2, 30].

Supplemental oxygen should be provided to keep the arterial oxygen saturation above 90% in infants older than ten minutes [53, 54]. Nasal continuous positive airway pressure (nCPAP) improves oxygenation and lung function in infants with respiratory distress [55, 56] and has been studied in infants presenting with signs of delayed transition or TTN [57, 58]. Remarkably, despite the high incidence of delayed transition and TTN, the number of studies on respiratory support and the evidence of its benefit in named clinical pictures are both low [59].

Diuretics and fluid restriction are plausible therapeutic approaches because delayed transition and TTN are associated with increased pulmonary fluid loads. Regarding diuretics, using one up to two doses of intravenously or orally administered furosemide (1 to 2 milligrams per kilogram per dose) did not affect the duration of TTN, oxygen requirement, or length of hospital stay [60-62]. Restricting fluid intake by about 20 milliliters per kilogram per day in near-term

infants may decrease the duration of respiratory support compared to a control group receiving standard volume care [63, 64]. However, a recent meta-analysis of four studies concluded insufficient evidence to support fluid restriction in near-term or term neonates with TTN [65].

As previously mentioned, beta-adrenergic receptors are at least partially involved in clearing lung liquid, leading to the use of inhaled beta-agonists in TTN [66]. While individual studies reported improvements in respiratory support, oxygen demand and clinical parameters with the use of inhaled salbutamol in infants with TTN [67-70], a recent systematic review concluded that determining whether salbutamol was safe or effective in TTN was impossible due to the limited and low certainty of evidence found in the literature [66]. Inhaled epinephrine was evaluated in a pilot study to examine adverse effects without adequate power to assess its efficacy as a therapeutic approach to TTN [71]. Regarding the use of budesonide, current data are inconclusive, thus preventing a recommendation for corticosteroids in TTN [72, 73].

Besides the mentioned therapeutic interventions, several studies evaluated the use of patient characteristics and clinical, laboratory and ultrasound findings to predict the duration and severity of TTN. Parameters associated with the need for mechanical ventilation were a low umbilical artery pH and a low Apgar score [74]. The former and an absence of labor are also associated with prolonged oxygen supplementation [36, 74]. Öztekin et al. associated a low pH and decreased PaO_2 and SpO_2 with prolonged respiratory support for more than five days in TTN [75]. Being male and having high respiratory rates led to a longer duration of TTN [51, 76, 77]. Low gestational age and prolonged tachypnea in neonates presenting with TTN were associated with longer stays in the neonatal intensive care unit (NICU) [51, 74]. Likewise, Ekmen et al. reported an elevated pCO_2 level and a decreased base excess on admission as risk factors for a prolonged NICU stay [78]. Elevated counts of nuclear red blood cells were found in neonates with TTN requiring intensified nCPAP therapy and prolonged courses of supplemental oxygen [79], whereas variances in platelet counts and platelet mass were associated with a longer duration of TTN [80]. Red cell distribution width and neutrophil-to-lymphocyte ratio were associated with more severe cases

of TTN [81]. Elevated levels of ischemia-modified albumin, an early biomarker for ischemic conditions, and N-terminal pro-B-type natriuretic peptide were associated with intensified respiratory support, prolonged oxygen therapy and hospitalization [82, 83]. Concerning ultrasound diagnostics, elevated right ventricular systolic pressures were associated with more severe cases of TTN [79]. To our knowledge, no prognostic factors have yet been described for delayed transition. However, we can assume that these are similar to TTN. It is also plausible that treatment outcomes are negatively influenced as multiple risk factors for developing TTN or delayed transition become more pronounced or even coincide.

1.6 Complications and consequences of delayed transition and transient tachypnea of the newborn

Despite their usually self-limiting and benign clinical course, delayed transition and TTN can lead to antibiotic treatment, prolonged hospital stays, and mother-child separation [2]. Requiring nCPAP therapy and supplemental oxygen might increase the risk of pneumothorax [84]. Reports of severe cases of TTN leading to respiratory failure and death exist [85], the latter being caused by the development of pulmonary hypertension due to resorption atelectasis under oxygen therapy and increased vasoreactivity of the pulmonary vascular bed [86]. In addition to the above association of an increased risk for TTN in the presence of maternal asthma, neonates who present with TTN after birth also have an increased risk of developing asthma themselves later in life [2, 24], suggesting a role of genetic determinants in the pathophysiology of TTN. In this regard, gene polymorphisms of the beta-2 adrenergic receptor have been associated with a higher risk for TTN [87].

1.7 Lung ultrasound in neonatology

In recent years, lung ultrasound has become an essential diagnostic tool in neonatology, providing fast point-of-care imaging without ionizing radiation [88, 89]. The European Society of Pediatric and Neonatal Intensive Care implemented lung ultrasound in their 2020 guidelines on point-of-care ultrasound for critically ill neonates and children [90].

The foundations for the current use of lung ultrasound were established in the mid-1990s by Lichtenstein et al., first in adults [91] and then in children and neonates [92, 93].

Due to the physical principles of (medical) ultrasound, in which sound waves are almost entirely reflected as soon as they encounter sudden changes in acoustic impedance, e.g., skin and muscle tissue of the chest wall vs. aerated lung tissue, lung ultrasound predominantly visualizes pleural or near-pleural findings and specific patterns of reverberation artifacts that represent physiological or pathological conditions of the lung [92, 94]. Describing said reverberation artifacts coined a nomenclature, although initially developed in adult medicine and specific to lung ultrasound, is applicable regardless of age group [92]. For illustrative purposes, only the lung ultrasound findings important to this study and used in neonatology are discussed below.

Concerning lung ultrasound in neonates, best results are obtained using a high-frequency linear transducer set at the respective device's lung ultrasound preset and placed over at least three areas on each hemithorax: anteriorly and posteriorly or both, and laterally along the longitudinal axis. Lung ultrasound visualizes skin, subcutaneous tissue, thoracic muscles and ribs, and in between the latter, the parietal and visceral pleura are depicted as an echogenic line called the pleural line (Figure 1). The pleural line is usually thin and regularly appearing, while certain neonatal respiratory disorders like respiratory distress syndrome due to surfactant deficiency and neonatal pneumonia are accompanied by pleural line abnormalities, i.e., the pleural line becoming thickened and irregular [95]. The lung displacement with each breath causes small shimmering artifacts when moving to and fro the craniocaudal axis, labeled lung sliding. So-called A-lines are horizontal reverberation artifacts of the pleural line representing the ultrasound finding of a normal, well-aerated lung (Figure 1). So-called B-lines originate from the pleural line and are depicted as vertical beam-like reverberations extending distally without fading, overlapping A-lines (Figure 2). While a small number of B-lines may also be observed in a healthy, well-aerated lung, they become more and more visible in case of increased intrapulmonary liquid content due to pulmonary interstitial liquid widening the intralobular septa.

With increasing intrapulmonary liquid content, the number of B-lines increases until they confluence to form compact or coalesced B-lines. This leads to a white lung in severe cases of interstitial and alveolar pulmonary fluid overload (Figure 3). Finally, so-called (extended) consolidations are visible in non-aerated alveoli due to atelectasis, pulmonary edema, or pneumonia and can differ in size and shape (Figure 4) [96-98].

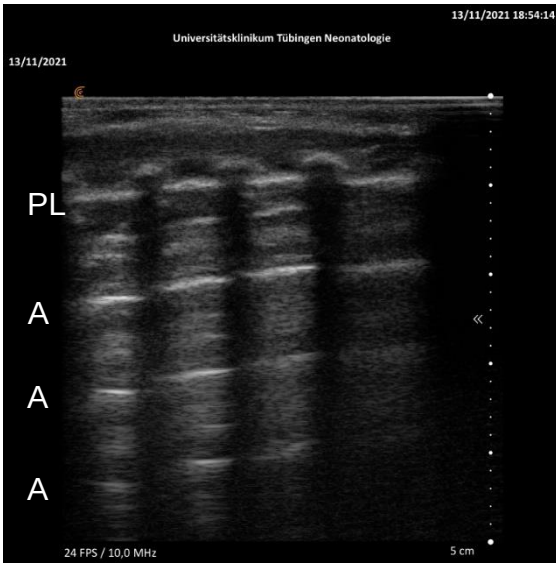

Figure 1: Normal pleural line (PL) and A-lines (A)

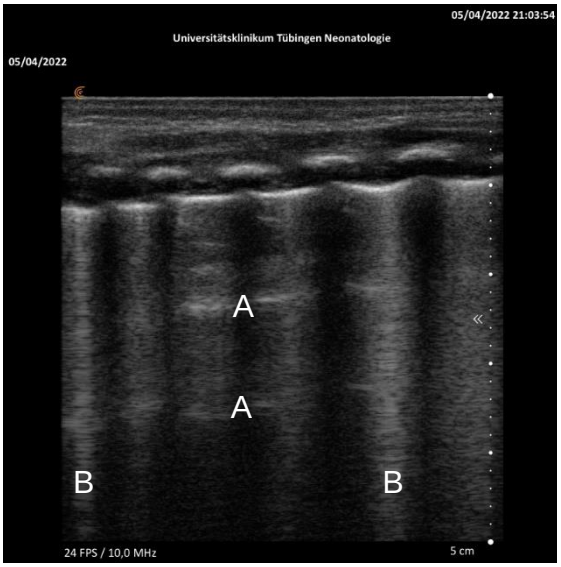

Figure 2: Multiple B-lines (B) with some A-lines (A) still visible

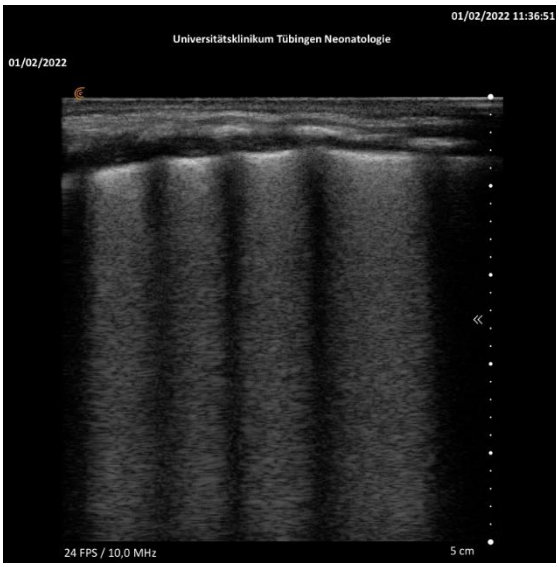

Figure 3: White lung

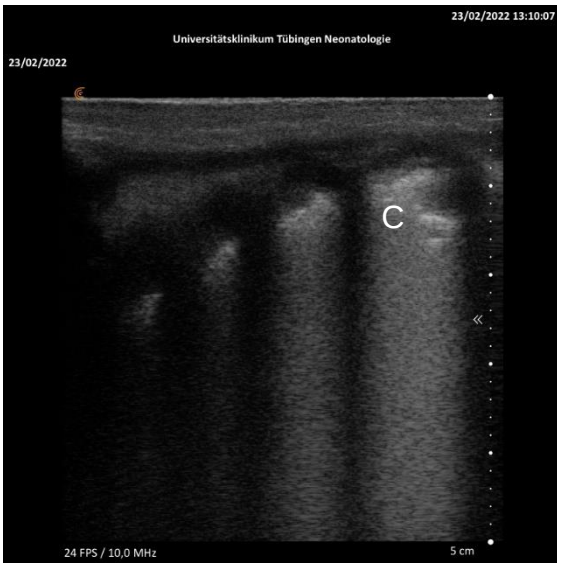

Figure 4: Subpleural consolidation (C)

Lung ultrasound has not only been used to describe the physiological pulmonary transition immediately after birth and in the following minutes or hours [21, 99] but also to describe a variety of neonatal lung diseases like TTN [97, 98, 100-102], respiratory distress syndrome [103], pneumothorax [104], and bronchopulmonary dysplasia [105]. Lung ultrasound was established as a validated prognostic tool to predict NICU admission [100, 106], the need for respiratory support or mechanical ventilation [107], surfactant therapy [103], or, in the longer term, the development of bronchopulmonary dysplasia [108]. In addition to its wide range of applications, lung ultrasound is easy to learn [89], can be efficiently established in centers with limited pre-existing experience concerning lung ultrasound [109], and shows both, strong intra- and inter-observer agreement [110], irrespective of the rater's expertise and the ultrasound probe used [111].

1.8 Lung ultrasound in delayed transition and transient tachypnea of the newborn

Lung ultrasound is an established tool in diagnosing TTN and its differentiation from other pulmonary pathologies like respiratory distress syndrome due to surfactant deficiency or pneumonia in newborns [100-102, 112-117]. Consistent with the underlying pathophysiology of TTN, increased lung liquid volumes are represented by an increasing number of unilateral or bilateral B-lines, showing a compact or coalesced pattern, depending on TTN severity. Usually, TTN is not accompanied by pleural line abnormalities, and subpleural (extended) consolidations are rare, although the data vary concerning the former [95, 96, 101, 118, 119]. The so-called "double lung point" is a common and specific lung ultrasound finding in TTN. It is composed of a pattern in which A- or non-compact B-lines are present in the superior lung fields, while compact B-lines can be visualized simultaneously in the inferior lung fields separated by a well-defined border (Figure 5) [97, 101, 117]. A yet rarely reported lung ultrasound finding in infants with postnatal respiratory distress is the so-called "backsliding." Several authors who used lung ultrasound scores to assess the severity of neonatal respiratory distress and lung aeration observed worsening lung ultrasound scores from one examination time point to the next. The significance of this phenomenon appearing early postnatally in healthy newborns and infants with TTN remains

unclear [21, 100]. Regarding delayed transition, no specific ultrasound findings are reported in the literature, but they are likely similar to TTN because of the same underlying pathophysiology.

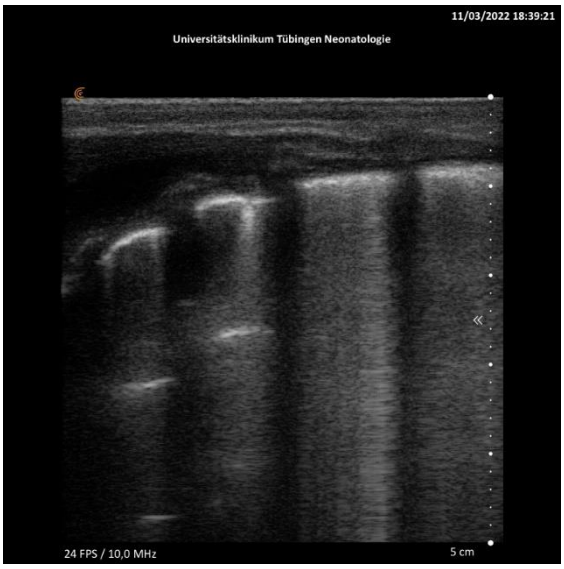

Figure 5: Double lung point with A-lines on the left and compact B-lines on the right

1.9 Study aims

As reported above, delayed transition and TTN are common and may result, despite usually bearing a benign clinical course, in NICU stays of varying duration and associated mother-child separation.

Although several studies identified prognostic factors for TTN duration, this is not the case for delayed transition [36, 51, 74, 75, 79]. Moreover, many studies evaluated laboratory parameters that make an early bedside prognosis difficult [79-83]. However, since delayed transition often has a short clinical course of several minutes to a few hours, identifying prognostic parameters that are available at the bedside and allow estimating the respective clinical course would be helpful.

We designed a prospective observational study to estimate the clinical course of term or near-term newborns with delayed transition and TTN within the first postnatal hour using bedside lung ultrasound in conjunction with readily available or at the time of birth already existing information. We set “duration of nCPAP

therapy" as our main outcome parameter mirroring the clinical course and defined short- and long-term clinical courses as nCPAP therapy < 1 hour and ≥ 1 hour, respectively. We chose two time points within the first postnatal hour, 30 and 60 minutes, at which the duration of nCPAP therapy and, thus, the clinical course of delayed transition and TTN were to be estimated based on the following parameters:

i. Lung ultrasound score adapted for neonates by Brat et al. [103]
ii. Silverman-Andersen score to assess respiratory distress in newborns [120]
iii. Respiratory rate [51]
iv. Fraction of inspired oxygen (FiO_2) [76]
v. Arterial oxygen saturation measured by pulse oximetry (SpO_2) [75]
vi. Respiratory acidosis in blood gas analysis [75]
vii. Birth weight, i.e., whether the neonate is small or large for gestational age [35, 36]
viii. Gestational age [35, 36, 74]
ix. pH in cord blood analysis [74]
x. 1-minute Apgar score [74]
xi. Sex [35, 51, 74]

We derived and adapted these parameters based on the current literature and our clinical experience. After dichotomization, we evaluated each parameter's influence on the risk of short- or long-term nCPAP therapy, i.e., a short or prolonged clinical course of delayed transition or TTN. We did so using univariate and multivariate analysis at the respective time points of 30 and 60 minutes postnatally. Additionally, we performed a Classification and Regression Tree (CART) analysis.

Additional study aims were a description of lung ultrasound findings in this cohort since lung ultrasound has yet only rarely been used in such a setting. Besides using an established lung ultrasound score encompassing findings like A- and B-lines and (extended) consolidations, we quantified the frequency of the double lung point, pleural line abnormalities, and backsliding. We evaluated the validity

by comparing lung ultrasound scores between neonatologists and pediatric radiologists by testing interrater agreement.

In summary, our study aims were:

- Identifying risk factors for prolonged nCPAP therapy in term or near-term infants with TTN and delayed transition
- Describing early lung ultrasound findings in infants with TTN and delayed transition
- Evaluating the interrater agreement of early lung ultrasound findings

The long-term goal of this and subsequent studies is to establish standardized NICU admission criteria for infants presenting with delayed transition and TTN by improving the predictability of the respective clinical course.

2 Materials and Methods

2.1 Study design

We designed our study as a single-center, prospective observational pilot study.

2.2 Location and timeframe

Our study took place at the Department of Obstetrics and the Department of Neonatology at the University Hospital Tübingen. Approximately 3,500 infants are born each year at the above institute. The initially estimated recruitment period was two years, starting on May 1, 2020. During the study, we extended patient recruitment to June 30, 2022. Data analysis took place from July to December 2022.

2.3 Ethics approval and consent to participate

We registered our study at the German Register of Clinical Trials (trial no. DRKS00020520) and obtained approval from the ethics committee of Tübingen University Hospital (application no. 741/2019BO1). Written informed parental consent was obtained upon patient recruitment.

2.4 Patients

The study population consisted of term newborns and late-preterm infants with a gestational age ≥ 36 0/7 weeks.

2.5 Inclusion criteria

- Gestational age ≥ 36 0/7 weeks
- Signs of respiratory distress including tachypnea, i.e., respiratory rate > 60/min, expiratory grunting, nasal flaring, cyanosis, intercostal, subxiphoid, and subcostal retractions, and need for supplementary oxygen
- Onset of respiratory distress within 30 minutes of birth
- Initiation of nCPAP therapy within 30 minutes of birth

2.6 Exclusion criteria

- Severe congenital malformations (chromosomal aberrations, heart defects, congenital airway and pulmonary malformations, abdominal wall defects, and neuromuscular diseases)

- Early onset sepsis or congenital pneumonia presenting with a C-reactive protein > 1 mg/dl and initiation of antibiotic treatment
- Respiratory distress due to surfactant deficiency in premature infants with concomitant surfactant replacement therapy
- Meconium aspiration syndrome as diagnosed by the neonatologist on call

2.7 Course of the study and equipment used

Newborns presenting with respiratory distress shortly after birth were treated by the neonatologist on call according to the department's guidelines based on the current European Resuscitation Council guidelines for newborn resuscitation and support of transition of infants at birth [54]. Resuscitation was initiated in the delivery room on a resuscitation unit with an implemented suctioning device and a radiant heater. After clearing the airway as needed, infants were predominantly placed in a 15° head-up tilt prone position. NCPAP was delivered via binasal prongs (EasyFLow, Fritz Stephan GmbH, Gackenbach, Germany) using a continuous flow ventilator (F120 mobil, Fritz Stephan GmbH, Gackenbach, Germany). The positive end-expiratory pressure (PEEP) level was set to 6 cmH_2O throughout. Oxygen was supplemented to achieve an SpO_2 > 90% within ten minutes postnatally. Besides respiratory support, patient positioning, swaddling, and providing a thermoneutral environment, we did not administer additional medication or infusions.

We monitored vital signs (heart rate, respiratory rate, SpO_2, blood pressure) using a continuous patient monitoring system (IntelliVue MP5 or X3, Koninklijke Philips N.V., Amsterdam, the Netherlands). The temperature was obtained using digital rectal thermometry (Fieberthermometer Meditemp digital, medgro GmbH & Co. KG, Wesel, Germany). We analyzed blood gas using a point-of-care blood gas analyzer (ABL800 FLEX, Radiometer, Copenhagen, Denmark). We performed lung ultrasound using a portable, high-frequency linear transducer with 15-Megahertz (L15 HD, Clarius Mobile Health, Vancouver, Canada). We recorded a two-second video clip using the lung ultrasound scan preset implemented within the Clarius ultrasound app (Clarius Mobile Health, Vancouver, Canada), which was installed on a tablet computer (iPad mini, Apple Inc., Cupertino, USA). In

case of persistent respiratory distress under ongoing nCPAP therapy or persistent need for oxygen supplementation, newborns were usually admitted to the NICU after 60 minutes of nCPAP therapy at the discretion of the attending neonatologist. During the NICU stay, nCPAP was continued using a continuous flow ventilator (Sophie, Fritz Stephan GmbH, Gackenbach, Germany). Also, we monitored vital signs as described above using a continuous patient monitoring system (M750, Koninklijke Philips N.V.). We discontinued nCPAP therapy according to our institutional guideline on nCPAP-weaning when newborns were breathing room air and signs of respiratory distress had regressed spontaneously.

During the delivery room and NICU stay, we collected patient data using a paper case report form (CRF), which we transferred to an electronic CRF. Our study was divided into two phases: phase one was in the delivery room, usually within the first postnatal hour, where we initiated nCPAP therapy, monitored the infant closely and performed lung ultrasound examinations. Phase two started upon admission to the NICU as soon as it became predictable from a clinical perspective that the respective infant would require nCPAP therapy for more than 60 minutes. Infants with shorter nCPAP courses were usually not admitted to the NICU, as was common practice in our department.

The general course of the study for an individual patient is shown in Figure 6. Table 1 shows the timing of determining the parameters collected for our study with the outcome parameters nCPAP therapy duration and lung ultrasound findings, including the lung ultrasound score, the presence of the double lung point, pleural line abnormalities, and backsliding.

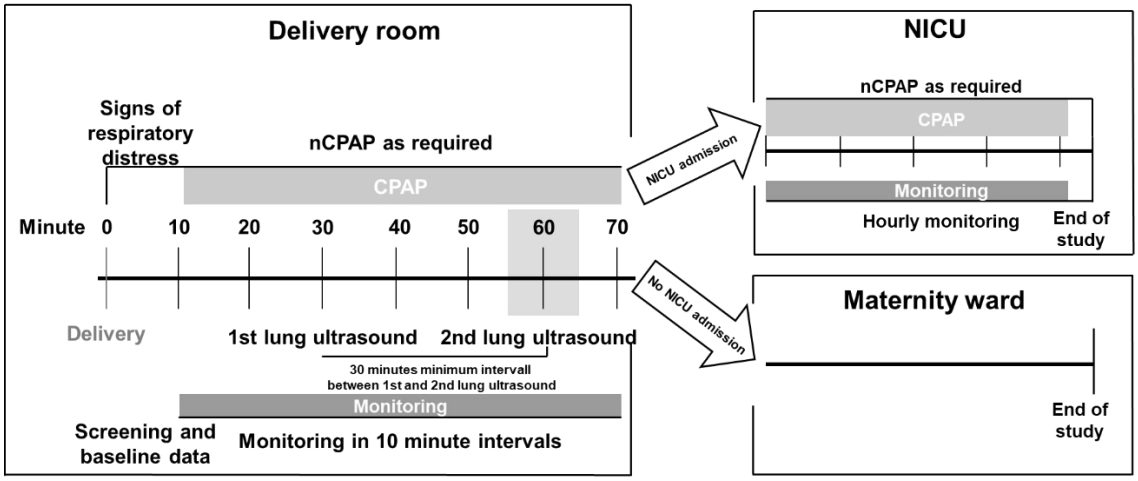

Figure 6 General course of the study in the delivery room with lung ultrasound examinations and short-interval data collection and the subsequent stay on either the NICU with hourly monitoring or maternity ward, depending on the need for NICU admittance. *nCPAP – nasal continuous positive airway pressure; NICU – neonatal intensive care unit*

Table 1 Collected data

	Study location and time interval of data collection									
			Delivery room						**NICU**	**End of study**
Parameter	**Screening**	**Baseline**	10	20	30	40	50	60	Hourly	
Inclusion criteria	x									
Exclusion criteria	x									
Parental consent	x									
Inclusion yes/no	x									
Reason for non-inclusion	x									
Date of birth		x								
Gestational age		x								
Male/female		x								
Multiple birth		x								

Birth weight (g)	x									
Length (cm)	x									
Head circumference (cm)	x									
Mode of delivery	x									
Apgar score	x									
Rupture of membranes	x									
An-/Oligo-/Polyhydramnios	x									
MASF	x									
Chorioamnionitis	x									
Maternal diabetes	x									
Maternal asthma	x									
Heartrate (bpm)		x	x	x	x	x	x		x	
Respiratory rate (/min)		x	x	x	x	x	x		x	
SpO_2 (%)		x	x	x	x	x	x		x	
MAD (mmHg)		x		x			x			
Temperature (°C)		x		x			x			
Silverman-Andersen score				x			x			
Lung ultrasound score				x			x			
Double lung point				x			x			
Pleural line abnormalities				x			x			
Backsliding										x
FiO_2		x	x	x	x	x	x	x	x	
nCPAP therapy (min)										x
pH	x			#						
pCO_2	x			#						
Base excess	x			#						
Lactate	x			#						
Date	x									x
Cause of study termination										x

At least one blood gas analysis within the first 60 postnatal minutes; *nCPAP – nasal continuous positive airway pressure; FiO2 – fracture of inspired oxygen; MAD – mean arterial blood pressure; MASF – meconium-stained amniotic fluid; NICU – neonatal intensive care unit; SpO_2 – arterial oxygen saturation measured by pulse oximetry*

2.8 Lung ultrasound

In almost all cases, we performed the lung ultrasound examinations in the prone position as this was part of our routine care for infants with respiratory distress.

In exceptional cases, we performed lung ultrasound examinations in the supine position. Regardless of body position, strict care was taken not to change the infant's position for at least 25 minutes before any lung ultrasound examination. We applied a lung ultrasound score established in newborns, dividing each lung into three areas (upper, lower, and lateral) and assigning 0 to 3 points at each position. Accordingly, a minimum score of 0 and a maximum score of 18 could have been achieved during a complete examination. Here, the score encompassed a spectrum of typical findings in newborns with respiratory distress: 0 indicating the "presence of only A-lines" (Figure 1; so-called A-pattern, representing a well-aerated lung); 1 indicating the "presence of ≥ 3 well-spaced B-lines" (Figure 2; so-called B-pattern, representing an increasing accumulation of intrapulmonary fluid); 2 indicating the "presence of crowded and coalescent B-lines with or without consolidations limited to the subpleural space" (Figure 3; so-called severe B-pattern or in severe cases white lung); 3 indicating extended consolidations (Figure 4; extended consolidations are caused by a large number of non-ventilated alveoli) [103]. We quantified the frequencies of the double lung point (A- or non-compact B-lines in the superior lung fields with compact B-lines in the inferior lung fields separated by a well-defined border), pleural line abnormalities (thickened or irregular pleural line), and backsliding (worsening of lung ultrasound score from the 30- to the 60-minute time point). During the lung ultrasound examination, we placed the transducer on the thorax in the longitudinal axis dorsally left and right in midline between the scapular and vertebral lines at the superior border of the scapula (upper area) and the level of the inferior angle (lower area). We examined the lateral lung area by placing the ultrasound probe at the left and right midaxillary lines at about the level of the sixth rib. We recorded a two-second video clip at each position in B-mode using the lung preset of the Clarius ultrasound app, which was set to a depth of five centimeters. By performing the lung ultrasound at 30 and 60 minutes postnatally, we acquired 12 two-second videos from each patient, which were pseudonymized and stored under a study ID in the digital study directory. Following patient recruitment, two neonatologists and two pediatric radiologists

independently scored the videos according to the above approach without knowledge of the respective clinical course.

2.9 Statistical analysis

2.9.1 Sample size calculation

Approximately 3,500 infants are born each year at the Department of Obstetrics of Tübingen University Women's Hospital. Eighty to 90 infants with a gestational age ≥ 36 0/7 weeks are admitted to the NICU due to respiratory distress after birth. Using the institution's patient information system, we calculated this figure through an a priori retrospective evaluation of patient records over two years. As our study was initiated as a pilot study, 150 patients were deemed sufficient to investigate the included parameters in a multivariate analysis, but no formal statistical power analysis was done.

2.9.2 Statistical significance

Due to our study being only hypothesis-generating, a p-value of < 0.05 was considered statistically significant and chosen as the inclusion criterion for multivariate analysis and the best model of multivariate analysis.

2.9.3 Missing data

If more than 20% of missing values occurred, we did not perform statistical testing or calculated confidence intervals.

2.9.4 Intention to treat population

Due to our study being an observational study analyzed by descriptive statistics, we performed all analyses and tabulations exclusively for the intention-to-treat (ITT) population. The ITT population consisted of all patients included in the study.

2.9.5 Statistical analysis

All data documented in the study database were included in the analysis. Continuous variables were described by statistical location parameters (number of patients, missing values, mean, standard deviation, median, minimum, maximum). Categorical variables were described by number and percentage. We evaluated group differences using Mann-Whitney-U-Test for non-normally

distributed data, and chi-square test or Fisher's exact test for categorical items. We dichotomized the risk factors to be evaluated for statistic modeling, as shown in Table 2. Except for the lung ultrasound score, dichotomization was determined prior to statistical analysis using data from the literature as well as the clinical experience of the authors. Since the lung ultrasound score has not yet been used in a comparable setting regarding timing and population, the best cutoff value was defined within the sample using Youden's index [121]. We excluded the risk factor SpO_2 before starting the statistical analysis.

Table 2 Dichotomization of the risk factors to be evaluated

Parameter		Dichotomization	Risk for nCPAP therapy ≥ 1h
i.	Lung ultrasound score at 30 and 60 minutes	≤ 5	No
		> 5	Yes
ii.	Silverman-Andersen score at 30 and 60 minutes	< 4 / < 5	No
		≥ 4 / ≥ 5	Yes
iii.	Respiratory rate (/min) at 30 and 60 minutes	≤ 60	No
		> 60	Yes
iv.	FiO_2 at 30 and 60 minutes	≤ 0.21	No
		> 0.21	Yes
v.	Respiratory acidosis within 60 minutes	No	No
		Yes	Yes
vi.	Birth weight (percentile)	≥ 10 and ≤ 90	No
		< 10 or > 90	Yes
vii.	Gestational age (weeks)	≥ 38	No
		< 38	Yes
viii.	pH in cord blood analysis	≥ 7.25	No
		< 7.25	Yes
ix.	1-minute Apgar score	≥ 7	No
		< 7	Yes
x.	Sex	female	No
		male	Yes

nCPAP – nasal continuous positive airway pressure; FiO_2 – fracture of inspired oxygen

Taking a two-step approach, we first analyzed the potential risk factors for prolonged nCPAP therapy obtained from our cohort (lung ultrasound score, Silverman-Andersen score, respiratory rate, FiO_2, and respiratory acidosis) using univariate logistic regression. Risk factors with a p-value < 0.05 in univariate analysis were then included in a multivariate logistic regression model, including the remaining risk factors mentioned in Table 2 (birth weight, gestational age, cord blood pH, 1-minute Apgar score, and sex). We then eliminated risk factors through a backward selection until the final model contained only those with a p-value < 0.05. This modeling was performed for the 30 and 60-minute time points after birth, respectively. By tabulating the estimated probabilities, sensitivity, specificity, and Youden's index, we determined the optimal probability cutoffs for nCPAP therapy ≥ 1 hour. We evaluated the diagnostic quality of our model by plotting a receiver operating characteristics curve.

Additionally, we performed a CART analysis [122]. Termination criteria were (i) no risk factor with a p-value < 0.05 and (ii) the number of the subgroup being smaller than the square root of the number of the entire group.

We used the intraclass correlation to evaluate interrater agreement according to Shrout and Fleiss [123].

3 Results

3.1 Patient recruitment

During this study, we screened 235 patients for eligibility (Figure 7). We excluded 105 patients: 74 were too old at the screening time point, i.e., the postnatal age was > 30 minutes, 14 patients met the infection exclusion criterion, and 14 had congenital malformations (Pierre Robin sequence or other severe facial abnormalities n = 5; congenital heart defects n = 5; chromosomal aberrations n = 2; congenital diaphragmatic hernia n = 1; esophagus atresia n = 1). Other reasons for exclusion were technical defects in two patients and meconium aspiration syndrome in one patient.

We recruited patients between May 01, 2020, and June 11, 2022. We failed to reach the recruitment target of 150 patients and terminated the study after including 130 patients.

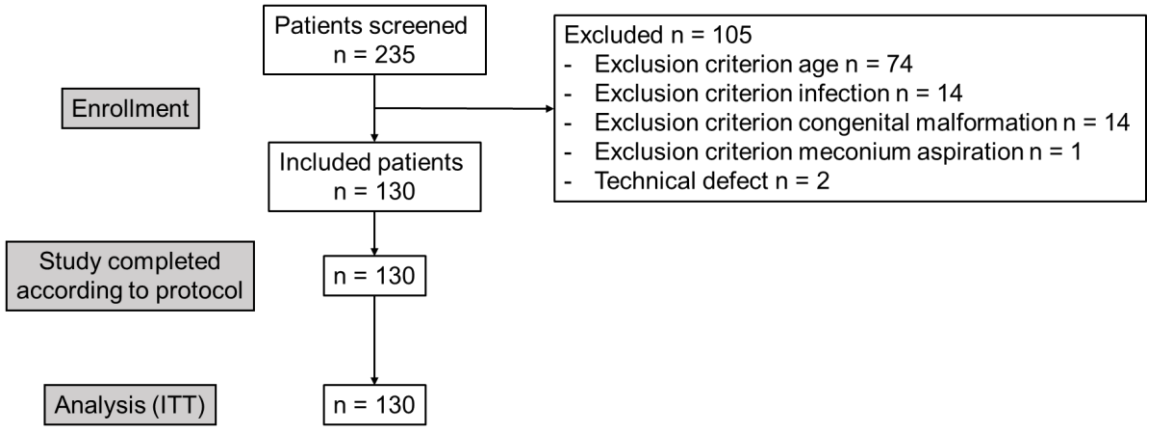

Figure 7 CONSORT flow diagram. All included patients completed the study according to protocol. *CONSORT – Consolidated standards of reporting trials; ITT – intention to treat*

3.2 Patient characteristics

Table 3 shows patient characteristics for all included patients, separated by nCPAP therapy duration. Coincidentally, both groups had the same size (n = 65).

Infants requiring nCPAP ≥ 1 hour were born at a lower gestational age and had higher birth weight percentiles than those with a shorter duration of respiratory support. While the proportion of male newborns predominated in our cohort

overall, the difference in terms of male vs. female was particularly pronounced in the group with nCPAP therapy ≥ 1 hour.

Elective cesarean section was performed more frequently in infants with longer nCPAP therapy.

Meconium-stained fluids and gestational diabetes were present in nearly a quarter of cases.

There were no clinically important differences between the groups regarding pH at birth and Apgar scores.

Table 3 Patient characteristics

	Duration of nCPAP			
Variable	**< 1 hour n = 65**	**≥ 1 hour n = 65**	**All n = 130**	**p-value**
Gestational age (w)	39.6 (36.4-42.1)	38.6 (36.0-41.3)	39.1 (36.0-42.1)	< 0.01
Weight (g)	3210 (2120-4350)	3320 (1850-4920)	3275 (1850-4920)	0.60
Weight percentile	33 (2-99)	47 (1-99)	41 (1-99)	0.32
Length (cm)	50.0 (42-58)	50.0 (43-57)	50.0 (42-58)	0.40
Head circum. (cm)	35.0 (31-38)	35.0 (30-38)	35.0 (30-38)	0.59
Female	31 (47.7%)	24 (36.9%)	55 (42.3%)	0.21
Male	34 (52.3%)	41 (63.1%)	75 (57.7%)	
Multiple births	6 (9.2%)	7 (10.8%)	13 (10.0%)	0.77
Vaginal birth	17 (26.2%)	13 (20.0%)	30 (23.1%)	0.41
Primary C/S	17 (26.2%)	30 (46.2%)	47 (36.2%)	0.02
Secondary C/S	19 (29.2%)	12 (18.5%)	31 (23.9%)	0.15
Emergency C/S	4 (6.2%)	0 (0.0%)	4 (3.1%)	0.04
Vacuum assisted	8 (12.3%)	10 (15.4%)	18 (13.9%)	0.61
ROM in h; mean	3.9 (± 10.4)	2.8 (± 6.5)	3.4 (± 8.7)	0.31
Polyhydramnios	0 (0.0%)	3 (4.6%)	3 (2.3%)	0.08
Oligohydramnios	0 (0.0%)	1 (1.5%)	1 (0.8%)	0.32
Anhydramnios	1 (1.5%)	0 (0.00%)	1 (0.8%)	0.32
MSAF	19 (29.2%)	12 (18.5%)	31 (23.9%)	0.15
Chorioamnionitis	8 (12.3%)	11 (16.9%)	19 (14.6%)	0.46
Maternal diabetes	14 (21.5%)	17 (26.2%)	31 (23.9%)	0.54
Maternal asthma	5 (7.7%)	1 (1.6%)	6 (4.6%)	0.15
pH at birth	7.24 (7.05-7.39)	7.24 (7.02-7.38)	7.24 (7.02-7.39)	0.79

Apgar 1	7 (2-10)	8 (2-10)	8 (2-10)	0.75
Apgar 5	9 (6-10)	8 (5-10)	9 (5-10)	0.32
Apgar 10	9 (8-10)	9 (7-10)	9 (7-10)	0.04

Data presented as mean (± standard deviation); median (minimum and maximum), or as the number of patients with percentages in parathesis. *C/S – cesarean section; MSAF – meconium-stained amniotic fluid; ROM - rupture of membranes*

3.3 Outcome parameters

Table 4 shows the outcome parameters for all included patients, separated by nCPAP therapy duration.

The lung ultrasound and Silverman-Andersen scores at 30 and 60 minutes after birth were higher in infants with long-term nCPAP therapy compared to the short-term nCPAP group. While an improvement in clinical symptoms over time was observed in both groups, represented by lower median Silverman-Andersen scores at 60 vs. 30 minutes postnatally, the difference in lung ultrasound scores was less pronounced. We observed the double lung point more frequently in the long-term nCPAP group. While in the latter group, the proportion of newborns with double lung points remained almost unchanged or increased over the two study time points, double lung point was less frequently visible 60 minutes postnatally in the short-term nCPAP group. The same was true for pleural line abnormalities. While backsliding occurred in about one-third of patients, consolidations were rare and limited to the long-term nCPAP group.

Infants in the long-term nCPAP group had a higher median respiratory rate 60 minutes postnatally than those in the short-term nCPAP group. They had a lower median SpO_2 and required more supplemental oxygen at both time points.

Compared with the short-term nCPAP group, respiratory acidosis was twice as common in the long-term nCPAP group.

We admitted two newborns originally assigned to the short-term nCPAP group to our NICU for observation or because of hypothermia and feeding difficulties for half a day and 17 days, respectively. The indication for NICU admission for all newborns from the long-term nCPAP group was the continuation of nCPAP

therapy initiated in the delivery room. Here, the respective NICU stay usually lasted only one day.

In infants with nCPAP therapy for ≥ 1 hour, the mean duration of supplemental oxygen therapy was about five hours. Due to outliers, the mean duration of nCPAP therapy was almost 20 times longer in the long-term nCPAP group compared to infants with nCPAP therapy for < 1 hour (mean 723.8 (± 1615.6) vs. 38.0 (± 10.4) minutes; $p < 0.01$), whereas the median treatment duration differed by a factor of six. NCPAP duration in the long-term nCPAP group exhibited a wide variation ranging from just over one hour to over six days.

Table 4 Outcome parameters

	Duration of nCPAP			
	< 1 hour	**≥ 1 hour**	**All**	**p-**
Variable	**n = 65**	**n = 65**	**n = 130**	**value**
LUS at 30 min.	2 (0-9)	9 (0-12)	4 (0-12)	< 0.01
LUS at 60 min.	2 (0-5)	8 (0-13)	4 (0-13)	< 0.01
DLP at 30 min.	34 (52.3%)	54 (83.1%)	88 (67.7%)	< 0.01
DLP at 60 min.	24 (36.9%)	58 (89.2%)	82 (63.1%)	< 0.01
Abnormal PL at 30 min.	26 (40.0%)	52 (80.0%)	78 (60.0%)	< 0.01
Abnormal PL at 60 min.	23 (35.4%)	54 (83.1%)	77 (59.2%)	< 0.01
Consolidation at 30 min.	0 (0.0%)	2 (3.1%)	2 (1.5%)	0.15
Consolidation at 60 min.	0 (0.0%)	3 (4.6%)	3 (2.3%)	0.80
Backsliding	21 (32.3%)	24 (36.9%)	45 (34.6%)	0.58
Silv.-And. score at 30 min.	6 (2-8)	7 (5-9)	6 (2-9)	< 0.01
Silv.-And. score at 60 min.	2 (0-5)	5 (2-8)	3 (0-8)	< 0.01
RR (/min) at 30 min.	65 (30-80)	65 (31-76)	65 (30-80)	0.10
RR (/min) at 60 min.	55 (25-65)	60 (42-73)	60 (25-73)	< 0.01
FiO_2 at 30 min.	0.21 (0.21-0.31)	0.21 (0.21-0.50)	0.21 (0.21-0.50)	< 0.01
FiO_2 at 60 min.	0.21 (0.21-0.21)	0.21 (0.21-0.40)	0.21 (0.21-0.40)	< 0.01
SpO_2 (%) at 30 min.	96 (88-100)	93 (85-100)	95 (85-100)	< 0.01
SpO_2 (%) at 60 min.	99 (93-100)	96 (90-100)	98 (90-100)	< 0.01
Respiratory acidosis	16 (24.6%)	32 (49.2%)	48 (36.9%)	0.04
Admission to NICU	2 (3.1%)	52 (80.0%)	54 (41.5%)	< 0.01
NICU stay in days	8.75 (0.5-17.0)	1.0 (0.5-17.0)	1.0 (0.5-17.0)	< 0.01
Supplemental oxygen (h)	0.0 (n/a)	5.1 (± 19.3)	5.1 (± 19.3)	(n/a)
Duration of nCPAP (min.)	38 (15-58)	240 (65-8767)	62 (15-8767)	< 0.01

Data presented as mean (± standard deviation); median (minimum and maximum), or as the number of patients with percentages in parathesis. *DLP – double lung point; FiO_2 – fracture of inspired oxygen; LUS – lung ultrasound score; NCPAP – nasal continuous positive airway pressure; NICU – neonatal intensive care unit; PL – pleural line; RR – respiratory rate; SpO_2 – arterial oxygen saturation measured by pulse oximetry*

3.4 Vital signs during the first postnatal hour

Figures 8 to 13 show the vital signs during the first postnatal hour. Infants with nCPAP therapy for ≥ 1 hour tended to have higher heart and respiratory rates, lower SpO_2 values and required higher FiO_2. We observed no significant differences concerning mean arterial blood pressure or temperature.

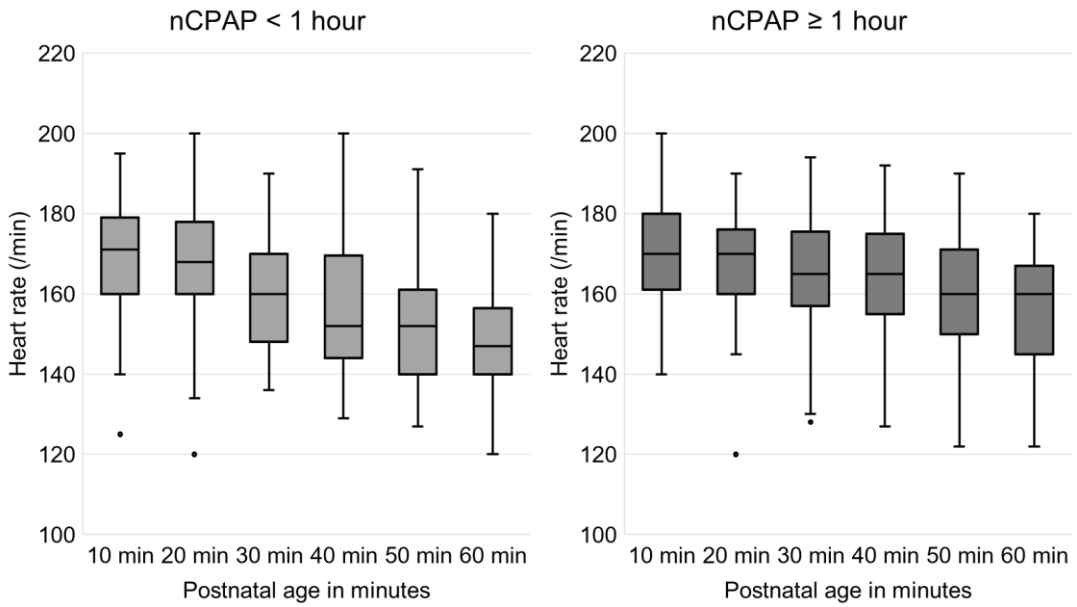

Figure 8 Box plots depicting heart rate in the first postnatal hour. *nCPAP – nasal continuous positive airway pressure*

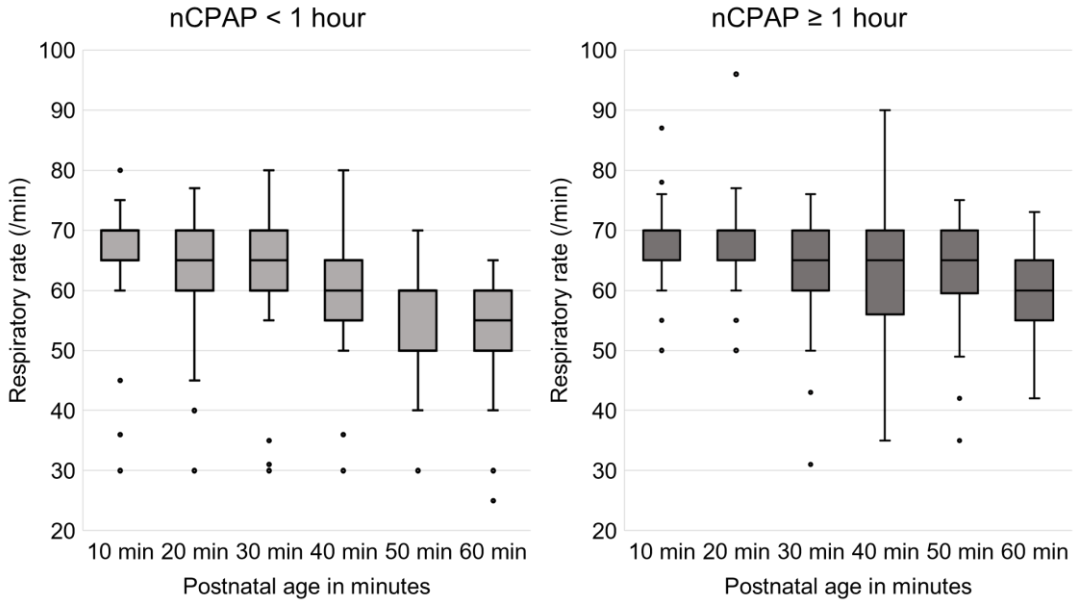

Figure 9 Box plots depicting respiratory rate in the first postnatal hour. *nCPAP – nasal continuous positive airway pressure*

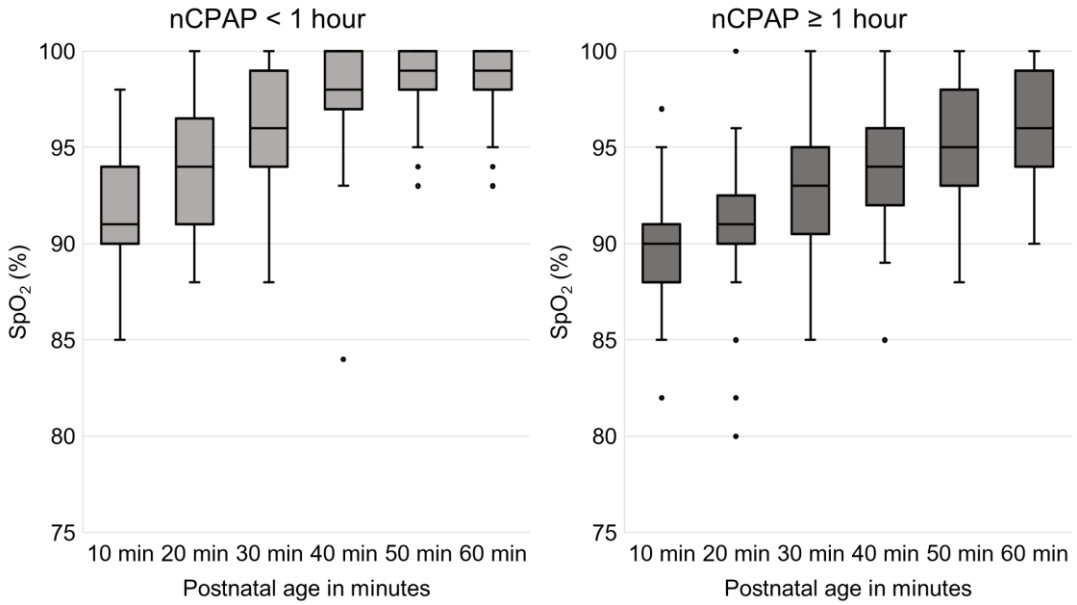

Figure 10 Box plots depicting SpO_2 in the first postnatal hour. *nCPAP – nasal continuous positive airway pressure; SpO_2 – arterial oxygen saturation measured by pulse oximetry*

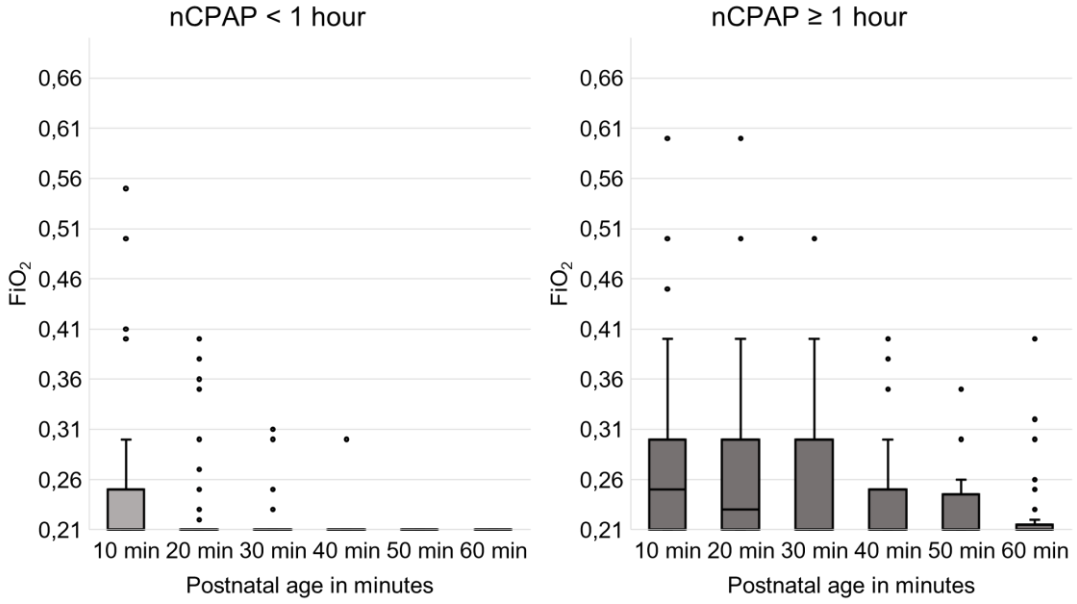

Figure 11 Box plots depicting FiO_2 in the first postnatal hour. *FiO_2 – fracture of inspired oxygen; nCPAP – nasal continuous positive airway pressure*

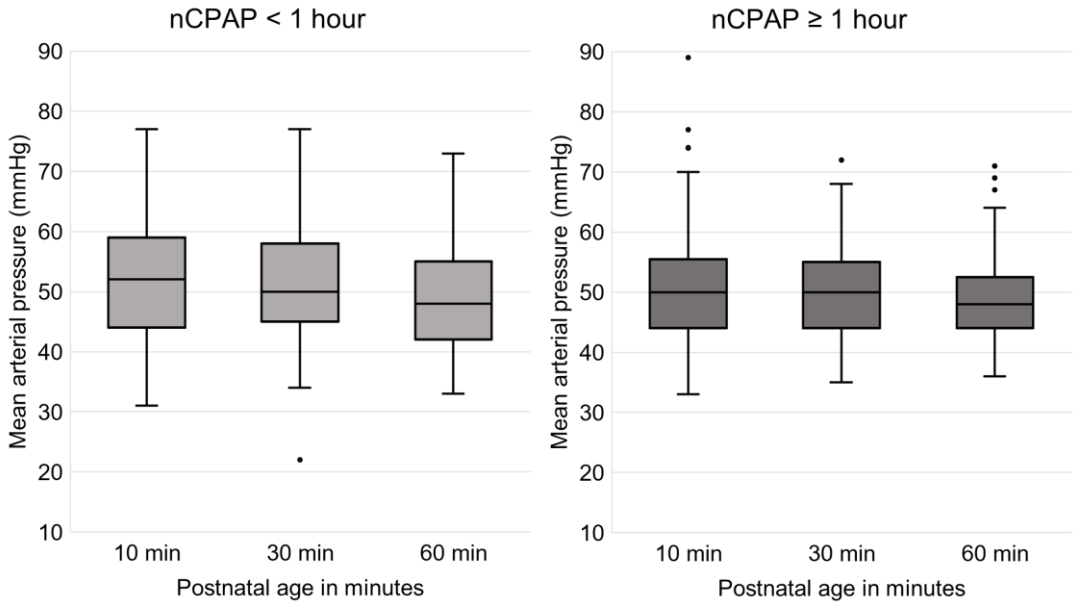

Figure 12 Box plots depicting mean arterial pressure in the first postnatal hour. *nCPAP – nasal continuous positive airway pressure*

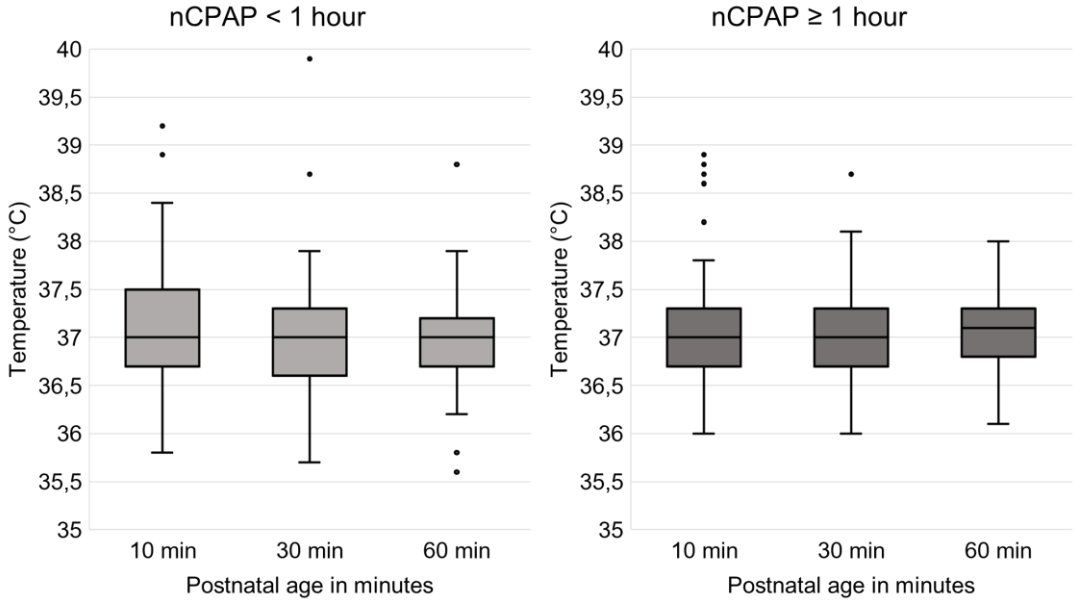

Figure 13 Box plots depicting rectal temperature in the first postnatal hour. *nCPAP – nasal continuous positive airway pressure*

3.5 Risk factors for nCPAP therapy ≥ 1 hour versus < 1 hour

3.5.1 Univariate analysis of risk factors 30 and 60 minutes postnatally

Taking the above-mentioned two-step approach analyzing the risk factors defined a priori for nCPAP therapy duration; we first included the lung ultrasound score, the Silverman-Andersen score, respiratory rate, FiO_2, and presence of respiratory acidosis in a univariate logistic regression. We analyzed all but the latter for the 30- and 60-minute time points. Table 5 shows the result of the univariate analysis. We had to exclude Silverman-Andersen scores with both cutoffs 4 and 5 from the 30-minute analysis and the parameters FiO_2 and lung ultrasound scores from the 60-minute analysis. Univariate modeling of named parameters was impossible since there was no infant with Silverman-Andersen scores < 4 or < 5 at the 30-minute time point who required nCPAP therapy for ≥ 1 hour. At 60 minutes, there was no infant receiving nCPAP for < 1 hour while either requiring supplemental oxygen or presenting with a lung ultrasound score > 5.

For further analysis at the 60 minutes time point, we used the Silverman-Andersen score with a cutoff of ≥ 5 due to a higher odds ratio with a similar p-value (subsequently named Silverman-Andersen $score_5$).

Table 5 Univariate analysis of the risk factors lung ultrasound score, Silverman-Andersen score, respiratory rate, FiO_2, and respiratory acidosis on increasing the risk for nCPAP therapy ≥ 1 hour

Risk factors at 30 minutes after birth		**p-value**	**Odds ratio**	**95% confidence interval**
Lung ultrasound score	> 5 vs. ≤ 5	< 0.01	14.36	6.04-34.12
Silverman-Andersen $score_4$	≥ 4 vs. < 4	n/a	n/a	n/a
Silverman-Andersen $score_5$	≥ 5 vs. < 5	n/a	n/a	n/a
Respiratory rate (/min)	> 60 vs. ≤ 60	0.11	1.79	0.88-3.66
FiO_2	> 0.21 vs. ≤ 0.21	< 0.01	9.55	3.61-25.16
Risk factors 60 minutes postnatally		**p-value**	**Odds ratio**	**95% confidence interval**
Lung ultrasound score	> 5 vs. ≤ 5	n/a	n/a	n/a
Silverman-Andersen $score_4$	≥ 4 vs. < 4	< 0.01	36.92	11.76-115.91
Silverman-Andersen $score_5$	≥ 5 vs. < 5	< 0.01	70.18	9.18-536.61
Respiratory rate (/min)	> 60 vs. ≤ 60	< 0.01	10.29	3.66-28.94

FiO_2	> 0.21 vs. ≤ 0.21	n/a	n/a	n/a
Risk factor within 60 minutes postnatally		**p-value**	**Odds ratio**	**95% confidence interval**
Respiratory acidosis	yes vs. no	< 0.01	2.97	1.41-6.25

nCPAP – nasal continuous positive airway pressure; FiO_2 – fracture of inspired oxygen

3.5.2 Multivariate analysis

During multivariate analysis, we tested all included risk factors for collinearity. The risk factors we included in the best model were tested for potential interactions. In both cases, we found neither collinearity nor interactions.

3.5.2.1 Multivariate analysis of risk factors at 30 minutes after birth

In the second step of our two-step approach analyzing risk factors on nCPAP therapy duration, we included risk factors with p-values < 0.05 from the univariate analysis into a complete model also containing the remaining risk factors birth weight, gestational age, pH in cord blood, 1-minute Apgar score, and sex (Table 6a). Here, only the risk factors FiO_2, lung ultrasound score, and respiratory acidosis showed a p-value < 0.05. Table 6b shows the best model results according to the Akaike Information Criterion (AIC) to estimate the quality of our statistical model, including the lung ultrasound score, FiO_2, and respiratory acidosis.

Table 7 shows the estimated probabilities for nCPAP therapy ≥ 1 hour for all combinations of risk factors identified at 30 minutes after birth. The best separation in terms of predicting nCPAP therapy ≥ 1 hour at 30 minutes postnatally was seen in our data at a probability cutoff of ≤ 0.66 versus > 0.66 (highest specificity with high sensitivity: 0.83 and 0.77, respectively; Youden's index 0.60) or at a probability cutoff of ≤ 0.46 versus > 0.46 (highest sensitivity with high specificity: 0.83 and 0.77, respectively; Youden's index 0.60). Figure 14 shows the receiver operating characteristic curve with an area under the curve of 0.87 (95 % confidence interval 0.81-0.93).

In summary, when evaluated at 30 minutes after birth, newborns with a lung ultrasound score ≤ 5 and one other risk factor (either FiO_2 > 0.21 or respiratory acidosis) were unlikely to require nCPAP therapy for ≥ 1 hour. In contrast,

newborns who presented either with a lung ultrasound score > 5 without other risk factors, or a lung ultrasound score ≤ 5 but two other risk factors, were more likely to have required respiratory support ≥ 1 hour. Newborns with a lung ultrasound score > 5 and one or two additional risk factors were increasingly likely to require nCPAP therapy for ≥ 1 hour.

Table 6a Multivariate analysis of risk factors for nCPAP therapy ≥ 1 hour at 30 minutes (complete model)

Risk factors evaluated at 30 minutes after birth		**p-value**	**Odds ratio**	**95% confidence interval**
Lung ultrasound score	> 5 vs. ≤ 5	< 0.01	15.71	5.33-46.31
FiO_2	> 0.21 vs. ≤ 0.21	< 0.01	8.05	2.40-26.97
Respiratory acidosis	yes vs. no	0.01	3.94	1.33-11.74
Birth weight	SGA or LGA vs. AGA	0.72	1.22	0.40-3.73
Gestational age (weeks)	< 38 vs. ≥ 38	0.29	1.80	0.61-5.30
pH in cord blood	< 7.25 vs. ≥ 7.25	0.84	0.90	0.33-2.46
1-minute Apgar	< 7 vs. ≥ 7	0.81	1.15	0.38-3.53
Sex	male vs. female	0.33	1.67	0.60-4.67

AGA – appropriate for gestational age; nCPAP – nasal continuous positive airway pressure; FiO_2 – fraction of inspired oxygen; LGA – large for gestational age; SGA – small for gestational age

Table 6b Multivariate analysis of risk factors on increasing the risk for nCPAP therapy ≥ 1 hour at 30 minutes (best model)

Risk factors evaluated at 30 minutes after birth		**p-value**	**Odds ratio**	**95% confidence interval**
Lung ultrasound score	> 5 vs. ≤ 5	< 0.01	16.32	5.82-45.76
FiO_2	> 0.21 vs. ≤ 0.21	< 0.01	7.36	2.24-24.16
Respiratory acidosis	yes vs. no	< 0.01	4.03	1.41-11.51

nCPAP – nasal continuous positive airway pressure; FiO_2 – fraction of inspired oxygen;

Table 7 Estimated probabilities for nCPAP therapy ≥ 1 hour for the risk factors lung ultrasound score, FiO_2, and respiratory acidosis at 30 minutes

Lung ultrasound score	FiO_2	Respiratory acidosis	Estimated probability for nCPAP ≥1 hour	95% confidence interval
≤ 5	≤ 0.21	No	0.11	0.05-0.22
≤ 5	≤ 0.21	Yes	0.33	0.17-0.53
≤ 5	> 0.21	No	0.47	0.22-0.73
> 5	≤ 0.21	No	0.66	0.48-0.81
≤ 5	> 0.21	Yes	0.78	0.50-0.93
> 5	≤ 0.21	Yes	0.89	0.71-0.96
> 5	> 0.21	No	0.94	0.80-0.98
> 5	> 0.21	Yes	0.98	0.92-0.99

nCPAP – nasal continuous positive airway pressure; FiO_2 – fraction of inspired oxygen

Figure 14 Receiver operating characteristic curve for the three risk factors on predicting nCPAP therapy ≥ 1 hour at 30 minutes

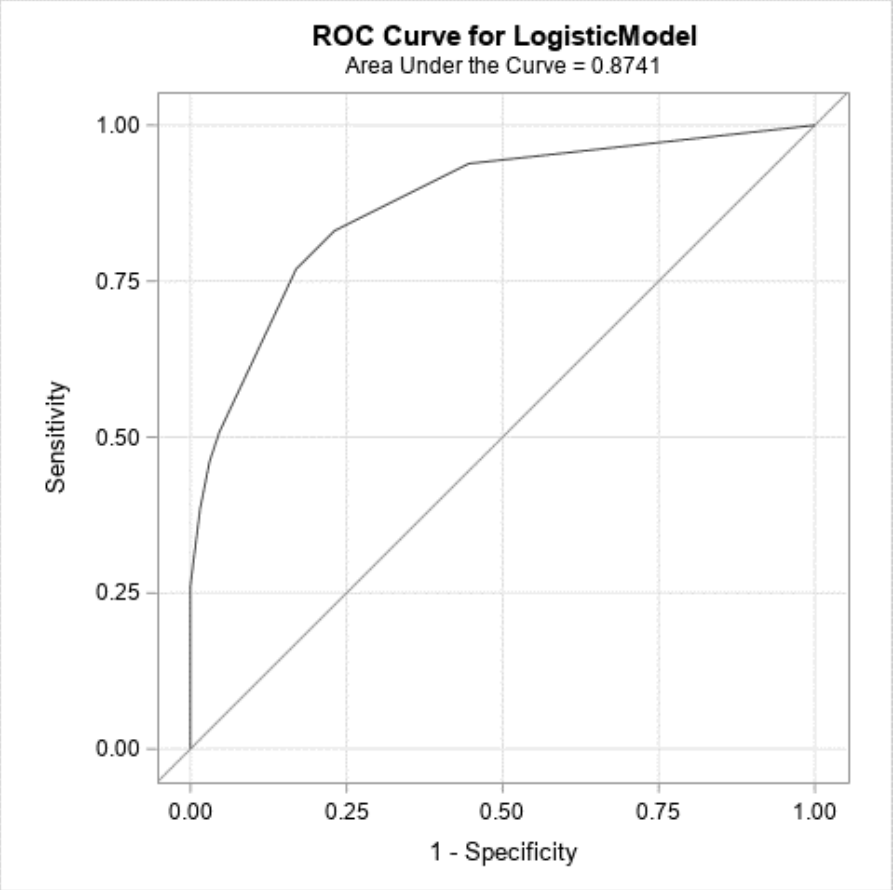

Figure 14 The curved grey line depicts the receiver operating characteristic curve for the risk factors lung ultrasound score, FiO_2, and respiratory acidosis on predicting nCPAP therapy ≥ 1 hour at 30 minutes. *FiO_2 – fraction of inspired oxygen; nCPAP – nasal continuous positive airway pressure; ROC – receiver operating characteristic*

3.5.2.2 Classification and regression tree analysis of the three risk factors for nCPAP therapy ≥ 1 hour at 30 minutes

The CART analysis confirmed our multivariate model (Figure 15).

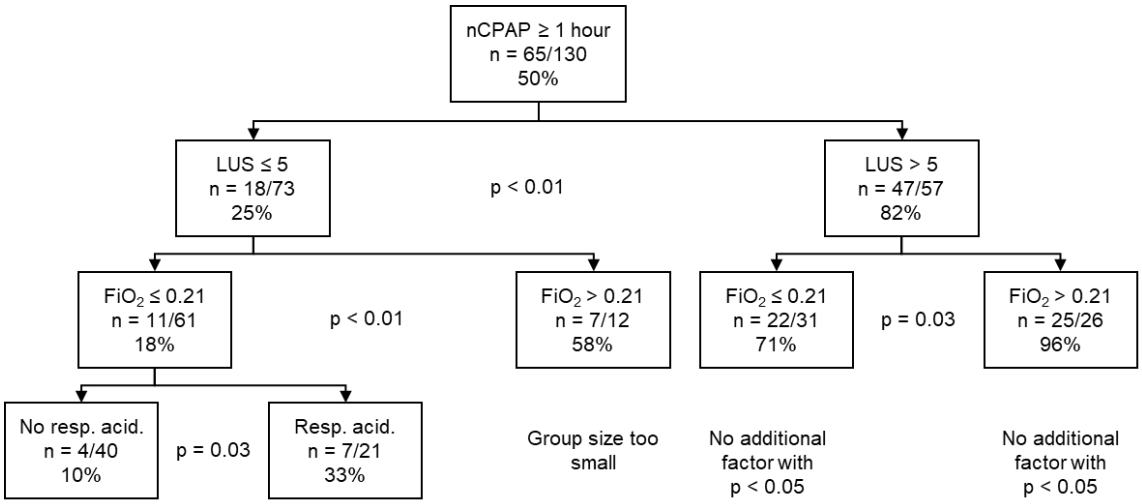

Figure 15 CART analysis; *CART – classification and regression tree; nCPAP – nasal continuous positive airway pressure; FiO_2 – fraction of inspired oxygen; LUS – lung ultrasound score*

3.5.2.3 Multivariate analysis of risk factors 60 minutes postnatally

Taking the same approach as outlined above, we included risk factors with p-values < 0.05 from the univariate analysis at 60 minutes into a complete model containing the remaining risk factors (Table 8a). Here, only the Silverman-Andersen $score_5$ and a respiratory rate > 60/min showed a p-value < 0.05. Table 8b shows the results of the best model according to the AIC, including only the Silverman-Andersen $score_5$ and respiratory rate.

Table 9 shows the estimated probabilities for nCPAP therapy ≥ 1 hour for all combinations of the risk factors identified at 60 minutes after birth.

In summary, when evaluated 60 minutes after birth, infants with a Silverman-Andersen $score_5$ < 5 and a respiratory rate ≤ 60/min were unlikely to require nCPAP therapy ≥ 1 hour. In contrast, newborns who presented either with a Silverman-Andersen $score_5$ ≥ 5 or a respiratory rate > 60/min or both were increasingly more likely to have required respiratory support ≥ 1 hour.

In univariate and multivariate analysis of risk factors at the 60-minute time point, the Silverman-Andersen score$_5$ showed an extremely high and implausible upper limit of the 95% confidence interval for the odds ratio (Tables 5, 8a, and 8b) due to an uneven distribution of the data. One of the four possible combinations of nCPAP therapy duration and the dichotomized Silverman-Andersen score$_5$ occurred in only one patient, destabilizing the statistical model (Table 8c). Therefore, we did not perform further analyses at the 60-minute time point.

Table 8a Multivariate analysis of risk factors on increasing the risk for nCPAP therapy ≥ 1 hour at 60 minutes (complete model)

Risk factors evaluated 60 minutes postnatally		**p-value**	**Odds ratio**	**95% confidence interval**
Silverman-Anders. score$_5$	≥ 5 vs. < 5	< 0.01	43.68	5.25-363.28
Respiratory rate (/min)	> 60 vs. ≤ 60	< 0.01	6.95	2.04-23.69
Respiratory acidosis	yes vs. no	0.41	1.54	0.56-4.24
Birth weight	SGA or LGA vs. AGA	0.93	1.05	0.35-3.10
Gestational age (weeks)	< 38 vs. ≥ 38	0.15	2.25	0.75-6.71
pH in cord blood	< 7.25 vs. ≥ 7.25	0.69	0.81	0.29-2.27
1-minute Apgar	< 7 vs. ≥ 7	0.83	1.12	0.40-3.16
Sex	male vs. female	0.84	0.91	0.35-2.35

AGA – appropriate for gestational age; nCPAP – nasal continuous positive airway pressure; FiO_2 – fraction of inspired oxygen; LGA – large for gestational age; SGA – small for gestational age

Table 8b Multivariate analysis of risk factors on increasing the risk for nCPAP therapy ≥ 1 hour at 60 minutes (best model)

Risk factors evaluated 60 minutes postnatally		**p-value**	**Odds ratio**	**95% confidence interval**
Silverman-Anders. score$_5$	≥ 5 vs. < 5	< 0.01	49.69	6.35-388.64
Respiratory rate (/min)	> 60 vs. ≤ 60	< 0.01	6.02	1.88-19.24

nCPAP – nasal continuous positive airway pressure

Table 8c Contingency table for the combinations of nCPAP therapy duration and the dichotomized Silverman-Andersen $score_5$ at 60 minutes

	Silverman-Anders. $score_5$ < 5	**Silverman-Anders. $score_5$ ≥ 5**	**Total**
nCPAP therapy < 1 hour	64	1	65
nCPAP therapy ≥ 1 hour	31	34	65
Total	95	35	130

Data presented as the number of patients. *nCPAP – nasal continuous positive airway pressure*

Table 9 Estimated probabilities for nCPAP therapy ≥ 1 hour for the risk factors Silverman-Andersen $score_5$ and respiratory rate at 60 minutes

Silverman-Andersen $score_5$	**Respiratory rate (/min)**	**Estimated probability for nCPAP ≥1 hour**	**95% confidence interval**
< 5	≤ 60	0.26	0.18-0.37
< 5	> 60	0.68	0.42-0.86
≥ 5	≤ 60	0.95	0.70-0.99
≥ 5	> 60	0.99	0.92-0.99

nCPAP – nasal continuous positive airway pressure

3.6 Interrater agreement

The intraclass correlation coefficient for interrater reliability of the lung ultrasound videos for four raters was 0.76 (95% confidence interval 0.72-0.89) and 0.77 (95% confidence interval 0.71-0.83) at 30 and 60 minutes, respectively, indicating good reliability according to Koo et al. [124].

4 Discussion

In this prospective observational study of newborns with respiratory distress due to delayed transition and TTN, we identified several risk factors for prolonged nCPAP therapy. Evaluated 30 minutes after birth, a lung ultrasound score > 5 or a need for supplemental oxygen coinciding with respiratory acidosis increased the risk for prolonged nCPAP therapy. Evaluated 60 minutes after birth, a respiratory rate > 60/min or a Silverman-Andersen score ≥ 5 increased the risk for prolonged nCPAP therapy, while the lung ultrasound score was now of little predictive value. Additionally, already-known risk factors for either the occurrence or a prolonged course of TTN were not associated with prolonged nCPAP therapy in our cohort.

Besides collecting data on vital signs during the first postnatal hour, we observed commonly described and lesser-known lung ultrasound findings, such as backsliding, in our cohort.

We demonstrated good interrater agreement for lung ultrasound video interpretation using an established lung ultrasound score.

4.1 Recruitment and study population

4.1.1 Recruitment

A large number of risk factors to be investigated necessitated a comparatively large sample size, although we planned our study as a pilot study. Given the annual number of infants born at our institution and the potentially eligible cases we identified a priori, we deemed our project, a single-center study over two years, feasible. The prerequisite for this was the inclusion of as many eligible patients as possible, which required parental consent in addition to the examinations relevant to the study. During the study plan's development, we knew that the early postnatal time our study was to start would be challenging since prospectively obtaining informed parental consent for study participation would have required us to approach all parents-to-be in advance. Also, obtaining consent shortly after birth may further burden parents in a per se stressful situation when their newborn presents with respiratory distress [125]. Due to our observational study design without any risk of harm and in agreement with the

ethics committee, we opted for deferred consent [125, 126], requiring us to obtain parental consent as soon as possible but within 72 hours after birth. The consent rate was 100%.

With choosing a gestational age ≥ 36 0/7 weeks as the inclusion criterion, we sought to reduce the area of overlap between respiratory distress caused by surfactant deficiency and that caused by TTN or delayed transition, as we focused on the latter [35]. Also, our cutoff meant including a significant proportion of infants with TTN or delayed transition in the designated study period and aligning with our institution's approach of routinely admitting only preterm infants < 36 weeks of gestation to the NICU [34, 35].

Due to the short time frame in which we had to initiate nCPAP therapy and perform the first lung ultrasound examination, we were forced to exclude almost one-third of eligible newborns as they were over 30 minutes old at the time of screening. In addition to cases with sepsis and pneumonia, we had to exclude patients with congenital malformations like congenital heart defects and a significant number of neonates with severe craniofacial malformations. The incidence of the latter was high since our institution focuses on treating such malformations. Also, binasal CPAP therapy, as required by the study protocol, was often not feasible in neonates with severe facial malformations. Additionally, one investigator became pregnant shortly after study initiation and could thus not participate further in patient recruitment. The above factors impaired recruitment and necessitated an extension of the recruitment period resulting in the enrollment of finally 130 instead of the initially aimed 150 patients. Coincidentally, the 130 cases were equally distributed between the short and long nCPAP groups, which was not apparent until after study completion since we did no interim analysis.

4.1.2. Study population

In our cohort, newborns requiring prolonged nCPAP therapy, thus mirroring more severe cases of delayed transition and TTN, were predominantly male, had a lower gestational age, and were frequently born by elective cesarean section, consistent with the literature [33, 35, 36]. Although the latter also had higher birth

weight percentiles than the short-term nCPAP group, the absolute birth weight difference was insignificant.

The percentage of newborns born to mothers with diabetes in pregnancy, which included type 1 and 2 diabetes in addition to gestational diabetes, was high, consistent with the at-risk population delivered at our institution [127]. In addition, gestational diabetes is a known risk factor for neonatal respiratory distress [39]. Although the percentage of mothers with asthma in our cohort matched the literature [128], we estimate our percentage to be too low because of inadequate documentation in patient records.

Nearly one-quarter of our cohort was born through some degree of meconium-stained amniotic fluid (MSAF), without us further grading the extent of MSAF. Although the reported MSAF incidence varies considerably [129, 130], our numbers surpass those of cohorts with similar gestational age (10.0-14.6%) [130, 131]. In addition to fetal maturation, MSAF is associated with hypoxic fetal stress and peripartum infections, all possible contributors to the pathogenesis of neonatal respiratory distress [129]. We excluded one newborn with meconium aspiration syndrome (MAS) needing mechanical ventilation and surfactant therapy, whereas the remaining MSAF cases were not considered MAS by the attending neonatologists.

Our cohort’s chorioamnionitis rate was also higher than reported in the literature, again considering that these vary markedly [132].

We believe our cohort’s high MSAF and chorioamnionitis rates result from our inclusion criteria requiring neonatal respiratory distress besides a certain gestational age, therefore, preselecting a population in which perinatal risk factors were more likely to be present. Additionally, as a university center, our institution cared for many high-risk pregnancies, increasing the prevalence of perinatal risk factors. Biasing our main study outcome, we estimate the effects of MSAF and chorioamnionitis as low, as we would have expected higher MSAF rates in the long-term nCPAP group and a more pronounced difference regarding chorioamnionitis rates.

Using umbilical artery pH as a surrogate marker for acute fetal stress and the Apgar score to provide an early assessment of the newborn, we did not observe clinically important differences between the short- and long-term nCPAP groups. Both our cohort's median umbilical artery pH and median Apgar scores were within the normal range. While the former does not reflect general fetal distress [133], Apgar scores, even within the normal range of 7 to 10, but lower than 10, as observed in our cohort, are associated with an increased risk for postnatal respiratory distress [134].

4.2 Outcome parameters

4.2.1 NCPAP therapy and duration, length of oxygen supplementation, and NICU stay

In our institution, nCPAP therapy is commenced early after birth, usually within minutes, in infants with signs of significant respiratory distress or need for supplemental oxygen. Routinely placed in a prone position on the resuscitation unit or in skin-to-skin with their mother, we supported all newborns with nCPAP therapy via binasal prongs and supplemental oxygen if needed. Our approach followed the concept that providing early distending pressure through nCPAP facilitates postnatal respiratory adaptation in infants with respiratory distress and may shorten the duration and severity of respiratory distress, thus avoiding NICU admission. While applying nCPAP for neonatal respiratory distress or TTN is a proven therapy and can improve the outcome of TTN, there are still many uncertainties regarding the timing of initiation of nCPAP therapy, the best nCPAP interface, or the required duration of nCPAP therapy [135]. Early postnatal nCPAP therapy has been investigated in similar populations [58, 136]. One applied nCPAP with a PEEP of 5 cmH_2O für 20 minutes after birth in near-term or term neonates with respiratory distress. Compared to a group of neonates receiving free-flow oxygen, the nCPAP group had a shorter duration of tachypnea and less frequent admissions to the NICU [136]. The other evaluated the effect of early prophylactic nCPAP therapy with a PEEP of 5 cmH_2O for 20 minutes in neonates after elective cesarean section, which led to fewer NICU admissions due to respiratory distress and a non-significant reduction in TTN rates compared to a group of neonates receiving no respiratory support [58].

Ultimately, despite the aforementioned studies, the evidence for the benefit of early nCPAP therapy in TTN is low or nonexistent concerning delayed transition [59]. Also, since early nCPAP therapy in the delivery room has been associated with an increased risk of pneumothorax, especially in near-term or term infants, it should be applied cautiously [84], highlighting the need for further studies concerning the use of nCPAP therapy in this population. Due to our study design, we could not evaluate the effectiveness of early nCPAP therapy in TTN or delayed transition; however, we also observed no clinically relevant pneumothoraces in our cohort of infants treated with early nCPAP therapy.

Comparing our main outcome parameter “nCPAP therapy duration”, as well as the length of oxygen supplementation and NICU stay to other studies, interpretation was hampered by our inclusion of the ill-defined clinical picture of delayed transition in addition to TTN and the high degree of heterogeneity in the literature regarding said outcomes [29, 135-141].

Concerning nCPAP duration, Demriel et al. recorded a mean duration of respiratory support of 32.2 (± 23.3 standard deviation (SD)) hours using nCPAP with a PEEP of 6 cmH_2O in a comparable cohort of (near-)term infants with TTN [138]. Applying nCPAP with a PEEP of 5 to 6 cmH_2O, Bekmez and Chiruvolu et al. reported median treatment durations of 31 (16-43 interquartile range (IQR)) and 27 (16-72 IQR) hours, respectively. However, both study populations had a significantly lower gestational age than ours, with 36 (35.5-38.0 IQR) and 36 (34.6-37.3 IQR) gestational weeks, respectively [140, 141].

With respect to oxygen supplementation, Dumas and Demriel et al. reported mean durations of 19.1 (± 8.1 SD) minutes and 29.0 (± 19.3 SD) hours in similar cohorts of newborns with tachypnea and TTN, respectively [137, 138]. Chiruvolu and colleagues documented a median duration of 6 (1-36 IQR) hours [141].

Regarding the duration of NICU stay, Demriel and Gizzi et al. reported means of 5.4 (± 2.0 SD) and 2.5 (± 2.0 SD) days, respectively, the latter applying nCPAP with a PEEP of 4 to 6 cmH_2O to term infants with TTN [138, 139]. Bekmez and Chiruvolu reported median values of 7 (5-9 IQR) and 7 (3-13 IQR) days, respectively, again in cohorts with a lower mean gestational age [140, 141].

Except for outliers, our cohort's range of nCPAP therapy duration was consistent with the above literature; however, the median treatment duration was comparatively short, even in the long-term nCPAP group. It is possible that the affected newborns benefited from our institution's early nCPAP therapy and the standardized weaning protocol, or our cohort generally had a more benign course of TTN and delayed transition. Ultimately, however, the reasons for the short nCPAP treatment duration remain unclear.

4.2.2 Respiratory rate, FiO_2, SpO_2, and additional vital signs

While we observed no difference in median respiratory rate between the groups 30 minutes postnatally, infants in the long-term nCPAP group had significantly higher respiratory rates 60 minutes postnatally, which correlated with the severity of respiratory distress. Respiratory rate in healthy newborns is normally at 30-60/min, averaging 46/min two hours postnatally [50, 142]. The respiratory rate varies markedly, reaching > 60/min transiently in healthy awake neonates, regardless of the mode of delivery. In TTN, respiratory rates of 60-80/min have been reported, sometimes extending to > 100/min [2, 142]. Interestingly, we did not observe the latter range within the first postnatal hour of our cohort.

Bekdas et al. associated higher respiratory rates with TTN durations lasting > 72 hours in a cohort of infants with a mean gestational age of 37.7 (± 1.8 SD) weeks without stating the exact time point of data collection. Infants in both groups (< 72 and > 72 hours) had significantly higher mean respiratory rates of 79.8/min (± 15.1 SD) and 105.2/min (± 17.4 SD), respectively, than our cohort. However, the authors included only infants requiring at least six hours of supplemental oxygen on their first day of life, presumably resulting in the inclusion of infants with a rather severe TTN course [51]. Also, retrospectively analyzing medical charts, Chang et al. identified a respiratory rate > 90/min within the first six postnatal hours as a risk factor for TTN durations > 72 hours in mostly late preterm infants with a mean gestational age of 36.4 (± 1.4 SD) weeks. In this study, the mean value for the highest respiratory rate seen within six hours of birth was also higher in both groups than in our cohort, with 90/min (± 18 SD) and 78/min (± 17 SD), respectively. However, unlike Bekdas et al., where all infants received respiratory support via high-flow nasal cannula or nCPAP, only 50% were treated with

“positive ventilation,” potentially affecting respiratory rate [76]. Also, utilizing an inclusion criterion preferring more severe cases of TTN, namely a 12-hour minimum duration of respiratory distress in a cohort of infants with a mean gestational age of 35.8 (± 3.1 SD) weeks, Köksal et al. reported a respiratory rate > 80/min as a risk factor for TTN duration > 72 hours. In their cohort of 108 neonates, only five of whom ultimately had a TTN duration > 72 hours, less than one-third received any respiratory support [77]. Lastly, in retrospective cohort analysis, Öztekin et al. did not find marked differences in respiratory rates at the time of NICU admission between two groups of infants requiring ≤ 5 or > 5 days of respiratory support or oxygen supplementation due to TTN. Stating conflicting time points of data acquisition either within the first postnatal hour or at the time of NICU admission, without specifying the latter, the authors reported mean respiratory rates of 67.5/min (± 18 SD) and 70.9/min (± 12.7 SD) in their cohorts of neonates with a mean gestational age of 38.1 (± 0.2 SD) and 38.0 (± 0.9 SD) weeks, respectively. The reported numbers were much closer to ours. However, the long treatment period and the inclusion criterion demanding persisting symptoms > 24 hours again suggested a study population affected by a more severe course of their TTN [75].

Even considering the heterogeneity of the above studies, it remains unclear why, in comparison, our median respiratory rates were significantly lower in the short- and long-term nCPAP groups. During the first postnatal hour, we determined the respiratory rate by counting thoracic excursions, potentially underestimating the actual respiratory rate.

Consistent with a more severe course of disease, infants in the long-term nCPAP group had higher median levels of oxygen supplementation, i.e., a higher FiO_2 and lower median SpO_2 at both time points; the latter, following international guidelines, had to be kept above 90% after the first ten postnatal minutes [54]. The above study by Chang et al. identified a maximum FiO_2 of > 0.4 within the first six postnatal hours as a risk factor for prolonged TTN, though without stating the targeted oxygen level [76]. In the above study by Öztekin et al., the authors reported mean SpO_2 levels of 95.8% (± 7.32 SD) and 89.2% (± 11.92 SD) during the first postnatal hour or at the time of NICU admission in their respective study

groups associating SpO_2 levels of ≤ 80% with a 5.7-fold increased risk for respiratory support for > 5 days [75].

While infants in the long-term nCPAP therapy group tended to have higher heart rates, presumably due to an increased respiratory distress, we observed no significant differences in mean arterial blood pressure and temperature. Heart rate decreased with increasing postnatal age in both groups. Comparing clinical data from neonates with short or long TTN courses, Chang et al. found no significant differences in maximum heart rates within the first six postnatal hours [76]. Therefore, the above parameters appeared poorly suited for evaluation as risk factors for prolonged nCPAP therapy or TTN and delayed transition courses.

4.2.3 Respiratory acidosis

We observed respiratory acidosis, defined as a pH < 7.2 and a pCO_2 > 60 mmHg, twice as often in the long-term nCPAP group compared to the short-term group, plausibly mirroring the increased severity of respiratory distress in the former. In a study by Hedstrom et al., higher mean pCO_2 within one hour of birth correlated to higher respiratory severity scores in neonates aged 24 to 41 weeks. The mean pCO_2 in the higher respiratory severity score group was 66.7 (± 17.3 SD) mmHg, and the latter group was also more likely to require increased respiratory support during the first 24 postnatal hours [143].

Concerning pH, Öztekin et al. also demonstrated an increased risk of prolonged respiratory support in infants with TTN if the respective pH was ≤ 7.22 in a blood gas analysis collected during the first postnatal hour. Although pCO_2 levels also tended to be higher in the group with longer respiratory support (mean 36.5 (± 6.57 SD) mmHg vs. 39.5 (± 8.62 SD)) mmHg, the authors did not find a significant relationship with the duration of treatment [75].

Without elucidating the reasons for prolonged NICU stays > 48 hours, Ekmen et al. reported an increased such risk in neonates with TTN and pCO_2 > 48.8 mmHg on admission [78].

We defined *respiratory acidosis* a priori as pH < 7.2 and CO_2 > 60 mmHg for practical reasons and to account for the wide variability in blood gas values

obtained in the early postnatal period and our assessment that, using the standard definition of pH < 7.35 and CO_2 > 45 mmHg, would have hampered the use of respiratory acidosis as a differentiating parameter due to the expectably large number of infants being labeled as respiratory acidotic [144, 145]. Additionally, we obtained all blood gas analyses from venous blood, which, despite showing a good correlation to arterial blood sampling as the gold standard, usually results in slightly lower and higher values for pH and CO_2, respectively [146, 147].

The timing of postnatal blood gas analysis is crucial since the obtained values may change rapidly and greatly, especially within 30 minutes of birth [144]. Since we designed our study to minimize alteration of the standard neonatal care and to avoid study-driven blood sampling at a fixed time point, when parental consent may not yet have been obtained, we solely set a time limit for blood sampling to be done anytime within the first postnatal hour. Therefore, we could only specify time frames for blood sampling with > 90% of blood gas analyses being performed in both the short- and long-term nCPAP group in infants older than 30 but younger than 60 minutes. The lack of minute-by-minute sampling time determination limits the interpretation of respiratory acidosis as a risk factor since its incidence expectably decreases over time, concomitant to an improvement in clinical symptoms.

4.2.4 Silverman-Andersen score

We used the Silverman-Andersen respiratory severity score as a clinical assessment tool since it included typical signs of neonatal respiratory distress like nasal flaring, chest retractions, and expiratory grunting, which is especially common in delayed transition [29, 120].

As expected, the respective scores at 30 and 60 minutes were higher in the long-term nCPAP group than in the short-term group. Both showed a decrease over time, matching the clinical improvement or the natural course of the disease or potentially also the effect of nCPAP therapy. However, the difference within each group between the 30- and 60-minute postnatal time points was less pronounced

in the long-term nCPAP group, with the latter presenting with a median score of 5 and the former with 2 at 60 minutes, respectively.

Our cohort's Silverman-Andersen scores were within the range reported under similar conditions concerning population, timing, and cause of respiratory distress while considering the heterogeneity of the existing data as far as possible [58, 101, 137, 148]. Scored within the first 30 postnatal minutes in term neonates with respiratory distress, Dumas De La Roque and Celebi et al. reported a median score of 5 (5-6 IQR) and a range of 5-7, respectively [58, 137]. In slightly older (mean postnatal age 1.7 (± 0.79 SD) hours) and less mature infants (mean gestational age 36.4 (± 1.8 SD) weeks) with TTN, Raimondi and colleagues reported a mean Silverman-Andersen score of 4.0 (± 1.8 SD) [101]. In a cohort of term newborns with TTN and need for respiratory support > 12 hours, Oskan et al. reported a median score of 8 (6-10 IQR) within the first two postnatal hours [148]. Utilizing the Silverman-Andersen score as a predictive tool within the first postnatal hour, Hedstrom et al. associated a score ≥ 5 with an increase in respiratory support during the first 24 hours in neonates with respiratory distress [143].

A point of critique was our use of the Silverman-Andersen score per se, since a different scoring system like the Downes score would have potentially better suited our study [149-151]. During the study planning, we chose the former, as it was already established in our institution.

4.3 Lung ultrasound findings

4.3.1 Lung ultrasound score

We used a lung ultrasound score first established in a general population of newborns by Brat et al. in 2015 [103]. Although initially intending to correlate the lung ultrasound score with oxygenation indices and trying to predict the need for surfactant in preterm infants, the score described lung aeration and oxygenation and encompassed lung ultrasound findings typical for TTN and presumably also for delayed transition. Additionally, the score was developed in neonates already treated with nCPAP, which corresponded to our study's setting [103]. The original score (or variations thereof) has been widely applied in newborns' pulmonary

diseases, including respiratory distress syndrome, bronchopulmonary dysplasia, and TTN [100, 152]. Deviating from the original score, we performed lung ultrasound almost exclusively in the prone position due to our institution's approach to treating respiratory distress in newborns. While applying lung ultrasound in the prone position is feasible, it is important to note that interpretation may be biased when lung ultrasound is performed immediately after a positional change. Transient shifts in aeration after positional changes necessitate a certain amount of resting time in the respective position for lung ultrasound to be diagnostically conclusive [153, 154]. In our study, we performed the lung ultrasound at least 25 minutes after the last positional change.

Concerning the total population, we observed median lung ultrasound scores similar to or slightly below those reported in the literature. However, few studies performed lung ultrasound examinations equally early after birth using the same scoring system. Brat et al. scored infants ≥ 34 weeks of gestation with respiratory distress at a mean postnatal age of 2.8 hours with a median lung ultrasound score of 5 (3-10 IQR) [103]. At 60 to 180 minutes of life, Raimondi and colleagues scored infants with TTN with a mean value of 6.7 (± 3.4 SD) [101], while Yoon et al. reported a median lung ultrasound score of 6 (5-8 IQR) in infants with TTN, without specifying the exact time when scoring took place [155].

Matching the severity of respiratory distress, infants needing prolonged nCPAP therapy had higher lung ultrasound scores than those with short-term nCPAP therapy. While the Silverman-Andersen score decreased significantly from the 30-minute time point to the 60-minute time point, we did not observe a comparable reduction in lung ultrasound score in either group. Our finding contrasts published data, where lung ultrasound and Silverman-Andersen scores followed similar trends, i.e., with an improvement in clinical symptoms, better lung aeration also became visible via ultrasound when lung ultrasound and clinical scoring were performed every 4 to 6 hours [101]. Possibly, our study's time intervals between the first and second lung ultrasound examinations were too short. However, at least in healthy newborns, relevant changes in lung aeration can be monitored in even shorter intervals, as Blank et al. showed using up to three examination time points within one hour of birth [21, 99].

4.3.2 Double lung point

We visualized the double lung point in about two-thirds of our cohort at both time points, with a significantly higher incidence in the long-term nCPAP group. Contrary to the above observations concerning the lung ultrasound score, double lung point frequency in the short-term nCPAP, but not the long-term nCPAP group, decreased between the 30- and 60-minutes time points. While the double lung point presumably mirrored a more severe clinical course in the latter, it potentially visualized improving lung aeration earlier than the lung ultrasound score.

Copetti et al. first described the double lung point as a specific finding in newborns with TTN in 2007. In their cohort with a mean gestational age of 34.2 (± 1.8 SD) weeks, all newborns with TTN showed said ultrasound finding within the first postnatal hour. The authors concluded that the double lung point had a 100% sensitivity and specificity for diagnosing TTN [97]. Subsequent studies reported the double lung point as a lung ultrasound sign highly specific for TTN, but not with 100% sensitivity [98, 118]. Without specifying the exact lung ultrasound examination time point and independent of the respective infant's position, Liu et al. detected the double lung point in 76.7% and 45.6% in two populations of term and preterm infants with TTN. The authors calculated the specificity and sensitivity of the double lung point for diagnosing TTN at 100% and 94.8%, respectively. In contrast to Copetti's data, Liu et al. visualized the double lung point also in infants with meconium aspiration syndrome, respiratory distress due to surfactant deficiency, and pneumonia, although only in small numbers [98, 101, 118]. In a cohort of near-term and term infants with a mean gestational age of 36.4 (± 1.8 SD) weeks initially scanned within the first two postnatal hours, Raimondi et al. detected the double lung point in 47.6%. While the percentage of neonates requiring nCPAP for TTN was the same independent of whether the double lung point was present, the duration of respiratory distress was longer in the double lung point group, corresponding to our observations [101].

Our results and those reported above indicate that the double lung point is a common yet not exclusive ultrasound sign in TTN and delayed transition. Being more frequently visualizable in prolonged courses of TTN, as reported by

Raimondi et al. and us [101], the double lung point is a potential additional prognostic factor for predicting TTN course to be evaluated in future studies.

4.3.3 Pleural line

Lung ultrasound depicts the pleural line of a healthy, well-aerated lung as a regular and thin linear hyperechoic line [119]. We detected pleural line abnormalities in 60% of cases. Again, like the lung ultrasound score and the double lung point, there were significantly higher incidences in the long-term nCPAP group, potentially representing the more severe course of delayed transition and TTN.

Reports on pleural line appearance in TTN vary, with some authors describing pleural line “thickening, fuzziness, and disappearance” or pleural line abnormalities in general in nearly all lung ultrasound examinations [98, 113, 119]. In contrast, other authors reported almost exclusively regular pleural lines in infants with TTN [97, 101].

In contrast to the now comparatively uniform nomenclature used describing general (neonatal) lung ultrasound findings like A- and B-lines or double lung point [96, 97], pleural line descriptions and data on pleural line thickness are yet rather vaguely described as “abnormal,” “thickened,” or “fuzzy” [98, 119, 156]; the latter ranging from < 0.5 to < 1.0 mm in “normal” pleural lines [95, 156]. Taking a systematic approach at defining reference values for pleural line thickness in healthy neonates and ten neonates with TTN, Alsonso-Ojembarrena et al. measured “normal” pleural line thickness in both groups to be < 1.0 mm [95].

Concerning the heterogeneity of describing and measuring the pleural line, it must be considered that the pleural line examination via ultrasound is particularly prone to error. Besides the equipment and transducer used (high vs. low-end equipment; < 10- vs. > 10-Megahertz ultrasound probe), body position (prone vs. supine) and transducer handling (scanning longitudinally vs. transversally; ultrasound probe angulation) all potentially influence the pleural line examination [157].

Given the above limitations, we refrained from including pleural line findings in our statistical analyses. Instead, based on the previously published descriptions, we only classified pleura line findings as normal or abnormal. Measuring pleural line thickness during the ultrasound exam was neither initially planned nor performed retrospectively. Therefore, our qualitative classification was subjective and of limited comparability, both limiting its use. However, due to the observed incidence, the detection of pleural line abnormalities, similar to the double lung point, appears to be a potential additional prognostic factor for predicting nCPAP duration and clinical course of delayed transition and TTN.

4.3.4 Extended consolidations

We observed extended consolidations in four term infants, one of whom had consolidations at both the 30 and 60-minute time points. All consolidations occurred in the long-term nCPAP group.

Extended consolidations are rare in TTN and are more commonly seen in respiratory distress syndrome due to surfactant deficiency, meconium aspiration syndrome, or neonatal pneumonia [101, 118, 119]. Although each was defined a priori as an exclusion criterion, no affected infant was treated for surfactant deficiency or neonatal pneumonia; one was born through meconium-stained fluids, potentially suffering from meconium aspiration syndrome, without the neonatologist in charge diagnosing it as such. Also, there is an overlap between TTN and surfactant-deficient respiratory distress syndrome, as reports exist of term neonates with prolonged TTN courses exhibiting a reduced surfactant function, potentially explaining our lung ultrasound findings [40, 101].

As stated in the pleural line section, detecting consolidations also depends on the equipment used and how lung ultrasound was performed [157]. With the increasing use of high-frequency linear transducers in the prone position optimally aligned to the relatively flat surface of the infant's back, conceivably more subpleural findings are visualized in clinical pictures previously not associated with consolidations.

4.3.5 Backsliding

Contrary to the expected clinical course, we observed an increase in lung ultrasound scores from the 30- to 60-minute time point in one-third of infants. “Backsliding,” i.e., worsening lung ultrasound grades from one point to the next, can be seen early postnatally in healthy neonates and infants presenting with respiratory distress [21, 100]. Through the observed changes in the respective infant’s activity, Blank et al. speculate that backsliding may result from reduced intrathoracic pressures in quietly breathing neonates compared with the initial state of vigorous crying, which correspondingly drives less lung liquid into the interstitium [21]. Backsliding could also be the lung ultrasound correlate of the above-described clearing and re-entry cycle of lung liquid during the normal postnatal transition [13]. Due to the paucity of data on backsliding, the significance of this lung ultrasound finding remains unclear. Since backsliding occurred at a similar frequency in the short- and long-term nCPAP groups, it does not seem to be associated with a longer course of TTN or delayed transition, at least in our population.

4.4 Identifying risk factors for prolonged nCPAP therapy

We conceptualized our study utilizing readily available neonatal data and bedside diagnostic tools to estimate nCPAP therapy duration within the first postnatal hour. We chose two checkpoints at 30 and 60 minutes postnatally, at which the prognostic assessment should be made based on the information available at the respective time points. Selecting these time points resulted from the following considerations: we assumed that healthcare providers should be able to stabilize the newborn and acquire the necessary information within the specified periods in everyday clinical practice outside of any study setting. Our approach further allowed the newborn to undergo neonatal transition without being categorized too early, as some degree of postnatal respiratory distress will resolve spontaneously or with little supportive care [29, 30, 158]. Lastly, for lung ultrasound to be informative early after birth, a certain time interval between delivery and lung ultrasound examination seemed necessary [21, 99].

We chose nCPAP therapy duration as the main outcome and surrogate for the clinical course of delayed transition and TTN since our institution's nCPAP weaning protocol ensured a standardized and patient-relevant study endpoint.

In the upfront selection of known risk factors that were to be included in our study, we focused on those that did not require a detailed maternal medical history, mirroring the potential unavailability of medical history data like maternal asthma, obesity, or diabetes in the first postnatal hour [37-39]. Furthermore, we attempted to include not only risk factors that have already been repeatedly described, like elective cesarean section [36], but also those with lesser-known impact on delayed transition and TTN. Ultimately, our selection of risk factors represented a compromise between the number of included factors and the subsequently larger sample size required to perform a valid statistical analysis.

We performed dichotomization of the risk factors birth weight, gestational age, pH in cord blood analysis, 1-minute Apgar score, and sex according to published data [35, 36, 51, 74]. Concerning respiratory rate, FiO_2, and respiratory acidosis, we adapted the respective risk factor cutoffs of the original publications to achieve more practical and intuitive cutoffs for daily practice [51, 75, 76]. We defined an increased respiratory rate as > 60/min, meeting the standard definition of tachypnea [50]. We rated $FiO_2 > 0.21$ as a risk factor for prolonged nCPAP since, at least in our experience, infants with delayed transition rarely require supplemental oxygen. Also, a limit of > 0.4 in infants with TTN, as reported by Chang et al., seemed too high as such cases rarely occur, at least in our setting [76]. We defined respiratory acidosis as indicated in the corresponding section. Due to the varying Silverman-Andersen score cutoffs in the literature, we included two cutoffs of 4 and 5 in univariate analysis to finally set the cutoff at 5 in the final analysis due to the latter's higher odds ratio [143, 159, 160]. As stated above, we could not rely on previously published cutoffs since the lung ultrasound score had not yet been used in a similar setting regarding timeframe and population. Thus, we determined cutoffs statistically from the data we collected, resulting in a major point of criticism of our study because the dichotomization used the same data as the subsequent statistical modeling. Therefore, our model has to be validated in an independent sample.

Contrary to the original draft, we refrained from including the risk factor SpO_2 < 90% vs. ≥ 90% in our statistical analysis. SpO_2 was directly influenced by FiO_2 and should have been maintained above 90% in infants older than 10 minutes, according to our institution's approach and international guidelines [54]. Therefore, we expected that almost all recorded SpO_2 values were above 90%, thus leaving this parameter uninformative.

4.4.1 Risk factors for nCPAP therapy ≥ 1 hour at 30 minutes postnatally

We identified a lung ultrasound score > 5, FiO_2 > 0.21, and respiratory acidosis as risk factors for prolonged nCPAP therapy (≥ 1 hour) at the 30-minute mark. Both, a need for supplemental oxygen and a lower pH or higher CO_2 were already associated with prolonged TTN courses or increased duration of respiratory support [75, 76]. Concerning the lung ultrasound score and cutoff value, a comparison to the existing literature is hampered due to varying study populations, designs, and application periods. However, our values seem to be within the range of those previously reported using the score by Brat et al. [152].

While higher respiratory rates have been linked to prolonged courses of TTN, we did not find a similar association if the respiratory rate was > 60/min at the 30-minutes time point [51].

As stated in the Results section, we could not include the 30-minute Silverman-Andersen score in the univariate analysis due to the uneven data distribution.

Typically, prolonged nCPAP therapy results in NICU admission, at least in our institution. Utilizing the identified three risk factors in clinical practice depends on the respective institution's approach: Both risk factors' estimated probability cutoffs of ≤ 0.66 vs. > 0.66 and ≤ 0.46 vs. 0.46 led to good sensitivity and specificity for predicting nCPAP therapy for ≥ 1 hour. If an institution's approach is to avoid NICU admissions, a high specificity and thus a high true-negative rate should be aimed for (in the sense of "expected nCPAP therapy not to be ≥ 1 hour"), thus utilizing the former cutoff. Alternatively, following a safety approach, a high sensitivity should be aimed for, i.e., a high true-positive rate, which ensures that as many infants as possible are detected who have an expected nCPAP therapy duration of ≥ 1 hour, subsequently admitting them to the NICU at an early

stage of delayed transition or TTN. Here, the estimated probability cutoff of ≤ 0.46 vs. > 0.46 seems more appropriate. With an area under the curve of 0.87, our statistical model can be considered a very good test and could serve as a basis for developing a prediction tool [161].

4.4.2 Risk factors for nCPAP therapy ≥ 1 hour at 60 minutes postnatally

We identified a Silverman-Andersen score ≥ 5 and a respiratory rate > 60/min as risk factors for prolonged nCPAP therapy ≥ 1 hour at the 60-minute mark.

We had to exclude the lung ultrasound score and FiO_2 at the 60-minute time point for the same reasons as the Silverman-Andersen score at 30 minutes postnatally.

Due to the literature reporting Silverman-Andersen score cutoffs ranging from ≥ 2 to > 6 as a contributory factor in diagnosing TTN, a threshold to initiate respiratory support in neonates with respiratory distress, and to indicate impending respiratory failure [101, 143, 151, 162-164], we included two cutoffs (< 4 vs. ≥ 4 and < 5 vs. ≥ 5) a priori. We used a cutoff of ≥ 5 as a risk factor for prolonged nCPAP therapy due to a higher odds ratio in our univariate analysis. Ultimately, we refrained from further analyses at the 60-minute point because one of the two remaining risk factors, the Silverman-Andersen score, destabilized the statistical model, again caused by unevenly distributed data. Using contingency tables, we ascertained that one of the four possible combinations between the duration of respiratory support and the dichotomized Silverman-Andersen score occurred in only one patient as depicted in the Results section.

For both study time points, none of the upfront selected and already known risk factors was associated with prolonged nCPAP therapy, which was an unexpected finding. Although infants requiring prolonged nCPAP therapy had a lower gestational age than those with shorter nCPAP therapy in our cohort, dichotomizing < 38 vs. ≥ 38 weeks of gestation based on the data of Bak et al. did not influence the risk for prolonged respiratory support [74]. Bak and colleagues had identified a gestational age < 38 weeks as a prognostic factor for longer hospitalization due to TTN [74]. Also, in the study by Bekdas et al., infants with an average gestational age < 38 weeks had a longer hospitalization due to TTN [51]. The association between low gestational age and longer inpatient stay

is plausible since increasing immaturity adds additional morbidity like hypothermia and feeding difficulties, besides a potential for respiratory distress, necessitating longer inpatient treatment [165]. Likewise, infants born small or large for gestational age (i.e., < 10^{th} or > 90^{th} birth weight percentile) have an increased risk for respiratory distress due to often being born via cesarean section [36, 45, 166]. While infants with prolonged nCPAP therapy had a higher average weight percentile than the short-term nCPAP group, being born small or large for gestational age did not alter our cohort's risk for prolonged nCPAP therapy. The same was valid for males despite the significantly greater proportion of males in the prolonged nCPAP group. Male sex has been previously reported as a risk factor for either TTN or prolonged courses of TTN [36, 51]. Finally, Bak et al. identified an umbilical artery pH < 7.25 and a 1-minute Apgar score < 7 as individual risk factors for prolonged respiratory support in TTN, which again we found no similar associations for in our cohort as umbilical artery pH and 1-minute Apgar scores did not significantly differ between the two groups [74].

Since we had not adjusted the cutoffs for the latter risk factors, our modifications did not explain the lack of associations. In general, studies identifying risk factors should be interpreted cautiously, especially when done retrospectively, as in the case of Bak and Bekdas et al., due to the inherent risk for bias [51, 74, 167, 168]. The herein-identified factors apply to the respective population and are only transferable to other populations to a limited extent. Nevertheless, they help generate hypotheses and serve as a basis for further studies.

4.5. Interrater agreement

The interrater agreement of the lung ultrasound videos among our four raters was good [124]. The high interrater agreement concerning the lung ultrasound score suggests method robustness when used by different practitioners, as previously demonstrated with the respective score and lung ultrasound scoring per se [103, 152].

4.6 Conclusion

We identified a lung ultrasound score > 5, the need for supplemental oxygen, and respiratory acidosis 30 minutes postnatally as risk factors for prolonged nCPAP

therapy. These risk factors could serve as the basis of a prediction tool. Using two statistical models, multivariate logistic regression and CART analysis, the mentioned risk factors showed comparable results, which supported the robustness of our model. Within our study population, we defined cutoffs that resulted in good sensitivity and specificity regarding the prediction of a prolonged nCPAP therapy in infants with TTN and delayed transition. Our study results now need to be validated in an independent sample. Although a higher Silverman-Andersen score ≥ 5 and a respiratory rate > 60/min evaluated 60 minutes postnatally seemed to increase the risk for prolonged nCPAP therapy, further analysis was impossible due to unevenly distributed data.

Additionally, we described clinical signs and lung ultrasound findings as additional factors present during the first postnatal hour. Concerning the latter, the double lung point and pleural line abnormalities could be investigated as potential additional risk factors for prolonged nCPAP therapy in future studies.

Finally, we showed good interrater agreement in evaluating lung ultrasound findings.

5 Abstract

Delayed transition and transient tachypnea of the newborn (TTN) are common causes of respiratory distress in term and near-term infants caused by delayed postnatal lung liquid clearance. Risk factors for delayed transition and TTN are prematurity, elective cesarean section, male sex, and perinatal asphyxia. Risk factors associated with a prolonged course of TTN and respiratory support are low umbilical cord pH, Apgar score, decreased SpO_2, increased respiratory rates, and increased CO_2. Treatment includes close cardiorespiratory monitoring, supplemental oxygen, and nasal continuous positive airway pressure (nCPAP). Usually bearing a benign clinical course, delayed transition and TTN may nonetheless lead to neonatal intensive care unit (NICU) admission with varying duration and associated mother-child separation. Identifying bedside applicable prognostic parameters to estimate the duration of nCPAP therapy as a surrogate for the clinical course of TTN and delayed transition potentially reduces NICU admission.

We designed a prospective observational study to estimate the duration of nCPAP therapy in term and near-term infants ≥ 36 0/7 weeks of gestation with delayed transition and TTN. The main outcome parameter was nCPAP therapy duration (< 1 vs. ≥ 1 hour). Additional study aims were clinical and lung ultrasound findings and evaluating interrater agreement of lung ultrasound scores. Thirty and 60 minutes postnatally, nCPAP duration was estimated based on the following parameters: lung ultrasound score, Silverman-Andersen score, respiratory rate, FiO_2, SpO_2, and respiratory acidosis in blood gas analysis. We also included the previously described risk factors birth weight, gestational age, pH in cord blood analysis, 1-minute Apgar score, and sex in our analysis. We used univariate and multivariate analysis to evaluate the risk factors' influence on nCPAP therapy duration and the intraclass correlation coefficient to test interrater agreement.

Thirty minutes postnatally, a lung ultrasound score > 5, FiO_2 > 0.21, and respiratory acidosis were associated with nCPAP therapy ≥ 1 hour. We determined two probability cutoffs aiming at either a high sensitivity or high specificity predicting nCPAP therapy ≥ 1 hour. We confirmed our model using

classification and regression tree analysis. With an area under the curve of 0.87 in receiver operating characteristic analysis, our model proved to be a good diagnostic test, potentially serving as a basis for developing a prognostic tool. Sixty minutes postnatally, a Silverman-Andersen-Score ≥ 5 and a respiratory rate > 60/min were associated with nCPAP therapy ≥ 1 hour. Due to unevenly distributed data, we refrained from further analyses at the 60-minute time point.

None of the already known risk factors were associated with prolonged nCPAP therapy in our cohort, but we confirmed several already known lung ultrasound findings in TTN and, for the first time, in delayed transition. We identified the double lung point and pleural line abnormalities as potential candidates for further prognostic studies in TTN and delayed transition. We demonstrated a good interrater agreement for lung ultrasound scoring between different raters: two neonatologists and two pediatric radiologists.

With regard to our study's main limitation of determining the lung ultrasound score cutoff statistically based on our cohort's data, our findings on risk factors for prolonged nCPAP therapy and their potential use as a diagnostic tool must be validated in an independent sample.

Zusammenfassung

Die respiratorische Anpassungsstörung, im Englischen und im Folgenden als delayed transition bezeichnet, und die transiente Tachypnoe des Neugeborenen (TTN) sind häufige Ursachen für Atemnot bei reifen oder nahezu reifen Neugeborenen. Sie werden durch eine verzögerte Mobilisation von intrapulmonaler Flüssigkeit verursacht. Risikofaktoren für die Entstehung dieser Krankheitsbilder sind Frühgeburtlichkeit, elektiver Kaiserschnitt, männliches Geschlecht und perinatale Asphyxie. Risikofaktoren für einen schweren Verlauf sowie einem erhöhten bzw. verlängerten Bedarf einer Atemunterstützung sind ein niedriger Nabelschnur-pH, niedriger Apgar-Score, ein verminderter SpO_2-Wert sowie eine erhöhte Atemfrequenz bzw. ein erhöhter CO_2-Wert. Zur Therapie gehören Monitoring, Sauerstoffsupplementierung und Atemunterstützung mittels

nasal appliziertem kontinuierlichen positiven Atemwegsdruck (nCPAP). Obwohl der Krankheitsverlauf in der Regel benigne ist, können die delayed transition und TTN zu stationären Aufenthalten auf der neonatologischen Intensivstation (NICU) von variabler Dauer und damit verbundener Trennung von Mutter und Kind führen. Die Identifizierung bettseitig erhobener Prognoseparameter zur Abschätzung der Dauer der nCPAP-Atemunterstützung bei delayed transition und TTN könnte die Aufnahme auf der Neugeborenen-Intensivstation (NICU) verringern.

Wir führten eine prospektive Beobachtungsstudie zur Abschätzung der Dauer einer nCPAP-Atemunterstützung bei Neugeborenen ≥ 36 0/7 Schwangerschaftswochen mit delayed transition und TTN durch. Das Primärergebnis war die nCPAP-Dauer (< 1 vs. ≥ 1 Stunde). Weitere Studienergebnisse waren die Erhebung klinischer Befunde sowie Beschreibung der Lungensonografie bei delayed transition und TTN. Außerdem überprüften wir die Interrater-Reliabilität bei der Erhebung des Lungenultraschall-Scores. Dreißig und 60 Minuten postnatal wurde der Einfluss folgender Parameter auf die nCPAP-Dauer evaluiert: Lungenultraschall-Score, Silverman-Andersen-Score, Atemfrequenz, FiO_2, SpO_2 und respiratorische Azidose in der Blutgasanalyse. Wir inkludierten zusätzlich bereits beschriebene Einflussfaktoren wie das Geburtsgewicht, Gestationsalter, pH-Wert in der Nabelschnur, 1-Minuten-Apgar und das Geschlecht in unserer Analyse. Wir verwendeten univariate und multivariate logistische Regressionsanalysen, um den Einfluss der Risikofaktoren auf die nCPAP-Dauer zu untersuchen und den Intraklassen-Korrelationskoeffizient zur Überprüfung der Interrater-Reliabilität.

Dreißig Minuten postnatal waren ein Lungenultraschall-Score > 5, FiO_2 > 0,21 und eine respiratorische Azidose mit einer nCPAP-Therapie für ≥ 1 Stunde assoziiert. Wir definierten zwei Wahrscheinlichkeitsgrenzwerte mit entweder hoher Sensitivität oder hoher Spezifität für die Vorhersage einer nCPAP-Therapie ≥ 1 Stunde. Zusätzlich bestätigten wir unser Modell mittels eines Classification and Regression Tree-Algorithmus. Mit einer area under the curve von 0,87 in der Receiver-Operating-Characteristics-Analyse erwies sich unser Modell als guter diagnostischer Test, der als Grundlage für die Entwicklung eines

Prognoseinstruments dienen könnte. Sechzig Minuten postnatal waren ein Silverman-Andersen-Score ≥ 5 und eine Atemfrequenz > 60/min mit einer nCPAP-Therapie von ≥ 1 Stunde assoziiert. Aufgrund der ungleichmäßigen Datenverteilung verzichteten wir auf weitere Analysen zum 60-Minuten-Zeitpunkt.

Keiner der im Vorfeld ausgewählten, bereits bekannten Risikofaktoren war in unserer Kohorte mit einer verlängerten nCPAP-Therapie assoziiert. Wir bestätigten mehrere bereits bekannte Lungenultraschallbefunde bei TTN und erstmals auch bei delayed transition und identifizierten den sogenannten double lung point und Unregelmäßigkeiten der Pleuralinie als potenzielle Kandidaten für zusätzliche Prognoseparameter in der Abschätzung des Verlaufs genannter Krankheitsbilder. Wir konnten eine gute Interrater-Übereinstimmung bei der Auswertung des Lungenultraschalls zwischen zwei Neonatologen und zwei pädiatrischen Radiologen nachweisen.

Im Hinblick auf die wichtigste Limitation unserer Studie, der statistischen Bestimmung des Cut-off für den Lungenultraschallscore aus den Daten unserer Kohorte, müssen unsere Ergebnisse bezüglich der identifizierten Risikofaktoren und des potenziellen Nutzens als diagnostisches Instrument in einer unabhängigen Stichprobe validiert werden.

6 Literature

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7 Statements

This study was conducted at the Department of Neonatology at the University Hospital Tübingen under the supervision of Prof. C. Poets, head of the Department of Neonatology.

I came up with the original idea for this study. I conceptualized the study design and developed the study plan with advice from Dr. B. Haase (Department of Neonatology), Dr. C. Engel (Center for Pediatric Clinical Studies), Prof. J. Schäfer (Head of the Department of Pediatric Radiology), and Prof. C. Poets (Head of the Department of Neonatology).

With the support of Prof. C. Poets, Dr. B. Haase and I acquired the lung ultrasound transducer and tablet computer used in this study.

Dr. C. Engel from the Center for Pediatric Clinical Studies and I developed the statistical analysis plan and performed the statistical analysis. Development and maintenance of the digital study database were done by the Center for Pediatric Clinical Studies. Patient recruitment, including informed parental consent, execution of the study-driven examinations, acquisition of necessary patient data as well as entries into the study database were carried out by me. Dr. B. Haase, Dr. M. Esser, Dr. J. Spogis, and myself rated the lung ultrasound videos.

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I certify writing this manuscript independently without using any sources other than those indicated by me.

Tübingen,

Maximilian Jonas Groß

8 Publications

Poster presentation at the 3rd LAUNCH – Lung Ultrasound in Neonates and Children 2021 in Paris. Poster title: “Is early lung ultrasound helpful in predicting how long (near-)term neonates will require nasal continuous positive airway pressure support?”

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