Statistical analysis of PICO study (CHI-PL-CUR-02)

REPORT

– Warsaw 2018 –

Version 1.3

The final statistical analysis of study results was performed by:

BioStat Sp. z o. o.

Kowalczyka 17

44-207 Rybnik

www.biostat.com.pl

statystyka@biostat.com.pl

Report's authors:

Mateusz Piechaczek, MSc – statistical analysis and description of study results

Barbara Gorzawska, MSc – description of study results

Dr Marian Płaszczyca, MSc, PhD – description of results and scientific consultation

Content

Abstract

The main aim of the PICO study was to determine the rate of nasal continuous positive airway pressure (NCPAP) failure, used as early respiratory support, in preterm infants at risk of respiratory distress syndrome (RDS). The study was performed in 29 neonatal intensive care units (NICUs) of reference level 3. The study involved observation of 394 preterm infants <30 weeks gestation, in which non-invasive respiratory support with NCPAP was initiated within 15 minutes from birth. Failure of an early NCPAP was defined as the need for endotracheal intubation and invasive ventilation within the first 72 hours of life.

The analysis of NCPAP efficacy was performed in 389 preterm infants with all available data. NCPAP failure was observed in 27.8% of preterm infants, and the rates depended on gestational age (failure rate of 50% at 23–24 weeks gestation down to 22.7% at 29 weeks gestation).

Secondary objectives involved the assessment of risk factors for NCPAP failure. Study results demonstrate the predictive value of maximum fraction of inspired oxygen (FiO_2) in the first hours of life and birth weight. The use of FiO_2 as a prognostic factor for NCPAP failure provides the best result when the risk assessment involves FiO_2 in the second hour of life or FiO_2 within the first two hours of life. The increase in the requirement for oxygen by 1 percentage point (p.p.) in the second hour of life results in the increase of risk of NCPAP failure by 7.5%. FiO_2 >0.29 in the second hour of life or >0.32 in the first two hours of life has a prognostic value for NCPAP failure. Birth weight has a substantial impact on the risk of NCPAP failure (odds reduction by 16% per each 100 g of weight).

In the study cohort, 81.9% (N=322) of hospitalised patients were discharged home, while 6.9% died (N=27). Overall, 44 neonates (11.2%) were transferred to another unit/hospital during the study, and thus lost to follow-up.

In preterm infants requiring treatment with exogenous surfactant (60.2%; N=237), FiO_2 at the moment of drug administration had a prognostic value for the occurrence of air-leak syndrome (risk increase by 2.5% for each p.p. of O_2); however, this parameter had no prognostic value for death, bronchopulmonary dysplasia (BPD), and severe retinopathy of prematurity (ROP).

The planned comparison of effects of an early and late caffeine therapy initiation (<2 hours vs. >12 hours of life) was not possible because the latter group comprised only 6.6% of premature infants.

Introduction and methods

PICO was a prospective, multicentre, non-interventional study collecting data on treatment of neonates with respiratory distress syndrome (RDS) conducted in daily practice with the use of early nasal continuous positive airway pressure (NCPAP), exogenous surfactant, and caffeine citrate. Since this was an observational study only collecting routinely available data from the hospital records and did not involve any direct intervention to participants. The study was sponsored by Chiesi, while the scientific part of the study was supervised by the Scientific Committee composed of the following members: Prof. M. K. Kornacka-Borszewska, Prof. E. Helwich, Prof. M. Rutkowska, Prof. E. Gulczyńska, Prof. R. Lauterbach.

Main aim of the study

The primary aim of this study was to determine the incidence of NCPAP failure in preterm infants at risk of RDS, in a routine practice setting, in Polish level-3 NICUs.

This study also aimed to assess clinical outcomes as well as the magnitude of required respiratory support in infants treated with a surfactant (SFT), depending on the oxygen demand at the moment of SFT administration.

For this study, ENCPAP was defined as maintaining continuous positive airway pressure of at least 5 cm H_2O with the use of any dedicated device and interface (e.g. nasal prongs or mask) available at the site, which is initiated within the first 15 minutes after birth.

Failure of ENCAP was defined as the need for endotracheal intubation and invasive ventilation within the first 72 hours of life.

Oxygen demand was defined as the fraction of inspired oxygen (FiO_2) necessary to maintain the oxygen saturation as measured by pulse oximetry, at the level which is acceptable according to local practice.

Secondary objectives

This study provided description of the methods of applying NCPAP in the Delivery Room and NICU at study sites, including device type, interface, initial pressure, availability and use of transport incubators, maintenance of CPAP during transfer to NICU, use of advanced CPAP modes (e.g. “biphasic” CPAP), in everyday practice.

Apart from that, specific secondary goals were also as follows:

- investigation of perinatal risk factors predictive of ENCPAP failure
- identification of the FiO_2 level at which SFT is administered, which best differentiates the occurrence of the following endpoints:
    - Death
    - Broncho-pulmonary dysplasia (BPD)
    - Air-Leak Syndrome
    - Severe retinopathy of prematurity (ROP)

In infants, who according to the assessment of the attending physician require administration of exogenous SFT, the relation between the magnitude of the initial dose and respiratory outcomes was assessed.

Also, a regimen of caffeine citrate therapy in current clinical practice was analysed, with particular attention to the timing of therapy initiation.

In infants in whom caffeine is started in the first day of life, the need of intubation in the first 12 hours of life and the rates of typical complications of prematurity was analysed, depending on the timing of therapy initiation: immediate post-delivery (<2h) vs later (>12 hours).

Inclusion and exclusion criteria

Inclusion criteria

Neonates qualified for observation had to fulfil all the following criteria:

1. Inborn infants at risk of RDS
2. Gestational age <30 weeks
3. NCPAP started within 15 min. from birth ("early NCPAP" – ENCPAP)

Exclusion criteria

1. Intubation at Delivery Room
2. Infants requiring mechanical ventilation from birth
3. Infants with clinically significant malformations, whether detected antenatally or visible in clinical examination

Primary study variables

The primary study variable was a proportion of infants requiring invasive ventilation (i.e. through an endotracheal tube) within the first 72 hours of life – „NCPAP failure".

Also, the rate of NCPAP failure depending on the gestational age was described.

In infants requiring administration of exogenous surfactant, an odds ratio (OR) for the occurrence of composite endpoint comprising different adverse endpoints was calculated; this OR was compared between the subgroup of patients obtained through stratification by FiO_2 value at the moment of surfactant (SFT) administration:

a. FiO_2 <0.35

b. FiO_2 0.35–0.45

c. FiO_2 >0.45–0.55

d. FiO_2 >0.55–0.65

e. FiO_2 >0.65

The composite endpoint was met in the occurrence of any of the below:

- Broncho-pulmonary dysplasia (BPD)
- Air-Leak Syndrome
- Intraventricular haemorrhage (IVH)
- Death

In the subgroup requiring exogenous surfactant, mean/median values of the following parameters defining the magnitude of necessary respiratory support were computed:

- Duration of invasive (requiring intubation) mechanical ventilation

- Maximal FiO_2 during mechanical ventilation
- Maximal Mean Airway Pressure (MAP)
- Maximal Positive End-Expiratory Pressure (PEEP), if applicable.

Results were also compared between the FiO_2 strata.

Secondary variables

1. Odds ratio describing the effect of the following factors, potentially predictive of ENCPAP failure:

    a. Gender

    b. Gestational age

    c. Birth weight

    d. Multiple birth

    e. Caesarean delivery

    f. Need for positive pressure ventilation at the Delivery Room

    g. Highest FiO_2 in the first hour of life

    h. Highest FiO_2 in the second hour of life

    i. CPAP initial level

2. Specificity, selectivity and area under ROC curve of the prognosis of death/ BPD/ Air-Leak Syndrome/ severe ROP, based on the FiO_2 level at SFT administration

3. Need for mechanical ventilation in infants receiving SFT at FiO_2 <0.45 vs>0.65

4. Age at initiation of caffeine citrate and duration of treatment

5. Proportion of infants requiring intubation within the first 12 hours of life in “early” (<2h) and “late” (>12h) caffeine subgroups

6. Specificity, selectivity and area under ROC curve of the prognosis of the need for endotracheal intubation in the first 12 hours of life, based on the infant’s age at caffeine therapy initiation

7. Rate of pulmonary complications

8. Incidence and severity of the following complications:

    a. BPD

    b. IVH

    c. Periventricular leukomalacia (PVL)

    d. Retinopathy of Prematurity – ROP (incl. necessity of laser therapy or photocoagulation)

    e. Patent Ductus Arteriosus – PDA

    f. Necrotizing Enterocolitis – NEC

9. Mortality rate

Statistical analysis of data

Continuous variables were described with the use of basic descriptive statistics: mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum. For categorical variables, however, frequencies and percentages – with consideration of lack of or missing data – were used.

Logistic regression analysis will be used to examine prediction of ENCPAP failure, with demographic and respiratory parameters as well as centre effect as independent variables. The odds ratios for each predictor will be reported with corresponding P values and 95% confidence intervals. Logistic regression models assessing the impact of FiO_2 value in the first, second hour of life, and overall on ENCPAP failure were evaluated with Receiver Operating Characteristic (ROC) curves.

Distribution of the qualitative variable was compared with the use of Pearson's chi-square test or Fisher's exact test. Non-parametric U Mann-Whitney test was used to compare the distribution of continuous variables between two groups.

A two-tailed level of significance (alpha value) will be set at 0.05 for all analyses. All analyses were performed with the use of R statistical software (version 3.4).

Data collection

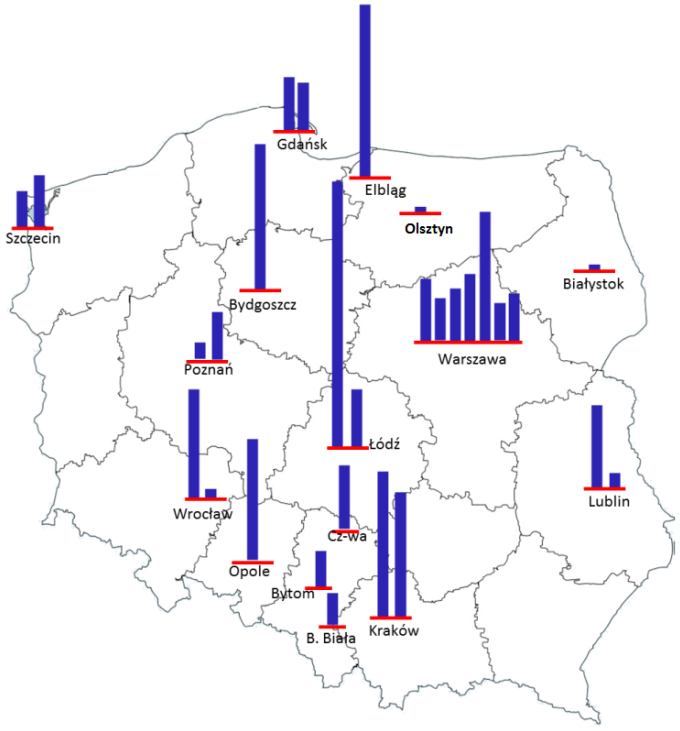
Overall, this study was conducted by 43 investigators from 29 sites.

Data were collected from October 2016 to March 2018, when hospitalisation of the last patient was completed.

Overall, data of 403 patients were recorded in the database, of whom nine subjects were excluded from the analysis due to not fulfilling enrolment criteria.

The list of trial sites according to the province is presented below.

Figure 1. Distribution of Neonatal Intensive Care Units (NICUs) participating in PICO study. The height of the bars is proportional to the number of enrolled patients.



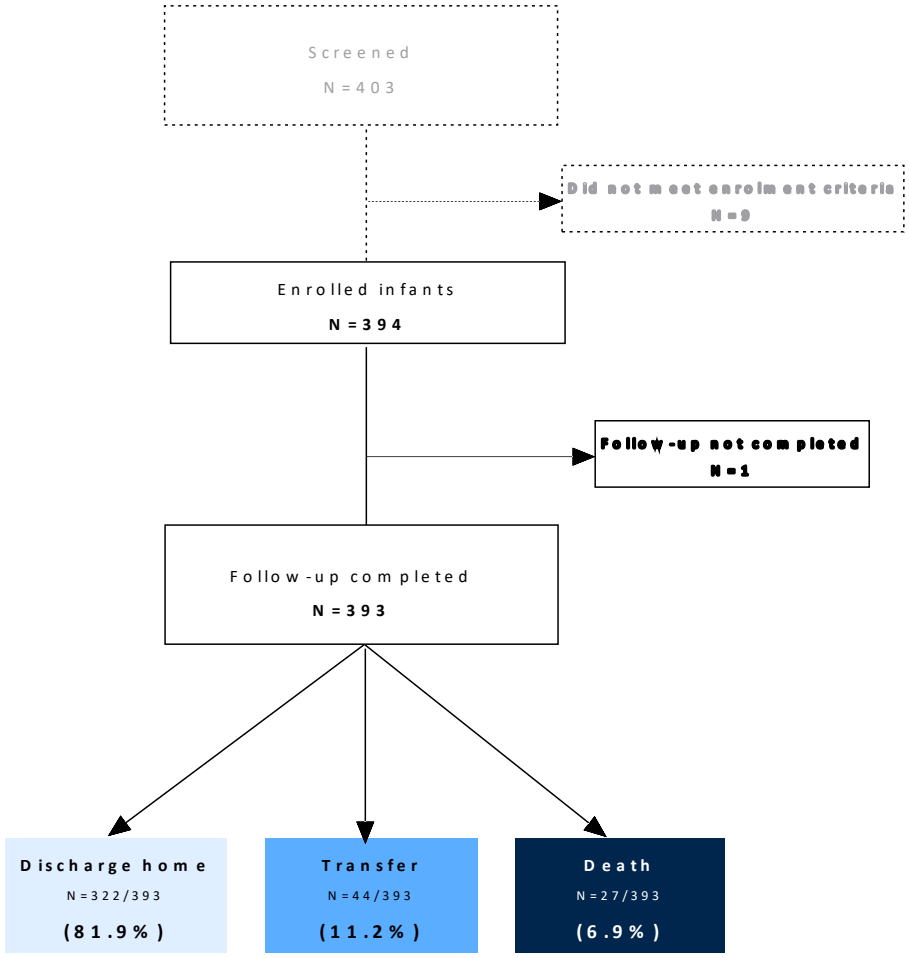
mazowieckie	7
śląskie	3
dolnośląskie	2
lubelskie	2
łódzkie	2
małopolskie	2
pomorskie	2
wielkopolskie	2
zachodniopomorskie	2
warmińsko-mazurskie	2
kujawsko-pomorskie	1
opolskie	1
podlaskie	1

Study group characteristics

Patient flow

The database included 403 neonates. Overall, nine (9) patients from this group did not fulfil all inclusion criteria or fulfilled some of the exclusion criteria defined in the study protocol. Therefore, this observation included 394 patients, of which one medical record did not contain any information on circumstances related to hospitalisation end. In the group of patients completing the observation period, 322 infants were discharged to their place of residence (81.9%); 44 neonates (11.2%) were transferred to another unit/hospital, while 27 died during the study (6.9%).

Figure 2. The flow of enrolled patients



Clinical characteristics

The gender ratio in the study cohort was balanced. The mean gestational age was 28.24 weeks (± 1.22 of standard deviation [SD]). The half of neonates were born between 27 weeks and 3 days and 29 weeks and 1 day of gestational age (interquartile range). The average birth weight was 1115.87g (± 269.8). Infants under observation achieved the mean 5 minute Apgar score of 7.49 (± 1.15) points.

Table 1. Descriptive characteristics of the study group

Variable	Parameter	Overall distribution	Distribution excluding missing data
Sex	F	197 (50%)	197 (50.1%)
	M	196 (49.7%)	196 (49.9%)
	No data	1 (0.3%)	
Gestational age [week]	Number of observations	394	
	Mean (standard deviation)	28.24 (1.22)	
	Median	28.43	
	IQR	27.43–29.14	
	Range	23.43–29.86	
	No data	0	
Birth weight [g]	Number of observations	394	
	Mean (standard deviation)	1115.87 (269.8)	
	Median	1120	
	IQR	940–1300	
	Range	400–1970	
	No data	0	
5 minute Apgar score	Number of observations	394	
	Mean (standard deviation)	7.49 (1.15)	
	Median	8	
	IQR	7–8	
	Range	4–10	
	No data	0	

Overall, 87 neonates (22.1%) were born from multiple pregnancies; in most cases, from twin pregnancies (88.5%; N=77). Only 16.5% (N=65) of infants were born by vaginal delivery.

Table 2. Descriptive characteristics of the study group – pregnancy and delivery

Variable	Parameter	Overall distribution	Distribution excluding missing data
Multiple birth	Yes	87 (22.1%)	87 (22.1%)
	No	307 (77.9%)	307 (77.9%)
	No data	0 (0%)	
Number of neonates	Twins	77 (88.5%)	77 (88.5%)
	Triplets	10 (11.5%)	10 (11.5%)
	No data	0 (0%)	
Delivery type	C-section	329 (83.5%)	329 (83.5%)
	Vaginal	65 (16.5%)	65 (16.5%)
	No data	0 (0%)	

Steroids were used in the majority of subjects (89.8%; N=354), while in more than half of patients (54.2%), the time between administration of the last dose and delivery ranged from 24 hours to 14 days (N=192). Overall, 81.9% of subjects received betamethasone (N=290), while dexamethasone was used in 68 (19.2%) patients. The full course of antenatal steroids was used in 281 subjects (79.4%).

Table 3. Descriptive characteristics of the study group – antenatal steroids

Variable	Parameter	Overall distribution	Distribution excluding missing data
Steroids	Yes	354 (89.8%)	354 (90.3%)
	No	38 (9.6%)	38 (9.7%)
	No data	2 (0.5%)	
Betamethasone	Yes	290 (81.9%)	290 (85.8%)
	No	48 (13.6%)	48 (14.2%)
	No data	16 (4.5%)	
Dexamethasone	Yes	68 (19.2%)	68 (23.2%)
	No	225 (63.6%)	225 (76.8%)
	No data	61 (17.2%)	
Full course of steroids	Yes	281 (79.4%)	281 (80.1%)
	No	70 (19.8%)	70 (19.9%)
	No data	3 (0.8%)	
Time of the last dose of steroids administration	<24 hours before birth	89 (25.1%)	89 (25.9%)
	24 hours–14 days before birth	192 (54.2%)	192 (55.8%)
	>14 days before birth	63 (17.8%)	63 (18.3%)
	No data	10 (2.8%)	

Seven neonates (1.8%) received cardiac massage, while only one received adrenalin (0.3%). Positive pressure breaths were used in 78.2% of infants (N=308), of which 76.0% (N=234) underwent constant pressure sustained inflation. The thermal assessment was used in 80.2% of neonates (N=316). Oxygen therapy in the Delivery Room was used in 213 infants (54.1%) with an average initial FiO_2 of 0.29 (± 0.08). In half of the infants, FiO_2 value ranged between 0.25 and 0.3. The mean highest FiO_2 value in the Delivery Room was 0.37 (± 0.11), while half of the values ranged between 0.3 and 0.4.

Table 4. Descriptive characteristics of the study group – procedures used

Variable	Parameter	Overall distribution	Distribution without missing data
Chest compressions	Yes	7 (1.8%)	7 (1.8%)
	No	387 (98.2%)	387 (98.2%)
	No data	0 (0%)	
Epinephrine	Yes	1 (0.3%)	1 (0.3%)
	No	393 (99.7%)	393 (99.7%)
	No data	0 (0%)	
Positive pressure breaths	Yes	308 (78.2%)	308 (78.2%)
	No	86 (21.8%)	86 (21.8%)
	No data	0 (0%)	
Mode of positive pressure breaths	Sustained inflation at constant pressure	234 (76%)	234 (79.6%)
	Bagging	60 (19.5%)	60 (20.4%)
	No data	14 (4.5%)	
Thermal protection	Yes	316 (80.2%)	316 (80.6%)
	No	76 (19.3%)	76 (19.4%)
	No data	2 (0.5%)	
Supplemental O_2 in the Delivery Room	Yes	213 (54.1%)	213 (54.3%)
	No	179 (45.4%)	179 (45.7%)
	No data	2 (0.5%)	
Initial FiO_2 in the Delivery Room	Number of observations	208	
	Mean (standard deviation)	0.29 (0.08)	
	Median	0.3	
	IQR	0.25–0.3	
	Range	0.21–1	
	No data	5	
Highest FiO_2 in the Delivery Room	Number of observations	209	
	Mean (standard deviation)	0.37 (0.11)	
	Median	0.3	
	IQR	0.3–0.4	
	Range	0.23–1	
	No data	4	

Demand for oxygen in the early postnatal period

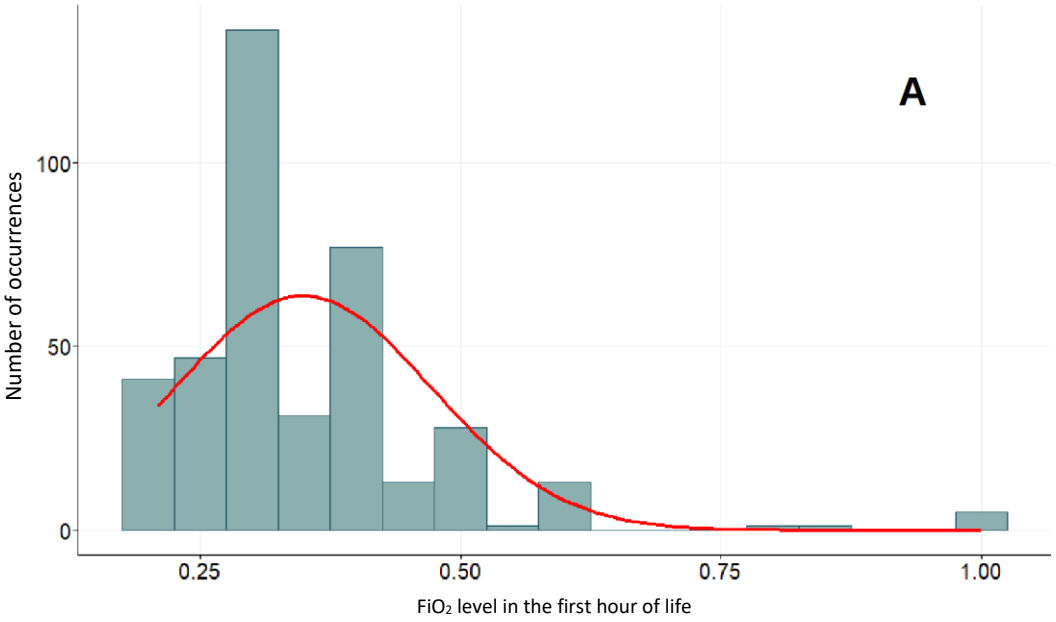
Median FiO_2, both in the first and second hour of life, was 0.3; however, the mean value was slightly higher 0.35 (± 0.12) in the first hour compared to the second hour of life 0.31 (± 0.11) – this difference was significant ($p<0.001$; Wilcoxon test).

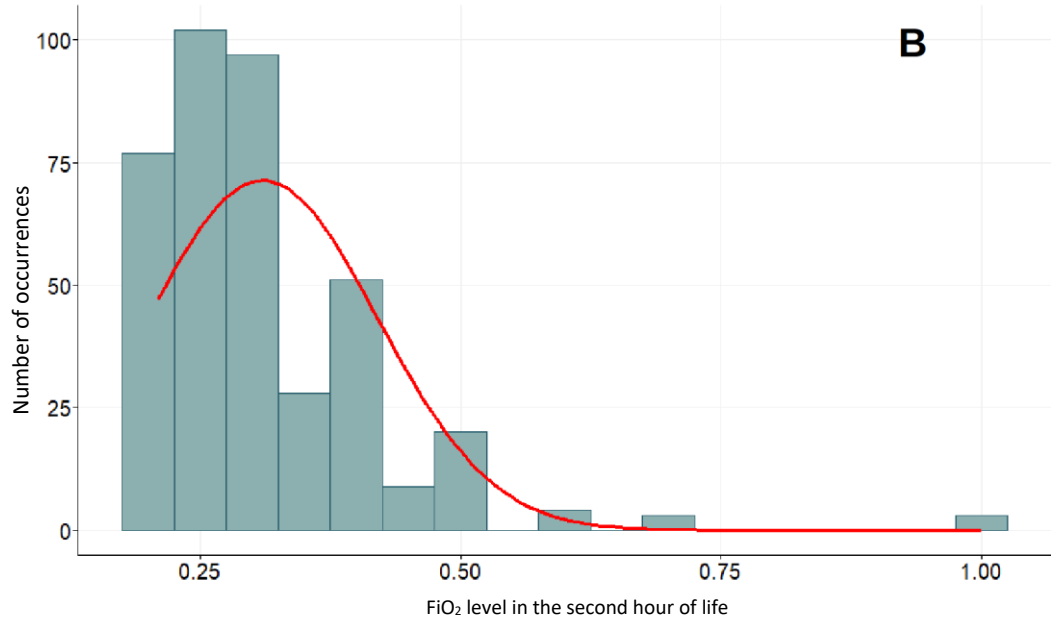
Table 5. Fraction of inspired oxygen (FiO_2) in the first and second hour of life

Variable	Parameter	Overall distribution
FiO_2 in the 1st hour of life	Number of observations	394
	Mean (standard deviation)	0.35 (0.12)
	Median	0.3
	IQR	0.3–0.4
	Range	0.21–1
	No data	0
FiO_2 in the 2nd hour of life	Number of observations	394
	Mean (standard deviation)	0.31 (0.11)
	Median	0.3
	IQR	0.24–0.35
	Range	0.21–1
	No data	0

Histograms demonstrating the distribution of FiO_2 values in the first and second hour of life are presented below.

Figure 3. Distribution of FiO_2 values in the first (A) and the second (B) hour of life





Non-invasive respiratory support

NCPAP

In the majority of patients, the use of NCPAP was initiated in the Delivery Room (95.2%; N=375) after a mean of 3.5 minutes (± 3.1) – in half of the neonates, respiratory support was initiated between 1 to 5 minutes after birth. In neonates initiating NCPAP in the NICU (4.8%; N=19), mean time to start was 9.63 minutes (± 3.42). In both locations, a variable flow CPAP was most often used, e.g. Infant Flow, MEDIN-CNO (Delivery Room: 79.7%, N=314; NICU: 78.4%, N=309). The half of infants underwent more than one CPAP cycle (50.3%; N=198). The median duration of CPAP was 12.9 days, and in half of the patients, it ranged between 3.4 and 29.5 days.

Table 6. Characteristics of non-invasive respiratory support

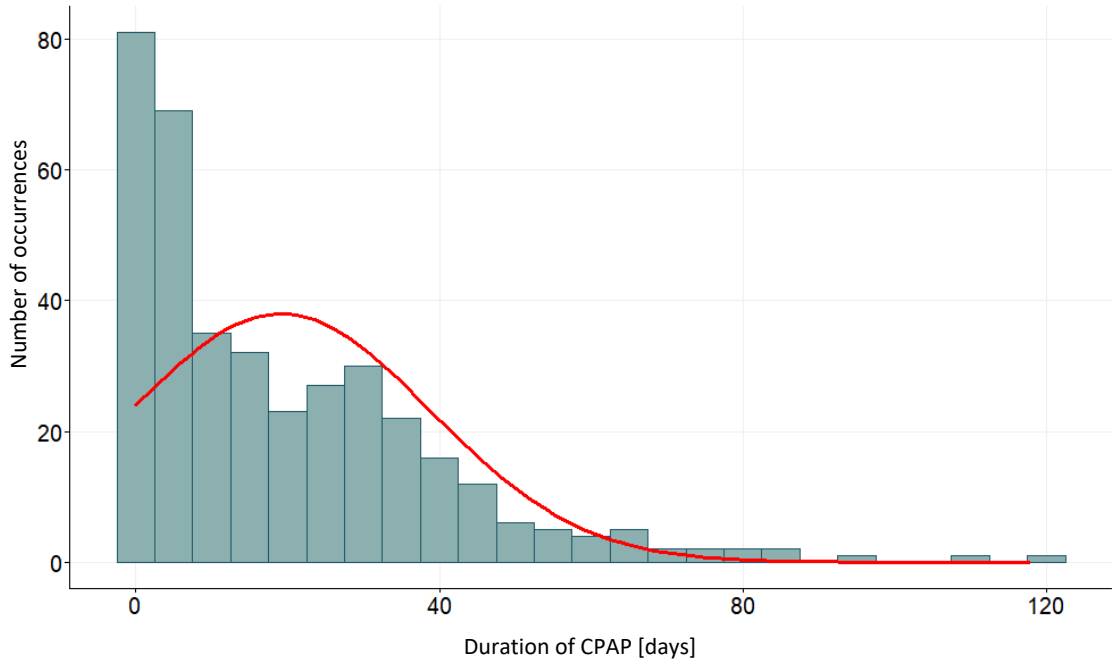
Variable	Parameter	Overall distribution	Distribution without missing data
Location of NCPAP initiation	NICU	19 (4.8%)	19 (4.8%)
	Delivery Room	375 (95.2%)	375 (95.2%)
	No data	0 (0%)	
Time to CPAP initiation in the Delivery Room [min]	Number of observations	374	
	Mean (standard deviation)	3.5 (3.1)	
	Median	2	
	IQR	1–5	
	Range	0–15	
	No data	1	
Time to CPAP initiation in the NICU [min]	Number of observations	19	
	Mean (standard deviation)	9.63 (3.42)	
	Median	10	
	IQR	7–12.5	
	Range	4–15	
	No data	0	
Type of CPAP device used in the Delivery Room	Bubble CPAP	7 (1.8%)	7 (1.9%)
	Constant flow CPAP (from the respirator)	54 (13.7%)	54 (14.4%)
	Variable flow CPAP, e.g. Infant Flow, MEDIN-CNO	314 (79.7%)	314 (83.7%)
	No data	19 (4.8%)	
Type of CPAP device used in the NICU	Bubble CPAP	5 (1.3%)	5 (1.3%)
	Constant flow CPAP (from the respirator)	76 (19.3%)	76 (19.5%)
	Variable flow CPAP, e.g. Infant Flow, MEDIN-CNO	309 (78.4%)	309 (79.2%)
	No data	4 (1%)	
Maintenance of CPAP during transfer to the NICU	Yes	368 (97.6%)	368 (98.1%)
	No	7 (1.9%)	7 (1.9%)
	No data	2 (0.5%)	
Nasal prongs	Yes	55 (14%)	55 (14%)
	No	339 (86%)	339 (86%)

Variable	Parameter	Overall distribution	Distribution without missing data
	No data	0 (0%)	

CPAP interface	Standard nasal prongs or mask	383 (97.2%)	383 (97.2%)
	RAM prongs	7 (1.8%)	7 (1.8%)
	Other	4 (1%)	4 (1%)
	No data	0 (0%)	
More than one CPAP cycle	Yes	198 (50.3%)	198 (50.5%)
	No	194 (49.2%)	194 (49.5%)
	No data	2 (0.5%)	
Duration of CPAP use [days]	Number of observations	378	
	Mean (standard deviation)	19.12 (19.85)	
	Median	12.91	
	IQR	3.38–29.49	
	Range	0–117.89	
	No data	16	

Histogram presenting duration of CPAP use is demonstrated below.

Figure 4. Distribution of CPAP duration



NIPPV

Nasal intermittent positive pressure ventilation (NIPPV) during hospitalisation was used in 143 neonates (36.3% overall) however, 67 (46,9%) of patients from this subgroup received more than one cycle. On average, NIPPV was used for 16.8 days (± 27.13) – in half of the patients, duration ranged between 1.9 to 21.2 days.

Table 7. NIPPV characteristics

Variable	Parameter	Overall distribution	Distribution without missing data
NIPPV	Yes	143 (36.3%)	143 (36.3%)
	No	251 (63.7%)	251 (63.7%)
	No data	0 (0%)	
More than one NIPPV cycle	Yes	67 (46.9%)	67 (46.9%)
	No	76 (53.1%)	76 (53.1%)
	No data	0 (0%)	
Duration of NIPPV use [days]	Number of observations	135	
	Mean (standard deviation)	16.84 (27.13)	
	Median	6.6	
	IQR	1.94–21.19	
	Range	0.01–216.42	
	No data	8	

Invasive respiratory support

Mechanical ventilation (MV) was used in two-thirds of intubated infants (67.8%; N=160); on average, MV was initiated in Day 5 after birth (mean 4.65 ± 9.66 days), while conventional mode was most often selected (82.5%; N=132). On average, MV was used for 10.87 days (± 17.66).

The mean maximal FiO_2 recorded during invasive ventilation was 0.56 (± 0.27); in half of the patients, this value ranged between 0.35 and 0.8.

In half of the patients, the highest mean airway pressure (MAP) was 8–14 cm H_2O, while the median was 10 cm H_2O.

Table 8. Characteristics of invasive respiratory support

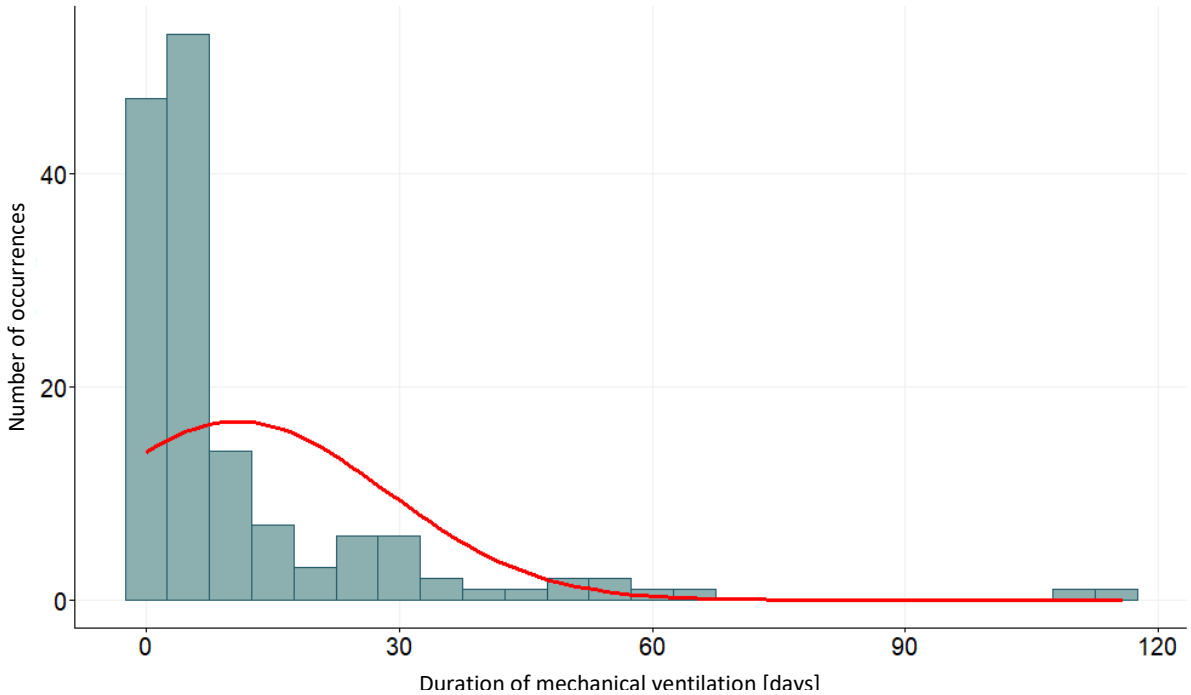
Variable	Parameter	Overall distribution	Distribution without missing data
Mechanical (invasive) ventilation	Yes	160 (40.6%)	160 (40.7%)
	No	233 (59.1%)	233 (59.3%)
	No data	1 (0.3%)	
Time from birth to mechanical ventilation [days]	Number of observations	156	
	Mean (standard deviation)	4.65 (9.66)	
	Median	1.02	
	IQR	0.08–4.39	
	Range	0.01–54.91	
	No data	4	
Ventilation mode	Conventional ventilation (IPPV)	132 (82.5%)	132 (83.5%)
	Oscillating ventilation (HFOV)	1 (0.6%)	1 (0.6%)
	IPPV + HFOV	25 (15.6%)	25 (15.8%)
	No data	2 (1.2%)	
Maximal FiO_2	Number of observations	160	
	Mean (standard deviation)	0.56 (0.27)	
	Median	0.5	
	IQR	0.35–0.8	
	Range	0.21–1	
	No data	0	
MAP [cm H_2O]	Number of observations	83	
	Mean (standard deviation)	13.37 (13)	
	Median	10	
	IQR	8–14	
	Range	7–93	
	No data	77	
PEEP use	Yes	160 (100%)	160 (100%)
	No data	0 (0%)	
Maximal PEEP [cm H_2O]	Number of observations	159	
	Mean (standard deviation)	5.61 (0.78)	
	Median	6	
	IQR	5–6	
	Range	4–9	

Variable	Parameter	Overall distribution	Distribution without missing data
	No data	1	
>1 cycle of invasive ventilation	Yes	36 (22.5%)	36 (23.1%)
	No	120 (75%)	120 (76.9%)
	No data	4 (2.5%)	

Duration of mechanical ventilation [days]	**Number of observations**	**148**	
	Mean (standard deviation)	10.87 (17.66)	
	Median	4.56	
	IQR	1.9–10.39	
	Range	0.01–115.79	
	No data	12	

Histogram demonstrating the distribution of time of invasive ventilation is presented below.

Figure 5. Distribution of duration of invasive ventilation



Typical complications of prematurity/ respiratory complications

Broncho-pulmonary dysplasia (BPD) was the most common complication with mild, moderate, and severe cases reported in 132 (33.5%), 38 (9.6%), and 8 (2%) infants, respectively. Retinopathy of prematurity (ROP) and intraventricular haemorrhage (IVH) were slightly less common, (34.5%; N=136) and (32.2%; N=127), respectively. Patent Ductus Arteriosus (PDA) was observed in 113 patients (28.7%), of which 59 (52,2) required medical treatment.

Table 9. Characteristics of complications

Variable	Parameter	Overall distribution	Distribution without missing data
Air-Leak Syndrome	Yes	17 (4.3%)	17 (4.3%)
	No	375 (95.2%)	375 (95.7%)
	No data	2 (0.5%)	
Air-Leak Syndrome – type	Pneumothorax	15 (88.2%)	15 (88.2%)
	Interstitial emphysema	2 (11.8%)	2 (11.8%)
	No data	0 (0%)	
Ventilation-associated pneumonia	Yes	43 (10.9%)	43 (11%)
	No	349 (88.6%)	349 (89%)
	No data	2 (0.5%)	
Broncho-pulmonary dysplasia płucna	No	207 (52.5%)	207 (53.8%)
	Mild	132 (33.5%)	132 (34.3%)
	Moderate	38 (9.6%)	38 (9.9%)
	Severe	8 (2%)	8 (2.1%)
	No data	9 (2.3%)	
Periventricular leukomalacia	Yes	25 (6.3%)	25 (6.4%)
	No	368 (93.4%)	368 (93.6%)
	No data	1 (0.3%)	
Periventricular leukomalacia – grade	No data on grade	2 (8%)	2 (8%)
	Grade I (noncystic leukomalacia, diffuse lesions in the middle area of the white matter which disturb its development)	4 (16%)	4 (16%)
	Grade II (small localised cystic lesions)	9 (36%)	9 (36%)
	Grade III (diffuse cystic lesions)	8 (32%)	8 (32%)
	Grade IV (extensive damage in the subcortical region)	2 (8%)	2 (8%)
	No data	0 (0%)	
Intraventricular haemorrhage	Yes	127 (32.2%)	127 (32.3%)
	No	266 (67.5%)	266 (67.7%)
	No data	1 (0.3%)	
Intraventricular haemorrhage – grade	Grade I (bleeding in the germinal matrix)	36 (28.3%)	36 (28.6%)
	Grade II (intraventricular bleeding occupies up to 50% of ventricular lumen volume)	56 (44.1%)	56 (44.4%)
	Grade III (intraventricular bleeding occupies >50% of the lumen of the lateral ventricular volume. It frequently enlarges the ventricle)	20 (15.7%)	20 (15.9%)

	Grade IV (haemorrhagic periventricular infarction [bleeding to the periventricular parenchyma])	14 (11%)	14 (11.1%)
	No data	1 (0.8%)	
Retinopathy of prematurity	Yes	136 (34.5%)	136 (35.1%)
	No	252 (64%)	252 (64.9%)
	No data	6 (1.5%)	
Retinopathy of prematurity – photocoagulation	Not requiring treatment	93 (68.4%)	93 (68.9%)
	Requiring treatment	42 (30.9%)	42 (31.1%)
	No data	1 (0.7%)	
Patent Ductus Arteriosus	Yes	113 (28.7%)	113 (28.8%)
	No	279 (70.8%)	279 (71.2%)
	No data	2 (0.5%)	
Patent Ductus Arteriosus – method of treatment	Need for surgical ligation	5 (4.4%)	5 (4.5%)
	Need for medical treatment	59 (52.2%)	59 (52.7%)
	Not requiring treatment	48 (42.5%)	48 (42.9%)
	No data	1 (0.9%)	
Necrotizing Enterocolitis	Yes	33 (8.4%)	33 (8.4%)
	No	359 (91.1%)	359 (91.6%)
	No data	2 (0.5%)	
Necrotizing Enterocolitis – grade	Grade I	14 (42.4%)	14 (42.4%)
	Grade IIA	7 (21.2%)	7 (21.2%)
	Grade IIB	3 (9.1%)	3 (9.1%)
	Grade IIIA	3 (9.1%)	3 (9.1%)
	Grade IIIB	6 (18.2%)	6 (18.2%)
	No data	0 (0%)	

Primary endpoints

NCPAP failures

The effect of NCPAP treatment was assessed in 389 infants. The analysis excluded data from 5 neonates, which were transferred to other unit/hospital in the first day of life or were lost to follow-up (N=4); or did not provide sufficient data (N=1).

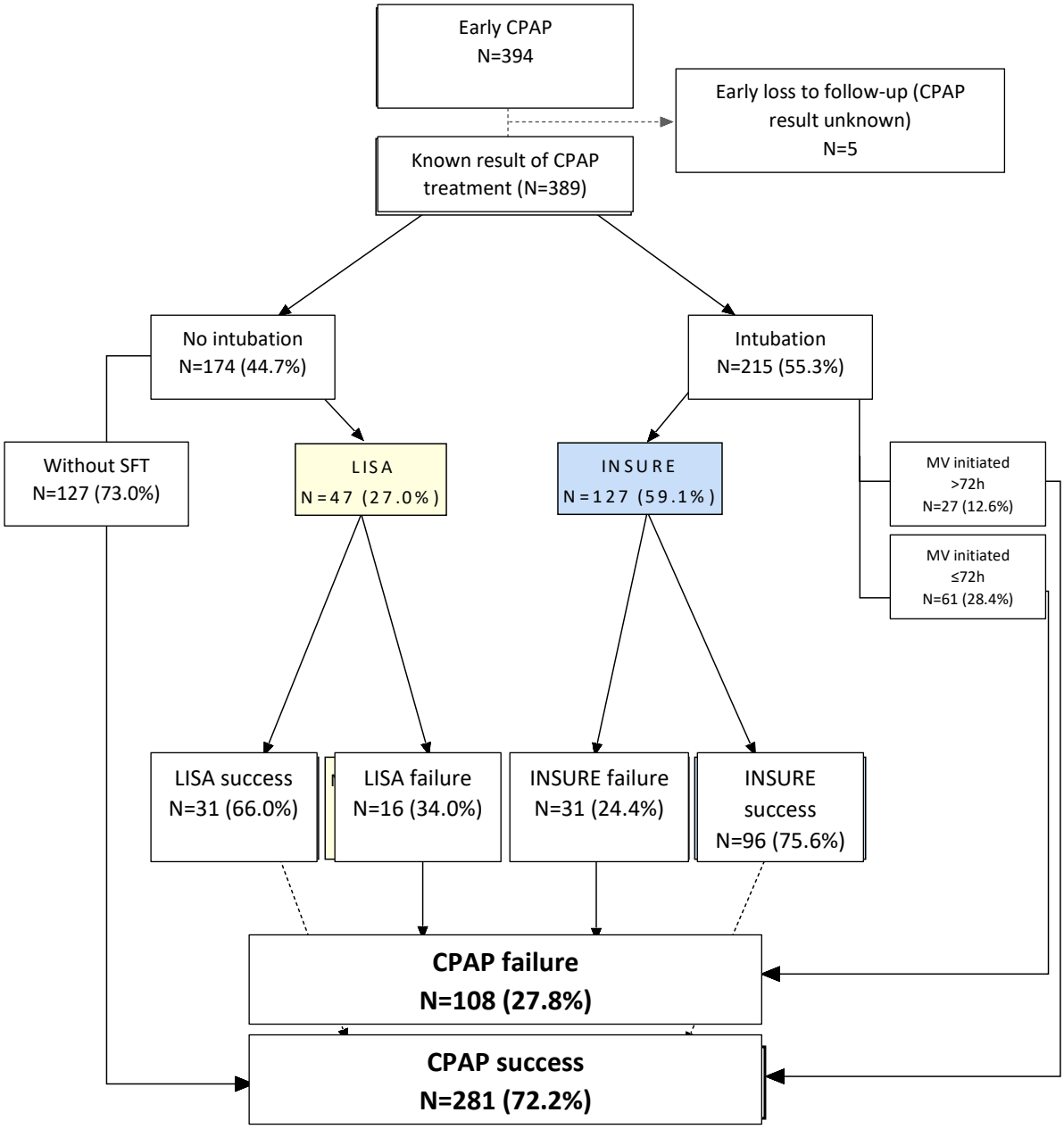
Early respiratory support with NCPAP was considered effective in 281 infants (72.7%), while failure was observed in 108 neonates (27.8%).

The proportion of infants with CPAP success was increasing along with a week of gestation, except the two youngest and smallest groups. In two neonates <23 weeks gestation CPAP was effective, while in two other infants <24 weeks gestation a CPAP failure was observed. In the group of the oldest infants (>27 weeks gestation), the rate of CPAP success was more than 70%.

Table 10. Proportion of neonates requiring invasive ventilation in the first 72 hours of life (CPAP failure) depending on week of gestation

Week of gestation	N=	CPAP failure N (%)	CPAP success N (%)
23–24	4	2 (50%)	2 (50%)
25	11	5 (45.5%)	6 (54.5%)
26	34	13 (38.2%)	21 (61.8%)
27	87	25 (28.7%)	62 (71.3%)
28	99	28 (28.3%)	71 (71.7%)
29	154	35 (22.7%)	119 (77.3%)

Figure 6. Diagram of study patient flow.



Definitions:

LISA success/INSURE success – patients receiving SFT with LISA or INSURE method without the need for invasive ventilation within 72 hours after birth

LISA failure/INSURE failure – patients receiving SFT with LISA or INSURE method with the need for invasive ventilation within 72 hours after birth

Impact of FiO_2 at the moment of SFT administration on complications

FiO_2 level at the moment of surfactant (SFT) administration as a continuous variable had a significant impact ($p<0.05$) on Air-Leak Syndrome. Each increase of FiO_2 level by 0.01 resulted in the increase of chances for the occurrence of Air-Leak Syndrome by 2.47%. (OR: 1.0247; 95% CI: 1.0017–1.0483). This

variable did not significantly impact other complications, BPF, IVH or death considered with the use of logistic regression.

Table 11. Odds ratio for the occurrence of specific conditions depending on FiO_2 level (treated as a continuous variable)

Dependent variable	OR	95% confidence interval	P value
Composite endpoint[1]	1.0026	0.986–1.021	0.7694
BPD	1.0047	0.9896–1.0205	0.5429
Air-Leak Syndrome	1.0247	1.0017–1.0483	0.0353
IVH	1.0007	0.985–1.0163	0.9246
Death	1.0009	0.9736–1.024	0.9445

The fi_{o2} level at the moment of SFT administration was used as a categorical variable in a logistic regression model – the following strata were determined: <0.35, 0.35–0.44, 0.45–0.54, 0.55–0.64, and >0.65. Such FiO_2 level at the moment of SFT administration did not impact specific complications. The table below contains the odds ratio (OR) values presented about the reference group of patients with the FiO_2 level at the moment of SFT administration below 0.35.

Table 12. Odds ratio for the occurrence of specific conditions depending on FiO_2 level (treated as a categorical variable)

Dependent variable	FiO_2 level before SFT administration	OR	95% confidence interval	P value
Composite endpoint	0.35–0.44	1.0235	0.4558–2.2337	0.954
	0.45–0.54	0.7854	0.3304–1.8359	0.5785
	0.55–0.64	0.6023	0.1962–1.9143	0.3776
	≥0.65	1.1946	0.3811–4.2059	0.7678
BPD	0.35–0.44	0.5578	0.2737–1.1189	0.103
	0.45–0.54	0.6429	0.2938–1.3895	0.2634
	0.55–0.64	0.7407	0.2538–2.1726	0.5802
	≥0,65	0.963	0.3482–2.7302	0.9422
Air-Leak Syndrome	0.35–0.44	1.4118	0.2920–10.1194	0.687
	0.45–0.54	2.449	0.5012–17.6785	0.2981
	0.55–0.64	1.3333	0.0598–14.759	0.8187
	≥0,65	5.3333	0.9567–40.935	0.0655
IVH	0.35–0.44	1.1471	0.5698–2.3353	0.702
	0.45–0.54	0.6711	0.2976–1.4974	0.3311
	0.55–0.64	1.35	0.4603–3.9408	0.5802
	≥0,65	0.8571	0.2945–2.3884	0.7707
Death	0.35–0.44	1.6013	0.5142–6.0407	0.4422
	0.45–0.54	1.15	0.2875–4.8925	0.842
	0.55–0.64	0.6389	0.0315–4.692	0.6974
	≥0,65	1.8158	0.3317–9.0112	0.462

The relation between the required respiratory support and FiO_2 level at the moment of surfactant administration (treated as a categorical variable) was also assessed. On average, the longest duration of mechanical ventilation (MV) was observed in infants with FiO_2 level ranging from 0.55 to 0.64

[1] Composite variable involving the occurrence of any of the following: BPD, Air-Leak Syndrome, IVH or death.

(median of 7.67 days); while the shortest duration of MV was noted in infants with FiO_2 of 0.45–0.54 (median of 2.86 days). On average, the maximal FiO_2 level during ventilation ranged from 0.31 (group median <0.35) to 0.95 (group median ≥0.65). On average, the Mean Airway Pressure (MAP) was almost equal in all subgroup (median ranged from 9.5 to 10.5) except for infants with FiO_2 level at the moment of surfactant (SFT) administration amounting to at least 0.65 – median was 15. In turn, the median of positive end-expiratory pressure (PEEP) was 5 (in <0.35 and 0.55–0.64 groups) or 6 (in other subgroups).

Table 13. Range of required respiratory support depending on the FiO_2 level at the moment of surfactant administration

	Parameter	**<0.35**	**0.35–0.44**	**0.45–0.54**	**0.55–0.64**	**≥0.65**
Duration of mechanical ventilation [days]	Number of observations	26	37	31	11	19
	Mean (standard deviation)	10.57 (21.63)	11.77 (15.69)	5.93 (10.73)	14.84 (16.05)	11.02 (11.95)
	Median	3.65	5.47	2.86	7.67	5.37
	IQR	2.07–9.61	2.65–12.94	0.81–5.52	2.58–25.16	2.8–21.53
	Range	0.01–109.51	0.04–63.01	0.02–55.83	0.27–49.94	0.28–33.86
	No data	1	5	3	0	0
Maximal FiO_2 during ventilation	Number of observations	27	42	34	11	19
	Mean (standard deviation)	0.44 (0.25)	0.63 (0.27)	0.52 (0.22)	0.62 (0.18)	0.82 (0.22)
	Median	0.31	0.5	0.5	0.6	0.95
	IQR	0.3–0.5	0.4–1	0.4–0.6	0.52–0.7	0.75–1
	Range	0.21–1	0.25–1	0.21–1	0.3–1	0.4–1
	No data	0	0	0	0	0
Mean Airway Pressure (MAP) [cm H_2O]	Number of observations	11	24	17	8	9
	Mean (standard deviation)	11.45 (3.72)	11.96 (6.06)	15.76 (20.15)	20.25 (27.89)	14.67 (4.03)
	Median	10	9.5	10	10.5	15
	IQR	9.5–12.5	8–12.75	9–12	8.75–12.75	12–17
	Range	8–20	7–28	7–93	8–89	9–20
	No data	16	18	17	3	10
Positive end-expiratory pressure [cm H_2O]	Number of observations	27	42	33	11	19
	Mean (standard deviation)	5.41 (0.75)	5.57 (0.77)	5.61 (0.61)	5.45 (0.82)	5.95 (0.85)
	Median	5	6	6	5	6
	IQR	5–6	5–6	5–6	5–6	5–6
	Range	4–7	4–7	5–7	4–7	5–8
	No data	0	0	1	0	0

Predictive factors for NCPAP failure

Univariate model

In the analysed univariate regression models explaining NCPAP failure, the following factors were significant: gestational age ($p<0.05$), birth weight ($p<0.001$), FiO_2 level in the first hour of life ($p<0.001$), FiO_2 in the second hour of life ($p<0.001$), and the highest FiO2 level within first 2h of life ($p<0.001$). An increase in birth weight and a later week of gestation reduced the risk for NCPAP failure; however, higher FiO_2 levels, both in the first and second hour of life, increased the chance for NCPAP failure.

Table 14. Impact of selected factors on NCPAP failure[2]

Factor	OR	95% confidence interval	P value
Male	1.0527	0.6749–1.6429	0.8208
Gestational age	0.8099	0.6767–0.9684	0.0206
Birth weight (100g)	0.8351	0.7631–0.9048	0
Multiple pregnancy	1.0092	0.5835–1.7047	0.9731
Mode of delivery – vaginal	0.6171	0.3093–1.1557	0.1481
CPAP in the Delivery Room	1.8352	0.5845–8.0776	0.3477
FiO_2 – first hour of life	1.0422	1.0231–1.0635	0
FiO_2 – second hour of life	1.0751	1.0495–1.1034	0
Highest FiO_2 in the first 2h of life	1.0006	1.0004–1.0008	0
CPAP initial level	1.0188	0.7255–1.4044	0.9112

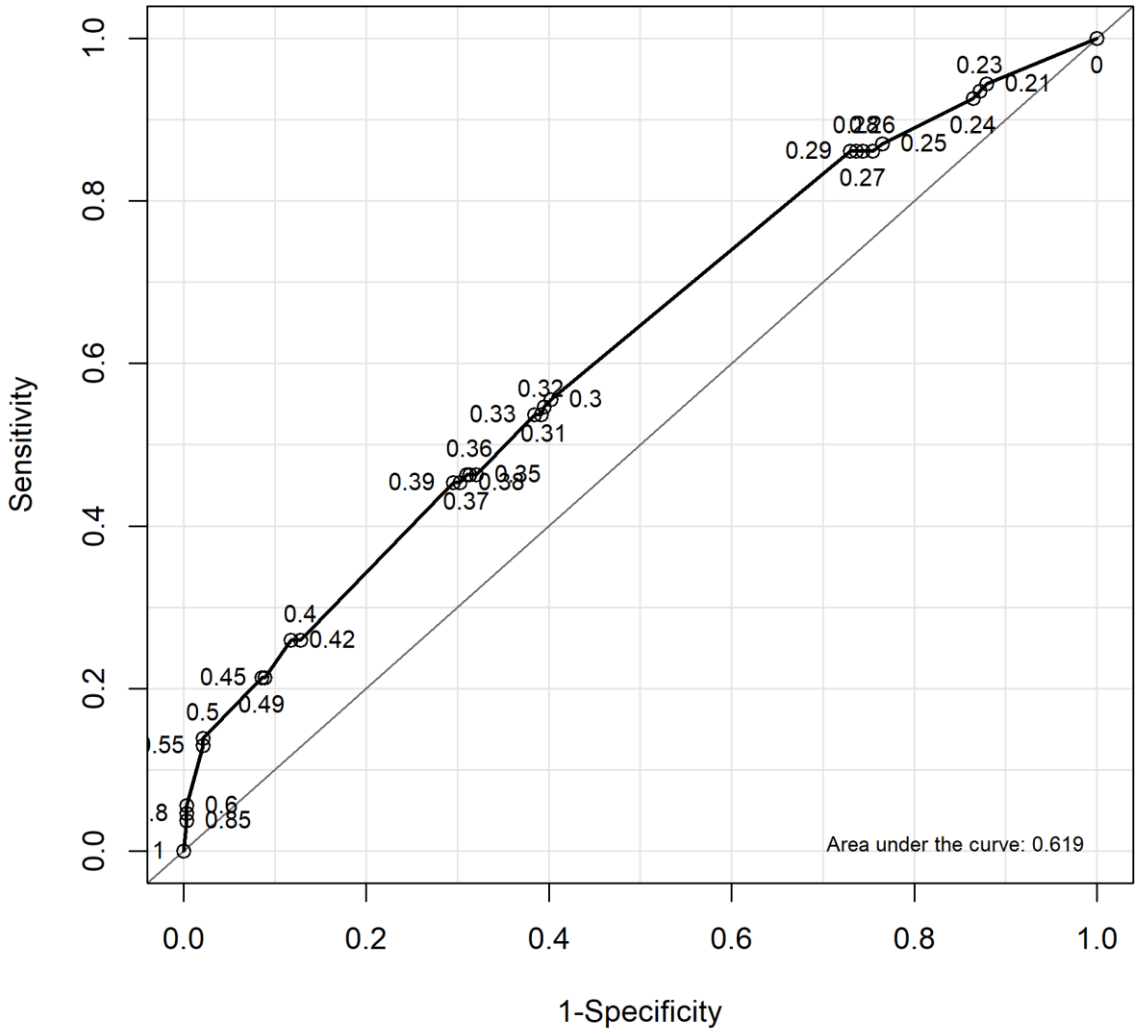
FiO_2 as a predictive factor for NCPAP failure

The quality of univariate models determining the predictive value of FiO_2 in the first two hours of life was analysed with the use of receiver operating characteristic (ROC) curves. The position of points on diagram depends on the proportion of false-positive results (1-Specificity) on the X-axis, and the proportion of true positive results (Sensitivity) on the Y axis for selected FiO_2 levels.

For FiO_2 level registered in the first hour of life, the predictive value for NCPAP failure occurrence is relatively small, which is confirmed by area under the curve (AUC) value amounting to 0.619 (where 0.5 indicates no predictive value, and 1 – perfect predictive value) with 95% confidence interval (CI) calculated with the the use of DeLong method ranging between 0.557 and 0.681. The cut-off point value is indicating maximal sensitivity and specificity amount to 0.39; however, it should be noted that for the range of 0.3–0.39 sensitivity and specificity are very similar.

[2] Odds ratios (OR) for continuous variables refer to a change by one unit – i.e. one week for gestational age, 100g for birth weight, and 0.01 for the FiO_2 level. The unit of initial CPAP pressure is 1 cm H_2O.

Figure 7. FiO_2 in the first hour of life as a predictive variable for the occurrence of NCPAP failure



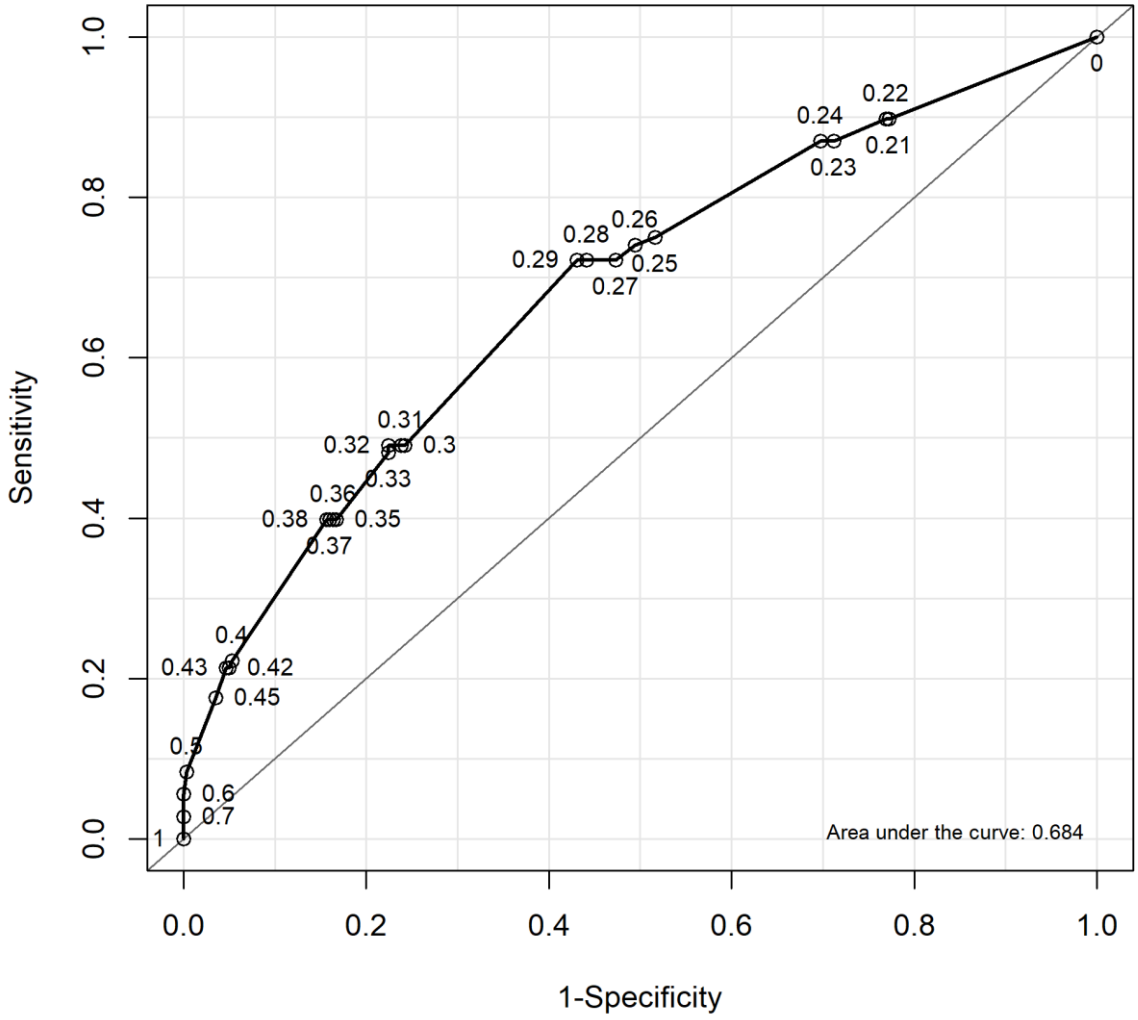
Data presented on the ROC curve are summarised in the table below. The positive predictive value refers to the ratio of true positive results to all positive results; while the negative predictive value refers to the ratio of true negative results to all negative results. The optimal cut-off point is marked with colour.

Table 15. ROC curve parameters for FiO_2 level recorded in the first hour of life

FiO_2 levels [first hour of life]	Sensitivity	Specificity	Positive predictive value	Negative predictive value
0.00	1.00	0.00	0.28	NA
0.21	0.94	0.12	0.29	0.85
0.23	0.94	0.13	0.29	0.84
0.24	0.93	0.14	0.29	0.83
0.25	0.87	0.23	0.30	0.83
0.26	0.86	0.25	0.30	0.82
0.27	0.86	0.26	0.31	0.83
0.28	0.86	0.26	0.31	0.83
0.29	0.86	0.27	0.31	0.84
0.30	0.56	0.60	0.35	0.78
0.31	0.55	0.60	0.35	0.78
0.32	0.54	0.61	0.35	0.77
0.33	0.54	0.62	0.35	0.78
0.35	0.46	0.68	0.36	0.77
0.36	0.46	0.69	0.36	0.77
0.37	0.46	0.69	0.36	0.77
0.38	0.45	0.70	0.37	0.77
0.39	**0.45**	**0.70**	**0.37**	**0.77**
0.40	0.26	0.87	0.44	0.75
0.42	0.26	0.88	0.46	0.76
0.45	0.21	0.91	0.48	0.75
0.49	0.21	0.91	0.49	0.75
0.50	0.14	0.98	0.71	0.75
0.55	0.13	0.98	0.70	0.75
0.60	0.06	1.00	0.86	0.73
0.80	0.05	1.00	0.83	0.73
0.85	0.04	1.00	0.80	0.73
1.00	0.00	1.00	NA	0.72

ROC curve analysis of the model determining the predictive value for the occurrence of NCPAP failure with the use of FiO_2 level in the second hour of life revealed that this parameter is a better predictor compared to the FiO_2 level in the first hour of life. The area under the curve is 0.684 (DeLong's 95% confidence interval: 0.624–0.744), and the cut-off point amounts to 0.29.

Figure 8. FiO_2 in the second hour of life as a predictive variable for the occurrence of NCPAP failure



Data presented on the ROC curve are summarised in the table below.

Table 16. ROC curve parameters for FiO_2 level recorded in the second hour of life

FiO_2 levels [first hour of life]	Sensitivity	Specificity	Positive predictive value	Negative predictive value
0	1.00	0.00	0.28	NA
0.21	0.90	0.23	0.31	0.85
0.22	0.90	0.23	0.31	0.86
0.23	0.87	0.29	0.32	0.85
0.24	0.87	0.30	0.32	0.86
0.25	0.75	0.48	0.36	0.83
0.26	0.74	0.51	0.37	0.84
0.27	0.72	0.53	0.37	0.83
0.28	0.72	0.56	0.39	0.84
0.29	**0.72**	**0.57**	**0.39**	**0.84**
0.3	0.49	0.76	0.44	0.79
0.31	0.49	0.76	0.44	0.80
0.32	0.49	0.78	0.46	0.80
0.33	0.48	0.78	0.45	0.80
0.35	0.40	0.83	0.48	0.78
0.36	0.40	0.84	0.48	0.78
0.37	0.40	0.84	0.49	0.78
0.38	0.40	0.84	0.49	0.78
0.4	0.22	0.95	0.62	0.76
0.42	0.21	0.95	0.62	0.76
0.43	0.21	0.95	0.64	0.76
0.45	0.18	0.96	0.66	0.75
0.5	0.08	1.00	0.90	0.74
0.6	0.06	1.00	1.00	0.73
0.7	0.03	1.00	1.00	0.73
1	0.00	1.00	NA	0.72

We also performed a ROC analysis considering the highest FiO_2 level recorded in the first 2h of life as a predictive factor for the occurrence of NCPAP failure. A similar predictive value characterises the obtained model compared to a model based on the FiO_2 level in the second hour of life (AUC amounts to 0.685 with DeLong's 95% confidence interval of 0.626–0.744). The cut-off point (indicating the highest sensitivity and specificity) amounts to 0.32.

Figure 9. Maximal FiO_2 level in the first two hours of life as a predictive variable for the occurrence of NCPAP failure

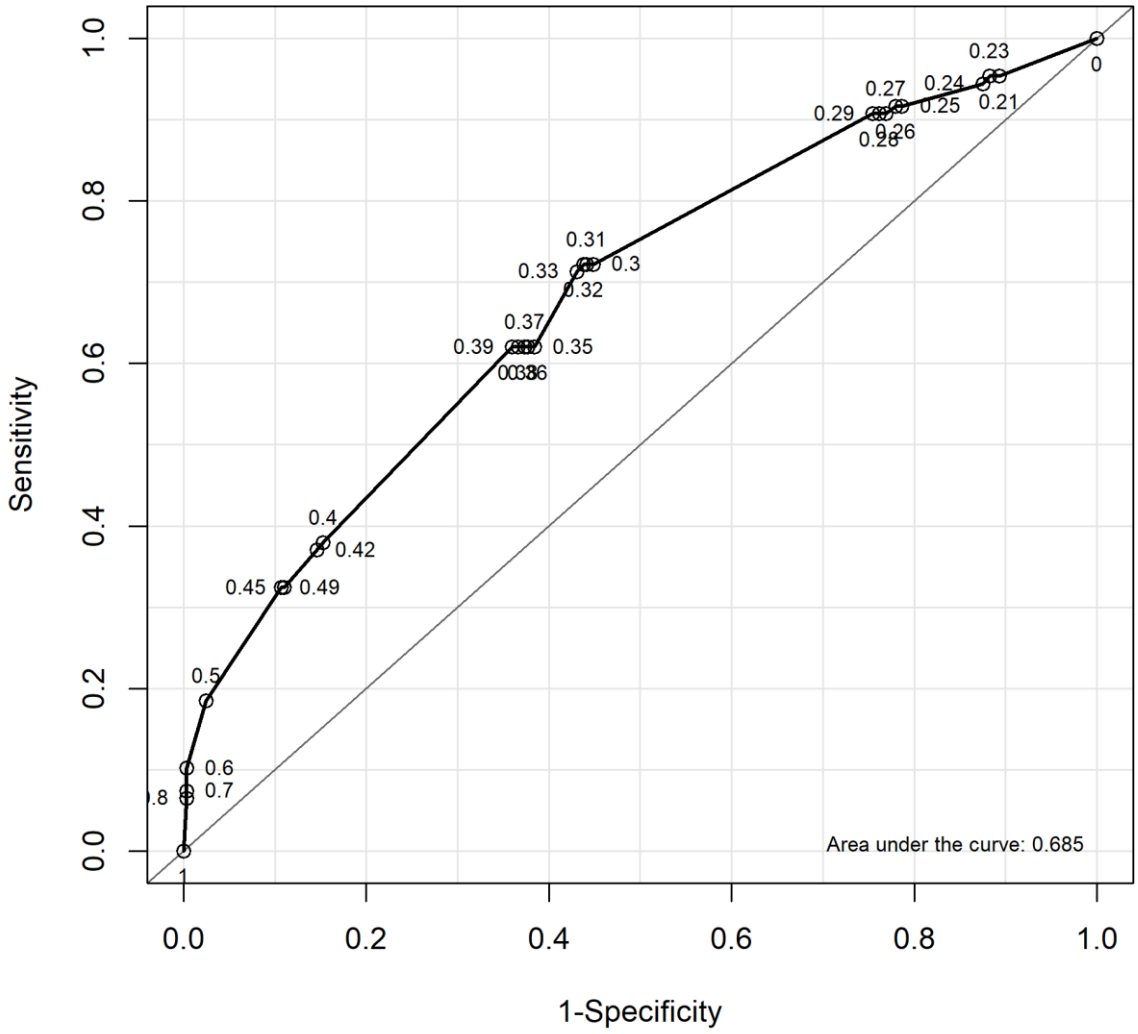


Table 17. ROC curve parameters for the maximal FiO_2 level recorded in the first two hours of life

FiO_2 levels [first hour of life]	Sensitivity	Specificity	Positive predictive value	Negative predictive value
0	1.00	0.00	0.28	NA
0.21	0.95	0.11	0.29	0.86
0.23	0.95	0.12	0.29	0.87
0.24	0.94	0.12	0.29	0.85
0.25	0.92	0.21	0.31	0.87
0.26	0.92	0.22	0.31	0.87
0.27	0.91	0.23	0.31	0.87
0.28	0.91	0.24	0.31	0.87
0.29	0.91	0.25	0.32	0.87
0.3	0.72	0.55	0.38	0.84
0.31	0.72	0.56	0.39	0.84
0.32	**0.72**	**0.56**	**0.39**	**0.84**
0.33	0.71	0.57	0.39	0.84
0.35	0.62	0.62	0.38	0.81
0.36	0.62	0.62	0.39	0.81
0.37	0.62	0.63	0.39	0.81
0.38	0.62	0.63	0.39	0.81
0.39	0.62	0.64	0.40	0.81
0.4	0.38	0.85	0.49	0.78
0.42	0.37	0.85	0.49	0.78
0.45	0.32	0.89	0.53	0.77
0.49	0.32	0.89	0.54	0.77
0.5	0.19	0.98	0.74	0.76
0.6	0.10	1.00	0.92	0.74
0.7	0.07	1.00	0.89	0.74
0.8	0.06	1.00	0.88	0.73
1	0.00	1.00	NA	0.72

Multivariate analysis

The next stage of the analysis comprised a multivariate model considering all potential variables explaining NCPAP failure. The baseline form of the model is presented in the table below.

Table 18. Impact of selected factors on NCPAP failure – multivariate model (baseline)

Factor	OR	95% confidence interval	P value
Intercept	0.2279	0.0003–166.2474	0.6623
male	1.0046	0.6077–1.6599	0.9856
gestational age [week]	0.992	0.7842–1.2578	0.9466
birth weight (100g)	0.852	0.7555–0.9512	0.0049
multiple pregnancy	0.9756	0.5252–1.773	0.9363
mode of delivery – vaginal	0.8317	0.3798–1.7348	0.6323
CPAP in the Delivery Room	1.1535	0.3326–5.3692	0.8352
FiO_2 – first hour of life	1.0191	0.9984–1.0411	0.0722
FiO_2 – second hour of life	1.0621	1.0352–1.0919	0
Initial CPAP level	0.9694	0.6688–1.3756	0.8648

The final model was obtained with the use of a stepwise backward selection method. In such a form, factors predicting NCPAP failure remained as follows: birth weight ($p<0.001$), FiO_2 level in the first hour of life (insignificant), and FiO_2 level in the second hour of life ($p<0.001$). An increase in birth weight reduced the chance for the occurrence of NCPAP failure; while the increase of FiO_2 level in the second hour of life increased the chance for the occurrence of NCPAP failure.

Table 19. Impact of selected factors on NCPAP failure – multivariate model (final)

Factor	OR	95% confidence interval	P value
Intercept	0.1801	0.0422–0.7281	0.0181
birth weight (100g)	0.8435	0.7708–0.9231	0.0004
FiO_2 – first hour of life	1.0196	0.9992–1.0412	0.061
FiO_2 – second hour of life	1.0618	1.0351–1.0915	0

Other characteristics

Treatment with surfactant and caffeine citrate

The surfactant was administered to 237 infants (60.2%); in almost all cases, neonates received poractant alpha (99.2%; N=235). On average, surfactant (SFT) was administered after 1.5h (median), while in more than a half of neonates (N=137; 57.8%), SFT was administered from 15 minutes to 2 hours after birth. In half of the cases, FiO_2 level measured before SFT administration ranged between 0.35 and 0.5, while the mean value was 0.45 (± 0.17) – 97 (40.9%) neonates received surfactant when the FiO_2 level was at least 0.45

More than a half of patients received surfactant with the use of INSURE method 53.6%; N=127). Mean dose of poractant alpha amounted to 177.64 mg/kg of body weight (BW) (±41.9); half of the neonates received a dose ranging from 158.42 to 200 mg/kg of BW. Only 15 (6.4%) patients received a dose of poractant alpha below 100 mg/kg of BW. In the majority of cases, surfactant was administered in the NICU (95.8%; N=227).

Table 20. Characteristics of treatment with surfactant

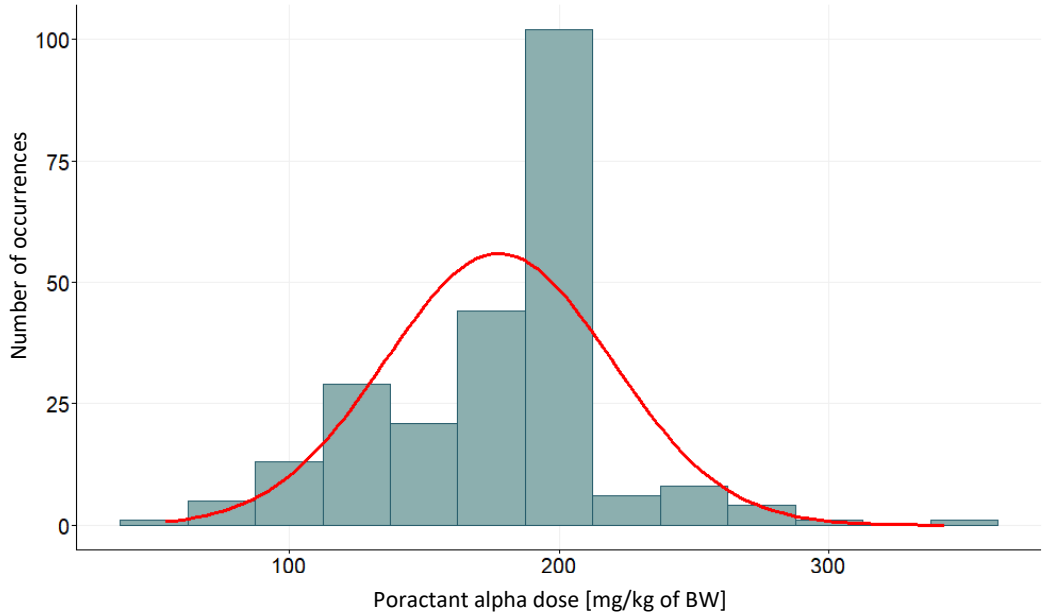
Variable	Parameter	Overall distribution	Distribution without missing data
Surfactant administration	Yes	237 (60.2%)	237 (60.2%)
	No	157 (39.8%)	157 (39.8%)
	No data	0 (0%)	
Type of surfactant	Beractant	2 (0.8%)	2 (0.8%)
	Poractant alpha	235 (99.2%)	235 (99.2%)
	No data	0 (0%)	
FiO_2 before surfactant administration	Number of observations	237	
	Mean (standard deviation)	0.45 (0.17)	
	Median	0.4	
	IQR	0.35–0.5	
	Range	0.21–1	
	No data	0	
SpO_2 before surfactant administration [%]	Number of observations	237	
	Mean (standard deviation)	86.28 (13.2)	
	Median	90	
	IQR	87–92	
	Range	23–98	
	No data	0	
Surfactant dose – poractant alpha [mg/kg]	Number of observations	235	
	Mean (standard deviation)	177.64 (41.9)	
	Median	190.48	
	IQR	158.42–200	
	Range	54.55–342.86	
	No data	1	
Surfactant dose – beractant [mg/kg]	Number of observations	2	
	Mean (standard deviation)	81.71 (27.17)	

Variable	Parameter	Overall distribution	Distribution without missing data
	Median	81.71	
	IQR	72.1–91.31	
	Range	62.5–100.92	
	No data	0	
Time of surfactant administration after birth [hours]	Number of observations	237	
	Mean (standard deviation)	6.76 (22.5)	
	Median	1.5	
	IQR	0.75–3.57	
	Range	0.05–300.38	
	No data	1	
Surfactant administration >24h after birth	Yes	15 (6.3%)	15 (6.3%)
	No	222 (93.3%)	222 (93.7%)
	No data	1 (0.4%)	
Surfactant administration >24h after birth – indication	Treatment of RDS	9 (60%)	9 (60%)
	Other indication	6 (40%)	6 (40%)
	No data	0 (0%)	
Number of surfactant doses	1	197 (82.8%)	197 (83.1%)
	2	32 (13.4%)	32 (13.5%)
	3	7 (2.9%)	7 (3%)
	5	1 (0.4%)	1 (0.4%)
	No data	1 (0.4%)	
Method of surfactant administration	INSURE (intubation + SF administration + extubation up to 1 hour)	127 (53.6%)	127 (53.8%)
	Intubation + SF administration + mechanical ventilation	62 (26.2%)	62 (26.3%)
	Administration with LISA/MIST method	47 (19.8%)	47 (19.9%)
	No data	1 (0.4%)	
Extubation time after surfactant administration (INSURE) [min]	Number of observations	122	
	Mean (standard deviation)	8.43 (11.76)	
	Median	5	
	IQR	2–10	
	Range	1–60	
	No data	5	
Re-intubation within 24h (INSURE)	Yes	11 (8.7%)	11 (8.7%)
	No	115 (90.6%)	115 (91.3%)
	No data	1 (0.8%)	
Re-intubation within 72h (INSURE)	Yes	17 (13.4%)	17 (13.5%)
	No	109 (85.8%)	109 (86.5%)
	No data	1 (0.8%)	

Variable	Parameter	Overall distribution	Distribution without missing data
Site of surfactant administration	NICU	227 (95.8%)	227 (95.8%)
	Delivery Room	10 (4.2%)	10 (4.2%)
	No data	0 (0%)	

Histogram demonstrating the distribution of doses of poractant alpha is presented below.

Figure 10. Distribution of poractant alpha dose



Caffeine citrate was used in almost all neonates (99.0%; N=390); 95.9% (N=374) received this treatment in the first day of life – in the majority of infants (64.4%), caffeine was administered in the first two hours after birth. In most cases, caffeine was administered with the use of combined intravenous and oral route (78.2%; N=305). Mean duration of treatment with caffeine was 39.19 days (±20.64); in half of the cases, treatment duration ranged from 26 to 52 days.

Table 21. Characteristics of treatment with caffeine citrate

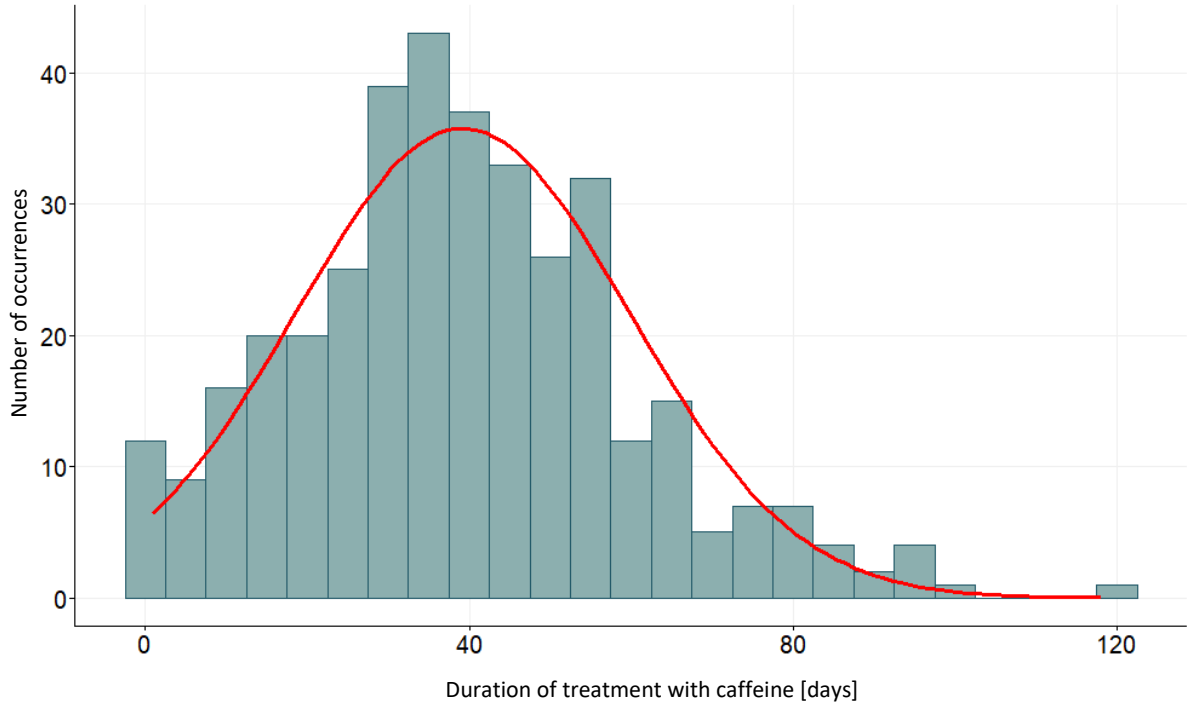
Variable	Parameter	Overall distribution	Distribution without missing data
Caffeine use	Yes	390 (99%)	390 (99%)
	No	4 (1%)	4 (1%)
	No data	0 (0%)	
Day of caffeine administration	First day of life	374 (95.9%)	374 (97.1%)
	Second day of life	4 (1%)	4 (1%)
	Third day of life	3 (0.8%)	3 (0.8%)
	Subsequent (>3) day of life	4 (1%)	4 (1%)
	No data	5 (1.3%)	
Route of caffeine administration	Intravenous and oral	305 (78.2%)	305 (78.2%)
	Oral only	3 (0.8%)	3 (0.8%)
	Intravenous only	82 (21%)	82 (21%)

Variable	Parameter	Overall distribution	Distribution without missing data
	No data	0 (0%)	
Time to caffeine administration [days]	Number of observations	385	
	Mean (standard deviation)	0.26 (1.72)	
	Median	0.06	
	IQR	0.03–0.11	
	Range	0–31.03	
	No data	5	

Duration caffeine treatment [days]	**Number of observations**	**370**	
	Mean (standard deviation)	39.19 (20.64)	
	Median	38	
	IQR	26–52	
	Range	1–118	
	No data	20	

Histogram demonstrating the distribution of duration of treatment with caffeine citrate is presented below.

Figure 11. Distribution of treatment with caffeine



CPAP results and complications rate

Relations between NCPAP success and treatment complications were assessed. Infants with NCPAP failure were more often discharged to their place of residence (89% vs. 66.7%; p<0.001). Infants with NCPAP failure more often experienced Air-Leak Syndrome (13.9% vs. 0.7%; p<0,001; OR 22.4; 95% confidence interval (CI): 5.0–99.9), ventilation-associated pneumonia (20.4% vs. 7.5%; p<0.001; OR 3.2; 95% CI: 1.65–6.0), moderate (16.7% vs. 7.5%) or severe (3.9% vs. 1.4%) broncho-pulmonary dysplasia (BPD) (p<0.05), intraventricular haemorrhages (47.2% vs. 26.7%; p<0.001; 2.5; 95% CI: 1.6–3.9), Patent Ductus Arteriosus (42.6% vs. 23.8%; p<0.001; OR 2.4; 95% CI: 1.5–3.8), and necrotizing enterocolitis (14.8% vs. 6%; p<0.05; OR 2.7; 95% CI: 1.3–5.6). For intraventricular haemorrhages, neonates with NCPAP failure more often experienced higher grades of disease (p<0.01).

Table 22. CPAP results and clinical outcome

Variable	Parameter	NCPAP failure (N=108)	NCPAP success (N=281)	Statistical test	P value
Termination of hospitalisation	Transfer to another hospital/unit	12 (11.1%)	28 (10%)	Fisher	0
	Hospital discharge	72 (66.7%)	250 (89%)		
	Death	24 (22.2%)	3 (1.1%)		
Air-Leak Syndrome	Yes	15 (13.9%)	2 (0.7%)	Fisher	0
	No	93 (86.1%)	278 (99.3%)		
Ventilation-associated pneumonia	Yes	22 (20.4%)	21 (7.5%)	Chi-square	0.0006
	No	86 (79.6%)	259 (92.5%)		
BPD	No	45 (44.1%)	158 (56.6%)	Fisher	0.013
	Mild	36 (35.3%)	96 (34.4%)		
	Moderate	17 (16.7%)	21 (7.5%)		
	Severe	4 (3.9%)	4 (1.4%)		
PVL	Yes	10 (9.3%)	15 (5.3%)	Chi-square	0.2374
	No	98 (90.7%)	266 (94.7%)		
PVL grade	No data on grade	1 (10%)	1 (6.7%)	Fisher	0.3699
	Grade I (noncystic leukomalacia, diffuse lesions in the middle area of the white matter which disturb its development)	2 (20%)	2 (13.3%)		
	Grade II (small localised cystic lesions)	2 (20%)	7 (46.7%)		
	Grade III (diffuse cystic lesions)	3 (30%)	5 (33.3%)		

	Grade IV (extensive damage in the subcortical region)	2 (20%)	0 (0%)		
IVH	Yes	51 (47.2%)	75 (26.7%)	Chi-square	0.0002
	No	57 (52.8%)	206 (73.3%)		
IVH grade	Grade I (bleeding in the germinal matrix)	8 (15.7%)	28 (37.8%)	Fisher	0.0061
	Grade II (intraventricular bleeding occupies up to 50% of ventricular lumen volume)	22 (43.1%)	33 (44.6%)		
	Grade III (intraventricular bleeding occupies >50% of the lumen of the lateral ventricular volume. It frequently enlarges the ventricle)	11 (21.6%)	9 (12.2%)		
	Grade IV (haemorrhagic periventricular infarction [bleeding to the periventricular parenchyma])	10 (19.6%)	4 (5.4%)		
ROP	Yes	39 (37.5%)	97 (34.5%)	Chi-square	0.6722
	No	65 (62.5%)	184 (65.5%)		
ROP – laser photocoagulation	Not requiring treatment	27 (69.2%)	66 (68.8%)	Chi-square	1
	Requiring treatment	12 (30.8%)	30 (31.2%)		
PDA	Yes	46 (42.6%)	67 (23.8%)	Chi-square	0.0004
	No	62 (57.4%)	214 (76.2%)		
PDA – method of treatment	Need for surgical ligation	3 (6.7%)	2 (3%)	Fisher	0.2503
	Need for medical treatment	27 (60%)	32 (47.8%)		
	Not requiring treatment	15 (33.3%)	33 (49.3%)		

NEC	Yes	16 (14.8%)	17 (6%)	Chi-square	0.01
	No	92 (85.2%)	264 (94%)		
NEC grade	Grade I	5 (31.2%)	9 (52.9%)	Fisher	0.6627
	Grade IIA	3 (18.8%)	4 (23.5%)		
	Grade IIB	2 (12.5%)	1 (5.9%)		
	Grade IIIA	2 (12.5%)	1 (5.9%)		
	Grade IIIB	4 (25%)	2 (11.8%)		

Confidence intervals for selected complications are presented in the table below:

Table 23. Odds ratios (OR) for death and complications

	OR	95% confidence interval
Death	26.5	7.8–90.1
Air-Leak Syndrome	22.4	5.0–99.9
Ventilation-associated pneumonia	3.2	1.7–6.0
BPD	1.7	1.0–2.6
IVH	2.5	1.5–3.9
PDA	2.4	1.5–3.8
NEC	2.7	1.3–5.6
IVH grade 3 or 4	3.3	1.4–7.4

Other analyses

The rate of mechanical ventilation (MV) increased along with the increase of FiO_2 level measured before surfactant administration. Although in infants with the FiO_2 level before SFT administration below 0.45 the rate of MV amounted to 49.3% (N=69), in the group of 22 infants with FiO_2 of at least 0.65 up to 19 (86.4%) neonates required MV.

Table 24. FiO_2 level before SFT administration and mechanical ventilation

FiO_2 level before surfactant administration	Yes	No
<0.45	69 (49.3%)	71 (50.7%)
0.45–0.64	45 (60.8%)	29 (39.2%)
≥0.65	19 (86.4%)	3 (13.6%)

The situation with NCPAP failure was similar. In almost two-thirds of patients with pre-SFT FiO_2 level <0.45, NCPAP was successful (65%; N=91); however, in the group of infants with the pre-SFT FiO_2 level of at least 0.65, NCPAP success was recorded in 5 of 22 subjects (22.7%).

Table 25. FiO_2 level before SFT administration and CPAP result

FiO_2 level before surfactant administration	NCPAP failure	NCPAP success
<0.45	49 (35%)	91 (65%)
0.45–0.64	37 (50%)	37 (50%)
≥0.65	17 (77.3%)	5 (22.7%)

Intubation in the first 12 hours of life was slightly more often in infants receiving early caffeine (i.e. within the first two hours of life) compared to neonates receiving late caffeine (>12h). Intubation rate was 30.3% (N=63) and 41.7% (N=10), in the first and second group, respectively.

Table 26. Intubation within the first 12h of life depending on the time of caffeine administration

	No	Yes
Late (>12h after birth)	14 (58.3%)	10 (41.7%)
Early (<2h after birth)	145 (69.7%)	63 (30.3%)

Regarding the fact that the majority of infants received caffeine citrate up to 2 hours after birth compared to >12h, it is not possible to perform a clear evaluation of the impact of administration of the first dose of caffeine on the need for intubation in the overall study population involving patients receiving such treatment.

Table 27. Impact of infant's age at the moment of caffeine treatment initiation on the need for the use of endotracheal intubation within first 12 hours of life

Factor	OR	95% confidence interval	P value
Time of first dose of caffeine administration[3]	0.9453	0.8279–1.0794	0.4062

Overall, during follow-up respiratory complications (i.e. occurrence of one or more of the following: Air-Leak Syndrome, ventilation-associated pneumonia, or bronchopulmonary dysplasia) occurred in 191 infants (49.1% of total population). Broncho-pulmonary dysplasia (BPD) was the most common complication that occurred in 178 patients (45.8% of total population) – most often in a mild form – 38 patients (33.9% of total). Ventilation-associated pneumonia (VAP) was diagnosed in 43 infants (11.1%), while Air-Leak Syndrome in 17 (4.4%) neonates.

Table 28. Respiratory complications

Variable	Parameter	Overall distribution	Distribution without missing data
Respiratory complications	Yes	191 (49.1%)	191 (49.2%)
	No	197 (50.6%)	197 (50.8%)
	No data	1 (0.3%)	
Air-Leak Syndrome	Yes	17 (4.4%)	17 (4.4%)
	No	371 (95.4%)	371 (95.6%)
	No data	1 (0.3%)	
Ventilation-associated pneumonia	Yes	43 (11.1%)	43 (11.1%)
	No	345 (88.7%)	345 (88.9%)
	No data	1 (0.3%)	
Broncho-pulmonary dysplasia	No	203 (52.2%)	203 (53.3%)
	Mild	132 (33.9%)	132 (34.6%)
	Moderate	38 (9.8%)	38 (10%)
	Severe	8 (2.1%)	8 (2.1%)
	No data	8 (2.1%)	

Termination of observation – the final effect of treatment

The majority of the observed cases was terminated with child discharge to his/her place of residence (81.7%; N=322), while mean follow-up time was 58.42 days (±27.19) – in half of the cases, follow-up time ranged between 44 from 74 days. In total, 27 deaths were observed (6.9%).

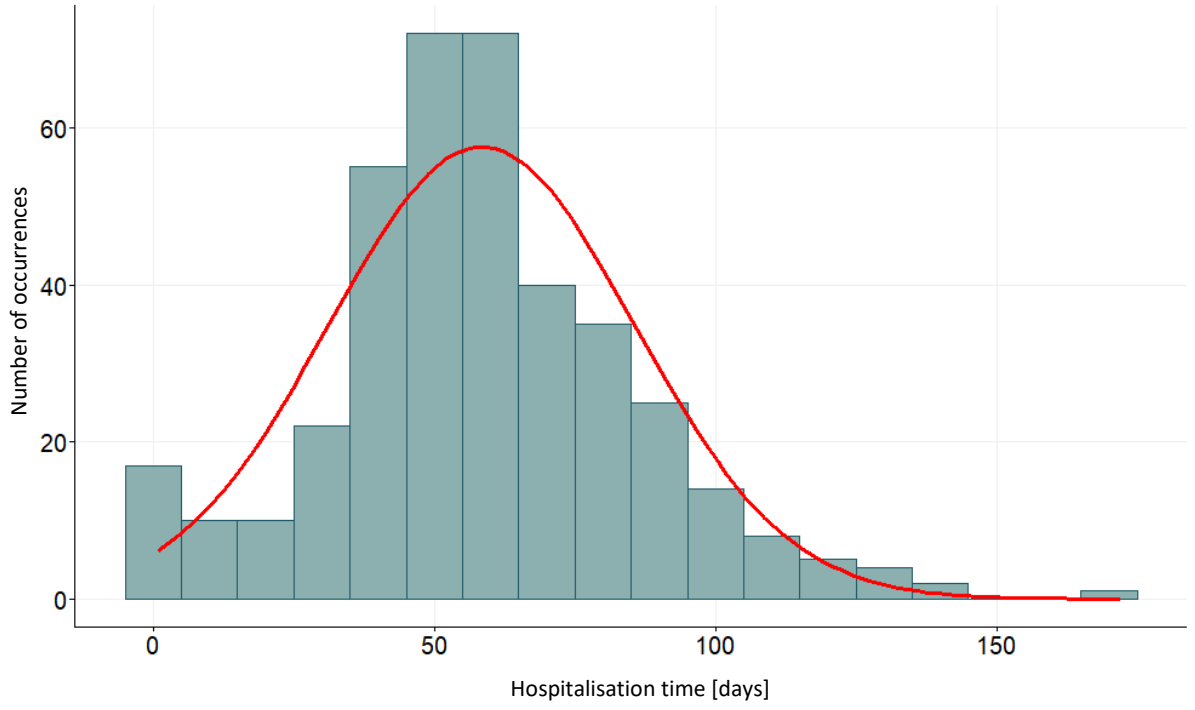
[3] OR provided for age change by one day.

Table 29. Characteristics of treatment completion

Variable	Parameter	Overall distribution	Distribution without missing data
Outcome	Transfer to another hospital/unit	44 (11.2%)	44 (11.2%)
	Hospital discharge	322 (81.7%)	322 (81.9%)
	Death	27 (6.9%)	27 (6.9%)
	No data	1 (0.3%)	
Duration of treatment [days]	Number of observations	392	
	Mean (standard deviation)	58.42 (27.19)	
	Median	56.5	
	IQR	44–74	
	Range	1–172	
	No data	2	
Cause of death	Other	13 (48.1%)	13 (48.1%)
	Intraventricular haemorrhage, grade III and IV	5 (18.5%)	5 (18.5%)
	Pulmonary haemorrhage	1 (3.7%)	1 (3.7%)
	NEC	3 (11.1%)	3 (11.1%)
	Sepsis	5 (18.5%)	5 (18.5%)
	No data	0 (0%)	

Distribution of hospitalisation time is presented on the histogram below.

Figure 12. Distribution of hospitalisation time



Appendix – *per protocol* population

Per protocol, the population included infants with data allowing for qualifying them in accordance to the primary endpoint to one of the following groups: NCPAP success or failure. This population comprised 389 of 394 patients. Of five patients excluded from this group, four neonates were transferred to another unit/hospital on the first day of life. These premature infants were lost to follow-up; thus their potential need for ventilation within the first 72 hours of life is unknown. In one case, all data on the final effect of treatment and method of therapy termination were missing.

Study group characteristics

Per protocol, the population included an identical number of boys and girls. The mean gestational age was 28.24 weeks (± 1.22 of standard deviation [SD]). Half of the infants were born between 27.43 and 29.14 weeks of gestation. Mean birth weight was 1,120g, and half of the infants weighted between 940 and 1,300g. In this population, the mean Apgar score was 7.49 (±1.15) points.

Table 30. Descriptive characteristics of the per-protocol group

Variable	Parameter	Overall distribution	Distribution without missing data
Gender	F	194 (49.9%)	194 (50%)
	M	194 (49.9%)	194 (50%)
	No data	1 (0.3%)	
Gestational age [week]	Number of observations	389	
	Mean (standard deviation)	28.24 (1.22)	
	Median	28.43	
	IQR	27.43–29.14	
	Range	23.43–29.86	
	No data	0	
Birth weight [g]	Number of observations	389	
	Mean (standard deviation)	1115.28 (270.61)	
	Median	1120	
	IQR	940–1300	
	Range	400–1970	
	No data	0	
5 minute Apgar score	Number of observations	389	
	Mean (standard deviation)	7.49 (1.15)	
	Median	8	
	IQR	7–8	
	Range	4–10	
	No data	0	

Less than every fourth infant was born from multiple pregnancy (22.1%) – most often from twin pregnancy (88.4%). In turn, 83.5% of infants were delivered by C-section.

Table 31. Descriptive characteristics of the per-protocol group – pregnancy and delivery

Variable	Parameter	Overall distribution	Distribution without missing data
Multiple birth	Yes	86 (22.1%)	86 (22.1%)
	No	303 (77.9%)	303 (77.9%)
	No data	0 (0%)	
Number of neonates	Twins	76 (88.4%)	76 (88.4%)
	Triplets	10 (11.6%)	10 (11.6%)
	No data	0 (0%)	
Delivery type	C-section	325 (83.5%)	325 (83.5%)
	Vaginal	64 (16.5%)	64 (16.5%)
	No data	0 (0%)	

In nine of ten cases, steroids were used (89.7%); 79.1% received the full course of treatment. In more than half of the cases, the last dose was administered from 24h to 14 days before birth (54.2%).

Table 32. Descriptive characteristics of the per-protocol group: antenatal steroids

Variable	Parameter	Overall distribution	Distribution without missing data
Steroids	Yes	349 (89.7%)	349 (90.2%)
	No	38 (9.8%)	38 (9.8%)
	No data	2 (0.5%)	
Betamethasone	Yes	286 (81.9%)	286 (85.9%)
	No	47 (13.5%)	47 (14.1%)
	No data	16 (4.6%)	
Dexamethasone	Yes	67 (19.2%)	67 (23.1%)
	No	223 (63.9%)	223 (76.9%)
	No data	59 (16.9%)	
Full course of steroids	Yes	276 (79.1%)	276 (79.8%)
	No	70 (20.1%)	70 (20.2%)
	No data	3 (0.9%)	
Time of the last dose of steroids administration	<24h before birth	88 (25.2%)	88 (25.9%)
	24 hours–14 days before birth	189 (54.2%)	189 (55.6%)
	>14 days before birth	63 (18.1%)	63 (18.5%)
	No data	9 (2.6%)	

Cardiac massage and adrenalin were infrequently used, in seven (1.8%) and one (0.3%) patient, respectively. In turn, positive pressure breaths (77.9%) and thermal protection (80.7%) were used in

the majority of children. Oxygen therapy in the Delivery Room was used in more than half of the cases. Median, both initial and the highest FiO_2 level in the Delivery Room, equalled to 0.3.

Table 33. Descriptive characteristics of the per-protocol group: procedures used

Variable	Parameter	Overall distribution	Distribution without missing data
Cardiac massage	Yes	7 (1.8%)	7 (1.8%)
	No	382 (98.2%)	382 (98.2%)
	No data	0 (0%)	
Adrenalin	Yes	1 (0.3%)	1 (0.3%)
	No	388 (99.7%)	388 (99.7%)
	No data	0 (0%)	
Positive pressure breaths	Yes	303 (77.9%)	303 (77.9%)
	No	86 (22.1%)	86 (22.1%)
	No data	0 (0%)	
Realization of positive pressure breaths	Sustained inflation at constant pressure	229 (75.6%)	229 (79.2%)
	Bagging	60 (19.8%)	60 (20.8%)
	No data	14 (4.6%)	
Thermal protection	Yes	314 (80.7%)	314 (81.1%)
	No	73 (18.8%)	73 (18.9%)
	No data	2 (0.5%)	
Oxygen therapy in the Delivery Room	Yes	211 (54.2%)	211 (54.5%)
	No	176 (45.2%)	176 (45.5%)
	No data	2 (0.5%)	
Initial FiO_2 in the Delivery Room	Number of observations	206	
	Mean (standard deviation)	0.29 (0.08)	
	Median	0.3	
	IQR	0.25–0.3	
	Range	0.21–1	
	No data	5	
Highest FiO_2 in the Delivery Room	Number of observations	207	
	Mean (standard deviation)	0.37 (0.11)	
	Median	0.3	
	IQR	0.3–0.4	
	Range	0.23–1	
	No data	4	

Non-invasive respiratory support

CPAP was used in 95.6% of infants in the Delivery Room, and in 99.2% of neonates in the NICU. In half of the neonates, CPAP in the Delivery Room was initiated from one to five minutes after birth. In turn,

in half of the cases, CPAP in the NICU was initiated between 7 and 12.5 minutes after birth. Nasal prongs were used in 13.9% of infants. In more than half of children, duration of CPAP ranged between 3.41 and 29.6 days. Approximately half of the neonates (50.6%) received more than one cycle of CPAP.

Table 34. Characteristics of non-invasive respiratory support – a per-protocol group

Variable	Parameter	Overall distribution	Distribution without missing data
CPAP in the Delivery Room	Yes	372 (95.6%)	372 (95.6%)
	No	17 (4.4%)	17 (4.4%)
	No data	0 (0%)	
CPAP in the NICU	Yes	386 (99.2%)	386 (99.2%)
	No	3 (0.8%)	3 (0.8%)
	No data	0 (0%)	
Site of CPAP initiation	NICU	19 (4.9%)	19 (4.9%)
	Delivery Room	370 (95.1%)	370 (95.1%)
	No data	0 (0%)	
Time to CPAP initiation in the Delivery Room [min]	Number of observations	369	
	Mean (standard deviation)	3.51 (3.11)	
	Median	2	
	IQR	1–5	
	Range	0–15	
	No data	1	
Time to CPAP initiation in the NICU [min]	Number of observations	19	
	Mean (standard deviation)	9.63 (3.42)	
	Median	10	
	IQR	7–12.5	
	Range	4–15	
	No data	0	
Type of CPAP device used in the Delivery Room	Bubble CPAP	7 (1.8%)	7 (1.9%)
	Constant flow CPAP (from the respirator)	53 (13.6%)	53 (14.3%)
	Variable flow CPAP, e.g. Infant Flow, MEDIN-CNO	310 (79.7%)	310 (83.8%)
	No data	19 (4.9%)	
Type of CPAP device used in the NICU	Bubble CPAP	5 (1.3%)	5 (1.3%)
	Constant flow CPAP (from the respirator)	72 (18.5%)	72 (18.7%)
	Variable flow CPAP, e.g. Infant Flow, MEDIN-CNO	308 (79.2%)	308 (80%)
	No data	4 (1%)	
Maintenance of CPAP until NICU admission	Yes	363 (97.6%)	363 (98.1%)
	No	7 (1.9%)	7 (1.9%)
	No data	2 (0.5%)	
Nasal prongs	Yes	54 (13.9%)	54 (13.9%)
	No	335 (86.1%)	335 (86.1%)
	No data	0 (0%)	

Variable	Parameter	Overall distribution	Distribution without missing data
CPAP connector	Other	4 (1%)	4 (1%)
	Standard nasal prongs or mask	378 (97.2%)	378 (97.2%)
	RAM prongs	7 (1.8%)	7 (1.8%)
	No data	0 (0%)	
More than one CPAP cycle	Yes	197 (50.6%)	197 (50.8%)
	No	191 (49.1%)	191 (49.2%)
	No data	1 (0.3%)	
Duration of CPAP use [days]	Number of observations	375	
	Mean (standard deviation)	19.27 (19.86)	
	Median	12.95	
	IQR	3.41–29.6	
	Range	0–117.89	
	No data	14	

Non-invasive positive pressure ventilation (NIPPV) was used in 36.8% of children. In total, 46.9% of neonates received more than one cycle of treatment. Duration of NIPPV in half of the patients ranged between 1.94 and 21.19 days.

Table 35. Characteristics of non-invasive positive pressure ventilation – a per-protocol group

Variable	Parameter	Overall distribution	Distribution without missing data
NIPPV	Yes	143 (36.8%)	143 (36.8%)
	No	246 (63.2%)	246 (63.2%)
	No data	0 (0%)	
More than one NIPPV cycle	Yes	67 (46.9%)	67 (46.9%)
	No	76 (53.1%)	76 (53.1%)
	No data	0 (0%)	
Duration of NIPPV use [days]	Number of observations	135	
	Mean (standard deviation)	16.84 (27.13)	
	Median	6.6	
	IQR	1.94–21.19	
	Range	0.01–216.42	
	No data	8	

Median FiO_2 level, both in the first as well as the second hour of life, was 0.3. The interquartile range (IQR) was higher in the first hour of life (0.3–0.4 vs 0.24–0.35), similarly to the value of the mean (0.35 vs 0.31). Differences were significant (Wilcoxon test; $p<0.001$).

Table 36. Fraction of inspired oxygen (FiO_2) in the first and second hour of life – a per-protocol group

Variable	Parameter	Overall distribution
FiO_2 in the first hour of life	Number of observations	389
	Mean (standard deviation)	0.35 (0.12)
	Median	0.3
	IQR	0.3–0.4
	Range	0.21–1
	No data	0
FiO_2 in the second hour of life	Number of observations	389
	Mean (standard deviation)	0.31 (0.11)
	Median	0.3
	IQR	0.24–0.35
	Range	0.21–1
	No data	0

Invasive respiratory support

In the study group, 60.4% of children were intubated. In half of the infants, the intubation time ranged from one hour to one day after birth. In total, 67.7% of intubated infants were receiving mechanical ventilation; in most cases with the use of conventional ventilation (83%). Median maximal FiO_2 during ventilation was 0.5, while IQR ranged from 0.35 to 0.8. Half of the patients were receiving mechanical ventilation from approximately 2 to 10.5 days. The median duration of invasive ventilation was 4.5 days.

Table 37. Characteristics of invasive respiratory support – a per-protocol group

Variable	Parameter	Overall distribution	Distribution without missing data
Time from birth to mechanical ventilation [days]	Number of observations	155	
	Mean (standard deviation)	4.68 (9.69)	
	Median	1.02	
	IQR	0.09–4.41	
	Range	0.01–54.91	
	No data	4	
Ventilation modes	Conventional ventilation	132 (83%)	132 (83.5%)
	Conventional ventilation, oscillating ventilation – HFOV	25 (15.7%)	25 (15.8%)
	Oscillating ventilation – HFOV	1 (0.6%)	1 (0.6%)
	No data	1 (0.6%)	
Maximal FiO_2	Number of observations	159	
	Mean (standard deviation)	0.56 (0.27)	

Variable	Parameter	Overall distribution	Distribution without missing data
	Median	0.5	
	IQR	0.35–0.8	
	Range	0.21–1	
	No data	0	
Invasive ventilation MAP [cm H_2O]	Number of observations	83	
	Mean (standard deviation)	13.37 (13)	
	Median	10	
	IQR	8–14	
	Range	7–93	
	No data	76	
PEEP	Yes	159 (100%)	159 (100%)
	No data	0 (0%)	
Maximal PEEP [cm H_2O]	Number of observations	158	
	Mean (standard deviation)	5.61 (0.78)	
	Median	6	
	IQR	5–6	
	Range	4–9	
	No data	1	
Cycle of invasive ventilation	Yes	36 (22.6%)	36 (23.2%)
	No	119 (74.8%)	119 (76.8%)
	No data	4 (2.5%)	
Duration of mechanical ventilation [days]	Number of observations	147	
	Mean (standard deviation)	10.91 (17.72)	
	Median	4.56	
	IQR	1.9–10.49	
	Range	0.01–115.79	
	No data	12	

Respiratory complications/ typical complications of prematurity

Air-Leak Syndrome was diagnosed in 4.4% of infants (most often pneumothorax), while ventilation-associated pneumonia in every tenth neonate (11.1%). Mild broncho-pulmonary dysplasia (BPD) occurred in 33.9% of infants. Moderate and severe BPD occurred less often (9.8% and 2.1%, respectively). Intraventricular haemorrhage was diagnosed in every third infant (32.4%). Retinopathy of prematurity was diagnosed slightly more often (35%), while the incidence of PDA was slightly lower (29%). Other complications, such as periventricular leukomalacia and necrotising enterocolitis were less often observed (6.4% and 8.5%, respectively).

Table 38. Characteristics of complications

Variable	Parameter	Overall distribution	Distribution without missing data

Air-Leak Syndrome	Yes	17 (4.4%)	17 (4.4%)
	No	371 (95.4%)	371 (95.6%)
	No data	1 (0.3%)	
Air-Leak Syndrome – type	Pneumothorax	15 (88.2%)	15 (88.2%)
	Interstitial emphysema	2 (11.8%)	2 (11.8%)
	No data	0 (0%)	
Ventilation-associated pneumonia	Yes	43 (11.1%)	43 (11.1%)
	No	345 (88.7%)	345 (88.9%)
	No data	1 (0.3%)	
Broncho-pulmonary dysplasia płucna	No	203 (52.2%)	203 (53.3%)
	Mild	132 (33.9%)	132 (34.6%)
	Moderate	38 (9.8%)	38 (10%)
	Severe	8 (2.1%)	8 (2.1%)
	No data	8 (2.1%)	
Periventricular leukomalacia	Yes	25 (6.4%)	25 (6.4%)
	No	364 (93.6%)	364 (93.6%)
	No data	0 (0%)	
Periventricular leukomalacia – grade	No data on grade	2 (8%)	2 (8%)
	Grade I (noncystic leukomalacia, diffuse lesions in the middle area of the white matter which disturb its development)	4 (16%)	4 (16%)
	Grade II (small localised cystic lesions)	9 (36%)	9 (36%)
	Grade III (diffuse cystic lesions)	8 (32%)	8 (32%)
	Grade IV (extensive damage in the subcortical region)	2 (8%)	2 (8%)
	No data	0 (0%)	
Intraventricular haemorrhage	Yes	126 (32.4%)	126 (32.4%)
	No	263 (67.6%)	263 (67.6%)
	No data	0 (0%)	
Intraventricular haemorrhage – grade	Grade I (bleeding in the germinal matrix)	36 (28.6%)	36 (28.8%)
	Grade II (intraventricular bleeding occupies up to 50% of ventricular lumen volume)	55 (43.7%)	55 (44%)
	Grade III (intraventricular bleeding occupies >50% of the lumen of the lateral ventricular volume. It frequently enlarges the ventricle)	20 (15.9%)	20 (16%)
	Grade IV (hemorrhagic periventricular infarction [bleeding to the periventricular parenchyma])	14 (11.1%)	14 (11.2%)
	No data	1 (0.8%)	
Retinopathy of prematurity	Yes	136 (35%)	136 (35.3%)
	No	249 (64%)	249 (64.7%)
	No data	4 (1%)	
Retinopathy of prematurity – photocoagulation	Not requiring treatment	93 (68.4%)	93 (68.9%)
	Requiring treatment	42 (30.9%)	42 (31.1%)
	No data	1 (0.7%)	

Patent Ductus Arteriosus	Yes	113 (29%)	113 (29%)
	No	276 (71%)	276 (71%)
	No data	0 (0%)	
Patent Ductus Arteriosus – method of treatment	Need for surgical ligation	5 (4.4%)	5 (4.5%)
	Need for medical treatment	59 (52.2%)	59 (52.7%)
	Not requiring treatment	48 (42.5%)	48 (42.9%)
	No data	1 (0.9%)	
Necrotizing Enterocolitis	Yes	33 (8.5%)	33 (8.5%)
	No	356 (91.5%)	356 (91.5%)
	No data	0 (0%)	
Necrotizing Enterocolitis – grade	Grade I	14 (42.4%)	14 (42.4%)
	Grade IIA	7 (21.2%)	7 (21.2%)
	Grade IIB	3 (9.1%)	3 (9.1%)
	Grade IIIA	3 (9.1%)	3 (9.1%)
	Grade IIIB	6 (18.2%)	6 (18.2%)
	No data	0 (0%)	

Follow-up termination

The majority of neonates was discharged to their place of residence (82.8%). Every tenth infant was transferred to another unit (10.3%), while 6.9% of neonates died. In half of the patients, duration of treatment ranged between 44 and 74.25 days.

Table 39. Characteristics of treatment completion

Variable	Parameter	Overall distribution	Distribution without missing data
Outcome	Transfer to another hospital/unit	40 (10.3%)	40 (10.3%)
	Hospital discharge	322 (82.8%)	322 (82.8%)
	Death	27 (6.9%)	27 (6.9%)
	No data	0 (0%)	
Duration of treatment [days]	Number of observations	388	
	Mean (standard deviation)	59.01 (26.69)	
	Median	57	
	IQR	44–74.25	
	Range	1–172	
	No data	1	
Cause of death	Other	13 (48.1%)	13 (48.1%)
	Intraventricular haemorrhage, grade III and IV	5 (18.5%)	5 (18.5%)
	Pulmonary haemorrhage	1 (3.7%)	1 (3.7%)
	NEC	3 (11.1%)	3 (11.1%)
	Sepsis	5 (18.5%)	5 (18.5%)
	No data	0 (0%)	

List of tables and figures