Neurodevelopmental Outcomes of Preterm Infants Born <29 weeks with Bronchopulmonary Dysplasia Associated Pulmonary Hypertension: A Multicenter Study

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Abstract

OBJECTIVE

To determine neurodevelopmental outcomes of preterm infants born at < 29 weeks gestational age (GA) with bronchopulmonary dysplasia and pulmonary hypertension (BPD-PH) at 18 to 24 months corrected age (CA).

STUDY DESIGN:

In this retrospective cohort study, preterm infants born at < 29 weeks GA between January 2016 and December 2019, admitted to level 3 Neonatal Intensive Care Units, who developed BPD and were evaluated at 18–24 months CA in the neonatal follow-up clinics were included. We compared demographic characteristics and neurodevelopmental- outcomes between the two groups: Group I: BPD with PH and Group II: BPD without PH, using univariate and multivariate regression models. The primary outcome was a composite of death or neurodevelopmental impairment (NDI). NDI was defined as any Bayley-III score < 85 on one or more of the cognitive, motor, or language composite scores.

RESULTS

Of 366 eligible infants, 116 (Group I [BPD-PH] = 7, Group II [BPD with no PH] = 109) were lost to follow-up. Of the remaining 250 infants, 51 in Group I and 199 in Group II were followed at 18–24 months CA. Group I and Group II had median (IQR) birth weights of 705 g (325) and 815g (317) [p = 0.003] and median gestational ages (IQR) were 25 weeks (2) and 26 weeks (2) [p = 0.015], respectively. Infants in the BPD-PH group (Group I) were more likely to have mortality or NDI (adjusted Odds Ratio [aOR] 3.63; 95% CI: 1.08–12.27).

CONCLUSION

BPD-PH in infants born at < 29 weeks GA is associated with increased odds of the composite outcome of death or NDI at 18–24 months CA.

Introduction

Bronchopulmonary dysplasia (BPD) is a common and serious problem in extremely premature infants. It is a multifactorial disease in premature infants related to the immaturity of lung structure and function and results from the inflammatory response to multiple iatrogenic interventions during neonatal care. In BPD, lungs are marked by alveolar simplification, variable interstitial fibrosis and vascular hyperplasia in premature infants [1]. The incidence of BPD in infants born at < 29 weeks GA in Canadian NICUs varies between 58%-73% [2, 3]. Early and late BPD complications include prolonged NICU stay, increased

mortality, growth failure, increased respiratory infections, need for home oxygen therapy, pulmonary hypertension (PH), frequent hospital visits, and the risk of hyperactive airway disease and neurodevelopmental impairment (NDI) [4–7]. PH is being increasingly recognized as a life-threatening complication in infants with BPD and increasing severity of BPD, needing complex multidisciplinary care and prolonging hospitalization. PH is estimated to occur in about 25% of infants with moderate to severe BPD [8, 9]. The risk of NDI and mortality due to PH in term infants varies between 18–46% and 14–40% respectively in different cohort studies [10–12]. The European Pediatric Pulmonary Vascular Disease Network (EPPVDN) consensus statement from 2019 recommends screening all infants with BPD at 34–36 weeks by echocardiography to detect PH [13]. Neonatal Intensive Care Units (NICUs) now commonly screen infants with BPD at 34–36 weeks to detect complications such as PH and nephrocalcinosis. Due to their complex neonatal course, these infants are followed up in follow-up clinics to assess neurodevelopmental outcomes. Therefore, we hypothesized BPD-PH might increase the risk of NDI compared to BPD alone. However, few studies with non-systematic follow-up and small sample sizes have reported neurodevelopmental outcomes in preterm infants with BPD-PH [14–16]. The purpose of this study was to determine neurodevelopmental outcomes of infants born at < 29 weeks GA with BPD-PH at 18 to 24 months CA.

Methods

Study Design

This was a retrospective cohort study based out of two-level 3 NICUs at Foothills Hospital in Calgary, Canada, and the University of Texas Medical Branch (UTMB) in Galveston, United States. The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary, and the UTMB Institutional Review Board. Both NICUs implemented a BPD screening program, including a cardiac care pathway to detect PH by echocardiography at 36 weeks postmenstrual age (PMA) in infants with BPD.

Study Population and sample

The study population included all infants born at < 29 weeks GA between January 2016 and December 2019, admitted to the NICUs at Foothills Medical Center in Calgary, Canada, and the University of Texas Medical Branch (UTMB) in Galveston, United States. Neonatal data of these infants were collected retrospectively; however, follow-up data on these infants were collected prospectively at 18–24 months CA. Infants with significant congenital anomalies, complex congenital heart disease and chromosomal disorders were excluded from the study.

Variables and measurement

The exposure variable of interest was PH. Infants were divided into two groups based on the presence of PH: **Group 1**: BPD with PH and **Group II**: BPD with no PH. All premature infants born at < 29 weeks are routinely followed up in the Neonatal follow up clinics (NFC), at both centers, at the ages of four months, eight months, 18–24 months, 36 months, and five years with a multidisciplinary team. Both centers use

the Bayley III for neurodevelopmental assessment at follow-up. From April 2020, routine Bayley assessments were stopped due to the COVID-19 pandemic. To enable ongoing developmental assessments of high-risk neonates, the neonatal follow-up clinics had to rely on the Ages and stages questionnaire version 3 (ASQ 3) as a screening tool. This was followed by tailored assessments in the follow-up clinics for infants identified as having concerns on ASQ 3. ASQ is an easy-to-use tool consisting of a set of questions to be answered by parents, which takes about 15 minutes to answer. ASQ has been studied as a screening tool to identify developmental issues in various populations and has shown modest agreement with other formal methods of neurodevelopmental assessment such as Bayley III and WPSSI [17, 18]. One study reported that the sensitivity, specificity, and correlations between measures improved in children with risk factors such as prematurity and increased age at assessment [18]. We used ASQ 3 scores for ND outcomes as a surrogate marker of NDI, especially in the pandemic period when infants did not have Bayley scores due to virtual follow-up.

Data Source

Standardized demographic, perinatal and neonatal data were collected from patients' medical records and a research coordinator and entered into a computerized neonatal follow-up clinic database upon discharge from the NICU. All surviving premature infants underwent comprehensive developmental assessment by a multidisciplinary team (consisting of a neonatologist or developmental pediatrician, psychologist, occupational therapist, physiotherapist, dietician, speech language pathologist, social worker, nurse, ophthalmologist, audiologist). The Bayley-III was administered at 18–24 months CA by a trained psychologist/psychometrist, audiologist and speech-language pathologist. Members of the multidisciplinary team were not blinded to the infant's neonatal hospital course details, which may introduce the risk of detection bias.

Definition of BPD and PH

Bronchopulmonary dysplasia was defined as oxygen dependency at 36 weeks' postmenstrual age (PMA). Infants with any degree of PH were included in the BPD-PH group. PH was diagnosed at 36 weeks' PMA based on echocardiography features of interventricular septal flattening, right ventricular systolic pressure /systemic systolic blood pressure ratio as measured by tricuspid regurgitation envelope and presence of main pulmonary artery dilation.

Outcome measures

The primary outcome for this study was a composite of mortality or NDI at 18–24 months of CA. Secondary outcomes included individual components (cognitive, language, motor) of the primary outcome, cerebral palsy, visual impairment, and sensorineural or mixed hearing loss.

NDI was defined as a Bayley-III score of < 85 on any one of the components (cognitive, language, motor composite score), and severe NDI defined as a score of < 70 on any one of the components.

Covariates

For infants in both groups, perinatal, birth and neonatal data were extracted from both centers' neonatal follow-up clinics' databases. Perinatal factors included maternal hypertension, maternal diabetes, chorioamnionitis, and antenatal corticosteroids (ANCS). Birth data included gestational age, sex, Apgar scores at 5 minutes and small for gestational age (SGA) status. Neonatal morbidities included respiratory distress syndrome (RDS), duration of mechanical ventilation, blood culture or CSF culture-proven sepsis, patent ductus arteriosus (PDA) and its treatment, necrotizing enterocolitis (NEC) Bell's criteria[19], intraventricular hemorrhage (IVH) grade 3 or higher as defined by Papile classification[20].

Statistical analysis

Maternal and neonatal characteristics and outcomes were compared between the two groups using the Chi-square test or Fisher's exact test for categorical variables and the t-test or Wilcoxon rank sum test for continuous variables. Logistic regression models were used to adjust for confounding variables. Confounders included gestational age at delivery, ANCS, SGA, PDA requiring treatment, chorioamnionitis and NEC. Bootstrap analysis was done to determine the confidence intervals (CI) of the adjusted odd ratio (aOR). Data were analyzed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Post hoc Power Calculations

We used a convenience sample of all eligible infants born in the study period for whom we had data for echocardiography screening for PH. With 58 infants in Group I and 308 in Group II, and 60% of infants with BPD without PH having the primary outcome, we had 80% power to detect a difference as small as 20% between the two groups.

Results

There were 402 neonates born at < 29 weeks GA, during the study period admitted to NICUs (Fig. 1). One hundred and fifty-two infants were excluded from the study [significant congenital anomalies (n = 3), complex congenital heart disease (n = 10), infants with missing screening echo at 36 weeks (n = 23), lost to follow-up (n = 116)]. We had 51 infants in group I and 199 infants in group II included in the analysis. Demographic characteristics, perinatal risk factors and incidence of neonatal morbidity among neonates in the BPD with PH and BPD without PH groups are described in Table 1.

Table 1
Characteristics of the study population

	BPD with PH Group I (n = 52)	BPD with no PH Group II (n = 202)	p-value*
Maternal characteristics			
Maternal age, years, mean (SD)	32 (5)	32 (6)	0.772
Smoking during pregnancy, n (%)	6 (12)	21/197 (11)	0.821
Gestational diabetes, n (%)	8 (16)	13/198 (7)	0.048
Gestational hypertension, n (%)	10 (20)	38 (19)	0.934
Antenatal steroids, n (%)	45 (88)	175 (88)	0.954
Chorioamnionitis, n (%)	5 (10)	31/197 (16)	0.284
Multiple birth, n (%)	13 (25)	60 (30)	0.514
C-section delivery, n (%)	37 (73)	134 (67)	0.475
Neonatal characteristics			
Gestational age, weeks, median (IQR)	25 (2)	26 (2)	0.015
Birth weight, grams, median (IQR)	705 (325)	815 (317)	0.003
Male, n (%)	30 (59)	112 (56)	0.744
SGA < 10th percentile, n (%)	12 (24)	23 (12)	0.028
5-minute Apgar score < 7, n (%)	17 (33)	73 (37)	0.657
RDS, n (%)	50 (98)	188 (94)	0.469
NEC, n (%)	11 (22)	17 (9)	0.009
PDA requiring treatment, n (%)	37 (73)	120 (60)	0.106
IVH Grade ≥ 3, n (%)	5 (10)	19 (10)	> 0.999

*Chi-square or Fisher's exact test for categorical variables, t-test or Wilcoxon rank sum test for continuous variables.

Different variables have different denominators due to missing/unknown values.

Abbreviations:

NEC; necrotizing enterocolitis; PDA; patent ductus arteriosus, RDS; respiratory distress syndrome, ROP; retinopathy of prematurity

	BPD with PH Group I (n = 52)	BPD with no PH Group II (n = 202)	p-value*
ROP Stage ≥ 3 or requiring treatment, n (%)	16 (31)	35 (18)	0.029
Confirmed sepsis, n (%)	8 (16)	26 (13)	0.626
Duration of mechanical ventilation, days, median (IQR)	22 (32)	11 (26)	0.001
Length of stay, days of those who survived to discharge, median (IQR)	122 (47)	104 (39)	0.002
Discharged home on oxygen, n (%)	24/44 (55)	64/198 (32)	0.006
*Chi-square or Fisher's exact test for categorical variables, t-test or Wilcoxon rank sum test for continuous variables.			
Different variables have different denominators due to missing/unknown values.			
Abbreviations:			
NEC; necrotizing enterocolitis; PDA; patent ductus arteriosus, RDS; respiratory distress syndrome, ROP; retinopathy of prematurity			

Maternal characteristics between the two groups were similar except for maternal diabetes, which was significantly higher in the BPD-PH group. Infants in the BPD-PH Group had lower gestational age (median 25 weeks versus 26 weeks) and birth weight and had a higher incidence of SGA, NEC, ROP stage ≥ 3 or needing treatment. Additionally, infants in the BPD-PH group also had a longer duration of mechanical ventilation and prolonged hospital stay (median 122 days versus 104 days) and were more likely to be discharged home on oxygen (55% versus 32%) (Table 1).

Comparison of the neurodevelopmental outcomes at 18–24 months CA between the two groups is shown in Table 2 and Fig. 2. For neurodevelopmental assessment at 18–24 months CA, 130 infants had Bayley III scores, and 67 babies had only ASQ3 scores. Eighty-seven percent of infants in the BPD-PH group had a composite of death, or NDI, compared to 60% in infants with BPD without PH (p = 0.007). Infants with BPD- PH had higher mortality (14% versus 1%) compared to BPD without PH group (p = < 0.001). Infants in group I had a higher proportion of Bayley III language composite score < 85, Bayley III Motor composite score < 85 and any Bayley cognitive, language, motor composite score < 85 scores compared to infants in group II (Fig. 2). The proportion of infants with severe NDI was higher in group I but this was not statistically significant (8/19 (42%) in group I versus 21/87 (24%) in group II, p = 0.112). Group I had a significantly higher proportion of Bayley III motor composite scores < 70 (7/23 (30%) in

group I versus 7/98 (7%) in group II, p = 0.005). There was no difference in the rates of cerebral palsy, visual impairment, or hearing impairment between the two groups (Calgary data only, as data was not available from UTMB).

Table 2
Outcomes at 18–24 months corrected age

	BPD with PH Group I (n = 51)	BPD with no PH Group II (n = 199)	*Adjusted OR (95% CI)	Bootstrap 95% CI†
Death or NDI (based on Bayley scores) n/N (%)	26/30 (87)	60/100 (60)	3.63 (1.08–12.27)	1.29–28.38
Death or any NDI (based on Bayley and ASQ scores) n/N (%)	32/45 (71)	90/152 (59)	1.39 (0.64–3.04)	0.58–3.34
Death before 24 months CGA, n (%)	7 (14)	2 (1)	#	#
Any Bayley cognitive, language, motor composite < 85, n/N (%)	19/23 (83)	58/98 (59)	2.70 (0.79–9.26)	0.97–27.33
Any Bayley score < 85, or any ASQ score below the cut-off, n/N (%)	25/38 (66)	88/150 (59)	1.14 (0.51–2.53)	0.49–2.92
Cerebral palsy, n/N (%)	0/36 (0)	8/173 (5)	#	#
Bayley-III cognitive composite score < 85, n/N (%)	11/24 (46)	32/115 (28)	1.85 (0.68–5.07)	0.54–6.23
Bayley-III language composite score < 85, n/N (%)	13/19 (68)	36/91 (40)	2.79 (0.90–8.70)	0.77–17.88
Bayley-III motor composite score < 85, n/N (%)	14/23 (61)	36/98 (37)	1.73 (0.59–5.05)	0.47–7.98
Visual impairment/blindness, n/N (%)	1/36 (3)	2/173 (1)	#	#
Hearing impairment/deafness, n/N (%)	0/36 (0)	2/173 (1)	#	#

Abbreviations: BPD; bronchopulmonary dysplasia, CGA; corrected gestational age, NDI; neurodevelopmental impairment, PH; pulmonary hypertension

* Adjusted for gestational age, antenatal steroids, small for gestational age, patent ductus arteriosus requiring treatment, chorioamnionitis and necrotizing enterocolitis.

† Percentile method, based on 1000 replications with sampling with replacement.

	BPD with PH Group I (n = 51)	BPD with no PH Group II (n = 199)	*Adjusted OR (95% CI)	Bootstrap 95% CI†
# For other secondary outcomes model could not be fit due to small numbers				
±Any NDI defined as above if Bayley scores available. If Bayley scores are not available, then on ASQ any NDI is defined as ASQ communication, gross motor, fine motor, problem-solving, or personal-social scores categorized as “below the cut-off”. This only applies to Calgary data as UTMB did not have ASQ scores				

Results of multivariate analysis controlling for GA at delivery, antenatal steroids, SGA, PDA requiring treatment, chorioamnionitis and NEC are shown in Table 2. The adjusted odds (aOR) of the primary outcome of death or NDI in-group I was 3.63 (95% confidence interval [CI] 1.08–12.27) when compared to group II.

We compared the demographic characteristic of the study population, and the population lost to follow-up, as shown in Table 3. There was no significant difference in the demographic characteristics between the two groups.

Table 3
Characteristics of infants lost to follow-up and infants included in the study

	Included in the study (n = 250)	Lost to follow-up at 21 months (n = 116)	p-value*
Maternal age, years, mean (SD)	32 (5)	30 (5)	0.076
Gestational age, weeks, median (IQR)	26 (2) Range 22–28	26 (2) Range 23–28	0.903
Birth weight, grams, median (IQR)	789 (325) Range 420–1430	774 (293) Range 505–1230	0.576
Male, n (%)	142 (57)	65 (56)	0.891
SGA < 10th percentile, n (%)	35 (14)	20 (17)	0.419
5-minute Apgar score < 7, n (%)	90 (36)	32 (28)	0.112
*Chi-square or Fisher’s exact test for categorical variables, Mann-Whitney U test for continuous variables. Different variables have different denominators due to missing/unknown values.			

The distribution of severity of BPD in groups I and II is shown in Table 4. BPD-no PH group had 18% mild, 66% moderate and 16% severe cases of BPD. There were no cases of mild BPD, 70% moderate, and 30% severe BPD cases in the BPD-PH group. The proportion of infants with the primary outcome was 63%, 57% and 64% for mild, moderate and severe BPD, respectively, in BPD-no PH group. The proportion of infants with the primary outcome was 0%, 78% and 100% for mild, moderate and severe BPD, respectively, in the BPD-PH group.

Table 4
Incidence and outcome percentages based on severity of BPD

BPD severity	Incidence in BPD with PH Group I	Incidence in BPD with no PH Group II	Primary outcome in BPD with PH Group I	Primary outcome in BPD with no PH Group II
Mild, n/N (%)	0/47 (0%)	34/190(18)	0	15/24 (63)
Moderate, n/N (%)	33/47 (70%)	125/190 (66)	14/18 (78)	33/58 (57)
Severe, n/N (%)	14/47 (30%)	31/190 (16)	9/9 (100)	7/11 (64)

Discussion

Preterm infants with BPD-PH were at increased risk of the composite outcome of death or NDI at 18–24 months CGA. This study has a substantial number of infants with BPD-PH, with structured ND outcome assessments.

The results of our study are consistent with a review on PH in BPD that reported an increased risk of mortality in the BPD-PH group, supporting our study's findings [8]. This systematic review did not address the neurodevelopmental outcome of infants with BPD-PH. However, this finding is in contrast with recent studies on BPD-PH, which found no increased risk of mortality, but small sample sizes limited these studies [14, 15].

Our study observed an increased risk of NDI on univariate analysis in the BPD-PH group. Infants with PH had an increased risk of having any NDI as measured by Bayley III composite score < 85. This was consistent with other studies, who reported increased NDI in infants with BPD-PH [14, 16]. The individual components of Bayley III, specifically the number of infants with language composite score < 85 was significantly higher in the BPD-PH group, which contrasts with the results of the study by Nakanishi et al and Choi et al [14, 16]. Unlike their study, we did not find significant differences in the cognitive scores < 85, but the difference in Bayley III motor scores < 85 was statistically significant. Other studies did not find any differences in the cognitive, language or motor scores between infants with BPD-PH compared to BPD alone [15, 16]. In a multivariate analysis, after adjusting for confounding factors (GA at delivery, antenatal steroids, SGA, PDA requiring treatment, chorioamnionitis and NEC), infants in the BPD-PH

group had increased odds of the composite outcome of death or NDI. Several plausible mechanisms explain the effect of PH on adverse neurodevelopmental outcomes, including increased inflammatory mediators, increased episodes of hypoxia, cardiac dysfunction leading to impaired cerebral perfusion or increased clinical/subclinical infection episodes associated with interventions such as mechanical ventilation [10, 13].

Among factors contributing to increased morbidity in the BPD-PH group, infants in the group I had an increased incidence of NEC and ROP ≥ stage 3. These morbidities have not shown a consistent pattern in previous studies, albeit limited by small numbers in these studies [14–16]. In our study, BPD-PH was associated with increased duration of mechanical ventilation, increased duration of hospitalization and increased home oxygen therapy. Similarly, Nakanishi et al. also reported increased hospitalization and home oxygen therapy duration in their BPD-PH group. In contrast, Choi et al. did not find the increased duration of hospitalization or any difference in respiratory support/ oxygen use. In contrast to other studies, we did not see any increase in the incidence of sepsis in BPD-PH [14–16].

Recent studies have shown a correlation between the severity of BPD and NDI, with severe BPD being associated with a higher incidence of NDI [21, 22]. In this study, we have not assessed the association between severity of BPD and NDI, which was not possible due to a low number of infants with severe BPD in our cohort. However, a higher proportion of infants with the primary outcome was associated with moderate and severe BPD in the BPD-PH group compared to the BPH without PH group.

During the COVID-19 pandemic, we were unable to complete Bayley III testing due to lockdown and restrictions. Therefore, neurodevelopmental outcomes were measured using Bayley III and ASQ scores, and they were not different between groups I and II. Validity studies between ASQ3 and Bayley III have shown a modest correlation in NDI detection. NDI assessment by ASQ3 must be interpreted with caution, considering the imitations of ASQ [18, 23].

The strengths of our study include a large number of infants with BPD-PH and being a multicenter study with standardized neurodevelopmental follow-up assessments. This study has a good follow-up rate despite the COVID-19 pandemic, is about twice the size of the two previous studies, and has a follow-up with multidisciplinary teams that reported on NDI in BPD-PH. The demographic characteristics of the study population lost to follow-up were similar to those and unlikely to affect the study results.

A major limitation was the inability to have Bayley III assessments in all our patients due to COVID-pandemic limitations to follow up, resulting in follow-up being on the virtual platform. In-person follow-up cases were minimal at the start of the pandemic and then opened to infants who, after virtual consults, were deemed to require occupational /physical therapy. At younger ages of 18–24 months, parental perception of developmental delays may be less reliable compared to the older pediatric population [24]. NDI, as assessed by ASQ3, is moderately reliable; however, this can be used in a pandemic situation where Bayley III could not be performed. The risk of detection bias was present as members of the multidisciplinary team were not blinded at the time of assessment.

Conclusion

In conclusion, our study found infants with BPD-PH were at a higher risk of death and/or NDI at 18–24 months of corrected age in infants born at < 29 weeks GA. These infants should be prioritized for closer follow-up and early intervention. The provided information will be helpful in counselling parents while the infants are in the NICU. However, further studies based on the severity of PH may better stratify the risks in this subgroup of infants, better understand the physiological basis for the NDI, and enable changes to clinical practices to optimize outcomes.

Declarations

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ETHICS APPROVAL

The study was approved by the Conjoint Health Research Ethics Board of the University of Calgary, and the University of Texas Medical Branch (UTMB) Institutional Review Board and the need for consent was waived as the study used de-identified data.

AVAILABILITY OF DATA AND MATERIALS

All data will be made available upon request to the corresponding author

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AUTHOR CONTRIBUTIONS

All the authors have contributed to the study design, data acquisition, interpretation of results, reviewing the manuscript and approval of the final version.

Financial disclosure

None

References

1. Jobe AH. Mechanisms of Lung Injury and Bronchopulmonary Dysplasia. Am J Perinatol 2016, **33**(11): 1076–1078.

2. Beltempo M SP, Yoon EW, Chan P, Balachandran N Annual Report 2019, Canadian Neonatal Network. Toronto, Canada; 2020.
3. Lee SK, Ye XY, Singhal N, De La Rue S, Lodha A, Shah PS. Higher altitude and risk of bronchopulmonary dysplasia among preterm infants. Am J Perinatol 2013, **30**(7): 601–606.
4. Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. Semin Perinatol 2006, **30**(4): 227–232.
5. Davidson LM, Berkelhamer SK. Bronchopulmonary Dysplasia: Chronic Lung Disease of Infancy and Long-Term Pulmonary Outcomes. J Clin Med 2017, **6**(1).
6. Jensen EA, Schmidt B. Epidemiology of bronchopulmonary dysplasia. Birth Defects Res A Clin Mol Teratol 2014, **100**(3): 145–157.
7. Lodha A, Sauvé R, Bhandari V, Tang S, Christianson H, Bhandari A, *et al.* Need for supplemental oxygen at discharge in infants with bronchopulmonary dysplasia is not associated with worse neurodevelopmental outcomes at 3 years corrected age. PLoS One 2014, **9**(3): e90843.
8. Al-Ghanem G, Shah P, Thomas S, Banfield L, El Helou S, Fusch C, *et al.* Bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis. J Perinatol 2017, **37**(4): 414–419.
9. Ambalavanan N, Mourani P. Pulmonary hypertension in bronchopulmonary dysplasia. Birth Defects Res A Clin Mol Teratol 2014, **100**(3): 240–246.
10. Lipkin PH, Davidson D, Spivak L, Straube R, Rhines J, Chang CT. Neurodevelopmental and medical outcomes of persistent pulmonary hypertension in term newborns treated with nitric oxide. J Pediatr 2002, **140**(3): 306–310.
11. Marron MJ, Crisafi MA, Driscoll JM, Jr., Wung JT, Driscoll YT, Fay TH, *et al.* Hearing and neurodevelopmental outcome in survivors of persistent pulmonary hypertension of the newborn. Pediatrics 1992, **90**(3): 392–396.
12. Rohana J, Boo NY, Chandran V, Sarvananthan R. Neurodevelopmental outcome of newborns with persistent pulmonary hypertension. Malays J Med Sci 2011, **18**(4): 58–62.
13. Hilgendorff A, Apitz C, Bonnet D, Hansmann G. Pulmonary hypertension associated with acute or chronic lung diseases in the preterm and term neonate and infant. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart 2016, **102 Suppl 2**: ii49-56.
14. Choi EK, Shin SH, Kim EK, Kim HS. Developmental outcomes of preterm infants with bronchopulmonary dysplasia-associated pulmonary hypertension at 18–24 months of corrected age. BMC Pediatr 2019, **19**(1): 26.
15. MacKenzie K, Cunningham K, Thomas S, Mondal T, El Helou S, Shah PS, *et al.* Incidence, risk factors, and outcomes of pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Paediatr Child Health 2020, **25**(4): 222–227.
16. Nakanishi H, Uchiyama A, Kusuda S. Impact of pulmonary hypertension on neurodevelopmental outcome in preterm infants with bronchopulmonary dysplasia: a cohort study. J Perinatol 2016, **36**(10): 890–896.

17. Klamer A, Lando A, Pinborg A, Greisen G. Ages and Stages Questionnaire used to measure cognitive deficit in children born extremely preterm. Acta Paediatr 2005, **94**(9): 1327–1329.
18. Schonhaut L, Armijo I, Schonstedt M, Alvarez J, Cordero M. Validity of the ages and stages questionnaires in term and preterm infants. Pediatrics 2013, **131**(5): e1468-1474.
19. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, *et al.* Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg 1978, **187**(1): 1–7.
20. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978, **92**(4): 529–534.
21. Katz TA, Vliegenthart RJS, Aarnoudse-Moens CSH, Leemhuis AG, Beuger S, Blok GJ, *et al.* Severity of Bronchopulmonary Dysplasia and Neurodevelopmental Outcome at 2 and 5 Years Corrected Age. J Pediatr 2022, **243**: 40–46 e42.
22. Malavolti AM, Bassler D, Arlettaz-Mieth R, Faldella G, Latal B, Natalucci G. Bronchopulmonary dysplasia-impact of severity and timing of diagnosis on neurodevelopment of preterm infants: a retrospective cohort study. BMJ Paediatr Open 2018, **2**(1): e000165.
23. Kwun Y, Park HW, Kim MJ, Lee BS, Kim EA. Validity of the ages and stages questionnaires in Korean compared to Bayley Scales of infant development-II for screening preterm infants at corrected age of 18–24 months for neurodevelopmental delay. J Korean Med Sci 2015, **30**(4): 450–455.
24. Raimundo DS CJ, Vasco J, Viveiros E. 470 Parental assessment on neurodevelopmental outcomes in children born late preterm at 2, 3, 5 and 8 years old. Archives of Disease in Childhood 2021, **106**: A197-198.

Figures

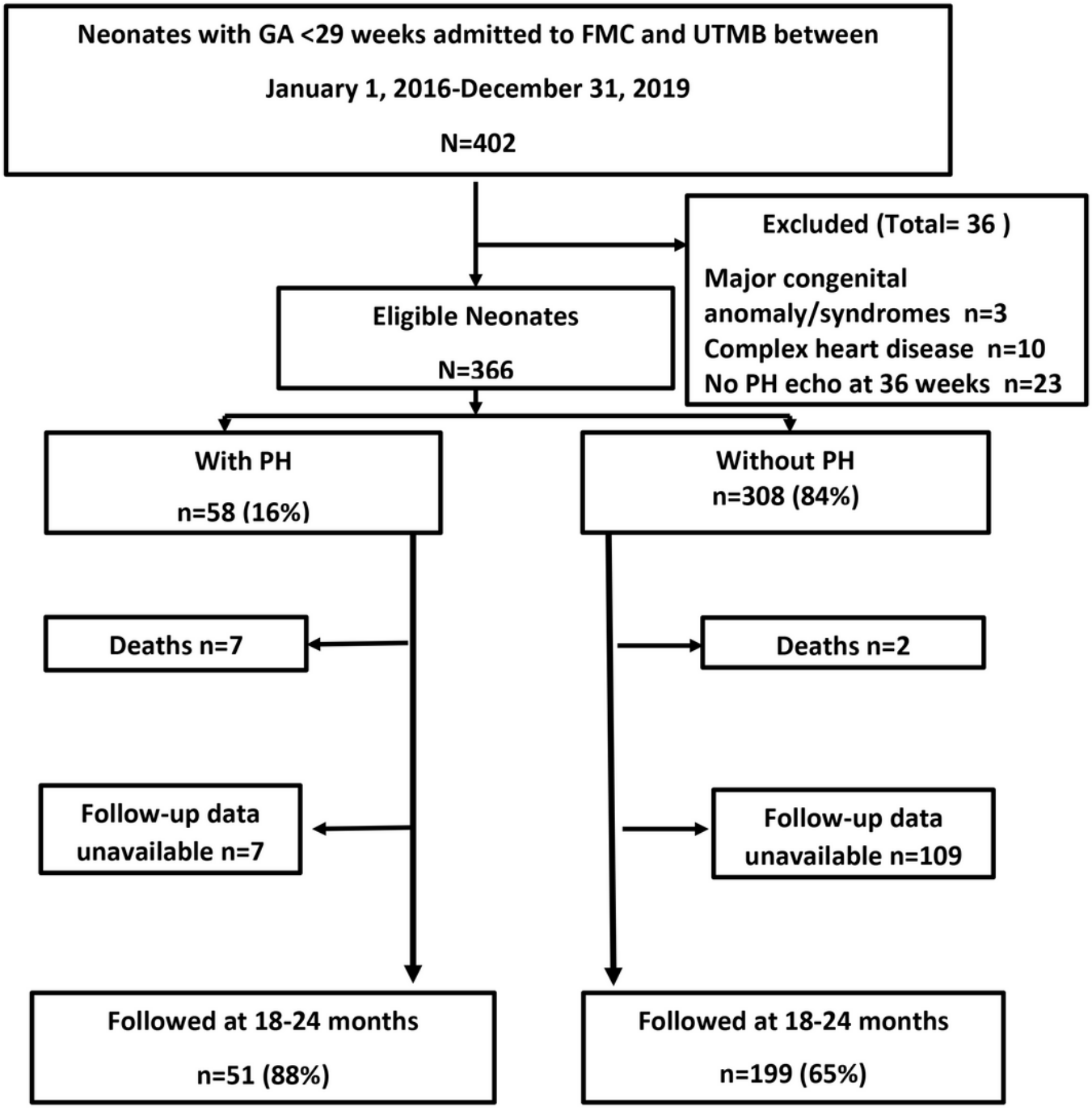

Figure 1

Flow diagram of the study population

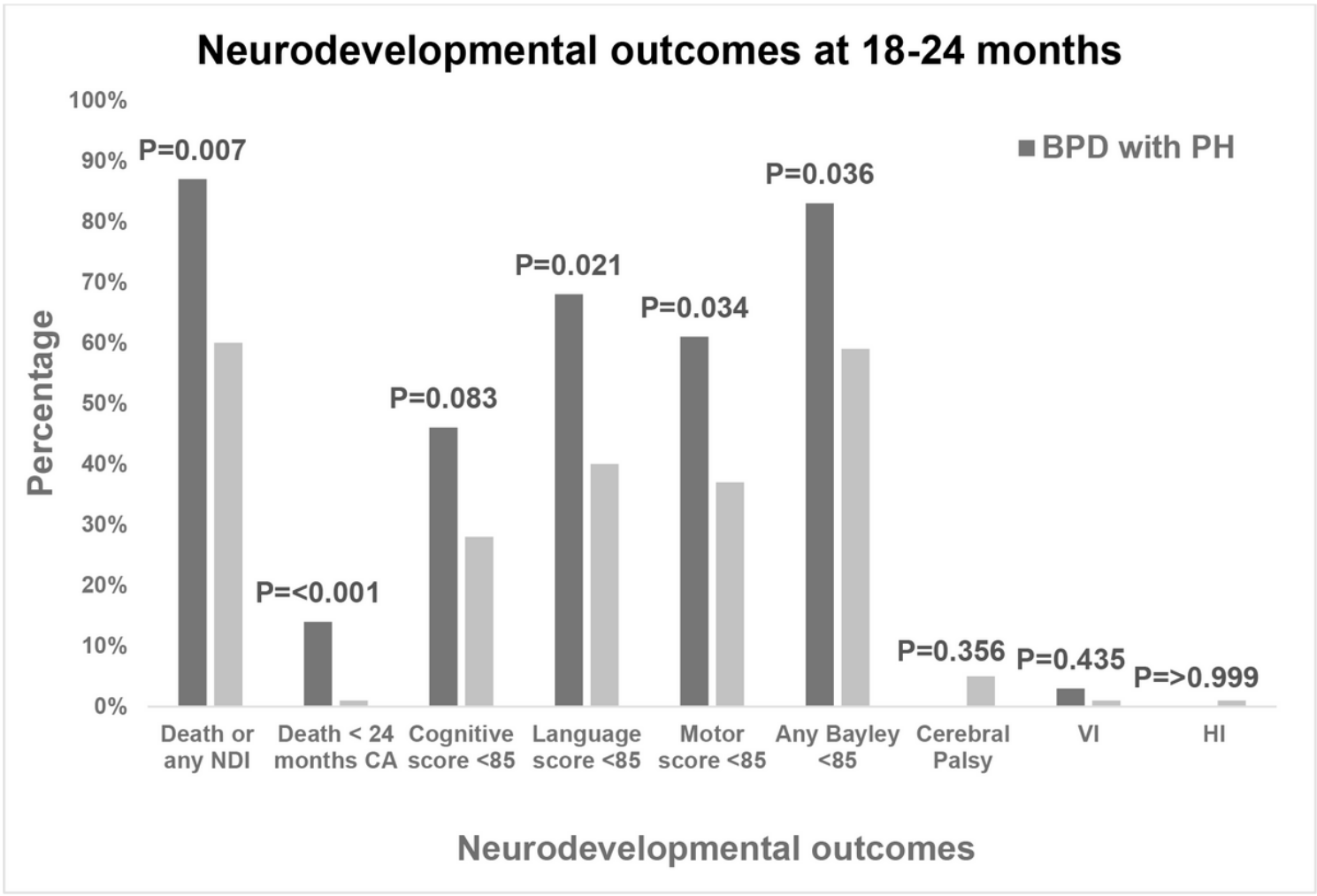

Figure 2

Neurodevelopmental outcomes at 18-24 months corrected age