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Original article

Persistent pulmonary hypertension – The neonatal period and evaluation at 2 years of age

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Abstract

Persistent pulmonary hypertension of the newborn (PPHN) is a condition in which the pulmonary vessels fail to dilate at birth. It can be the consequence of a wide array of diseases, such as pneumonia, congenital diaphragmatic hernia, meconium aspiration syndrome and hyaline membrane disease. It has an incidence of 1-2 per 1,000 newborns and it can have pulmonary, neurologic and developmental consequences. We conducted a retrospective study with the aim of analyzing the causes, morbidities and comorbidities, management and mortality of PPHN in newborns hospitalized in our neonatal intensive care unit (NICU) and to evaluate respiratory, neurologic and developmental morbidity at 2 years of age. A total of 77 children, born between 1996 and 2012, were studied. Twenty-six (33.8%) deceased. The mortality, as well as the need for resuscitation, inhaled nitric oxide (iNO), diuretics, and vasopressor support, was higher in patients with the severe form of PPHN. The need for vasopressor support was the only factor associated with a higher mortality. We found a reduction of 17.8% in mortality rates after the introduction of iNO, sildenafil and extracorporeal membrane oxygenation (ECMO). Congenital diaphragmatic hernia was the most common cause of PPHN. Pneumonia was more frequent before 2003. There was no significant difference in the morbidity and mortality between the two time periods (before and after 2003). On the follow-up of 37 of the remaining 51 patients, we did not find differences in the morbidity of patients comparing those with the severe vs. non-severe forms of the condition.

An evaluation over the years of admitted newborns with PPHN in our NICU is mandatory to confirm a relationship between the new treatment strategies and the better outcome of the patients.

Keywords

Persistent pulmonary hypertension of the newborn, inhaled nitric oxide, sildenafil, extracorporeal membrane oxygenation, Mary Sheridan Scale, congenital diaphragmatic hernia.

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Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a serious condition resulting from a defective transition to air breathing, with a failure of the pulmonary vasculature to dilate at birth [1-6]. It affects about 2/1,000 live born infants [2, 3, 7-13]. It results in a hypoxemic respiratory failure [2, 3, 7, 8, 10] and is characterized by a sustained elevation of the pulmonary vascular resistance [1-3, 5, 6, 8, 9]. A right-to-left blood shunt through the foramen ovale and the ductus arteriosus may also be present [1-3, 7-10], contributing to the hypoxemia and labile oxygen saturations [8].

It has a multitude of etiologies, including abnormally constricted pulmonary vasculature caused by parenchymal diseases, hypoplastic pulmonary vasculature and normal parenchyma with remodeled pulmonary vasculature [1, 5, 8-10, 12, 14]. When remodeled vessels and hypoxia are observed in the absence of parenchymal changes, it can be named primary or idiopathic PPHN [1, 3, 8, 10, 15]. Secondary PPHN occurs due to clinical conditions such as pneumonia, sepsis, meconium aspiration syndrome or to underdevelopment, such as oligohydramnios [1, 10, 12].

Early recognition of the condition is of prime importance. The management focuses on treating the hypoxia and reducing the pulmonary vasoconstriction. In order to do so, the treatment options include oxygen ventilation, vasorelaxants (e.g. inhaled nitric oxide [iNO], sildenafil and prostanoids), sedation and extracorporeal membrane oxygenation (ECMO) when medical treatment fails [1-4, 6-13, 16, 17]. When treated with ECMO and iNO, mortality is reduced from 25-50% to 10-15% [9].

Causes of morbidity and death related to the condition include intracranial hemorrhage, chronic lung disease, and right ventricular hypertrophy [10, 11]. Despite being less common [18], hearing and neurodevelopmental disabilities, as well as brain injuries, are also sequelae that make long term follow-up essential in infants with PPHN [8, 9].

There is a lack of information regarding the follow-up of these children, namely respiratory, neurological, or developmental morbidities at 2 years of age.

With this study, we aim to assess the neonatal morbidity and mortality as well as the pulmonary and neurodevelopmental status at 2 years of age of the PPHN survivors.

Methods

Neonates with the diagnosis of PPHN, admitted to a level III neonatal intensive care unit (NICU) between 1996 and 2012, were included. Data were collected from the database of our NICU, a tertiary referral center for neonatal cardiac and pediatric surgery in the north of Portugal. Gestational data, demographic data, the cause of PPHN, treatment, days of NICU stay, neonatal outcome, and necropsy findings of the deceased neonates were retrieved from the clinical charts and retrospectively reviewed. Children with congenital heart malformations were excluded [14, 19].

The diagnosis of PPHN was made based on clinical data, chest X-ray images, arterial blood gases analysis and 2D-echographic criteria, with a methodology similar to the one used in a previous study at our center in 2012 [20]. Pulmonary artery systolic pressure (PASP) values were estimated as the right ventricle to right atrium gradient + 15 mmHg (assuming the right atrium pressure was 15 mmHg). Pulmonary hypertension was stratified as mild if estimated PASP was less than 40 mmHg, moderate if between 40 and 60 mmHg, and severe if higher than 60 mmHg [20]. Additionally, other parameters were evaluated to help in definition of the severity of PPHN: (i) ductus arteriosus or foramen ovale shunt direction (left-to-right shunt was considered normal, bidirectional shunt was considered mild to moderate PPHN and right to left shunt was considered severe PPHN); (ii) ventricular septum orientation (left-to-right orientation was considered normal, septum rectification was indicative of mild-to-moderate PPHN, and when the septum budge from right-to-left a severe PPHN was likely), and (iii) systolic function of the left ventricle, through the left ventricular ejection fraction (in cases of moderate PPHN it was expected a hypercontractil left ventricle whilst in severe PPHN usually we

found a decrease on left ventricle ejection fraction) [1, 3, 7-9, 12, 20]. All of these parameters were daily evaluated. The presence of congenital heart disease was also excluded or confirmed by ultrasound.

iNO (usually starting with 20 ppm; only rarely there is benefit in using higher doses [1, 3, 9, 12, 13]) has been administrated since 2003 when severe PPHN was diagnosed [3, 13] and when the oxygenation index (mean airway pressure × fraction of inspired oxygen × 100 / partial arterial pressure of oxygen) was over 20 [3]. Sildenafil was used when the response to iNO was weak or as an adjuvant therapy for weaning of iNO [3]. Both iNO and sildenafil have been used since 2003 [20] and a comparison of the survival rates between the two epochs (1996-2002 and 2003-2012) was made.

A daily water intake of 60-80 mL/kg/day (with progression of fluids according to the underlying disease and clinical situation of the patient, namely fluid balance, renal function, blood pressure, hemodynamic status and estimate pulmonary pressure) and a perfusion of dopamine 5-20 mcg/kg/min [9] have been used since 2003, in order to keep a systemic blood pressure over 40 mmHg. The hematocrit is kept higher or equal to 45% (haemoglobin ≥ 15 g/dL). In case of myocardial dysfunction, a perfusion of dobutamine (5-10 mcg/kg/min) is started. Higher doses of dopamine and dobutamine or epinephrine perfusion are used if clinical criteria demand it. Minimum stimulation, sedation and analgesia are usually performed [8-10]. Paralyzing agents are usually avoided, except for selected cases as a rescue ventilation adjunct therapy. In the eventual need for mechanical ventilation, conventional ventilation is preferred, while high-frequency oscillation ventilation is used as a rescue ventilation [7]. The mechanical ventilation aims to maintain a PaO_2 of 60-90 mmHg [1, 3, 4, 8] and a $PaCO_2$ > 35 mmHg (usually 35-50 mmHg), in order to avoid oxidative stress and hypocapnia. Treatment with ECMO is available at our center since 2010 [20].

Congenital diaphragmatic hernia was diagnosed when abdominal organs were observed in the thoracic cavity in the ultrasound [21]. Meconium aspiration syndrome was diagnosed when infants presented respiratory distress with no apparent cause other than meconium in the amniotic fluid [22]. When the infant had a 5th minute Apgar score lower than 6 and an umbilical cord artery pH inferior to 7.00, perinatal asphyxia was diagnosed [23]. Pneumonia was diagnosed based on clinical and radiographic findings [24]. Sepsis was diagnosed according to clinical signs and laboratorial results [25]. RDS was diagnosed based on chest X-ray findings and clinical signs like increased oxygen need, grunts and retraction [26].

Bronchopulmonary dysplasia was diagnosed based on the National Institute of Child Health and Human Development criteria [27]. Patent ductus arteriosus was diagnosed by bi-dimensional heart ultrasound, using Doppler to analyze the blood flow and show the presence of shunt [28-30]. Necrotizing enterocolitis was graded and diagnosed according to the modified Bell criteria [31]. When present, retinopathy of prematurity was diagnosed based on the 2005 revised International Classification [32]. The grade of intraventricular haemorrhage was based on the presence (grade III) or absence (grade II) of ventricular dilatation and the observation of parenchymal involvement (grade IV) in the cranial ultrasound [26]. When hypoechoic cysts were observed in the periventricular white mass, cystic periventricular leukomalacia was diagnosed [26].

We analyzed all the variables studied (demographic, pregnancy and delivery data, morbidity and management of the patients) to assess the risk factors of severity and death of PPHN, comparing the data before and after 2003 (1996-2003 and 2003-2012).

In order to assess the respiratory, neurological and development status at 2 years of age, we analyzed the patients' clinical files and contacted the parents by phone using a questionnaire (**Appendix A**) during the interviews to complete clinical data.

The statistical analysis was performed using SPSS® for Windows®, version 20. Continuous variables were characterized by mean (± standard deviation) or median (medium-maximum) if they had symmetric or asymmetric distribution respectively and categorical variables by absolute and relative frequencies. To compare continuous variables parametric testes (independent t test) or non-parametric tests (Mann-Whitney U test) were used if they had symmetric or asymmetric distribution, respectively. To compare categorical variables, Chi-Squared or Fisher's exact test were used, the latter for expected values less than 5. A multivariate analysis by logistic regression was performed to evaluate predictive factors for death. A p-value less than 0.05 was considered statistically significant.

This study has been approved by the ethics committee of our institution.

Results

Seventy-seven children born between January 1st 1996 and October 31st 2012 were treated for PPHN during the neonatal period at our service, out of which 26 died. We analyzed the autopsy findings of the 14 patients that underwent autopsy. At 2 years evaluation, we observed 37 patients.

The demographics of the target population and the pregnancy and delivery data are shown in **Tab. 1**. There were no statistically significant differences between both time periods in any of the demographic parameters. The use of peripartum antibiotics was more frequent in the 2003-2012 period (p = 0.016)

The neonatal morbidity, treatment and mortality data are shown in **Tab. 2**. The most common cause of PPHN was congenital diaphragmatic hernia (23.4%), followed by pneumonia (22.1%). Pneumonia was a significantly more frequent cause of PPHN in the 1996-2002 period. Meconium aspiration syndrome was significantly more frequent in the 2003-2012 period (p = 0.035). During the NICU stay, 39.3% had an abnormal neurological exam and before 2003 the abnormal findings were significantly more frequent (p = 0.038). Dopamine was significantly more used after 2002 (p = 0.023). The duration of both mechanical ventilation and oxygen therapy were significantly higher after 2002

Table 1. Demographic characteristics and pregnancy and delivery data.

	Total (n = 77)	1996-2002 (n = 35)	2003-2012 (n = 42)	P
Gender, n (%)				
Male	51 (66.2)	22 (62.9)	29 (69.0)	0.567[a]
Female	26 (33.8)	13 (37.1)	13 (31.0)	
Gestational Age (weeks), median (min-max)	39 (28-41)	38 (30-41)	39 (28-41)	0.820[c]
Preterm (< 37 weeks), n (%)	17 (22.1)	8 (22.9)	9 (21.4)	0.880[a]
Birth weight (grams), mean (± SD)	2,944 (± 624)	2,901 (± 616)	2,981 (± 637)	0.578[d]
Small for gestational age, n (%)	11 (14.3)	4 (11.4)	7 (16.7)	0.745[b]
Surveillance during pregnancy, n (%)	69 (92.0)	33 (97.1)	36 (87.8)	0.212[b]
Parity, n (%)				
Single	74 (96.1)	34 (97.1)	40 (95.2)	0.999[b]
Multiple	3 (3.9)	1 (2.9)	2 (4.8)	
Steroids use, n (%)	10 (13.7)	5 (15.6)	5 (12.2)	0.672[a]
Full cycle	6 (60.0)	2 (40.0)	4 (80.0)	0.524[b]
Smoking during pregnancy, n (%)	1 (1.4)	0	1 (2.7)	0.999[b]
Maternal diseases, n (%)				
Hepatitis C	1 (1.4)	0	1 (2.5)	0.999[b]
Gestational diabetes	1 (1.4)	1 (3.0)	2 (5.1)	0.471[b]
Chronic hypertension	1 (1.4)	0	1 (2.7)	0.999[b]
HELLP syndrome	1 (1.4)	1 (3.0)	0	0.471[b]
Placental abruption	1 (5.0)	0	1 (5.0)	0.999[b]
Positive Streptococcus Group B screening, n (%)	9 (19.1)	2 (8.3)	7 (30.4)	0.072[b]
Premature membrane rupture, n (%)	7 (10.0)	2 (6.7)	5 (12.5)	0.690[b]
Peripartum antibiotics, n (%)	14 (19.2)	2 (6.3)	12 (29.3)	0.016[b]
Delivery, n (%)				
Vaginal	27 (35.1)	14 (40.0)	13 (31.0)	0.407[a]
C-section	50 (64.9)	21 (60.0)	29 (69.0)	
Apgar score, n (%)				
1st minute < 7	33 (42.9)	13 (37.1)	20 (47.6)	0.355[a]
5th minute < 7	18 (23.4)	5 (14.3)	13 (31.0)	0.085[a]
Resuscitation, n (%)	48 (63.2)	18 (52.9)	30 (71.4)	0.097[a]
Endotracheal tube	31 (64.6)	11 (64.7)	20 (69.0)	0.766[a]

[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test; [d]Independent t test.

Table 2. Neonatal morbidity, treatment, and mortality during hospitalization.

	Total (n = 77)	1996-2002 (n = 35)	2003-2012 (n = 42)	p
PPHN, n (%)				
Non severe	37 (48.1)	18 (51.4)	19 (45.2)	0.588[e]
Severe	40 (51.9)	17 (48.6)	23 (54.8)	
Causes of PPHN, n (%)				
Congenital diaphragmatic hernia	18 (23.4)	8 (22.9)	10 (23.8)	0.922[e]
Pneumonia	17 (22.1)	12 (34.3)	5 (11.9)	0.018[e]
Sepsis	8 (10.4)	6 (17.1)	2 (4.8)	0.131[f]
Meconium aspiration syndrome	9 (11.7)	1 (2.9)	8 (19.0)	0.035[f]
Perinatal asphyxia	6 (7.8)	3 (8.6)	3 (7.1)	0.999[f]
Hyaline membrane disease	7 (9.1)	5 (14.3)	2 (4.8)	0.235[f]
Fetal tachyarrhythmia	4 (5.2)	3 (8.6)	1 (2.4)	0.325[f]
Other[a]	19 (24.7)	9 (25.7)	10 (23.8)	0.847[e]
Unknown aetiology	9 (11.7)	2 (5.7)	7 (16.7)	0.170[f]
Major congenital malformation, n (%)[b]	14 (18.2)	8 (22.9)	6 (14.3)	0.332[e]
Chromosomopathy, n (%)[c]	4 (5.2)	1 (2.9)	3 (7.1)	0.621[f]
Associated neonatal morbidities, n (%)				
Bronchopulmonary dysplasia	4 (5.2)	1 (2.9)	3 (7.1)	0.621[f]
Patent ductus arteriosus with surgical ligation need	2 (2.6)	0	2 (4.8)	0.999[f]
Necrotizing enterocolitis ≥ grade 2	1 (1.3)	0	1 (2.4)	0.999[f]
Intraventricular hemorrhage ≥ grade 3	1 (1.3)	0	1 (2.4)	0.999[f]
Periventricular leukomalacia	7 (11.9)	3 (12.5)	4 (11.4)	0.999[f]
Retinopathy of prematurity ≥ grade 2	0	0	0	-
Abnormal neurological examination, n (%)	22 (39.3)	14 (53.8)	8 (26.7)	0.038[e]
Abnormal cerebral ultrasound, n (%)	10 (16.1)	3 (10.7)	7 (20.6)	0.490[f]
Pharmacological treatment, n (%)				
Inhaled nitric oxide	20 (26.0)	0	20 (47.6)	< 0.001[f]
Surfactant	26 (33.8)	9 (25.7)	17 (40.5)	0.173[e]
Dopamine	48 (62.3)	17 (48.6)	31 (73.8)	0.023[e]
Dobutamine	32 (41.6)	14 (40)	18 (42.9)	0.800[e]
Epinephrine	3 (3.9)	1 (2.9)	2 (4.8)	0.999[f]
Sildenafil	9 (11.7)	0	9 (21.4)	0.003[f]
Diuretics	31 (40.3)	16 (45.7)	15 (35.7)	0.373[e]
Prostaglandins	10 (13.0)	3 (8.6)	7 (16.7)	0.293[f]
Other	19 (24.7)	7 (20.0)	12 (28.6)	0.385[e]
Maximum FiO_2, median (min-max)	100 (25-100)	100 (25-100)	100 (30-100)	0.680[g]
Oxygen therapy (days), median (min-max)	6 (1-162)	4 (1-67)	8 (1-162)	0.033[g]
Mechanical ventilation, n (%)	66 (85.7)	27 (77.1)	39 (92.9)	0.099[f]
Mechanical ventilation (days), median (min-max)	7 (1-114)	5 (1-33)	10 (1-114)	0.007[g]
ECMO, n (%)[d]	2 (9.5)	0	2 (14.3)	0.533[f]
Parenteral feeding, n (%)	45 (58.4)	13 (37.1)	32 (76.2)	0.001[e]
Parenteral feeding (days), median (min-max)	10 (1-95)	10 (2-34)	10 (1-95)	0.415[g]
Stay in NICU (days), median (min-max)	11 (1-167)	8 (1-67)	14 (1-167)	0.026[g]
Sildenafil at discharge, n (%)	4 (7.8)	0	4 (13.8)	0.124[f]
Deceased, n (%)	26 (33.8)	13 (52.0)	13 (34.2)	0.161[e]
Autopsy	14 (53.9)	9 (69.2)	5 (38.5)	0.238[f]

PPHN: persistent pulmonary hypertension of the newborn; ECMO: extracorporeal membrane oxygenation; NICU: neonatal intensive care unit.
[a] Other causes: Galen vein malformation (2), meningitis (1), cerebral arteriovenous malformation (1), idiopathic arterial calcification (1), pulmonary hemorrhage (2), aspiration pneumonia (2), closure of patent ductus arteriosus with indomethacin (1), pleural effusion (1), pneumothorax (1), malformative syndrome (7).
[b] Malformative syndrome (7), interventricular communication (3) aeosophageal atresia (2), cleft palate (1), pectus excavatum (1), onphalocele (1), coarctation of the aorta (1), interauricular communication (1).
[c] Cat-eye syndrome (1), 8q11.22-q11.23 and Xp21.2-p11.4 microdeletion (1), short arm tetrasomy of chromosome 9 (1), chromosome 13 trisomy (1).
[d] Treatment with ECMO is available at our center since 2010.
[e] Chi-square test; [f] Fisher's exact test; [g] Mann-Whitney U test.

(p = 0.007 and p = 0.033, respectively). There was also a significantly larger number of infants with parenteral feeding (p = 0.001), but there was no significant difference in its duration. The duration of the stay at the NICU was significantly higher in the 2003-2012 period with a median of 14 days for the latter period and 8 days in the 1996-2002 period (p = 0.026). Four infants continued sildenafil treatment after discharge. Two patients went through ECMO.

Twenty-six (96.2%) deceased patients received vasopressor support vs. 21 (56.8%) of the non-deceased ones (OR = 17.6, 95% CI [1.9-157.3]). The need of vasopressor support was the only predictive factor for death.

Tab. 3 shows the comparison between the clinical data according to severity of PPHN. The percentage of deceased patients was significantly higher in the group with the severe form of PPHN (p < 0.0001). iNO, vasopressor support and diuretics were significantly more used in the patients with the severe form (p = 0.016, p < 0.0001 and p = 0.002, respectively).

Six patients died of pneumonia, the most common cause of death according to the autopsies. Pulmonary hypoplasia was the death cause of 3 patients. Sepsis, bronchopulmonary dysplasia, pulmonary artery thrombosis, idiopathic arterial calcification and necrotizing bronchiolitis were the death causes of 1 patient each.

Out of the 14 infants lost to the follow-up, 10 patients were born before 2003. Two patients had a severe form of PPHN, both of them were born after 2003. Twelve patients, including these 2 infants, were cured or improved their condition during the NICU stay. The other 2 patients, both born before 2003, were transferred to other hospitals in the first week of life. Of the aforementioned 12 patients, 6 were sent home while the other 6 were admitted into the pediatric ward or sent to other hospitals. One of the patients that were sent home was being medicated with captopril, salbutamol and beclomethasone. One of the infants with the severe form of PPHN, who was sent to another hospital, was being medicated with sildenafil. The other patients, including the remaining infant with the severe form, were on no cardiovascular or respiratory medication.

Tables 4, **5** and **6** compare the follow-up during the first 2 years of life for infants who had severe PPHN and those who had non-severe PPHN. **Tab. 4** shows the demographic and risk factors for morbidity in the first 2 years of life. **Tab. 5** reports the morbidity and therapy in the first 2 years of life. **Tab. 6** shows the Mary Sheridan Scale at 2 years of age. There were no statistically significant differences between the two groups of children regarding the follow-up.

On the follow-up of 37 of the remaining 51 patients, we did not find differences in the morbidity of patients comparing those with the severe vs. non-severe forms of the condition.

Discussion

In our study, congenital diaphragmatic hernia was the main cause of PPHN (23.4%) along all the years. This disease leads to pulmonary hypoplasia, a condition that occurs with deficient vasculogenesis and angiogenesis [3, 8, 10, 12, 33]. Despite the high morbidity and mortality when in the presence of pulmonary hypertension, the prevalence of congenital diaphragmatic hernias in PPHN series is yet not known [34].

Congenital pneumonia was the second most common cause of PPNH in our study (22.1%), and it was significantly less frequent in the 2003-2012 period than in the 1996-2002 period (p = 0.018). This fact is probably related to the higher and regular use of peripartum antibiotics after 2003 (p

Table 3. Significant clinical data according to severity of PPHN.

	Total (n = 77)	Severe PPHN (n = 40)	Non-severe PPHN (n = 37)	p
Resuscitation, n (%)	48 (62.3)	30 (75.0)	18 (50.0)	0.024[a]
Pharmacological treatment, n (%)				
iNO	20 (26.0)	15 (37.5)	5 (13.5)	0.016[a]
Vasopressor support	49 (63.6)	33 (82.5)	16 (43.2)	< 0.0001[a]
Diuretics	31 (40.3)	23 (57.5)	8 (21.6)	0.002[a]
Deceased (all causes included), n (%)	26 (33.8)	23 (60.5)	3 (12.0)	< 0.0001[b]

PPHN: persistent pulmonary hypertension of the newborn; iNO: inhaled nitric oxide.
[a] Chi-square test; [b] Fisher's exact test.

Table 4. Demographic and risk factors for morbidity in the first 2 years of life.

Demographics	Total (n = 37)	Severe PPHN (n = 15)	Non-severe PPHN (n = 22)	p
Gender, n (%)				
Male	27 (73.0)	10 (66.7)	17 (77.3)	0.476[a]
Female	10 (27.0)	5 (33.3)	5 (22.7)	
Major congenital malformation, n (%)	5 (13.5)	3 (20.0)	2 (9.1)	0.317[b]
Chromosomopathy, n (%)	2 (5.4)	1 (6.7)	1 (4.5)	0.999[b]
Breastfeeding ≥ 1 month, n (%)	16 (57.1)	4 (44.4)	12 (63.2)	0.432[b]
Duration (months), median (min-max)	4 (1-24)	2 (1-24)	5 (1-24)	0.559[c]
Preventive measures after discharge, n (%)	26 (92.9)	8 (88.9)	18 (94.7)	0.999[b]
Pneumococcal polysaccharide conjugate vaccine	21 (91.3)	7 (100)	14 (87.5)	0.999[a]
Pavalizumab, n (%)	5 (23.8)	1 (14.3)	4 (28.6)	0.624[b]
Influenza vaccine, n (%)	10 (37.0)	3 (33.3)	7 (38.9)	0.999[b]
People in the household, median (min-max)	4 (3-7)	4 (3-7)	4 (3-5)	0.357[c]
Preschool aged siblings, n (%)	1 (3.6)	0	1 (5.3)	0.999[b]
Attendance of daycare, n (%)	10 (35.7)	3 (33.3)	7 (36.8)	0.999[b]
Age at beginning (months), median (min-max)	9 (0-24)	9 (0-24)	9 (0-24)	0.554[c]
Smokers in household, n (%)	15 (53.6)	5 (55.6)	10 (52.6)	0.999[b]
Fireplace in household, n (%)	16 (57.1)	7 (77.8)	9 (47.4)	0.223[b]
Family history of asthma, n (%)	6 (21.4)	2 (22.2)	4 (21.1)	0.999[b]
Maternal asthma, n (%)	3 (10.7)	0	3 (15.8)	0.530[b]
Family history of atopy, n (%)	9 (32.1)	3 (33.3)	6 (31.6)	0.999[b]
Maternal atopy, n (%)	6 (21.4)	3 (33.3)	3 (15.8)	0.352[b]
Parents' education, n (%)				
≤ 9 y	8 (29.6)	3 (37.5)	5 (26.3)	0.999[b]
10-12 y	11 (40.7)	3 (37.5)	8 (42.1)	
> 12 y	8 (29.6)	2 (25.0)	6 (31.6)	
Graffar, n (%)				
Low class	2 (7.1)	1 (11.1)	1 (5.3)	0.999[b]
Middle class	6 (21.4)	2 (22.2)	4 (21.1)	
High class	20 (71.4)	6 (66.7)	14 (73.7)	

PPHN: persistent pulmonary hypertension of the newborn.
[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test.

= 0.016). According to the literature, pneumonia, when associated with either hyaline membrane disease or sepsis, is responsible for 13-14% of the cases of PPHN [3, 7]. We had a similar pneumonia prevalence (11.9%) in the second time period.

Clinical conditions like pneumonia, surfactant deficiency and meconium aspiration [3, 8, 10, 12] are associated to detrimental parenchymal changes resulting in vasoconstriction and consequent PPHN [10].

Despite the recent reduction in its prevalence [8, 24], in our study meconium aspiration syndrome was more frequent after 2003 (p = 0.035). Unless the retrospective collection of data has distorted the results, we were not able to find an explanation for this fact, since there were no significant differences in Apgar scores, gender or gestational age between the two studied epochs [24]. Although meconium aspiration syndrome is the condition most frequently associated with PPHN in the literature [3, 8, 12], in our study it was the cause in only 11.7% of the cases, being just the third most common cause. This may be due to the absence of post-term infants in our study, which can probably be explained by the improvement of follow-up observed in the Portuguese perinatal healthcare over the last decades.

Remodeled pulmonary vasculature, the least common cause of PPHN, is usually the consequence of more chronic, long-acting conditions that lead to changes in the vessels' wall, turning it thicker, with reduced lumen diameter and elevated resistance

Table 5. Morbidity and therapy in the first 2 years of life.

	Total (n = 37)	Severe PPHN (n = 15)	Non-severe PPHN (n = 22)	p
Symptoms, n (%)				
Frequent cough	6 (17.6)	3 (23.1)	3 (14.3)	0.653[b]
Frequent wheeze	10 (29.4)	4 (30.8)	6 (28.6)	0.999[b]
Cough, wheeze or dyspnea with exercise	9 (26.5)	2 (15.4)	7 (33.3)	0.427[b]
Waking with cough	6 (17.6)	2 (15.4)	4 (19.0)	0.999[b]
Waking with wheeze	6 (17.6)	2 (15.4)	4 (19.0)	0.999[b]
Waking with dyspnea	5 (14.7)	2 (15.4)	3 (14.3)	0.999[b]
Medication, n (%)				
Sildenafil	2 (5.4)	2 (13.3)	0	0.158[b]
Inhaled long acting β agonists	2 (5.9)	0	2 (9.5)	0.513[b]
Chronic use	2 (100)	0	2 (100)	0.400[b]
Steroids	10 (29.4)	4 (30.8)	6 (28.6)	0.999[b]
Inhaled	7 (70.0)	3 (75.0)	4 (66.7)	0.999[b]
Oral	3 (30.0)	1 (25.0)	2 (33.3)	0.999[b]
Chronic use	5 (50.0)	2 (50.0)	3 (50.0)	0.567[b]
Inhaled short acting β agonists	10 (29.4)	4 (30.8)	6 (28.6)	0.999[b]
Chronic use	4 (40.0)	1 (25.0)	3 (50.0)	0.286[b]
Inhaled antimuscarinics	7 (20.6)	2 (15.4)	5 (23.8)	0.682[b]
Chronic use	3 (42.9)	1 (50.0)	2 (40.0)	0.381[b]
Oral antihistamines	5 (14.7)	2 (15.4)	3 (14.3)	0.999[b]
Chronic use	1 (20.0)	1 (50.0)	0	0.545[b]
Leukotriene antagonists	1 (2.9)	0	1 (4.8)	0.999[b]
Health care need due to respiratory causes, n (%)				
Any health care utilization	16 (45.7)	5 (35.7)	11 (52.4)	0.491[a]
Additional outpatient visits	12 (35.3)	3 (23.6)	9 (42.9)	0.292[b]
Emergency Department attendance	11 (32.3)	5 (23.8)	6 (28.6)	0.999[b]
Bronchiolitis	9 (81.8)	5 (100)	4 (66.7)	0.432[a]
Pneumonia	5 (45.5)	2 (50.0)	3 (75.0)	0.999[b]
Hospital admission	6 (17.6)	2 (15.4)	4 (19.0)	0.999[b]
Bronchiolitis	4 (66.7)	1 (50.0)	3 (75.0)	0.999[b]
Pneumonia	3 (50.0)	0	3 (75.0)	0.270[b]
Follow-up in pediatric cardiology outpatient department, n (%)	16 (64.0)	8 (88.9)	8 (50.0)	0.088[b]
Cerebral palsy, n (%)	0	0	0	-
Glasses, n (%)	4 (10.8)	1 (7.7)	3 (14.3)	0.999[b]
Squint	4 (10.8)	2 (15.4)	2 (9.5)	0.627[b]
Myopia	1 (2.7)	1 (7.7)	0	0.382[b]
Other	4 (10.8)	1 (7.7)	3 (14.3)	0.999[b]
Hearing loss, n (%)	1 (2.9)	0	1 (4.8)	0.513[b]
Hearing aid	1 (100)	0	1 (100)	0.999[b]

PPHN: persistent pulmonary hypertension of the newborn.
[a] Chi-square test; [b] Fisher's exact test.

to blood flow. This type of vasoconstriction can, also, be the underlying cause of pulmonary hypertension caused by parenchymal diseases, making the classification of PPHN etiologies confusing [8, 12]. This sequence of events tends to occur in hypoxemic contexts, like prematurely closed ductus arteriosus, chronic fetal hypoxemia or drug exposure [8, 10, 12].

Perinatal asphyxia was diagnosed in 6 (7.8%) patients of this study. One patient had in-uterus indomethacin-induced closure of the patent ductus arteriosus and 1 had idiopathic arterial calcification observed at necropsy study. We had no knowledge of maternal drug exposure. We did not find any information regarding the prevalence of each of these diseases in PPHN series.

Table 6. Mary Sheridan Scale at 2 years of age.

Mary Sheridan Scale, n (%)	Total (n = 37)	Severe PPHN (n = 15)	Non severe PPHN (n = 22)	p
Runs	28 (82.4)	11 (84.6)	17 (81.0)	0.999[a]
Goes up and down the stairs with both feet at the time	28 (82.4)	11 (84.6)	17 (81.0)	0.999[a]
Builds 6 block towers	28 (82.4)	13 (100)	15 (71.4)	0.062[a]
Draws circles	26 (76.5)	10 (76.9)	16 (76.2)	0.999[a]
Likes books	32 (94.1)	13 (100)	19 (90.5)	0.513[a]
Turns one page at the time	30 (88.2)	12 (92.3)	18 (85.7)	0.999[a]
Mentions his/her first name	25 (75.8)	10 (83.3)	15 (71.4)	0.678[a]
Speaks to himself while playing	27 (79.4)	11 (84.6)	16 (76.2)	0.682[a]
Builds shot sentences with two or three words	29 (85.3)	12 (92.3)	17 (81.0)	0.627[a]
Names objects	25 (73.5)	10 (76.9)	15 (71.4)	0.999[a]
Incomprehensible speech	29 (85.3)	12 (92.3)	17 (81.0)	0.627[a]
Puts hat and shoes on	30 (88.2)	13 (100)	17 (81.0)	0.144[a]
Uses the spoon	31 (91.2)	13 (100)	18 (85.7)	0.270[a]
Drinks from a glass with spilling	31 (91.2)	13 (100)	18 (85.7)	0.270[a]
Unable to walk alone	3 (8.8)	1 (7.7)	2 (9.5)	0.999[a]
Throws away objects	1 (2.9)	0	1 (4.8)	0.999[a]
Doesn't seem to understand what he/she is told	1 (2.9)	0	1 (4.8)	0.999[a]
Can't pronounce understandable words	5 (14.7)	1 (7.7)	4 (19.0)	0.627[a]
Has no interest in his/hers surroundings	2 (5.9)	0	2 (9.5)	0.513[a]
Doesn't establish contact	1 (2.9)	0	1 (4.8)	0.999[a]
Can't mimic	1 (2.9)	0	1 (4.8)	0.999[a]

[a] Fisher's exact test

There was a significantly higher amount of abnormal neurological examinations before 2003. The improvement in the management of these high risk newborns is probably the reason for the better neurological outcome in the last epoch.

The hospitalizations were, however, longer after 2003, as well as the duration of the oxygen therapy. This could be explained by a higher percentage of infants with the severe form of PPHN after 2003 (54.8% vs. 48.6%). Longer oxygenation periods could also be part of more aggressive treatment strategies applied after 2003. Likewise, due to severity of patients, a higher number of infants were also submitted to parenteral feeding in this period.

The global mortality was 33.8%. The mortality was higher before the introduction of iNO and ECMO (52% vs. 34.2%), but this difference was not statistically significant (p = 0.161). This 17.8% reduction in mortality matches figures of the literature [9], but the global mortality remains higher than that observed in some centers, which is around 10-20% [3, 4, 12]. The explanation for this difference is the high mortality associated to CDH, the most frequent cause of PPNH in this study.

The survival rates of patients treated with ECMO described in the literature is superior to 80% [16], but only 2 patients received this type of treatment at our center. The influence of ECMO in mortality hasn't yet been established in our center. Sildenafil was proven to reduce mortality in centers where iNO was not available. Despite improving certain ventilation parameters and reducing the need for ECMO, iNO was not proven to reduce mortality [7, 8, 17]. The introduction of these two drug therapies was, probably, the most important factor associated to the reduction in mortality observed in our study.

When comparing between severe and non-severe PPHN, it was observed that mortality was significantly higher in the severe forms, as we expected. Also, children with the severe forms of PPHN also had an increased need for resuscitation, iNO therapy, diuretics and vasopressor support.

Vasopressor support using dopamine, dobutamine and adrenaline is essential when treating PPHN because it increases the systemic blood pressure, reduces the right left shunting, improves oxygenation and increases right ventricular contractility [3, 11,

35]. In our study, the need for vasopressor support was the only factor associated with a higher mortality (OR = 17.6, 95% CI = 1.9-157.3).

There was no significant statistical difference between any respiratory follow-up data when comparing children who had severe PPHN with those who had non-severe PPHN.

Knowing that out of 14 infants lost to the follow-up at least 10 seemed to have a good prognosis, probably the results would also be similar when comparing the two epochs.

The most frequent respiratory comorbidity was frequent wheezing (29.4%), followed by exercise-induced symptoms (26.5%). The most used drugs were steroids (mainly in the inhaled form) and inhaled short acting β agonists, with both being used in 29.4% of the patients. Sixteen (45.7%) patients needed some form of health care for respiratory causes. Bronchiolitis was the most common reason for both emergency department visits and hospital admissions. We found no information in the literature regarding the respiratory morbidities at 2 years of life to compare with our data.

None of the infants developed cerebral palsy. There was only 1 (2.9%) child with severe PPHN that developed hearing loss; none of the children with the non-severe form developed this condition. There isn't much information about this outcome, but the incidence of 2.9% in our study was inferior to some values we found in the literature, which ranged from 6.4% [1] to 24% [3]. Hearing loss may be an adverse effect of certain therapies, namely diuretics (which, in our study, were more used in the severe form), antibiotics (especially aminoglycosides), and mechanical ventilation [33, 36]. The patient that had sensorineural hearing loss was born after 2003, a period associated with increased duration of mechanical ventilation and oxygen treatment, which were strongly associated with this type of hearing loss [37]. Gentamicin, an aminoglycoside, was also administrated to this patient.

There was no statistically significant difference between the severe and non-severe forms of PPHN regarding the Mary Sheridan parameters (**Tab. 6**). The most common alarm sign was the inability to pronounce understandable words (14.7%).

There are studies that access the neurological outcomes at 18 to 24 months of age of children treated with iNO in the neonatal period [38-40] that came to the conclusion that iNO treatment did not increase neurological morbidity. In our study, however, only 26% of our patients were treated with iNO, so it is unreasonable to compare the data. A study by Marron et al., published in 1992, evaluated the neurological development and hearing loss [41]. However, the others only analyzed infants that underwent conservative treatment and the infants' neurological abilities with IQ tests at 1 year of age, a method very different from that we used in our study. These series did not report any patient sensorineural hearing loss. Our study identified 1 patient. Some studies also claim that congenital diaphragmatic hernia may also lead to a delay in neurodevelopment as well as greater likelihood of respiratory infections and inflammatory respiratory symptoms [21, 33]. This study had some limitations. The first was the fact that this was a retrospective study, meaning that it was subject to loss of data or lack of important information. Secondly, contacting the parents by phone meant there was a possibility that the parents were unable to provide objective and correct answers about their children's health status. Thirdly, we were unable to contact some families, meaning an even smaller sample size for the 2-year evaluation. Finally, we used the Mary Sheridan Scale to evaluate the children's development, but it lacks a measurable quantification.

Conclusion

Our study showed that after 2003 we had more therapeutic solutions for the management of PPHN, with the introduction of sildenafil, iNO and ECMO. We observed a reduction of 17.8% in mortality after 2003, although it was not statistically significant.

Despite the significantly higher mortality in patients with severe PPHN before discharge, there were no differences in the follow-up of the survivors at 2 years of age between those with severe and non-severe forms of the disease.

An evaluation over the years of admitted newborns with PPHN in our NICU is mandatory to confirm a relationship between the new treatment strategies and mortality reduction as well as the long-term morbidity.

Declaration of interest

The Authors declare that there is no conflict of interest.

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Appendix A. Questionnaire about prenatal, perinatal, and neonatal data; respiratory, neurological, and developmental morbidities; morbidity at 2 years of age.

PRENATAL, PERINATAL AND NEONATAL DATA

ID: _____

1. DEMOGRAPHICS

Birth date: ___ / ___ / _____
Sex ❑ $F_{(0)}$ ❑ $M_{(1)}$
Gestational age: _____ weeks
Birth weight: _____ g
IUGR (birth weight < 3 P - Fenton curves) ❑ $no_{(0)}$ ❑ $yes_{(1)}$

2. GESTATION

Multiple gestation ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Vigilance ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Prenatal corticosteroids ❑ $no_{(0)}$ ❑ Complete cycle (two betamethasone/four dexametasone administrations)$_{(1)}$
Smoking during pregnancy ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Drugs during pregnancy ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Gestational diabetes ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Chronic maternal hypertension ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Pre-eclampsia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Eclampsia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
HELLP syndromee ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Streptococcus agalactiae (group B) ❑ $no_{(0)}$ ❑ $yes_{(1)}$

3. DELIVERY

Mode of delivery ❑ Vaginal $_{(0)}$ ❑ Cesarean $_{(1)}$
Premature ruprture of membranes ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Intrapartum antibiotics ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Justification: _____
APGAR (1st and 5th minutes) ____ / ____
Resuscitation ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Endotracheal Tube ❑ $no_{(0)}$ ❑ $yes_{(1)}$

3. NEONATAL PERIOD

Pulmonary hypertension ❑ $no_{(0)}$ ❑ Non Severe$_{(1)}$ ❑ Severe$_{(2)}$
Cause of Pulmonary Hypertension: _____
Congenital hemodiaphragmatic hernia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Sepsis ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Pneumonia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Respiratory distress syndrome ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Perinatal asphyxia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Hyaline membrane disease ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Fetal tachyarrhythmia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Other: _____
Major Congenital Malformation ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Chromosomopathy ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Associated neonatal morbidities: _____
Bronchopulmonary dysplasia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Patent ductus arteriosus with surgical ligation need ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Necrotizing enterocolitis (grade ≥ 2A Bell) ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Retinopathy of prematurity (grade ≥ 2) ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Intraventricular hemorrhage (grade ≥ 3) ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Periventricular cystic/leukomalacia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Heart Ultrasound ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Neurological exam ❑ $no_{(0)}$ ❑ $yes_{(1)}$
❑ Normal $_{(0)}$ ❑ Changes$_{(1)}$ _____
Cranial Ultrasound ❑ $no_{(0)}$ ❑ $yes_{(1)}$
❑ Normal $_{(0)}$ ❑ Changes$_{(1)}$ _____

Treatment:

Inhaled Nitric Oxide ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Sildenafil ❑ no $_{(0)}$ ❑ yes $_{(1)}$
Prostagladins ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Dopamine ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Dobutamine ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Epinephrine ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Diuretics ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Other ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Conventional mechanical ventilation (> 12 h) ❑ $no_{(0)}$ ❑ yes $_{(1)}$ ❑ Duration: _____ days
Higher FiO_2 (> 24 h): _____

Appendix A (continued). Questionnaire about prenatal, perinatal, and neonatal data; respiratory, neurological, and developmental morbidities; morbidity at 2 years of age.

Duration of oxygen supplementation: _____
Extracorporeal Membrane Oxygenation ❑ no(0) ❑ yes(1)
Parenteral Feeding ❑ no(0) ❑ yes(1)
Duration: ____ days
Days at NICU: _____
Sildenafil at discharge ❑ no (0) ❑ yes (1)
Deceased ❑ no(0) ❑ yes(1)
Autopsy ❑ no(0) ❑ yes(1)
Autopsy findings ❑ no(0) ❑ yes(1)

RESPIRATORY MORBIDITY IN THE FIRST 2 YEARS OF LIFE

1. CARE AND EVOLUTION

Breastfeeding (≥ 1 month) ❑ no (0) ❑ yes (1) Duration: _____ months
Preventive measures after discharge (avoidance of crowded spaces, avoidance of tobacco smoke exposure, adequate hand hygiene) ❑ no(0) ❑ yes(1)
Pneumococcal polysaccharide conjugate vaccine ❑ no(0) ❑ yes(1)
Pavalizumab ❑ no(0) ❑ yes(1)
Influenza vaccine ❑ no(0) ❑ yes(1)

2. SOCIAL AND FAMILIAL FACTORS

Number of people in the household (patient included): _____
Any preschool aged siblings ❑ no(0) ❑ yes(1)
Attended daycare ❑ no(0) ❑ yes(1)
Age at beginning of daycare attendance: ___ months
Any smokers in the household ❑ no(0) ❑ yes(1)
Fireplace in the household ❑ no(0) ❑ yes(1)
Family history of asthma ❑ no(0) ❑ yes(1)
Maternal asthma ❑ no(0) ❑ yes(1)
Family history of atopy ❑ no(0) ❑ yes(1)
Maternal atopy ❑ no(0) ❑ yes(1)
Parents' education: ❑ ≤ 9 years (0) ❑ 10-12 years (1) ❑ > 12 years (2)
Parents' profession: _____
Graffar: ❑ Low class(0) ❑ Middle Class(1) ❑ High Class(2)

3. RESPIRATORY MORBIDITY

3.1) SYMPTOMS

Frequent cough ❑ no (0) ❑ yes (1)
Frequent wheeze ❑ no(0) ❑ yes(1)
Cough, wheeze or dyspnea with exertion ❑ no(0) ❑ yes(1)
Waking with cough ❑ no(0) ❑ yes(1)
Waking with wheeze ❑ no(0) ❑ yes(1)
Waking with dyspnea ❑ no(0) ❑ yes(1)

3.2) MEDICATION

Inhaled long acting β agonists ❑ no(0) ❑ yes(1)
Chronic use: ❑ no(0) ❑ yes(1)
Corticosteroids ❑ no(0) ❑ yes(1)
Oral CCT ❑ no(0) ❑ yes(1)
Inhaled CCT ❑ no(0) ❑ yes(1)
Chronic use: ❑ no(0) ❑ yes(1)
Inhaled short acting β agonists ❑ no(0) ❑ yes(1)
Chronic use: ❑ no(0) ❑ yes(1)
Inhaled antimuscarinics ❑ no(0) ❑ yes(1)
Chronic use: ❑ no(0) ❑ yes(1)
Oral antihistamines ❑ no(0) ❑ yes(1)
Chronic use: ❑ no(0) ❑ yes(1)
Leukotriene antagonists ❑ no(0) ❑ yes(1)
Other ❑ no(0) ❑ yes(1) _____

3.3) HEALTH CARE UTILIZATION

Any health care utilization for respiratory causes ❑ no(0) ❑ yes(1)

OUTPATIENT VISITS

Followed at pediatric cardiology (outpatient) ❑ no(0) ❑ yes(1)
Additional outpatient visits for respiratory causes ❑ no(0) ❑ yes(1)

EMERGENCY DEPARTMENT (ED)

Any ED attendance for respiratory causes ❑ no(0) ❑ yes(1)

Appendix A (continued). Questionnaire about prenatal, perinatal, and neonatal data; respiratory, neurological, and developmental morbidities; morbidity at 2 years of age.

Any ED attendance for bronchiolitis ❑ no(0) ❑ yes(1)
Any ED attendance for pneumonia ❑ no(0) ❑ yes(1)

HOSPITAL ADMISSIONS

Any hospital admission for respiratory causes ❑ no(0) ❑ yes(1)
Any hospital admission for bronchiolitis ❑ no(0) ❑ yes(1)
Any hospital admission for pneumonia ❑ no(0) ❑ yes(1)
Any hospital admission for other respiratory causes ❑ no(0) ❑ yes(1)

NEUROLOGICAL AND DEVELOPMENT STATUS AT 2 YEARS OF AGE

Cerebral Palsy (Gross Motor Function Classification System): ❑ no(0) ❑ Type I(1) ❑ Type II(2) ❑ Type III(3) ❑ Type IV(4) ❑ Type V(5)

Vision

Glasses ❑ no(0) ❑ yes(1)
Squint ❑ no(0) ❑ yes(1)
Myopia ❑ no(0) ❑ yes(1)
Other ❑ no(0) ❑ yes(1) _____

Hearing

Hearing loss ❑ no(0) ❑ yes(1)
Hearing aid ❑ no(0) ❑ yes(1)

Mary Sheridan Scale

Runs ❑ no(0) ❑ yes(1)
Goes up and down the stairs with both feet at the time ❑ no(0) ❑ yes(1)
Builds 6 block towers ❑ no(0) ❑ yes(1)
Draws circles ❑ no(0) ❑ yes(1)
Likes books ❑ no(0) ❑ yes(1)
Turns one page at the time ❑ no(0) ❑ yes(1)
Mentions his/her first name ❑ no(0) ❑ yes(1)
Speaks to himself while playing ❑ no(0) ❑ yes(1)
Builds shot sentences with two or three words ❑ no(0) ❑ yes(1)
Names objects ❑ no(0) ❑ yes(1)
Incomprehensible speech ❑ no(0) ❑ yes(1)
Puts hat and shoes on ❑ no(0) ❑ yes(1)
Uses the spoon ❑ no(0) ❑ yes(1)
Drinks from a glass with spilling ❑ no(0) ❑ yes(1)

Unable to walk alone ❑ no(0) ❑ yes(1)
Throws away objects ❑ no(0) ❑ yes(1)
Doesn't seem to understand what he/she is told ❑ no(0) ❑ yes(1)
Can't pronounce understandable words ❑ no(0) ❑ yes(1)
Has no interest in his/hers surroundings ❑ no(0) ❑ yes(1)
Doesn't establish contact ❑ no(0) ❑ yes(1)
Can't mimic ❑ no(0) ❑ yes(1)