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Risk Factors Associated With the Development of Late Pulmonary Artery Hypertension in Extremely Premature Infants

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ABSTRACT

Objective: To identify risk factors for late pulmonary artery hypertension (PH) at 36 weeks' postmenstrual age (PMA) in infants born before 28 weeks' gestation.

Design/Methods: A retrospective cohort study included infants born < 28 weeks' gestation who underwent PH screening echocardiography at 36 weeks' PMA. We compared characteristics between infants with and without late PH to determine associations.

Results: Of 99 infants, 20 (20%) developed late PH. The FiO2% requirement at 4 weeks of age, home oxygen use, and procedural patent ductus arteriosus closure were associated with late PH. Bronchopulmonary dysplasia (BPD) severity was linearly associated with late PH, with each 1-point increase in BPD severity corresponding to a 3.5-fold increased odds of late PH diagnosis.

Conclusion(s): One in five extremely premature infants developed late PH. Markers of respiratory disease severity, including the BPD grade, were associated with the development of late PH.

1 | Introduction

Bronchopulmonary dysplasia (BPD), a common complication affecting approximately 45% of surviving extremely premature infants born before 28 weeks' gestational age (GA) [1], is frequently associated with late pulmonary artery hypertension (PH). This serious condition, characterized by increased pressure in the pulmonary arteries that develops at or after 36 weeks' postmenstrual age (PMA), is linked to heightened morbidity and mortality [2–5]. Infants with late PH and BPD have been shown to have increased readmission rates in the first year post neonatal intensive care unit discharge and 2- and 3-year mortality rates of 26%–47% [6, 7].

Despite the severe consequences of late PH, there is no standardized approach for its screening and diagnosis in neonates [8–10]. The timing of late PH screening and the selection criteria for infants is widely variable. Diagnosis of late PH is

primarily made using echocardiography, but the specific echocardiographic parameters used to assess and determine the pulmonary artery pressure differ between centers [5, 8–10].

Multiple hypotheses exist regarding the development of late PH, with some researchers focusing on abnormal pulmonary angiogenesis and others implicating factors like hypoxia, hyperoxia, and inflammation [11–14]. While the exact pathogenesis of late PH is likely multifactorial, a clear understanding of the specific risk factors associated with late PH remains elusive.

This study aims to address this knowledge gap by identifying risk factors and their relationship to the development of late PH in premature infants born before 28 weeks' gestation. By identifying modifiable and non-modifiable risk factors, this research seeks to inform early detection strategies, optimize interventions, and ultimately improve long-term outcomes for this vulnerable patient population.

2 | Methods

2.1 | Patients

This retrospective cohort study was conducted at the UnityPoint Health Meriter (UPHM) Hospital Neonatal Intensive Care Unit (NICU). The UPHM NICU is a 44-bed level III NICU in Wisconsin's largest birthing hospital, with approximately 5000 births per year. The study period spanned from January 1, 2017, to December 31, 2021, and included all neonates born at less than 28 weeks' gestational age (GA) admitted to the NICU, excluding those with major congenital anomalies or those undergoing extensive cardiac surgery. A late PH screening echocardiogram was obtained at 36 weeks' PMA for all surviving neonates and their pulmonary hypertension status was assessed. Demographic and clinical characteristics were compared in relation to the infant's late PH status to assess for correlation with late PH development. Institutional Review Boards at UPHM and the University of Wisconsin School of Medicine and Public Health granted exemption status for this study and waiver for informed consent due to low risk.

2.2 | Pulmonary Hypertension Screening Echocardiogram

In 2017, the UPHM NICU adopted a standard practice of obtaining a PH screening echocardiogram for all former neonates born at < 28 weeks' GA once they reached 36 weeks' PMA. These echocardiograms were interpreted by pediatric cardiologists at the University of Wisconsin Department of Pediatric Cardiology.

2.3 | Data Abstraction

Subjects were identified through existing institutional databases of neonates born < 28 weeks' GA. Data collected included infant and maternal demographic characteristics, infant outcomes, respiratory support at 1 week, 4 weeks, and 36 weeks' PMA, patent ductus arteriosus (PDA) status and treatment, and PH screening echocardiogram findings. Diagnoses, clinical findings, therapies, and echocardiogram results were gathered from progress notes, clinical electronic medical records documentation, and echo reports. Data was deidentified and entered into a shared database.

2.4 | Study Definitions

PH was determined based on multiple echo parameters, including pulmonary artery acceleration time (PAAT), ventricular septal position, and systemic pressures estimated within the right heart from shunt gradients and tricuspid valve jet regurgitation velocity. An echocardiographic diagnosis of PH was made by the interpreting cardiologist based on their assessment of these parameters, with the value of each parameter weighed on a case-by-case basis depending on the available imaging and underlying anatomy.

BPD was defined by the Jensen criteria, with BPD severity determined by the level of respiratory support at 36 weeks' PMA [15].

2.5 | Statistical Analysis

Demographic characteristics, and potential exposures including maternal steroid use and chorioamnionitis, and risk factors of interest including respiratory status and oxygen needs were tabulated separately for neonates with and without late PH. Frequencies and percentages were used for categorical factors, while the mean and standard deviation or median and interquartile range (IQR) were used for continuous characteristics. Generalized estimating equations were used to account for potential correlations between twins from the same pregnancy, considering shared characteristics like gestational age, race, maternal age, exposure to antenatal steroids, pre-eclampsia.

Risk factors occurring at the individual neonate level were compared between groups using chi-square or Fisher's exact tests for categorical factors and *t*-tests or rank-sum procedures for continuous and ordinal variables. Analyses were performed using R (v.4.2.1), with p-values reported without adjustment for multiplicity due to the exploratory nature of the research. A p-value < 0.05 was considered statistically significant.

3 | Results

3.1 | Infants Included in the Analysis

From January 2017 to December 2021, 118 neonates with gestational age < 28 weeks were admitted to the UPHM NICU. The median gestational age was 25.7 weeks and the median birthweight was 780 grams. The length of stay ranged from 1 to 244 days (median [IQR] of 93 [76–113] days). There were 19 deaths observed during this period. Nineteen neonates were excluded due to unknown late PH status: 17 died before 36 weeks, one required cardiac surgery, one missed the late PH screening.

Among the remaining 99 infants, 20 (20%) developed late PH. No significant associations were found between maternal or neonatal characteristics and the development of late PH (Table 1).

3.2 | Echocardiography Characteristics Used to Identify PH

The diagnosis of late PH was most frequently based on septal flattening (8/20; 40% of diagnoses), followed by assessments PDA gradient (35%), VSD (15%), tricuspid valve jet velocity (25%), PAAT (5%) and the PAAT/RVET ratio (15%). A summary of echocardiographic findings for the infants with late PH is provided in Table 2.

3.3 | Respiratory Support and BPD Severity

Respiratory support, specifically the need for invasive ventilation, at one and 4 weeks of age was not significantly associated with the development of late PH ($p > 0.60$ for both time points). At 1 week of age, 55% of infants who developed late PH and 54% who did not develop late PH required invasive ventilation. At 4 weeks of age, this proportion remained similar for infants with late PH (55%), while it decreased to 43% for those without late PH. Although the FiO2% at 1 week was slightly higher in infants who developed late PH, this difference was not statistically significant ($p = 0.08$). However, by 4 weeks of age, the FiO2% was significantly higher in infants with PH compared to those without ($p = 0.004$).

Late PH was detected in 5% with no BPD, 6% of grade 1 BPD, and 33% of infants with grade 2–3 BPD. The severity of BPD was significantly associated with late PH status ($p = 0.003$), with a linear relationship observed: each 1-point increase in BPD severity corresponded to a 3.5-fold increased odds of late PH diagnosis (OR 3.48, 95% CI: 1.70–8.41) (Figure 1).

3.4 | BPD Therapies and Co-Morbidities and Their Association With PH

Postnatal steroid use was also associated with late PH ($p < 0.001$), though this finding was imprecise due to small numbers (OR15.5, 95% CI: 2.98–285). Home oxygen support was more common in infants with late PH (80% vs. 58%, $p = 0.04$). While a higher proportion of infants with late PH required PDA treatment, this difference was not statistically significant (80% vs. 58%, $p = 0.06$). However, procedural PDA management was significantly associated with late PH development (OR 3.72, 95% CI: 1.24–11.1, $p = 0.02$).

3.5 | Prematurity Co-Morbidities and Their Association With PH

No significant differences were found between infants who developed late PH and those who did not in their incidence of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), sepsis, and intraventricular hemorrhage (IVH) of any degree. However, the median length of hospital stay was

TABLE 1 | Demographic comparisons between infants who developed late PH and those who did not within the cohort.

Demographics	PH ($n = 20$)	No PH ($n = 79$)	p value
Gestational age, weeks (SD)	25.9 (1.4)	25.7 (1.3)	0.62
Birthweight, g (SD)	751 (183.4)	830.5 (192.3)	0.10
Size, *n* (%)			
SGA	3 (43)	4 (57)	0.24
AGA	17 (39)	72 (81)	
LGA	0 (0)	3 (100)	
Sex			0.65
Female, *n* (%)	10 (22)	35 (78)	
Male, *n* (%)	10 (19)	44 (81)	
Race, *n* (%)			
Black	6 (30)	14 (70)	0.57
White	11 (19)	48 (81)	
Other	3 (15)	17 (85)	
Antenatal steroids, *n* (%)			
No, unknown	5 (33)	10 (67)	0.33
Partial	3 (12)	22 (88)	
Complete	12 (20)	47 (80)	
Chorioamnionitis, *n* (%)			
No	16 (17)	78 (83)	0.06
Yes	4 (80)	1 (20)	

TABLE 2 | Echocardiographic parameters for all subjects with late PH and description of how diagnosis was made.

PDA gradient	RV enlargement	Septal flattening	PAAT	PAAT/RVET	TR JET	TAPSE	VSD gradient	PH diagnosis made by:
n/a	Top normal	Yes	55 ms	0.24	1.1 m/s	1.04 cm	n/a	TR jet/septal flattening
32.3 mmHg (left to right)	No		66 ms	0.3		1.02 cm	n/a	PDA gradient
n/a	No	Yes	40 ms	0.2	2.75 m/s	0.99 cm	n/a	Septal flattening
n/a			55 ms	0.3		1.24 cm	40 mm/hg	VSD gradient
n/a	No		34 ms	0.17	3.21 m/s		29 mmHg	VSD gradient
n/a	Yes	Yes	66 ms	0.33	3.0 m/s	0.92 cm	n/a	TR jet
n/a	No	Yes	48 ms	0.26			n/a	Septal flattening/PAAT/RVET ratio
Bidirectional			28 ms	0.21			n/a	PDA gradient
n/a	No		53 ms	0.26	2.7 m/s		n/a	PAAT and RVET
n/a	No	Yes	82 ms	0.43	2.3 m/s	0.9 cm	n/a	Septal flattening
n/a			62 ms	0.27		0.95 cm	n/a	Septal flattening/PA doppler pattern
n/a	No		56 ms	0.21		0.85 cm	n/a	Septal flattening/PAAT/PAAT/RVET
46.5 mmHg (left to right)	No		83 ms	0.49			Not reported	PDA gradient
35.6 mmHg (left to right)	No	No	53 ms	0.3			n/a	PDA gradient
n/a	No		42 ms	0.21	2.66 m/s	0.94 cm	Not reported	TR jet
Left to right	No	Yes	88 ms	0.49		1.04 cm	n/a	Septal flattening/PDA gradient
n/a	No	yes	58 ms	0.35		0.5 cm	n/a	Septal flattening
Not reported	No		61 ms	0.4	2.1 m/s	0.87 cm	n/a	TR jet
7.8 mmHg (bidirectional)	Yes		45 ms	0.25		0.49 cm	4 mmHg	VSD gradient/PDA gradient
36 mmHg (left to right)	Yes		48 ms	0.28	3.32 m/s	1.1 cm	n/a	TR jet/PDA gradient

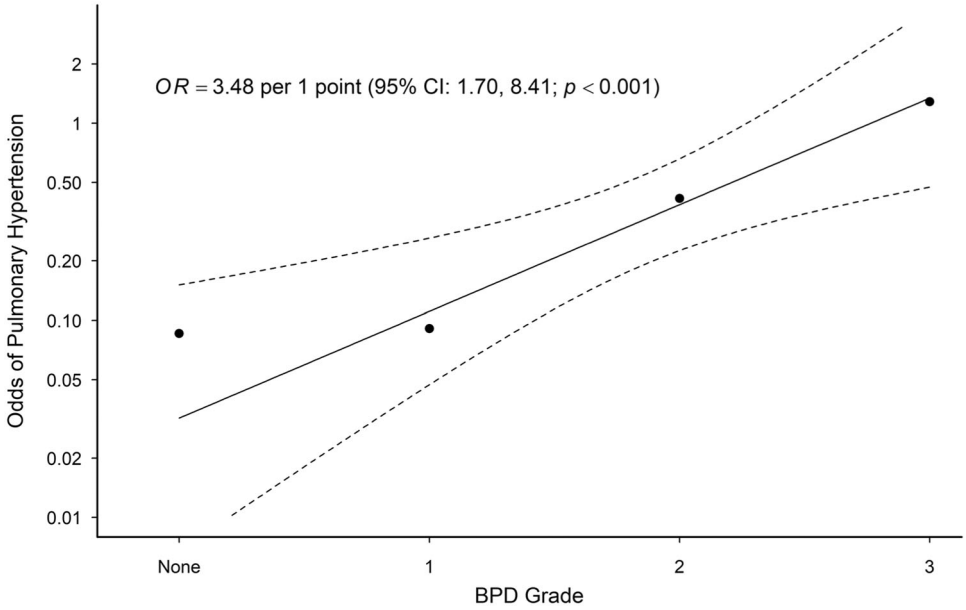

FIGURE 1 | Relationship between odds of developing late pulmonary hypertension and BPD grade.

21% longer for infants with late PH (122 days) compared to those without (99 days) (95% CI: 4.5%–40%, $p = 0.01$). These associations between clinical, respiratory, cardiovascular outcomes and late PH are summarized in Table 3.

4 | Discussion

This exploratory research found a strong association between BPD severity and late PH in preterm neonates born at less than 28 weeks' GA. Each 1-point increase in BPD grade associated with 3.5-fold increase in the odds of developing late PH, suggesting that impaired vascular proliferation associated with heterogeneous ventilation in BPD may contribute to the pathogenesis of late PH. Markers of increased respiratory disease severity, such as elevated FiO2 requirement at 4 weeks of age, postnatal steroid use, home oxygen need, and procedural PDA intervention, were also associated with late PH. This highlights the link between worsening respiratory status over time late PH development.

Given that BPD grade is a modifiable risk factor, measures should be taken within units to decrease BPD rates and severity, which would likely influence late PH rates. Measures that improve rates of more severe BPD could be avenues to study the effect on rates of late PH.

We did not find that gestational age, birthweight, antenatal steroid exposure, or maternal chorioamnionitis status were related to being diagnosed with late PH. Although Nagiub et al. reported a strong association with birthweight less than 600 g, our data did not replicate this finding. However, consistent with prior research, we observed a strong association between BPD severity and late PH [16], with an incidence of 33% in infants with grade II or III BPD, aligning with previous reports of 20%–40% in infants with BPD [6, 7, 17].

Our findings have implications for PH screening programs, suggesting that targeted screening of infants with moderate to severe BPD (grade II or III) may be more effective than universal screening of all preterm infants. This approach could significantly reduce healthcare costs while focusing resources on the highest-risk population screening. Mehler et al. developed a screening program to detect late PH in extremely low birthweight infants, finding that 41% of their cohort did not have PH detected on the screening echo at 36 weeks' but were diagnosed at discharge. This emphasizes the importance of close follow up with primary care physicians for this high-risk group but does not support broad NICU screening [10]. Given our results highlighting the strong association between late PH moderate to severe BPD, it may be reasonable to limit screening to these infants and closely monitor those with mild BPD (grade I) after discharge. Through targeted implementation of a PH screening programs, healthcare costs associated with echocardiograms could be reduced by limiting screening to infants with BPD, or further narrowing the criteria to those with severe BPD, rather than screening all neonates as was initially done at our center. Centers with low BPD rates that currently screen all preterm neonates born at less than 28 weeks' GA could see significant cost savings by transitioning to a more targeted screening strategy.

Identifying which infants to continue to monitor and screen post-discharge has not been well evaluated in current literature. At our institution we recommend continued screening for infants who discharge on home oxygen therapy every two to 3 months while still needing oxygen. If infants remain on oxygen in the hospital and do not meet PH criteria at the initial 36-week screen, we also recommend continued screening monthly while hospitalized. Additional considerations for post-discharge screening include screening those infants with poor post-discharge weight gain given that infants who are developing late PH may experience impaired growth due to increased metabolic demands. Likewise, these high-risk infants born at less than 28 weeks' gestational age should undergo screening if they are admitted for respiratory illness following discharge.

While infants with late PH had longer hospital stays and higher FiO2% requirements at 4 weeks of age, we did not find

TABLE 3 | Clinical outcomes, including respiratory outcomes, compared between infants who developed late PH and those who did not within the cohort.

	PH ($n = 20$)	No PH ($n = 79$)	p value
Clinical outcomes			
IVH, *n* (%)			0.90
No	14 (70)	51 (65)	
Mild	3 (15)	14 (18)	
Severe	3 (15)	14 (18)	
NEC, *n* (%)			0.60
No	18 (90)	75 (95)	
Yes	2 (10)	4 (5)	
Sepsis, *n* (%)			0.07
No	12 (65)	64 (81)	
Yes	8 (35)	15 (19)	
ROP, *n* (%)			0.72
No	9 (45)	41 (53)	
Mild	5 (25)	20 (26)	
Severe	6 (35)	17 (22)	
PDA requiring treatment, *n* (%)			0.06
No	4 (20)	33 (42)	
Yes	16 (80)	46 (58)	
PDA requiring surgical intervention, *n* (%)			0.02
No	12 (60)	67 (85)	
Yes	8 (40)	12 (15)	
Length of stay, days median [IQR]	122 [95, 144]	99 [83, 112]	0.01
Respiratory outcomes			
Surfactant, *n* (%)			0.20
No	0 (0)	9 (11)	
Yes	20 (100)	70 (89)	
Resp. support at 1 week, *n* (%)			0.64
ET	11 (55)	43 (54)	
NIPPV/NAVA	1 (5)	9 (11)	
CPAP/HFNC	8 (40)	27 (34)	
FiO2% at 1 week median [IQR]	30 [25, 50]	27 [23, 33]	0.09
Resp. support at 4 weeks, *n* (%)			0.63
ET	11 (55)	34 (43)	
NIPPV/NAVA	3 (15)	16 (20)	
CPAP/HFNC	6 (30)	29 (37)	
FiO2% at 4 weeks median [IQR]	40 [30, 45]	30 [25, 40]	0.004
Steroid administration for pulmonary reasons, *n* (%)			< 0.001
No	1 (5)	35 (45)	
Yes	19 (95)	43 (55)	

(Continues)

TABLE 3 | (Continued)

	PH ($n = 20$)	No PH ($n = 79$)	p value
Home oxygen, n (%)			0.04
No	4 (20)	32 (42)	
Yes	15 (75)	44 (58)	
ET	1 (5)	0 (0)	
BPD, n (%)			0.003
No	1 (5)	17 (22)	
Grade 1	2 (10)	27 (34)	
Grade 2	13 (65)	32 (41)	
Grade 3	4 (20)	3 (4)	

differences in other clinical outcomes like NEC, sepsis, and IVH rates, compared to infants without late PH. This contrasts with previous studies reporting associations between these conditions and late PH [16, 18]. Consistent with prior research, infants with late PH were more likely to be discharged home on oxygen therapy [5], likely reflecting the strong association with BPD. Additionally, procedural PDA treatment was more common among infants with late PH, suggesting a potential role of PDA shunt burden in late PH development as reported by Gentle et al [19]. This association may reflect the time period studied, before the widespread availability of transcatheter PDA closure; however, a recent meta-analysis by Mascarenhas et al also found rates of PH were higher among infants with BPD who were exposed to PDA ligation [20]. Infants who underwent invasive PDA closure had thoracotomies as a part of their surgical procedure, which may have caused lung injury and increased rates of late PH and BPD development. As transcatheter closure becomes more common and is performed earlier, the incidence of late PH may decrease. This trend should be evaluated further in large randomized controlled trials and future observational studies.

The gold standard for diagnosis of PH is with cardiac catheterization. Given the potential risks associated with that procedure, echocardiograms have been used as a second option to try to obtain similar physiologic data. However, because this is an indirect measure of three dimensional and dynamic structures, the diagnosis of PH on echocardiography is variable, with subjective interpretations contributing to the diagnosis. Other studies have determined late PH with various measures, noting the subjectivity of septal wall flattening in the diagnosis [4, 5, 17, 21, 22]. Abraham et al. found the eccentricity index to be a more reliable assessment of PH compared to septal flattening, however, this measurement is not used in our institution [23]. Variability in the inclusion of parameters such as the PAAT and differences between echocardiographic and cardiac catheterization measurements, as previously shown by Mourani et al [24], further complicate the diagnosis. Future work should aim to better understand the relationship between echocardiogram variables and specific outcomes to establish a consistent PH definition.

This study has several limitations. Its retrospective design and data collection over 5 years (2017–2021) introduce the possibility of evolving clinical practices, potentially influencing the reported BPD rates. Notably, the NICU's shift towards continuing CPAP until 32 weeks' gestation during this period, may have influenced BPD incidence. As a single center study, the findings may not be generalizable to other NICU settings. The lack of a universally accepted PH definition and variability in echocardiogram interpretation introduce uncertainty in PH diagnoses. While all screening echocardiograms in the PH group showed signs of elevated right heart pressure, not all met strict diagnostic criteria for PH. However, these signs were absent in the echocardiograms of the non-PH group. Lastly, this study lacks long term follow-up data for infants diagnosed with PH, limiting our ability to assess the condition's long-term impact and potential for resolution.

In conclusion, this retrospective cohort study found a strong association between late PH and BPD severity in extremely preterm infants, reinforcing the concept of a shared pathophysiological mechanism. Given the increased morbidity and mortality with late PH, we recommend implementing a targeted screening program for all infants with BPD at 36 weeks' PMA to evaluate for late PH followed by close monitoring after discharge. Further research is needed to develop effective strategies to prevent and mitigate BPD severity, thereby reducing the incidence of late PH and improving outcomes in this vulnerable population.

Author Contributions

Paige E. Condit was involved in designing the study, obtained the data, assisted with data analysis, drafted and approved the final manuscript as submitted. John S. Hokanson was involved in designing of the study, assisted with data analysis, reviewed and approved final manuscript as submitted. Vivek Balasubramaniam was involved in designing of the study, reviewed and approved final manuscript as submitted. David J. McCulley was involved in designing of the study, reviewed and approved final manuscript as submitted. Michael Lasarev was involved in designing of the study, did the data analysis, reviewed and approved final manuscript as submitted. Luke Lamers was involved in designing of the study, reviewed and approved final manuscript as submitted. Ryan M. McAdams was involved in designing of the study, reviewed and approved final manuscript as submitted. Dinushan C. Kaluarachchi designed the study, drafted the project proposal, reviewed and approved final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflicts of Interest

D.K. serves as a consultant for ONY Biotech. The remaining authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. E. A. Jensen, E. M. Edwards, L. T. Greenberg, R. F. Soll, D. E. Y. Ehret, and J. D. Horbar, "Severity of Bronchopulmonary Dysplasia Among Very Preterm Infants in the United States," *Pediatrics* 148, no. 1 (2021): e2020030007.

2. H. S. An, E. J. Bae, G. B. Kim, et al., "Pulmonary Hypertension in Preterm Infants With Bronchopulmonary Dysplasia," *Korean Circulation Journal* 40, no. 3 (2010): 131–136.

3. C. D. Baker, S. H. Abman, and P. M. Mourani, "Pulmonary Hypertension in Preterm Infants With Bronchopulmonary Dysplasia," *Pediatric Allergy, Immunology, and Pulmonology* 27, no. 1 (2014): 8–16.

4. R. Bhat, A. A. Salas, C. Foster, W. A. Carlo, and N. Ambalavanan, "Prospective Analysis of Pulmonary Hypertension in Extremely Low Birth Weight Infants," *Pediatrics* 129, no. 3 (2012): e682–e689.

5. P. M. Mourani, M. K. Sontag, A. Younoszai, et al., "Early Pulmonary Vascular Disease in Preterm Infants at Risk for Bronchopulmonary Dysplasia," *American Journal of Respiratory and Critical Care Medicine* 191, no. 1 (2015): 87–95.

6. E. Khemani, D. B. McElhinney, L. Rhein, et al., "Pulmonary Artery Hypertension in Formerly Premature Infants With Bronchopulmonary Dysplasia: Clinical Features and Outcomes in the Surfactant Era," *Pediatrics* 120, no. 6 (2007): 1260–1269.

7. J. M. Lagatta, E. B. Hysinger, I. Zaniletti, et al., "The Impact of Pulmonary Hypertension in Preterm Infants With Severe Bronchopulmonary Dysplasia Through 1 Year," *Journal of Pediatrics* 203 (2018): 218–224.e3.

8. C. G. Weismann, J. D. Asnes, A. Bazzy-Asaad, C. Tolomeo, R. A. Ehrenkranz, and M. J. Bizzarro, "Pulmonary Hypertension in Preterm Infants: Results of a Prospective Screening Program," *Journal of Perinatology* 37, no. 5 (2017): 572–577.

9. D. Kaluarachchi, K. Woo, and T. Colaizy, "Role of Early Pulmonary Hypertension as a Risk Factor for Late Pulmonary Hypertension in Extremely Preterm Infants," *American Journal of Perinatology* 35, no. 2 (2018): 120–126.

10. K. Mehler, F. E. Udink Ten Cate, T. Keller, U. Bangen, A. Kribs, and A. Oberthuer, "An Echocardiographic Screening Program Helps to Identify Pulmonary Hypertension in Extremely Low Birthweight Infants With and Without Bronchopulmonary Dysplasia: A Single-Center Experience," *Neonatology* 113, no. 1 (2018): 81–88.

11. M. Jakkula, T. D. Le Cras, S. Gebb, et al., "Inhibition of Angiogenesis Decreases Alveolarization in the Developing Rat Lung," *American Journal of Physiology-Lung Cellular and Molecular Physiology* 279, no. 3 (2000): L600–L607.

12. E. Lignelli, F. Palumbo, D. Myti, and R. E. Morty, "Recent Advances in Our Understanding of the Mechanisms of Lung Alveolarization and Bronchopulmonary Dysplasia," *American Journal of Physiology-Lung Cellular and Molecular Physiology* 317, no. 6 (2019): L832–L887.

13. G. Hansmann, H. Sallmon, C. C. Roehr, S. Kourembanas, E. D. Austin, and M. Koestenberger, "Pulmonary Hypertension in Bronchopulmonary Dysplasia," *Pediatric Research* 89, no. 3 (2021): 446–455.

14. C. B. Bui, M. Kolodziej, E. Lamanna, et al., "Interleukin-1 Receptor Antagonist Protects Newborn Mice Against Pulmonary Hypertension," *Frontiers in Immunology* 10 (2019): 1480.

15. E. A. Jensen, K. Dysart, M. G. Gantz, et al., "The Diagnosis of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-Based Approach," *American Journal of Respiratory and Critical Care Medicine* 200, no. 6 (2019): 751–759.

16. M. Nagiub, U. Kanaan, D. Simon, and L. Guglani, "Risk Factors for Development of Pulmonary Hypertension in Infants With Bronchopulmonary Dysplasia: Systematic Review and Meta-Analysis," *Paediatric Respiratory Reviews* 23 (2017): 27–32.

17. J. L. Slaughter, T. Pakrashi, D. E. Jones, A. P. South, and T. A. Shah, "Echocardiographic Detection of Pulmonary Hypertension in Extremely Low Birth Weight Infants With Bronchopulmonary Dysplasia Requiring Prolonged Positive Pressure Ventilation," *Journal of Perinatology* 31, no. 10 (2011): 635–640.

18. Y. Chen, D. Zhang, Y. Li, et al., "Risk Factors and Outcomes of Pulmonary Hypertension in Infants With Bronchopulmonary Dysplasia: A Meta-Analysis," *Frontiers in Pediatrics* 9 (2021): 695610.

19. S. J. Gentle, C. P. Travers, M. Clark, W. A. Carlo, and N. Ambalavanan, "Patent Ductus Arteriosus and Development of Bronchopulmonary Dysplasia-Associated Pulmonary Hypertension," *American Journal of Respiratory and Critical Care Medicine* 207, no. 7 (2023): 921–928.

20. D. Mascarenhas, M. Al-Balushi, A. Al-Sabahi, D. E. Weisz, A. Jain, and B. Jasani "Pulmonary Hypertension in Preterm Neonates With Bronchopulmonary Dysplasia: A Meta-Analysis," Archives of Disease in Childhood—Fetal and Neonatal Edition 2024: fetalneonatal-2024-327547.

21. J. Check, N. Gotteiner, X. Liu, et al., "Fetal Growth Restriction and Pulmonary Hypertension in Premature Infants With Bronchopulmonary Dysplasia," *Journal of Perinatology* 33, no. 7 (2013): 553–557.

22. L. F. Ling, N. A. Obuchowski, L. Rodriguez, Z. Popovic, D. Kwon, and T. H. Marwick, "Accuracy and Interobserver Concordance of Echocardiographic Assessment of Right Ventricular Size and Systolic Function: A Quality Control Exercise," *Journal of the American Society of Echocardiography* 25, no. 7 (2012): 709–713.

23. S. Abraham and C. G. Weismann, "Left Ventricular End-Systolic Eccentricity Index for Assessment of Pulmonary Hypertension in Infants," *Echocardiography* 33, no. 6 (2016): 910–915.

24. P. M. Mourani, M. K. Sontag, A. Younoszai, D. D. Ivy, and S. H. Abman, "Clinical Utility of Echocardiography for the Diagnosis and Management of Pulmonary Vascular Disease in Young Children With Chronic Lung Disease," *Pediatrics* 121, no. 2 (2008): 317–325.