

Title: Does severity of bronchopulmonary dysplasia predict neurodevelopmental impairments at age 5 years in infants born at <27 weeks' gestation?

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Background: Despite improvements in perinatal care of extremely preterm infants and improved ventilator approaches and nutritional management, there continues to be evidence of poorer neurodevelopmental (ND) outcomes in extremely preterm children with BPD. However, there is no sufficient evidence to predict long-term neurodevelopmental outcomes of infants with BPD at five years of age.

Objective: To compare composite outcome of death after discharge from hospital and or ND outcomes in infants born <27 weeks with no BPD (NBPD), mild BPD (MBPD) and severe BPD (SBPD) at 5 years of age. At our center, MBPD was defined as oxygen at 36 wk postmenstrual age with no home oxygen and SBPD was defined as chronic oxygen dependence following discharge home.

Methods: In a prospective population-based follow-up cohort study at our regional center, all surviving babies born from Jan 1995 to Dec 2014 at <27 weeks' gestation were enrolled in the study. Demographic, neonatal and ND outcome data were compared between the three groups. NDI was defined as cerebral palsy, visual impairment or blindness, sensorineural hearing impairment or deafness, or cognitive delay >1 standard deviation below the mean on standardized testing. Outcomes were compared across all 3 groups using univariate analysis, however, multivariable regression analysis is still underway and we will present at the time of conference.

Results: Of 1033 births, 216 died before discharge home, 817 survived to age 5 years and followed in our follow-up clinic. A total of 68 were excluded due to congenital anomalies or unknown BPD status. Outcome data were available for 608/749 (81.2%), grouped as follows: NBPD (N=105), MBPD (N=188) and SBPD (N=315). . Mean BWs for the three groups were 848g, 757g and 722g ($p<0.001$); median GAs were 26, 25, and 25 wk. respectively ($p<0.001$). The demographic characteristics and neurodevelopmental outcomes are shown in the Table 1 and Table 2 respectively. Proportion with composite outcome of death or NDI at age 5 was 40%, 47%, and 57% respectively ($p=0.008$). We are still continuing the multivariable regression modelling and will present the results at the time of meeting in June.

Conclusion: Increased severity of BPD is associated with higher prevalence of composite outcome of death after discharge or NDI in preterm children at age 5.

Table 1: MATERNAL CHARACTERISTICS

	No BPD (n=105)	BPD (n=188)	COD (n=315)	p-value*	Confidence Intervals for Pairwise Differences§		
					No BPD vs. BPD	No BPD vs. COD	BPD vs. COD
Maternal age, mean (SD)	30 (6) Range 16-42	29 (6) Range 17-48	30 (6) Range 14-45	0.615	-1.2 to 2.1	-1.6 to 1.4	-1.8 to 0.7
Nulliparous, n (%)	36/101 (36%)	61/185 (33%)	96/306 (31%)	0.724	-11% to 17%	-9% to 17%	-9% to 12%
Smoking during pregnancy, n (%)	25/103 (24%)	36/185 (19%)	59/304 (19%)	0.539	-7% to 17%	-7% to 16%	-9% to 9%
Antenatal steroids, n (%)	95/104 (91%)	167/186 (90%)	261/309 (84%)	0.090	-7% to 10%	-1% to 15%	-2% to 13%
Maternal antihypertensives, n (%)	5/104 (5%)	10/184 (5%)	38/310 (12%)	0.010	-7% to 6%	-14% to -1%	-13% to -1%
Maternal antibiotics, n (%)	85/104 (82%)	135/184 (73%)	193/310 (62%)	<0.001	-4% to 20%	8% to 31%	1% to 21%
Chorioamnionitis, n (%)	36/100 (36%)	73/179 (41%)	91/305 (30%)	0.046	-19% to 10%	-7% to 19%	0.2% to 22%
Multiple birth, n (%)	28 (27%)	59 (31%)	93 (30%)	0.697	-18% to 8%	-15% to 9%	-8% to 12%
C-section delivery, n (%)	56 (53%)	103 (55%)	147/314 (47%)	0.181	-16% to 13%	-7% to 20%	-3% to 19%
Maternal education post-secondary or more†	67/100 (67%)	120/182 (66%)	188/301 (62%)	0.614	-13% to 15%	-9% to 18%	-7% to 14%

†Available only for those who survived and were seen in follow-up.

*Chi-square for categorical variables, ANOVA or Kruskal-Wallis test for continuous variables.

§Bonferroni correction applied to adjust for the three pairwise comparisons, thus confidence intervals are reported at the $(1 - 0.05/3)\%$ level.

Table 2: NEONATAL CHARACTERISTICS

	No BPD (n=105)	BPD (n=188)	COD (n=315)	p-value*	Confidence Intervals for Pairwise Differences§		
					No BPD vs. BPD	No BPD vs. COD	BPD vs. COD
Gestational age in weeks, n (%)				<0.001			
23-24	9 (9%)	55 (29%)	113 (36%)		-31% to -10%	-37% to -18%	-17% to 4%
25-26	96 (91%)	133 (71%)	202 (64%)				
Birth weight in grams, mean (SD)	848 (131) Range 418-1240	757 (134) Range 440-1156	722 (136) Range 436-1140	<0.001	53 to 130	91 to 162	6 to 64
Birth length in cm, mean (SD)	33.7 (2.2) Range 27.0-38.0	32.6 (2.3) Range 22.0-38.0	32.1 (2.3) Range 26.0-38.5	<0.001	0.4 to 1.7	0.9 to 2.2	-0.0003 to 1.0
Birth head circumference in cm, mean (SD)	23.6 (1.3) Range 18.5-27.5	23.0 (1.6) Range 19.2-33.5	22.7 (1.5) Range 18.5-28.0	<0.001	0.2 to 1.0	0.5 to 1.3	-0.02 to 0.6
Male, n (%)	46 (44%)	88 (47%)	177 (56%)	0.032	-18% to 12%	-26% to 1%	-20% to 2%
Outborn, n (%)	13 (12%)	23 (12%)	37 (12%)	0.979	-9% to 10%	-8% to 9%	-7% to 8%
5 minute Apgar score <7, n (%)	33 (31%)	76/187 (41%)	130/311 (42%)	0.162	-23% to 5%	-23% to 2%	-12% to 10%
Caffeine, n (%)	91/103 (88%)	169/187 (90%)	260/309 (84%)	0.122	-11% to 7%	-5% to 13%	-1% to 13%
Postnatal steroids, n (%)	16 (15%)	58 (31%)	156/314 (50%)	<0.001	-27% to -4%	-45% to -24%	-29% to -8%
Diuretics, n (%)	69/103 (67%)	165 (88%)	301/309 (97%)	<0.001	-33% to -8%	-42% to -19%	-16% to -4%
Surfactant, n (%)	61 (58%)	120 (64%)	242/314 (77%)	<0.001	-20% to 9%	-32% to -6%	-23% to -3%
PDA, n (%)	65 (62%)	138 (73%)	269 (85%)	<0.001	-25% to 2%	-36% to -11%	-21% to -3%
PDA ligation, n (%)	15 (14%)	53 (28%)	165 (52%)	<0.001	-25% to -3%	-49% to -28%	-35% to -14%
SGA <10 th percentile, n (%)	3 (3%)	8 (4%)	34 (11%)	0.004	-7% to 4%	-14% to -2%	-12% to -1%
NEC	13 (12%)	33 (18%)	46/314 (15%)	0.465	-15% to 5%	-11% to 7%	-5% to 11%
IVH Grade III/IV	12 (11%)	33/187 (18%)	48 (15%)	0.367	-16% to 4%	-13% to 5%	-6% to 11%
ROP stage 3 or higher or treated ROP	14/84 (17%)	72/153 (47%)	129/259 (50%)	<0.001	-44% to -17%	-45% to -21%	-15% to 9%
Confirmed sepsis	24/104 (23%)	53/187 (28%)	109/310 (35%)	0.045	-18% to 7%	-24% to -0.3%	-17% to 3%
Length of hospital stay, median (IQR)	85 (22) Range 55-155	105 (30) Range 44-412	110 (34) Range 55-351	<0.001	-27 to -16	-29 to -18	-7 to 3
Days on respiratory support, median (IQR)	57 (22) Range 1-291	91 (25) Range 65-548	241 (149) Range 64-1596	<0.001	-45 to -34	-220 to -172	-167 to -131
Days on ventilation/CPAP/High Flow, median (IQR)	33 (30) Range 0-110	56 (36) Range 3-119	54 (34) Range 2-153	<0.001	-31 to -17	-31 to -18	-7 to 5
Number blood transfusions, median (IQR)	1 (2) Range 0-10	4 (3) Range 0-18	5 (4) Range 0-17	<0.001	-2 to -1	-4 to -3	-3 to -1

*Chi-square for categorical variables, ANOVA or Kruskal-Wallis test for continuous variables.

§Bonferroni correction applied to adjust for the three pairwise comparisons, thus confidence intervals are reported at the (1 – 0.05/3)% level.

Table 3: NEURODEVELOPMENTAL OUTCOMES AT 5 YEARS OF AGE

	No BPD (n=105)	BPD (n=188)	COD (n=315)	p-value*
Primary outcome at 5 years				
Death after discharge or any NDI	40/100 (40%)	83/176 (47%)	170/300 (57%)	0.008
Secondary outcomes				
Death after discharge	1 (1%)	2 (1%)	1 (0.3%)	0.501
Any NDI				0.019
None	60/99 (61%)	93/174 (53%)	130/299 (43%)	
Milder	28/99 (28%)	51/174 (29%)	102/299 (34%)	
Severe	11/99 (11%)	30/174 (17%)	67/299 (22%)	
Cognitive Score				0.482
≥85	65/99 (66%)	99/165 (60%)	161/275 (59%)	
70-84	27/99 (27%)	47/165 (28%)	76/275 (28%)	
<70	7/99 (7%)	19/165 (12%)	38/275 (14%)	
Cerebral Palsy				0.234
None	95 (90%)	169 (90%)	268/314 (85%)	
Mild	7 (7%)	7 (4%)	24/314 (8%)	
Moderate/Severe	3 (3%)	12 (6%)	22/314 (7%)	
Visual Impairment				<0.001
None	103 (98%)	175 (93%)	260/314 (83%)	
Mild	2 (2%)	10 (5%)	43/314 (14%)	
Bilateral blindness	0 (0%)	3 (2%)	11/314 (4%)	
Hearing Impairment				0.054
None	103 (98%)	182 (97%)	290/311 (93%)	
Mild	1 (1%)	3 (2%)	3/311 (1%)	
Bilateral deafness	1 (1%)	3 (2%)	18/311 (6%)	
Weight <5 th percentile§	13/97 (13%)	36/169 (21%)	72/277 (26%)	0.035
Height <5 th percentile§	10/98 (10%)	32/169 (19%)	75/275 (27%)	0.001

*Chi-square or Fisher's exact test.

§Based on WHO growth standard.