Title:

Neurodevelopmental Outcomes of Preterm Infants Born <29 weeks with Bronchopulmonary Dysplasia Associated Pulmonary Hypertension: A Multicenter Study

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Background:

More than 1 in 4 preterm infants with bronchopulmonary dysplasia (BPD) develop BPD-associated pulmonary hypertension (BPD-PH) that is associated with significant morbidity. Data regarding neurodevelopmental outcomes with BPD-PH in preterm infants are lacking.

Objective

To determine neurodevelopmental outcomes of preterm infants born < 29 weeks gestational age (GA) with BPD associated pulmonary hypertension at 18 to 24 months corrected gestational age (CGA).

Methods:

In this retrospective cohort study, preterm infants born < 29 weeks GA between January 2016 and December 2019 at level 3 Neonatal Intensive Care Units at Foothills Hospital in Calgary and the University of Texas Medical Branch (UTMB) in Galveston, who were evaluated at 18-24 months CGA in the neonatal follow-up clinics were included. We compared demographic factors, neurodevelopmental status including Bayley-III scores and sensory impairments between the two groups based on the presence of PH at 36 weeks CGA: Group I: BPD with PH and Group II: BPD without PH, using univariate and multivariable regression models. The primary outcome was a composite of death or neurodevelopmental impairments (NDI). NDI was defined as any cerebral palsy (GMFCS≥1), Bayley-III score < 85 on one or more of the cognitive, motor, or language composite scores, sensorineural or mixed hearing impairment or unilateral or bilateral visual impairment.

Results:

Of 372 eligible infants, 118 (Group I [BPD-PH] =7, Group II [BPD with no PH] =111) were lost to follow up. Of the remaining 254 infants, 52 in Group I and 202 in Group II were followed at 18-24 months CGA. Group I and Group II had median (IQR) birth weight of 710g (323) and 815g (314) [p=0.004] and median gestational ages (IQR) were 25 weeks (2) and 26 weeks (2) [p=0.020], respectively (Table 1). Rates of associated impairments are shown in Figure 1. Infants in BPD-PH group (Group I) were more likely to have mortality or NDI (adjusted Odds Ratio [aOR] 3.82; 95% CI: 1.17-12.41) (Table 2).

Conclusion:

BPD-PH in preterm infants born < 29 weeks GA is associated with increased odds of the composite outcome of death or neurodevelopmental impairment and language delay at 18-24 months CGA.

Table 1: Demographic characteristics of the study population

	BPD with PH Group I (n=52)	**BPD with no PH Group II** (n=202)	p-value*
Maternal characteristics			
Maternal age, mean (SD)	32 (±5)	32 (±6)	0.772
Smoking during pregnancy, n (%)	6 (12%)	21/200 (11%)	0.829
Gestational diabetes, n (%)	8 (15%)	13/201 (6%)	0.049
Gestational hypertension, n (%)	10 (19%)	38 (19%)	0.945
Antenatal steroids, n (%)	46 (88%)	176 (87%)	0.796
Chorioamnionitis, n (%)	5 (10%)	31/200 (16%)	0.280
Multiple birth, n (%)	14 (27%)	60 (30%)	0.694
C-section delivery, n (%)	38 (73%)	136 (67%)	0.426
Neonatal characteristics			
Gestational age, weeks, median (IQR)	25 (2)	26 (2)	0.020
Birth weight, grams, median (IQR)	710 (323)	815 (314)	0.004
Male, n (%)	30 (58%)	113 (56%)	0.820
SGA <10th percentile, n (%)	12 (23%)	24 (12%)	0.039
5-minute Apgar score <7, n (%)	17 (33%)	73 (36%)	0.643
RDS, n (%)	51 (98%)	191 (95%)	0.469
NEC, n (%)	11 (21%)	18 (9%)	0.013
PDA requiring treatment, n (%)	37 (71%)	120 (59%)	0.120
IVH Grade 3/4, n (%)	5 (10%)	19 (9%)	0.963
ROP Stage ≥3± requiring treatment, n (%)	16 (31%)	35 (17%)	0.031
Confirmed sepsis, n (%)	8 (15%)	27 (13%)	0.707
Duration of mechanical ventilation, days, median (IQR)	22 (32)	11 (26)	<0.001
Length of stay, days, median (IQR)	120 (46)	104 (38)	0.003
Discharged home on O2, n (%)	24/45 (53%)	67/201 (33%)	0.012

*Chi-square or Fisher's exact test for categorical variables, Mann-Whitney U test for continuous variables.
**Different variables have different denominators due to missing/unknown values.
Abbreviations: IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, RDS: Respiratory distress syndrome, ROP: Retinopathy of prematurity

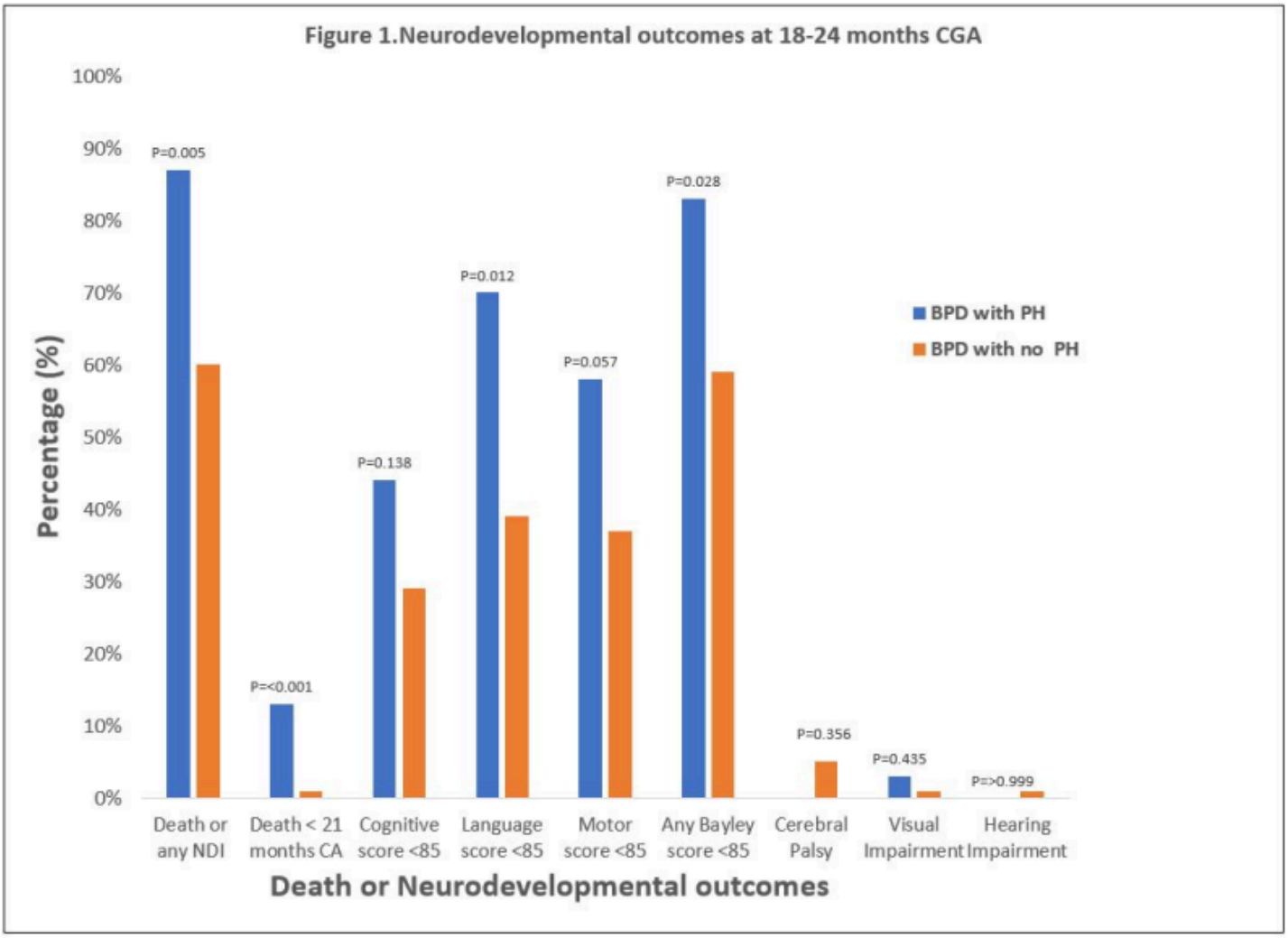

Table 2. Death or Neurodevelopmental outcomes at 18-24 months CGA

	BPD with PH Group I (n=52)	BPD with no PH Group II (n=202)	*Adjusted OR (95% CI)
Death or NDI, n (%)	27/31 (87%)	62/103 (60%)	3.82 (1.17-12.41)
Death before 21 months CGA, n (%)	7 (13%)	2 (1%)	#
Any NDI, n (%)	20/24 (83%)	60/101 (59%)	2.94 (0.89-9.70)
Cerebral palsy, n (%)	0/36 (0%)	8/173 (5%)	#
Bayley-III cognitive composite score <85, n (%)	11/25 (44%)	34/118 (29%)	1.76 (0.67-4.61)
Bayley-III language composite score <85, n (%)	14/20 (70%)	37/94 (39%)	3.05 (1.02-9.14)
Bayley-III motor composite score <85, n (%)	14/24 (58%)	37/100 (37%)	1.61 (0.56-4.61)
Visual impairment/blindness, n (%)	1/36 (3%)	2/173 (1%)	#
Hearing impairment/deafness, n (%)	0/36 (0%)	2/173 (1%)	#

Abbreviations: BPD; bronchopulmonary dysplasia, CGA; corrected gestational age, NDI; neurodevelopmental impairment, PH; pulmonary hypertension

* Adjusted for gestational age, antenatal steroids, Small for gestational age, patent ductus arteriosus requiring treatment, and necrotizing enterocolitis.

**Different variables have different denominators due to missing/unknown values.

For other secondary outcomes model could not be fit due to small numbers