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ARTICLE

Factors associated with development of early and late pulmonary hypertension in preterm infants with bronchopulmonary dysplasia

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Abstract

Objective To investigate factors associated with development of early and late pulmonary hypertension (E/LPH) in preterm infants with bronchopulmonary dysplasia (BPD).

Study design A retrospective case-control observational study of preterm infants with BPD admitted to a level IV referral neonatal intensive care unit over 5 years. We compared pre- and postnatal characteristics between infants with or without BPD-associated EPH and LPH.

Results Fifty-nine out of 220 infants (26.8%) had LPH, while 85 out of 193 neonates (44%) had EPH. On multiple logistic regression, novel factors associated with development of BPD–LPH included presence of maternal diabetes, EPH, tracheostomy, tracheitis, intraventricular hemorrhage (IVH, grade ≥3) and systemic steroid use. For EPH, these were maternal diabetes, IVH grade ≥3, high frequency ventilator use, and absence of maternal antibiotics use.

Conclusion We identified novel factors and confirmed previously established factors with development of LPH and EPH, which can help develop a screening strategy in BPD patients.

Introduction

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy in the United States with an incidence of over 30% in extremely preterm infants, resulting in 10,000–15,000 new cases annually in the United States [1]. Prenatal steroids, gentle ventilation techniques, as well as exogenous surfactant have increased survival rates in preterm infants and decreased the severity of lung injury [2]. Over the last two decades, while survival rates of extremely low birth weight (ELBW) infants has steadily improved, the number of patients with BPD has remained the same or even increased [3, 4]. BPD is associated with increased mortality, poor neurodevelopmental outcome, and long-term respiratory complications in survivors [4–6].

Among the cardiovascular sequelae, pulmonary hypertension (PH) contributes significantly to the high morbidity and mortality in BPD patients. Vascular remodeling, reduced alveolar–capillary surface area, altered distribution of vessels, and abnormal vascular tone and reactivity result in an increase in pulmonary vascular resistance (PVR) [7]. Increased PVR leads to increased pulmonary arterial pressure and subsequently right ventricular (RV) hypertrophy and RV failure. There have been multiple retrospective and prospective studies which have recognized various risk factors for the development of PH in infants with BPD such as LBW, small for gestational age (SGA), duration of mechanical ventilation, use of high frequency ventilation, longer duration of antibiotics, surgical closure of patent ductus arteriosus and severe BPD [8–12]. However some of these studies used a limited number of perinatal factors to seek association with the development of PH. There have been limited studies to find the factors associated with Early PH (EPH) and also the relationship of EPH with Late PH (LPH) and BPD [9, 13–15]. We conducted a retrospective case-control observational study on a fairly large sample size to investigate the association of multiple perinatal factors using standardized

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definitions for development of EPH and LPH using defined echocardiographic criteria in preterm infants with BPD. We used a comprehensive list of pre- and postnatal variables with the goal of a detailed analysis of all potential risk factors contributing to E/LPH. In addition, we investigated the relationship between EPH and LPH, with the aim of an earlier detection of BPD–LPH for a potential future utility of an improved therapeutic approach to identify and manage BPD–LPH to decrease morbidity/mortality in these infants.

Material and methods

Study design

This study was approved by the Institutional Review Board at St. Christopher's Hospital for Children in Philadelphia, PA and Drexel University College of Medicine, Philadelphia PA. The study population was a retrospective, observational cohort of patients at St. Christopher's Hospital for Children (SCHC) from January 2012 to December 2016. SCHC is an academic, urban hospital in Philadelphia, PA, USA with a 39-bed level IV neonatal intensive care unit (NICU), which has around 300 admissions a year referred from adjacent level I, II and III NICUs as well as from emergency rooms. Infants <32 weeks gestational age (GA) at birth, and with a birth weight (BW) of <1500 g were identified using electronic medical records. Patients were excluded if they died <28 day of life (DOL), medical records were missing or if they had multiple anomalies/aneuploidy, congenital heart disease (CHD, other than atrial septal defect (ASD), ventricular septal defect (VSD), or PDA), or congenital lung disease.

Definitions

Bronchopulmonary dysplasia

The BPD consensus definition for infants with GA <32 weeks was used to categorize and classify our patient population [16], i.e., treatment with oxygen for at least 28 days with categorization into the following three subgroups at 36 weeks' postmenstrual age (PMA): (1) mild (breathing room air); (2) moderate (need for a <0.3 fraction of inspired oxygen (FiO_2)), and (3) severe (need for ≥0.3 FiO_2 and/or positive pressure support). Infants with BPD who died of respiratory causes before the assessment date (i.e., after 28 DOL and before 36 weeks PMA) were included in the analysis and considered to have "severe disease" [17, 18].

Pulmonary hypertension (PH)

The primary outcome was Late PH (LPH), defined as PH diagnosed ≥28 DOL, while we divided Early PH (EPH) in three categories. (1) EPH I: PH diagnosed ≤7 DOL, (2) EPH II: PH diagnosed ≤14 DOL and (3) EPH III: PH diagnosed <28 DOL. PH was defined based on the following echocardiogram criteria [10, 19]: (1) RV systolic pressure (SP) >40 mmHg; (2) RVSP/systemic systolic blood pressure ratio >0.5; (3) Any VSD or PDA with bidirectional or right-to-left shunting; (4) If no tricuspid regurgitation (TR) jet or shunt present then two out of following three criteria: (a) Any degree of interventricular septal flattening; (b) RV dilatation; (c) RV hypertrophy. As per our NICU protocol, all the echocardiograms in NICU are transthoracic complete echocardiograms (CEs) with color doppler unless specified by a neonatologist or a cardiologist to be a limited echocardiogram to look for specific pathology. As part of our NICU protocol, which was implemented in July 2015, CEs to screen for PH are performed at corrected 36 weeks PMA and interpreted by pediatric cardiologists for the patients who are diagnosed with any stage of BPD.

Echocardiographic variables

Interpretation of all the CEs performed on the infants were reviewed by the study team. Directionality of the shunt through an ASD, patent foramen ovale (PFO), VSD, or PDA was entered as (1) left-to-right (2) right-to-left or (3) bidirectional. Right ventricular dilatation, hypertrophy, septal flattening, and TR jet were defined as either present or absent. Reported RV pressure and systemic pressures were recorded as numerical. ASDs were categorized as (1) none (2) PFO, (3) PFO vs. ASD or (4) ASD. PDA was defined as (1) none (2) small (3) moderate (4) large as defined by Ramos et al. [20]. Hemodynamically significant PDA was defined as per Zonnenberg et al. [21].

Clinical variables

Data abstracted from the patient's chart included maternal history, prenatal characteristics, intrapartum history, postpartum history, and postnatal NICU course along with multiple complications as shown in Tables 1 and 2. Antenatal diagnoses such as gestational diabetes, intrauterine growth restriction (IUGR), preeclampsia, preterm premature rupture of the membranes (PPROM), and chorioamnionitis were defined as per the American College of Obstetricians and Gynecologists (ACOG) guidelines [22–26]. Maternal diabetes included preexisting as well as gestational diabetes. Maternal antibiotics included any antibiotics given to the mother in the antenatal period except if given for presurgical prophylaxis. Tracheitis was defined as following: (1) absence of clinical or radiographic evidence of pneumonia, AND (2) a positive culture obtained by deep tracheal aspirate or bronchoscopy, AND (3) ≥2 of the following signs or symptoms with no other

Table 1 General characteristics

Characteristics	Total sample ($N = 220$)	
	Number (%)	Median (IQR)
Prenatal characteristics		
Maternal age		26 (15–46)
Antenatal steroid (≥1 dose)	152 (69.1)	
IUGR	23 (10.5)	
Preeclampsia	49 (22.3)	
Maternal diabetes	13 (5.9)	
Oligohydramnios	15 (6.8)	
Tobacco/alcohol use	25 (11.4)	
Substance use	38 (17.3)	
Prolonged ROM (>18 h)	36 (16.4)	
PPROM	58 (26.4)	
Chorioamnionitis	26 (11.8)	
C-section	151 (68.6)	
Postnatal characteristics		
GA at birth (weeks)		25 + 6 (22–31 + 0)
Birth weight (grams)		750 (330–1460)
Sex		
Male	129 (58.6)	
Female	91 (41.4)	
Race		
White	27 (12.3)	
African American	96 (43.6)	
Hispanic	41 (18.6)	
Asian	8 (3.6)	
Other	48 (21.8)	
Small for gestational age	28 (12.7)	
Multiple births	56 (25.5)	
APGAR		
1 min		4 (0–9)
5 min		6.5 (0–9)
10 min		7 (1–10)
Morbidity and mortality		
Death	17 (7.7)	
Tracheostomy	27 (12.3)	
Bacteremia	77 (35.0)	
Tracheitis	88 (40)	
Pneumothorax	21 (9.5)	
IVH (Grade 3–4)	39 (17.7)	
NEC (Any stage)	64 (29.1)	
Gastrostomy-tube	66 (30)	
Hemodynamically significant PDA	109 (49.5)	
PDA- Surgical closure	42 (19.1)	
ROP- laser or avastin use	79 (35.9)	
Bronchopulmonary dysplasia		
Mild	28 (12.7)	
Moderate	21 (9.5)	
Severe	171 (77.7)	
Pulmonary hypertension		
EPH I (≤7 DOL)	62 (43)	
EPH II (≤14 DOL)	72 (40.9)	
EPH III (<28 DOL)	85 (44)	
LPH (>28 DOL)	59 (26.8)	

IQR interquartile range, *IUGR* intrauterine growth retardation, *PPROM* preterm premature rupture of the membranes, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *PDA* patent ductus arteriosus, *C-section* cesarean section, *DOL* day of life, *EPH* early pulmonary hypertension, *LPH* late pulmonary hypertension

recognized cause: temperature >38 or < 36 °C, new or increased sputum production, rhonchi, or wheezing, respiratory distress, apnea, or bradycardia (<100 bpm) [27, 28]. In our NICU, it is usual clinical practice to collect tracheal culture in the presence of any of above symptoms in the absence of pneumonia findings on chest x-ray. It is a routine clinical practice in our NICU to administer tapering doses of dexamethasone for 10 days as per the DART protocol for BPD patients requiring prolonged invasive mechanical ventilation [29]. Bacteremia was defined as any positive blood culture during the NICU stay for the patient. Intraventricular hemorrhage (IVH) was classified as per Papile et al., while periventricular leukomalacia (PVL) was defined as described by Banker et al. [30, 31]. IVH intervention included ventricular reservoir and/or ventriculoperitoneal shunt placements. Modified Bell's criteria were used to classify necrotizing enterocolitis (NEC), while International Classification for Retinopathy of Prematurity was used to diagnose and classify retinopathy of prematurity (ROP) [32, 33].

Descriptive statistics

All data were retrospectively collected using the electronic medical records. Chi-square test was used to assess the association between categorical variables unless the cell frequency was ≤5, in which case the Fisher's exact test was used. Distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous variables were analyzed using independent sample *t*-test, while Mann–Whitney U test was used for non-normal distributions. To determine the effect of all the prenatal and postnatal variables on the outcome of LPH and EPH, binomial logistic regression was used to arrive at odds ratios (OR), and 95% confidence intervals (CI). Adjusted OR

Table 2 Factors associated with development of LPH

Variables	LPH ($N = 59$) *n* (%)	No LPH ($N = 161$) *n* (%)	*P* value	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)
Maternal factors						
Maternal age, mean (SD)	26.2 (5.0)	27.5 (6.5)	0.179	0.966 (0.918–1.016)	0.100	0.956 (0.906–1.009)
Gravida, mean (SD)	3 (1.8)	3.34 (2.2)	0.293	0.922 (0.793–1.073)	0.407	0.935 (0.798–1.096)
Para, mean (SD)	2.2 (1.3)	2.2 (1.3)	0.625	0.943 (0.745–1.1193)	0.969	1.005 (0.782–1.291)
Antenatal steroid (≥1 dose)	45 (76.3)	107 (66.5)	0.165	1.622 (0.819–3.212)	0.411	1.346 (0.662–2.736)
IUGR	9 (15.3)	14 (8.7)	0.164	1.890 (0.771–4.634)	0.693	1.215 (0.462–3.195)
Preeclampsia	15 (25.4)	34 (21.1)	0.497	1.273 (0.634–2.558)	0.668	0.847 (0.397–1.808)
Magnesium sulfate use	35 (59.3)	72 (44.7)	0.056	1.803 (0.984–3.302)	0.150	1.584 (0.846–2.966)
Maternal diabetes	**7 (11.9)**	**6 (3.7)**	**0.031***	**3.478 (1.118–10.817)**	**0.047***	**3.412 (1.016–11.456)**
Oligohydroamnios	4 (6.8)	11 (6.8)	0.989	0.992 (0.303–3.245)	0.670	0.763 (0.220–2.651)
Tobacco/Alcohol use	10 (16.9)	15 (9.3)	0.119	1.986 (0.838–4.709)	0.055	2.441 (0.980–6.081)
Substance use	9 (15.3)	29 (18)	0.632	0.819 (0.362–1.852)	0.551	0.775 (0.335–1.793)
Prolonged ROM (>18 h)	7 (11.9)	29 (18)	0.278	0.613 (0.253–1.485)	0.310	0.626 (0.253–1.547)
PPROM	15 (25.4)	43 (26.7)	0.848	0.936 (0.473–1.851)	0.985	0.993 (0.491–2.007)
Chorioamnionitis	6 (10.2)	20 (12.4)	0.647	0.798 (0.304–2.096)	0.837	0.900 (0.330–2.454)
Maternal antibiotics	21 (35.6)	62 (38.5)	0.77	0.914 (0.499–1.673)	0.784	0.914 (0.480–1.739)
C-section	39 (66.1)	112 (69.6)	0.486	0.802 (0.432–1.491)	0.391	0.748 (0.385–1.453)
Newborn history						
GA at birth, mean (SD)	25 + 4 (11 days)	26 + 0 (12 days)	0.105	0.863 (0.722–1.031)	0.507	1.083 (0.856–1.371)
BW, grams, mean (SD)	**690 (224)**	**807 (206)**	**0.001***	**0.997 (0.996–0.999)**	**0.003***	**0.997 (0.996–0.999)**
Sex (female)	32 (54.2)	59 (36.6)	0.020	2.049 (1.120–3.749)	0.148	1.598 (0.846–3.018)
SGA	**16 (27.1)**	**12 (7.5)**	**0.000***	**4.620 (2.031–10.509)**	**0.042***	**2.703 (1.036–7.057)**
Multiple births	15 (25.4)	41 (25.5)	0.995	0.998 (0.503–1.979)	0.581	1.224 (0.597–2.507)
Delivery room (DR) resuscitation						
Meconium stained amniotic fluid	2 (3.4)	4 (2.5)	0.926	1.072 (0.249–4.625)	0.643	1.414 (0.326–6.138)
1 min, mean (SD)	3.5 (2.1)	3.7 (2.4)	0.139	0.904 (0.792–1.033)	0.297	0.928 (0.806–1.068)
5 min, mean (SD)	5.6 (2.3)	6.5 (2.1)	0.017	0.849 (0.742–0.971)	0.087	0.884 (0.768–1.018)
CPAP in DR	52 (89.7)	150 (93.2)	0.395	0.636 (0.224–1.804)	0.276	0.545 (0.183–1.624)
PPV in DR	54 (91.5)	134 (83.2)	0.129	2.176 (0.796– 5.946)	0.413	1.548 (0.543–4.413)
Intubation in DR	52 (88.1)	123 (76.4)	0.061	2.295 (0.963–5.472)	0.294	1.637 (0.653–4.105)
Surfactant in DR	29 (49.2)	81 (50.6)	0.847	0.943 (0.519–1.713)	0.272	0.695 (0.364–1.329)
NICU course						
Surfactant doses (≥1 dose)	53 (89.8)	134 (83.2)	0.165	1.622 (0.819–3.212)	0.411	1.346 (0.662–2.736)
HFOV use	**51 (86.4)**	**69 (43.4)**	**0.000***	**8.315 (3.704–18.666)**	**0.000***	**7.072 (3.053–16.381)**
PPV use (>30 days)	31 (52.5)	99 (61.5)	0.233	0.693 (0.380–1.265)	0.185	0.655 (0.350–1.225)
NC use (>30 days)	9 (15.3)	28 (17.4)	0.708	0.855 (0.377–1.938)	0.929	1.039 (0.452–2.386)
Mechanical Ventilation (>30 days)	**47 (79.7)**	**84 (52.2)**	**0.000***	**3.590 (1.773–7.268)**	**0.008***	**2.781 (1.302–5.944)**
Tracheostomy	**17 (28.8)**	**10 (6.2)**	**0.000***	**6.112 (2.605–14.338)**	**0.000***	**5.141 (2.105–12.554)**
Caffeine use	56 (94.9)	159 (98.8)	0.118	0.235 (0.038–1.442)	0.106	0.208 (0.031–1.395)
Bacteremia	23 (39)	54 (33.5)	0.454	1.266 (0.683–2.346)	0.812	1.082 (0.566–2.069)
Antibiotic days (>30 days)	**34 (57.6)**	**55 (34.2)**	**0.002***	**2.621 (1.423–4.826)**	**0.019***	**2.177 (1.138–4.166)**
Tracheitis	**33 (55.9)**	**55 (34.2)**	**0.004***	**2.446 (1.331–4.495)**	**0.045***	**1.934 (1.016–3.683)**
Pneumonia	7 (12.1)	14 (8.7)	0.456	1.441 (0.551–3.770)	0.607	1.300 (0.478–3.540)
Pneumothorax	10 (16.9)	11 (6.8)	0.028	2.783 (1.115–6.949)	0.052	2.614 (0.993–6.882)

Table 2 (continued)

Variables	LPH ($N = 59$) n (%)	No LPH ($N = 161$) n (%)	P value	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)
IVH ≥ Grade III	**17 (28.8)**	**22 (13.7)**	**0.011***	**2.557 (1.244–5.259)**	**0.012***	**2.616 (1.235–5.541)**
IVH intervention	4 (6.8)	9 (5.6)	0.741	1.228 (0.364–4.150)	0.597	1.410 (0.395–5.039)
PVL	9 (15.3)	11 (6.8)	0.060	2.455 (0.961–6.267)	0.056	2.578 (0.976–6.811)
NEC	19 (32.2)	45 (28.0)	0.539	1.224 (0.642–2.335)	0.915	0.964 (0.488–1.903)
Intestinal perforation	13 (22)	25 (15.5)	0.260	1.537 (0.727–3.251)	0.615	1.226 (0.555–2.708)
ROP (any stage)	43 (72.9)	97 (60.2)	0.087	1.773 (0.921–3.414)	0.520	1.264 (0.620–2.576)
Laser and/or Avastin	26 (44.1)	53 (33.5)	0.148	1.552 (0.856–2.811)	0.790	1.096 (0.558–2.151)
Gastrostomy-tube	**27 (45.8)**	**39 (24.2)**	**0.002***	**2.639 (1.411–4.938)**	**0.013***	**2.272 (1.187–4.348)**
Hemodynamically significant PDA	31 (52.5)	78 (48.4)	0.591	1.178 (0.648–2.141)	0.787	0.917 (0.487–1.724)
EPH I (≤7 days) ($n = 144$)	20 (51.3)	42 (40.0)	0.226	1.579 (0.754–3.307)	0.097	1.941 (0.886– 4.253)
EPH II (≤14 days) ($n = 176$)	**24 (52.2)**	**48 (36.9)**	**0.072**	**1.864 (0.945–3.676)**	**0.035***	**2.175 (1.056–4.477)**
EPH III* (<28 days) ($n = 193$)	**31 (63.3)**	**54 (37.5)**	**0.002***	**2.870 (1.456–5.619)**	**0.002***	**3.178 (1.554–6.500)**
PDA surgical closure (any)	17 (28.8)	25 (15.5)	0.029	2.202 (1.086–4.464)	0.087	1.897 (0.912–3.946)
BPD (severe)	**56 (94.9)**	**115 (71.4)**	**0.001***	**7.467 (2.225–25.059)**	**0.005***	**5.763 (1.684–19.717)**
Steroid use for BPD (>7 days)	**26 (44.1)**	**22 (13.7)**	**0.000***	**4.978 (2.515–9.855)**	**0.000***	**4.230 (2.085–8.583)**
Death	10 (16.9)	7 (4.3)	0.004	4.490 (1.622–12.426)	0.067	2.729 (0.931–7.999)

BPD bronchopulmonary dysplasia, *LPH* late pulmonary hypertension, *OR* odds ratio, *CI* confidence interval, *IUGR* intrauterine growth retardation, *PPROM* preterm premature rupture of the membranes, *GA* gestational age, *BW* birth weight, *SD* standard deviation, *SGA* small for gestational age, *CPAP* continuous positive airway pressure, *PPV* positive pressure ventilation, *HFOV* high frequency oscillator ventilator, *NC* nasal cannula, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *PDA* patent ductus arteriosus, *EPH* early pulmonary hypertension, *C-section* cesarean section

Bold values indicate statistical significance $p \le 0.05$

were determined by multiple logistic regression, to control for possible confounding effects of other variables. In the multivariate model, LPH (yes or no) and EPH (yes or no) were considered as the dependent variables separately, and all the prenatal and postnatal variables were analyzed as independent variables, which were adjusted for BW and sex as covariates. We also replaced BW with GA, with no major impact in our results. All data were analyzed with SPSS 24.0 for Windows (SPSS Inc, Chicago, IL). All statistical tests were two-tailed, and P values ≤ 0.05 were considered statistically significant. The Hosmer–Lemeshow test was conducted to determine the model's goodness of fit.

Results

Patient selection

As per Figure 1, over a 5-year-period after using inclusion and exclusion criteria, we found 258 patients with BPD, who fit the NIH consensus definition. We had to exclude 38 patients as none of them received any CE ≥ 28 DOL. The median GA at birth was 25 + 6 weeks (range, 22–31 + 0 weeks), and the median BW was 750 g (range, 330–1460 g). Out of 220 patients, 144, 176, and 193 patients had received at least one CE ≤ 7 DOL, ≤ 14 DOL, and < 28 DOL, respectively. So, while analyzing data with EPH I, II, and III, we considered only those patients who received at least one CE in their respective time period. The pre- and postnatal characteristics of the infants studied are presented in Table 1.

Pulmonary hypertension

As the PH screening protocol was implemented in middle of the study period, not all patients included in the study received a screening echocardiogram at 36 weeks of GA. Instead, all 220 patients had at least one CE ≥ 28 DOL. CEs done before 28 DOL were performed for various indications including evaluating for PH, PDA, heart function, as well as to rule out CHD. Being a referral center, patients were admitted at different ages; hence, the total number of CEs received by each patient was different. Median age to diagnose LPH was 37 + 4 adjusted weeks of gestation (range, 26 + 4–73 + 6) and 79 DOL (range, 29–328 DOL). Out of all the LPH cases, 45.8%,

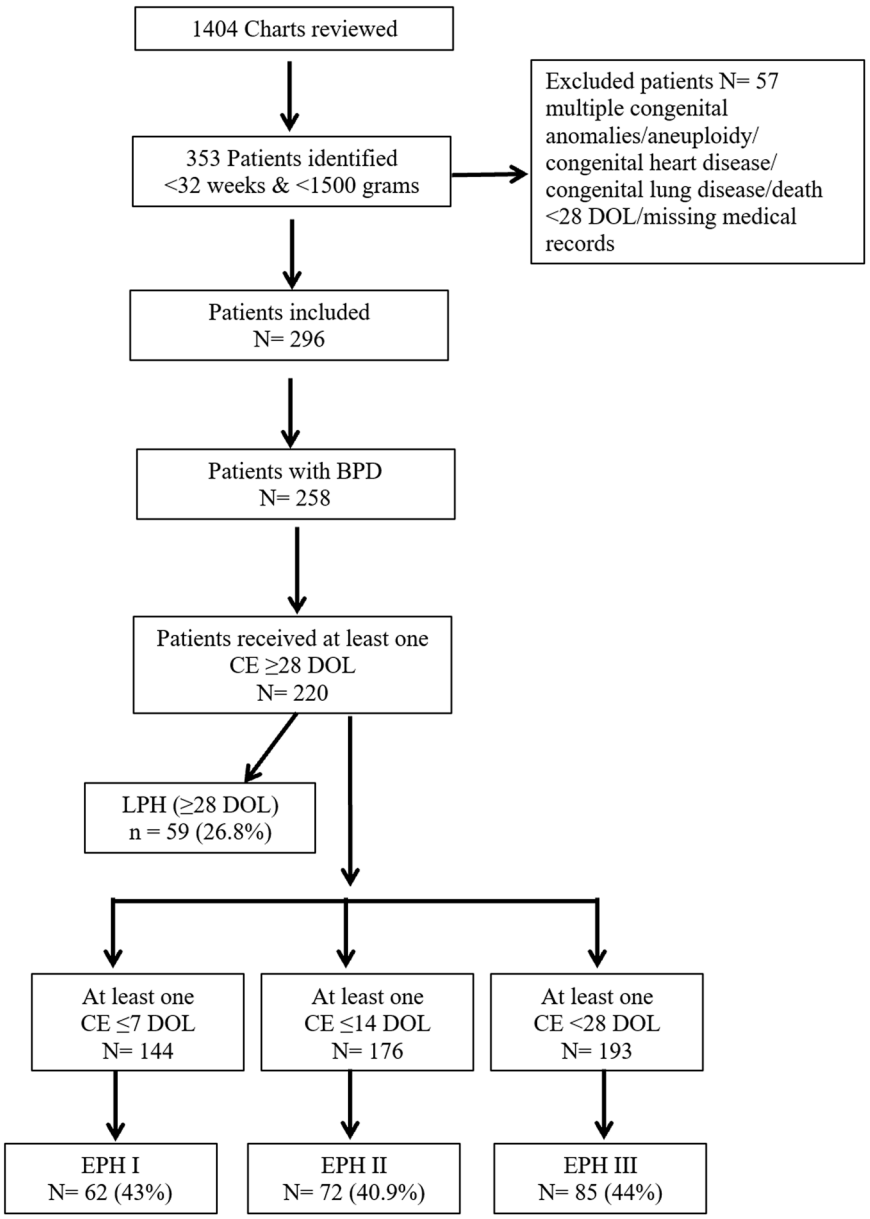

Fig. 1 Flowchart of study patient selection

15.3%, 15.3%, and 23.7% were diagnosed using criteria 1, 2, 3 and 4 respectively, while out of all EPH cases 27.1%, 28.2%, 25.9%, and 18.8% were diagnosed using criteria 1, 2, 3, and 4 respectively. Figure 2 shows the distribution of LPH with the degree of BPD severity.

Factors associated with LPH and EPH II in patients with BPD

Comparison of characteristics between those with or without LPH has been shown in Table 2. Excluding infants who died (i.e., after 28 DOL and before 36 weeks PMA; $n = 6$) did not impact our results. The novel factors associated with development in LPH in our study were maternal diabetes (OR, 95% CI; 3.412, 1.016–11.456), EPH II and III ($p < 0.05$), tracheostomy (5.141, 2.105–12.554), tracheitis (1.934, 1.016–3.683), IVH grade ≥3 (2.616, 1.235–5.541), Gastrostomy-tube (G-tube) placement (2.272, 1.187–4.348), and systemic steroid use for BPD (4.230, 2.085–8.583. Table 3 shows comparison of characteristics between those with or without EPH II. Only 176 out of 220 patients were included as they received at least one CE ≤ 14 DOL.

Association of PDA surgical closure with LPH and BPD

Supplemental Table 1 shows the relationship of different PDA surgical closure timing with development of LPH; we

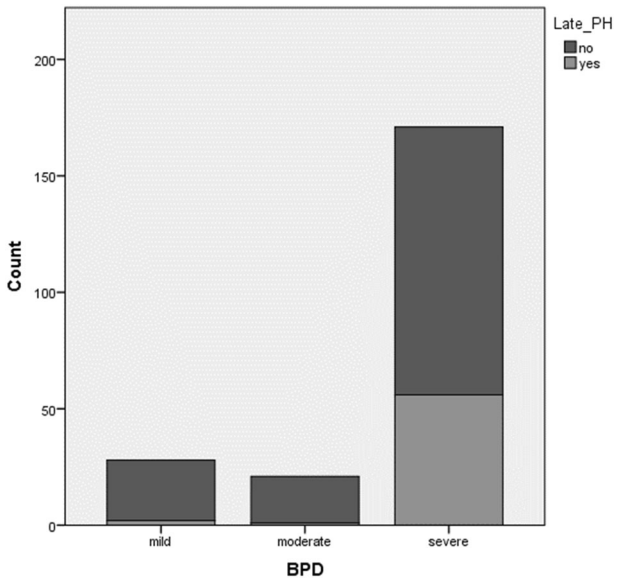

Fig. 2 The development of LPH with the degree of BPD severity

did not find any association of early vs. late surgical closure of PDA with development of LPH in later life.

Discussion

This study was carried out to comprehensively evaluate multiple pre- and postnatal factors that could impact the development of LPH and EPH in infants with BPD. We confirmed several well-known factors [34], and determined several novel factors associated with the development of LPH and EPH in patients with BPD.

Different studies have defined LPH as PH diagnosed after 2, 4, 36 weeks PMA or on final echocardiograms before discharge [9, 13–15, 35]. To qualify for the BPD definition, an infant should require treatment with >0.21 FiO_2 for at least 28 days and then classified at 36 weeks PMA [16]. On that basis, we used the cutoff at 28 DOL to define LPH and EPH. There have been a few studies, which have defined EPH as PH diagnosed within first week, 2 weeks or 4 weeks of life [8, 9, 13–15]. It is possible that different pathways could be at play contributing to the pathogenesis of PH diagnosed during these time periods; hence, we divided EPH in three different categories to see if any of them could predict the development of LPH in BPD patients.

As previously shown, we confirmed several factors associated with development of LPH, including LBW, SGA, high frequency oscillatory ventilation (HFOV), longer use of mechanical ventilation, longer use of antibiotics, and severe BPD [8, 10–12, 36]. However, in contrast to previously described associations, we did not find a significant association with development of LPH with the use of antenatal steroids, IUGR, oligohydramnios, PPROM, modes of resuscitation used in delivery room, APGAR scores, surfactant use, surgical closure of PDA, or multiple gestation [9, 10, 35, 37–39]. A number of reasons could explain the lack of significant association with the factors noted above; among them, the most likely one is probably the differences in our patient/referral population, compared with other studies. In addition, we did not find any difference in incidence of developing LPH with different timing of PDA surgical closure (Supplemental Table 1).

Of note, maternal diabetes appeared to be an independent risk factor for the development of LPH. Out of 13 diabetic mothers, 6 had type II diabetes and 7 had gestational diabetes. To the best of our knowledge, such a relationship between maternal diabetes and LPH has not been previously reported. Maternal diabetes has been associated with persistent pulmonary hypertension in term newborn infants [40]. Recently, it has been proposed that BPD has its origins during fetal life and antenatal events including maternal placental under-perfusion are determining factors of the development of BPD [41–44]. Diabetes can result in endothelial dysfunction and vascular inflammation [45], which might be associated with maternal under-perfusion and in turn be associated with BPD as well as LPH in these infants. As the screening test for gestational diabetes is done from 24 to 28 weeks of GA unless at high risk for diabetes, we might have missed some of the mothers who potentially would have been diagnosed with gestational diabetes later during pregnancy [22].

There might be a different pathogenesis for PH diagnosed within 1, 2 or 4 weeks of life, but interestingly PH diagnosed within 2 and 4 weeks of life (EPH II and III) were significantly associated with development of LPH in preterm infants with BPD in our study.

Surprisingly, when we compared the characteristics from the same dataset to assess the factors associated with EPH II (Table 3), there were a few that overlapped with that of LPH: maternal diabetes, HFOV use and IVH ≥grade 3 and absence of maternal antibiotic use. Most of these factors were consistently associated with EPH I and III. Multiple theories including maternal placental under-perfusion, disruption of normal angiogenesis etc. can be applied to this association. In the clinical setting, early CE < 28 DOL can be very useful for the early identification of preterm infants at high risk for BPD and LPH.

The presence of tracheitis, IVH grade ≥3, G-tube placement, systemic steroid use for BPD, and tracheostomy were additional novel factors in our study. These conditions might be associated with high risk of developing LPH due to the presence and persistence of inflammation in the airway and lung parenchyma, as well as due to severity of illness. Fourteen (82%) out of 17 patients who required tracheostomy were already diagnosed with LPH before

Table 3 Factors associated with development of EPH II

Variable	EPH II ($N = 72$) *n* (%)	No EPH II ($N = 104$) *n* (%)	*P* value	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)
Maternal Factors						
Maternal age, mean (SD)	27 (6.2)	27.3 (5.7)	0.749	0.992 (0.942–1.044)	0.717	0.991 (0.941–1.043)
Gravida, mean (SD)	3.3 (2.4)	3.4 (2.0)	0.889	0.990 (0.861–1.139)	0.769	0.979 (0.849–1.128)
Para, mean (SD)	2.2 (1.2)	2.3 (1.3)	0.440	0.910 (0.715–1.157)	0.335	0.886 (0.694–1.132)
Antenatal steroid (≥1 dose)	46 (63.9)	75 (72.1)	0.248	0.684 (0.359–1.303)	0.295	0.705 (0.366–1.357)
IUGR	10 (13.9)	8 (7.7)	0.188	1.935 (0.724–5.173)	0.104	2.358 (0.839–6.626)
Preeclampsia	17 (23.6)	22 (21.2)	0.700	1.152 (0.561–2.365)	0.550	1.255 (0.596–2.642)
Magnesium sulfate use	36 (50.0)	50 (48.1)	0.802	1.080 (0.592–1.970)	0.714	1.121 (0.610–2.060)
Maternal Diabetes	**7 (9.7)**	**3 (2.9)**	**0.069**	**3.626 (0.905–14.527)**	**0.044***	**4.251 (1.040–17.375)**
Oligohydramnios	4 (5.6)	8 (7.7)	0.582	0.706 (0.204–2.439)	0.726	0.799 (0.227–2.811)
Tobacco/Alcohol use	11 (15.3)	12 (11.5)	0.471	1.383 (0.574–3.332)	0.446	1.417 (0.578–3.471)
Substance use	13 (18.1)	17 (16.3)	0.767	1.128 (0.510–2.495)	0.751	1.138 (0.512–2.526)
Prolonged ROM (>18 h)	8 (11.1)	20 (19.2)	0.152	0.525 (0.217–1.268)	0.160	0.530 (0.219–1.284)
PPROM	18 (25.0)	27 (26.0)	0.886	0.951 (0.477–1.896)	0.887	0.951 (0.475–1.902)
Chorioamnionitis	5 (6.9)	16 (15.4)	0.098	0.410 (0.143–1.177)	0.105	0.415 (0.143–1.203)
Maternal antibiotics	**19 (26.4)**	**45 (43.3)**	**0.023***	**0.470 (0.245–0.902)**	**0.023***	**0.467 (0.243–0.900)**
C-section	51 (70.8)	72 (69.2)	0.820	1.079 (0.560–2.082)	0.810	1.084 (0.559–2.102)
Newborn history						
GA at birth, mean (SD)	26 + 0 (12 days)	25 + 3 (11 days)	0.039	1.216 (1.010–1.464)	0.090	1.232 (0.968–1.569)
BW, grams, mean (SD)	774.1 (226)	728.6 (185)	0.250	1.001 (0.999–1.002)	0.214	1.001 (0.999–1.002)
Sex (female)	31 (43.1)	43 (41.3)	0.821	1.073 (0.584-1.971)	0.597	1.186 (0.631–2.230)
SGA	9 (12.5)	14 (13.5)	0.852	0.918 (0.374–2.252)	0.687	1.235 (0.442–3.453)
Multiple births	15 (20.8)	34 (32.7)	0.087	0.542 (0.269–1.092)	0.058	0.500 (0.244–1.025)
Delivery room (DR) resuscitation						
Meconium stained amniotic fluid	1 (1.4)	4 (3.8)	0.355	0.352 (0.039–3.217)	0.331	0.332 (0.036–3.062)
1 min, mean (SD)	3.9 (2.3)	4 (2.4)	0.794	0.983 (0.863–1.119)	0.631	0.968 (0.849–1.105)
5 min, mean (SD)	6.2 (2.2)	6.2 (2.3)	0.966	0.997 (0.872–1.141)	0.817	0.984 (0.858–1.128)
CPAP in DR	64 (88.9)	95 (92.2)	0.452	0.674 (0.241–1.887)	0.500	0.701 (0.249–1.971)
PPV in DR	62 (86.1)	87 (83.7)	0.657	1.211 (0.520–2.824)	0.501	1.347 (0.565–3.213)
Intubation in DR	60 (83.3)	78 (75.0)	0.189	1.667 (0.778–3.572)	0.066	2.178 (0.948–5.000)
Surfactant in DR	33 (45.8)	54 (52.4)	0.391	0.768 (0.420–1.404)	0.625	0.853 (0.450–1.615)
NICU course						
Surfactant doses (≥1 dose)	65 (90.3)	86 (82.7)	0.162	1.944 (0.766–4.929)	0.131	2.066 (0.806–5.297)
HFOV use	**46 (63.9)**	**52 (50.5)**	**0.080**	**1.735 (0.936–3.215)**	**0.031***	**2.069 (1.068–4.009)**
PPV (>30 days)	40 (55.6)	62 (59.6)	0.592	0.847 (0.461–1.555)	0.710	0.890 (0.481–1.647)
NC (>30 days)	11 (15.3)	17 (16.3)	0.849	0.923 (0.404–2.108)	0.755	0.876 (0.380–2.019)
Mechenical ventilation (>30 days)	45 (62.5)	64 (61.5)	0.897	1.042 (0.561–1.935)	0.549	1.227 (0.629–2.393)
Caffeine use	71 (98.6)	101 (97.1)	0.522	2.109 (0.215–20.689)	0.546	2.021 (0.206–19.881)
Bacteremia	24 (33.3)	42 (40.4)	0.343	0.738 (0.394–1.382)	0.430	0.775 (0.411–1.461)
Antibiotic days (>30 days)	28 (38.9)	47 (45.2)	0.412	0.999 (0.997–1.001)	0.574	0.835 (0.445–1.566)
Tracheitis	26 (36.1)	45 (43.3)	0.342	0.741 (0.400–1.375)	0.516	0.808 (0.425–1.536)
Pneumonia	6 (8.3)	9 (8.7)	0.925	0.949 (0.322–2.796)	0.936	1.047 (0.346–3.166)

Table 3 (continued)

Variable	EPH II ($N = 72$) *n* (%)	No EPH II ($N = 104$) *n* (%)	*P* value	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)
Pneumothorax	4 (5.6)	13 (12.5)	0.315	0.412 (0.129–1.319)	0.154	0.427 (0.133–1.377)
IVH ≥ Grade III	**20 (27.8)**	**12 (11.5)**	**0.007***	**2.949 (1.335–6.513)**	**0.007***	**3.015 (1.358–6.693)**
IVH intervention	4 (5.6)	5 (4.8)	0.825	1.165 (0.302–4.495)	0.865	1.124 (0.290–4.361)
PVL	9 (12.5)	7 (6.7)	0.197	1.980 (0.702–5.586)	0.183	2.037 (0.714–5.808)
NEC	20 (27.8)	33 (31.7)	0.574	0.828 (0.427–1.602)	0.745	0.894 (0.454–1.759)
Intestinal perforation	15 (20.8)	17 (16.3)	0.449	1.347 (0.623–2.910)	0.317	1.500 (0.678–3.316)
ROP (any stage)	48 (66.7)	73 (70.2)	0.620	0.849 (0.445–1.620)	0.904	0.959 (0.485–1.895)
Hemodynamically significant PDA	42 (58.3)	57 (54.8)	0.643	1.154 (0.629–2.119)	0.471	1.258 (0.674–2.350)
PDA surgical closure (any)	15 (20.8)	19 (18.3)	0.672	1.177 (0.553–2.506)	0.621	1.212 (0.565–2.601)
BPD (severe)	58 (80.6)	78 (75.0)	0.388	1.381 (0.663–2.875)	0.230	1.603 (0.742–3.463)

BPD bronchopulmonary dysplasia, *OR* odds ratio, *CI* confidence interval, *IUGR* Intrauterine growth retardation, *PPROM* preterm premature rupture of the membranes, *GA* gestational age, *BW* birth weight, *SD* standard deviation, *SGA* small for gestational age, *CPAP* continuous positive airway pressure, *PPV* positive pressure ventilation, *HFOV* high frequency oscillator ventilator, *NC* nasal cannula, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *PDA* patent ductus arteriosus, *EPH* early pulmonary hypertension, *C-section* cesarean section

Bold values indicate statistical significance $p \leq 0.05$

placement of the tracheostomy tube. This might suggest these infants are at a high risk of having long-term ventilator dependency and so at risk of getting a tracheostomy.

In our cohort, the number of severe BPD patients was slightly higher than many other studies. We attribute this skewness to the severity of illness of patients admitted to the level IV referral based NICU serving most of the underserved population of Philadelphia, PA. Cardiac catheterization has been accepted as the gold standard for diagnosing PH, however it is invasive and is not easily performed in premature neonates, and hence serial echocardiography is recommended as the main tool to screen for PH in BPD patients despite its limitations [46–48]. In our study, the diagnosis of E/LPH was made solely from echocardiography reports read by different pediatric cardiologists, which can cause inter-observer variability. A number of limitations of the BPD definition have been described; however, given its current universal practical value, we chose the NIH consensus definition for our study [49]. Another limitation of our study was that being a retrospective study, we could not control factors such as the consistent timing to get a CE. Despite these limitations, we report some important findings, which could potentially improve the earlier identification and management of premature patients with BPD. The other strengths of our study include the use of standardized definitions and a large sample size of our study cohort. Furthermore, the characteristics of our study population (racial distribution etc.) as well as the management of these infants remained reasonably consistent over the time period at our urban NICU.

Conclusion

Our study identified novel factors and confirmed some of the previously identified factors for development of BPD-associated LPH and EPH. Based on these results, a risk-based scoring system, which would potentially include pre- and postnatal factors, can be formulated to screen for premature infants at risk for BPD and LPH. We propose to have at least one echocardiogram done to screen for PH < 28 DOL in premature neonates requiring respiratory support with $FiO_2 > 0.21$, which can help strategize identification and management of BPD and LPH. Prospective studies are needed to validate this approach.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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