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Original article

Respiratory morbidity in very preterm and very low birth weight infants: the first 2 years of life

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Abstract

Respiratory morbidity in the first two years of life, including recurrent symptoms and frequent hospitalizations, is a common problem in very preterm and very low birth weight (VLBW) infants. We conducted a retrospective cohort study aiming to describe the respiratory morbidity at 2 years of corrected age for very preterm and VLBW infants and to identify potential risk factors for its development in a Portuguese based population born in a tertiary referral center between 2009 and 2011. Data were collected from patient's clinical files and using a standardized questionnaire-based clinical interview for parents. A total 59 children were included. Thirteen (22.0%) had recurrent respiratory symptoms and 12 (20.3%) were using chronic respiratory medication. Health care utilization for respiratory causes was frequent (57.6%), particularly emergency department attendance (50.8%). Twenty seven (45.8%) had additional outpatient visits for respiratory causes and hospital admission was necessary for 8 (13.6%) patients. Factors associated with increased recurrent respiratory symptoms included maternal hypertensive disorders during pregnancy, umbilical artery flow disturbances, being small for gestational age, bronchopulmonary dysplasia, retinopathy of prematurity, intraventricular hemorrhage and a weight percentile below 3 at 6, 12 and 24 months of corrected age. Premature rupture of membranes was negatively associated with respiratory morbidity. Respiratory morbidity at 2 years of age is a common problem in very preterm and VLBW children from our population. Several perinatal and developmental risk factors were identified for respiratory morbidity. Further studies are needed to clarify the importance of these factors, as they can lead to changes in healthcare guidelines.

Keywords

Preterm infants, very low birth weight, small for gestational age, bronchopulmonary dysplasia, respiratory tract infections, wheezing.

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Introduction

Preterm birth has increased over the last 20 years and survival rates have improved [1-4]. Chronic respiratory problems remain a common complication of prematurity, and very preterm [1, 2, 4] and very low birth weight (VLBW) [5, 6] infants are especially vulnerable.

These children often experience recurrent respiratory symptoms, with wheezing being the most frequently described outcome. Recurrent cough is also common, as is the need for bronchodilators and inhaled corticosteroids. Rates of hospitalization are considerably higher in this population, with respiratory illnesses being the most common cause of admission [5-10].

Several perinatal, neonatal and familial factors, as well as early life exposures have also been associated with increased respiratory morbidity in the first years of life [7, 11-17].

Hospitalization rates usually decline after the second year of life and by school age symptoms typically become mild [1, 2]. However, in some individuals recurrent wheezing and pulmonary function impairment may persist throughout childhood and early adulthood [18-21].

The aim of this study is to describe the respiratory morbidity at 2 years of corrected age for very preterm and VLBW infants and to identify potential risk factors for its development in a Portuguese based population born in the modern neonatal care era.

Patients and methods

This retrospective cohort study was conducted in a neonatal intensive care unit (NICU) of a tertiary referral center hospital in Porto, Portugal – "Centro Hospitalar de São João".

All children born at our hospital between January 1, 2009 and December 31, 2011 with less than 32 weeks of gestational age or less than 1,500 g at birth, and admitted to the NICU of the hospital were included. Exclusion criteria were: major malformations, chromosomal disorders, congenital TORCH infection, death during NICU stay and transfer to another hospital before completing 7 days at the local NICU.

All information was collected retrospectively. Patients' clinical files were consulted and data about demographics, perinatal and neonatal characteristics were recorded (**Appendix A**).

Gestational age was defined by menstrual age (women with regular menstrual cycles), ultrasound examination (in the absence of a menstrual date or when a difference of two or more weeks existed between menstrual age and that derived sonographically), or by the New Ballard Score (in the absence of obstetrical indexes) [22, 23]. Small for gestational age (SGA) was defined as a birth weight below the 10th centile of Fenton's fetal growth charts [24].

Histological chorioamnionitis was classified according to Blanc [25] (stage I: intervilositis; stage II: chorionitis; stage III: chorioamnionitis, funisitis [polymorphonuclear leukocytes in the Wharton's jelly or umbilical vessel walls], vasculitis [polymorphonuclear leukocytes in chorionic or umbilical blood vessel walls]).

Diagnosis of respiratory distress syndrome (RDS) was made using clinical and radiological criteria [26]: (1) PaO_2 < 50 mmHg in room air, central cyanosis in room air, a requirement for supplemental oxygen to maintain PaO_2 > 50 mmHg or a requirement for supplemental oxygen to maintain a pulse oximeter saturation over 85% within the first 24 h of life and (2) a chest radiograph consistent with RDS (reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 h of life. RDS was classified as light, moderate or severe according to X ray appearance ranging from a light reticulogranular pattern with air bronchograms to white lungs, an adaptation from the classification by Couchard et al. [27].

Bronchopulmonary dysplasia (BPD) was defined according to the National Institute of Child Health and Human Development consensus criteria [28, 29]. Patent ductus arteriosus (PDA) was considered when a hemodynamically significant defect was diagnosed on echocardiography. Diagnosis and staging of necrotizing enterocolitis (NEC) was made using the modified Bell criteria [30]. Retinopathy of prematurity (ROP) was staged according to the

International Classification [31]. Proven neonatal sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture. Intraventricular hemorrhage (IVH) was classified according to Papile et al. [32] (grade I: germinal matrix hemorrhage; grade II: IVH without ventricular dilation; grade III: IVH with ventricular dilation; grade IV: germinal matrix hemorrhage or IVH with parenchymal involvement).

Afterwards, information about respiratory morbidity, care and evolution during the first 2 years of life (**Appendix B**) was collected in a single interview with the patients' parents conducted at a routine hospital visit for the child or telephonically for those who had no scheduled visits or missed their appointments.

Weight percentiles at 6, 12 and 24 months of corrected age were defined according to the World Health Organization Child Growth Standards [33]. Socioeconomical status was graded using the Graffar classification as adapted to the Portuguese population [34].

Written or oral consent was obtained after the parents were fully informed about the study's design and purpose.

This study was approved by the Centro Hospitalar de São João's ethics committee.

Statistical analysis was performed using *SPSS® 19* (IBM®, New York, USA). Categorical variables were described using absolute and relative frequencies. Continuous variables (with non symmetrical distribution) were described using median and range. We used Chi square test to explore associations for categorical variables and Mann Whitney test for continuous variables. Results are presented as odds ratio (OR) with the respective 95% confidence intervals (95% CI). A p value < 0.05 was considered significant.

Results

A total of 119 patients met the inclusion criteria. Thirteen were excluded for malformations, 5 for chromosomal disorders, 13 for death during NICU stay and 16 for transfer to another hospital before completing 7 days at the local NICU. Additionally, 12 children were excluded for loss of follow up and 1 for parents' refusal to participate. In the end, a total of 59 children were included.

The populations' demographics, perinatal and neonatal data are summarized in **Tab. 1**. **Tab. 2** describes the participants' care and evolution after discharge, social and familiar characteristics.

According to **Tab. 3**, in the first 2 years of life, 13 (22.0%) had recurrent respiratory symptoms and 12 (20.3%) were using chronic respiratory medication. Health care use for respiratory causes was frequent (57.6%), particularly emergency department attendance (50.8%). Hospital admission was necessary for 8 (13.6%) patients. Twenty seven (45.8%) had additional outpatient visits for respiratory causes. Eighteen (30.5%) parents had to miss at least 1 day at work for their child's respiratory problems (**Tab. 3**).

Table 1. Demographics, perinatal and neonatal characteristics of the study population (continues on the next page).

	Total (n = 59)	
DEMOGRAPHICS		
Female, n (%)	36	(61.0)
Gestational age (weeks), median (range)	30	(25-37)
Birth weight (g), median (range)	1,195	(520-2,435)
SGA (small for gestational age), n (%)	26	(44.1)
Asymmetrical SGA (small for gestational age), n (%)	7	(11.9)
GESTATION		
Multiple gestation, n (%)	21	(35.6)
Prenatal corticosteroids, n (%)	54	(91.5)
Incomplete cycle, n (%)	9	(15.3)
Complete cycle, n (%)	45	(76.3)
Smoking during pregnancy, n (%)	9	(15.3)
Gestational diabetes, n (%)	5	(8.5)
Chronic maternal hypertension, n (%)	3	(5.1)
Hypertensive disorders of pregnancy, n (%)	11	(18.6)
Pre eclampsia, n (%)	9	(15.3)
Eclampsia, n (%)	1	(1.7)
HELLP syndrome, n (%)	2	(3.4)
Histological chorioamnionitis, n (%)	19	(32.2)
Funisitis and/or chorionic vasculitis, n (%)	10	(16.9)
Clinical chorioamnionitis, n (%)	2	(3.4)
Placental abruption, n (%)	3	(5.1)
Umbilical artery flow disturbances[a], n (%)	14	(23.7)
DELIVERY		
Cesarean section, n (%)	49	(83.1)
Premature rupture of membranes, n (%)	10	(16.9)
Hours of membrane rupture, median (range)	62	(3-1,992)
Intrapartum antibiotics for premature rupture of membranes, n (%)	6	(10.2)
APGAR (1st minute)		
0-3, n (%)	6	(10.2)
4-6, n (%)	15	(25.4)
7-10, n (%)	38	(64.4)
APGAR (5th minute)[b]		
0-3, n (%)	1	(1.7)
4-6, n (%)	6	(10.2)
7-10, n (%)	51	(87.9)
Need for resuscitation, n (%)	30	(50.8)
Early CPAP, n (%)	27	(45.8)

[a]Includes umbilical artery flow absence or inversion; [b]n = 58.

Table 1. Demographics, perinatal and neonatal characteristics of the study population (continues from the previous page).

	Total (n = 59)	
NEONATAL PERIOD (NICU STAY)		
SNAPPE II score[c]		
0-9, n (%)	32	(54.2)
10-19, n (%)	6	(10.2)
20-29, n (%)	8	(13.6)
30-39, n (%)	3	(5.1)
40-49, n (%)	2	(3.4)
50-59, n (%)	1	(1.7)
60-69, n (%)	1	(1.7)
70-79, n (%)	0	(0.0)
≥ 80, n (%)	0	(0.0)
CRIB score[c]		
0-5, n (%)	47	(79.7)
6-10, n (%)	6	(10.2)
11-15, n (%)	0	(0.0)
≥ 16, n (%)	0	(0.0)
RDS (respiratory distress syndrome), n (%)	29	(49.2)
Mild, n (%)	13	(22.0)
Moderate, n (%)	11	(18.6)
Severe, n (%)	5	(8.5)
Surfactant administration, n (%)	29	(49.2)
Conventional mechanical ventilation, n (%)	27	(45.8)
Invasive ventilation only, n (%)	1	(1.7)
Invasive ventilation and nCPAP, n (%)	26	(44.1)
nCPAP only, n (%)	24	(40.7)
Days of conventional mechanical ventilation, median (range)	7	(1-59)
Days of nCPAP, median (range)	27	(2-62)
Supplemental oxygen, n (%)	29	(49.2)
Maximal fraction of inspired O_2, median (range)	0.21	(0.21-1.00)
Days of supplemental oxygen, median (range)	7	(1-121)
Supplemental oxygen on discharge, n (%)	1	(1.7)
BPD (bronchopulmonary dysplasia), n (%)	6	(10.2)
Mild, n (%)	2	(3.4)
Moderate, n (%)	1	(1.7)
Severe, n (%)	3	(5.1)
PDA (patent ductus arteriosus), n (%)	14	(23.7)
NEC (necrotizing enterocolitis) (≥ 2A), n (%)	3	(5.1)
ROP (retinopathy of prematurity) (≥ II), n (%)	8	(13.6)
IVH (intraventricular hemorrhage) (≥ III), n (%)	3	(5.1)
Hydrocephalus, n (%)	2	(3.4)
Periventricular cystic leukomalacia, n (%)	6	(10.2)
Sepsis, n (%)	23	(39.0)
Days at the NICU, median (range)	43	(7-154)
Weight on discharge (g), median (range)	1,920	(848-2,800)
Weight percentile on discharge		
< 3, n (%)	43	(72.9)
≥ 3, n (%)	16	(27.1)
Season of discharge		
Spring, n (%)	22	(37.3)
Summer, n (%)	14	(23.7)
Autumn, n (%)	8	(13.6)
Winter, n (%)	15	(25.4)

[c]n = 53.

Table 2. Care and evolution after discharge from NICU.

	Total (n = 59)	
Breastfeeding, n (%)	34	(57.6)
Duration of breastfeeding (months), median (range)	3	(1-27)
Isolation during first winter season, n (%)	17	(28.8)
Other preventive measures, n (%)	35	(59.3)
Antipneumococcal vaccine, n (%)	57	(96.6)
Palivizumab, n (%)	47	(79.7)
Influenza vaccine, n (%)	20	(33.9)
Weight percentile at 6 months of corrected age[a]		
< 3, n (%)	12	(20.7)
≥ 3, n (%)	46	(79.3)
Weight percentile at 12 months of corrected age[b]		
< 3, n (%)	9	(16.1)
≥ 3, n (%)	47	(83.9)
Weight percentile at 24 months of corrected age[c]		
< 3, n (%)	5	(8.8)
≥ 3, n (%)	52	(91.2)
SOCIAL AND FAMILIAR CHARACTERISTICS		
Socioeconomical status (Graffar classification)		
Class I, n (%)	17	(28.8)
Class II, n (%)	20	(33.9)
Class III, n (%)	18	(30.5)
Class IV, n (%)	4	(6.8)
Class V, n (%)	0	(0.0)
Number of people in the household, median (range)	4	(2-7)
Preschool aged siblings, n (%)	24	(40.7)
Stayed at home during the first two years of life, n (%)	44	(74.6)
Day care attendance, n (%)	15	(25.4)
Age at beginning of day care attendance, median (range)	9	(0-20)
Any smokers in the household, n (%)	27	(45.8)
Fireplace in the household, n (%)	26	(44.1)
Family history of asthma, n (%)	24	(40.7)
Maternal, n (%)	13	(22.0)
Family history of atopy, n (%)	22	(37.3)
Maternal, n (%)	12	(20.3)

[a]n = 58; [b]n = 56; [c]n = 57.

Being SGA was significantly associated with the presence of recurrent respiratory symptoms (OR: 3.84, 95% CI: 1.02-14.37), as were maternal hypertensive disorders during pregnancy (OR: 4.17, 95% CI: 1.02-17.05) and umbilical artery flow disturbances (OR: 10.67, 95% CI: 2.61-43.64). Premature rupture of membranes (PROM) was negatively associated with the presence of respiratory symptoms in the first 2 years of life (**Tab. 4**).

BPD (OR: 9.78, 95% CI: 1.55-61.73), ROP (stage ≥ II) (OR: 5.00, 95% CI: 1.03-24.30) and IVH (grade ≥ III) had significant positive associations with respiratory morbidity, as did a weight percentile below 3 at 6, 12 and 24 months of corrected age (**Tab. 4**).

Table 3. Respiratory morbidity in the first two years of life.

	Total (n = 59)	
SYMPTOMS		
Recurrent respiratory symptoms, n (%)	13	(22.0)
Recurrent cough, n (%)	4	(6.8)
Recurrent wheeze, n (%)	3	(5.1)
Recurrent respiratory symptoms on exertion, n (%)	10	(16.9)
Waking with cough, n (%)	4	(6.8)
Waking with wheeze, n (%)	3	(5.1)
Waking with dyspnea, n (%)	4	(6.8)
Respiratory symptoms with respiratory illness only, n (%)	30	(50.8)
Cough, n (%)	33	(55.9)
Wheeze, n (%)	28	(47.5)
NEED FOR RESPIRATORY MEDICATION		
Chronic respiratory medication[a], n (%)	12	(20.3)
Long acting β agonists, n (%)	0	(0.0)
Daily inhaled corticosteroids, n (%)	5	(8.5)
Daily short acting β agonists, n (%)	2	(3.4)
Frequent inhaled antimuscarinics use, n (%)	2	(3.4)
Daily leukotriene antagonists use, n (%)	2	(3.4)
Frequent antihistamines use, n (%)	5	(8.5)
Respiratory medication for respiratory illness only[b], n (%)	25	(42.4)
HEALTH CARE UTILIZATION		
Health care utilization for respiratory causes, n (%)	34	(57.6)
Additional outpatient visits for respiratory causes, n (%)	27	(45.8)
Emergency department attendance for respiratory causes, n (%)[c]	30	(50.8)
Emergency department attendance for bronchiolitis, n (%)	16	(27.1)
Emergency department attendance for pneumonia, n (%)	2	(3.4)
Emergency department attendance for other respiratory causes, n (%)	17	(28.8)
Hospital admission for respiratory causes, n (%)[d]	8	(13.6)
Hospital admission for bronchiolitis, n (%)	7	(11.9)
Hospital admission for pneumonia, n (%)	1	(1.7)
Hospital admission for other respiratory causes, n (%)	3	(5.1)
IMPACT ON PARENTS' LIFE		
Any missed days at work, n (%)	18	(30.5)
Number of days missed at work by parents, median (range)	7	(2-10)

[a]Includes inhaled long and short acting β agonists, inhaled antimuscarinics, inhaled corticosteroids, oral leukotriene antagonists and oral antihistamines; [b]includes inhaled long and short acting β agonists, inhaled antimuscarinics, inhaled corticosteroids, and oral antihistamines; [c]in the subsection "Emergency department attendance for respiratory causes", 30 refers to the number of children who had *any* (≥ 1) emergency department attendance for respiratory causes during their first two years of life; since some of these children had *more than one* attendance, and those attendances were frequently for different illnesses, the sum exceeds 30 (for example, if a child had one attendance for bronchiolitis and another for pneumonia, they were considered as having "emergency department attendance for respiratory causes", "emergency department attendance for bronchiolitis" and also "emergency department attendance for pneumonia"); [d]the same applies to the subsection "Hospital admission for respiratory causes", in which 8 is the number of children who had *any* (≥ 1) hospital admission for respiratory causes, and some children had *more than one* admission, for different reasons.

Table 4. Factors associated with respiratory morbidity in the first two years of life (continues on the next page).

How to read **Tab. 4**: the percentages represent the proportion of children in each category that developed recurrent respiratory symptoms. For example, in the case of "Chronic maternal hypertension": 3 children had a maternal history of chronic hypertension, of whom 2 developed recurrent respiratory symptoms (2/3 = 66.7%); on the other hand, of the 56 children with no maternal history of chronic hypertension, only 11 went on to develop recurrent respiratory symptoms (11/56 = 19.6%). The same applies for the other variables. We didn't include the "n" for each category in **Tab. 4** as they can be found in **Tables 1** and **2**.

	Recurrent respiratory symptoms, n (%)	OR (95% CI)	p
Overall	13 (22.0)		
Sex			
Female	9 (25.0)	1.00 (ref)	0.49
Male	4 (17.4)	0.63 (0.17-2.36)	
SGA (small for gestational age)			
No	4 (12.1)	1.00 (ref)	**0.04**
Yes	9 (34.6)	**3.84 (1.02-14.37)**	
Assymetrical SGA (small for gestational age)			0.58
No	12 (23.1)	1.00 (ref)	
Yes	1 (14.3)	0.56 (0.06-5.08)	
Prenatal corticosteroids			
No	0 (0.0)	1.00 (ref)	0.21
1 dose	3 (33.3)	n.a.	
2 doses	10 (22.2)	n.a.	
Smoking during pregnancy			
No	12 (24.0)	1.00 (ref)	0.36
Yes	1 (11.1)	0.40 (0.05-3.49)	
Gestational diabetes			
No	13 (24.1)	1.00 (ref)	0.11
Yes	0 (0.0)	n.a.	
Chronic maternal hypertension			
No	11 (19.6)	1.00 (ref)	0.06
Yes	2 (66.7)	8.18 (0.68-98.62)	
Hypertensive disorders of pregnancy			**0.04**
No	8 (16.7)	1.00 (ref)	
Yes	5 (45.5)	**4.17 (1.02-17.05)**	
Placental disorders[a]			
No	9 (23.1)	1.00 (ref)	0.79
Yes	4 (20.0)	0.83 (0.22-3.14)	
Umbilical artery flow disturbances[b]			**0.001**
No	5 (11.1)	1.00 (ref)	
Yes	8 (57.1)	**10.67 (2.61-43.64)**	
Cesarean section			
No	0 (0.0)	1.00 (ref)	**0.02**
Yes	13 (26.5)	n.a.	
PROM (premature rupture of membranes)			**0.02**
No	13 (26.5)	1.00 (ref)	
Yes	0 (0.0)	n.a.	
APGAR (5th minute)			
0-6	2 (28.6)	1.00 (ref)	0.68
≥ 7	11 (21.6)	0.69 (0.12-4.04)	
Need for resuscitation			
No	5 (17.2)	1.00 (ref)	0.38
Yes	8 (26.7)	1.75 (0.50-6.14)	

[a]Includes histological chorioamnionitis, funisitis and chorionic vasculitis; [b]includes umbilical artery flow absence or inversion.

Table 4. Factors associated with respiratory morbidity in the first two years of life (continues from the previous page).

	Recurrent respiratory symptoms, n (%)	OR (95%CI)	p
Early CPAP			
No	10 (31.3)	1.00 (ref)	0.06
Yes	3 (11.1)	0.28 (0.70-1.13)	
RDS (respiratory distress syndrome)			
No	8 (26.7)	1.00 (ref)	0.38
Yes	5 (17.2)	0.57 (0.16-2.02)	
Surfactant administration			
No	7 (23.3)	1.00 (ref)	0.81
Yes	6 (20.7)	0.86 (0.25-2.95)	
Conventional mechanical ventilation			
No	7 (21.9)	1.00 (ref)	0.97
Yes	6 (22.2)	1.02 (0.30-3.51)	
nCPAP only			
No	10 (28.6)	1.00 (ref)	0.13
Yes	3 (12.5)	0.36 (0.09-1.47)	
Supplemental oxygen			
No	6 (20.0)	1.00 (ref)	0.70
Yes	7 (24.1)	1.27 (0.37-4.37)	
BPD (bronchopulmonary dysplasia)			
No	9 (17.0)	1.00 (ref)	**0.01**
Yes	4 (66.7)	**9.78 (1.55-61.73)**	
PDA (patent ductus arteriosus)			
No	10 (22.2)	1.00 (ref)	0.95
Yes	3 (21.4)	0.96 (0.22-4.10)	
NEC (necrotizing enterocolitis) (≥ 2A)			
No	12 (21.4)	1.00 (ref)	0.64
Yes	1 (33.3)	1.83 (0.15-21.98)	
ROP (retinopathy of prematurity) (≥ II)			
No	8 (16.7)	1.00 (ref)	**0.05**
Yes	4 (50.0)	**5.00 (1.03-24.30)**	
IVH (intraventricular hemorrhage) (≥ III)			
No	11 (19.3)	1.00 (ref)	**0.01**
Yes	2 (100.0)	n.a.	
Hydrocephalus			
No	12 (21.1)	1.00 (ref)	0.38
Yes	1 (50.0)	3.75 (0.22-64.44)	
Periventricular cystic leukomalacia			
No	12 (24.0)	1.00 (ref)	0.36
Yes	1 (11.1)	0.40 (0.05-3.49)	
Sepsis			
No	6 (16.7)	1.00 (ref)	0.22
Yes	7 (30.4)	2.19 (0.63-7.62)	
Weight percentile on discharge			
< 3	10 (23.3)	1.00 (ref)	0.71
≥ 3	3 (18.8)	0.76 (0.18-3.22)	
Season of discharge			
Spring	4 (18.2)	1.00 (ref)	
Summer	4 (28.6)	1.80 (0.37-8.80)	0.90
Autumn	2 (25.0)	1.50 (0.22 10.36)	
Winter	3 (20.0)	1.13 (0.21-5.95)	

Table 4. Factors associated with respiratory morbidity in the first two years of life (continues from the previous column).

	Recurrent respiratory symptoms, n (%)	OR (95%CI)	p
Breastfeeding			
No	7 (28.0)	1.00 (ref)	0.35
Yes	6 (17.6)	0.55 (0.16-1.91)	
Isolation during first winter season			
No	10 (23.8)	1.00 (ref)	0.60
Yes	3 (17.6)	0.67 (0.16-2.88)	
Antipneumococcal vaccine			
No[c]	2 (40.0)	1.00 (ref)	0.34
Yes	11 (20.4)	0.38 (0.06-2.59)	
Palivizumab			
No	4 (33.3)	1.00 (ref)	0.31
Yes	9 (19.1)	0.47 (0.12-1.93)	
Influenza vaccine			
No	8 (18.6)	1.00 (ref)	0.31
Yes	5 (31.3)	1.99 (0.54-7.35)	
Weight percentile at 6 months of corrected age			**0.002**
< 3	7 (58.3)	1.00 (ref)	
≥ 3	6 (13.0)	**0.11 (0.03-0.45)**	
Weight percentile at 12 months of corrected age			**0.001**
< 3	6 (66.7)	1.00 (ref)	
≥ 3	6 (12.8)	**0.07 (0.01-0.37)**	
Weight percentile at 24 months of corrected age			**0.004**
< 3	4 (80.0)	1.00 (ref)	
≥ 3	9 (17.3)	**0.05 (0.01-0.53)**	
Socioeconomical status (Graffar classification)			
Class I	4 (23.5)	1.00 (ref)	0.35
Class II	2 (10.0)	0.36 (0.06-2.28)	
Class III	6 (33.3)	1.63 (0.37-7.20)	
Class IV	1 (25.0)	1.08 (0.09-13.54)	
Preschool aged siblings			
No	10 (28.6)	1.00 (ref)	0.13
Yes	3 (12.5)	0.36 (0.09-1.47)	
Day care attendance			
No	11 (25.0)	1.00 (ref)	0.33
Yes	2 (13.3)	0.46 (0.09-2.37)	
Any smokers in the household			
No	7 (21.9)	1.00 (ref)	0.97
Yes	6 (22.2)	1.02 (0.30-3.51)	
Fireplace in the household			
No	9 (27.3)	1.00 (ref)	0.27
Yes	4 (15.4)	0.49 (0.13-1.80)	
Family history of asthma			
No	8 (22.9)	1.00 (ref)	0.85
Yes	5 (20.8)	0.89 (0.25-3.14)	
Family history of atopy			
No	6 (16.2)	1.00 (ref)	0.17
Yes	7 (31.8)	2.41 (0.69-8.44)	

[c]Incomplete immunization (1 or 2 doses) or no immunization.

We found no significant associations for gestational age, birth weight, SNAPPE II and CRIB scores, maximal fraction of inspired O_2 during NICU stay, duration of NICU stay, duration of breastfeeding, number of people in the household and age at beginning of daycare attendance (data not shown).

Discussion

We aimed to describe the respiratory morbidity at 2 years of corrected age in a Portuguese population of very preterm and VLBW infants. The prevalence of recurrent respiratory symptoms was 22.0%, with symptoms on exertion being the most frequent manifestation (16.9%). Twelve patients (20.3%) required chronic respiratory medication and 57.6% had health care utilization for respiratory causes in the first 2 years of life.

The prevalence of respiratory symptoms and chronic respiratory medication use in our population is lower than that described in most studies [4, 8, 9, 13, 35, 36]. The great variability among studies' inclusion and exclusion criteria, definition of outcomes and age at evaluation makes it difficult to compare results. Still, the fact that our population is highly selected, excluding outborn patients with potentially more severe neonatal disease justifying their transfer to a tertiary center, could explain some of the differences observed. Also, the low prevalence of BPD in our population (10.2%), although comparable to a previous Portuguese study (12.9%) [37], could contribute to the overall low respiratory morbidity. However, rates described for preterm children without BPD are still higher than those we found [8, 36]. Differences in prescription criteria could explain some variations in medication use as well.

The rate of hospital admissions for respiratory causes was also lower than that found in previous studies, although similar rates have been described [1, 8, 35, 36, 38]. Once again, differences in inclusion and exclusion criteria, age at evaluation and admission criteria make any conclusive comparisons difficult.

We found a significant association between being SGA and recurrent respiratory symptoms. While some have found a significant association between intrauterine growth restriction (IUGR) and persistent wheezing, others failed to confirm it [14, 39]. Still, our results are supported by animal studies showing an association between IUGR and persisting alterations in lung structure and function and by findings of abnormal lung function in school-aged children born SGA [40, 41].

While no studies have described an association between umbilical artery flow disturbances and respiratory morbidity during infancy, we believe our results to be consistent with those by Hartung et al. [42] describing a positive association between absent or reversed end diastolic umbilical artery flow and BPD. Also, our findings of a positive association between hypertensive disorders of pregnancy and recurrent respiratory symptoms are in line with those by Rusconi et al. [43].

It is possible that IUGR, hypertensive disorders of pregnancy and umbilical artery flow abnormalities represent to some extent a common pathway of placental insufficiency and altered angiogenesis, as proposed by others [44, 45]. However, more studies are necessary to confirm this.

Cesarean section has been associated with the development of asthma and recurrent wheezing [46, 47]. The lack of exposure to vaginal flora could alter immune system development in these children, with a subsequent increased risk for asthma and atopy [46, 47]. Because we studied a very young population, we didn't include asthma diagnosis as a respiratory outcome; follow up of this population is crucial to clarify whether those with recurrent respiratory symptoms during infancy are diagnosed with asthma in the future [47, 48].

We found a negative association between PROM and recurrent symptoms. Teune et al. [11] found the opposite and Williams et al. [49] described an increased incidence of hospital admissions for respiratory causes in these infants. However, PROM has been associated with a reduced risk of RDS. The proposed biological mechanism behind this association states PROM as an inflammation inducer that accelerates lung maturity [1, 50]. Therefore, although lacking support from epidemiological studies, we believe that our findings are biologically plausible as infants with PROM may present with less RDS and need less aggressive respiratory interventions, and therefore develop less respiratory morbidity.

Our findings of a positive association between BPD and respiratory morbidity during infancy are in line with what has been described [3, 8, 14, 15].

ROP and IVH were also significantly associated with recurrent respiratory symptoms. We found no studies describing a relation between these disorders and respiratory morbidity in the first years of life. However, they appear to share common risk factors and an association between ROP and BPD has been described [37, 51-53]. Also, because we didn't exclude children with neurological disorders,

it is possible that infants with ROP and particularly IVH represent those with the worst neurological outcome, which may account for their increased respiratory morbidity [54-56].

Having a weight percentile below 3 at 6, 12 or 24 months was significantly associated with respiratory morbidity. Most studies have described the negative effects of rapid weight gain or being overweight on pulmonary function and the development of asthma and recurrent wheezing [57-59]. However, these findings are not universal [60] and a study by Zhang et al. [61] found that being overweight during the first 2 years of life was associated with a decreased risk of asthma and better lung function. Proposed explanations emphasized the influence of a well nourished state in promoting maximal postnatal lung development at an age when great alveolar development and multiplication occurs [61]. Because we chose to focus on the effects of poor weight evolution and underweight persistence, the extent to which our results may be compared to previous reports is limited.

We chose to define outcomes as reported by parents, a method frequently used in other studies [3]; however, it creates the potential for information bias. Also, the study's retrospective design creates the possibility of recall bias.

Still, the small number of participants is one of our study's major limitations and it may justify the lack of significant associations between respiratory morbidity and several of the factors we tested for. Many such factors have been associated, albeit inconsistently, with increased respiratory morbidity in the first years of life. These include the duration of stay at the NICU [3, 10], the use and duration of mechanical ventilation [6, 14] and ventilator parameters such as a high peak inspiratory pressure [35]. Pre- and postnatal exposure to maternal tobacco smoke during pregnancy [1, 4, 7, 10, 11, 15], having preschool aged siblings or attending daycare [15, 16] and having a lower socioeconomical status [7, 17] have all been associated with recurrent respiratory symptoms; a positive association with family history of atopy has also been described [14, 15, 17], although there is conflicting evidence [7, 16]. On the other hand, breastfeeding has been described by many as having a protective effect on pulmonary outcomes [6], reducing the severity of lower respiratory tract infections and the incidence of clinical asthma [62]; however, its benefits on recurrent respiratory symptoms during the first year of life haven't been confirmed by all [4]. Palivizumab administration is recommended for very preterm infants, as they are at increased risk for severe respiratory syncytial virus (RSV) lower respiratory tract illness [63]. RSV infection has been associated with both short- and long-term respiratory morbidity, including recurrent wheezing, and there is evidence that palivizumab may also have a protective effect on these outcomes [64, 65].

Future studies with larger samples are needed to clarify the significance of our findings. Particularly, it would be of great value to include multiple Portuguese NICU's in a similar study. Also, the creation of predictive models for respiratory morbidity in the first years but also later in life would be an interesting goal, allowing a more accurate identification of children who might benefit from closer follow up and specific preventive measures, and therefore promoting better allocation of health resources.

Declaration of interest

The Authors declare that there is no conflict of interest.

References

1. Kwinta P, Pietrzyk JJ. Preterm birth and respiratory disease in later life. Expert Rev Respir Med. 2010;4(5):593-604.
2. Greenough A. Long-term respiratory consequences of premature birth at less than 32 weeks of gestation. Early Hum Dev. 2013;89(Suppl 2):S25-7.
3. de Mello RR, Dutra MV, Lopes JM. [Respiratory morbidity in the first year of life of preterm infants discharged from a neonatal intensive care unit]. [Article in Portuguese]. J Pediatr (Rio J). 2004;80(6):503-10.
4. Elder DE, Hagan R, Evans SF, Benninger HR, French NP. Recurrent wheezing in very preterm infants. Arch Dis Child Fetal Neonatal Ed. 1996;74(3):F165-71.
5. McLeod A, Ross P, Mitchell S, Tay D, Hunter L, Hall A, Paton J, Mutch L. Respiratory health in a total very low birthweight cohort and their classroom controls. Arch Dis Child. 1996;74(3):188-94.
6. Chalfun G, Mello RR, Dutra MV, Andreozzi VL, Silva KS. [Risk factors for respiratory morbidity at 12 to 36 months in very low birth weight premature infants previously admitted to a public neonatal intensive care unit]. [Article in Portuguese]. Cad Saude Publica. 2009;25(6):1399-408.
7. Greenough A, Limb E, Marston L, Marlow N, Calvert S, Peacock J. Risk factors for respiratory morbidity in infancy after very premature birth. Arch Dis Child Fetal Neonatal Ed. 2005;90(4):F320-3.
8. Perez Perez G, Navarro Merino M, Romero Perez MM, Saenz Reguera C, Pons Tubio A, Polo Padillo J. [Respiratory morbidity after hospital discharge in premature infants born at < or = 32 weeks gestation with bronchopulmonary dysplasia]. [Article in Spanish]. An Pediatr (Barc). 2004;60(2):117-24.
9. Greenough A. Late respiratory outcomes after preterm birth. Early Hum Dev. 2007;83(12):785-8.

10. Resch B, Pasnocht A, Gusenleitner W, Muller W. Rehospitalisations for respiratory disease and respiratory syncytial virus infection in preterm infants of 29-36 weeks gestational age. J Infect. 2005;50(5):397-403.
11. Teune MJ, van Wassenaer AG, van Buuren S, Mol BW, Opmeer BC, Dutch PCSG. Perinatal risk-indicators for long-term respiratory morbidity among preterm or very low birth weight neonates. Eur J Obstet Gynecol Reprod Biol. 2012;163(2):134-41.
12. Rocha G, Proença E, Quintas C, Rodrigues T, Guimarães H. Histological chorioamnionitis and lung damage in preterm newborns. Arq Med. 2005;19:15-21.
13. Kumar R, Yu Y, Story RE, Pongracic JA, Gupta R, Pearson C, Ortiz K, Bauchner HC, Wang X. Prematurity, chorioamnionitis, and the development of recurrent wheezing: a prospective birth cohort study. J Allergy Clin Immunol. 2008;121(4):878-84.e6.
14. Broughton S, Thomas MR, Marston L, Calvert SA, Marlow N, Peacock JL, Rafferty GF, Greenough A. Very prematurely born infants wheezing at follow-up: lung function and risk factors. Arch Dis Child. 2007;92(9):776-80.
15. Hagen EW, Sadek-Badawi M, Palta M. Daycare attendance and risk for respiratory morbidity among young very low birth weight children. Pediatr Pulmonol. 2009;44(11):1093-9.
16. Latzin P, Frey U, Roiha HL, Baldwin DN, Regamey N, Strippoli MP, Zwahlen M, Kuehni CE; Swiss Paediatric Respiratory Research Group. Prospectively assessed incidence, severity, and determinants of respiratory symptoms in the first year of life. Pediatr Pulmonol. 2007;42(1):41-50.
17. Belanger K, Beckett W, Triche E, Bracken MB, Holford T, Ren P, McSharry JE, Gold DR, Platts-Mills TA, Leaderer BP. Symptoms of wheeze and persistent cough in the first year of life: associations with indoor allergens, air contaminants, and maternal history of asthma. Am J Epidemiol. 2003;158(3):195-202.
18. Guimarães H, Rocha G, Pissarra S, Guedes MB, Nunes T, Vitor B. Respiratory outcomes and atopy in school-age children who were preterm at birth, with and without bronchopulmonary dysplasia. Clinics. 2011;66(3):425-30.
19. Choukroun ML, Feghali H, Vautrat S, Marquant F, Nacka F, Leroy V, Demarquez JL, Fayon MJ. Pulmonary outcome and its correlates in school-aged children born with a gestational age </= 32 weeks. Respir Med. 2013;107(12):1966-76.
20. Baraldi E, Filippone M. Chronic lung disease after premature birth. N Engl J Med. 2007;357(19):1946-55.
21. Doyle LW, Anderson PJ. Adult outcome of extremely preterm infants. Pediatrics. 2010;126(2):342-51.
22. MacDonald H, American Academy of Pediatrics. Committee on F, Newborn. Perinatal care at the threshold of viability. Pediatrics. 2002;110(5):1024-7.
23. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119(3):417-23.
24. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr. 2013;13:59.
25. Blanc WA. Pathology of the placenta, membranes, and umbilical cord in bacterial, fungal, and viral infections in man. Monogr Pathol. 1981;(22):67-132.
26. Rodriguez RJ, Martin RJ, Fanaroff AA. Respiratory distress syndrome and its management. In: Fanaroff AA, Martin RJ (Eds.). Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 7th ed. St. Louis, MO: Mosby, 2002, pp. 1001-11.
27. Couchard M, Polge J, Bomsel F. [Hyaline membrane disease: diagnosis, radiologic surveillance, treatment and complications]. [Article in French]. Ann Radiol (Paris). 1974;17(7):669-83.
28. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163(7):1723-9.
29. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, Wrage LA, Poole K; National Institutes of Child Health and Human Development Neonatal Research Network. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005;116(6):1353-60.
30. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am. 1986;33(1): 179-201.
31. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991-9.
32. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978;92(4):529-34.
33. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006.
34. Amaro F. A classificação das famílias segundo a Escala de Graffar. Lisboa: Fundação Nossa Senhora do Bom Sucesso, 2001.
35. Pramana IA, Latzin P, Schlapbach LJ, Hafen G, Kuehni CE, Nelle M, Riedel T, Frey U. Respiratory symptoms in preterm infants: burden of disease in the first year of life. Eur J Med Res. 2011;16(5):223-30.
36. Vrijlandt EJ, Boezen HM, Gerritsen J, Stremmelaar EF, Duiverman EJ. Respiratory health in prematurely born preschool children with and without bronchopulmonary dysplasia. J Pediatr. 2007;150(3):256-61.
37. Guimarães H, Rocha G, Vasconcellos G, Proença E, Carreira ML, Sossai Mdo R, Morais B, Martins I, Rodrigues T, Severo M. Risk factors for bronchopulmonary dysplasia in five Portuguese neonatal intensive care units. Rev Port Pneumol. 2010;16(3):419-30.
38. Rhein LM, Konnikova L, McGeachey A, Pruchniewski M, Smith VC. The role of pulmonary follow-up in reducing health care utilization in infants with bronchopulmonary dysplasia. Clin Pediatr (Phila). 2012;51(7):645-50.
39. Rusconi F, Galassi C, Corbo GM, Forastiere F, Biggeri A, Ciccone G, Renzoni E. Risk factors for early, persistent, and late-onset wheezing in young children. SIDRIA Collaborative Group. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1617-22.
40. Pike K, Jane Pillow J, Lucas JS. Long term respiratory consequences of intrauterine growth restriction. Semin Fetal Neonatal Med. 2012;17(2):92-8.

41. Rona RJ, Gulliford MC, Chinn S. Effects of prematurity and intrauterine growth on respiratory health and lung function in childhood. BMJ. 1993;306(6881):817-20.
42. Hartung J, Kalache KD, Heyna C, Heling KS, Kuhlig M, Wauer R, Bollmann R, Chaoui R. Outcome of 60 neonates who had ARED flow prenatally compared with a matched control group of appropriate-for-gestational age preterm neonates. Ultrasound Obstet Gynecol. 2005;25(6):566-72.
43. Rusconi F, Galassi C, Forastiere F, Bellasio M, De Sario M, Ciccone G, Brunetti L, Chellini E, Corbo G, La Grutta S, Lombardi E, Piffer S, Talassi F, Biggeri A, Pearce N. Maternal complications and procedures in pregnancy and at birth and wheezing phenotypes in children. Am J Respir Crit Care Med. 2007;175(1):16-21.
44. Hansen AR, Barnes CM, Folkman J, McElrath TF. Maternal preeclampsia predicts the development of bronchopulmonary dysplasia. J Pediatr. 2010;156(4):532-6.
45. Wang KG, Chen CY, Chen YY. The effects of absent or reversed end-diastolic umbilical artery Doppler flow velocity. Taiwan J Obstet Gynecol. 2009;48(3):225-31.
46. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy. 2008;38(4):629-33.
47. Negele K, Heinrich J, Borte M, von Berg A, Schaaf B, Lehmann I, Wichmann HE, Bolte G; LISA Study Group. Mode of delivery and development of atopic disease during the first 2 years of life. Pediatr Allergy Immunol. 2004;15(1):48-54.
48. Magnus MC, Haberg SE, Stigum H, Nafstad P, London SJ, Vangen S, Nystad W. Delivery by Cesarean section and early childhood respiratory symptoms and disorders: the Norwegian mother and child cohort study. Am J Epidemiol. 2011;174(11):1275-85.
49. Williams O, Michel B, Hutchings G, Debauche C, Hubinont C. Two-year neonatal outcome following PPROM prior to 25 weeks with a prolonged period of oligohydramnios. Early Hum Dev. 2012;88(8):657-61.
50. Sims EJ, Vermillion ST, Soper DE. Preterm premature rupture of the membranes is associated with a reduction in neonatal respiratory distress syndrome. Am J Obstet Gynecol. 2002;187(2):268-72.
51. Giapros V, Drougia A, Asproudis I, Theocharis P, Andronikou S. Low gestational age and chronic lung disease are synergistic risk factors for retinopathy of prematurity. Early Hum Dev. 2011;87(10):653-7.
52. Yang CY, Lien R, Yang PH, Chu SM, Hsu JF, Fu RH, Chiang MC. Analysis of incidence and risk factors of retinopathy of prematurity among very-low-birth-weight infants in North Taiwan. Pediatr Neonatol. 2011;52(6):321-6.
53. Aly H, Hammad TA, Essers J, Wung JT. Is mechanical ventilation associated with intraventricular hemorrhage in preterm infants? Brain Dev. 2012;34(3):201-5.
54. Sugimoto S, Furukawa A, Hatsukawa Y, Yanagihara K, Saito Y. Weak association between retinopathy of prematurity and neurological disorders in childhood. Jpn J Ophthalmol. 1998;42(2):142-5.
55. Sherlock RL, Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. Early Hum Dev. 2005;81(11):909-16.
56. Fitzgerald DA, Follett J, Van Asperen PP. Assessing and managing lung disease and sleep disordered breathing in children with cerebral palsy. Paediatr Respir Rev. 2009;10(1):18-24.
57. Lucas JS, Inskip HM, Godfrey KM, Foreman CT, Warner JO, Gregson RK, Clough JB. Small size at birth and greater postnatal weight gain: relationships to diminished infant lung function. Am J Respir Crit Care Med. 2004;170(5):534-40.
58. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, Basterrechea M, Bisgaard H, Chatzi L, Corpeleijn E, Correia S, Craig LC, Devereux G, Dogaru C, Dostal M, Duchen K, Eggesbø M, van der Ent CK, Fantini MP, Forastiere F, Frey U, Gehring U, Gori D, van der Gugten AC, Hanke W, Henderson AJ, Heude B, Iñiguez C, Inskip HM, Keil T, Kelleher CC, Kogevinas M, Kreiner-Møller E, Kuehni CE, Küpers LK, Lancz K, Larsen PS, Lau S, Ludvigsson J, Mommers M, Nybo Andersen AM, Palkovicova L, Pike KC, Pizzi C, Polanska K, Porta D, Richiardi L, Roberts G, Schmidt A, Sram RJ, Sunyer J, Thijs C, Torrent M, Viljoen K, Wijga AH, Vrijheid M, Jaddoe VW, Duijts L. Preterm birth, infant weight gain, and childhood asthma risk: A meta-analysis of 147,000 European children. J Allergy Clin Immunol. 2014;133(5):1317-29.
59. Turner S, Zhang G, Young S, Cox M, Goldblatt J, Landau L, Le Souëf P. Associations between postnatal weight gain, change in postnatal pulmonary function, formula feeding and early asthma. Thorax. 2008;63(3):234-9.
60. Scholtens S, Wijga AH, Seidell JC, Brunekreef B, de Jongste JC, Gehring U, Postma DS, Kerkhof M, Smit HA. Overweight and changes in weight status during childhood in relation to asthma symptoms at 8 years of age. J Allergy Clin Immunol. 2009;123(6):1312-8.e2.
61. Zhang Z, Lai HJ, Roberg KA, Gangnon RE, Evans MD, Anderson EL, Pappas TE, Dasilva DF, Tisler CJ, Salazar LP, Gern JE, Lemanske RF Jr. Early childhood weight status in relation to asthma development in high-risk children. J Allergy Clin Immunol. 2010;126(6):1157-62.
62. Section on Breastfeeding. Breastfeeding and the use of human milk. Pediatrics. 2012;129(3):e827-41.
63. Committee on Infectious Diseases. From the American Academy of Pediatrics: Policy statements – Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. Pediatrics. 2009;124(6):1694-701.
64. Simoes EA, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick L, Groothuis JR; Palivizumab Long-Term Respiratory Outcomes Study Group. The effect of respiratory syncytial virus on subsequent recurrent wheezing in atopic and nonatopic children. J Allergy Clin Immunol. 2010;126(2):256-62.
65. Simoes EA, Groothuis JR, Carbonell-Estrany X, Rieger CH, Mitchell I, Fredrick LM, Kimpen JL; Palivizumab Long-Term Respiratory Outcomes Study Group. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr. 2007;151(1):34-42, 42.e1.

Appendix A. Questionnaire about demographic, perinatal and neonatal data.

RESPIRATORY MORBIDITY IN VERY PRETERM AND VERY LOW BIRTH WEIGHT INFANTS – THE FIRST TWO YEARS OF LIFE

ID: _____

DEMOGRAPHICS

Birth date: ___ / ___ / _____
Sex ❑ F (0) ❑ M (1)
Gestational age: _____ days
Birth weight: _____ g
Small for gestational age (SGA) ❑ no (0) ❑ yes (1)
Assymetrical SGA ❑ no (0) ❑ yes (1)

GESTATION

Multiple gestation ❑ no (0) ❑ yes (1)

Prenatal corticosteroids ❑ no (0) ❑ incomplete cycle (one betamethasone administration) (1) ❑ Complete cycle (two betamethasone administrations) (2)

Smoking 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 syndrome ❑ no(0) ❑ yes(1)

Placental histology
Histological chorioamnionitis ❑ no(0) ❑ stage I (1) ❑ stage II (2) ❑ stage III (3)
Funisitis ❑ no(0) ❑ yes(1)
Chorionic vasculitis ❑ no(0) ❑ yes(1)

Clinical chorioamnionitis ❑ no(0) ❑ yes(1)
Placental abruption ❑ no(0) ❑ yes(1)
Umbilical artery flow disturbances (absence, inversion) ❑ no(0) ❑ yes(1)

DELIVERY

Type of delivery ❑ eutocic (0) ❑ cesarean section (1)

Premature rupture of membranes ❑ no(0) ❑ yes(1)

Intrapartum antibiotics ❑ no(0) ❑ yes(1) Justification: _____

APGAR (1st and 5th minutes): ____ / ____ / ____

Resuscitation ❑ no(0) ❑ yes(1)

NEONATAL PERIOD

SNAPPE-II: _____ CRIB: _____

Respiratory distress syndrome ❑ no (0) ❑ light (1) ❑ moderate (2) ❑ severe (3)

Surfactant administration ❑ no (0) ❑ yes(1)

Conventional mechanical ventilation (> 12 h) ❑ no(0) ❑ yes(1) Duration: _____days
nCPAP (> 12 h) ❑ no(0) ❑ yes(1) Duration: _____days

Higher FiO_2 (> 24 h): _____
Duration of oxygen supplementation: _____ days

Bronchopulmonary dysplasia ❑ no (0) ❑ light(1) ❑ moderate(2) ❑ severe(3)

Persistent ductus arteriosus ❑ no(0) ❑ yes(1)

Necrotizing enterocolitis (grade ≥ 2A Bell) ❑ no(0) ❑ yes(1)

Retinopathy of prematurity (higher stage) ❑ no(0) ❑ stage I (1) ❑ stage II (2) ❑ stage III (3) ❑ stage IV (4) ❑ stage V (5)

Intraventriculary hemorrhage ❑ no (0) ❑ stage I (1) ❑ stage II (2) ❑ stage III (3) ❑ stage IV (4)
Hydrocephalus (with ventriculoperitoneal derivation) ❑ no(0) ❑ yes(1)
Periventricular leukomalacia ❑ no(0) ❑ yes(1)

Sepsis ❑ no(0) ❑ yes(1)

Days at NICU: _____

Weight on discharge: _____ g
Weight percentile on discharge (Fenton curves) ❑ < 3 (0) ❑ ≥ 3 (1)

Season of NICU discharge ❑ Spring (0) ❑ Summer (1) ❑ Autumn (2) ❑ Winter (3)

Appendix B. Questionnaire about social and familiar data and follow-up in the first two years of life.

RESPIRATORY MORBIDITY IN VERY PRETERM AND VERY LOW BIRTH WEIGHT INFANTS – THE FIRST TWO YEARS OF LIFE

ID: _____

Date at two years of corrected age: _____

FOLLOW-UP AFTER NICU DISCHARGE (FIRST TWO YEARS OF LIFE)

1. CARE AND EVOLUTION

Breastfeeding (≥ one month) ❑ $no_{(0)}$ ❑ $yes_{(1)}$ Duration: _____ months

Isolation during first winter season ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Other preventive measures after discharge (avoidance of crowded spaces, avoidance of tobacco smoke exposure, adequate hand hygiene) ❑ $no_{(0)}$ ❑ $yes_{(1)}$

Antipneumococcal vaccine ❑ $no_{(0)}$ ❑ complete (3 administrations)$_{(1)}$ ❑ incomplete (< 3 administrations)$_{(2)}$
Palivizumab ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Influenza vaccine ❑ $no_{(0)}$ ❑ $yes_{(1)}$

Weight percentile at 6 months of corrected age (WHO curves) ❑ $< 3_{(0)}$ ❑ $\geq 3_{(1)}$
Weight percentile at 12 months of corrected age (WHO curves) ❑ $< 3_{(0)}$ ❑ $\geq 3_{(1)}$
Weight percentile at 24 months of corrected age (WHO curves) ❑ $< 3_{(0)}$ ❑ $\geq 3_{(1)}$

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 ❑ $no_{(0)}$ ❑ $yes_{(1)}$

Graffar classification (according to: Amaro F. A classificação das famílias segundo a Escala de Graffar. Lisboa: Fundação Nossa Senhora do Bom Sucesso, 2001): ❑ Class $I_{(1)}$ ❑ Class $II_{(2)}$ ❑ Class $III_{(3)}$ ❑ Class $IV_{(4)}$ ❑ Class $V_{(5)}$

Family history of asthma ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Maternal asthma ❑ $no_{(0)}$ ❑ $yes_{(1)}$

Family history of atopy ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Maternal atopy ❑ $no_{(0)}$ ❑ $yes_{(1)}$

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 ❑ $no_{(0)}$ ❑ $yes_{(1)}$

Cough with respiratory illness only ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Wheeze with respiratory illness only ❑ $no_{(0)}$ ❑ $yes_{(1)}$

3.2) MEDICATION

Inhaled long acting β agonists ❑ $no_{(0)}$ ❑ chronic use$_{(1)}$ ❑ use for respiratory illness only$_{(2)}$
Inhaled corticosteroids ❑ $no_{(0)}$ ❑ chronic use$_{(1)}$ ❑ use for respiratory illness only$_{(2)}$
Inhaled short acting β agonists ❑ $no_{(0)}$ ❑ chronic use$_{(1)}$ ❑ use for respiratory illness only$_{(2)}$
Inhaled antimuscarinics ❑ $no_{(0)}$ ❑ chronic use$_{(1)}$ ❑ use for respiratory illness only$_{(2)}$
Oral antihistamines ❑ $no_{(0)}$ ❑ chronic use$_{(1)}$ ❑ use for respiratory illness only$_{(2)}$
Leukotriene antagonists ❑ $no_{(0)}$ ❑ $yes_{(1)}$

3.3) HEALTH CARE UTILIZATION

Any health care utilization for respiratory causes ❑ $no_{(0)}$ ❑ $yes_{(1)}$

OUTPATIENT VISITS

Additional outpatient visits for respiratory causes ❑ $no_{(0)}$ ❑ $yes_{(1)}$

EMERGENCY DEPARTMENT (ED)

Any ED attendance for respiratory causes ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Any ED attendance for bronchiolitis ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Any ED attendance for pneumonia ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Any ED attendance for other respiratory causes ❑ $no_{(0)}$ ❑ $yes_{(1)}$

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 ❑ $no_{(0)}$ ❑ $yes_{(1)}$

3.4) IMPACT ON PARENTS' LIFE

Any days missed at work for the child's respiratory problems ❑ $no_{(0)}$ ❑ $yes_{(1)}$
Number of days missed at work for the child's respiratory problems: ____ days