CRIB Scores as a Tool for Assessing Risk for the Development of Pulmonary Hypertension in Extremely Preterm Infants with Bronchopulmonary Dysplasia

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Abstract

Objective Bronchopulmonary dysplasia (BPD) increases the risk for developing pulmonary hypertension (PH). However, the risk factors associated with BPD-associated PH remain unclear. Our primary aim was to determine perinatal risk factors associated with the development of PH in infants with BPD.

Study Design We retrospectively reviewed medical records of 303 infants born at ≤ 28 weeks' gestation. Infants were categorized as having no, mild, moderate, or severe BPD. PH was diagnosed by echocardiogram. Data were analyzed using Fisher exact test, two-sample *t*-test, and multivariable logistic regression.

Results The incidence of PH in our cohort was 12%. Infants with PH had lower birth weights and gestational ages ($p < 0.001$). After controlling for confounding variables, severe BPD ($p < 0.001$), and higher Clinical Risk Index for Babies (CRIB) scores ($p = 0.04$) were associated with the development of PH.

Conclusion Severe BPD increases the risk for developing PH. Higher CRIB scores correlate with PH development in infants with BPD. We speculate that CRIB scores may allow for early categorization of preterm infants with a higher likelihood of developing PH.

Keywords
- neonatal
- bronchopulmonary dysplasia
- pulmonary hypertension

Bronchopulmonary dysplasia (BPD), a chronic lung disease of infancy, impacts the pulmonary and overall health and development of thousands of infants each year.[1] It is one of the most common complications of extreme preterm birth and results in significant morbidity and mortality in extremely low birth weight infants.[2–5] Risk factors associated with the development of severe BPD includes lower gestational ages (GAs) and birth weights.[6] Previous studies have suggested that infants with BPD are at increased risk for developing cardiovascular complications including pulmonary hypertension (PH), cor pulmonale, and death.[7–10]

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There is a paucity of information about the risk factors, pathogenesis, and natural history of BPD-associated PH. Although vascular remodeling, increased vasomotor tone, and reduced alveolar capillary coupling have been implicated in the pathogenesis of PH, the precise mechanism by which BPD-associated PH develops remains poorly elucidated.[8,9,11,12] Infants with severe BPD appear to be at highest risk for developing PH suggesting that higher inspired oxygen concentrations and inflammation may play a role in its pathogenesis.[1,13–15] Other proposed mechanisms for BPD-associated PH include growth restriction, exposure to certain drugs such as selective serotonin reuptake inhibitors (SSRIs), genetic predisposition, and cardiovascular shunts.[11,16,17] Recently, elevated maternal α-fetoprotein (AFP) and human chorionic gonadotropin (HCG), as well as decreased unconjugated estriol (uE3) have been shown to be associated with an increased risk of developing BPD suggesting that a prenatal predisposition for BPD may exist.[18]

At present, there is no consensus on the definition, screening, or management of clinically significant PH in extremely preterm infants.[19] Although cardiac catheterization is the gold standard for diagnosing PH,[10] it is often avoided in fragile premature infants as it is an invasive procedure. PH definitions range widely from the isolated right ventricular hypertrophy (RVH) to more stringent criteria of elevated tricuspid regurgitation jet and ventricular septal flattening in addition to RVH.[11,20,21] Routine screening for BPD-associated PH has not been universally adopted because of questions regarding the optimal timing for screening. In a recent study of extremely low birth weight infants, BPD-associated PH was seen in 6% of infants at 4 weeks of life; an additional 12% of patients were diagnosed with PH beyond 4 weeks of life.[22]

In this study, we examined the maternal and neonatal characteristics of infants born at $\leq$ 28 weeks' GA admitted to the intensive care nursery at the Children's Hospital at Montefiore, Weiler Division, between 2006 and 2012, who developed BPD-associated PH. Our objective was to identify maternal and neonatal risk factors associated with the development of PH in extremely premature infants. In this study of infants born at $\leq$ 28 weeks' gestation with a screening echocardiogram obtained at or after 36 weeks' corrected GA, we hypothesized that infants with severe BPD were at the highest risk for developing PH and that certain targeted neonatal characteristics would help to better identify preterm infants with evolving chronic lung disease who would benefit from routine, and possibly earlier, screening for PH.

Patients and Methods

This is an observational, retrospective cohort study of all the infants with GA $\leq$ 28 weeks' who were admitted to the neonatal intensive care unit at the Children's Hospital at Montefiore, Weiler Division, from 2006 to 2012. Eligible infants were identified from our comprehensive neonatal database. Infants were excluded from the study if they met the following criteria: (1) death within 28 days of birth, (2) transfer to an outside hospital within the first week of life, (3) echo not obtained at or after 36 weeks' corrected GA, or (4) presence of any congenital conditions that would predispose the infant to developing PH or worsen preexisting PH such as congenital heart disease and diaphragmatic hernia. During the study period, screening echocardiograms to diagnose BPD-associated PH were performed at the discretion of the attending neonatologist. Therefore, all infants born at less than 28 weeks' gestation did not have PH screening.

Baseline maternal and neonatal demographic information were obtained from our database and chart review. Maternal characteristics analyzed included age, quad screen results (AFP, HCG, estriol, and inhibin), antenatal steroid administration, and the presence or absence of obesity, diabetes, hypertension, preeclampsia, chorioamnionitis, preterm premature rupture of membranes (PPROM), depression requiring medication, and toxic habits (tobacco, alcohol, and/or illicit drug use). Neonatal characteristics recorded included GA, birth weight (BW), gender, race, small for GA (SGA) status, and Apgar score $\leq$ 5 at 5 minutes of life. Additional neonatal characteristics analyzed were Clinical Risk Index for Babies (CRIB) scores as an indicator of illness severity in the first 12 hours of life; the presence of a patent ductus arteriosus (PDA) with or without the need for surgical ligation, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and gastrointestinal perforation; severity of intraventricular hemorrhage (IVH); and average fluid intake over the first 2 weeks of life. For each patient, the presence or absence of BPD was noted. Each infant was then categorized by severity of BPD based on validated NICHD criteria. The four groups included no BPD, mild BPD (oxygen requirement at 28 days of life), moderate BPD (F_{IO_2} of $<$ 30% at 36 weeks' postmenstrual age), and severe BPD (F_{IO_2} $\geq$ 30% or need for continuous positive airway pressure, high flow nasal cannula, or ventilator support at 36 weeks' postmenstrual age).[23]

The primary outcome measure was development of PH in preterm infants born at $\leq$ 28 weeks' gestation. The definition of PH was met if a patient had elevated right ventricular pressures on echocardiogram, defined as the presence of two or more of the following criteria: RV pressure greater than 25 mm Hg in the presence of a tricuspid regurgitation jet, right ventricular hypertrophy, and intraventricular septal flattening.[24–26] Patients were included only if an echocardiogram was obtained at 36 weeks' corrected GA or greater, at which time physiologic postnatal PH should no longer be evident and moderate or severe BPD can be diagnosed.

Data Analysis

The *p* values for comparison across PH and non-PH patients were tabulated by Fisher exact test for categorical variables and by two-sample *t*-test for continuous variables. Multivariable logistic regression was utilized to assess the independent effects of the various risk factors for PH and to control for potential confounders. The predictor variables included in the model were severity of BPD, CRIB scores, PDA, PDA ligation, severity of ROP, GA, BW, and maternal age. Statistical significance was considered at $p < 0.05$. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

The Children's Hospital at Montefiore treats patients in a large urban area with a diverse population. A total of 351 infants were screened for the study of which 303 infants met inclusion criteria. Overall, 48 infants (14%) were excluded—6 infants (2%) secondary to death before 28 days of life and 42 infants (12%) because of lack of echocardiogram results at or after 36 weeks' corrected GA (►**Fig. 1**). Of the 303 infants studied, the incidence of PH was 12% (►**Table 1**). The overall incidence of BPD of any severity was 89% (270/303) with 37% (112/303) of infants categorized as having severe BPD. Infants with PH had lower BW ($p < 0.001$) and lower GA ($p < 0.001$) (►**Table 1**). Although there was a trend toward an increase in PH in SGA infants, this was not statistically significant ($p = 0.09$; ►**Table 1**).

To understand how maternal health may impact the development of PH in extremely preterm infants, we examined the presence of maternal comorbidities and the subsequent development of PH in preterm infants. Maternal morbidities such as obesity, diabetes mellitus, hypertension, preeclampsia, and chorioamnionitis were not associated with PH development as indicated in ►**Table 2**. Of note, unlike previous reports, we did not observe an association between maternal use of SSRI's for depression and the development of PH in our cohort of patients. However, only four patients in our cohort reported a history of taking SSRIs for depression (►**Table 2**). No relationship was demonstrated between quad screen results and the development of BPD or PH.

Because pulmonary disease is associated with the development of PH, we evaluated the relationship between BPD severity and PH. Severe BPD was positively associated with the development of PH (►**Table 3**). BPD-associated PH was diagnosed at a median age of 96 days (range, 66–179 days). To better understand the relationship between illness severity and the development of PH, we assessed the relationship between CRIB scores, a marker of illness severity within the first 12 hours of life,[27] and PH. Elevated CRIB scores were noted to be significantly associated with the subsequent development of PH ($p < 0.001$; ►**Table 3**). There was no association between the degree of elevation of CRIB scores and the timing of the diagnosis of PH. Interestingly, other neonatal morbidities including NEC, gastrointestinal perforation, and severity of IVH were not associated with the development of PH in our cohort.

A multivariable logistic regression model was used to assess the independent effects of the various risk factors for PH and to control for potential confounders. In this model, severe BPD and higher CRIB scores remained significantly associated with PH development (►**Table 4**). The odds of developing PH were 4.7-fold higher in infants with severe BPD compared with those without (odds ratio [OR] = 4.74; 95% confidence interval [CI], 1.68–13.4).

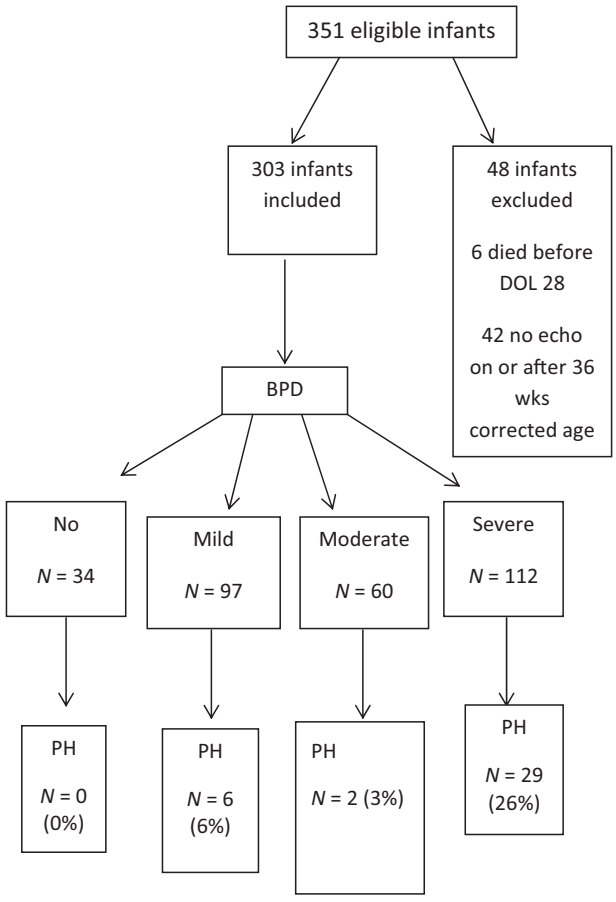

Fig. 1 Flow diagram of infant categorization.

Discussion

In this single center, retrospective review of extremely preterm infants, we observed that the development of PH was associated with severe BPD and neonatal disease severity as measured by CRIB scores. Previously published studies of infants with BPD describes an incidence of PH ranging from 17.9 to 43%.[13,28] In comparison, we found a PH incidence of 12% in our study cohort. This lower incidence may be related, at least in part, to our more stringent criteria for diagnosing PH in the study patients. In this study, infants had to meet two or more echocardiographic criteria to be diagnosed with PH whereas other studies required only one echocardiographic finding.[13,22] The median age at diagnosis of PH was 96 days of life (range, 66–179 days) suggesting that it may take a few weeks to months for echocardiographic evidence of PH to manifest in the presence of significant lung disease.

Infants with severe BPD were at higher risk for developing PH than infants with no BPD or BPD of lesser severity. Although 26% of patients with severe BPD developed PH, a few patients with mild and moderate BPD also developed PH (6 and 3%, respectively). This is likely related to the fact that the development of PH is a multifactorial process. Infants with the most significant lung disease may be impacted for several reasons. Impaired lung development may coincide with impaired development of the pulmonary vasculature, as premature infants are born at early developmental stages.[29] Altered pulmonary and vascular development may lead to an inability of both the respiratory and cardiovascular systems to adequately support the infant's needs during growth. This

Table 1 Neonatal demographic and clinical characteristics

	No PH ($n = 266$)	PH ($n = 37$)	p value
Gestational age (mean), wks	26.7 ± 1.4	25.7 ± 1.6	< 0.001
Birth Weight (g), mean ± SD	872 ± 202	695 ± 222	< 0.001
Male, *n* (%)	127 (48)	17 (46)	0.86
SGA, *n* (%)	39 (15)	10 (27)	0.09
Black, *n* (%)	155 (58)	23(62)	0.5
Apgar ≤ 5 at 5 min, *n* (%)	23 (9)	6 (16)	0.14

Abbreviations: *N*, number; PH, pulmonary hypertension; SD, standard deviation; SGA, small for gestational age.

Table 2 Maternal demographics and risk factors ($N = 303$)

	No PH ($n = 266$)	PH ($n = 37$)	p value
Maternal age, mean ± SD (y)	29.2 ± 6.0	31.2 ± 5.9	0.06
ANS complete, *n* (%)	159 (60)	18 (49)	0.22
Obesity, *n* (%)	108 (41)	19 (53)	0.4
Diabetes mellitus, *n* (%)	26 (10)	4 (11)	0.77
Hypertension, *n* (%)	48 (18)	10 (27)	0.19
Preeclampsia, *n* (%)	61 (23)	6 (16)	0.4
Chorioamnionitis, *n* (%)	47 (18)	9 (24)	0.37
Prolonged PPROM, *n* (%)	92 (35)	8 (22)	0.14
Depression meds, *n* (%)	4 (2)	0 (0)	1.00
Toxic habits, *n* (%)	29 (10)	4 (11)	1.00

Abbreviations: ANS, antenatal steroid; *N*, number; PH, pulmonary hypertension; PPROM, preterm premature rupture of membranes; SD, standard deviation.
Note: Toxic habits include tobacco, alcohol, and/or illicit drug use.

Table 3 Neonatal characteristics and risk factors (Total $N = 303$)

	No PH ($n = 266$)	PH ($n = 37$)	p value
BPD			
Nonsevere, *n* (%)	183 (69)	8 (22)	< 0.001
Severe, *n* (%)	83 (31)	29 (78)	
CRIB, mean ± SD	10.7 ± 0.2	13.3 ± 0.4	< 0.001
PDA, *n* (%)	176 (66)	32 (89)	0.006
PDA with ligation, *n* (%)	64 (24)	20 (56)	< 0.001
ROP, *n* (%)	33 (12)	9 (24)	< 0.001
Vent support 36 wks, *n* (%)	11 (4)	9 (26)	< 0.001
Fluid intake, 1st wk[a]	140 mL/k/d (± 18)	147 mL/k/d (± 20)	0.02
Fluid intake, 2nd wk[a]	148 mL/kg/d (± 15)	146 mL/k/d (± 13)	0.4

Abbreviations: BPD, bronchopulmonary dysplasia; CRIB, Clinical Risk Index for Babies; PDA, patent ductus arteriosus; PH, pulmonary hypertension; ROP, retinopathy of prematurity.
[a]Average fluid intake per day for 1st and 2nd week of life.

may be further impaired by the severity of the infant's illness and comorbid conditions.[12] Alternatively, more severe postnatal lung disease may lead to PH. Abnormal gas exchange and increased pulmonary arterial pressure in the lungs may lead to pulmonary artery hypertrophy, increased right-sided heart pressures, and ultimately PH.[11,30]

Higher illness severity, as estimated by CRIB scores, was associated with an increased likelihood of PH development.

Table 4 Multivariable logistic regression analysis of risk factors for PH

	OR (95% CI)	P-value
BPD		
Nonsevere	Reference	0.003
Severe	4.74 (1.68–13.4)	
CRIB	1.24 (1.01–1.52)	0.04
PDA	0.66 (0.19–2.31)	0.515
PDA ligation	0.93 (0.36–2.42)	0.885
ROP	1.11 (0.66–1.85)	0.696
Maternal age	1.06 (0.99–1.13–1.15)	0.088
Gestational age	1.34 (0.86–2.08)	0.2
Birth weight	0.999 (0.996–1.002)	0.387

Abbreviations: BPD, bronchopulmonary dysplasia; CRIB, Clinical Risk Index for Babies; PDA, patent ductus arteriosus; PH, pulmonary hypertension; ROP, retinopathy of prematurity.

This is the first study to demonstrate a relationship between early illness severity as characterized by CRIB scores and the development of PH in extremely premature neonates (►**Table 4**; 1.2-fold increased risk of developing PH in infants with higher CRIB scores; $p = 0.04$). CRIB scores are used as indicators of early illness severity and risk of mortality. They are compiled based on GA, BW, gender, admission temperature, and greatest base deficit in the first 12 hours of life. One may hypothesize that, in addition to GA and BW, initial temperature abnormalities/instability and acidosis may contribute significantly to long-term infant morbidity and mortality. A score of < 10 is generally considered to indicate a less sick infant, whereas scores > 15 are associated with increased mortality.[31] As our non-PH group had a mean score of 10.7 versus the PH group with an average score of 13.3, one can envision how a CRIB score of greater than 11 may be used as an indicator for a higher likelihood of developing PH. CRIB scores have recently been shown to be superior to other illness severity scores including the Score for Neonatal Acute Physiology (SNAP)[32]; they have demonstrated a greater ability to discriminate illness severity, possess good predictive value, and are less time intensive to compile.[33,34] SNAP scores have recently been reported to be associated with BPD or death. However, as CRIB scores are based on 5 parameters versus 28 parameters used in calculating SNAP scores, CRIB scores are more likely to be utilized in the clinical arena because of the ease of calculation.[35]

On the basis of our findings of a positive correlation between CRIB scores and PH development, we propose that CRIB scores may be used as an early screening tool for future PH development as they can be calculated on the first day of life. Currently, BPD is diagnosed after a chronological age of 28 days for mild BPD and 36 weeks' postconceptual age for moderate-to-severe BPD. With the early identification of preterm infants at the greatest risk of developing PH, targeted interventions can be provided earlier to the "at risk" population, thus improving short- and long-term health outcomes.

Infants with growth restriction have previously been reported to be at risk for the development of both BPD and PH. Mechanisms for this association may be related to poor overall growth in these infants leading to incomplete alveolarization and pulmonary vascular development. African American mothers, even after controlling for risk status, are 2.6 times more likely to give birth to SGA infants compared with their White counterparts.[16] Overall, 49% of our cohort was African American. However, we did not observe a significant association between growth restriction and the development of PH (►**Table 1**; $p = 0.09$). This may be related to the relatively small numbers of SGA infants in the study (49 SGA subjects, 22/49 African American); however, these findings warrant further exploration in a larger cohort.

There are several limitations to our study. The retrospective nature of this study may predispose our findings to being impacted by various confounders and bias. As this is a single center study, our patient population, primarily underserved and racially diverse, may not reflect the patient characteristics seen elsewhere. Although our sample size of 303 infants is robust, some of the trends that we observed may have achieved significance if the sample size was larger. In addition, the absence of a correlation between various prematurity-related comorbidities and BPD-associated PH may be related to the fact that the study was not powered to detect differences for these variables. Finally, during the study period, all infants born at less than 28 weeks' gestation did not have screening echocardiograms to evaluate for BPD-associated PH. However, the eligible infants who did not have screening echocardiograms at 36 weeks' corrected GA were low-risk infants with low CRIB scores for whom the attending neonatologist deemed screening for PH not of high utility. Thus, the exclusion of these infants should not affect the predictive value of the high CRIB score. At the conclusion of this study, we have since instituted standardized PH screening guidelines in our unit. Our screening guidelines are indicated for infants born at < 30 weeks' gestation or those infants diagnosed with BPD at 28 days of life. These infants

have a screening echocardiogram at 6 weeks' chronological age and if PH is diagnosed at this time, therapeutic measures such as adjusting respiratory support or oxygen saturation targets when appropriate, and institution of diuretic therapy are undertaken. Patients with diagnosed PH at 28 days of life are routinely screened with echocardiograms every 2 weeks, or earlier if clinically indicated. If PH is not diagnosed, then routine screening echocardiograms are obtained every 4 weeks until the infant is in room air and PH is not present.

In conclusion, after controlling for potential confounding factors, severe BPD and higher CRIB scores were associated with an increased likelihood of development of PH. We speculate that CRIB scores may represent a reliable and quantifiable screening tool for early identification of infants most at risk of developing PH that may allow for possible interventions to prevent its development or progression.

Authors' Contributions

Dr. Bruno was responsible for the study concept and design, acquisition of the data, analysis, and interpretation of the data, drafting of the article, and critical revision of the article for important intellectual content.

Dr. Meerkov was responsible for acquisition of the data, analysis, and interpretation of the data, drafting of the article, and critical revision of the article for important intellectual content.

Dr. Capone was responsible for acquisition of the data, analysis and interpretation of the data, and critical revision of the article for important intellectual content.

Ms. Vega was responsible for acquisition of the data, critical revision of the article for important intellectual content, and administrative, technical, and material support.

Dr. Sutton was responsible for the study concept and design, analysis and interpretation of the data, and critical revision of the article for important intellectual content.

Dr. Kim was responsible for statistical analysis and interpretation of the data and critical revision of the article for important intellectual content.

Ms. Wang was responsible for statistical analysis and interpretation of the data and critical revision of the article for important intellectual content.

Dr. Fuloria was responsible for the study concept and design, drafting of the article, critical revision of the article for important intellectual content, and study supervision.

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