Pulmonary Hemodynamics and Long-Term Outcomes in Children with Pulmonary Hypertension-Associated Bronchopulmonary Dysplasia

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Objective To determine whether the severity of pulmonary hypertension (PH), assessed at cardiac catheterization, is associated with bronchopulmonary dysplasia (BPD) severity and mortality.

Study design We analyzed clinical data from subjects with BPD-PH enrolled in the PPHNet Registry between 2014 and 2024. BPD severity was based on the Neonatal Research Network grading system at 36 weeks postmenstrual age. Survival and clinical associations were estimated using Cox proportional hazards regression with delayed entry-to-risk-set and competing risk methodologies.

Results The study included 320 subjects (gestational age, 25.8 ± 2.0 weeks (range 22.2 to 31.6 weeks); postnatal age 5.0 months (IQR 3.3, 8.6; range birth to 12 years) at the time of PH diagnosis. The severity of BPD was 27% (grade 1), 44% (grade 2), and 29% grade 3. Twenty-two percent (n = 69) of subjects underwent cardiac catheterization within 1 month of echocardiographic diagnosis of PH. Hemodynamic features by cardiac catheterization were similar between grades of BPD severity. Five-year survival postdiagnosis was 94%, 94%, and 87%, respectively, for Grades 1, 2, and 3 BPD. Twenty-five of 320 (8%) subjects died, including 6 with pulmonary vein stenosis.

Conclusions Among subjects with BPD-PH undergoing cardiac catheterization, more deaths occurred among children with Grade 3 BPD. However, there were no substantive differences in invasive measurements of pulmonary hemodynamics based on BPD severity. *(J Pediatr 2026;289:114869)*.

Bronchopulmonary dysplasia (BPD) is the chronic lung disease of prematurity and associates with significant morbidity and mortality.[1,2] Although survival of infants born extremely preterm has improved, the incidence of BPD has not decreased over the past decades despite concurrent reductions in other major morbidities, including severe intraventricular hemorrhage and necrotizing enterocolitis.[3] A disease of multifactorial origins, BPD and its severity are defined by the prolonged need for higher levels of respiratory support at 36 weeks postmenstrual age (PMA), which reflect various cardiopulmonary features that include distal lung disease, airways obstruction, pulmonary hypertension (PH) and other factors.[4] Long-term survivors of preterm birth with BPD remain at high risk for late respiratory and cardiovascular disease, as well as adverse neurodevelopmental, mental health and other outcomes of preterm birth.[5-7]

PH is common in infants with BPD, with a prevalence of 6-39% at 36 weeks PMA.[4,8,9] The prevalence of PH increases with increasing severity of BPD, ap-

AVT	Acute vasodilator testing	NRN	Neonatal Research Network
ASD	Atrial septal defect	PAH	Pulmonary arterial hypertension
BPD	Bronchopulmonary dysplasia	PDA	Patent ductus arteriosus
BPD-PH	Bronchopulmonary dysplasia-associated pulmonary hypertension	PH	Pulmonary hypertension
		PPHNet	Pediatric Pulmonary Hypertension Network
CHD	Congenital heart disease	PVRi	Pulmonary vascular resistance indexed
CI	Cardiac index		
mPAP	Mean pulmonary artery pressure	WSPH	World Symposium on Pulmonary Hypertension
mRAP	Mean right atrial pressure		

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proaching 40% of infants with severe BPD by previous classification schemes.[10-13] The majority of subjects described to date with PH have been diagnosed during infancy, as recently described by multiple investigators.[8] However, PH can be identified in older children and adults who were born preterm.[12,14-18] Cardiac catheterization remains the gold standard procedure to diagnose PH, yet the procedure is not without risk, particularly for infants and young children. As a result, in most cases, diagnosis of PH in infants with BPD is based on echocardiogram without cardiac catheterization.[19] Therefore, published studies of patients with BPD-associated PH (BPD-PH) that confirm the diagnosis and include detailed invasive hemodynamic metrics are lacking. However, clinical indications for cardiac catheterization in the BPD population are well described and recently reviewed.[20,21]

Recently, a data-driven, severity-based definition of BPD was proposed by investigators in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NRN), defining BPD severity as grades 1, 2 and 3, as based on the mode of respiratory support required by a premature infants as assessed at 36 weeks PMA.[22] Despite numerous studies showing that PH is more common in more severe forms of BPD, PH was not incorporated into the NRN grade of BPD severity; and the relative differences in pulmonary hemodynamics as defined by cardiac catheterization according to grade of BPD severity has not been previously studied.[23,24]

The Pediatric Pulmonary Hypertension Network (PPHNet) recently published a report describing a registry of 1475 subjects with all forms of PH. BPD-PH was the primary classification for 320 (22%) of cases, making it the second most common subtype of PH.[25] Given its size and derivation from PH specialty care centers, the PPHNet research cohort provides a powerful opportunity to study BPD-PH and its potential variation according to BPD severity beyond the neonatal intensive care unit environment. We hypothesized that BPD-PH subjects with grade 3 BPD would have more severe hemodynamic indices of PH, as assessed by cardiac catheterization near the time of diagnosis, and worse survival. To investigate this hypothesis, we sought to: (a) study the epidemiology of patients diagnosed with BPD-PH, incorporating the new BPD grading system; (b) evaluate invasive hemodynamic metrics by cardiac catheterization around the time of PH diagnosis in BPD-PH patients and stratified according to BPD severity grade; and (c) examine the relationship of invasive hemodynamic metrics at diagnosis with long-term outcome, including survival.

Methods

Study Sample

This study is based on data collected from subjects born at less than 32 weeks gestational age (GA) with a diagnosis of PH who consented to participate in a multicenter longitudinal study (PPHNet Registry) conducted at 14 pediatric PH centers distributed across North America that are members of the PPHNet. As previously described, subjects were eligible for enrollment in the PPHNet Registry if they had a PH diagnosis confirmed by the PH specialty program at the enrolling center with echocardiographic or hemodynamic evidence of PH.[25] Subjects were enrolled starting in January 2014 and this report includes follow-up through April 2024. Written parental consent was obtained for all subjects following institutional review board approval of the protocol at each participating institution. Clinical data were entered into a secure database platform (Medidata Solutions, Inc.)[25] and REDCap.

The PPHNet research cohort includes subjects diagnosed with PH prior to age 21 years according to established guidelines for pediatric PH as previously described.[25] The diagnosis of PH was made by echocardiogram performed at the discretion of the treating pediatric PH physician specialist. A standardized electronic case report form was used to capture specialized information relevant to subjects born at less than 32 weeks GA. Subjects were clinically classified by each center's principal investigator according to the 2013 World Symposium on PH (Nice) Classification Scheme.[26] Subjects with PH and a confirmed GA of less than 32 weeks formed the analytic cohort for this report. Exclusion criteria included: (1) lack of a completed electronic case report form for subjects born less than 32 weeks; (2) diagnosis of congenital diaphragmatic hernia; (3) diagnosis of omphalocele; and (4) diagnosis of a defined genetic syndrome, such as Trisomy 21, DiGeorge Syndrome, or Noonan Syndrome. There were 366 subjects with a GA of less than 32 weeks and 46 met exclusion criteria; hence, the sample size of the analytic cohort was n = 320.

Definitions

The diagnosis of BPD and its severity were determined at 36 weeks PMA. BPD severity was classified by each center according to the recently proposed criteria that updated the older National Institutes of Health (NIH) definitions.[22] Specifically, subjects were categorized by BPD severity according to the mode of respiratory support administered at 36 weeks PMA, which includes the use of nasal cannula support with flow <2 L per minute (grade 1); nasal cannula support with flow ≥2 L per minute or noninvasive positive airway pressure support including continuous positive airway pressure delivery (grade 2); or the use of invasive mechanical ventilation (grade 3).

The use of PH-specific medications for each subject was recorded, as based on the following classes of medication: (a) calcium channel blockers; (b) inhaled nitric oxide; (c) phosphodiesterase 5 inhibitors; (d) endothelin receptor antagonists; (d) any delivery form of prostacyclin or treprostinil; and, (e) selexipag (a type of prostacyclin receptor agonist).

Cardiac catheterization was not a requirement for enrollment in this study and was performed at the discretion of the clinical team at each of the enrolling institutions. For those who underwent cardiac catheterization, when available, the response to acute vasodilator testing (AVT) was determined to be reactive or non-reactive according to 3 well-

established standards: the Sitbon, Barst, and Modified Barst criteria,[27-29] as previously described.[19]

Outcomes

The primary outcome was the composite of time to the earliest occurrence of either death or lung transplant according to BPD severity. A secondary analysis evaluated 3 competing risks: death, lung transplant, and PH resolution. PH resolution was defined as cessation of PH medications (see PH medication definition above).

Statistical Analysis

Descriptive statistics include counts and percentages for categorical variables and mean ± SD or median and IQR for continuous variables. Characteristics of groups defined by age at diagnosis or BPD severity were compared using a chi-square test for categorical measures and Student's t-test or the Wilcoxon rank sum test for continuous measures. Comparison of medication use according to BPD severity was conducted using a Mantel-Haenszel test for linear trend.

Kaplan–Meier methodology with delayed-entry to risk set methodology was used to estimate the distribution of time to the composite outcome of death or lung transplant, with group comparisons performed using the score test from the corresponding Cox proportional hazards model. Follow-up time was calculated as the time between PH diagnosis and the latest physical exam date if no death or lung transplant occurred; otherwise, follow-up ended at the time of death or lung transplant. In addition, the sub-distribution proportional hazards model of Fine and Gray was used to estimate time to event in a competing risks framework (death vs lung transplant vs PH resolution defined as cessation of PH medications).[30]

A *P*-value less than or equal to 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute) and R version 3.5.1 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing. URL https://www.R-project.org/).

Results

Of the 1457 subjects in the PPHNet Registry, 366 subjects had a GA of less than 32 weeks and 46 met exclusion criteria; hence, the sample size of the analytic cohort was n = 320 (**Supplemental Figure 1**; available at www.jpeds.com). The subjects were born at a mean GA of 25.8 ± 2.0 weeks (range 22.2 to 31.6 weeks) and mean birth weight was 721 ± 466 g. Nearly all (295, 92%) subjects were assigned a primary WSPH diagnostic classification of Group 3.5, which is PH due to lung disease and/or hypoxia due to a developmental lung disorder.[31]

Table I. Study demographics of 320 patients with BPD-PH

	All subjects	Grade 1*	Grade 2*	Grade 3*	
Variable	n (%) or median (IQR)	n (%) or median (IQR)	n (%) or median (IQR)	n (%) or median (IQR)	*P* value
N	320	75 of 278 (27%)	121 of 278 (44%)	82 of 278 (29%)	
Gestational age, wks	25.8 ± 2.0	25.9 ± 2.1	25.8 ± 1.8	25.9 ± 2.1	.91
Birth weight, grams (n = 285)	721 ± 466	725.7 ± 239.1	675.3 ± 218.0	705.6 ± 537.6	.64
Male sex	172 (53.8%)	35 (46.7%)	65 (53.7%)	48 (58.5%)	.33
Age at PH diagnosis (mo), median (IQR)	5.0 (3.3, 8.6)	5.2 (3.2, 8.9)	4.9 (3.2, 7.2)	4.9 (3.6, 8.8)	.24
Hispanic (n = 283)	38 (13.4%)	12 (18.8%)	10 (8.9%)	11 (15.1%)	.15
Race					.22
White	147 (45.9%)	35 (46.7%)	56 (46.3%)	33 (40.2%)	
Black	81 (25.3%)	21 (28.0%)	28 (23.1%)	26 (31.7%)	
Asian	30 (9.4%)	2 (2.7%)	16 (13.2%)	9 (11.0%)	
Other/Unknown	62 (19.3%)	17 (22.7%)	21 (17.3%)	14 (17.1%)	
Prenatal History					
Antenatal Steroids	128 (46.0%)	34 (45.3%)	56 (46.3%)	38 (46.3%)	1.00
Chorioamnionitis	27 (8.4%)	5 (6.7%)	12 (9.9%)	9 (11.0%)	.65
Maternal vascular disease	121 (37.8%)	27 (36.0%)	46 (38.0%)	38 (46.3%)	.36
Preeclampsia	70 (21.9%)	15 (20.0%)	27 (22.3%)	19 (23.2%)	.90
HELLP syndrome	25 (7.8%)	4 (5.3%)	12 (9.9%)	7 (8.5%)	.53
Maternal systemic hypertension	69 (21.6%)	17 (22.7%)	24 (19.8%)	25 (30.5%)	.21
Maternal cigarette smoker	18 (5.6%)	9 (12.0%)	3 (2.5%)	6 (7.3%)	.02
Maternal gestational diabetes	16 (5.0%)	3 (4.0%)	6 (5.0%)	6 (7.3%)	.63
Prolonged (>24 h) rupture of membranes	57 (17.8%)	10 (13.3%)	27 (22.3%)	15 (18.3%)	.30
Neonatal and Infant Conditions					
SGA (n = 285)					.30
Yes	86 (30.2%)	14 (22.6%)	36 (31.6%)	26 (34.2%)	
No	199 (69.8%)	48 (77.4%)	78 (68.4%)	50 (65.8%)	
Necrotizing enterocolitis	53 (16.6%)	12 (16.0%)	12 (9.9%)	23 (28.0%)	.004
Patent ductus arteriosus					.67
Untreated	85 (33.6%)	22 (33.3%)	36 (37.9%)	20 (31.3%)	
Treated (medically or surgically)	168 (66.4%)	44 (66.7%)	59 (62.1%)	44 (68.8%)	
Pulmonary vein stenosis (≥1 affected vein)	35 (10.9%)	6 (8.0%)	10 (8.3%)	13 (15.9%)	.18

SGA, small for gestational age.
*BPD Grade was determined for 278 of the 320 study participants.

Table II. Cardiopulmonary medications overall and by BPD severity*, concurrent with or initiated within 30 days of PH diagnosis

Medication type	Total cohort n = 320	Grade 1 n = 75	Grade 2 n = 121	Grade 3 n = 82	P value
PH-specific medications					
Inhaled nitric oxide (NO)	33 (10.3%)	3 (4.0%)	13 (10.7%)	15 (18.3%)	.01
Prostacyclin or prostacyclin derivative	13 (4.1%)	4 (5.3%)	3 (2.5%)	4 (4.9%)	.91
Phosphodiesterase 5 inhibitor	120 (37.5%)	28 (37.3%)	49 (40.5%)	28 (34.1%)	.66
Endothelin receptor antagonist	20 (6.3%)	2 (2.7%)	8 (6.6%)	5 (6.1%)	.47
Calcium channel blocker	2 (0.6%)	0 (0%)	1 (0.8%)	1 (1.2%)	.35
No PH-specific medications	174 (54.4%)	45 (25.9%)	63 (36.2%)	42 (24.1%)	.37
Related medications					
Diuretics	154 (48.1%)	34 (45.3%)	70 (57.9%)	37 (45.1%)	.11
Iron supplementation	66 (20.6%)	18 (24.0%)	30 (24.8%)	14 (17.1%)	.40
Levothyroxine	5 (1.6%)	0 (0%)	2 (1.7%)	3 (3.7%)	.08
Milrinone	2 (0.6%)	1 (1.3%)	0 (0%)	1 (1.2%)	.96
Dopamine	11 (3.4%)	3 (4.0%)	3 (2.5%)	5 (6.1%)	.48
Digoxin	11 (3.4%)	3 (4.0%)	7 (5.8%)	0 (0%)	.16

*BPD grade was determined for 278 of the 320 study participants.

Table I describes the full cohort. Although the majority of children were diagnosed during infancy (median 5.0, IQR 3.3-8.6 months chronologic age), 57 children (18%) were diagnosed with PH at greater than 12 months of age (Figure 1). One hundred and seventy-two (54%) subjects were male. Sufficient data were available to determine the grade of BPD at 36 weeks PMA for 278 subjects (87%); of these, 75 (27%) subjects were categorized as grade 1, 121 (44%) as grade 2, and 82 subjects (29%) as grade 3. There were no significant differences among the grades of BPD

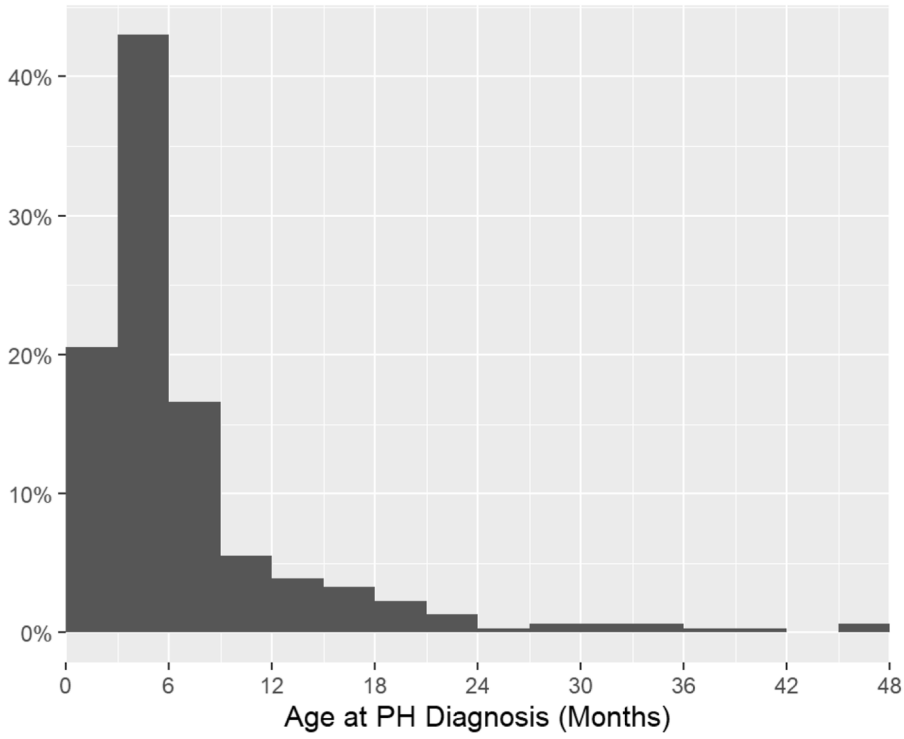

Figure 1. Distribution of age at PH diagnosis for the analytic cohort (gestational age less than 32 weeks, n = 320). Although the median age at diagnosis was 5.0 months, 57 subjects (18%) were diagnosed at greater than 12 months of age. Thirteen cases with age at PH diagnosis over 4 years are not shown.

represented for sex, age at diagnosis, Hispanic ethnicity, or race. Prenatal history was not notably different among grades 1, 2 or 3. Among early neonatal and infant conditions, a history of necrotizing enterocolitis was more prevalent among those with grade 3 BPD (28% grade 3 BPD vs 16% and 10%, respectively, for grades 1 and 2; $P = .004$). Thirty percent were small for gestational age; this rate did not vary by BPD grade ($P = .30$).

PH-specific medication use within a month of diagnosis is presented in **Table II**. Of these subjects, 112 (35%) were treated with a single PH-specific drug. Thirty-four (11%) were treated with 2 or more PH-specific drugs. Half of the subjects (174; 54%) were not treated any PH-specific drugs around the time of diagnosis.

The median follow-up in the full cohort was 3.6 years (IQR 1.6-7.4). During follow-up, 144 (48%) of the 320 subjects underwent cardiac catheterization at least one time. More than one-third of subjects underwent 2 (92 of 297; 31%) or 3 (24 of 297; 8%) catheterization procedures during the study period. Sixty-nine of the 320 (22%) subjects underwent catheterization within 1 month of the PH diagnosis, at median age of 0.7 years (IQR 0.4, 1.2) (**Supplemental Table 1**; available at www.jpeds.com); hemodynamic measurements for these subjects are provided in **Table III**. Findings were consistent with precapillary pulmonary hypertension, as defined by an elevated mean pulmonary artery pressure (mean ± SD of 39.6 ± 12.5 mmHg) and pulmonary vascular resistance indexed 7.2 ± 4.3 WU m^2 without elevation of pulmonary capillary wedge pressure (9.4 ± 4.2 mmHg). The cardiac index (CI) was 3.8 ± 1.3. The mean pulmonary to systemic blood flow ratio (Qp:Qs) was 1.32 ± 0.54; 10 (14.5%) subjects had a Qp:Qs > 1.5. Data to determine AVT response during CC were available for 46 of the 69 subjects. Of those tested, regardless of the criteria used, few subjects met criteria for a positive response to AVT (9%, 7%, and 4%, respectively.[31-33]

Twenty-five of the 320 subjects (8%) died during the study. Although BPD grade was not determined for 3 subjects who died, of the 22 subjects with a BPD grade, 13 (59%) were grade 3, 5 (23%) were grade 2, and 4 (18%) were grade 1. Six of the 25 (24%) had a concurrent diagnosis of pulmonary vein stenosis (PVS); BPD grade was unknown for one of

Table III. Hemodynamic assessment for those with cardiac catheterization within 1 month of diagnosis, categorized by BPD grade (n = 59/69 subjects with BPD Grade)*

Variable	Overall (n = 69)	Grade 1 (n = 19)	Grade 2 (n = 20)	Grade 3 (n = 20)	*P* value
Age at cath, mo, n	69	19	20	20	
Median (IQR)	7.6 (4.4, 11.5)	7.6 (5.0, 10.2)	6.6 (4.2, 13.7)	6.6 (4.2, 13.7)	.93
mRAP, mm Hg, n	54	14	16	17	
Mean ± SD	7.96 ± 6.81	6.93 ± 1.86	10.25 ± 11.78	6.94 ± 2.82	.33
RVEDP, mm Hg, n	37	8	12	14	
Mean ± SD	9.46 ± 3.48	9.63 ± 2.72	9.75 ± 4.00	9.14 ± 3.86	.91
RVSP, mm Hg, n	40	9	12	15	
Mean ± SD	55.8 ± 17.8	55.4 ± 22.1	51.1 ± 9.6	58.5 ± 21.3	.59
mPAP, mmHg, n	58	16	20	14	
Mean ± SD	39.6 ± 12.5	38.9 ± 14.2	37.9 ± 10.6	43.4 ± 14.5	.45
mPCWP, mm Hg, n	41	12	11	13	
Mean ± SD	9.39 ± 4.18	8.79 ± 4.14	10.14 ± 4.69	9.46 ± 4.14	.76
CI, L/min/m^2, n	51	14	16	14	
Mean ± SD	3.82 ± 1.34	3.83 ± 1.73	3.67 ± 0.63	3.98 ± 1.64	.83
PVRi, WU m2	55	17	17	15	
Mean ± SD	7.18 ± 4.29	7.24 ± 4.51	7.57 ± 4.76	6.40 ± 4.12	.75
SVRi, WU m2, n	48	15	15	13	
Mean ± SD	14.2 ± 4.7	15.5 ± 5.6	13.8 ± 4.1	13.8 ± 4.5	.54
mSAP, mm Hg, n	46	17	11	13	
Mean ± SD	55.6 ± 11.8	56.9 ± 8.9	58.4 ± 11.4	52.5 ± 16.3	.48
Ratio of mPAP/mSAP, n	40	15	11	10	
Mean ± SD	0.66 ± 0.23	0.67 ± 0.30	0.64 ± 0.18	0.68 ± 0.21	.92
Qp:Qs > 1.5, n					.09
Yes	10 (14.5%)	1 (5.3%)	4 (20.0%)	3 (15.0%)	
No	36 (52.2%)	13 (68.4%)	13 (65.0%)	7 (35.0%)	
Unknown	23 (33.3%)	5 (26.3%)	3 (15.0%)	10 (50.0%)	
AVT responsivity	46	14	13	12	
Sitbon					.75
Yes	4 (8.7%)	1 (7.1%)	2 (15.4%)	1 (8.3%)	
No	42 (91.3%)	13 (92.9%)	11 (84.6%)	11 (91.7%)	
Barst criteria					.35
Yes	3 (6.5%)	1 (7.1%)	2 (15.4%)	0 (0%)	
No	43 (93.5%)	13 (92.9%)	11 (84.6%)	12 (100%)	
Modified Barst criteria					.61
Yes	2 (4.4%)	1 (7.1%)	1 (8.3%)	0 (0%)	
No	43 (95.6%)	13 (92.9%)	11 (91.7%)	12 (100%)	

IQR, interquartile range; *mPAP*, mean pulmonary artery pressure; *mRAP*, mean right atrial pressure; *PCWP*, pulmonary capillary wedge pressure; *RVEDP*, right ventricular end diastolic pressure; *CI*, cardiac index; *TD*, thermodilution; *PVRi*, pulmonary vascular resistance index; *SVRi*, systemic vascular resistance index; *Qp*, pulmonary blood flow; *Qs*, systemic blood flow.
*Not all subjects have a recorded value for each variable.

Table IV. Features of the 25 subjects in the analytic cohort (n = 320) with death during study follow-up

			grade	Contributors to death			
Subject*	Age at death (yrs)	BPD	RV failure	Acute respir Failure	Acute on chronic respir failure	PVS	Other
1	0.5	3	✓			✓	
2	0.5	3			✓		
3	0.6	3			✓		
4	0.7	3	✓				
5	1.0	3	✓				
6	1.3	3		✓		✓	
7	1.6	3	✓		✓		
8	1.6	3		✓			
9	1.7	3				✓	Arrhythmic arrest
10	2.0	3	✓		✓		
11	2.4	3			✓	✓	
12	2.5	3	✓			✓	
13	15.7	3			✓		
14	0.7	2	✓				Arrhythmic arrest
15	0.7	2	✓		✓		
16	0.7	2			✓		
17	3.8	2		✓			
18	9.5	2					Cancer
19	2.1	1	✓				
20	4.2	1	✓				
21	14.8	1	✓				
22	16.0	1			✓		Acute pulmonary hemorrhage
23	1.3	ND	✓			✓	
24	1.3	ND		✓			
25	10.6	ND			✓		

ND, not determined.
*Exact Subject IDs masked.

the patients who died with PVS, and was grade 3 for the remaining 5. Twelve (45%) subjects had acute respiratory failure; of those, 7 had grade 3 BPD (versus 3 with Grade 2, 1 with grade 1, and 1 not determined). Ten subjects (40%) had progressive right heart failure; of those, 5 had grade 3 BPD (versus 2 with grade 2, 2 with grade 1, and 1 not determined). Of 3 subjects who died during cardiac catheterization, 2 had grade 3 BPD (BPD grade was not determined for the third CC death) (Table IV).

We sought to explore the relationship between BPD grade and time to death or lung transplant, using the 278 subjects in Table I for whom BPD grade was determined. At 5 years post-diagnosis, the transplant-free survival rate was 94% for BPD grades 1 and 2, vs 87% for those with BPD grade 3 (P = .16). In addition, competing risk analyses were conducted to incorporate both PH-specific medication use and time to death/lung transplant for the cohort overall (Figure 2, Left Panel) as well as stratified according to BPD severity grade (Figure 2, Right Panel). Although time to cessation of PH-specific medications increased from grade 1 to grade 2 to grade 3 BPD severity, this was not significant (P = .07). Consistent with the overall transplant-free survival rate, the time to death/lung transplant did not differ according to BPD grade (P = .17).

We also examined hemodynamic data at the time of diagnosis according to BPD severity grade (Table III and Supplemental Figure 1; available at www.jpeds.com). Of the 69 subjects who underwent cardiac catheterization within 1 month of diagnosis, 59 had sufficient data to determine the BPD severity grade. Grade 1 BPD was diagnosed in 19 (32%), grade 2 in 20 (34%) and grade 3 in 20 (34%). Hemodynamic parameters did not differ according to BPD severity grade at the time of diagnosis.

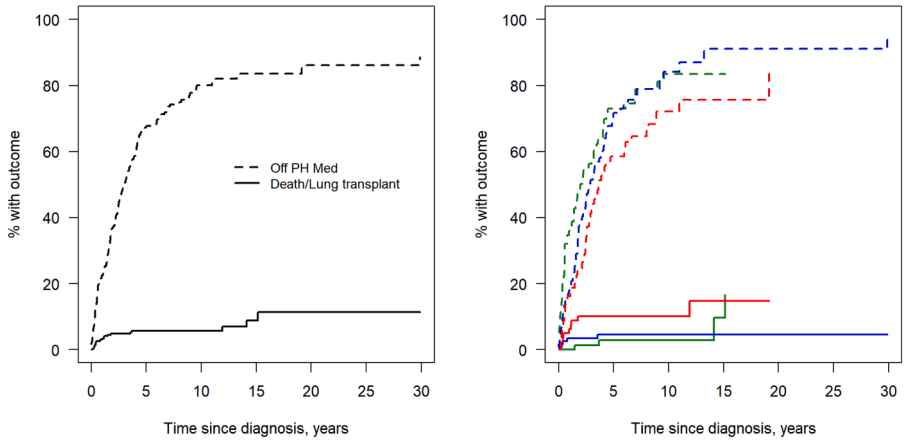

Figure 2. Estimated freedom from death/lung transplant by BPD severity grade (P = .16), calculated using delayed entry-to-risk-set methodology. A total of 25 deaths and 1 lung transplant were observed during a median follow-up of 3.6 years (IQR 1.6-7.4) amongst the 278 subjects with a BPD grade determined. Event rates at 5 years postdiagnosis were grade 1, 94% (95% CI: 80%, 99%), vs grade 2, 94% (95% CI: 80%, 98%) vs grade 3, 87% (95% CI 54%, 87%).

Table V. Hemodynamic assessment for those with cardiac catheterization within 1 month of PH diagnosis (n = 69), categorized according to death (n = 12) or survival (n = 57)*

Variable	All	Survivor	Nonsurvivor	*P* value
Age at diagnosis, mo	69	57	12	
Median (IQR)	7.6 (4.6, 14.7)	8.2 (5.0, 15.3)	5.2 (4.1, 9.8)	.97
mRAP, mm Hg, n	54	45	9	
Mean ± SD	7.96 ± 6.81	8.04 ± 7.39	7.56 ± 2.55	.33
RVEDP, mm Hg, n	37	28	9	
Mean ± SD	9.46 ± 3.48	9.29 ± 3.67	10.00 ± 2.96	.91
RVSP, mm Hg, n	40	31	9	
Mean ± SD	55.83 ± 17.82	51.55 ± 14.63	70.56 ± 20.76	.59
mPAP, mmHg, n	58	47	11	
Mean ± SD	39.62 ± 12.53	38.38 ± 11.48	44.91 ± 15.81	.45
mPCWP, mm Hg, n	41	36	5	
Mean ± SD	9.39 ± 4.18	9.42 ± 4.44	9.20 ± 1.30	.76
mLAP, mm Hg, n	23	19	4	
Median (IQR)	8.00 (6.00, 12.00)	8.00 (6.00, 12.00)	8.50 (6.50, 10.00)	.68
mLVEDP, mm Hg, n	16	12	4	
Mean ± SD	11.69 ± 3.50	11.17 ± 3.69	13.25 ± 2.63	.71
CI, L/min/m^2, n	51	43	8	
Mean ± SD	3.82 ± 1.34	3.80 ± 1.34	3.89 ± 1.43	.83
PVRi, WU m^2v	55	46	9	
Mean ± SD	7.18 ± 4.29	6.83 ± 4.09	8.93 ± 5.10	.75
SVRi, WU m^2, n	48	40	8	
Mean ± SD	14.25 ± 4.66	14.20 ± 4.63	14.49 ± 5.14	.54
mSAP, mm Hg, n	46	39	7	
Mean ± SD	55.57 ± 11.75	55.56 ± 11.73	55.57 ± 12.82	.48
Ratio of mPAP/mSAP, n	40	34	6	
Mean ± SD	0.66 ± 0.23	0.64 ± 0.20	0.79 ± 0.32	.92
Qp:Qs, n	46	37	9	
Median (IQR)	1.15 (1.00, 1.42)	1.16 (1.00, 1.35)	1.03 (1.00, 1.46)	.43
AVT responsivity				
Sitbon				.28
Yes	4 (8.7%)	4 (10.8%)	0 (0%)	
No	42 (91.3%)	33 (89.2%)	9 (100%)	
Barst criteria				.36
Yes	3 (6.5%)	3 (8.1%)	0 (0%)	
No	43 (93.5%)	34 (91.9%)	9 (100%)	
Modified Barst criteria				.45
Yes	2 (4.4%)	2 (5.6%)	0 (0%)	
No	43 (95.6%)	34 (94.4%)	9 (100%)	

IQR, interquartile range; *mPAP*, mean pulmonary artery pressure; *mRAP*, mean right atrial pressure; *mSAP*, mean systemic Arterial pressure; *PCWP*, pulmonary capillary wedge pressure; *RVEDP*, right ventricular end diastolic pressure; *LVEDP*, left ventricular end diastolic pressure; *CI*, cardiac index; *PVRi*, pulmonary vascular resistance index; *RVSP*, right ventricular systolic pressure; *SVRi*, systemic vascular resistance index; *LVEDP*, left ventricular end diastolic pressure; *Qp*, pulmonary blood flow; *Qs*, systemic blood flow.
*Not all subjects have a recorded value for each variable.

Furthermore, the usage of PH medications at the time of catheterization was similar in the 3 groups (53% in grade 1; 75% in grade 2; and 65% in grade 3). Arterial oxygen saturation tended to be lower with increasing BPD severity grade (median 93, 88, 85% for grades 1 to 3, respectively), and the prevalence of Qp:Qs > 1.5 was 2% in grade 1, 20% in grade 2, and 15% in grade 3.

Among the 69 subjects that had cardiac catheterization within 1 month of diagnosis, we explored the relationship between deleterious outcomes (including death, lung transplantation, and PH-related hospitalization) and invasive hemodynamic metrics. For this group, 12 of 69 (17%) subjects died during follow up. No hemodynamic metrics at diagnosis were associated with death (Table V). Further, the distribution of number of PH medications prescribed was similar for the 12 patients who died and the 57 survivors. In addition, 32 of the 69 underwent 2 or more catheterization procedures. Mixed effects modeling was employed and found no association between change in hemodynamics over time and death (data not shown).

Discussion

BPD-PH is a major burden for children and families, accounting for 22% of PH cases enrolled in the PPHNet Research Cohort.[25] Although past studies showed high rates of PH in severe BPD,[4] the natural history and relationship between BPD severity and PH remains unclear. In addition, whether invasive hemodynamic metrics are worse for those infants with more severe BPD is unknown. Evaluating data from 320 subjects born preterm at less than 32 weeks PMA in the PPHNet Research Cohort, we found: (a) an equal representation of subjects from all 3 grades of BPD Severity[22]; (b) a precapillary hemodynamic condition for the 69 subjects who underwent CC within 1 month of diagnosis; and (c) that

neither hemodynamic metrics nor survival were statistically different across BPD severity grades.

Our findings are important for several reasons, including the derivation of data from a real-world PH-focused cohort of participants from a large multicenter registry from 14 major interdisciplinary pediatric PH centers in North America. The participants were diagnosed and cared for by PH-focused specialists, with rigidly documented PH.[25] This report includes the largest series of BPD-PH patients who underwent cardiac catheterization and supports clinical evidence that most patients with BPD-PH have a precapillary condition that typically responds favorably to pulmonary vasodilator therapy in the absence of obvious contraindications (eg, multivessel PVS disease).[19,20,32,33] Prior studies found that the most severe forms of BPD were represented in higher proportion among BPD-PH patients[4]; in this study, we found all 3 BPD grades represented fairly equally in our cohort. Furthermore, grade 3, the most severe respiratory form of BPD determined at 36 weeks PMA, had similar invasive hemodynamic metrics to grades 1 and 2 at the time of diagnosis. The severity of lung disease at 36 weeks PMA (when BPD is determined and graded) is not directly indicative of the severity of pulmonary vascular disease. Furthermore, the factors which drive outcome among BPD-PH patients may derive more from nonvascular drivers than PH itself, which historically is identified as the primary cause of deleterious outcome.[34] Although it would be reasonable to assert that subjects with grade 3 BPD had similar hemodynamic features of PH due to more aggressive PH-specific medication use at the time of CC, this was not the case in our cohort. Finally, our finding that a significant proportion of BPD-PH cases were diagnosed by expert PH centers after infancy is consistent with a growing body of data to suggest that formerly preterm individuals have a risk of PH emergence that extends into childhood and beyond.[6,35,36]

Since its initial description by Northway in 1967, efforts have been made to stratify BPD into levels of severity with an eye toward long-term outcomes, with more recent focus upon the duration and degree of respiratory support required up to 36 weeks PMA.[1,13,37] Recently, Jensen and Neonatal Research Network colleagues proposed a 3-grade system that predicted death or serious respiratory morbidity for 81% of study subjects, including 20% mortality by 18-26 months corrected age for subjects with the most severe form, grade 3 BPD.[23] However, this grading system did not incorporate PH diagnosis, a potentially crucial driver of outcomes for formerly preterm subjects.[38] The BPD Collaborative recently explored the outcome of patients with BPD-PH discharged from the neonatal intensive care unit on mechanical ventilation via tracheostomy, the majority of whom were presumably grade 3 BPD. In that study of 154 subjects (40% BPD vs 60% BPD-PH), the majority of infants with BPD-PH requiring chronic ventilation via tracheostomy survived after their initial hospital discharge with gradual improvement; BPD-PH did not associate with later liberation from oxygen or mechanical ventilatory support compared with those with BPD alone, suggesting that PH was not the key driver of respiratory support requirement.[39]

Although not uniformly employed at the time of diagnosis for formerly premature subjects, cardiac catheterization is an important component of the PH diagnostic process to assess invasive hemodynamic parameters as well as assessment of the degree (if any) intracardiac shunt, aortopulmonary collateral vessels, pulmonary veins, and LV diastolic function.[20,32,40] However, literature providing invasive hemodynamic metrics remains limited and typically restricted to small subject samples, with variable clinical characteristics including a high percentage of prevalent BPD-PH cases on PH-specific therapy for variable lengths of time.[15,18,38,41-45] Of the nearly 300 subjects in the current cohort, we closely examined the 69 subjects with cardiac catheterization data within 1 month of PH diagnosis by echocardiogram. We chose this time course as we aimed to capture subjects more naïve to PH-specific therapies and disease duration. We found a precapillary PH hemodynamic condition with severe elevation of mean pulmonary artery pressure and pulmonary vascular resistance indexed, and much lower rates of responsivity to formal acute vasodilatory testing (AVT) compared with prior studies (8-10% in this study depending on criteria, compared with 30-82% in previous reports).[15,18,27-29,41-45] For example, Frank et al in a single-center study found that 35% of 26 BPD-PH subjects had a positive AVT, which associated with lower events of death or tracheostomy at 2 years; although pulmonary hemodynamics did not otherwise associate with deleterious outcomes.[33]

Even though 25 of 320 (8%) participants died (and one underwent lung transplant), freedom from death or lung transplant in this study was slightly higher than most other studies over the past 15 years.[8,15,45,46] Three subjects died during cardiac catheterization, emphasizing that the procedure is not without risk.[47] We found no statistically significant difference according to BPD severity grade, although the majority of deaths during the time of follow up occurred among those with grade 3 BPD. This is consistent with studies demonstrating higher mortality for those with grade 3 BPD and other severe BPD definitions.[8,12,14-16,46,48-50] Data from cardiac catheterization allowed us to explore this further: we found similar hemodynamic metrics across BPD severity grades, but those subjects who died were more likely to be grade 3 BPD. Ultimately, PVS and/or progressive right ventricular failure were common findings among those who died, and enriched in those with grade 3 PH. This may suggest that subjects with grade 3 BPD require enhanced vigilance for PVS monitoring in the setting of PH, although further studies are required for this potential association. In addition, it may also be the case that subjects with grade 3 BPD more poorly tolerate elevated RV pressures, leading to progressive right ventricular failure and higher risk of death. Thus, although we do not advocate for the inclusion of PH into the determination of BPD severity, it may be an important risk assessment tool for those who meet grade 3 BPD designation. Furthermore, we do not believe that this

information undermines the importance of the decision to proceed to cardiac catheterization to address critical physiologic questions for some patients with BPD-PH, as recently reviewed by the Pediatric Task Force of the seventh World Symposium on Pulmonary Hypertension.[21]

Although several prior studies carefully described groups of patients with BPD-PH,[8,10,15,38,45,46,51] our study provides the largest and most comprehensive prospective cohort of subjects actively followed as inpatients and outpatients by PH specialty teams. These subjects, carefully phenotyped at PH specialty centers, were born with a median PMA < 26 weeks and median birth weight of 721 g. A high proportion had PH formally diagnosed after 1 year of life, which is consistent with the growing recognition that formerly premature subjects have risk of PH expression subsequent to infancy, including even otherwise healthy subjects with an occult pulmonary hypertensive phenotype into adulthood.[52] What remains unclear is if (and when) formerly premature subjects should be routinely screened for PH by noninvasive means such as echocardiogram at distinct intervals during childhood. Of the 320 subjects in this cohort, 57 (18%) were diagnosed after 12 months of age, with some presenting well into childhood. In contrast, prior studies of BPD-PH reported smaller cohorts of children with an earlier age at diagnosis. For example, Arjaans et al recently reported their experience with BPD-PH patients diagnosed at or beyond 36 weeks PMA, describing 28 children born at 26.4 weeks GA and 790 g, a sample similar to the current cohort in terms of GA and birth weight. However, those children were diagnosed at a median of 2.5 months and skewed toward more severe BPD (23 (82%) of children met the 2001 NIH standard definition of BPD[13]).[38] Similarly, del Cerro et al reported 29 patient with BPD-PH of similar GA and birth weight, of whom 22 (76%) were categorized as severe BPD by the same 2001 NIH criteria.[13] Those subjects were also diagnosed during infancy, at a median age of 4.5 months (IQR 2.4–7.8).[45] Likewise, neonatal-driven studies have focused on those subjects diagnosed during early infancy.[46,53]

Potential limitations include the observational nature of this study and incomplete data for a subset of subjects in the Registry. Further, the associations described herein do not assure causation. In addition, subjects were cared for at tertiary referral centers for pediatric PH care across North America, which may not fully represent BPD-PH patients and care patterns.[54] This was not a study of all premature subjects from the time of birth, which may enhance survival bias as some subjects may have died or resolved PH prior to enrollment; rather, subjects were enrolled upon engagement with specialty PH providers at each center. Cardiac catheterization was conducted according to local center decision-making rather than by shared protocol; hence selection bias may be present with respect to BPD severity. It is also possible that some subjects had indices consistent with PH prior to involvement of the PH specialists, such that PH diagnosis may have been delayed for some subjects which may inflate the size of the group of subjects diagnosed after infancy. In addition, even though BPD grade was determined according to respiratory support provided at 36 weeks PMA,[22] it was unavailable for some children and the NRN grading system used may not precisely describe BPD beyond infancy. Resolution of PH was defined as cessation of PH therapy; however, this may underestimate the exact percentage of subjects with PH resolution, because in some cases medications may have been conservatively continued beyond resolution of PH. Finally, although echocardiographic data were used by each PH Center to assign the initial diagnosis of PH, imaging and laboratory data were not systematically collected and blindly evaluated—thus, we lack noninvasive metrics assessed over time. Each of these limitations highlight the importance of continued multispecialty and multicenter collaborations, particularly as preterm births increase, to help us better understand the causes and consequences of BPD-PH across the lifespan.[5,55]

In conclusion, using a large multicenter cohort of subjects with BPD-PH, we found a similar distribution of grade 1, grade 2, and grade 3 BPD-PH, with a high proportion with freedom from death or lung transplant. Among those undergoing cardiac catheterization, invasive hemodynamic profiles did not associate with BPD severity grade, although the majority of deaths occurred among those with grade 3 BPD. Further studies are warranted. Reduced survival among those with grade 3 BPD and PH may be driven by factors independent of pulmonary vascular hemodynamic parameters. ■

CRediT authorship contribution statement

Eric D. Austin: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Mary P. Mullen:** Writing – review & editing, Resources, Investigation, Conceptualization. **Catherine M. Avitabile:** Writing – review & editing, Resources, Investigation, Conceptualization. **Usha S. Krishnan:** Writing – review & editing, Resources, Investigation, Conceptualization. **Erika B. Rosenzweig:** Writing – review & editing, Resources, Investigation, Conceptualization. **Roberta L. Keller:** Writing – review & editing, Resources, Investigation, Conceptualization. **John P. Kinsella:** Writing – review & editing, Resources, Investigation, Conceptualization. **Delphine Yung:** Writing – review & editing, Resources, Investigation, Conceptualization. **Lea Steffes:** Writing – review & editing, Resources, Investigation, Conceptualization. **Angela Bates:** Writing – review & editing, Resources, Investigation, Conceptualization. **Eleni G. Elia:** Writing – review & editing, Visualization, Validation, Methodology, Formal analysis, Data curation. **Lewis H. Romer:** Writing – review & editing, Resources, Investigation. **Sharon McGrath-Morrow:** Writing – review & editing, Resources, Investigation. **Meghan L. Bernier:** Writing – review & editing, Investigation. **Kenneth D. Mandl:** Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **J. Usha Raj:** Writing – review & editing, Resources, Investigation, Conceptualization. **Lynn A. Sleeper:** Writing – review & editing, Writing – original draft,

Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Steven H. Abman:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

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References

1. Northway WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 1967;276:357-68.
2. Geetha O, Rajadurai VS, Anand AJ, Dela Puerta R, Huey Quek B, Khoo PC, et al. New BPD-prevalence and risk factors for bronchopulmonary dysplasia/mortality in extremely low gestational age infants ≤28 weeks. J Perinatol 2021;41:1943-50.
3. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. Birth Defects Research A, Clin Mol teratology 2014;100:145.
4. Thébaud B, Goss KN, Laughon M, Whitsett JA, Abman SH, Steinhorn RH, et al. Bronchopulmonary dysplasia. Nat Rev Dis Primers 2019;5:1-23.
5. Barton GP, Torres LA, Goss KN, Eldridge MW, Fain SB. Pulmonary microvascular changes in adult survivors of prematurity: utility of dynamic contrast-enhanced magnetic resonance imaging. Am J Respir Crit Care Med 2020;202:1471-3.
6. Goss KN, Beshish AG, Barton GP, Haraldsdottir K, Levin TS, Tetri LH, et al. Early pulmonary vascular disease in young adults born preterm. Am J Respir Crit Care Med 2018;198:1549-58.
7. Kelly MM. National perspective of health outcomes of 8- to 11-Year-Old children born prematurely and their full-term peers. J Pediatr Nurs 2016;31:422-9.
8. Arjaans S, Zwart EAH, Ploegstra MJ, Bos AF, Kooi EMW, Hillege HL, et al. Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 2018;32:258-67.
9. Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J 2024;64:2401324. https://doi.org/10.1183/13993003.01324-2024
10. An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J 2010;40:131-6.
11. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics 2012;129:e682-9.
12. Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am J Respir Crit Care Med 2015;191:87-95.
13. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
14. Arjaans S, Fries MWF, Schoots MH, Schilte CFM, Roofthooft MTR, Vrijlandt EJLE, et al. Clinical significance of early pulmonary hypertension in preterm infants. J Pediatr 2022;251:74-81.e3.
15. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007;120:1260-9.
16. Mirza H, Ziegler J, Ford S, Padbury J, Tucker R, Laptook A. Pulmonary hypertension in preterm infants: prevalence and association with bronchopulmonary dysplasia. J Pediatr 2014;165:909-14.e1.
17. Abman SH. Pulmonary hypertension: the hidden danger for newborns. Neonatology 2021;118:211-7.
18. Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. Am J Respir Crit Care Med 2004;170:1006-13.
19. Rosenzweig EB, Bates A, Mullen MP, Abman SH, Austin ED, Everett A, et al. Cardiac catheterization and hemodynamics in a multicenter cohort of children with pulmonary hypertension. Ann Am Thorac Soc 2022;19:1000-12.
20. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric Pulmonary Hypertension: guidelines from the American heart Association and American thoracic Society. Circulation 2015;132:2037-99.
21. Ivy D, Rosenzweig EB, Abman SH, Beghetti M, Bonnet D, Douwes JM, et al. Embracing the challenges of neonatal and paediatric pulmonary hypertension. Eur Respir J 2024;64:2401345.
22. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach. Am J Resp Crit Care 2019;200:751-9.
23. Jensen EA, Edwards EM, Greenberg LT, Soll RF, Ehret DEY, Horbar JD. Severity of bronchopulmonary dysplasia among very preterm infants in the United States. Pediatrics 2021;148:e2020030007.
24. Vyas-Read S, Logan JW, Cuna AC, Machry J, Leeman KT, Rose RS, et al. A comparison of newer classifications of bronchopulmonary dysplasia: findings from the Children's Hospitals Neonatal Consortium Severe BPD Group. J Perinatol 2022;42:58-64.
25. Abman SH, Mullen MP, Sleeper LA, Austin ED, Rosenzweig EB, Kinsella JP, et al. Characterisation of paediatric pulmonary hypertensive vascular disease from the PPHNet Registry. Eur Respir J 2022;59:2003337.
26. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34-41.
27. Barst RJ. Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. Chest 1986;89:497-503.
28. Apitz C, Hansmann G, Schranz D. Hemodynamic assessment and acute pulmonary vasoreactivity testing in the evaluation of children with pulmonary vascular disease. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016;102:ii23-9.
29. Sitbon O, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 2005;111:3105-11.

30. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.
31. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019;53:1801913.
32. Hansmann G, Koestenberger M, Alastalo TP, Apitz C, Austin ED, Bonnet D, et al. 2019 Updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: the European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. J Heart Lung Transpl 2019;38:879-901.
33. Frank BS, Schäfer M, Grenolds A, Ivy DD, Abman SH, Darst JR. Acute vasoreactivity testing during cardiac catheterization of neonates with bronchopulmonary Dysplasia-Associated pulmonary hypertension. J Pediatr 2019;208:127-33.
34. Torok RD, Gardner RA, Barker PCA, McCrary AW, Li JS, Hornik CP, et al. Correlating severity of pulmonary hypertension by echocardiogram with mortality in premature infants with bronchopulmonary dysplasia. Am J Perinatol 2024;41:2206-13.
35. Naumburg E, Soderstrom L. Increased risk of pulmonary hypertension following premature birth. BMC Pediatr 2019;19:288.
36. Mohlkert LA, Hallberg J, Broberg O, Sjöberg G, Rydberg A, Liuba P, et al. Right heart structure, geometry and function assessed by echocardiography in 6-Year-Old children born extremely Preterm-A population-based cohort Study. J Clin Med 2020;10:122.
37. Shennan AT, Dunn MS, Ohlsson A, Lennox K, Hoskins EM. Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics 1988;82:527-32.
38. Arjaans S, Haarman MG, Roofthooft MTR, Fries MWF, Kooi EMW, Bos AF, et al. Fate of pulmonary hypertension associated with bronchopulmonary dysplasia beyond 36 weeks postmenstrual age. Arch Dis Child Fetal Neonatal Ed 2021;106:45-50.
39. Akangire GG, Manimtim W, Agarwal A, Alexiou S, Aoyama BC, Austin ED, et al. Outcomes of infants and children with bronchopulmonary dysplasia-associated pulmonary hypertension who required home ventilation. Pediatr Res 2025;97:387-94.
40. Hansmann G, Sallmon H, Roehr CC, Kourembanas S, Austin ED, Koestenberger M, European Pediatric Pulmonary Vascular Disease Network EPPVDN. Pulmonary hypertension in bronchopulmonary dysplasia. Pediatr Res 2021;89:446-55.
41. Mourani PM, Sontag MK, Ivy DD, Abman SH. Effects of long-term Sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr 2008;154:379.
42. Mourani PM, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. Pediatrics 2008;121:317.
43. Steurer MA, Nawaytou H, Guslits E, Colglazier E, Teitel D, Fineman JR, et al. Mortality in infants with bronchopulmonary dysplasia: data from cardiac catheterization. Pediatr Pulmonol 2019;54:804-13. https://doi.org/10.1002/ppul.24297
44. Mahgoub L, Kaddoura T, Kameny AR, Lopez Ortego P, Vanderlaan RD, Kakadekar A, et al. Pulmonary vein stenosis of ex-premature infants with pulmonary hypertension and bronchopulmonary dysplasia, epidemiology, and survival from a multicenter cohort. Pediatr Pulmonol 2017;52:1063-70.
45. del Cerro MJ, Sabaté Rotés A, Cartón A, Deiros L, Bret M, Cordeiro M, et al. Pulmonary hypertension in bronchopulmonary dysplasia: clinical findings, cardiovascular anomalies and outcomes. Pediatr Pulmonol 2014;49:49-59.
46. Lagatta JM, Hysinger EB, Zaniletti I, Wymore EM, Vyas-Read S, Yallapragada S, et al. The impact of pulmonary hypertension in preterm infants with severe bronchopulmonary dysplasia through 1 year. J Pediatr 2018;203:218-24.e3.
47. Varghese NP, Austin ED, Galambos C, Mullen MP, Yung D, Guillerman RP, et al. An interdisciplinary consensus approach to pulmonary hypertension in developmental lung disease. Eur Respir J 2024;64:2400639.
48. Seth SA, Soraisham AS, Harabor A. Risk factors and outcomes of early pulmonary hypertension in preterm infants. J Matern Fetal Neonatal Med 2018;31:3147-52.
49. Kaluarachchi DC, Woo KM, Colaizy TT. Role of early pulmonary hypertension as a risk factor for late pulmonary hypertension in extremely preterm infants. Am J Perinatol 2018;35:120-6.
50. Mirza H, Garcia JA, Crawford E, Pepe J, Zussman M, Wadhawan R, et al. Natural history of postnatal cardiopulmonary adaptation in infants born extremely preterm and risk for death or bronchopulmonary dysplasia. J Pediatr 2018;198:187-93.e1.
51. Kwon HW, Kim HS, An HS, Kwon BS, Kim GB, Shin SH, et al. Long-Term outcomes of pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Neonatology 2016;110:181-9.
52. Yallapragada SG, Savani RC, Goss KN. Cardiovascular impact and sequelae of bronchopulmonary dysplasia. Pediatr Pulmonol 2021;56:3453-63. https://doi.org/10.1002/ppul.25370
53. Altit G, Bhombal S, Hopper RK, Tacy TA, Feinstein J. Death or resolution: the 'natural history' of pulmonary hypertension in bronchopulmonary dysplasia. J Perinatol 2019;39:415-25.
54. Ong MS, Abman S, Austin ED, Feinstein JA, Hopper RK, Krishnan US, et al. Racial and ethnic differences in pediatric pulmonary hypertension: an analysis of the pediatric pulmonary hypertension network registry. J Pediatr 2019;211:63-71.e6.
55. Bates ML, Levy PT, Nuyt AM, Goss KN, Lewandowski AJ, McNamara PJ. Adult cardiovascular health risk and cardiovascular phenotypes of prematurity. J Pediatr 2020;227:17-30.