Persistent pulmonary hypertension of the newborn in extremely preterm infants: a Japanese cohort study

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ABSTRACT

Objective To investigate the characteristics of persistent pulmonary hypertension of the newborn (PPHN) in extremely preterm infants and its impact on neurodevelopmental outcomes at 3 years of age.

Design A retrospective multicentre cohort study.

Settings 202 tertiary perinatal centres registered in the Neonatal Research Network of Japan (NRNJ).

Patients Infants born at <28 weeks of gestational age (GA), between 2003 and 2012, were extracted from tertiary perinatal centres participating in NRNJ.

Main outcome measures Demographic characteristics, morbidity, interventions and mortality were compared for infants with and without PPHN. Multivariable logistic analysis was performed to evaluate the impact of PPHN on long-term neurodevelopmental outcomes (the prevalence rate of cerebral palsy, need for home oxygen therapy, and visual, hearing and cognitive impairment) at 3 years of age.

Results The prevalence of PPHN among the 12 954 extremely preterm infants enrolled was 8.1% (95% CI 7.7% to 8.6%), with the trend increasing annually, and a higher proportion as GA decreased: 18.5% (range, 15.2% to 22.4%) for infants born at 22 weeks compared with 4.4% (range, 3.8% to 5.2%) for those born at 27 weeks. Clinical chorioamnionitis and premature rupture of membranes were associated with PPHN. On multivariate analysis of the data from 5923 infants followed up for 3 years, PPHN was a significant independent risk factor for visual impairment (adjusted OR, 1.42, 95% CI 1.03 to 1.97).

Conclusions The prevalence of PPHN in extremely preterm infants has been increasing over the past decade in Japan. Clinicians should be aware of visual impairments as a neurodevelopmental abnormality among infants with PPHN.

What is already known on this topic?

- Persistent pulmonary hypertension of the newborn (PPHN) is associated with high mortality and serious long-term neurodevelopmental problems, even in term infants.
- However, the impact of PPHN on the long-term outcomes of extremely preterm infants, using a large cohort, has not been evaluated.

What this study adds?

- To our knowledge, this is the first large-cohort study describing the prevalence, trend and long-term neurodevelopmental outcomes of PPHN among extremely preterm infants.
- PPHN is a significant independent risk factor for visual impairment at 3 years of age in this group.

INTRODUCTION

Persistent pulmonary hypertension of the newborn (PPHN) is caused by failed circulatory adaptation at birth, increasing mortality and morbidity. The prevalence of PPHN is higher among late preterm (5.4 per 1000 live births) than term (1.6 per 1000 live births) infants.[1 2] PPHN is also prevalent among extremely preterm infants, in whom PPHN is frequently associated with sepsis or pulmonary hypoplasia secondary to the preterm rupture of membranes (PROM) or oligohydramnios.[3] Even when extremely preterm infants survive, PPHN remains a strong risk factor for severe bronchopulmonary dysplasia (BPD).[4] However, the prevalence of PPHN among a large cohort of extremely preterm infants and the impact of PPHN on the long-term prognosis of these infants are unknown.

The Neonatal Research Network of Japan (NRNJ) was created in 2003 and includes the clinical information of infants with a birth weight ≤1500 g who received treatment in participating neonatal centres.[5] In this study, we retrospectively analysed NRNJ data to determine the prevalence of PPHN among extremely preterm infants in Japan over a 10-year period, from 2003 to 2012. We also analysed longer-term data to evaluate the impact of PPHN on the growth and neurodevelopmental outcomes of extremely preterm infants.

METHODS

Study cohort

Between 2003 and 2012, 40 806 infants with a birth weight ≤1500 g were registered in the NRNJ from 202 tertiary perinatal centres. Among these infants, 12 954 extremely preterm infants, born at <28 weeks gestational age (GA), from 160 tertiary perinatal centres were enrolled, after excluding cases with congenital anomaly, a birth outside of hospital, perinatal death or incomplete medical records. Included infants were classified into four groups to examine the impact of PPHN on BPD: PPHN(−)BPD(−), PPHN(−)BPD(+), PPHN(+)BPD(−) and PPHN(+)BPD(+). Among the 12 954 infants enrolled, 11 488 survived at discharge. Of

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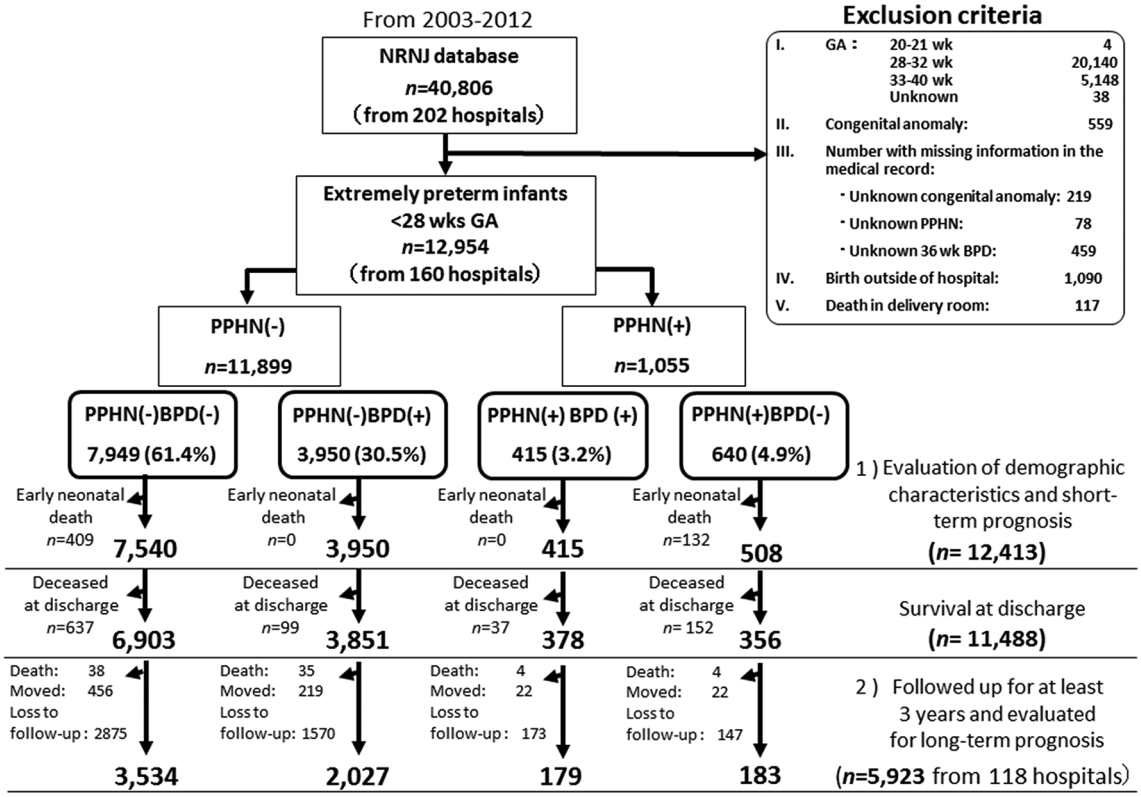

Figure 1 Flowchart of the study. BPD, bronchopulmonary dysplasia; GA, gestational age; NRNJ, Neonatal Research Network of Japan; PPHN, persistent pulmonary hypertension of the newborn.

these infants, 5565 were excluded from the evaluation of long-term prognosis at 3 years of age for the following reasons: 81 deaths, 719 transferred to another institution and 4765 lost to follow-up. Therefore, our long-term analysis of growth and neurodevelopmental outcomes included 5923 infants from 118 tertiary perinatal centres (figure 1).

PPHN and BPD diagnosis

PPHN was diagnosed in the perinatal period in all infants, with no case of structural heart disease identified. PPHN diagnosis was based on echocardiogram and clinical findings as follows: a >10% difference between preductal and postductal SpO_2, despite optimal treatment of the patient's lung disease (mechanical ventilation and high concentration of oxygen); an estimated peak systolic pulmonary artery pressure >35 mm Hg, or more than two-thirds of the systemic systolic pressure, as indicated by the presence of a tricuspid regurgitation jet; and a right-to-left patent ductus arteriosus or atrial-level shunt.[6] Pulmonary hypertension that developed later in the clinical course of BPD was not included in the PPHN diagnosis, where BPD was defined as oxygen dependency at 36 weeks of postmenstrual age.[7]

Definitions

All measured outcomes were defined according to the standardised NRNJ manual,[8–12] with a brief description as follows: GA, determined by ultrasonography early during pregnancy or based on the last menstrual period; clinical chorioamnionitis (CAM), maternal fever, leukocytosis and local pain[13]; retinopathy of prematurity (ROP), according to the International Classification for Retinopathy of Prematurity[14]; cerebral palsy (CP), defined at 3 years of age according to the clinical features described by Bax[15]; visual impairment, absence of functional vision in one or both eyes; and hearing impairment, need for amplification.

Long-term growth and neurodevelopmental assessment

Long-term prognosis at 3 years of age was based on the following criteria: prevalence of CP; home oxygen therapy (HOT); visual or hearing impairment; somatic growth, including height, body weight and head circumference; and developmental testing, using the Kyoto Scale of Psychological Development (KSPD),[12 16] with a developmental quotient (DQ) <70, which is equivalent to a Bayley III Cognitive score of <85, indicative of a significant delay.[16]

Statistical analysis

Statistical analysis was performed using JMP V.13 (SAS Institute). Considering that our large cohort would increase the likelihood of detecting significant between-group differences, we transformed our prevalence data into means and percentage (%) of involved infants, and included the 95% CI for our aggregated cohort data. Significant between-group differences were identified by the absence of an overlap of the 95% CI between groups ($P<0.05$). Between-group differences for variables with a non-normal distribution were evaluated using the Wilcoxon Mann-Whitney test or Kruskal-Wallis one-way analysis of variance. A χ^2 analysis was performed to evaluate yearly trends for proportions (Cochran-Armitage test), and to determine the prevalence of PPHN over time.

To identify interventions associated with mortality among infants with PPHN, multivariable logistic regression models were fitted to the data for the 1055 infants with PPHN, with mortality at discharge as the dependent variable and perinatal interventions (high-frequency oscillatory ventilation (HFOV),

inhaled nitric oxide (iNO) and HFOV+iNO, intubation at birth, surfactant administration and intravenous hyper-alimentation) as the independent variables. This analysis was adjusted for significant perinatal risk factors identified in the multivariable analysis using a stepwise approach according to the minimum Akaike information criterion.

To evaluate the impact of PPHN on the long-term prognosis at 3 years of age (defined by the prevalence rate of CP, HOT, visual and hearing impairment, and a DQ <70), an additional multivariable regression analysis was performed using the following factors: antenatal steroid (ANS) and clinical CAM, which were considered perinatal factors[17 18]; GA, small for gestational age (SGA) and multiple pregnancy, which were considered birth factors[12 19]; male sex, which has been reported to influence growth and development[20]; severe ROP (≥stage 3), severe intraventricular haemorrhage (IVH) (≥grade 3) and periventricular leukomalacia (PVL), which were considered as extracardiopulmonary factors[21–23]; and severe BPD, which was considered a cardiopulmonary factor.[24] A P<0.05 was considered significant, and all tests were two-sided. ORs (95% CI) were calculated to enhance interpretation of significant test results.

Ethics

Written informed consent was obtained from the parents or guardians of all infants in the NRNJ. All information about the infants was collected anonymously, and the analysed data were unlinked from individual data.

RESULTS

Prevalence and trend of PPHN

PPHN was diagnosed in 8.1% (95% CI 7.7% to 8.6%) of the 12 954 infants enrolled, with the prevalence increasing as GA decreased: 18.5% (15.2–22.4%) among the 448 infants born at 22 weeks; 13.1% (11.5–15.0%) among the 1468 born at 23 weeks; 11.1% (9.8–12.5%) among the 2098 born at 24 weeks; 8.1% (7.1–9.2%) among the 2532 born at 25 weeks; 6.4% (5.6–7.3%) among the 3004 born at 26 weeks and 4.4% (3.8–5.2%) among the 3404 born at 27 weeks (online supplemental figure A). The annual incidence rate of preterm infants with PPHN increased over time, from 54 cases (7.5% (5.8–9.7%)) in 2003 to 147 cases (9.0% (7.7–10.5%)) in 2012, with a specific annual increase among infants born at a GA of 22–24 weeks (P=0.048; online supplemental figure B).

Prenatal and perinatal correlates

Prenatal and perinatal correlates of PPHN are reported in table 1. Birth weight and GA were significantly lower in the BPD than non-BPD groups, with the lowest birth weight and GA for infants with both PPHN and BPD. The prevalence of male sex was higher in the BPD than non-BPD groups, regardless of PPHN status.

The prevalence of PROM and clinical CAM was higher in the PPHN than in non-PPHN groups, while the prevalence of maternal hypertension was lower in the PPHN groups, regardless of BPD status. The prevalence of maternal or gestational diabetes mellitus (DM) was lower in the PPHN(+)BPD(+) than in the other groups.

Postnatal correlates

Postnatal correlates of PPHN are reported in table 2. Regarding morbidities, the PPHN groups had a significantly higher prevalence of pulmonary air leak, pulmonary haemorrhage, severe IVH and necrotizing enterocolitis/gastrointestinal perforation than the non-PPHN groups.

The severity of respiratory disorder was highest among infants with both PPHN and BPD, as indicated by the highest prevalence of steroid treatment for BPD, HFOV use and HOT at discharge, and longer duration of mechanical ventilation, O_2 supplementation and hospital stay. Moreover, time to establishment of enteral feeding was longer in the PPHN than non-PPHN groups.

ROP ≥stage 3 was more prevalent in BPD than non-BPD groups, with the greatest severity of ROP in the PPHN(+)BPD(+) groups. Hearing impairment at discharge was more prevalent in BPD than non-BPD groups, without any additional influences by PPHN status. The prevalence of PVL in infants with BPD was not influenced by PPHN status. However, mortality was higher in the PPHN groups.

Long-term growth and neurodevelopmental outcomes

The long-term growth and developmental status is reported in table 3. Visual impairment was more prevalent in PPHN than non-PPHN groups, with no between-group difference for hearing impairment. HOT was more prevalent in BPD than non-BPD groups, with no additional influences by PPHN. Significant between-group differences in body weight, height and head circumference at 3 years of age were identified. In particular, body weight and head circumference were lower among infants with BPD than those without BPD, and specifically lower in the PPHN(+)BPD(+) groups. The DQ score was significantly lower in infants with BPD than non-BPD groups with an additional decrease by PPHN status.

Interventions associated with mortality in extremely preterm infants with PPHN

Results of the multiple logistic analysis are reported in online supplemental table. The first model used death as the dependent variable, with potential perinatal risk factors entered as independent variables in a stepwise manner. The following factors were independently associated with death: GA (1 week increment; OR 0.76, 95% CI 0.70 to 0.81), birth weight (100 g increment; OR 0.74, 95% CI 0.69 to 0.79), male sex (OR 1.38, 95% CI 1.22 to 1.75), SGA (OR 1.28, 95% CI 1.01 to 1.63), Apgar score <4 at 1 min (OR 1.53, 95% CI 1.33 to 1.75), Apgar score <4 at 5 min (OR 1.84, 95% CI 1.56 to 2.17), multiple pregnancies (OR 1.42, 95% CI 1.23 to 1.65), ANS (OR 0.63, 95% CI 0.56 to 0.71), clinical CAM (OR 0.78, 95% CI 0.68 to 0.90), non-reassuring fetal status OR 1.47, 95% CI 1.28 to 1.68) and caesarean section (OR 0.82, 95% CI 0.71 to 0.94). A second model used the same independent variables but was adjusted for HFOV, iNO, HFOV +iNO, intubation at birth, surfactant administration and intravenous hyperalimentation, to identify potential interventions that might be associated with decreased mortality among the 1055 infants with PPHN. HFOV (adjusted OR (AOR) 0.62, 95% CI 0.43 to 0.89) and intravenous hyperalimentation (AOR 0.24, 95% CI 0.17 to 0.34) were independent interventions associated with mortality among infants with PPHN. In contrast, iNO was not a significant factor (AOR 1.11, 95% CI 0.82 to 1.50), even when combined with HFOV (AOR 0.91, 95% CI 0.68 to 1.24).

Impact of PPHN on neurodevelopmental outcomes

Neurodevelopmental outcomes measured at 3 years of age are reported in table 4. To evaluate the impact of PPHN on neurodevelopmental outcomes at 3 years of age, a multiple regression analysis was performed with PPHN as the independent variable and CP, HOT at 3 years of age, visual impairment, hearing

Table 1 Prenatal and perinatal correlates among extremely preterm infants, with or without persistent pulmonary hypertension of the newborn

	PPHN (–)				PPHN (+)			
	BPD (–)		BPD (+)		BPD (–)		BPD (+)	
	n=7540		n=3950		n=508		n=415	
Basic characteristics								
Birth weight (g), mean (95% CI)	808 (803 to 812)		715 (709 to 720) [a]		737 (720 to 755)[a]		687 (670 to 704) [a,b,c]	
GA (weeks), mean (95% CI)	26.0 (26.0 to 26.1)		25.4 (25.4 to 25.5)[a]		25.3 (25.1 to 25.4)[a]		25.0 (24.9 to 25.1)[a,b]	
Male sex, % (95% CI), n*	51.3 (50.2 to 52.5)	7536	55.6 (54.1 to 57.2)[a]	3949	51.8 (47.4 to 56.1)	508	57.6 (52.8 to 62.3)[a]	415
SGA, % (95% CI), n*	10.5 (9.8 to 11.2)	7506	15.9 (14.8 to 17.0)[a]	3925	9.7 (7.4 to 12.5)[b]	507	12.0 (9.2 to 15.5)	408
Apgar score								
At 1 min,<4, % (95% CI), n*	34.9 (33.8 to 36.0)	7452	42.4 (40.9 to 44.0)[a]	3939	54.0 (50.0 to 58.2)[a,b]	506	53.6 (48.8 to 58.4)[a,b]	414
At 5 min,<4, % (95% CI), n*	6.4 (5.9 to 7.0)	7311	10.0 (9.1 to 11.0)[a]	3924	17.1 (14.1 to 20.8)[a,b]	484	18.4 (15.0 to 22.4)[a,b]	413
Perinatal characteristics								
Maternal age, mean (95% CI)	31.0 (30.9 to 31.2)		31.2 (31.0 to 31.4)		31.3 (30.9 to 31.8)		30.8 (30.3 to 31.3)	
Primipara, % (95% CI), n*	52.7 (51.6 to 53.8)	7476	50.7 (49.2 to 52.3)	3939	45.5 (41.2 to 49.8)[a]	508	49.2 (44.4 to 54.0)	415
Multiple pregnancy, % (95% CI), n*	21.0 (20.1 to 21.9)	7540	19.6 (18.4 to 20.9)	3950	19.3 (16.1 to 22.9)	508	12.0 (9.3 to 15.5)[a,b,c]	415
Maternal hypertension, % (95% CI), n*	10.7 (10.0 to 11.4)	7531	13.4 (12.4 to 14.5)[a]	3948	4.9 (3.4 to 7.2)[a,b]	507	5.6 (3.7 to 8.2)[a,b]	412
Maternal DM/gestational DM, % (95% CI), n*	2.3 (1.9 to 2.6)	7512	2.4 (2.0 to 3.0)	3935	2.2 (1.2 to 3.8)	508	0.5 (0.1 to 1.8)[a,b]	411
PROM, % (95% CI), n*	35.7 (34.6 to 36.8)	7530	40.9 (39.3 to 42.4)[a]	3946	54.8 (50.5 to 59.1)[a,b]	507	64.1 (59.4 to 68.6)[a,b,c]	415
ANS, % (95% CI), n*	49.6 (48.5 to 50.8)	7492	56.7 (55.1 to 58.2)[a]	3931	47.0 (42.7 to 51.4)[b]	504	54.3 (49.4 to 59.0)	411
Clinical CAM, % (95% CI), n*	25.3 (24.4 to 26.3)	7381	32.8 (31.3 to 34.3)[a]	3859	40.2 (36.0 to 44.6)[a,b]	495	46.0 (41.2 to 50.9)[a,b]	402
NRFS, % (95% CI), n*	21.5 (20.6 to 22.5)	7432	24.4 (23.1 to 25.8)[a]	3892	27.2 (23.5 to 31.3)[a]	496	26.3 (22.2 to 30.8)	407
Head presentation, % (95% CI), n*	63.5 (62.4 to 64.6)	7540	63.4 (61.9 to 64.9)	3950	63.2 (58.9 to 67.3)	508	61.7 (56.9 to 66.2)	415
Caesarean section, % (95% CI), n*	72.6 (71.6 to 73.6)	7529	75.6 (74.2 to 76.9)	3947	71.0 (66.9 to 74.8)	507	72.5 (68.0 to 76.5)	414

[a]P<0.05 versus PPHN(–)BPD(–), [b]P<0.05 versus PPHN(–)BPD(+), [c]P<0.05 versus PPHN(+)BPD(–).

*The number of infants included in the denominator for statistical analysis for each group; PPHN(–)BPD(–), PPHN(–)BPD(+), PPHN(+)BPD(–) and PPHN(+)BPD(+).

ANS, antenatal steroid; BPD, bronchopulmonary dysplasia; CAM, chorioamnionitis; DM, diabetes mellitus; GA, gestational age; NRFS, non-reassuring fetal status; PPHN, persistent pulmonary hypertension of the newborn; PROM, premature rupture of membranes; SGA, small for gestational age.

Table 2 Postnatal correlates including morbidities, interventions, and mortality among extremely preterm infants, with or without persistent pulmonary hypertension of the newborn

	PPHN (–)				PPHN (+)			
	BPD (–)		BPD (+)		BPD (–)		BPD (+)	
	n=7540		n=3950		n=508		n=415	
Morbidities								
RDS, %(95% CI), n*	73.7 (72.7 to 74.7)	7538	76.8 (75.5 to 78.1)[a]	3950	82.1 (78.5 to 85.2)[a,b]	508	73.4 (69.0 to 77.5)[c]	414
Pulmonary air leak, %(95% CI), n*	2.5 (2.2 to 2.9)	7533	3.5 (3.0 to 4.1)[a]	3949	12.8 (10.2 to 16.0)[a,b]	507	15.2 (12.0 to 19.0)[a,b]	415
Pulmonary haemorrhage, %(95% CI), n*	4.6 (4.1 to 5.0)	7530	4.9 (4.2 to 5.6)	3950	12.6 (10.0 to 15.8)[a,b]	508	9.2 (6.8 to 12.4)[a,b]	413
Late-onset AOP, %(95% CI), n*	13.4 (12.6 to 14.2)	7527	21.7 (20.4 to 23.0)[a]	3942	14.8 (12.0 to 18.1)[b]	507	29.0 (24.8 to 33.5)[a,b,c]	411
PDA, %(95% CI), n*	51.6 (50.5 to 52.8)	7533	60.5 (58.9 to 62.0)[a]	3948	56.1 (51.8 to 60.4)	508	52.5 (47.7 to 57.3)[b]	415
Sepsis, %(95% CI), n*	12.6 (11.8 to 13.3)	7529	14.1 (13.0 to 15.2)	3944	28.2 (24.4 to 32.2)[a,b]	508	21.1 (17.4 to 25.3)[a,b]	413
IVH, %(95% CI), n*	21.8 (20.9 to 22.8)	7535	23.0 (21.7 to 24.4)	3945	48.2 (43.9 to 52.6)[a,b]	508	38.6 (34.1 to 43.4)[a,b,c]	414
Grade≥3, %(95% CI), n*	7.2 (6.6 to 7.8)	7478	6.5 (5.8 to 7.3)	3935	26.7 (23.0 to 30.8)[a,b]	505	14.7 (11.6 to 18.5)[a,b,c]	414
NEC/gastrointestinal perforation, %(95% CI), n*	6.0 (5.4 to 6.5)	7540	4.9 (4.3 to 5.7)	3950	14.0 (11.2 to 17.3)[a,b]	508	9.4 (7.0 to 12.6)[a,b]	415
BPD								
Oxygen at 28 days of age, %(95% CI), n*	48.9 (47.8 to 50.0)	7536	100[a]	3950	55.7 (51.4 to 60.0)[a,b]	508	100 [a,c]	415
Oxygen at 36 weeks' PMA, %(95% CI), n*	0	7540	100[a]	3950	0[b]	508	100 [a,c]	415
Severity								
Severe, %(95% CI), n*	0	7536	18.5 (17.3 to 19.7)[a]	3950	0[b]	508	29.6 (25.4 to 34.2)[a,b,c]	415
O2 concentration at 36 weeks' PMA, mean (95% CI)	21 (21 to 21)		26.1 (25.9 to 26.4)[a]		21 (21 to 21)[b]		28.7 (27.5 to 29.8)[a,b,c]	
PVL, %(95% CI), n*	4.0 (3.6 to 4.5)	7530	4.7 (4.1 to 5.4)	3944	9.0 (6.9 to 11.9)[a,b]	507	6.0 (4.1 to 8.8)	414
ROP≥stage 3, %(95% CI), *n**	19.5 (18.6 to 20.4)	7359	30.7 (29.3 to 32.2)[a]	3895	21.4 (18.0 to 25.2)[b]	501	40.2 (35.6 to 45.0)[a,b,c]	408
Hearing impairment at discharge, %(95% CI), n*	9.5 (8.8 to 10.3)	5765	14.9 (13.7 to 16.1)[a]	3514	9.5 (6.8 to 13.2)[b]	325	15.4 (12.0 to 19.6)[a]	344
Seizure, %(95% CI), n*	4.9 (4.5 to 5.4)	7535	4.5 (3.9 to 5.2)	3948	11.2 (8.8 to 14.3)[a,b]	507	7.8 (5.5 to 10.7)[a,b]	414
Intervention								
Steroid treatment for BPD, %(95% CI), n*	29.2 (27.8 to 30.7)	3893	48.0 (46.5 to 49.6)[a]	3930	35.1 (29.9 to 40.7)[b]	296	59.0 (54.2 to 63.6)[a,b,c]	412
HFOV use, %(95% CI), n*	45.0 (43.9 to 46.2)	7361	66.7 (65.2 to 68.1)[a]	3892	77.9 (74.1 to 81.3)[a,b]	502	88.9 (85.5 to 91.6)[a,b,c]	407
Surfactant administration, %(95% CI), n*	73.3 (72.3 to 74.3)	7524	81.6 (80.4 to 82.8)[a]	3945	90.6 (87.7 to 92.8)[a,b]	508	90.3 (87.1 to 92.8)[a,b]	413
Inhaled NO use, %(95% CI), n*	2.6 (2.3 to 3.0)	7410	3.9 (3.3 to 4.5)[a]	3894	60.1 (55.8 to 64.3)[a,b]	506	67.9 (63.2 to 72.2)[a,b]	411
Days of ventilation, median (IQR)†	28 (9 to 46)		52 (36 to 71)[a]		35 (17 to 53)[a,b]		64 (45 to 113)[a,b,c]	
Days of O_2 supplementation, median (IQR)†	47 (16 to 65)		97 (80 to 128)[a]		48 (20 to 68)[a,b]		118 (92 to 164)[a,b,c]	
Time to establishment of enteral feeding, median days (IQR)†	15 (11 to 21)		15 (11 to 22)[a]		16 (13 to 23)[a]		16 (12 to 26)[a,b]	
Hospital stay, median (IQR)†	107 (88 to 131)		137 (116 to 167)[a]		106 (50 to 136)[b]		149 (126 to 190)[a,b,c]	
HOT at discharge, %(95% CI), n*	2.1 (1.8 to 2.5)	7443	24.7 (23.4 to 26.1)[a]	3877	4.6 (3.0 to 6.8)[a,b]	483	43.1 (38.3 to 48.1)[a,b,c]	394
Tracheotomy, %(95% CI), n*	0.9 (0.7 to 1.2)	7443	2.0 (1.6 to 2.4)[a]	3882	1.2 (0.6 to 2.7)	483	3.2 (1.9 to 5.5)[a]	395
Mortality								
Deceased at discharge, %(95% CI), n*	8.4 (7.8 to 9.1)	7540	2.5 (2.1 to 3.0)[a]	3950	29.9 (26.1 to 34.0)[a,b]	508	8.9 (6.5 to 12.0)[b,c]	415

[a]P<0.05 versus PPHN(–)BPD(–), [b]P<0.05 versus PPHN(–)BPD(+), [c]P<0.05 versus PPHN(+)BPD(–).

*The number of infants included in the denominator for statistical analysis in each group; PPHN(–)BPD(–), PPHN(–)BPD(+), PPHN(+)BPD(–) and PPHN(+)BPD(+).

†Variables with non-normal distribution were analysed by Kruskal–Wallis one-way analysis of variance.

AOP, adrenal insufficiency of prematurity; BPD, bronchopulmonary dysplasia; HFOV, high-frequency oscillatory ventilation; HOT, home oxygen therapy; IVH, intraventricular haemorrhage; NEC, necrotizing enterocolitis; NO, nitric oxide; PDA, patent ductus arteriosus; PMA, postmenstrual age; PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

Table 3 Long-term growth and neurodevelomental outcomes among extremely preterm infants, with or without persistent pulmonary hypertension of the newborn

	PPHN (–)				PPHN (+)			
	BPD (–)		BPD (+)		BPD (–)		BPD (+)	
	n=3534		n=2027		n=183		n=179	
Long-term prognosis at 3 years								
CP, % (95% CI), n*	11.3 (10.3 to 12.4)	3363	15.2 (13.7 to 16.9)[a]	1933	19.7 (14.4 to 26.2)[a]	173	16.3 (11.5 to 22.5)	172
HOT, % (95% CI), n*	0.9 (0.6 to 1.4)	2613	5.5 (4.5 to 6.7)[a]	1604	2.0 (0.7 to 6.0)	143	9.5 (5.8 to 15.4)[a]	147
Visual impairment, % (95% CI), n*	9.5 (8.6 to 10.6)	3214	12.0 (10.6 to 13.5)[a]	1849	18.4 (13.2 to 25.1)[a]	163	20.2 (14.8 to 27.1)[a,b]	163
Hearing impairment, % (95% CI), n*	1.9 (1.5 to 2.5)	2578	3.7 (2.8 to 4.7)[a]	1451	2.3 (0.8 to 6.6)	130	2.2 (0.7 to 6.2)	139
Growth at 3 years								
Body weight (kg), mean (95% CI)	12.1 (12.0 to 12.2)		11.7 (11.5 to 11.9)[a]		11.5 (11.2 to 11.7)[a]		11.2 (11.0 to 11.4)[a,b]	
Height (cm), mean (95% CI)	89.3 (89.1 to 89.4)		88.1 (87.9 to 88.3)[a]		88.1 (87.5 to 88.8)[a]		87.6 (87.0 to 88.2)[a]	
HC (cm), mean (95% CI)	48.2 (48.1 to 48.2)		47.9 (47.8 to 48.0)[a]		47.6 (47.3 to 48.0)[a]		47.4 (47.1 to 47.7)[a,b]	
Cognitive development at 3 years								
KSPD DQ, mean (95% CI)	81.3 (80.7 to 81.9)		76.2 (75.3 to 77.2)[a]		74.8 (71.6 to 77.9)[a]		71.3 (68.1 to 74.4)[a,b]	
KSPD DQ<70, % (95% CI), n*	19.7 (18.4 to 21.3)	2982	31.5 (29.3 to 33.8)[a]	1667	30.1 (23.5 to 37.7)[a]	156	39.0 (31.8 to 46.7)[a]	159

[a]P<0.05 versus PPHN(–)BPD(–), [b]P<0.05 versus PPHN(–)BPD(+).
*The number of infants included in the denominator for statistical analysis in each group; PPHN(–)BPD(–), PPHN(–)BPD(+), PPHN(+)BPD(–) and PPHN(+)BPD(+).
BPD, bronchopulmonary dysplasia; cerebral palsy; CP, cerebral palsy; DQ, developmental quotient; HC, head circumference; HOT, home oxygen therapy; KSPD, Kyoto Scale of Psychological Development; PPHN, persistent pulmonary hypertension of the newborn.

impairment and KSPD DQ <70 as dependent variables. The model was adjusted for GA, male sex, multiple gestation, clinical CAM, ANS, SGA, severe BPD, severe IVH, severe ROP and PVL. In this analysis, PPHN was identified as a significant independent risk factor for visual impairment (AOR: 1.42, 95% CI 1.03 to 1.97).

DISCUSSION

Our multicentre, retrospective cohort study provides national epidemiological data on PPHN in extremely preterm infants in Japan. The number of registered infants in the NRNJ database has been increasing since 2003,[11] with 70% of delivered preterm infants, having a birth weight ≤1500 g in 2012. In our large cohort, we identified PPHN as an independent risk factor for visual impairment, even after adjustment for severe ROP (≥stage 3), a well-established risk factor for long-term visual impairment.[22] Given the high prevalence of PPHN in this GA group, effective therapies for PPHN could have major impact in improving the survival and neurodevelopmental outcomes of premature infants.

For analysis, we considered the coexistence of PPHN and BPD, with an aim to elucidate the impact of PPHN on the clinical characteristics of BPD. The pulmonary microvasculature in the developing lung is highly susceptible to oxidative damage and, therefore could be easily injured by exposure to intrauterine infection and cytokines,[25 26] with the resulting abnormal pulmonary microvasculature being linked to BPD pathogenesis.[27] Moreover, we identified a significant correlation between PPHN and PROM and clinical CAM, an indicator of intrauterine infection,[13 28] which might explain a shared pathway between PPHN and BPD. Therefore, exposure to antenatal inflammation, due to clinical CAM, might cause preterm delivery and vascular remodelling, contributing to the development of PPHN and severe BPD, with PPHN preceding BPD.

Prior to the regular use of iNO, hyperventilation and alkali infusion were standard practices, with hearing impairment being the most prevalent impairment of PPHN.[29] Now, iNO treatment and lung protective strategies are widely implemented in NICUs, lowering the incidence of neurodevelopmental impairments among PPHN survivors by avoiding excessive hypocapnia.[30] However, a high concentration of oxygen during PPHN management might cause microvascular degeneration in retinal vessels, increasing the risk for visual impairments.[31] HFOV, with or without iNO, is also a safe and effective treatment in infants with PPHN-associated parenchymal lung disease.[32] However, we did not identify a benefit of iNO therapy on survival in our cohort, even when combined with HFOV. The efficacy of iNO on mortality and BPD among extremely preterm infants remains controversial.[33] It is possible that the NO signalling cascade might be poorly developed or expressed in the injured developing lung, limiting the efficacy of iNO in sick preterm infants.[34 35] A recent Japanese survey demonstrated that treatment with iNO was as effective in improving oxygenation in preterm neonates of <34 weeks' GA, with hypoxic respiratory failure and pulmonary hypertension, as for late preterm and term neonates, without a negative impact on the incidence of other comorbidities or survival.[36] Therefore, our results do not discourage the use of iNO in extremely preterm infants, but do underline the need for future therapeutic trials to evaluate the use of iNO in preterm neonates.

Table 4 Impact of persistent pulmonary hypertension of the newborn on neurodevelopmental outcomes at 3 years of age

Outcome at 3 years	Crude OR	Adjusted OR*	95% CI	P value
CP	1.52	1.04	0.73 to 1.47	0.831
HOT	2.28	1.64	0.92 to 2.92	0.094
Visual impairment	2.06	1.42	1.03 to 1.97	0.033
Hearing impairment	0.87	0.72	0.31 to 1.67	0.443
KSPD DQ<70	1.68	1.25	0.95 to 1.64	0.108

*Adjusted for gestational age, Male sex, Multiple pregnancy, Clinical CAM, ANS, SGA, Severe BPD, Severe IVH, Severe ROP, and PVL
ANS, antenatal steroid; BPD, bronchopulmonary dysplasia; CAM, chorioamnionitis; CI, confideince interval; CP, cerebral palsy; DQ, developmental quotient; HOT, home oxygen therapy; IVH, intraventricular hemorrhage; KSPD, Kyoto Scale of Psychological Development; OR, odds ratio; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SGA, small for gestational age.

The limitations of our study should be acknowledged. Due to the design of the NRNJ database, the aetiology or severity of PPHN could not be characterised but could have influenced our results. In some cases, systemic hypotension due to perinatal infection might be an important cause of PPHN and of functional and/or anatomical pulmonary hypoplasia, due to prolonged drainage of lung fluid after PROM. The prevalence of DM and maternal hypertension was low in our cohort, especially among infants with PPHN. In contrast, a previous study reported that maternal DM likely induced endothelial dysfunction and inflammation as a cause of abnormal fetal lung development leading to PPHN.[37] The timing of delivery might explain this discrepancy, with an earlier birth for infants with PPHN, partly due to intrauterine infection, as indicated by the high prevalence of PROM and clinical CAM, compared with infants without PPHN. Therefore, intrauterine infection might be the most important mechanism of PPHN in extremely preterm infants. Another important issue was the low follow-up rate (52% at 3 years of age among surviving infants). Although loss to follow-up is an inevitable problem of most cohort studies,[38–40] considerable effort should be put into improving the follow-up rate in NRNJ. Therefore, our findings will need careful interpretation.

CONCLUSION

In a large Japanese cohort, extremely premature infants were at higher risk of PPHN than term infants, with PPHN being an independent risk factor of visual impairment at 3 years of age. As the number of preterm infants with PPHN is increasing, early management of PPHN is important to improve survival of extremely preterm infants.

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