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Respiratory distress management in moderate and late preterm infants: the NEOBS Study

Short title: The NEOBS Study

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Abstract

Objective: To investigate the characteristics and management of respiratory failure (RF) in moderate-to-late preterm infants.

Methods: NEOBS was a prospective, multicenter, observational study conducted in 46 neonatal intensive care units caring for preterm infants (30+0/7 to 36+6/7 weeks of gestation [WG]) in France in 2018. The cohort was stratified into two groups: 30–33 WG (group 1) and 34–36 WG (group 2). Infants with early neonatal RF were included and the outcomes assessed were maternal, pregnancy, and delivery characteristics and how RF was managed.

Results: Of the 560 infants analyzed, 279 were in group 1 and 281 were in group 2. Most pregnancies were singleton (64.1%), and 67.4% of women received prenatal corticosteroids (mostly two doses). Infants were delivered by cesarean section in 59.6% of cases; 91.7% of the infants had an Apgar score ≥ 7 at 5 min. More than 90% of infants were hospitalized post-birth (median duration, 36 and 15 days for groups 1 and 2, respectively). Medical intervention was required for 95.7% and 90.4% of the infants in group 1 and group 2, respectively, and included noninvasive ventilation (continuous positive airway pressure [CPAP]: 88.5% and 82.9%; high-flow nasal cannula: 55.0% and 44.7%, or other) and invasive ventilation (19.7% and 13.2%). The two main diagnoses of RF were respiratory distress syndrome (39.8%) and transient tachypnea of the newborn (57.3%). Surfactant was administered to 22.5% of the infants, using the less invasive surfactant administration (LISA) method for 34.4% of the patients. In the

overall population, 8.6% of the infants had respiratory and/or hemodynamic complications.

Conclusions: The NEOBS study demonstrated that CPAP was widely used in the delivery room and the LISA method was chosen for 34.4% of the surfactant administrations for the management of RF in moderate-to-late preterm infants. The incidence of RF-related complications was low.

Key words: Outcomes; moderate/late preterm; respiratory distress syndrome

1 Introduction

Most of the guidelines regarding the management of respiratory distress syndrome (RDS) following preterm birth are focused on extremely or very preterm infants (<28 and 28–32 weeks of gestation [WG], respectively) [1, 2]. However, RDS can occur in the late preterm population (defined by a birth ≥ 34 WG) and controversies exist regarding its management. For example, the administration of prenatal corticosteroids, especially in the case of planned cesarean section, remains a significant problem after 34 WG [3]. Because chronic lung disease is less frequent in late preterm infants, the use of noninvasive ventilation (NIV, such as high-flow nasal cannula, continuous positive airway pressure [CPAP], or intermittent positive pressure ventilation) and administration of surfactant is less defined for these newborns, in comparison with very preterm infants. However, the incidence of RDS is approximately 8–10% for those born

at 35–36 WG [4, 5]. Moderate (32–34 WG) to late (34–36 WG) preterm births account for 85% of all preterm births, comprising 12.75 million babies worldwide each year [6]. In France, preterm birth rates increased between 1995 and 2016, with infants born <37 WG accounting for 7.5% of all live births in 2016 [7]. Consequently, the number of moderate-to-late preterm infants requiring respiratory support for RDS is very high.

Several studies focusing on this population have been published during the last decade but very often in comparison with early- or full-term infants [8, 9]. While these studies clearly indicate an increase in respiratory morbidity for late preterm compared with full-term infants, the management of respiratory failure (RF), whatever its cause, is not well documented.

To move forward on this issue, we conducted a multicenter, observational study on RF in a large population comprising moderate-to-late preterm infants in France. Our objective was (i) to describe the characteristics of RF in these infants and assess the proportion of RDS according to gestational age, and (ii) to compare the different strategies used in French neonatal intensive care units (NICUs) for the management of RF.

2 Methods

NEOBS was a prospective, multicenter observational study conducted in 46 neonatal units (level 2 or 3) caring for preterm infants in France.

2.1 *Population studied*

Newborn infants were included if they were born between 30+0/7 and 36+6/7 WG, had early neonatal RF defined by the requirement for ventilatory support, such as nasal cannula, CPAP, or invasive ventilation (IV), during the first 24 h after birth (whether the ventilator was still ongoing at 24 h or not), were hospitalized at the investigating site within the first 24 h of life, and had verbal informed consent to participate, obtained from either the parents or legal guardians.

Patients were not included in the study if they were a neonate receiving ventilatory support for a nonrespiratory disease or a malformation disorder, a neonate deceased within the first 24 h of life, or a neonate included in a clinical trial with a ventilatory care impact.

2.2 *Study objectives*

The main objective of the study was to describe the different procedures for ventilatory management in a large French population of preterm infants of ≥ 30 WG. The secondary objectives were (i) to estimate the proportion of RDS and other diagnoses for RF; (ii) to describe the proportion of neonates with respiratory or hemodynamic complications (pneumothorax, hemodynamic disorders with recourse to amines) during hospitalization; and (iii) to estimate the time to neonate independence.

2.3 *Study design and data collection*

Participation in the study was offered to all eligible infants hospitalized in the

participating sites. On average ten infants per site were expected. The maximum number of inclusions per site was limited to 25 to avoid a site effect. Newborns were included chronologically according to their admission date in the NICUs. No registry of eligible nonincluded patients was used in this study. A national stratification according to gestational age at birth, 30+0/7 to 33+6/7 WG (group 1) and 34+0/7 to 36+6/7 WG (group 2) was performed to obtain two equivalent-sized samples in order to carry out separate analyses in each group.

The inclusion visit (V0) was performed at 24 h of life, and the infants were followed up at 72 h (V1), on day 7 (V2) and at hospital discharge to home or on day 60 (if the infant was still in hospital) (V3).

Data were recorded by local investigators or a member of their team using an electronic case report form. Maternal, pregnancy, and delivery characteristics were recorded, as well as management in the delivery room, ventilatory supports used, duration of ventilation, the maximum fraction of inspired oxygen (FiO₂) value, surfactant administration, and time to withdrawal of all respiratory support. The diagnosis of RF (provided by the investigators according to their own usual criteria) was recorded at 72 h and on day 7 in order to take into account the patient's progression. Details of the data collected are presented in **Supplementary Table S1**.

2.4 Statistical analysis

Descriptive analyses were conducted according to gestational age and in the full population. A sample size of 270 infants per gestational age group (a total of 540

infants) was deemed adequate to describe the different endpoints with acceptable precision in each group. Qualitative variables were presented as the number and percentage of patients, and quantitative variables were presented as median and interquartile range (Q1–Q3). Analyses were performed using the available data, with no imputation of missing data. SAS® software (version 9.4, SAS Institute, Cary, NC USA) was used for all analyses.

2.5 Ethics approval

The study was approved in October 2017 by the West V Rennes Research Ethics Committee (*Comités de Protection des Personnes*, CPP) and on July 13th, 2017, by the French Data Protection Authority (*Commission Nationale de l'Informatique et des Libertés*, CNIL).

3 Results

3.1 Patient characteristics

Between February 9th, and October 31st, 2018, a total of 575 infants were included in the study (Figure 1). A total of 560 infants had complete data and were analyzed. The number of infants in each gestational age category (30, 31, 32, 33, 34, 35, and 36 WG) was 71, 71, 81, 56, 140, 87, and 54, respectively.

For the preterm infants included, the characteristics of gestation, birth, and early outcome are presented in Table 1. We observed that most of the pregnancies were singleton (64.1%), and 67.4% of the women had received treatment with prenatal

corticosteroids (mostly two doses). Cesarean section occurred in 59.6% of the cases. A complication during pregnancy was common (87.8%), with the most frequent reason being hospitalization for risk of preterm birth.

3.2 *Management in the delivery room*

For the overall population, 91.7% of the infants had an Apgar score ≥ 7 at 5 min (Table 1). A medical intervention was undertaken for 95.7% of the infants born between 30+0/7 and 33+6/7 WG (group 1) and 90.4% of the infants born between 34+0/7 and 36+6/7 WG (group 2). NIV in the delivery room was administered to 91.8% and 83.6% of group 1 and 2 infants, respectively, while IV was initiated in 6.1% and 3.9%. Surfactant was administered in the delivery room to 9.7% and 2.8% of the infants in groups 1 and 2.

More than 90% of the infants in the overall population were initially admitted to the hospital of their birth. Of the infants in groups 1 and 2, 64.6% and 42.0%, respectively, were transferred to a level III NICU, 28.3% and 37.2% were transferred to a level II NICU, and 7.1% and 17.2% were transferred to a neonatology unit.

3.3 *Causes of respiratory failure according to gestational age*

The most common RF diagnoses were RDS and transient tachypnea of the newborn (TTN; Figure 2). RDS was more frequent in those of younger gestational age.

3.4 Management and severity of respiratory failure during hospitalization

The details of RF management are presented in Table 2. During hospitalization, NIV and IV were administered to 98.7% and 16.4% of the total infant population, respectively. NIV was introduced at a median time of 0.3 h, with CPAP treatment the most common type of NIV used, and IV was initiated at a median time of 3.7 h with conventional mechanical ventilation the most common IV used (Table 2). For 44.3% of the total population, a maximum $\text{FiO}_2 \geq 40\%$ was recorded at least once (group 1 vs group 2: 47.7% vs 40.8%). The median (Q1–Q3) duration of hospitalization was 36 (27–46) and 15 (11–22) days for groups 1 and 2, respectively. The age of neonates for independent feeding was 31 (24.7–38) and 10.7 (5–16) days, respectively.

Surfactant was administered to 126 out of 560 (22.5%) infants of the overall population. Among infants diagnosed with RDS ($n=222$), the use of surfactant was observed in 50%. The use of surfactant appears to be associated with gestational age: 52.1% of the infants born at 30 WG, ~20% of infants born at 31–33 WG, and ~10% of infants born at 35–36 WG were treated. The majority of the patients treated (92%) received a single dose of surfactant at a median (Q1–Q3) time from birth of 4 (1–13) h. For 27.8% of them, it was administered in the delivery room. Surfactant was administered using the less invasive surfactant administration (LISA) method in 34.4% of the infants, the Intubation SURfactant Extubation (INSURE) method in 21.9%, or during conventional mechanical ventilation in 43.7%. The median (Q1–Q3) for FiO_2 at the time of surfactant administration was 40% (34.5–50). Sedation was administered before the first administration for 74 out of 110 (67.3%); when the LISA method was chosen ($n=41$),

ketamine was the most frequently used medication (31.7%). Caffeine was administered to 51% of the overall population (83.8% vs 18.1% for groups 1 and 2, respectively).

3.5 *Complications during hospitalization*

In the overall population, 8.6% of the infants had a respiratory and/or hemodynamic complication. Two infants died during the study, one from a grade IV intraventricular hemorrhage and one from fulminant necrotizing enterocolitis (Table 3).

4 Discussion

In this prospective study of a large French population of preterm infants aged ≤ 30 WG with RF, we observed that NIV and IV were performed for 98.7% and 16.4% of infants, respectively. Surfactant was administered to 22.5% of the overall population. Two main diagnoses were recorded in the population: RDS in 39.8% and TTN in 57.3%. Other etiologies, such as pneumothorax, occurred in less than 5% of the infants. In the two groups, NIV management was widely used and the frequency of IV was comparable.

To our knowledge, this is the first report that details the practices for the management of RF, particularly in moderate-to-late-preterm infants. Although respiratory morbidity is a known issue in moderate-to-late preterm infants [10], our findings show that most of these infants were treated with NIV, usually in the delivery room. While it is difficult to compare the results of this study with others, because most of them included all the moderate-to-late preterm infants in their institutions [10-12], whereas ours focused on the infants with RF, the timeliness of the treatment with NIV after the birth is a

significant factor that contributes to better management of the RF [13, 14]. We found that the French NICUs that participated in the study typically followed the published literature, given that the time from birth to the first NIV was short, between 0.3 and 0.5 h depending on the WG group.

In late preterm infants with RDS, the use of surfactant was typically low in previously published clinical studies, below 10% [5, 15-17]. However, it is very important to consider the denominator of the population studied, which in most cases included all late preterm infants, with and without RDS. In a more recent study focused on late preterm infants with RDS, 45% of the infants were treated with surfactant [18]. In contrast, our rate of surfactant use was 22%. However, if we consider only the babies with RDS and not TTN in the present study, the rate of treatment with surfactant was 50%, closer to that observed by Dani and colleagues [18]. The median 40% FiO₂ at the time of surfactant administration was close to the 2013 European guidelines on the management of neonatal RDS in preterm infants, where the threshold of FiO₂ used to decide whether to administer surfactant was based on the maturity of the babies (FiO₂ >30% in infants born at <26 WG and FiO₂ >40% in infants born at >26 WG) [19]. In the updated 2019 guidelines, surfactant is recommended with a FiO₂ >30% in all babies, irrespective of maturity [2]. Another interesting point is that the LISA method was used to administer surfactant in 34.4% of the preterm infants in this study, a finding that is close to a previous French single-center study, which found the LISA technique was used in 33.5% of patients [20]. For very preterm infants, the main argument for using the LISA method is that it reduces the rate of chronic lung disease (CLD) [21, 22]. In

late preterm infants, the risk/benefit ratio for the LISA method to prevent CLD is much lower. However, the use of LISA is still recommended in this population [2], mainly because the LISA catheter is less aggressive than a tracheal tube used for the INSURE procedure, and other morbidities observed in very preterm infants such as shorter ventilation duration could also benefit late preterm infants [21-24].

The comparison of the etiology of the RF in the two WG groups in this study shows a greater proportion of RDS in the more immature infants. The distinction between RDS and TTN is not always easy because the natural course of some cases of RDS could be modified with a prenatal corticosteroid and early management of the RF with NIV.

Moreover, our classification was based on data from medical records without a centralized reading of the pulmonary x-rays, which is a limitation of this study.

However, while no imaging confirmation of the diagnoses was obtained, the clinical diagnosis by the infants' physicians remained consistent throughout the course of the infants' observation period (i.e., on Day 3 and Day 7), irrespective of disease severity or NIV weaning status. Another limitation of the NEOBS study is its observational nature, which cannot allow for relationship analysis such as between the respiratory support strategy and the outcome. Furthermore, no data regarding the eligible infant population were gathered due to the absence of a registry of eligible but non-included infants, leading to a potential selection bias. Moreover, this multicenter study included 46 centers in France and we cannot claim that our results reflect those of the entire nation. However, these centers were carefully selected to range across all of France and reflected the sampling observed in other descriptive studies, such as EPIPAGE 2 [25].

Finally, there may be some selection bias due to including newborn mostly from level 3 neonatal units: one could argue that infants admitted to level 3 units are sicker than those admitted to lower-level units. However, in France very few infants with RDS are treated in level 1 and 2 units, and infants admitted to level 2 units are often quickly weaned from NIV because they have rapidly evolving RDS and therefore do not have many support issues. In the study reported by Iacobelli et al., which included all preterm infants born from 32 WG in the year 2011 in France, the most frequent places of hospitalization were intermediate neonatal (level 2) units, but not intensive care (level 3) units [26]. We would argue that including level 3 units means that our sample is more representative of infants with prolonged RDS.

5 Conclusion

The NEOBS study presents the first data on RF management in late preterm infants in a large sample of French NICUs. CPAP in the delivery room and the LISA method for surfactant administration were widely used. The incidence of RF-related complications was low. Further studies should be conducted to assess the implementation of the 2019 European guidelines for management of RF.

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Author contributions All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. All authors were involved in patient enrollment, design of the study, and analysis of the data, and read and approved all drafts of the manuscript.

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Tables

Table 1. Characteristics of the patients included in the NEOBS study

Characteristics		30+0/7 to 33+6/7 WG (n=279)	34+0/7 to 36+6/7 WG (n=281)	Total population (n=560)
Mother	Age years, median (Q1–Q3)	31 (27–35)	31 (28–34)	31 (28–35)
	Gravidity >1, <i>n</i> (%)	177 (63.4)	194 (69.0)	371 (66.2)
	Parity (with included neonates) >1, <i>n</i> (%)	179 (64.1)	191 (68.0)	370 (66.1)
	Smoker during pregnancy, <i>n</i> (%)	37 (13.5)	40 (14.7)	77 (14.1)
	Medically assisted procreation, <i>n</i> (%)	56 (20.1)	31 (11)	87 (15.5)
	Multiple pregnancy, <i>n</i> (%)	103 (36.9)	98 (34.8)	201 (35.9)
Gestation	Complication during pregnancy, <i>n</i> (%)	257 (92.4)	233 (83.2)	490 (87.8)
	Gestational diabetes	36 (12.9)	41 (14.6)	77 (13.8)
	Pre-eclampsia	58 (20.8)	47 (16.7)	105 (18.8)
	Chorioamnionitis	6 (2.2)	2 (0.7)	8 (1.4)
	Eclampsia	0	2 (0.7)	2 (0.4)
	Hospitalization for risk of preterm delivery	133 (47.7)	71 (25.3)	204 (36.4)
	Prenatal corticosteroid use, <i>n</i> (%)	251 (90.6)	124 (44.4)	375 (67.4)
	Number of doses received, <i>n</i> (%)			
	1	57 (20.4)	10 (3.6)	67 (12.0)
	2	171 (61.3)	101 (35.9)	272 (48.6)
	≥2	20 (7.2)	11 (3.9)	31 (5.5)
	Time between the last corticosteroid dose received and delivery, <i>n</i> (%)			
	<24 h	50 (20.7)	4 (3.3)	54 (15.0)
	1–7 days	105 (43.6)	32 (26.7)	137 (38.0)
	Mode of delivery, <i>n</i> (%)			
	Vaginal	105 (37.6)	121 (43.1)	226 (40.4)
	Vaginal with instrument	13 (12.9)	21 (18.3)	34 (15.7)
	Caesarean	174 (62.4)	160 (56.9)	334 (59.6)
	Emergency cesarean	156 (55.9)	113 (40.2)	269 (48.0)
Newborn infant	Location of the birth, <i>n</i> (%)			
	NICU (maternity type III)	230 (82.4)	190 (67.6)	420 (75)
	NICU (maternity type II)	31 (11.1)	56 (19.9)	87 (15.5)
	Others	18 (6.5)	35 (12.5)	53 (9.5)
	Male sex, <i>n</i> (%)	152 (54.5)	166 (59.1)	318 (56.8)
	WG, median (Q1–Q3)	31 (30–32)	35 (34–35)	34 (31–35)
	Weight g, median (Q1–Q3)	1560 (1340– 1865)	2300 (1970– 2620)	1898 (1500– 2350)
	Apgar score ≥7 at 5 min, <i>n</i> (%)	254 (92)	255 (91.4)	509 (91.7)

NICU: neonatal intensive care unit; Q: quartile; WG: weeks of gestation

Table 2. Management of respiratory distress in the NEOBS study

	30+0/7 to 33+6/7 WG (n=279)	34+0/7 to 36+6/7 WG (n=281)	Total population (n=560)
Noninvasive ventilation, n (%)	278 (99.6)	275 (97.8)	553 (98.7)
Time from birth to first NIV, hours, median (Q1–Q3)	0.3 (0.1–0.6)	0.5 (0.2–1.0)	0.3 (0.1–0.8)
Silverman score at first NIV, median (Q1–Q3)	3 (2–4)	4 (2–4)	3 (2–4)
FiO ₂ ≥30% at first NIV, n (%)	59 (29.4)	74 (33.2)	133 (31.4)
Ventilation support before first NIV, n (%)			
No support	262 (94.2)	263 (95.6)	525 (94.9)
Invasive ventilation	16 (5.8)	5 (1.8)	21 (3.8)
Mechanical ventilation	16 (5.8)	5 (1.8)	21 (3.8)
Nasal cannula oxygen	0	4 (1.5)	4 (0.7)
Other (simple oxygen therapy)	0	3 (1.1)	3 (0.5)
Type of NIV, n (%)			
HFNC	153 (55.0)	123 (44.7)	276 (49.9)
CPAP	246 (88.5)	228 (82.9)	474 (85.7)
IPV	109 (39.2)	65 (23.6)	174 (31.5)
Duration of first NIV hours, median (Q1–Q3)	167.1 (27.9–455)	45.5 (18.1–95.6)	78.7 (25–216)
NIV stopped before hour 24, n (%)	138 (50.4)	169 (62.6)	307 (56.4)
Invasive ventilation, n (%)	55 (19.7)	37 (13.2)	92 (16.4)
Time from birth to first IV, hours, median (Q1–Q3)	3 (0.4–21.8)	4.4 (0.5–18)	3.7 (0.5–21)
FiO ₂ ≥30% at first IV, n (%)	33 (71.7)	19 (65.5)	52 (69.3)
Type of IV, n (%)			
Conventional mechanical ventilation	55 (100)	35 (94.6)	90 (97.8)
High-frequency oscillatory ventilation	6 (10.9)	4 (10.8)	10 (10.9)

Data are missing for the following factors: Silverman score, $n=262$; FiO_2 before first NIV, $n=129$; duration of first NIV, $n=273$; FiO_2 at first IV, $n=17$. CPAP: continuous positive airway pressure; FIO_2 : fraction of inspired oxygen; HFNC: high-flow nasal cannula; IPV: intermittent pressure ventilation; IV: invasive ventilation; NIV: noninvasive ventilation; Q: quartile; WG: weeks of gestation

Table 3. Respiratory failure-related complications in the NEOBS study

Complication, <i>n</i> (%)	30+0/7 to 33+6/7 WG (<i>n</i>=279)	34+0/7 to 36+6/7 WG (<i>n</i>=281)	Total population (<i>n</i>=560)
Presence of ≥ 1 respiratory or hemodynamic complication	30 (10.8)	18 (6.4)	48 (8.6)
Pneumothorax	9 (3.2)	9 (3.2)	18 (3.2)
Pulmonary hypertension treated with NO	1 (0.4)	3 (1.1)	4 (0.7)
Administration of amines	11 (3.9)	3 (1.1)	14 (2.5)
Vascular filling	24 (8.6)	8 (2.8)	32 (5.7)
Intraventricular hemorrhage of any grade	9 (3.2)	2 (0.7)	11 (2)
Intraventricular hemorrhage Grade IV	2 (28.6)	0 (0)	2 (22.2)
Transfusion of RBCs	20 (7.2)	6 (2.1)	26 (4.6)
Other complications	59 (21.1)	36 (12.8)	95 (17)
Death	2 (0.7)	0 (0)	2 (0.4)
Cause of death			
Intraventricular hemorrhage Grade IV	1 (0.4)	0	1 (0.2)
Fulminant necrotizing enterocolitis	1 (0.4)	0	1 (0.2)

NO: nitric oxide; RBC: red blood cells; WG: weeks of gestation

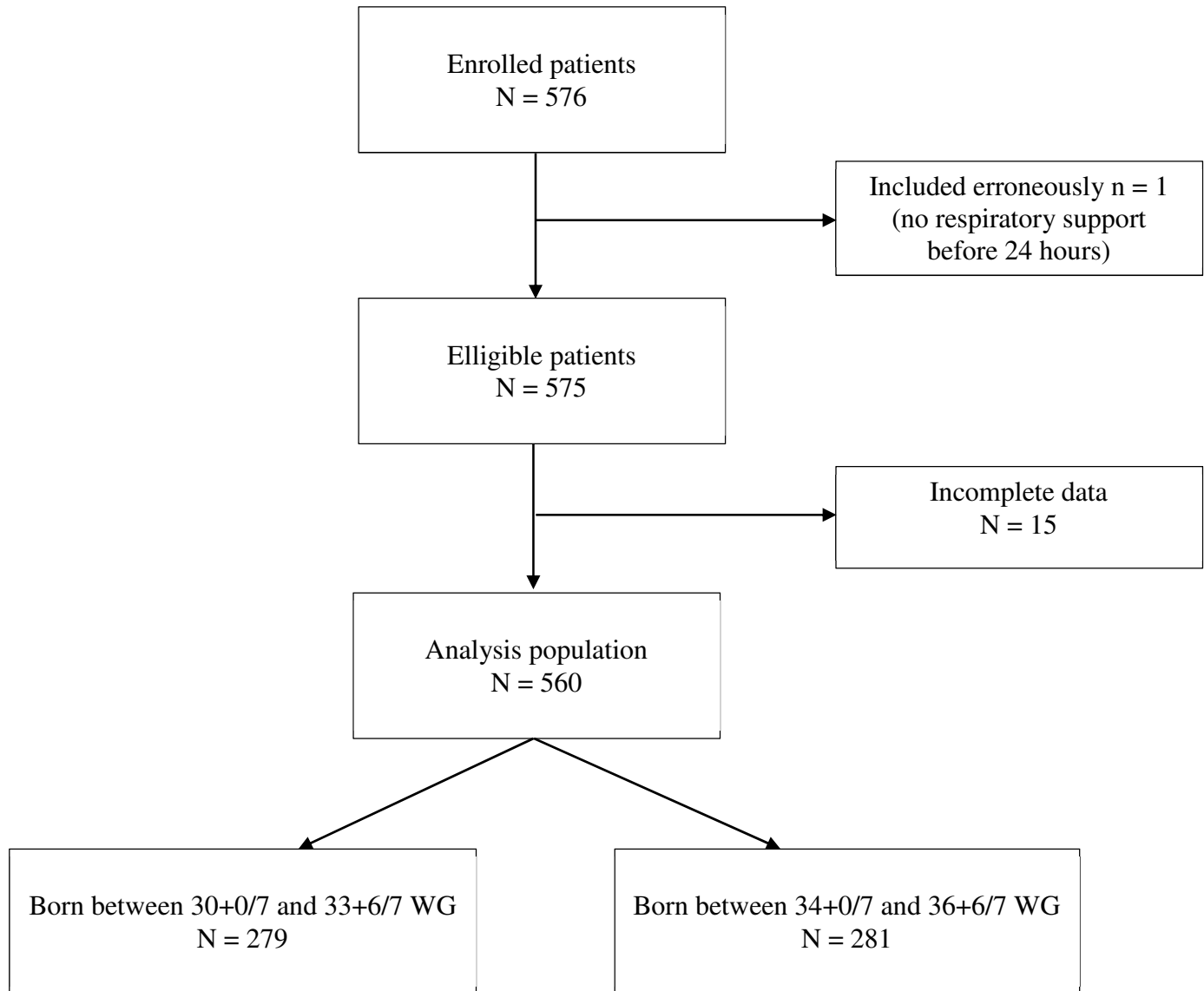
Figure legends

Figure 1. Patient distribution in the NEOBS study.

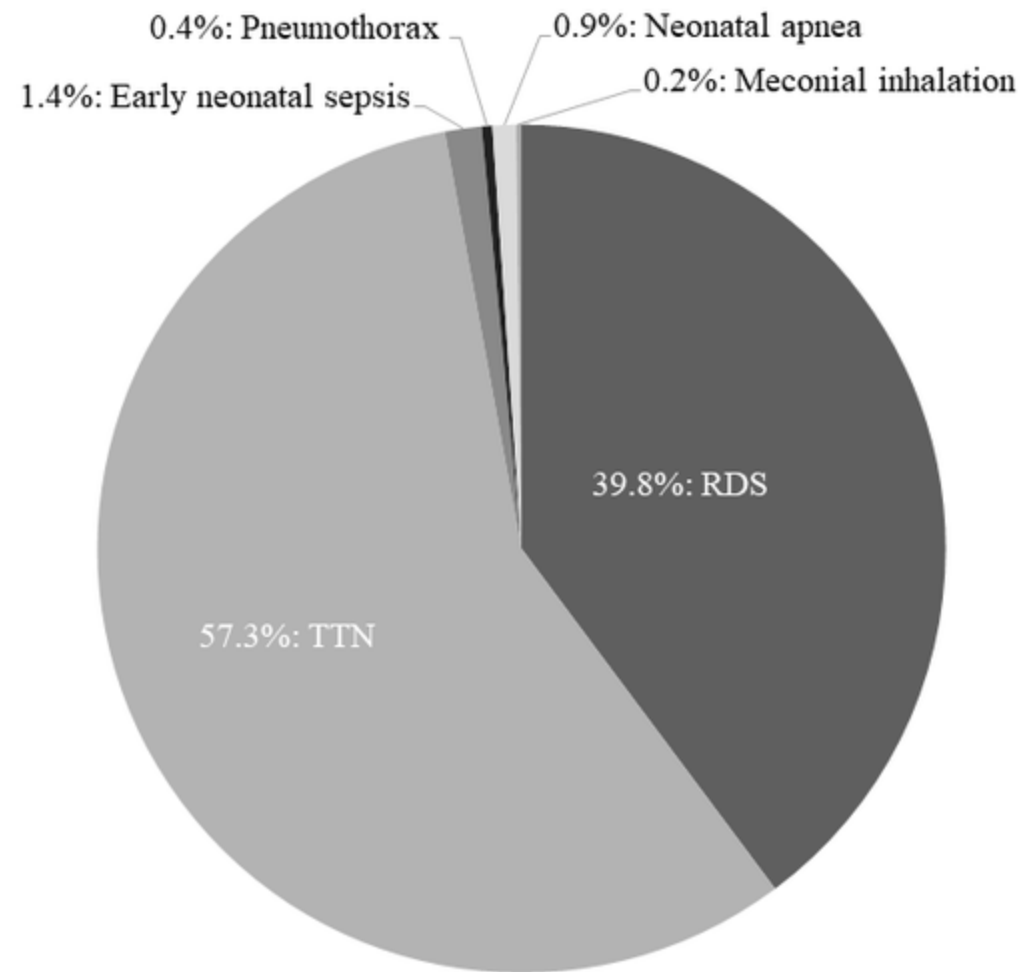
WG: weeks of gestation.

Figure 2. Etiological diagnosis of the respiratory failure in the NEOBS study.

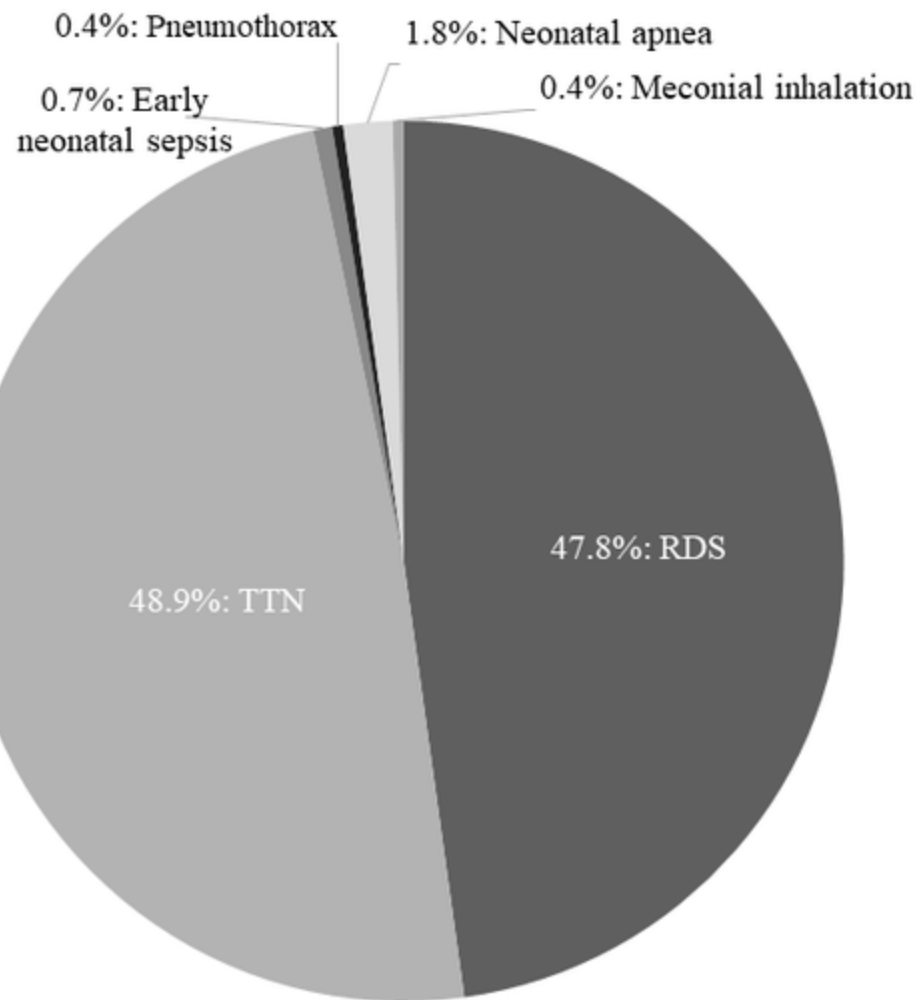
RDS: respiratory distress syndrome; TTN: transient tachypnea of the newborn; WG: weeks of gestation.



Total population



30+0/7 to 33+6/7 WG



34+0/7 to 36+6/7 WG

