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Respiratory morbidity and therapy in very preterm infants – a population-based study from 2009-2018

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Preface

During medical school we have gained an increased interest in pediatrics, which is why we wanted our master thesis to concern children, especially preterm children. During our second-year assignment we both did a literature review. For our master thesis we wanted to do a quantitative study with statistical analyses and interpretations. Having the opportunity to acquire knowledge about statistical analyses and be able to interpret the results is something we considered a great benefit, which may come in handy later in our career.

After our first meeting with our supervisor, Claus Klingenberg, we were presented with the opportunity to make use of data on premature infants collected by the Norwegian Neonatal Network. This was a great opportunity for us, and we chose to seize it. The purpose of this study was to analyse respiratory morbidity and therapy in preterm infants, born week 22-31 gestation age. For us as students it was a great bonus to learn more about the topic.

Our thesis has not required any financial support. The data in our thesis are part of a larger study on preterm infants in Norway and processing of data is approved by REK (Regional Committees for medical and Health Research Ethics, South-East 2012/944).

Acknowledgements:
We want to give our deepest gratitude to our supervisor Claus Klingenberg, who has been very supportive and encouraging throughout our master thesis, and for helping us with statistical analyses and new angles when things have been difficult. We also want to thank each other for a fantastic collaboration.

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Abstract

Introduction

Preterm infants have immature and vulnerable lungs. The association between respiratory support and lung diseases is known. In our thesis we aimed to analyse pulmonary morbidity and respiratory care including duration of non-invasive respiratory support and mechanical ventilation (MV) in Norwegian very preterm infants. We also aimed to evaluate regional differences in respiratory care and outcomes.

Materials and methods

The study is a nationwide population-based registry study and contains preterm infants born between gestation week 22-31 in the period 2009-2018. The data is gathered from the Norwegian Neonatal Network and the data-extract obtains all patient stays until discharge to the home or death. We included all live-born premature infants born between gestation age (GA) 22-31 in the given period.

Results

A total of 5296 premature infants (45% girls) were included. Among these, 1397 (85%) preterm infants born before week 28 and 949 (26%) of those born between week 28-31 received MV. Among infants diagnosed with bronchopulmonary dysplasia (BPD) 654 (92%) born before week 28 received MV and 246 (64%) born week 28-31. Infants born before 28 weeks and with moderate BPD had as a group the longest duration on non-invasive respiratory support; median (IQR) of 68 (57-81) days. Infants with severe BPD born before 28 weeks had the longest duration on MV; median (IQR) of 86 (53-113) days. Infants cared for in the West region had the shortest median duration on MV for infants born before week 28 and the lowest number of infants with moderate-severe BPD.

Conclusion

This study provides evidence that non-invasive respiratory support is the most used ventilation management for all preterm infants. We found association between lower rates of moderate-severe BPD in the west region which also had the lowest median duration of MV. Practice variations can be used to inform on guidelines for improved therapy.

Abbreviations

BPD – Bronchopulmonary dysplasia

GA – Gestation age

RDS – Respiratory distress syndrom

PMA – Postmenstrual age

nHFT – Nasal High-Flow therapy

NICUs – Neonatal intensive care units

MV – Mechanical ventilation

DA – Ductus arteriosus

PDA – Persistent ductus arteriosus

EOS – Early-onset sepsis

LOS – Late-onset sepsis

CoNS – Coagulase negative staphylococci

CRIB2 – Clinical Risk Index for Babies Scoring system

nCPAP – nasal continuous positive airway pressure

PC-AC – Pressures controlled-assisted controlled

VTV – Volume targeted ventilation

PIP – Peak inspiratory pressure

VG – Volume guarantee

HFV – High frequency ventilation

MAP – Mean airway pressure

INSURE – Intubate-Surfactant-Extubate

MIST – Minimally invasive surfactant therapy

LISA – Less invasive surfactant administration

CPAP – Continuous positive airway pressure

NNN – Norwegian Neonatal Network

IQR – Interquartile range

NIPPV – Non-invasive positive pressure ventilation

1 Introduction

Respiratory morbidity and lung disease frequently affects preterm infants and have both short- and long-term consequences. It can affect the quality of life of an infant who already has a weaker starting point due to its prematurity. In this study we therefore wanted to evaluate this in the whole study population and in infants later diagnosed with bronchopulmonary dysplasia (BPD), and compare the differences, if any, between the groups. We also want to analyse variations in duration of different ventilation managements and regional differences.

1.1 Prematurity

A normal pregnancy has a length of 37-41 weeks (1). Preterm birth is defined as a birth before 37+0 completed weeks (2). In Norway 5-6% of all live births are preterm, a percentage that has been stable for many years. Gestational age (GA) defines the degree of prematurity. Every child born before week 37 is defined as premature. Very premature is defined as birth before week 32, and extremely premature is birth before week 28 (3).

Many preterm births are without a clear cause and occur spontaneously, but some factors can predispose. Around 40% are due to infections, less than 10% are due to cervical insufficiency and 16% due to multiple pregnancies. Other predisposing factors include smoking, short time between births (<6 months), placenta previa and abruptio placenta. Preeclampsia and subsequent fetal growth restriction is also a common cause of preterm birth due to risks for the mother and/or the fetus itself (4). The most important risk factor that can predict early birth is previous history of preterm birth (5, 6).

Survival of extremely preterm has increased in high-income countries. Antenatal use of corticosteroids to accelerate the lung maturation of the child increases survival, as does the use of surfactant and receiving care in neonatal units with great competence (7, 8). However, the most premature children who survive have a high risk of diseases and injuries that are of great importance for subsequent health and development. This includes lung disease, nutritional and deficient growth, sensory impairments, severe brain damage and difficulties associated with learning, language, mental health and motor skills. The risk increases with decreasing GA, if the child also has a low weight in relation to average for GA (small for gestational age), the risk is also increased (1).

1.2 Lung maturation

In the fourth week of gestation, the fetal respiratory system begins to take shape by forming a laryngotracheal pit. From the endodermal part of the pit, a laryngotracheal diverticulum grows from the ventral wall of the forearm, and the caudal part of the diverticulum develops into a respiratory diverticulum. At the end of the fourth gestational week, two primary bronchial buds develop from the respiratory diverticulum. The bronchial buds, together with the splenic mesoderm, will differentiate into bronchi (9, 10).

1.2.1 Maturation phases

The fetal maturation of the lung is divided into four different phases: pseudoglandular phase, canalicular phase, saccular phase and alveolar phase (10).

The **pseudoglandular phase** takes place in gestational week 6-17 where bronchioles and terminal bronchioles develop, respiratory parenchyma and type I and II pneumocytes are also formed. In addition to the development of the lung and lung parenchyma, vascularization near the parenchyma will increase. By the end of the pseudoglandular phase, all major anatomical features will be complete, with the exception of respiratory bronchioles. Gas exchange is not possible and a fetus born in the pseudoglandular phase will therefore not survive (9).

The **canalicular phase** is the second respiratory maturation phase and begins in gestational week 16 and lasts approximately until week 25. The canalicular phase overlaps with the pseudoglandular phase as cranial lung tissue develops faster than caudal lung tissue. In this phase, the size of the lumen increases both in the bronchi and in terminal bronchioles. Also increases vascularization of the pulmonary parenchyma and development of alveolar epithelium. When the fetus is in gestational week 24, each terminal bronchiole will have formed two to four respiratory bronchioles, and each respiratory bronchiole is associated with three to six terminal alveoli. Terminal alveoli will later become alveoli. The wall of the terminal alveoli is thin and richly vascularized at the end of the canalicular phase, this makes gas exchange possible. A fetus born at the end of the canalicular phase will be able to survive, but the risk of death is high as a result of a relatively immature respiratory system (9, 10).

The **saccular phase** begins around gestational week 24 and lasts until the late fetal period. In this third phase several terminal alveoli are developed, and the alveolar septum becomes even thinner. The capillaries in the lung parenchyma begins to penetrate the alveolar sacs and this gives a shorter distance for gas exchange. At week 26, the alveolar epithelium is mainly covered by type I pneumocytes. Scattered around the type I pneumocytes are some type II

pneumocytes, which are secretory epithelial cells that secrete surfactant. Surfactant is a substance consisting of phospholipids and proteins that coats the inside of terminal alveoli and reduces surface tension. The reduced surface tension enables expansion of the terminal alveoli and coexistence of alveoli of different sizes. The amount of surfactant increases with increasing GA and an adequate amount of surfactant is not achieved until the later part of the fetal period (10).

The **alveolar phase** is the fourth and final maturation phase, it starts around gestation week 36 and lasts until around the age of 8 years. At the beginning of the fourth phase, each respiratory bronchiole will end in a cluster of terminal alveoli separated by loose connective tissue. After birth, the terminal alveoli will increase in size as the lungs fill with air, and most of the lung growth is due to increased formation of alveoli and respiratory bronchioles. The terminal alveoli mature into alveoli with thinner alveolar septa. The alveolar development is almost complete by the age of 3 years and is fully completed by the age of 8 years (10).

1.3 Lung diseases in premature infants

1.3.1 Respiratory distress syndrome

Babies born prematurely need stabilization and postpartum support. Respiratory distress syndrome (RDS) is a condition that mainly affects children born prematurely (11). It is characterized by structural immature lungs with deficiency or dysfunctional surfactant (12). Without surfactant, high surface tension in the alveoli will lead to collapse of the lungs on expiration, low lung volume and reduced compliance, resulting in insufficient gas exchange (11).

In the early 1990s, surfactant became part of the routine treatment of RDS in children born prematurely in Norway and has since contributed to increased survival in these children. The surfactant used in treatment today is natural surfactant extracted from the lungs of pigs or cattle (13). Synthetic surfactant is also available, but the natural variant has been shown to work better (14). Surfactant is given to children with GA <32 weeks who are intubated due to RDS (13). Premature babies also often receive different types of respiratory support (11). There are two main forms; i) non-invasive respiratory support which is given via a nasal masks, prongs or cannulae or ii) invasive respiratory support which is usually given via endotracheal tube (15).

1.3.2 Bronchopulmonary dysplasia

BPD or neonatal chronic lung disease is a major cause of respiratory morbidity that premature babies may develop in the first weeks and months of life. Most newborns who develop BPD have received treatment for RDS (16).

Originally, in the 1960s BPD was described in children born after week 32. If the children were still in need of oxygen after 28 days, the diagnosis was made. In addition, the child had to be ventilated for RDS for at least three days in the first week of life and have clinical signs of lung disease shown by rapid respiration, retractions and foreign sounds by auscultation as well as radiological lung changes in the form of densities, decreased air content and/or hyperinflated areas (17). Since then, steroid treatment of the mother and treatment with surfactant have resulted in a reduction in acute morbidity in premature infants. At the same time, there has been an increase in the proportion of more premature babies who survive (18).

The diagnostic criteria for BPD have changed since they were first described. Today, a distinction is made between the degree of prematurity (above or below 32 weeks) and the degree of oxygen dependence or respiratory support after 28 days postnatal age as well as at 36 weeks postmenstrual age (PMA). The requirement for respiratory treatment in the first week of life has been removed as a criterion for BPD. No lower limit for oxygen saturation has been defined as an indication of oxygen demand (19). This can lead to differences in perception of the desired oxygen saturation from hospital to hospital and can contribute to variation in the incidence of BPD. In Norway, an oxygen saturation of 90-94% is considered to be best for a growing preterm infant (18). In 2019 a new set of criteria were suggested, based on the implementation of nasal high flow therapy (nHFT) in many neonatal intensive care units (NICUs). These new criteria now classify BPD based on the preterm infants need of respiratory support at 36 weeks PMA, as this best predicts death and respiratory morbidity at 18-26 months age (20):

- BPD grade 1: nHFT < 2 L/min
- BPD grade 2: nHFT $\geq$ 2 L/min or other non-invasive respiration support with positive airway pressure
- BPD grade 3: Invasive mechanical ventilation

BPD is characterized by damage to the lung structure including dysmorphic vascularization, hypertrophic musculature of arterioles and bronchioles and decreased alveolar formation. This

results in a combined restrictive-obstructive lung disease (19). The etiology is multifactorial, postnatal factors such as pressure and volume trauma during respiratory support, oxygen toxicity and infections are among the most common causes (11). Respiratory support is a well-known risk factor for later development of BPD in premature infants. The use of respiratory support has changed remarkable over the years. Research have shown that invasive mechanical ventilation (MV) poses the greatest risk for lung injury and development of BPD, and the use of non-invasive respiratory support is thus increasing (21, 22).

1.4 Risk factors for bronchopulmonary dysplasia

1.4.1 Persistent ductus arteriosus

Ductus arteriosus (DA) is one of the fetal shunts; shunting from the pulmonary artery to the aorta (23). The resistance in the pulmonary circulation will decrease immediately after birth. In the first days of life, the bloodstream in DA can be bidirectional since the resistance in the systemic- and the pulmonary circulation is pretty similar (24). After a period, the resistance in aorta will increase, and decrease in the pulmonary artery. As a result, the bloodstream in DA, if it remains open, will go from the aorta to the pulmonary artery; a so-called left-right-shunt. Within the first day of life the DA usually closes, and the ductal blood flow will normally cease a couple of days after birth. In some cases DA fails to contract and close spontaneously, and when it remains open it is coined as a persistent (or patent) DA (PDA) (23).

PDA is more frequent in very premature infants, approximately 50-60% of preterm infants born before week 29 or with a birthweight <1000 gram are diagnosed with a PDA (25). The consequence of PDA in premature infants will often be observed earlier compared to term born infants, since the compensatory mechanisms are poorer in premature infants. As a result, strain on the left ventricle and pulmonary edema occurs earlier in premature infants (24). Depending on the size of shunt-volume, different kinds of symptoms and findings can appear. If the shunt-volume is large, the infant can have symptoms like high respiratory rate and little weight gain. The diagnosis of PDA and its hemodynamic consequences are best evaluated with echocardiography. The effects of PDA are also evaluated with a chest x-ray, blood pressure- and pulse oximeter measurement. After the diagnosis is verified, the PDA can be closed in different ways, mainly medical or surgical/catheter-based, or one may decide not to attempt treatment. Currently, there is a great controversy whether treating a PDA is of any benefit at all (23).

1.4.2 Neonatal sepsis

Sepsis in premature infants can lead to serious illness and, at worst, death. The diagnosis of sepsis is made if there is growth of microbes in the blood or in the cerebrospinal fluid. If no bacteria are detected in the blood or cerebrospinal fluid, but the clinical picture indicates sepsis, according to the Norwegian Pediatric society four criteria must be fulfilled if the diagnosis sepsis can be set (13).

- Clinical picture compatible with infection
- CRP > 30 mg/l during the course
- Minimum 5 days antibiotic treatment, or death from clinical sepsis before 5 days
- Other causes are ruled out

Neonatal sepsis is often divided into: early-onset sepsis (EOS) and late-onset sepsis (LOS). EOS is defined as an infection that occurs within the first 72 hours of life. LOS is if the infection takes place 72 hours after birth. Depending on when the sepsis occurs, the type of microbes is a slight difference. In EOS bacteria from the birth canal that are vertically transmitted to the child, in particular group B streptococci and *E. coli,* dominate. LOS is usually a nosocomial/hospital acquired infection and in LOS coagulase negative staphylococci (CoNS), *S. aureus* and other Gram-negative bacteria are frequently found (13).

It is often difficult to distinguish between being sick of sepsis or sick because of being premature. Clinically the children may appear with breathing difficulty, temperature lability, low blood pressure, lethargy, poor ability to suck and irritability.

Treatment for premature infants with EOS is often penicillin G and gentamicin. LOS in Tromsø is treated with 1st generation cephalosporins and gentamicin. Treatment is usually given for a period of 5 days if “clinical sepsis” but the presence of microbes is not confirmed, and 7-10 days when it is a culture proven sepsis (13).

1.5 Clinical Risk index for Babies Scoring System

Clinical Risk Index for Babies Scoring system (CRIB2) is used to anticipate mortality risk among infants with low birthweight. Factors that are considered in the CRIB2 is birthweight, GA, body temperature, base excess and the infant’s sex; all obtained within one hour of admission. The scoring range is between 0-27, higher scores anticipate increased risk of

mortality (26). When evaluating the risk of an outcome in preterm infants and/or comparing different groups of preterm infants it is common and important to adjust for the background disease severity, for instance by using the CRIB2 score.

1.6 Respiratory support and surfactant treatment

1.6.1 Nasal High-Flow therapy

nHFT is respiratory support that delivers humidified gas with a flow of $\geq$ 2 L/min. It is given through nasal catheters/cannulae. It is easier to use and perceived as more comfortable for the babies than nasal continuous positive airway pressure (nCPAP). It is preferred by parents and nurses (27). In recent years, the popularity of nHFT has increased and it is used today in several neonatal wards around the world. nHFT works by "washing out" CO_2 from the respiratory dead space and replacing it with O_2, which lowers pCO_2. nHFT also generates a certain pressure. Albeit difficult to measure, this pressure may contribute to increase end-expiratory lung volume which improves oxygenation and reduces respiratory work (13, 28).

Studies have shown that nHFT has approximately the same effect compared to nCPAP in stable premature infants, including after extubation (8). On the other hand, nHFT is associated with significantly higher treatment failure than nCPAP when used as primary treatment of RDS, and nCPAP is therefore usually preferred (29).

1.6.2 Nasal Continuous Positive Airway Pressure

nCPAP is a non-invasive method that provides positive end expiratory pressure throughout the respiratory cycle. It keeps the airways open, thus preventing atelectasis. Non-invasive methods have partially replaced the invasive methods such as intubation and MV. nCPAP is frequently used and has been shown to be more effective, with lower mortality and reduced risk of BPD compared with intubation, both with and without surfactant administration (30).

Patients with neonatal RDS treated with nCPAP and who do not respond may require intubation and treatment with surfactant. The proportion of cases where nCPAP has no effect increase in parallel with decreasing GA and are associated with increased mortality and morbidity (30).

1.6.3 Mechanical ventilation

The most immature premature newborns do often not respond satisfactory to nCPAP and must be treated on a ventilator. MV can damage the lungs in the form of volume trauma, pressure trauma and oxygen toxicity and is a risk factor for later development of BPD in premature infants. The goal is to minimize the potential damage, but at the same time open the lungs and achieve an oxygen saturation of between 90-94% (30).

A conventional ventilator can be set to different modes. The ventilator has a trigger-function that registers the child's attempt to breathe spontaneously and gives a machine-inflations coordinated with the breathing attempt. The modern ventilators recognizes the child's attempt of breathing by a small inflow of air into a flow sensor placed closed to the patient at the wye-piece of the endotracheal tube (31). Numerous different ventilation modes exist. In Tromsø the most frequently used mode is pressure-controlled assist-controlled (PC-AC). This kind of ventilation gives support to every breath the child takes. You also set a back-up frequency as a minimum for how many inflations the ventilator gives every minute, for example if apnea or insufficient triggering occurs, but the child itself decide the frequency as long it is above the back-up frequency. The inflation time is set and used despite the patient's spontaneous inspiration time. If the inflation time is too long the child may get out of synch with the ventilator and start the expiration while the machine still blows air in. This is unfavorable and the inflation time should be reduced (13). PC-AC is usually in Tromsø combined with a volume-targeted ventilation (VTV) approach where you set your wanted tidal volume and then the ventilator automatically measures which peak inflating pressure (PIP) is necessary to reach the set tidal volume; this is also in some ventilators called volume guarantee (VG) (32). Benefits with VG is that PIP automatically adjusts down, and you avoid big tidal volumes and risk of overdistention when the compliance improves (13).

High-frequency ventilation (HFV) is a different mode of ventilation. During HFV there is a constant distending pressure (mean airway pressure, MAP), with pressure variations that fluctuate (oscillates) around MAP with a high frequency. This makes the alveoli inflate with a more constant pressure, without big variances in inspiration and expiration. With HFV small tidal volumes are generated, they are often smaller, the same or only a tiny bit larger than physiological dead space (33). Tidal volumes required for effective gas exchange depends on frequency (34). With HFV the tidal volumes are delivered with a high frequency of 5-15 Hz,

that is frequencies of 300-900/min. HFV requires close monitoring. A chest x-ray is the best method to control the volume of the lung and especially signs of hyperinflation (33).

Most NICUs in Norway use conventional ventilation and not HFV as primary mode of choice for RDS. However, some big centers in for example Amsterdam and Stockholm use HFV as primary mode and with good results (33).

1.6.4 Surfactant treatment

The level of surfactant is related to when in pregnancy the child was born. A child born at term has a surfactant stock of 100 mg/kg. The corresponding surfactant stock will be reduced at a lower GA. In addition to the surfactant storage, positive end-expiratory pressure (e.g. by using nCPAP) will improve pulmonary distribution, which in turn amplifies the effect of surfactant (7).

Indications for surfactant treatment for premature infants are (13):

- Established RDS in premature infants <32 weeks - given to everyone on a ventilator
- Premature ≥27 weeks with moderate-severe RDS treated with nCPAP
- Other causes of lung failure with inactivation of surfactant

There are various methods of administering surfactant to premature infants. A prophylactic method, particularly suitable for premature infants with GA ≥27 weeks, is Intubate-Surfactant-Extubate (INSURE) (13). In INSURE, the child is intubated and surfactant is administered through an endotracheal tube. Some minutes after treatment, the endotracheal tube is removed to minimize the harmful effect of MV on the lung tissue (7). Less invasive forms of treatment are coined as Minimally invasive surfactant therapy (MIST) or Less invasive surfactant administration (LISA). MIST uses a rigid small catheter that is passed between the vocal cords, and surfactant is administered. The form of treatment can be given to children who breathe spontaneously (GA <27 weeks) on continuous positive airway pressure (CPAP), with a need of >30% O2 to keep SpO2 >90%. MIST is a preventive form of treatment and means that some children are overtreated with surfactant. LISA uses a thin, soft catheter that is inserted intratracheally while the child breathes spontaneously (13). LISA is built into a package of measures aimed at avoiding overpressure ventilation and has similar indication as MIST (7).

2 Materials and method

The study is a nationwide population-based registry study including all preterm infants born before 32 weeks gestation in Norway between 2009-2018. The overall aim is to evaluate respiratory morbidity and management in this vulnerable population.

The data is obtained from the Norwegian Neonatal Network (NNN). NNN is a national medical network established in 2004. All 21 NICUs in Norway are entering data. The attending physician in the NICU are registering data concerning investigation, treatment and diagnosing on all hospitalized infants daily. The data-extract obtains all patient stays until discharge to the home or death. The elements in the data are aggregated and summarized throughout the patient pathway (35).

2.1 Participants

We included all live-born premature infants born between GA 22-31 in the period 2009-2018.

2.2 Data

The data is based on NNN´s collection on multiple variables. In this thesis we have used both categorical and numerical variables, such as health region, gender, birthweight, GA, Apgar score 5 minutes, CRIB2, death on discharge, PMA at discharge, BPD, total days on systemic steroids against BPD, PDA therapy, non-invasive respiratory support, total days on MV (defined as conventional ventilator + oscillator) and conventional ventilator or HFV separately.

Non-invasive respiratory support includes nCPAP, nasal Bi-level Positive Airway Pressure and nHFT. We acknowledge that premature infants who received non-invasive respiratory support not necessarily have received all variants, but we assume that they most likely received nCPAP. At 36 weeks PMA we defined BPD into three groups:

- BPD1: Only need for oxygen supplementation
- BPD2: Receiving non-invasive respiratory support
- BPD3: Receiving MV

2.3 Statistics

We used SPSS for all statistical analyses (IBM SPSS-28). We analysed the relationship between variables as GA, health regions and if the patient developed BPD or not with variables as time spent on non-invasive respiratory support and MV, CRIB2 and total days with systemic steroids against BPD.

We divided the cohort in two groups; GA <28 weeks = extremely premature and GA 28 to 31 weeks = very premature.

For the variables showing total days of non-invasive respiratory support, MV, conventional ventilator and HFV we filtered away all the children who received zero days of support.

Shapiro Wilk-test showed that most data were not normally distributed. We therefore report data as median and interquartile range (IQR) and used non-parametric testing like Mann-Whitney U for comparing different groups. To compare more than two groups (e.g. region of birth) we used Kruskal Wallis test. When testing for significance between two categorical variables we used Pearson's chi square. Statistical significance is defined as $p<0.05$.

2.4 Ethics

Data for NNN is personally identifiable. It is collected under the medical birth register regulation and is free from requirement of consent (35).

3 Results

A total of 5296 live born preterm infants (45% girls) were included; 1650 (31%) were born before week 28 and 3646 (69%) were born week 28-31. More background information about our study population is included in **table 1**.

We are missing data from two patients and therefore 5294 patients are included in most of our analyses. In all analyzes regarding respiratory support only the infants receiving one day or more with support are included, unless otherwise stated.

3.1 Non-invasive respiratory support and mechanical ventilation

In total 4708 (89%) of all included patients received one day or more of non-invasive respiratory support with a median duration of 21 (IQR 6-43) days. A total of 2346 (44%) of the patients received one day or more of MV with a median duration 5 (IQR 2-16) days. Most who received MV were treated with conventional ventilation (n=2242), median duration 4 (IQR 2-11) days. A lower proportion (n=1147) also received HFV with median duration 5 (IQR 2-14) days.

In total 4977 (94%) preterm infants received any kind of respiratory support. The median duration for all types of respiratory support was 20 (IQR 6-47) days.

1397 (85%) of the premature infants born before week 28 received MV and 949 (26%) of those born between week 28-31 (**Table 2**). Among infants with BPD 1-3, 654 (92%) born before week 28 received MV and 246 (64%) born week 28 to 31.

Figure 1 presents the median of total days on non-invasive respiratory support and MV for every gestational week from 22-31. Here we restricted the analyses to only include the preterm infants still alive when discharged, as we expect many of the extremely preterm infants, especially those born week 22 and 23, to have died only few days after birth, and therefore would have biased the estimates on median duration. It shows that the extremely premature infants spent the most time on both MV and non-invasive respiratory support. The

preterm infants born between week 28-31 have a median duration of 0 days on MV, and duration of non-invasive respiratory support is decreasing week by week.

Premature infants born before 28 weeks gestation spent more time on respiratory support regardless of type (**Table 2**). Overall, **Table 2** shows that there were significant differences in duration of all kinds of respiratory support between infants born extremely premature (<28 weeks) versus infants born very premature (28-31 weeks).

3.2 Bronchopulmonary dysplasia

In total there were 1096 (21%) infants registered with a BPD diagnosis. In our study we subclassified BPD from BPD1 to BPD3 depending on severity.

Table 3 presents infant characteristics in relation to BPD grade 1-3. The infants born between week 28-31 had overall higher Apgar-5 and lower CRIB2 scores and lower PMA at discharge versus those born before week 28. For preterm infants born before week 28; those with BPD3 received the most days of systemic steroids against BPD. There were statistically significant differences between the GA groups for both BPD1 and BPD2. There were also significant differences for most characteristics between the infants in the two GA groups with BPD3.

For infants on non-invasive respiratory support, those born before 28 weeks and with BPD2 had the longest median duration on non-invasive respiratory support (**Table 4**).

For all types of respiratory support and therapy, the infants with BPD3 born before 28 weeks had the longest median duration (**Table 4**). As extremely premature infants with BPD3 are the sickest this was not unexpected. Infants with BPD1 and BPD2 born before 28 weeks had a longer median duration on all types of respiratory support compared to those born between week 28-31.

For all BPD patients (grade 1-3) just about half of them received PDA therapy. Slightly more infants born before week 28 with BPD2 received PDA therapy compared to those born before week 28 with BPD1 (**Table 5**).

There was a statistically significant difference (p=0.026) between regions and how many infants who received PDA therapy (**Table 6**). The West region had the lowest proportion (25%) and the Central region the highest proportion (35%) of extremely preterm infants receiving PDA therapy.

3.3 Regional differences

The South-East region was the largest region with the most patients, but each region had about the same percentage of infants in the two GA groups, with 31% born before week 28 in the South-East region, 30% in West and Central and 33% in the North region.

Preterm infants born before week 28 had the longest median duration for all ventilation types (**Table 7**). When comparing the health regions there were significant differences between the regions regarding duration of MV for the infants born before week 28 ($p<0.001$). The significance was made up by differences between the West and South-East regions and West and Central regions, and infants cared for in the West had the shortest median duration (**Figure 2**). For infants born between week 28-31 there was a significant difference ($p<0.001$) in duration of non-invasive respiratory support, made up by West and Central and South-East and Central, where the Central region had the longest duration (**Figure 3**).

When comparing proportion of cases of BPD in the different regions there were no significant differences for BPD1. However, for BPD2/3 the West had a lower proportion compared to all other regions (**Table 8**).

We compared total days of systemic steroids against BPD in the regions for infants born before week 28 (**Table 9**). The median duration was similar in all regions. North had the highest percentage of infants receiving steroids (41%) and West the lowest (28%).

4 Discussion

We have in this thesis evaluated respiratory morbidity in premature infants. Our purpose was to evaluate proportions of infants receiving all kinds of respiratory support and duration of different types of support in the whole study population and in preterm infants diagnosed with BPD. We have also analysed use of steroids and PDA therapy; a known risk factor for developing BPD. The extremely premature infants had the highest overall morbidity and the longest duration of both non-invasive and invasive respiratory support. There were also a higher number of patients in this group that developed BPD than the group of very preterm infants born week 28 to 31. These results were as expected.

4.1 Respiratory support

Almost all patients (94%) in our study received some kind of respiratory support. The European consensus guidelines on the management of RDS recommends spontaneously breathing babies to be started on CPAP rather than be intubated to reduce the risk of BPD (36). In our study 89% of the infants received non-invasive respiratory support during the hospitalization, compared to 42% receiving conventional ventilation and 22% HFV. This corresponds to a study from the Italian neonatal network, where 71.6%, 53.2% and 15.8% received non-invasive respiratory support, conventional ventilation and HFV, respectively. However, they had a slightly different study population, looking at infants born week 23-30 and with birthweight lower than 1501 grams enrolled in the Italian neonatal network in 2009 and 2010 (37).

Premature infants in our study had a long duration of non-invasive respiratory support, with a median duration of 50 days for the extremely premature newborns. We could, however, not differentiate different subtypes of non-invasive respiratory support. A Cochrane study from 2016 states that nCPAP reduces the need for MV. The authors discuss that non-invasive positive pressure ventilation (NIPPV) is better than nCPAP in preventing apnea, respiratory failure and intubation in preterm infants who have been extubated from MV (8). The European guidelines also prefer non-invasive respiratory support (not specified which type) for premature infants breathing on their own at birth, as the risk of lung injury with MV is greater. They however acknowledge there's a lack of evidence to determine the most effective method and recommends nCPAP as the first choice of respiratory support (36).

Despite increasing use of non-invasive respiratory support over the past years, a large portion of premature infants are still treated with MV. In our analyses 85% of the extremely premature infants received MV during their admission, and 28% born between week 28 to 31. If we look at the different gestational weeks separately, we also see that the most premature, week 22-25, spends the most time on both MV and non-invasive respiratory support, while the preterm infants born week 28-31 spends a median of zero days on MV and duration of non-invasive respiratory support decreases for every week increase of GA. This clearly shows that the extremely preterm infants are the ones with the highest pulmonary morbidity and most dependent on invasive respiratory support to survive.

There are two main types of MV; conventional ventilation and HFV. Our analyses did not include specific conventional ventilation modalities, but this is of importance for the infants as optimal application of MV is important to reduce risk of ventilator induced injury. Both extensive and insufficient tidal volumes can increase the risk of ventilator induced lung injury in preterm infants (38). Studies have shown that VTV, a form for conventional ventilation, has been shown to significantly reduce the combined outcome of chronic lung disease, death and duration of ventilation. Compared to pressure-limited ventilation, VTV offered many important benefits with minimal side effects (8, 39). Infants born before week 28 had a longer median duration on conventional ventilation, compared to the ones born week 28-31 in our analyses. Less patients received HFV compared to conventional ventilation. HFV is often used as a rescue ventilation, when conventional ventilation fails (40). This can explain why more patients, especially those born before week 28, are given HFV, as they have more underdeveloped lungs, higher morbidity and intubated longer (41). There are limited studies on HFV in preterm infants. Generally, HFV is thought to be gentler to the preterm developing lungs when compared to conventional ventilation and may result in a small reduction of chronic lung disease. Use of HFV requires knowledge on lung physiology and close monitoring of the infant. Studies show there is still insufficient evidence to recommend HFV over conventional ventilation for preterm infants (42).

In our analyses we see that infants spends a considerably longer period on non-invasive respiratory support than MV, which can suggest that they are put on non-invasive respiratory support as a first choice or as soon as they no longer need MV. Increasing use of non-invasive respiratory support is a strategy to reduce lung injury, and implemented in most western countries over the last 10-20 years. A study from Stoll et. al showed a decrease in the use of

conventional ventilation and increase in non-invasive respiratory support from 2002-2012 (43). Studies over the past years have shown that MV is posing the greatest risk for lung injury in the premature infant (21).

4.2 Bronchopulmonary dysplasia

Among extremely preterm infants, BPD is one of the most common morbidities (44). The relationship between MV and BPD is well documented in numerous studies (43, 45). In our study, we have looked at premature infants born before week 28 and between 28-31 weeks and duration of non-invasive respiratory support and MV in the whole study cohort and specifically for infants later diagnosed with BPD.

4.2.1 Non-invasive respiratory support and bronchopulmonary dysplasia

Non-invasive respiratory support reduces the risk of infection, volume- and barotrauma since use of an endotracheal tube is not necessary (46). As presented above non-invasive respiratory support is the most used type of ventilation support among premature infants in our analyses. When studying infants diagnosed with BPD, non-invasive respiratory support is still the most used respiratory support compared to all other types of ventilation for infants with BPD1 and BPD2. For infants with BPD3, the median duration was the longest for MV compared to the other ventilation types, regardless of GA. This was no surprise considering the diagnostic criteria for BPD3. Nor was it surprising that infants diagnosed with BPD2 had the longest duration on non-invasive respiratory support in both GA groups out of all the types of ventilation support, evaluating the diagnostic criteria for BPD2.

The portion of preterm infants born before 28 weeks have increased over the years (46). In the period 2001-2010 in Germany, there was an increase of 65% premature infants born before 28 weeks (47). GA and birthweight are inversely proportional to the risk of BPD, and it was natural to look at these factors and duration of different types of ventilation support (44, 46). When analysing birthweight, the tendency for the whole study-population were decreasing birthweight among infants born before week 28 and with increasing BPD severity.

Our thesis does not specifically evaluate the risk of developing BPD as a consequence of treatment with non-invasive and invasive respiratory support. That said, it is important and interesting to investigate different respiratory outcomes due to different respiratory

managements. Pas et al. analysed the difference in pulmonary outcome depending on whether premature infants, GA 25-32 weeks, received early nCPAP or was intubated. The study revealed that infants in the early nCPAP group had a reduced risk of developing BPD compared to infants who were intubated immediately after birth (48). Similar results were also observed in one meta-analysis where nCPAP compared to intubation, initiated in the delivery room in very preterm infants was associated with a significantly reduced risk for death or BPD (49).

Premature infants who participated in the NICHD SUPPORT Trial were evaluated with pulmonary outcome after 18-22 months corrected age. The follow-up showed that premature infants initially treated with CPAP rather than intubation/surfactant had fewer periods of wheezing and fewer physician visits. There was a significant difference for infants with or without BPD and the incidence of wheezing and cough. The study concluded that the pulmonary outcome was significantly different for premature infants with and without BPD (50). Our thesis does not address follow-up of respiratory outcomes, but it would be interesting to see it done for this study population in the future.

4.2.1.1 Mechanical ventilation and bronchopulmonary dysplasia

An American study from 2015 presented that a total of 82% of infants born before 29 weeks received MV (43). This matches our results, which showed that 85% of infants born before 28 weeks received MV, compared to 26% of infants born between week 28-31. Looking at the preterm infants diagnosed with BPD, the percentages of those receiving MV predictably increases a lot, with 92% of infants born before week 28 and 64% between week 28-31.

We observed that the extremely premature infants with BPD1 had a slightly higher Apgar value compared to BPD3. A study by Kidman et al. presented that 85% of extremely premature infants who experienced extubation failure had BPD, compared to 50% of extremely preterm infants who extubated with success, and Apgar and birthweight was lower for the extremely preterm infants who underwent extubation failure compared to those with success (41). Low Apgar score are associated with BPD and these infants are often in a poorer general condition at birth (46). It is not unexpected that Apgar score was lower for the extremely preterm infants with BPD3 as these have a higher morbidity, and we can expect

that the infants with the highest severity of BPD in our analyses underwent extubation failure, as this is the group with the longest duration of MV.

The CRIB2 score was higher among extremely premature infants, where a higher severity of BPD was associated with a higher score. These results were in line with Ezz-Eldin et al. who presented a significant association between lower CRIB2 score and higher mortality rate, in addition to a longer hospitalization (26).

Infants in both GA groups who were diagnosed with BPD had a higher median duration of MV, conventional ventilation and HFV compared to the whole study population. For MV the median duration also increased for BPD grade 1-3. It can be difficult to identify whether the development of BPD this is due to the long-lasting duration of MV, or if the infants had such underdeveloped lungs that they had a high risk of developing BPD and MV was a necessity, but it is probably a combination of both.

A Cochrane systematic review from 2015 compared differences in BPD incidence in premature infants treated with HFV versus conventional ventilation. The review contains multiple studies and revealed no significant difference in duration between conventional ventilation and HFV, which corresponds with our results. Ventilation with HFV had a small, but statistically significant decrease in BPD compared to conventional ventilation. Further, HFV had a short, but advantageous pulmonary effect (42). Another review from 2020 showed similar results, where preterm infants who received HFV had a small risk reduction of BPD compared to infants who received conventional ventilation (51).

Courtney et al. found in a study that infants with low birthweight had shorter duration on HFV compared to conventional ventilation. So, infants in the HFV group had an increased survival without BPD (52). These results support the evidence that premature infants who have shorter duration on HFV may also have reduced risk of surviving without BPD, compared to conventional ventilation.

4.2.2 Steroids against bronchopulmonary dysplasia

Steroids as an approach to reduce risk of BPD or to treat BPD in preterm infants have been studied numerous times (53, 54). Because of their anti-inflammatory effects, steroids play a

role in the management of BPD but have also been associated with adverse neurological development outcomes and other adverse side effects such as gastrointestinal bleeding and perforation (53). As expected in our analyses, preterm infants born before week 28 and with BPD3 had the largest median duration of systemic steroids. In general, preterm infants born before week 28 had much higher exposure to steroids compared to the infants born between week 28-31. However, not all infants with a BPD diagnosis received steroids. This may be due to the risk of adverse side effects and long-term outcomes is considered greater than the benefits of an acute improvement in respiratory function at that moment. One can also presume it is due to various preferences of the different physicians involved in the treatment.

Our thesis does not contain any data regarding the type of steroids used, but this is important as the various steroids have been shown to have different effects and outcomes. Studies have been conducted on both dexamethasone, hydrocortisone and budesonide, as well as whether to administer systemic or inhaled (53-57). The use of dexamethasone is associated with a reduced need for MV and reduction in BPD if given seven days after birth and in low doses, to avoid long-term side effects such as cerebral palsy and short-term side effects such as bleeding from the stomach and hypertension. However, it is uncertain whether it improves survival among infants developing BPD (54). Studies have been conducted on inhaled budesonide, which has demonstrated good effects and reduced risk of both BPD and PDA. But a worrying trend towards increased mortality was seen (55). However, this was later discarded in a metanalysis which presented good effects of budesonide and reduced risk of BPD, without increased mortality and concluded that based on the current evidence, budesonide may safely be used in BPD therapy (58). As there are no specific guidelines to follow on postnatal steroids, the practice in various NICUs probably vary a lot.

4.2.3 Persistent ductus arteriosus

It is acknowledged an association between PDA and the risk of developing BPD (44, 59). In our analyses we found that about half of preterm infants with BPD received PDA therapy. One review discussed that RCTs for the most part explored the efficacy of PDA treatment regarding PDA closure, and not the effect that PDA had on mortality and morbidity related to BPD (44). Despite this, the causal relationship between PDA and BPD has been investigated by some studies (60). A systematic review and a metanalysis found a positive correlation between PDA and BPD. It also presented a positive association between PDA and MV, low

birthweight, and lower GA (25, 44). The association between PDA and mentioned variables were not surprising since the largest portion of infants with BPD are born before week 28, have a low birthweight and also received MV. The size of the PDA and its risk effect on BPD has also been assessed by another study, which presented an increased risk of developing BPD with the presence of a moderate to large PDA shunt (59). However, the same results have not been established for smaller PDA shunts (61).

Despite early treatment of PDA, the incidence of BPD has not been reduced (62). Based on this, one can assume that infants with an existing moderate to large PDA have an increased risk of developing BPD, even if they receive treatment, and is therefore an unalterable risk factor for BPD until better treatment options becomes available.

4.3 Regional differences

The duration of non-invasive respiratory support was about the same in all four regions. For overall MV, conventional ventilation and HFV there were some variations. Duration of MV were highest in the Central region for those born before week 28, with a median duration of 5 days more than nationwide. The variation in use of invasive ventilation modalities is similar to other studies (37, 63) and probably reflects on different approaches to the preterm infants, a physician driven variation, which again originate from the lack of solid data to guide therapeutic decisions regarding invasive ventilation in preterm infants, especially in the most prematures born before week 28. For infants born between week 28-31 there were no differences between the regions and nationwide in our analyses.

Analysing BPD in the regions, the Central region had the most cases of BPD3. This might reflect that infants in this region had the longest median duration of MV. The opposite can be seen in the West region, which had the least cases of BPD2-3 and the shortest median duration of MV. Our results substantiate the claim that invasive ventilation pose an increased risk of lung injury in premature infants. It also makes us question where the differences lie, whether it is just coincidences or if the West region has a better strategy treating preterm infants in relation to lung outcome. Infants could benefit from further studies on this topic.

Comparing duration of systemic steroids between the regions there are no striking differences. The North region, however, have a higher percentage of infants receiving steroids than other regions, which can reflect on a more liberal use.

There are also some regional differences in the number of preterm infants born before week 28 and PDA therapy, where Central region had the highest portion of PDA therapy and West region had the lowest number receiving therapy. This may be a contributing factor to the West region diagnosing fewer infants with BPD, and opposite in the Central region.

4.4 Strength and weaknesses

Strengths of this study is that it is based on 10-years of material including all preterm infants born in this period in Norway, which gives no risk of selection bias. It includes a large number of infants and a day-to-day prospective collection of data with a standardized electronic registration system. The inclusion of all preterm births on a national basis allows us to explore regional differences in care practices and compare with other population-based studies.

A weakness is that this study uses a BPD-definition not used in all other studies and that infants in the data material can be registered with up to all three degrees of BPD, which can make the analyses regarding BPD severity and comparison with other studies somewhat inaccurate. It is also a weakness of the study that there are no data on when in the course the different types of ventilation were initiated and long-term outcome of lung morbidity. This type of data would shed light on whether the various ventilation managements over time have provided better long-term results. Some groups contain only a few patients, like when analysing preterm infants with BPD3, and it is important to bear in mind that we because of this sometimes can have assumed that the null hypothesis is true, even though it is actually false, so-called type-II errors.

5 Conclusion

There have been major technological and medical advances in recent years. Despite this there is still a lack of knowledge about what is the best treatment of preterm infants in many areas, to spare them for morbidity known to be associated with both short- and long-term adverse consequences. This study provides evidence that non-invasive respiratory management is the most used respiratory management for all preterm infants and preterm infants later diagnosed with BPD, which is in line with other studies and guidelines. MV is most used in extremely preterm infants, compared to very preterm infants. Furthermore, there were notable trends indicating a well-known association between shorter duration of MV and lower risk of severe BPD.

This study also provides results of respiratory support methods and a few other influential factors for preterm infants in Norway. There are a few differences between the health regions, but the West region had the shortest duration of MV, least cases of severe BPD and least patients receiving PDA therapy. With more studies on the matter there will be possible to implement general guidelines with the aim of reducing variation between NICUs and physicians, which ultimately will benefit preterm infants.

Respiratory- and BPD-management remains an extremely challenging task. For future studies to analyse the effects of different managements it would be ideal with a follow-up program to assess long-term pulmonary outcomes.

6 References

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7 Tables

Table 1. Background information about the study population

	n	*Percent (%)*
Girls	*2381*	*45.0*
Boys	*2915*	*55.0*
Single	*3713*	*70.1*
Twin	*1424*	*26.9*
Triplet	*159*	*3.0*
Extremely premature (<28 weeks)	*1650*	*31.2*
Very premature (28-31 weeks)	*3646*	*68.8*
Birthweight ≤1000g	*1807*	*34.1*
Birthweight >1000g	*3489*	*65.9*
PDA therapy; medical and/or surgical	*629*	*11.9*
Received antenatal steroids	*4429*	*85.5*
Not received antenatal steroids	*752*	*14.5*
Dead when discharged	*464*	*8.7*
Alive when discharged	*4833*	*91.3*
South-East region	*2919*	*55.1*
West region	*1217*	*23.0*
Central region	*730*	*13.8*
North region	*430*	*8.1*

Table 2. Proportion of infants and duration (days) of respiratory support, and systemic steroids against BPD

Treatment	*<28 weeks n=1649*	*28-31 weeks n=3645*	*P-value*
Non-invasiv respiratory support	*n=1425 (86%)*	*n=3283 (90%)*	
Median (IQR) duration days	*50 (38-62)*	*10 (4-27)*	*<0.001*
Mechanical ventilation*	*n=1397 (85%)*	*n=949 (26%)*	
Median (IQR) duration days	*10 (3-26)*	*3 (2-6)*	*<0.001*
Conventional ventilation	*n=1336 (81%)*	*n=906 (25%)*	
Median (IQR) duration days	*7 (2-16)*	*2 (2-5)*	*<0.001*
HFV	*n=849 (51%)*	*n=307 (8%)*	
Median (IQR) duration days	*7 (3-16)*	*3 (2-5)*	*<0.001*
Steroids for BPD	*n=572 (35%)*	*n=55 (1.5%)*	
Median (IQR) duration days	*11 (7-19)*	*7 (3-10)*	*<0.001*

*MV = Conventional ventilation + HFV

Table 2 includes the infants who received one day or more of each respiratory support management. For duration of steroids against BPD the analyses include the infants receiving one day or more with steroids. All analyses include both those alive and dead when discharged.

Table 3. Infant characteristics in relation to different BPD severities

Background	***BPD1***		***BPD2***		***BPD3***	
	<28 weeks n=623	*28-31 weeks n=304*	*<28 weeks n=440*	*28-31 weeks n=219*	*<28 weeks n=39*	*28-31 weeks n=22*
Birthweight						
Median (IQR)	*735 (615-876)*	*1128 (880-1353)*	*710 (595-864)*	*1149 (890-1355)*	*680 (600-800)*	*1253 (1081-1430)*
Apgar 5						
Median (IQR)	*7 (5-8)*	*8 (6-9)*	*7 (5-8)*	*8 (6-9)*	*6 (5-8)*	*8 (6-9)*
CRIB 2						
Median (IQR)	*12 (10-14)*	*7 (5-8)*	*12 (10-14)*	*7 (5-8)*	*13 (11-15)*	*5 (3-6)*
PMA w/ discharged						
Median (IQR)	*40 (39-43)*	*39 (38-41)*	*41 (40-44)*	*40 (39-42)*	*46 (43-53)*	*42 (39-51)*
Days steroids for BPD						
Median (IQR)	*7 (0-16)*	*0 (0-0)*	*10 (0-18)*	*0 (0-0)*	*14 (5-34)*	*0 (0-1)*

A total of 14 infants are included in all three BPD groups. For duration of steroids against BPD the analyses include the infants receiving one day or more with steroids.

The three degrees of BPD are evaluated on 36 weeks PMA and defined as:

- BPD1: Only need for oxygen supplementation
- BPD2: Receiving non-invasive respiratory support
- BPD3: Receiving mechanical ventilation

Table 4. Duration of respiratory support and BPD severity

	BPD 1		***BPD 2***		***BPD 3***	
	<28 weeks n=624	*28-31 weeks n=304*	*<28 weeks n=440*	*28-31 weeks n=219*	*<28 weeks n=39*	*28-31 weeks n=22*
Non-invasive respiratory support						
Median (IQR)	*60 (49-72)*	*42 (29-55)*	*68 (57-81)*	*50 (40 -60)*	*59 (38-68)*	*25 (11-41)*
Mechanical ventilation*						
Median (IQR)	*21 (8-39)*	*5 (2-11)*	*25 (12-41)*	*6 (3-12)*	*86 (53-113)*	*28 (12-71)*
Conventional ventilation						
Median (IQR)	*12 (5-23)*	*4 (2 -7)*	*15 (7-25)*	*5 (2-9)*	*33 (11-78)*	*15 (6-55)*
HFV						
Median (IQR)	*12 (5-25)*	*4 (3-10)*	*13 (6-24)*	*5 (2-12)*	*39 (9-74)*	*17 (11-34)*
Total days of resp. support						
Median (IQR)	*79 (64-98)*	*46 (33-60)*	*89 (76-105)*	*55 (44-66)*	*112 (92-154)*	*67 (35-92)*

*MV= Conventional ventilation + HFV

Table 4 includes the infants who received one day or more of each respiratory support management. All analyses include both those alive and dead when discharged.

The three degrees of BPD are evaluated on 36 weeks PMA and defined as:

- BPD1: Only need for oxygen supplementation
- BPD2: Receiving non-invasive respiratory support
- BPD3: Receiving MV

Table 5. Preterm infants born before week 28 diagnosed with BPD, and the proportion of these receiving PDA therapy for increasing severity of BPD

PDA therapy; medical and/or surgical	*n (%)*
BPD1	*291 (47)*
BPD2	*229 (52)*
BPD3	*20 (51)*

Table 6. Number of infants born before week 28 who received PDA therapy within each region

	South-East *n (%)*	***West*** *n (%)*	***Central*** *n (%)*	***North*** *n (%)*	*P-value*
PDA therapy; medical and/or surgical	*302/910 (33)*	*95/374 (25)*	*79/223 (35)*	*46/143 (32)*	*0.026**

*Significance made up by differences between the West and South-East region where the West region had the lowest number of infants receiving therapy.

Table 7. Median duration of respiratory support and comparison between the four health regions

	South-East		***West***		***Central***		***North***	
	<28 weeks n=910	*28-31 n=2009*	*<28 weeks n=374*	*28-31 n=843*	*<28 weeks n=223*	*28-31 n=507*	*<28 weeks n=143*	*28-31 n=287*
Non-invasive respiratory support								
Median (IQR)	*51 (39-63)*	*10 (4-27)*	*48 (37-61)*	*8 (4 -25)*	*49 (38- 58)*	*14 (6-29)*	*50 (39-66)*	*10 (5-28)*
Mechanical ventilation*								
Median (IQR)	*12 (4-30)*	*3 (2-6)*	*6 (3-14)*	*3 (2-5)*	*15 (5-32)*	*3 (5-31)*	*7 (3-29)*	*4 (2-6)*
Conventional ventilation								
Median (IQR)	*9 (3-17)*	*3 (2-5)*	*3 (2-6)*	*2 (1-3)*	*10 (3-21)*	*2 (2-6)*	*7 (2-25)*	*3 (2-6)*
HFV								
Median (IQR)	*8 (3-19)*	*3 (2-5)*	*6 (3-12)*	*3 (2-5)*	*7 (3-20)*	*3 (2-6)*	*6 (2-13)*	*3 (3-6)*

*MV= Conventional ventilation + HFV

Table 7 includes the infants who received one day or more of each respiratory support management, and both infants alive and dead when discharged.

Table 8. Proportion of infants diagnosed with BPD1 and BPD2/3 for each health region

	South-East n (%)	*West n (%)*	*Central n (%)*	*North n (%)*	*P-value*
BPD1					
n=927	*499 (17)*	*234 (19)*	*119 (16)*	*75 (17)*	*0.307*
BPD2/3					
n=704	*406 (14)*	*119 (10)*	*103 (14)*	*76 (18)*	*<0.001**

*Significance made up by West and South-East, West and Central and West-North, where West had the least cases of BPD2/3

Table 9. Median duration of systemic steroids in the four health regions for preterm infants born before week 28

	South-East n=343 (38%)	*West n=107 (29%)*	*Central n=63 (28%)*	*North n=59 (41%)*	*P-value*
Duration (days) steroids for BPD					
Median (IQR)	*11 (6-20)*	*11 (6-16)*	*11 (9-14)*	*12 (8-23)*	*0.182*

The analyses include only those receiving one day or more with steroids.

8 Figures

Figure 1. Median days on non-invasive respiratory support and mechanical ventilation for preterm infants

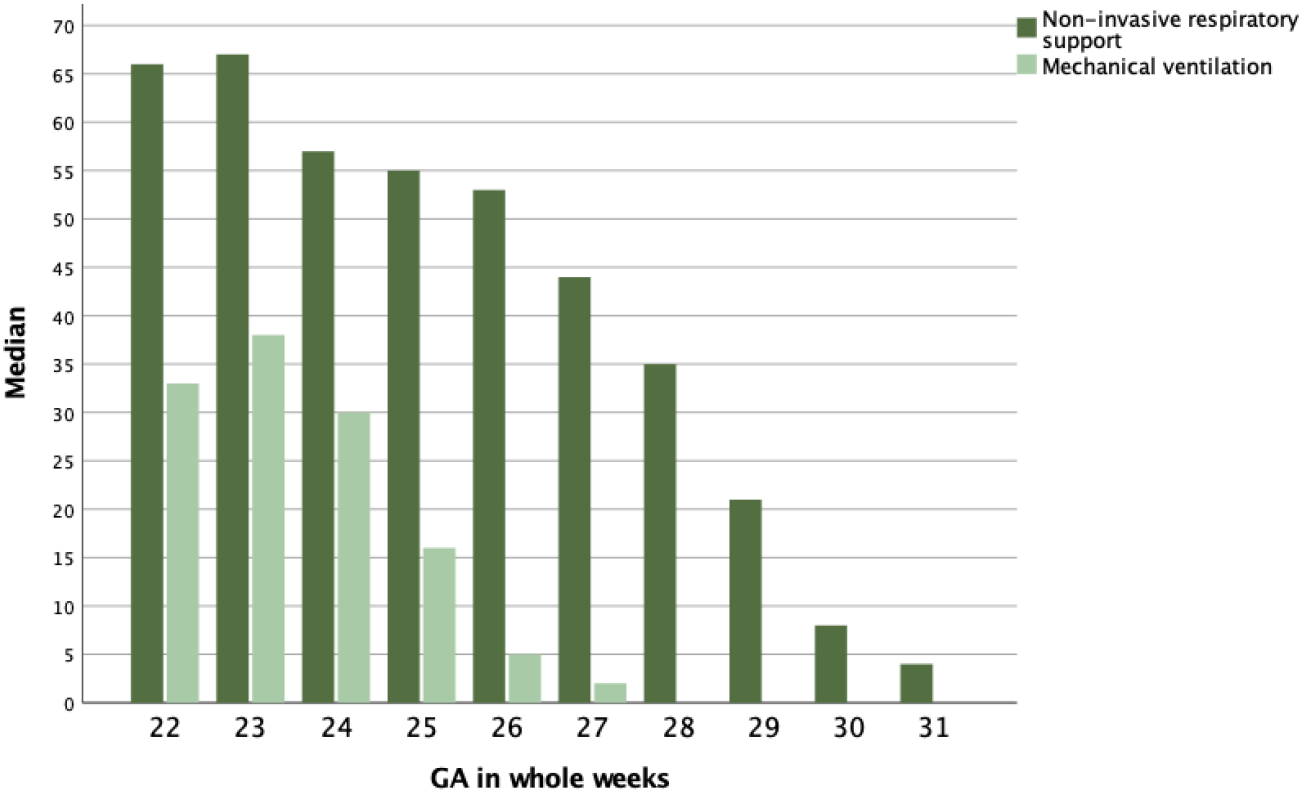
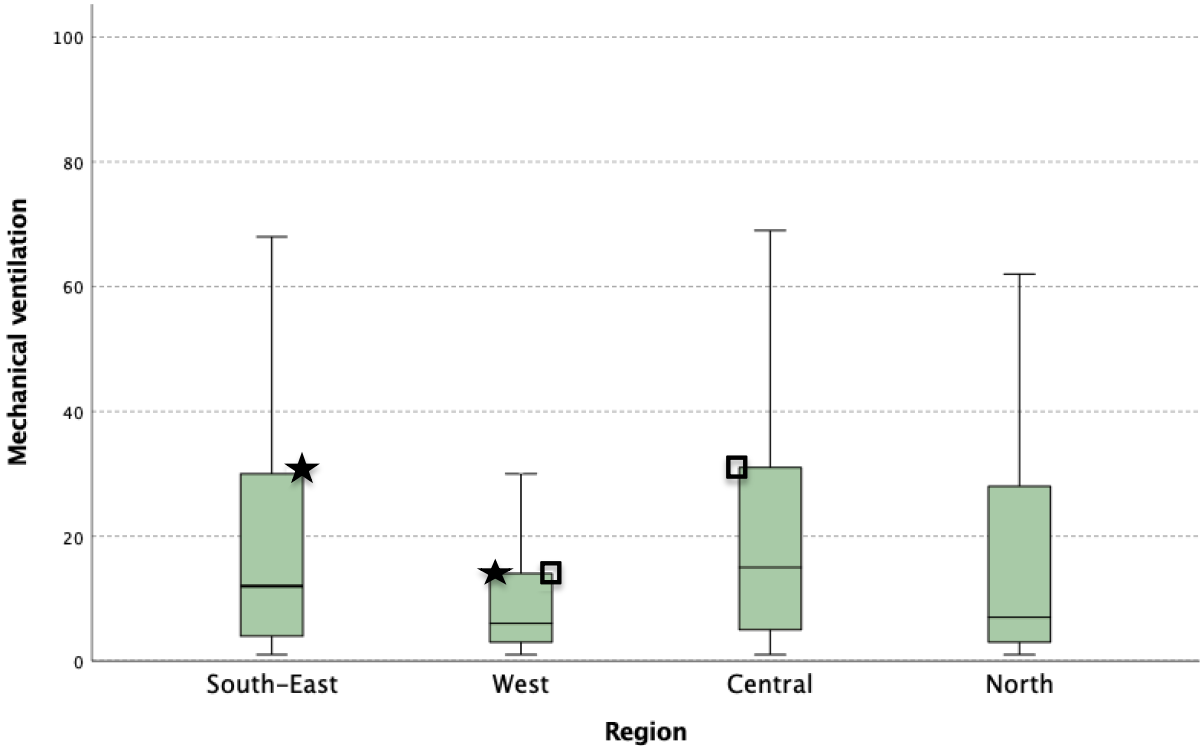


Figure 2 includes only infants alive when discharged and who received one day or more with non-invasive respiratory support or mechanical ventilation.

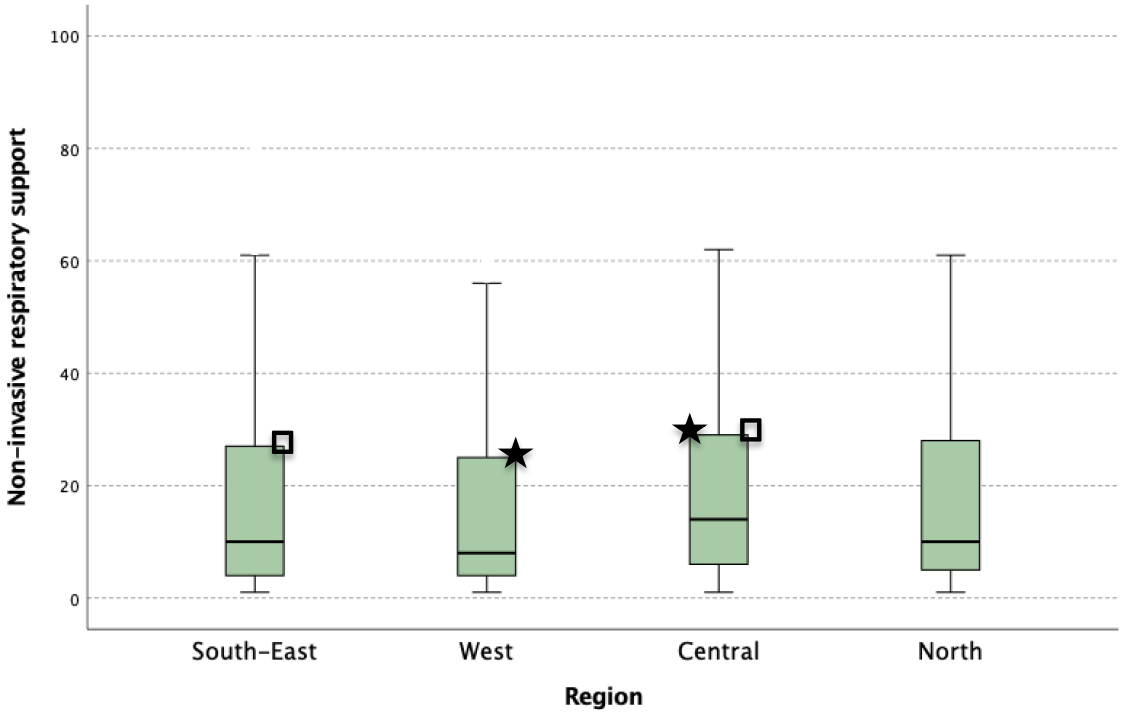
Figure 2. Regional differences regarding duration of mechanical ventilation for infants born before week 28



The significance was made up by differences between the West and South-East regions (★) and West and Central regions (□), where West had the median shortest duration.

Figure 3 includes infants born before week 28 who received one day or more with mechanical ventilation and includes both infants alive and dead when discharged.

Figure 3. Regional differences regarding duration of non-invasive respiratory support for infants born between week 28-31



Statistically significance was made up by West and Central regions (★) and South-East and Central regions (□), where the Central region had the longest duration.

Figure 4 includes infants born between week 28-31 who received one day or more with non-invasive respiratory support and includes both infants alive and dead when discharged.