ORIGINAL ARTICLE

# Patent Ductus Arteriosus and Development of Bronchopulmonary Dysplasia–associated Pulmonary Hypertension

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## Abstract

**Rationale:** Extremely preterm infants with evolving bronchopulmonary dysplasia (BPD) are at risk for development of BPD-associated pulmonary hypertension (BPD-PH). A patent ductus arteriosus (PDA) shunt may be a modifiable risk factor for BPD-PH development.

**Objective:** To determine whether the presence and duration of ductus arteriosus patency differs between extremely preterm infants with and without BPD-PH.

**Methods:** We conducted a retrospective case-control study among preterm infants of gestational age 22 weeks, 0 days, to 28 weeks, 6 days, who remained on respiratory support on postnatal day 28 at the University of Alabama at Birmingham from 2017 to 2020. Infants who were diagnosed with PH (cases) by echocardiography were compared with infants without PH (control subjects). Data from echocardiograms performed during the hospitalization after postnatal day 28 were included. Logistic regression adjusted for covariates that differed significantly between groups. A probit analysis related the duration of ductal patency to the development of BPD-PH.

**Measurements and Main Results:** A total of 138 infants developed BPD alone, and 82 infants developed BPD-PH. After adjustment for differing covariates between groups, both PDA (adjusted odds ratio, 4.29; 95% confidence interval, 1.89–9.77) and moderate to large PDA (adjusted odds ratio, 4.15; 95% confidence interval, 1.78–9.64) remained significantly related to BPD-PH at discharge. By probit analysis, each additional month of PDA and hemodynamically significant PDA exposure was associated with an increased probability for the composite outcome of BPD-PH at discharge or death with coefficients of 0.40 ($P < 0.001$) and 0.45 ($P < 0.001$), respectively.

**Conclusions:** In extremely preterm infants on respiratory support on postnatal day 28, both the presence of and a longer duration of ductus arteriosus patency were associated with the development of BPD-PH.

**Keywords:** bronchopulmonary dysplasia; prematurity; patent ductus arteriosus; pulmonary hypertension

Bronchopulmonary dysplasia (BPD) is one of the most common morbidities of prematurity, occurring in ∼40% of infants born at less than 28 weeks' gestation (1). Rather than a monomorphic disease, multiple endotypes have been described (2), including BPD associated with pulmonary hypertension (BPD-PH), which occurs in ∼17% of infants with BPD (3). Infants who develop BPD-PH are at higher risk for long-term neurodevelopmental impairment (4) and mortality (3). Given the severity of adverse outcomes associated with BPD-PH, identification of specific risk factors for BPD-PH development is needed.

Demographic characteristics reported to be associated with the development of BPD-PH include lower gestational age and lower birth weight (3). Although the presence (5) and hemodynamic significance (6) of a

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## At a Glance Commentary

**Scientific Knowledge on the Subject:** Few studies have systematically detailed the association between the presence and duration of ductus arteriosus patency and the development of pulmonary hypertension in preterm infants.

**What This Study Adds to the Field:** In this case-control study, we report that the presence of a patent ductus arteriosus may be one of the strongest risk factors for pulmonary hypertension development.

patent ductus arteriosus (PDA) have been associated with the development of BPD, there is limited evidence for whether the presence and persistence of a PDA may be uniquely associated with the BPD-PH phenotype (4, 7). Moreover, few of these studies analyzed the duration of ductal patency and risk for BPD-PH (8). Because ductal patency varies over time, with up to 85% of PDAs closing by hospital discharge in very low birth weight infants (9), characterization of the duration of ductal patency may further define the potential association between a PDA and BPD-PH.

We conducted a retrospective, case-control study in infants with (cases) and without (control subjects) BPD-PH born between 22 0/7 weeks' and 28 6/7 weeks' gestation on respiratory support on postnatal day 28. We hypothesized that among infants with evolving BPD, the presence and duration of ductus arteriosus patency would be associated with the development of BPD-PH after adjusting for differences in baseline characteristics.

## Methods

### Study Design

This was a retrospective case-control study of prospectively collected data in preterm infants born at the University of Alabama at Birmingham between 2017 and 2020. Institutional review board approval was obtained before the investigation. Infants were included if born between 22 0/7 and 28 6/7 weeks' gestation, if they were receiving respiratory support on postnatal day 28, if they had at least one echocardiogram performed after postnatal day 28, and if they remained on respiratory support at 36 weeks' postmenstrual age (PMA). Infants who died before postnatal day 28, did not have an echocardiogram performed, or had major congenital anomalies (including hemodynamically significant cardiac lesions) were excluded. Cases were defined as infants with evidence of PH diagnosed by cardiology-reviewed echocardiograms at any time during hospitalization after postnatal day 28, whereas infants with echocardiograms but without evidence of PH were defined as control subjects.

At the University of Alabama at Birmingham, all preterm infants receiving respiratory support on postnatal day 28 are assessed for PH by echocardiogram, after which monthly echocardiographic assessment is performed until discharge. Infants are not systematically screened for a PDA before this postnatal time point, with ~35% of infants being pharmacologically treated upon PDA diagnosis during the study period. Infants both with and without BPD-PH may receive a trial of inhaled nitric oxide if they develop refractory hypoxemia while receiving 100% $FI_{O_2}$ through invasive ventilation.

### Covariate Definitions

Demographic and birth characteristics compared between cases and control subjects included gestational age, birth weight, small for gestational age, race, sex, preterm premature rupture of membranes (>24 h before delivery), and histologic chorioamnionitis by placental pathology. Small for gestational age was defined as birth weight below the 10th percentile for gestational age (10). Clinical exposures compared between cases and control subjects included respiratory support (at postnatal day 28 and 36 weeks' PMA) and pharmacologic exposures (corticosteroids for BPD and inhaled nitric oxide). Morbidities of comparison included BPD at 36 weeks' PMA using Jensen criteria (11), grades 3 to 4 intracranial hemorrhage (12), and necrotizing enterocolitis stage ⩾2 using modified Bell's criteria (13, 14).

For characterization of PDAs that persisted beyond 28 days, all echocardiograms performed on or after postnatal day 28 were included for the analysis. Echocardiographic diagnoses (e.g., PDA) derived from echocardiograms performed before postnatal day 28 were not included. A PDA was further characterized as moderate to large if the ductal diameter was ⩾1.5 mm with any of the following:

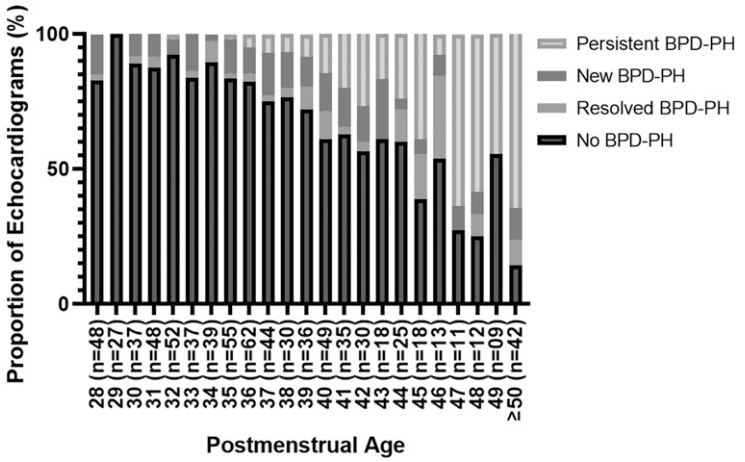


**Figure 1.** Timing of echocardiographic bronchopulmonary dysplasia–associated pulmonary hypertension (BPD-PH) diagnosis and subsequent disease trajectory for included patients. Infants were stratified into the following dynamic groups: *1*) new diagnosis of BPD-PH (postmenstrual age [PMA] at which BPD-PH was first diagnosed), *2*) resolved BPD-PH (previously present on prior echocardiogram without evidence at indicated PMA), *3*) persistent BPD-PH (noted on a previous and indicated PMA echocardiogram), and *4*) no BPD-PH (with no evidence at indicated PMA echocardiogram and either any prior echocardiogram or, in infants with previous evidence of BPD-PH, the echocardiogram is subsequent to a prior study indicating BPD-PH resolution). The median postnatal age at BPD-PH diagnosis in cases was 38 weeks' PMA (interquartile range, 33–41). Infants with BPD with and without PH had a similar number of echocardiograms performed between PMAs of 28 and 40 weeks.

**Table 1.** Demographic and Clinical Characteristics of Included Patients

| | BPD with No PH (*n* = 138) | BPD-PH (*n* = 82) | *P* Value |
|---|---|---|---|
| Demographic characteristics, *n* (%) | | | |
| Gestational age, wk* | 26 ± 2 | 25 ± 2 | <0.001 |
| Birth weight, g* | 806 ± 209 | 655 ± 169 | <0.001 |
| Multiple gestation | 30 (22) | 15 (18) | 0.54 |
| Male sex | 80 (58) | 38 (46) | 0.09 |
| White race | 60 (44) | 25 (31) | 0.06 |
| Antenatal corticosteroids | 127 (92) | 75 (92) | 0.88 |
| Cesarean section | 97 (70) | 50 (61) | 0.16 |
| Histologic chorioamnionitis | 64 (46) | 42 (51) | 0.49 |
| Small for gestational age | 18 (13) | 17 (21) | 0.13 |
| Prolonged rupture of membranes | 36 (27) | 16 (20) | 0.23 |
| Clinical exposures, *n* (%) | | | |
| Inhaled nitric oxide | 18 (13) | 34 (42) | <0.001 |
| Corticosteroids for BPD | 44 (32) | 62 (76) | <0.001 |
| Pharmacologic treatment of PDA | 19 (14) | 20 (24) | 0.05 |
| Respiratory support at Day 28 | | | |
| Nasal cannula | 28 (20) | 8 (10) | 0.04 |
| CPAP or NIPPV | 69 (50) | 26 (32) | 0.008 |
| Invasive support | 41 (30) | 48 (59) | <0.001 |
| $F_{IO_2}$ at postnatal day 28* | 0.44 ± 0.23 | 0.59 ± 0.27 | <0.001 |
| BPD severity at 36 wk PMA | | | |
| Grade I | 90 (65) | 38 (46) | 0.006 |
| Grade II | 34 (25) | 28 (34) | 0.13 |
| Grade III | 14 (10) | 16 (20) | 0.05 |
| Other outcomes, *n* (%) | | | |
| Patent ductus arteriosus | 29 (21) | 36 (44) | <0.001 |
| Moderate to large PDA | 19 (14) | 32 (39) | <0.001 |
| Weeks of PDA exposure† | 6 (5–9) | 12 (7–23) | <0.001 |
| Grades 3–4 intracranial hemorrhage | 13 (9) | 11 (13) | 0.36 |
| Early-onset sepsis | 3 (2) | 2 (2) | 0.90 |
| Late-onset sepsis | 18 (13) | 21 (26) | 0.02 |
| Severe retinopathy of prematurity | 22 (16) | 21 (26) | 0.08 |
| Necrotizing enterocolitis stage ⩾2 | 11 (8) | 14 (17) | 0.04 |
| Death | 6 (4) | 19 (23) | <0.001 |

*Definition of abbreviations*: BPD = bronchopulmonary dysplasia; CPAP = continuous positive airway pressure; NIPPV = noninvasive positive pressure ventilation; PDA = patent ductus arteriosus; PMA = postmenstrual age.
*Average (SD).
†Median (interquartile range) in infants with echocardiographic PDA that persisted beyond 28 days.

*1*) ductal systolic flow velocity ⩽2.8 m/s, *2*) reverse diastolic flow in the descending aorta, or *3*) ratio of left atrium to aortic root ⩾1.6. The time of ductal closure was defined as the postnatal age at which ductal patency was last identified by echocardiogram.

### Outcome Definitions

Infants were diagnosed with BPD-PH if any of the following echocardiographic findings (15) were present: *1*) elevated right ventricular pressures as estimated by tricuspid jet velocity measurement (with right ventricular systolic pressure estimate of ⩾35 mm Hg), *2*) bidirectional flow through the patent foramen ovale or PDA, or *3*) interventricular septum flattening based on end-systolic eccentricity index >1.0.

An additional exploratory analysis was performed in infants with BPD-PH to further define the longitudinal relationship between a PDA and BPD-PH persistence and resolution. Infants with BPD-PH were stratified into infants with resolution of BPD-PH, infants with persistence of BPD-PH, and infants who died. Infants were characterized as having resolved or persistent BPD-PH based on the presence or absence of PH on the last echocardiogram performed during the hospitalization.

### Statistical Analysis

To determine an adequate sample size, we used a two-sided confidence interval (CI) of 95%, 80% power, an expected ratio of control subjects to cases of 2:1, and preliminary estimates for the rates of PDA within control subjects (20%) and cases (40%). Using these calculations, we estimated that 58 infants with BPD-PH and 115 infants with BPD would be needed for this analysis.

For comparisons of PDAs that persisted beyond 28 days between cases and control subjects, the following three classifications were used: *1*) PDA as a binary outcome, *2*) moderate or large PDA as a binary outcome, and *3*) the PMA in weeks at which a PDA was last identified. To further examine the relationship between the duration of PDA exposure and BPD-PH development, parallel analyses were performed by PDA status, PDA hemodynamic significance, and strata of PDA exposure days for the outcomes of BPD-PH at 28 postnatal days, subsequent BPD-PH development, persistent BPD-PH at discharge, and death.

A probit regression was conducted to calculate the probability for persistent BPD-PH or death using months of *1*) any or *2*) hemodynamically significant ductus arteriosus patency exposure as the dose variable. This regression was performed to identify whether an increase in the number of months of PDA exposure (the predictor variable) was associated with a higher probability of BPD-PH development or death. However, to assess for nonlinear associations between categorical ranges of PDA exposure and BPD-PH–related outcomes, additional analyses by logistic regression were employed as next described.

Additional bivariate analyses were conducted comparing baseline demographic and clinical characteristics between cases and control subjects. After tests of normality, continuous data were analyzed using a *t* test or Mann-Whitney test. A chi-square test was used for categorical variables. The Box-Tidwell procedure was used to determine the linearity of continuous covariates from which the appropriate regression model was selected. In considering the most appropriate regression model, separate logistic regression models were employed for the outcomes of *1*) BPD-PH at discharge, *2*) BPD-PH at discharge or death, and *3*) prespecified strata of PDA exposure duration (<4 wk, 4–7 wk, 8–11 wk, and ⩾12 wk). Models incorporated both categorical and continuous demographic characteristics that differed between cases and control subjects ($P < 0.10$) after calculation of bivariate correlation and variance inflation factor testing for multicollinearity.

**Table 2.** Bronchopulmonary Dysplasia Association with Pulmonary Hypertension Outcomes, by Patent Ductus Arteriosus Status

| | | | | | | Duration of PDA* Exposure | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *P* Value | | 4–7 wk | | 8–11 wk | | ≥12 wk | | *P* Value | | | |
| | No PDA* (*n* = 155) | PDA* (*n* = 65) | HPDA* (*n* = 51) | PDA† | HPDA‡ | PDA (*n* = 28) | HPDA (*n* = 27) | PDA (*n* = 15) | HPDA (*n* = 8) | PDA (*n* = 22) | HPDA (*n* = 16) | PDA§ | HPDA‖ | | |
| BPD-PH persistence at discharge or death | 26 (17) | 24 (37) | 21 (41) | 0.001 | <0.001 | 5 (18) | 7 (26) | 4 (27) | 1 (13) | 15 (68) | 13 (81) | <0.001 | <0.001 | | |
| BPD-PH persistence at discharge | 21 (14) | 21 (32) | 19 (37) | 0.001 | <0.001 | 4 (14) | 7 (26) | 4 (14) | 1 (13) | 13 (59) | 11 (69) | <0.001 | <0.001 | | |
| Death | 11 (7) | 14 (22) | 13 (26) | 0.002 | <0.001 | 3 (11) | 3 (11) | 1 (7) | 0 (0) | 10 (46) | 10 (63) | <0.001 | <0.001 | | |
| BPD-PH persistence at discharge | 6 (4) | 11 (17) | 11 (22) | 0.001 | <0.001 | 2 (7) | 3 (11) | 1 (7) | 0 (0) | 8 (36) | 8 (50) | <0.001 | <0.001 | | |
| BPD-PH resolution at discharge | 1 (1) | 1 (2) | 1 (2) | 0.12 | 0.07 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (5) | 1 (6) | 0.01 | 0.003 | | |
| No BPD-PH during hospitalization | 4 (3) | 2 (3) | 1 (2) | 0.84 | 0.70 | 1 (4) | 0 (0) | 0 (0) | 0 (0) | 1 (5) | 1 (6) | 0.80 | 0.84 | | |
| BPD-PH during hospitalization | 46 (30) | 36 (55) | 32 (63) | <0.001 | <0.001 | 10 (36) | 13 (48) | 8 (53) | 4 (50) | 18 (82) | 15 (94) | <0.001 | <0.001 | | |
| Diagnosed at 28 d | 2 (1) | 4 (6) | 4 (8) | 0.04 | 0.01 | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 4 (18) | 4 (18) | <0.001 | <0.001 | | |
| Diagnosed after 28 d | 44 (28) | 32 (49) | 28 (55) | 0.003 | <0.001 | 10 (36) | 13 (48) | 8 (53) | 4 (50) | 14 (64) | 11 (69) | <0.001 | <0.001 | | |

*Definition of abbreviations*: BPD-PH = bronchopulmonary dysplasia–associated hypertension; HPDA = moderate to large patent ductus arteriosus; PDA = patent ductus arteriosus.
*PDA status based on echocardiogram performed at ⩾28 postnatal days.
†By chi-square comparison between infants with and without PDA.
‡By chi-square comparison between infants with and without moderate to large PDA.
§By chi-square linear-by-linear test for trend comparison by duration of PDA exposure.
‖By chi-square linear-by-linear test for trend comparison by duration of hemodynamically significant PDA exposure.

Results were summarized using odds ratios, 95% CIs, and *P* values defining significance as $<0.05$. Analyses were conducted using IBM SPSS Statistics 26 for Windows, GraphPad Prism, and MedCalc.

Given the collinearity between demographic characteristics and both spontaneous ductal closure and PH, a mediation analysis was performed between a PDA and BPD-PH using birth weight as the mediator variable. This assessed whether the association between PDA persistence beyond 28 days and BPD-PH resulted from indirect effects between a PDA and birth weight or birth weight and BPD-PH.

## Results

Of the 398 infants born during the inclusion period, 82 infants met case criteria for BPD-PH, 138 infants met control criteria for BPD alone, and 178 infants did not develop BPD. A total of 463 echocardiograms from cases were reviewed (median of 5 echocardiograms per patient) and 461 echocardiograms from control subjects were reviewed (median of 3 echocardiograms per patient). The median postnatal age at BPD-PH diagnosis in cases was 38 weeks' PMA (interquartile range, 33–41), with the distribution of postnatal age at BPD-PH diagnosis, resolution, and persistence further depicted in Figure 1. The median intervals between patients' echocardiograms in infants with BPD and BPD-PH were 30 and 29 days, respectively.

The mean gestational age differed between cases ($25 \pm 2$) and control subjects ($26 \pm 2$; $P < 0.001$), and cases were born at a lower birth weight ($655 \pm 169$ g vs. $806 \pm 209$ g; $P < 0.001$) (Table 1). Regarding clinical exposures, cases were more frequently exposed to invasive ventilation (59% vs. 30%) and had a higher $F_{IO_2}$ (0.59 vs. 0.44) on postnatal day 28. More cases had a PDA (44% vs. 21%) and a moderate to large PDA (39% vs. 14%). The PDA was more frequently treated with pharmacotherapy in cases than in control subjects (24% vs. 14%) (Table 1).

For analyses by PDA status, the presence of a PDA persistent beyond 28 postnatal days was associated with a higher frequency of subsequent BPD-PH development (49% vs. 28%; $P = 0.003$), persistence of BPD-PH at discharge (34% vs. 14%; $P < 0.001$), and death or BPD-PH at discharge (39% vs. 17%; $P < 0.001$) compared with infants without a PDA.

**Table 3.** Odds Ratios of Bronchopulmonary Dysplasia–associated Hypertension–related Outcomes, by Clinical Covariates

| | BPD-PH at Discharge | | | | BPD-PH at Discharge or Death | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95% CI | | | | 95% CI | | |
| Variable | Adjusted OR* | Lower | Upper | *P* Value | Adjusted OR* | Lower | Upper | *P* Value |
| Birth weight† | 0.75 | 0.59 | 0.95 | 0.02 | 0.77 | 0.61 | 0.97 | 0.03 |
| Gestational age‡ | 1.23 | 0.94 | 1.62 | 0.13 | 1.12 | 0.86 | 1.45 | 0.40 |
| Male sex | 1.13 | 0.53 | 2.42 | 0.75 | 1.79 | 0.86 | 3.71 | 0.12 |
| White race | 0.76 | 0.33 | 1.75 | 0.52 | 0.65 | 0.30 | 1.43 | 0.28 |
| $F_{IO_2}$ at postnatal day 28§ | 1.29 | 1.07 | 1.55 | 0.007 | 1.18 | 1.00 | 1.40 | 0.05 |
| Invasive ventilation day 28 | 1.16 | 0.45 | 3.01 | 0.76 | 1.71 | 0.71 | 4.11 | 0.23 |
| PDA | 4.29 | 1.89 | 9.77 | <0.001 | 3.50 | 1.64 | 7.49 | 0.001 |
| Moderate to large PDA‖ | 4.15 | 1.78 | 9.64 | <0.001 | 3.02 | 1.38 | 6.59 | 0.005 |
| PDA exposure duration¶ | | | | | | | | |
| 4–7 wk | | | | | | | | |
| PDA | 1.50 | 0.16 | 14.04 | 0.72 | 1.81 | 0.31 | 10.58 | 0.51 |
| HPDA | 6.12 | 1.28 | 29.27 | 0.02 | 3.88 | 0.79 | 19.03 | 0.10 |
| 8–11 wk | | | | | | | | |
| PDA | 3.15 | 1.09 | 9.11 | 0.03 | 2.30 | 0.82 | 6.39 | 0.11 |
| HPDA | NS | NS | NS | NS | NS | NS | NS | NS |
| ⩾12 wk | | | | | | | | |
| PDA | 6.95 | 2.48 | 19.47 | <0.001 | 6.22 | 2.31 | 16.76 | <0.001 |
| HPDA | 3.78 | 1.28 | 11.14 | 0.02 | 3.21 | 1.12 | 9.21 | 0.03 |

*Definition of abbreviations*: BPD-PH = bronchopulmonary dysplasia–associated hypertension; CI = confidence interval; HPDA = moderate to large patent ductus arteriosus; NS = not significant; OR = odds ratio; PDA = patent ductus arteriosus.

*Analysis by logistic regression adjusting for birth weight, gestational age, White race, male sex, invasive respiratory support at postnatal day 28, $F_{IO_2}$ at postnatal day 28, and PDA.

†For every 100-g change in birth weight.

‡For every week of gestation.

§For every 10% change in $F_{IO_2}$.

‖Adjusted OR for moderate or large PDA by logistic regression adjusting for birth weight, gestational age, White race, male sex, invasive respiratory support at postnatal day 28, and $F_{IO_2}$ at postnatal day 28. Coefficients for covariates are available in Table E1.

¶Logistic regression for duration of PDA and HPDA exposure using a four-level categorical variable: <4 wk, 4–7 wk, 8–11 wk, and ⩾12 wk adjusting for birth weight, gestational age, White race, male sex, invasive respiratory support at postnatal day 28, and $F_{IO_2}$ at postnatal day 28. Coefficients for covariates are available in Tables E2 and E3.

Similarly, a hemodynamically significant PDA was associated with persistence of BPD-PH at discharge (37% vs. 14%; $P < 0.001$) and death or BPD-PH at discharge (41% vs. 18%; $P < 0.001$) compared with infants without a hemodynamically significant PDA. There was an associated increase in BPD-PH at discharge and death in infants with BPD-PH with longer durations of PDA or hemodynamically significant PDA exposures (Table 2).

Tests for multicollinearity in covariates differing between cases and control subjects were nonsignificant, for which all variates were retained. Logistic regression models adjusted for birth weight, gestational age, White race, male sex, $F_{IO_2}$, and invasive ventilation on postnatal day 28 between cases and control subjects (Table 3). Invasive ventilation and $F_{IO_2}$ exposure on postnatal day 28 were included to discriminate whether the presence of a persistent PDA reflected pulmonary disease independent of PH status. The following covariates remained significantly associated with the BPD-PH at discharge: PDA (adjusted odds ratio [aOR], 4.29; 95% CI, 1.89–9.77), a moderate to large PDA (aOR, 4.15; 95% CI, 1.78–9.64), birth weight (aOR, 0.75; 95% CI, 0.59–0.95), and $F_{IO_2}$ at postnatal day 28 (aOR, 1.29; 95% CI, 1.07–1.55). The same covariates were significant for the outcome of BPD-PH at discharge or death. Regression analyses by PDA exposure duration were most significant for exposure ⩾12 weeks for both PDA and moderate to large PDA duration (Table 3). Covariate coefficients for regression models for moderate to large PDA and strata of PDA exposure duration can be found in Tables E1–E3 in the online supplement.

By probit analysis, the duration of PDA and hemodynamically significant PDA exposure increased the probability of BPD-PH at discharge or death with coefficients of 0.40 ($P < 0.001$) and 0.45 ($P < 0.001$), respectively (Figure 2). As coefficients were positive, this translates to each additional month of PDA exposure increases the probability of BPD-PH at discharge or death; however, this does not provide a magnitude of effect, given the nonlinearity of probit analysis (e.g., the change in predicted probability of BPD-PH at discharge or death is not constant between months of PDA exposure).

In characterizing the trajectory of BPD-PH in cases, BPD-PH resolved in 39 infants (48%) and persisted in 43 infants (52%), of whom 19 (23%) infants died. Among infants with BPD-PH, those with a moderate to large PDA that persisted beyond 28 days were more likely to die (12 of 32; 38%) than those without a moderate to large PDA (7 of 46; 15%; $P = 0.01$) (Table 2).

For the mediation analysis, indirect effects were assessed between a PDA and birth weight and between birth weight and

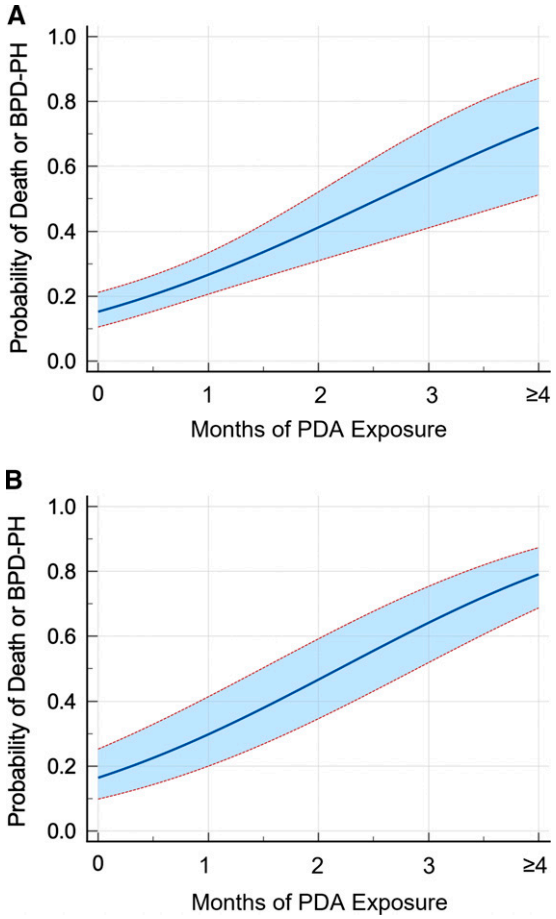


**Figure 2.** Probit analysis of bronchopulmonary dysplasia–associated pulmonary hypertension (BPD-PH) probability by duration of patent ductus arteriosus (PDA) exposure (*A*) and moderate to large PDA (HPDA) exposure (*B*). Longer durations of PDA and HPDA exposure were associated with a higher probability of BPD-PH. The probability and 95% confidence interval are indicated at each corresponding duration of PDA exposure.

BPD-PH with correlation coefficients of −32 and −0.004, respectively, which were not significant (β, 0.14; 95% CI, −0.12 to 0.44), because the CI was inclusive of zero. This indicates that the association between a PDA and BPD-PH is not, in part, the result of the mediating variable of birth weight. Conversely, the direct effect of PDA exposure on BPD-PH, excluding the mediator variable of birth weight, was significant (β, 1.11; 95% CI, 0.47–1.76).

## Discussion

In this case-control study of infants born between 22 0/7 and 28 6/7 weeks' gestation with an echocardiogram performed after postnatal day 28, infants with BPD-PH (cases) more frequently had a PDA that persisted beyond 28 days than did infants with BPD alone (control subjects). The association between both a persistent PDA and a persistent moderate to large PDA and BPD-PH remained significant after adjustment for baseline characteristics by logistic regression. We also determined that the duration of PDA persistence was associated with BPD-PH. In further analyses stratifying cases to infants with resolution, persistence, or death associated with BPD-PH, a PDA was associated with both persistence of BPD-PH and death.

Several identified baseline characteristics that differed between cases and control subjects in the present study have been reported previously. Compared with control subjects, cases were more likely to be born at a lower birth weight and gestational age. In our previous cohort study of extremely low birth weight infants in which an echocardiogram was performed to screen for BPD-PH, infants with BPD-PH were born at a lower birth weight ($P < 0.001$) and small for gestational age ($P < 0.01$) compared with infants without BPD-PH (16). Other cohort studies have reported that infants with BPD-PH are more frequently born small for gestational age (15) and/or are born at a lower birth weight (8, 17, 18). In contrast, few studies (19) have reported female sex more commonly in infants with BPD-PH; most cohort studies have reported similar rates of BPD-PH by sex (8, 16, 17).

Previous investigators have reported an association between a PDA and BPD-PH. A systematic review and meta-analysis identified PDA as a characteristic associated with an increased risk ratio of BPD-PH of 1.2 (95% CI, 1.0–1.5) in infants with BPD (3). However, there was significant variation regarding the association between a PDA and BPD-PH in those studies that were included. Mourani and colleagues (8) prospectively screened preterm infants ($n = 277$) born between 500 and 1,250 g for the presence of PH, of whom 39 infants (14%) had BPD-PH at 36 weeks' PMA. Comparing infants with and without BPD-PH, a PDA was identified on postnatal day 7 in 47% of infants who developed BPD-PH and in 40% of infants who did not develop BPD-PH ($P = 0.41$). A PDA at this postnatal time point was not associated with BPD-PH at 36 weeks' PMA. A single-center study of 116 preterm infants with BPD reported a higher prevalence of surgical PDA closure in infants with BPD-PH (48% vs. 27%; $P = 0.025$) (20). In the present study, compared with infants with BPD alone, preterm infants who developed BPD-PH had a higher rate of a PDA that persisted beyond 28 days (43% vs. 22%) and a higher rate of a persistent moderate to large PDA (29% vs. 11%). Moreover, infants with longer durations of ductus arteriosus patency were more likely to have a persistent BPD-PH and BPD-PH–associated mortality.

The duration of ductus arteriosus patency and risk for BPD alone has also been reported in preterm infants, which remains relevant to the present analysis because BPD-PH is a common endotype in infants with moderate to severe BPD (3). In a study of infants born at <28 weeks' gestation that stratified PDA exposure to <7 days, 7 to 13 days, and ⩾14 days, infants with a moderate to large PDA for 7 to 13 days had an increased odds ratio for BPD or death compared with infants with a PDA for <7 days; however, exposure for ⩾14 days

was not associated with worse outcomes (21). Another study of preterm infants born at <29 weeks' gestation stratified infants' exposure by <1 week, 1–2 weeks, and >2 weeks and by logistic regression reported an association between a PDA duration and death or BPD (aOR, 1.37; 95% CI, 1.03–1.82) (22). Because other postnatal exposures may further compound infants' BPD risk, additional data from this investigatory group have identified prolonged invasive ventilation >10 days as a critical coexposure to prolonged PDA exposure that may mediate infants' risk for BPD (23, 24). In the present study, the duration of PDA exposure was associated with BPD-PH after adjustment for baseline characteristics, suggesting that prolonged PDA exposure may be specifically associated with the BPD-PH phenotype.

In a recent investigation of 28 infants with BPD-PH characterizing survival and resolution, Arjaans and colleagues reported that suprasystemic pulmonary artery pressures were associated with death. The proportion of infants with a PDA did not differ between infants who died (10 of 11; 91%) and survived 11 of 17 (73%; $P = 0.36$) (25); however, the postnatal age at diagnosis was not reported. In an observational investigation of the clinical impact between early and late PDA closure, infants with late closure were more likely to develop BPD-PH (52% vs. 0%) with a later median procedural age at closure (84 vs. 32 d; $P < 0.001$) (26). In the present study, infants with BPD-PH at discharge or death more frequently had a PDA that persisted beyond 28 days after adjusting for baseline differences. Moreover, the risk of BPD-PH at discharge or death was higher among infants exposed to a PDA for ≥12 weeks, but not among those with shorter durations of exposure. Probit regression modeling further substantiated the association between longer durations of PDA exposure and risk for BPD-PH. Therefore, longitudinal monitoring of ductal patency may provide an additional and potentially earlier marker for BPD-PH persistence and death.

The primary limitation of this study is that conclusions are limited to associations. It is unknown whether latent patency of a ductus arteriosus in infants with BPD-PH contributes to disease severity whereby ductal ligation would mitigate BPD-PH persistence, severity, or death. The presence and persistence of a PDA may only implicate underlying BPD-PH with ductal patency maintained by elevated right ventricular pressures. The therapeutic utility of early PDA closure has not been shown to reduce BPD after early prophylactic treatment (27) or selective use in infants with a hemodynamically significant PDA (28). However, a conservative approach to a PDA persistent beyond 28 postnatal days may increase risk for the development of BPD-PH based on the present study findings. In addition, the months' duration between echocardiograms limited the precision to which duration of PDA exposure could be associated with BPD-PH development.

In this case-control investigation of extremely preterm infants, the presence of a PDA beyond 28 postnatal days was associated with BPD-PH but also with the persistence of BPD-PH and death in infants with BPD-PH. Longitudinal monitoring of a PDA may provide an additional echocardiographic marker for BPD-PH development. Because these inferences are limited to association, further study of PDA closure in infants at >28 postnatal days' age would be needed to determine whether a reduction in PDA exposure may prevent both BPD-PH and death in infants with established BPD-PH. ■

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