

Factors in the Neonatal Period Associated With Pulmonary Hypertension at 28 Days of Life in Broncho-Pulmonary Dysplasia

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Nguyen Thi Hai Anh, MD¹, Tran Minh Dien, PhD², Le Thi Ha, MD²,
Pham Thao Nguyen, MD^{1,2}, and Dang Thi Hai Van, PhD^{1,2}

Abstract

Objectives. To identify factors associated with pulmonary hypertension (PH) at 28 days of life in preterm infants with bronchopulmonary dysplasia (BPD). **Methods.** This observational study included 128 premature infants with BPD between January 2022 and February 2023 from the neonatal intensive care unit of Vietnam National Children's Hospital. **Results.** PH was observed using echocardiography in 29 patients (22.66%). The prevalence of severe BPD in the PH group (62.07%) was significantly higher than that in the non-PH group (18.18%). The multivariate logistic regression showed 2 predictors of PH in BPD: invasive mechanical ventilation up to 28 days of life (odds ratio [OR]: 9.440; 95% confidence interval [CI]: 3.090–28.833; $P < .001$) and history of shock (OR: 2.962; 95% CI: 1.067–8.225; $P = .037$). **Conclusion.** We found 2 predictors of PH at 28 days of life in BPD: invasive mechanical ventilation up to 28 days of life and history of shock.

Keywords

pulmonary hypertension, bronchopulmonary dysplasia, preterm, neonate, Vietnam

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Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease among premature infants who have incomplete alveolarization and require mechanical ventilation and oxygen therapy.¹ The advanced development in perinatal medicine has dramatically reduced preterm infant mortality. The strategy of gentle ventilation combined with steroids and surfactant therapy, to limit lung injury, is emphasized in the resuscitation of premature infants to protect their lungs.² However, the rate of BPD was still high, ranging from 18% to 40%, depending on the study.^{3,4} According to the consensus of the National Heart, Lung, and Blood Institute, the National Institute of Child Health and Human Development, and the US Office of Rare Diseases (NHLBI/NICHD/ORD) in 2001, the criteria for the diagnosis of BPD are oxygen dependence or ventilatory support for more than the first 28 days of life. These criteria are still commonly applied worldwide.⁵

Pulmonary hypertension (PH) is a common and severe cardiovascular complication of BPD, with approximately 25% of patients with moderate-to-severe BPD having PH.^{6–8} Pulmonary circulation in premature infants is characterized by decreased vascularization, epithelial proliferation, and vascular smooth muscle thickening, resulting in a predisposition to PH.^{9,10} Lack of respiratory membrane reduces gas exchange capacity and increases the need for oxygen support and prolonged ventilation. Moreover, severe respiratory failure

¹Ha Noi Medical University, Hanoi, Vietnam

²Vietnam National Children's Hospital, Hanoi, Vietnam

Corresponding Authors:

Tran Minh Dien, Vietnam National Children's Hospital, Dong Da, Hanoi, 100000, Vietnam.
Email: dientm@nch.gov.vn

Dang Thi Hai Van, Ha Noi Medical University, Dong Da, Hanoi, 100000, Vietnam.
Email: haivan@hmu.edu.vn



aggravates PH symptoms.^{9,10} PH is associated with poor outcomes in patients with BPD.^{11,12} Cardiac catheterization remains the gold standard for PH diagnosis; however, it is difficult to commonly apply in premature infants with respiratory failure and very low birth weight. Alternatively, echocardiography is a non-invasive and widely used method that is recommended for PH screening in premature infants.^{8,13} Early PH detection and treatment, aiming to maintain appropriate target oxygen saturation and avoid hypercapnia, may reduce the disease burden for preterm infants with BPD.^{14,15} Therefore, this study was conducted to determine the risk factors and consequences of PH at 28 days of life in preterm infants with BPD during the neonatal period.

Materials and Methods

This observational study involved all preterm infants with BPD treated in the neonatal intensive care unit (NICU) of Vietnam National Children's Hospital between January 2022 and February 2023. The BPD diagnostic criteria used in this study followed the consensus of NICHD/NHLBI/ORD in 2001, that is, preterm infants were oxygen-dependent for at least the first 28 days of life. BPD grades were classified into mild, moderate, and severe forms at 36 weeks of postmenstrual age, as described by Jobe and Bancalari.⁵ Mild BPD was defined as the absence of supplemental oxygen, moderate BPD as the need for <30% oxygen, and severe BPD as the use of positive pressure ventilation or the need for $\geq 30\%$ oxygen.⁵ The exclusion criteria included severe congenital malformations that could cause PH, such as the following: isolated lungs, congenital pulmonary dysplasia, congenital diaphragmatic hernia, and congenital heart disease. To screen for PH, echocardiography was performed at approximately 28 days of life.

PH Diagnosis

The diagnostic criterion of PH in preterm infants with BPD met one of the following criteria: (1) velocity of tricuspid regurgitation flow >2.5 m/s; (2) presence of a right to left or bidirectional shunt via a ventricular septal defect or ductus arteriosus; and (3) left ventricle end-systolic eccentricity index (LV-sEi) >1 , pulmonary artery acceleration (PAAT) <70 ms, and pulmonary artery acceleration/right ventricular ejection time (PAAT/RVET) <0.31 . PH was not diagnosed if the child had any evidence of pulmonary arterial or venous stenosis.^{8,13} Patients were divided into 2 groups: PH and non-PH. All patients were treated with the same hospital-approved

strategy for preterm BPD, with an oxygen saturation target of $\geq 92\%$ for the non-PH group and $\geq 95\%$ for the PH group, and followed during the neonatal period until they could be discharged.

Research Variables

Clinical variables included sex, gestational age at birth, birth weight, type of delivery, multiple pregnancies, obstetric history, and history of large patent ductus arteriosus (large PDA). The levels of mechanical ventilation support included high-frequency mechanical ventilation (HFO), invasive mechanical ventilation, non-invasive mechanical ventilation, and oxygen ventilation. This study defined pneumonia based on chest X-ray lesions and evidence of bacteria in the endotracheal fluid; history of shock during the first 28 days of life based on a hypotension status requiring the maintenance of at least one inotropic support; and necrotizing enterocolitis based on gastric residual, bloody stools, and abdominal tenderness, portal venous gas, or pneumoperitoneum.

Statistical Analysis

Data were collected using RedCap and analyzed using SPSS software. The differences between the PH and non-PH groups were analyzed using the chi-squared or Fisher's exact tests, as appropriate. The mean of non-normally distributed variables, including gestational age, birth weight, and total invasive ventilation duration, were compared using the Mann-Whitney U test. The mean total non-invasive respiration support duration and length of stay were compared using the T-test. Potentially influential variables, such as gestational age, history of shock, and invasive mechanical ventilation at 28 days of age, were used in the multivariate logistic regression analysis. Multivariate analyses were conducted using logistic regression. A P -value $<.05$ was considered statistically significant.

Ethical Considerations and Parental Consent

This study was approved by the Ethics Committee of the Vietnam National Children's Hospital (approval number: VNCH – TRICH – 2022 – 45). Written parental consent was obtained from the parents of all participants before collecting data.

Results

A total of 128 preterm infants with BPD were included in this study. Only 11.7% of patients could be measured for the full spectrum of tricuspid regurgitation, while

Table 1. Demographic and Obstetric Characteristics of the Participants Based on Their PH status.

Variable	PH group (n=29)	Non-PH group (n=99)	P value
Sex (male)	19 (65.52%)	55 (55.56%)	.339
Gestational age (weeks)	27.45 ± 2.37	28.27 ± 1.78	<i>P</i> = .013**, <i>U</i> = 1005.50, <i>Z</i> = -2.490
Birth weight (grams)	973.14 ± 371.27	1080.70 ± 281.11	<i>P</i> = .012**, <i>U</i> = 998.50, <i>Z</i> = -2.507
Gestational age at the time of echocardiogram (weeks)	33.64 ± 3.08	33.23 ± 3.16	.537
Cesarean section	21 (72.41%)	62 (62.63%)	.332
Multiple pregnancies	6 (20.69%)	21 (21.21%)	.952
In-vitro fertilization	4 (13.79%)	9 (9.09%)	.489
Maternal hypertension	1 (3.45%)	5 (5.05%)	>.05*
Maternal diabetes	1 (3.45%)	4 (4.04%)	>.05*
Maternal COVID-19	3 (10.34%)	14 (14.14%)	.857*
Vaginosis	7 (24.14%)	18 (18.18%)	.684
Antenatal steroids	9 (31.03%)	36 (36.46%)	.148*

Abbreviations: COVID-19, coronavirus disease 2019; PH, pulmonary hypertension.

*Fisher's exact test.

**Mann Whitney U test.

1.6% estimated pulmonary artery pressure through a shunt of a ventricular septal defect or ductus arteriosus. In the remaining cases, PH was determined based on LV-sEi < 1, PAAT < 70 ms, and PAAT/RVET < 0.31. The study identified 29 patients with PH at 28 days of life, accounting for 22.66% of all patients. The mean PAAT index of the PH and non-PH groups were 55.3 ± 8.1 and 69.3 ± 15.1 ms, respectively. The average PAAT/REVT ratio of the PH and non-PH groups were 0.268 ± 0.043 and 0.343 ± 0.076 ms, respectively. The mean LV-sEi of the PH and non-PH groups were 1.078 ± 0.168 and 0.967 ± 0.061, respectively. The mean tricuspid annular plane systolic excursion of the 2 groups was equivalent to 8.5 ± 1.6 mm.

The mean gestational age of all patients was 28.09 weeks, and the mean birthweight was 1056.33 g. The mean gestational age of the PH group (27.45 ± 2.37 weeks) was lower than that of the non-PH group (28.27 ± 1.78 weeks) (*P* = .013). According to the Fenton growth chart, the birthweight by gestational age of the PH and non-PH groups were at 42.83% ± 25.66% and 46.94% ± 23.74%, respectively (*P* < .05). The proportion of multiple pregnancies was relatively high (21.09%). Four patients had maternal polyhydramnios and 2 had maternal oligohydramnios. There were no differences between the groups, with respect to obstetric history (Table 1).

The mean duration of invasive ventilation was 18.95 days. The PH group had a longer total invasive ventilation duration (45.48 ± 41.51 days) than the non-PH group (11.18 ± 10.78 days) (*P* < .001). The PH group had a higher rate of invasive mechanical ventilation up to 28 days of life, higher rate of shock, and incidence of large PDA (Table 2).

The prevalence of severe, moderate, and mild BPD in the PH and non-PH groups was 62.07%, 31.03%, and 6.90% and 18.18%, 41.41%, and 40.41%, respectively (*P* < .001) (Figure 1).

History of shock was associated with pneumonia or large PDA with a rate of 68.4% and 25.0% in pneumonia and non-pneumonia groups and 44.3% and 17.9% in the large PDA and non-PDA groups, respectively. The multivariate logistic regression showed that invasive mechanical ventilation at 28 days of age and history of shock were independent risk factors for PH at 28 days of life with an adjusted odds ratio (OR) of 9.440 (95% confidence interval [CI]: 3.090-28.833) and 2.962 (95% CI: 1.067-8.225), respectively (Table 3).

Discussion

This study did not use the gold standard right heart catheterization for diagnosing PH as this procedure is invasive and impractical in the NICU. For infants with very low birth weights, echocardiography is recommended as the primary screening tool for PH in patients with BPD; however, even ultrasound screening for PH in preterm infants is challenging. One reason for this is the difficulty in measuring the full spectrum of tricuspid regurgitation.¹⁶ Therefore, other criteria such as PAAT/RVET, LV-sEi, right-to-left or bidirectional shunt via a PDA, and ventricular septum defect guided by PPHNet and EPPVDN are very useful.^{9,14,15} We also applied recently recommended parameters and criteria to increase the accuracy of screening results.

In our study, the mean gestational age was 28.09 weeks, and the mean birth weight was 1056.33 g. Our center

Table 2. Characteristics of Treatment in the NICU of the Participants Based on Their PH Status.

Variable	PH group (n=29)	Non-PH group (n=99)	P value
HFO	1 (3.45%)	11 (11.11%)	.295*
Invasive mechanical ventilation up to 28 days of life	16 (55.17%)	9 (9.09%)	<.001
Pneumonia	8 (27.59%)	11 (11.11%)	.039*
History of shock	18 (62.07%)	22 (22.22%)	<.001
Necrotizing enterocolitis	3 (10.3%)	16 (16.16%)	.562*
History of large PDA	20 (68.97%)	41 (41.41%)	.009
Total invasive ventilation duration (days)	45.48 ± 41.51	11.18 ± 10.78	$P < .001^{**}$, $U = 529.50$, $Z = -5.163$
Total non-invasive respiration support duration (days)	45.80 ± 31.78	46.26 ± 19.43	.925
Length of stay (days)	95.77 ± 37.90	65.23 ± 19.30	<.001
Death	9 (31.0%)	7 (7.1%)	.002

Abbreviations: HFO, high-frequency mechanical ventilation; PDA, patent ductus arteriosus; PH, pulmonary hypertension.

*Fisher exact test.

**Mann Whitney U test.

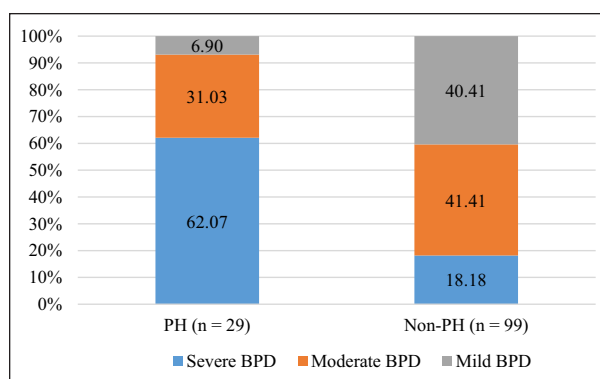


Figure 1. Association between PH at 28 days of life and severity of BPD at 36 weeks of postmenstrual age.

Abbreviations: BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension.

receives premature babies from other localities of the country, especially extremely premature babies with very low gestational age, with some even 25 weeks premature. However, the mean gestational age in this study was higher than that reported in other studies worldwide. In the study by Vayaltrikkovil et al,¹⁶ patients with BPD had an average gestational age of 26.1 weeks and weight of 858 g, and in the study by Collaco et al,¹² patients with BPD had an average gestational age of 27.1 weeks and weight of 994 g.

The prevalence of severe BPD in the PH group was 62.07%, which was significantly higher than that in the non-PH group at 18.18%. A recent study by Hien et al, showed the association between PH and severity of BPD. They found that the risk of PH in severe BPD was 5.71 times higher than that in mild BPD. However, we

assessed PH earlier than that in Hien et al's¹⁷ study at hospitalization after the neonatal period. In our study, a longitudinal follow-up only was performed at the neonatal center and we assessed for PH at approximately 28 days of age; furthermore, additional parameters such as LV-sEi, PAAT, and PAAT/RVET ratio were applied to evaluate PH. We also found that patients with PH at 28 days of life could still progress to mild BPD; moreover, their PH could resolve spontaneously without a pulmonary vasodilator.

Previous studies have demonstrated an association between PH and maternal pregnancy factors, such as low gestational age,¹⁶ oligohydramnios,¹⁸ and low weight for gestational age.^{18,19} In this study, the PH group had a lower gestational age than the non-PH group, similar to the results of Vayaltrikkovil et al¹⁶ who studied 126 preterm infants under 30 weeks of gestational age in Canada (25.4 vs 26.3 weeks). Oligohydramnios was rare and did not differ between the groups in our study. In contrast, Kim et al¹⁸ found that oligohydramnios was a risk factor for PH (risk ratio=7.7). Other factors, such as birth weight, polyhydramnios, maternal hypertension, maternal diabetes, and vaginosis, were also not associated with PH in our study. This may be due to the small sample size and earlier PH assessment time of our study compared with others.

Infants with BPD often experience diffuse fibrotic lung damage and respiratory failure, which may require prolonged or high-frequency mechanical ventilation. Mechanical and biological trauma to the immature lung results in a severe inflammatory response in the alveolar lumen and promotes the constriction and proliferation of the pulmonary vasculature. The association between the need for high-frequency mechanical ventilation and the

Table 3. Multivariate Logistic Regression Analysis on Factors Related to PH at 28 Days of Life.

Factor	OR	P value	95% CI
Gestational age	0.772	.060	0.589-1.011
History of shock	2.962	.037	1.067-8.225
Invasive mechanical ventilation up to 28 days of life	9.440	<.001	3.090-28.833

Abbreviations: CI, confidence interval; OR, odds ratio; PDA, patent ductus arteriosus; PH, pulmonary hypertension.

occurrence of PH was demonstrated in a study by Nagiub et al²⁰ but was not shown in our study. However, we observed a strong association between invasive mechanical ventilation up to 28 days of life and the occurrence of PH.

PDA is more common in premature infants than in full-term infants because the smooth muscle of the ductus arteriosus in preterm infants is less responsive to increased blood oxygen levels after birth. A ductus with a significant left-right shunt causes pulmonary circulation overload, is a risk factor for PH,¹² and may increase the need for mechanical ventilation. In our center, a large PDA with a left-right shunt was closed within 1 to 2 weeks of life with ibuprofen or paracetamol. If the patient was unresponsive, surgery or catheter closure was performed. At the time of enrollment, PDA treatment was complete except for 1 patient with a small PDA. Nearly half of the patients underwent PDA closure with paracetamol or ibuprofen, whereas 13.28% underwent surgical ligation. The incidence of a large PDA may be influenced by gestational age at birth. The role of a large PDA in PH occurrence has not been demonstrated in previous studies.²¹ Severe conditions in the NICU, such as necrotizing enterocolitis or sepsis, were more common in premature infants but did not differ between the groups with and without PH. However, the 2 groups differed in pneumonia, large PDA, history of shock, mechanical ventilation up to 28 days of age, and severe BPD. These problems were more severe in the PH group. However, when the related factors found in our study were included in a multivariate regression analysis model, only mechanical ventilation up to 28 days of age and history of shock were found to be independent prognostic factors for PH. Vayalthrikkovil et al¹⁶ also found that ventilator-associated pneumonia and severe BPD were risk factors for PH, with ORs of 17.9 and 3.3, respectively.

In this study, we found that PH increased the intubation time and length of stay in the neonatal unit by 4 and 1.5 times, respectively. Furthermore, overall mortality (severe pneumonia, PH, and sepsis) was 4 times higher in the PH group than in the non-PH group, comparable

with previous estimates by MacKenzie et al¹¹ and Collaco et al.¹²

This study was limited by its small sample size. Moreover, we did not perform sample size calculations and simply surveyed all patients who met the eligibility criteria during the study period. Future studies with a larger sample may yield interesting results.

Conclusion

The prevalence of PH at 28 days of life was 22.66% in preterm infants with BPD. In the PH group, 62.07% patients had severe BPD; however, only 18.18% in the non-PH group had severe BPD. Some factors associated with PH were low gestational age, invasive mechanical ventilation until 28 days of life, history of large PDA, pneumonia, and history of shock. However, the multivariate regression logistic showed that only invasive mechanical ventilation up to 28 days of life and history of shock were predictors of PH. Therefore, we found that PH at 28 days of life is associated with a prolonged duration of invasive mechanical ventilation, length of stay, and increased mortality in preterm infants with BPD.

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Author Contributions

Nguyen Thi Hai Anh, Tran Minh Dien, and Dang Thi Hai Van contributed equally to this work: conceived and designed the study, recruited the patients, collected the data, analyzed the data, and prepared the manuscript. Le Thi Ha and Pham Thao Nguyen participated in the data collection and following the patients. All authors reviewed and approved the final version of the manuscript.

Declaration of Conflicting Interests

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ORCID iDs

Nguyen Thi Hai Anh  <https://orcid.org/0009-0007-3266-9701>

Dang Thi Hai Van  <https://orcid.org/0009-0007-2574-7839>

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