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Original Article

Incidence, risk factors, and outcomes of pulmonary hypertension in preterm infants with bronchopulmonary dysplasia

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Abstract

Objectives: To determine the incidence and risk factors for pulmonary hypertension (PH) in preterm infants with moderate to severe bronchopulmonary dysplasia (BPD) and to compare short-term outcomes.

Methods: Preterm infants <32 weeks gestation born August 2013 through July 2015 with moderate to severe BPD at 36 weeks postmenstrual age were categorized into BPD-PH (exposure) and BPD-noPH (control) groups.

Results: Of 92 infants with BPD, 87 had echocardiographic assessment, of whom 24 (28%) had PH. On multiple logistic regression after adjustment for gestational age and sex, no significant risk factors for PH were identified based on data from this cohort. There were no differences in resource utilization or clinical outcomes including survival to discharge.

Conclusion: Approximately one out of four patients with moderate to severe BPD were identified as having PH. No significant risk factors for PH were identified. No differences in outcomes were identified for those with and without PH.

Keywords: *Chronic lung disease; Echocardiography; Morbidity; Resource utilization; Screening.*

Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity, affecting up to 40% of preterm infants <29 weeks' GA, with more than 10,000 infants diagnosed annually in the USA (1). Despite advances in neonatal care, including the increased use of noninvasive respiratory support, the incidence of BPD has remained relatively stagnant (2). BPD is associated with significant short- and long-term morbidity (3). One of the most concerning short-term complications which is known to occur in up to 28% of patients with moderate to severe BPD is BPD-associated pulmonary hypertension (BPD-PH) (4,5).

Presence of BPD-PH may be associated with increased mortality and possibly increased morbidity, but there are significant limitations in the current literature, as delineated in a recent systematic review and meta-analysis on the topic (5). One of the most important limitations in the literature is the significant variability in the criteria for screening for pulmonary hypertension (PH), which leads to uncertainty around the incidence of the complication (6). Furthermore, there are currently no consensus criteria for diagnosis of BPD-PH based on echocardiogram, despite there being suggested criteria in paediatrics and infants > 3 months' age (7,8), with resultant tremendous

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variability in criteria for neonatal BPD-PH in existing literature (5). Little is known about the natural history of BPD-PH and its lifelong implications for preterm survivors.

Despite the knowledge-gap in our current understanding of BPD-PH, screening for PH among BPD patients is increasingly performed and endorsed by the American Heart Association (8). However, it is unclear whether a targeted approach to screening for BPD-PH based on BPD severity and/or presence of risk factors is more efficient compared to screening all neonates with BPD. At our institution, neonates with moderate to severe BPD are screened for PH by echocardiogram at 36 weeks postmenstrual age during initial neonatal intensive care unit (NICU) hospitalization. The definition of BPD was in accordance with the 2001 NICHD criteria (9); moderate BPD was defined by the need for < 30% supplemental oxygen and severe BPD as the need for ≥ 30% supplemental oxygen and/or positive pressure at 36 weeks postmenstrual age (PMA), which includes high flow nasal cannula. Our study aimed to determine the incidence of BPD-PH in this population and to identify risk factors for BPD-PH and to compare clinical outcomes up to 18 to 22 months corrected gestational age among BPD patients with and without PH.

METHODS

Study design

This was a retrospective cohort study. The study protocol was approved by a research ethics board.

Population

All infants born at gestational age < 32 weeks admitted to McMaster Children's NICU August 2013 through July 2015 with a diagnosis of moderate to severe BPD were included. Patients with major congenital malformations or suspected/confirmed genetic/chromosomal abnormalities were excluded. The initial time point of August 2013 was chosen because this is when all moderate to severe BPD patients—diagnosed as such at 36 weeks PMA—started having routine screening for PH at our institution.

Classification of cohort

The above cohort of infants with BPD was divided into 'exposure' (BPD-PH) and control (BPD-noPH) groups based on results of the BPD screen conducted at 36 weeks PMA. The BPD screen consisted of an electrocardiogram (EKG), a chest radiograph, and an echocardiogram (ECHO). Results of the ECHO were reviewed to designate a classification of definite PH, possible PH, or no PH for each subject with a completed BPD screen at 36 weeks PMA. Definite PH was defined as right ventricular systolic pressure (RVSP) > 40 mmHg (regardless of status of septum) or septum flattening/bowing towards left ventricle in absence of RVSP data. Possible PH was defined as RVSP between 30 and 40 mmHg with normal or unknown septal dynamics, or a RVSP of ≤ 40 mmHg with septal flattening or bowing toward left ventricle. If none of the above findings were present, the infant was classified as not having PH. These definitions were devised in collaboration between physicians in neonatology (A.M.) and cardiology (T.M.). Subjects with both definite and possible PH were designated under the BPD-PH group for the main analysis.

Outcomes

The primary outcome was the incidence of PH in patients with moderate to severe BPD. Secondary outcomes included delineation of respiratory support levels at time of BPD-PH diagnosis, as well as a comparison of short and long-term neonatal outcomes and NICU resource utilization between BPD-PH and BPD-noPH infants for the following: survival to discharge, need for home oxygen at discharge, length of hospital stay in NICU, days on invasive respiratory support, days on any respiratory support, days on supplemental oxygen, growth parameters at discharge and at follow-up visits (3, 6, and 12 months corrected gestational age), and neurodevelopmental outcomes at 18 to 22 months corrected age using Bayley Scales of Infant development III. In addition, follow-up assessments with ECHO including medical management (including pharmacotherapy and/or supplemental oxygen) of BPD-PH patients was sought up to 36 months post-discharge to evaluate impact in early childhood. Finally, we sought to determine predictors for the development of PH among BPD patients from the list of demographic factors collected, which are listed in Table 1.

Data abstraction and analysis

Eligible subjects based on gestational age at birth on admission to McMaster Children Hospital's NICU and without exclusion criteria were identified from the Canadian Neonatal Network's (CNN) local institutional database. All patients on either supplemental oxygen and/or positive pressure were identified. Demographic and outcome data listed above were captured from the local CNN database, electronic/paper chart assessment when needed, and from the local Canadian Neonatal Follow-Up Network (CNFUN) database. Each echocardiogram was reviewed from the electronic patient chart and an assessment of PH classification was made as described earlier by K.M.

A-priori sample size calculation was not performed as a convenience sample is being used. Based on data from a previous systematic review on this topic, a sample size of 190 subjects (with equal distribution of cohort) would have been required to detect a fourfold increase in mortality rate from 4 to 16% (5). Patient demographics and outcome variables were compared using univariate analyses among the

Table 1. Baseline demographics among BPD infants with and without PH

Variable*	BPD-PH n=24	No PH n=63	P value
Gestational Age (weeks)	24.7 (2.3)	26.4 (3.7)	0.02
Birthweight (grams)	765 (220)	840 (344)	0.20
Sex (Female)	37.5 (9/24)	37.1 (23/62)	0.97
Antenatal Steroids	91.7 (22/24)	88.9 (56/63)	1.00
Suspected Chorioamnionitis	50.0 (11/22)	22.0 (13/59)	0.01
PROM	29.2 (7/24)	20.6 (13/63)	0.40
Oligohydramnios	4.2 (1/24)	14.3 (9/63)	0.27
Maternal diabetes	4.2 (1/24)	10.0 (6/60)	0.67
Maternal hypertension	8.7 (2/23)	31.2 (19/61)	0.03
Maternal GBS positive	28.6 (2/7)	29.4 (5/17)	1.00
Caesarean section	41.7 (10/24)	66.7 (42/63)	0.03
PPV (mask)	91.7 (22/24)	88.9 (56/63)	1.00
Apgar 1 min	4 (4)	5 (3)	0.32
Apgar 5 min	7 (2)	7 (3)	0.07
SNAP II Score	14.0 (24.0)	16.0 (16.0)	0.94
Number of Surfactant			
0 or 1 dose	58.3 (14/24)	73.0 (46/63)	0.19
>1 doses	41.7 (10/24)	27.0 (17/63)	
Postnatal steroids	45.8 (11/24)	39.7 (25/63)	0.60
Severe ROP†	33.3 (8/24)	22.6 (14/62)	0.31
NEC	8.3 (2/24)	6.4 (4/63)	0.67
Sepsis£	37.5 (9/24)	31.8 (20/63)	0.61
Severe IVH§	25 (6/24)	4.8 (3/63)	0.01

BPD Bronchopulmonary dysplasia; GBS Group B streptococcus; IVH Intraventricular hemorrhage; NEC Necrotizing enterocolitis; PH Pulmonary hypertension; PPV Positive ventilation ventilation; PROM Prolonged rupture of membranes; ROP Retinopathy of prematurity; SNAP Score for neonatal acute physiology.

*All continuous variables expressed as medians (IQR) and categorical variables as % (n/N).

†Defined as stage 3 or greater, or treatment in either eye.

£Defined as presence of either positive blood or cerebral spinal fluid culture.

§Defined as the presence of periventricular or parenchymal hemorrhage on either side.

exposure and control groups, utilizing chi-squared/Fisher's exact and Student t/Wilcoxon rank sum tests for categorical and continuous data as appropriate, respectively (normality of continuous data assessed using Shapiro-Wilk test). Logistic regression models were conducted for demographic variables with P value < 0.3 on univariate analyses and biological plausibility for causation after accounting for gestational age at birth and sex as correcting factors with primary outcome of BPD-PH to determine risk factors. Finally, follow-up assessments of the exposure patients for management and persistence of PH were presented using descriptive methods. All analyses were conducted using SAS version 9.4 (Cary, NC) and a P-value < 0.05 was considered statistically significant. A sensitivity analysis by re-classifying possible PH into the control group was conducted for univariate analyses only using similar methods as described above.

RESULTS

During the study period, 92 patients met the study criteria, of whom 87 had the PH screening performed including an ECHO. Twenty-four of these 87 patients (28%) had definite (n=9) or possible (n=15) PH. The baseline characteristics were similar in the two groups, with the exception of gestational age (lower in BPD-PH), chorioamnionitis (higher in BPD-PH), maternal hypertension (lower in BPD-PH), caesarean section (lower in BPD-PH), and rate of severe intraventricular hemorrhage (higher in BPD-PH), as shown in Table 1. Among those with BPD-PH, the respiratory support settings at 36 weeks PMA were highly variable. Fifteen (62.5%) infants were on either high flow nasal cannula, low flow nasal cannula or nasal CPAP ≤6 cmH_2O, while the remainder were on higher levels of respiratory support (only one infant was on endotracheal mechanical ventilation).

There were no significant differences in outcomes, as shown in Table 2. These findings were similar for sensitivity analysis by re-classifying cases of possible PH into the control group (data shown in Supplementary Table S1). All BPD-PH patients had at least one follow-up ECHO at our institution. Of these, 11 (46%) infants had documented resolution. Among infants with resolution of BPD-PH, the median (IQR) time to resolution was 8 (10) months. There were 12 infants with residual PH on the last ECHO, of which 3 had definite PH (median [IQR] age at final follow-up of 9 (6) months) and 9 had possible PH (median [IQR] age at final follow-up at our institution of 4 (5.5) months). In one subject, the follow-up ECHO report was inconclusive. Oxygen supplementation was provided to 5 of 24 BPD-PH infants at the time of hospital discharge, with one patient requiring tracheostomy insertion prior to discharge (in addition to one patient without BPD-PH who also required tracheostomy). Supplemental oxygen was required for four infants with BPD-PH at 6 months and 1 at 12 months postdischarge. Sildenafil was administered to one neonate with BPD-PH and nitric oxide was administered to two patients with definite PH and three patients with possible PH as inpatients prior to discharge home.

Logistic regression models (each adjusting for gestational age and sex) to ascertain risk factors for development of BPD-PH were conducted for following four variables based on P values on univariate analyses: chorioamnionitis, oligohydramnios, maternal hypertension, and number of surfactant doses. Delivery mode and severe IVH were not included as these were not considered to have biological plausibility toward the outcome. None of presence of maternal hypertension (adjusted odds ratio [OR] 0.28, 95% confidence interval [CI] 0.06 to 1.43, P=0.13), receipt of more than one dose (compared to none or one dose) of surfactant (adjusted OR 2.61, 95% CI 0.87 to 7.87, P=0.09), antenatal history of oligohydramnios (adjusted OR 0.30, 95% CI 0.03 to 2.65, P=0.28) or presence of chorioamnionitis (adjusted OR 2.02, 95% CI 0.65 to 6.26, P=0.22) were significant predictors of BPD-PH in this study cohort.

DISCUSSION

The incidence of BPD-PH among infants with moderate to severe BPD was 28% in our cohort, which is in keeping with previous published reports (5). Short- and long-term outcomes were not found to differ between those with and without BPD-PH. None of the variables tested were predictive of BPD-PH, likely reflective of the relatively small sample size in this cohort. Finally, an evaluation of follow-up of infants with BPD-PH in this cohort

Table 2. Outcomes and resource utilization data

Variable	BPD-PH n=24	No PH n=63	P value
Survival to Discharge*	100 (24/24)	96.8 (61/63)	1.00
Discharged on Oxygen	33.3 (8/24)	25.4 (16/63)	0.46
Length of Stay (day)	99.5 (36.0)	91.0 (40.0)	0.17
Total Endotracheal Ventilation Duration (days)	30.5 (44.0)	13.0 (34.0)	0.18
Total Noninvasive Respiratory Support Duration (days)	67.0 (22.0)	59.0 (28.0)	0.17
Total Duration Receiving Oxygen (days)	81.0 (52.5)	66.0 (45.0)	0.18
Discharge Weight (grams)	3470 (689)	3092 (974)	0.12
Discharge Head circumference (cm)	34.8 (1.5)	33.5 (3.3)	0.07
Weight 3 months (grams)†	5538 (909)	5513 (957)	0.92
Length 3 months (cm)†	56.7 (3.5)	57.0 (3.3)	0.74
Head circumference 3 months (cm)†	39.7 (1.9)	40.0 (1.6)	0.57
Weight 6 months (grams)†	7394 (1154)	7167 (1061)	0.43
Length 6 months (cm)	62.5 (4.5)	63.5 (3.5)	0.81
Head circumference 6 months (cm)	43.4 (2.7)	43.0 (2.3)	0.99
Weight 12 months (grams)	9100 (1050)	9020 (1300)	0.75
Length 12 months (cm)	73.5 (3.3)	72.5 (4.0)	0.16
Head circumference 12 months (cm)	45.7 (2.0)	46.0 (1.9)	0.44
Cognitive score composite	90 (15)	100 (15)	0.13
Motor score composite	88 (18)	97 (15)	0.35
Language score composite†	84 (19)	89 (17)	0.46

All continuous outcomes expressed as median (IQR) unless otherwise indicated and all categorical variables expressed as % (n/N).

*Cause of death – patient 1: cardiopulmonary arrest following one way extubation and planned palliative care; patient 2: respiratory failure secondary to severe bronchopulmonary dysplasia.

†Expressed as mean (SD) as data were normally distributed on Shapiro-Wilk test.

showed that approximately half had documented resolution of the PH within 36 months post-discharge.

While previous reports have suggested that incidence of PH increases with severity of BPD (10,11), others have reported cases of PH even in mild BPD (12,13). However due to variable reporting (5), the true incidence of PH associated with mild BPD is unknown. Even in our cohort that encompassed moderate to severe BPD as per the 2001 NICHD classification (9), there was a wide range of respiratory settings indicative of a spectrum of BPD within this group. It is also important to note that in addition to any "dose-dependency" of PH incidence in relation to severity of BPD that may exist, factors contributing to the development of PH in BPD are still poorly understood. The role of genetic, epigenetic, and environmental factors remain to be fully elucidated (4,6).

Previous studies evaluating adjusted risk factors for development on PH in BPD patients have reported the following: postnatal infection, birthweight <25th percentile, oligohydramnios, and low APGAR scores ≤6 (14–16). Our study evaluated four risk factors based on differences in univariate analysis and biological plausibility: chorioamnionitis, maternal hypertension, oligohydramnios, and >1 doses of surfactant received, after adjustment for gestational age and sex. None of these variables were found to be predictive in our cohort. Further work is needed toward elucidation of risk factors that may allow for closer monitoring and possibly intervention at earlier stages, as well as having the potential to target screening among those at highest risk of BPD-PH. Very little is known about the natural history of BPD-PH, partly due to variability in screening and diagnostic practices reported in existing literature, and largely due to lack of data reporting this. We attempted to evaluate both in this study; it was interesting to note that many cases of BPD-PH resolved over time.

It has been previously reported that PH increases the mortality of BPD (11,17,18). In our cohort of patients with moderate to severe BPD, there were two cases of mortality (Table 2, both in the control arm), albeit this is a relatively small sample size. The effect of PH on short-term and long-term morbidities has been inconsistent in previous reports. A 2017 systematic review and meta-analysis reported no increased morbidity, which may be partly attributable to variable screening regimens and definitions of PH (5). In the absence of a universally agreed upon evidence-based criteria, our study used local consensus expert opinion extrapolated from criteria based on PH findings in infants and children > 3 months' age (7,8). The definitions of definite and probable PH were determined locally, but there is currently no 'gold standard' ECHO-based definition of PH in neonates (5), and performing cardiac catheterization is impractical for screening purposes. Using this definition to classify our cohort, we reported on a wide range of outcomes including NICU resource utilization as well as clinical outcomes including predischarge mortality, growth parameters, and neurodevelopment outcomes at 18 to 22 months. Outcomes evaluated were not different between BPD patients with and without PH. However, all studies to date have been limited by their relatively small sample size, in addition to the limitations described earlier (5).

The major limitation of our study is the small sample size. This precluded our ability to determine the value of targeted versus universal screening. As discussed, definitions of PH are inconsistent. The echocardiograms were read by different cardiologists. Finally, not all infants had their echocardiogram follow-ups completed at our institution, which limits our ability to delineate the natural history BPD-PH, nor comment on predictors of resolution over time. A strength of our study is that we applied specific criteria for PH screening and the vast majority of eligible infants had screening completed. We describe neurodevelopment outcomes which have only received limited attention to date, and attempted to characterize the natural history of BPD-PH. Finally, work from this study has served as the foundation for a more standardized and unified approach to instituting cardiology consultation, initiation of medical therapy, and institution of a regimented follow-up visit schedule and echocardiograms based on the results of initial PH screening.

In conclusion, while BPD-PH is a commonly identified complication of moderate to severe BPD, its true significance on outcomes remains unclear. Approximately one out of four patients with moderate to severe BPD were identified as having PH at our centre. No significant predictors for BPD-PH and no differences in clinical outcomes were identified for those with and without PH. In this study, we add to the growing body of knowledge in this field and describe the results from a single centre's screening practice. This work, with resultant standardization of diagnosis and follow-up at our institution, makes the case for a national-level standardized approach to screening, diagnosis, and evaluating long-term outcomes of patients with BPD-PH.

SUPPLEMENTARY DATA

Supplementary data are available at *Paediatrics & Child Health* Online.

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References

1. Stenmark KR, Abman SH. Lung vascular development: Implications for the pathogenesis of bronchopulmonary dysplasia. Annu Rev Physiol 2005;67:623–61.
2. Shah PS, Sankaran K, Aziz K, et al.; Canadian Neonatal Network. Outcomes of preterm infants <29 weeks gestation over 10-year period in Canada: A cause for concern? J Perinatol 2012;32(2):132–8.
3. Jobe AJ. The new BPD: An arrest of lung development. Pediatr Res 1999;46(6):641–3.
4. Bui CB, Pang MA, Sehgal A, et al. Pulmonary hypertension associated with bronchopulmonary dysplasia in preterm infants. J Reprod Immunol 2017;124:21–9.
5. Al-Ghanem G, Shah P, Thomas S, et al. Bronchopulmonary dysplasia and pulmonary hypertension: A meta-analysis. J Perinatol 2017;37(4):414–9.
6. Altit G, Dancea A, Renaud C, Perreault T, Lands LC, Sant'Anna G. Pathophysiology, screening and diagnosis of pulmonary hypertension in infants with bronchopulmonary dysplasia - a review of the literature. Paediatr Respir Rev 2017;23:16–26.
7. Galiè N, Hoeper MM, Humbert M, et al.; ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the international society of heart and lung transplantation (ISHLT). Eur Heart J 2009;30(20):2493–537.
8. Abman SH, Hansmann G, Archer SL, et al.; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Surgery and Anesthesia; and the American Thoracic Society. Pediatric pulmonary hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132(21):2037–99.
9. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163(7):1723–9.
10. An HS, Bae EJ, Kim GB, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J 2010;40(3):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(3):e682–9.
12. Khemani E, McElhinney DB, Rhein L, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: Clinical features and outcomes in the surfactant era. Pediatrics 2007;120(6):1260–9.
13. Weismann CG, Asnes JD, Bazzy-Asaad A, Tolomeo C, Ehrenkranz RA, Bizzarro MJ. Pulmonary hypertension in preterm infants: Results of a prospective screening program. J Perinatol 2017;37(5):572–7.
14. Ali Z, Schmidt P, Dodd J, Jeppesen DL. Predictors of bronchopulmonary dysplasia and pulmonary hypertension in newborn children. Dan Med J 2013;60(8):A4688.
15. Check J, Gotteiner N, Liu X, et al. Fetal growth restriction and pulmonary hypertension in premature infants with bronchopulmonary dysplasia. J Perinatol 2013;33(7):553–7.
16. Kim DH, Kim HS, Choi CW, Kim EK, Kim BI, Choi JH. Risk factors for pulmonary artery hypertension in preterm infants with moderate or severe bronchopulmonary dysplasia. Neonatology 2012;101(1):40–6.
17. Slaughter JL, Pakrashi T, Jones DE, South AP, Shah TA. Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation. J Perinatol 2011;31(10):635–40.
18. Choi EK, Jung YH, Kim HS, et al. The impact of atrial left-to-right shunt on pulmonary hypertension in preterm infants with moderate or severe bronchopulmonary dysplasia. Pediatr Neonatol 2015;56(5):317–23.