Original Paper

Two-Year Outcomes in Preterm Infants Suffering from Moderate to Severe Bronchopulmonary Dysplasia with or without Associated Pulmonary Hypertension

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ABSTRACT: Objectives: to assess the impact of pulmonary hypertension (PH) on short and long-term respiratory and neurodevelopmental outcomes in extremely preterm infants, diagnosed with moderate to severe bronchopulmonary dysplasia (MSBPD). Study design: cohort study, with retrospective analysis of the medical records of infants born at ≤32 weeks gestation admitted to a single neonatal tertiary centre from 2010 to 2020. Primary outcome was consistent with hospital re-admissions by 2 years post menstrual age. Neurodevelopment was assessed using Bayley's Scales of Infant and Toddler Development 3rd edition (Bayley-III) as a secondary outcome. Results: 201 infants with no PH and 23 infants with PH were analysed. The PH group showed higher risk for respiratory and paediatric intensive care unit re-admission (65%) during the first 2 years of life (OR: 3.15; 95% CI: 1.28 to 7.78; p<0.5). In contrast to current published literature, our study showed that pulmonary hypertension complicating moderate to severe bronchopulmonary dysplasia had no negative impact on neurodevelopmental outcomes (OR: 1.87; 95% CI: 0.72 to 4.88; p value=0.19). However, in our population, ethnicity, chorioamnionitis and need for persistent ductus arteriosus treatment were all independently associated with poor neurodevelopmental outcomes (p values <0.5). Conclusion: infants with MSBPD associated pulmonary hypertension (MSBPD-PH) are more likely to need intensive care and respiratory hospital re-admissions. Ethnicity, chorioamnionitis and need for ductus arteriosus treatment are independently associated with poor neurodevelopmental outcomes regardless of the pulmonary hypertension status.

KEYWORDS: *Extreme prematurity, pulmonary hypertension, bronchopulmonary dysplasia, 2-years' outcomes.*

Introduction

Pulmonary hypertension in the neonatal population is caused by various and potentially life-threatening cardio-respiratory illness with increased mortality and associated comorbidities. Most of these causes present with respiratory failure due to an acute hypoxic event, which is clinically evident within hours from birth. Others can have a late presentation following a short period of clinical stability known as 'the honeymoon period' [1-2].

However, conditions like bronchopulmonary dysplasia of prematurity display a wide range of clinical variation due to the degree of the gestational age, lung impairment and associated triggers [3-4].

The all too well known 'spiral of death' from acute pulmonary hypertension is characterised by a significant ventilation/oxygenation mismatch, followed by worsening hypoxia, systemic hypotension, and acidosis, thus damaging the cardiac function.

Although there is a fair amount of specialty literature describing the acute settings of pulmonary hypertension, there isn't enough evidence-based medicine available in the current literature providing information on the evolution of chronic pulmonary hypertension, with specific applicability for the extreme preterm infants surviving from MSBPD-PH. We are yet to determine how pulmonary hypertension evolves into early childhood and finally what the known impact on long-term outcomes and subsequent quality of life for these extreme preterm survivors is [6-8].

Specialised follow up clinics for paediatric pulmonary hypertension are available in very few tertiary centres throughout the world-undoubtedly, this has a clear impact in regards of the management and subsequent outcomes of these complex entities [9].

Current data to depict long term outcomes for infants suffering from MSBPD-PH is insufficient, whilst up to 10% of preterm infants are being sent home from the neonatal intensive care unit on oxygen. Nowadays, it is common knowledge that ex premature babies with bronchopulmonary dysplasia have a higher re-admission rate, despite novel management techniques [10-13].

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Nevertheless, the risk of re-hospitalisation within this particular population is very difficult to establish since prematurity comes with its own co-morbidities and further clinical complication that require ongoing specialty management [14].

Understanding this risk would be very helpful for anticipating clinical course and subsequent guidance, managing local resources better and planning future interventions that would hopefully lead to better long-term outcomes.

This is a retrospective study with a 3-stage project, who looked in the 1st instance at the immediate neonatal outcomes in babies with moderate to severe BPD associated PH [15], followed by a 2nd stage of early childhood outcomes up to 2 years of age-that include duration of oxygen need, PICU admissions and need for hospital re-admissions. The 3rd phase was looking at neurodevelopmental outcomes at 2 years of age, in the hope to develop a screening protocol to identify and target the babies at high risk early on.

The objective of this study was to establish if pulmonary hypertension was associated with any risk differences in preterm infants suffering from MSBPD. We were particularly interested in pulmonary and intensive care unit re-admissions to hospital.

Material and Methods

Cohort study, with retrospective analysis of the medical records of infants born at ≤32 weeks gestation diagnosed with MSBPD, admitted to a single centre tertiary neonatal unit from 2010 to 2020. Primary outcome was consistent with hospital re-admissions by 2 years corrected gestational age. Neurodevelopment was assessed using Bayley's Scales of Infant and Toddler Development 3rd edition (Bayley-III) as a secondary outcome.

Clinical data was collected using patient electronic medical records, as well as the UK national data base consistent with Badger Net, which allowed real time access to standardised maternal, neonatal and child records. Data collection included gender, ethnicity, birth weight, presence of maternal illness (such as chorioamnionitis or diabetes mellitus), steroid use (both antenatally and postnatally), mode of ventilation, need for tracheostomy, use of broncho-vasodilators (such as sildenafil or inhaled nitric oxide), patent ductus arteriosus treatment, associated co-morbidities (such as necrotising enterocolitis or grade III/IV intraventricular haemorrhage), as well as need of respiratory support at discharge.

Bronchopulmonary dysplasia severity was classified using the NICHD (United States National Institute of Child Health and Human Development), as well as NHLBI (United States National Heart, Lung, and Blood Institute) regulations. (Table 1) [15].

Table 1. BPD definition criteria.

BPD severity	Criteria
Mild	O2 required ≥28 days, terminated by 36weeks cGA or discharge
Moderate	O2 required ≥28 days, <30% at 36weeks cGA or discharge
Severe	O2 required ≥28 days, ≥30% and/or continuous positive airway pressure or mechanical ventilation at 36weeks cGA or discharge

Neurodevelopmental assessment was evaluated using Bayley-III scale. Cognitive, language and motor delays are defined using the composite score <85 (1 standard deviation below 100 mean).

However, since there was considerable variability among the assessors who performed the Bayley-III evaluation, not all infants had composite or growth z-scores recorded.

Therefore, we proposed for this study, a pragmatic definition that allowed us to divide the infants into two subgroups: moderate and severe neurodevelopmental disability, as shown in Table 2.

Table 2. Disability criteria.

	Moderate Disability	Severe Disability
Motor	Cerebral Palsy GMFCS level 2	Cerebral Palsy GMFCS level 3/4/5
Cognitive	< -2SD to -3SD (DQ 55-70)	< -3DS below norm (DQ <55)
Hearing	Hearing loss corrected with aids (moderate 40-70 dBHL), or Some hearing but loss not corrected by aids (70-90 dBHL)	No useful hearing even with aids (profound > 90 dBHL)
Vision	Moderately reduced vision, or Blind in one eye with good vision in the contralateral eye	Blind, or Can only perceive light or light reflecting objects
Speech and Language	Less than 5 words/signs, or Unable to comprehend un-cued command, but able to comprehend a cued command	No meaningful words/signs, or Unable to comprehend cued command
Respiratory	Limited exercise tolerance	Continuous respiratory support or oxygen
Gastrointestinal	On special diets or has stoma	Requires TPN/NG/PEG feeding
Renal	Impairment needing treatment or special diet	Requires dialysis, or Awaiting organ transplant

Statistical analysis

Patient characteristics were depicted using descriptive statistics. Based on distribution, data were presented as mean±standard deviation (SD), or frequencies with percentages. Correlation between pulmonary hypertension and independent variables was assessed. Anderson-Darling test was carried out to assess the normal distribution of the samples. Because most of the numerical variables showed non-gaussian distributions, we used the nonparametric test Kruskal-Wallis. Proportions were tested using chi-squared test and p values <0.05 were considered statistically significant. Univariate regression was performed to determine the association between PH and adverse outcomes (need for PICU/respiratory hospital re-admissions and disability). Independent association between pulmonary hypertension and outcomes of interest was assessed using logistic regression, with subsequent aim to develop a prediction model.

Results

A total of 268 infants with MSBPD were enrolled in this study. Out of these, 23 patients died and 21 were lost to follow up, with a remaining total number of 224 extreme preterm infants that were followed up to 2 years of corrected gestational age (cGA). All patients had echocardiographic assessment done before 32 weeks post-menstrual age, for pulmonary hypertension, prior to this study: 23 with-and 201 without pulmonary hypertension (Figure 1).

Infants with missing neurodevelopmental assessment and incomplete medical records were excluded (Figure 2).

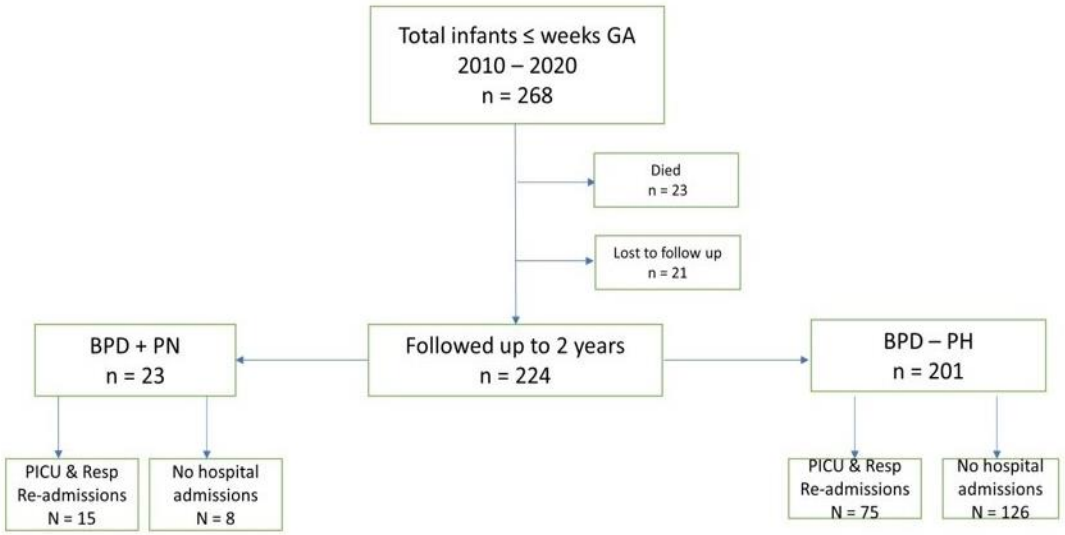

Figure 1. Flow Chart of the study population-respiratory outcomes.

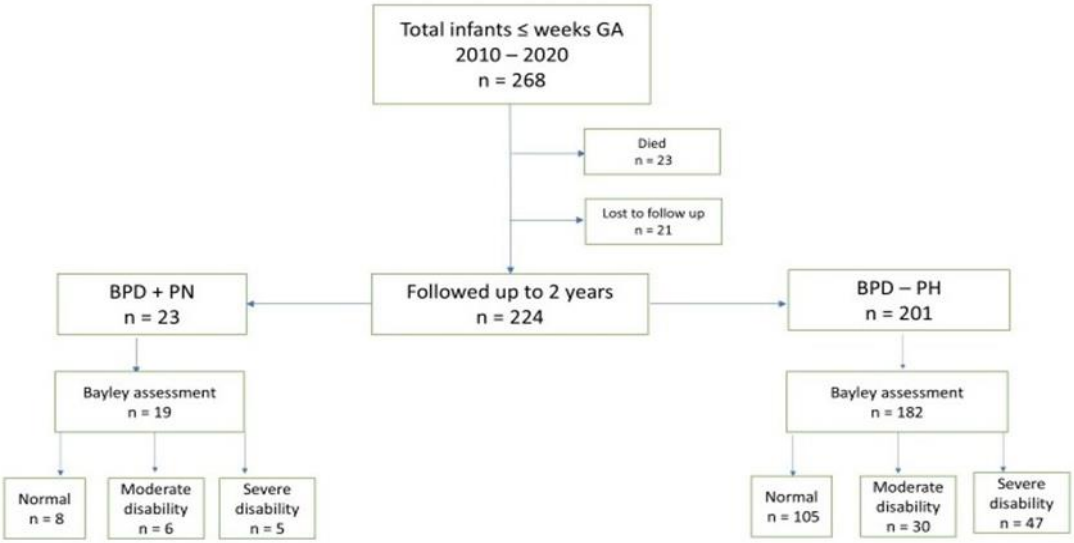

Figure 2. Flow Chart of the study population-disability outcomes.

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Hospital re-admissions

From the non-PH group: 75 infants (37.31%) were re-admitted due to respiratory illness, either onto the general respiratory ward, or to the Paediatric Intensive Care Unit (PICU) for oxygen requirement and/or respiratory support. The PH group had almost the double re-admission rate, with 65.22% (15 patients). Out of these, 7 cases (46.66%) required initial respiratory ward admission, with a subsequent need for escalation of care onto PICU. The presence of pulmonary hypertension in extreme infants diagnosed with moderate-to-severe bronchopulmonary dysplasia was associated with increased hospital re-admissions due to respiratory illness (Figure 3), leading to intensive care (OR: 3.15; 95% CI: 1.28 to 7.78; p=0.0097).

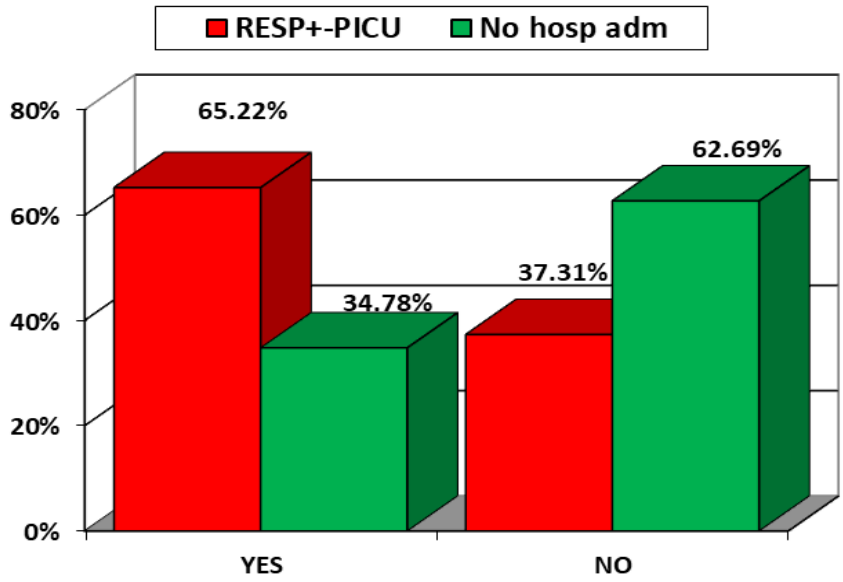

Figure 3. Relationship between initial PH and 2-years hospital admissions.

On univariate analysis, most of the qualitative variables studied within the PH group, were associated with poorer respiratory outcome. Prevalence for the male gender, non-Caucasian ethnicity, growth restriction, chorioamnionitis, use of antenatal steroids and patent ductus arteriosus, as well as associated co-morbidities such as necrotising enterocolitis or grade III/IV intra ventricular haemorrhage had no statistical significance. Babies who required postnatal steroids treatment or those who were on invasive type of ventilation at 36 weeks cGA, were more likely to need hospital re-admissions during the first 2 years of life (Table 3).

We also analysed the differences of the quantitative variables between the three groups (Table 4).

Table 3. Data analysis of respiratory outcomes - qualitative variables.

Variable	No admissions (n=134)	Respiratory admissions (n=60)	PICU admissions (n=30)	p value Chi^2	p value univariate logistic regression
Maternal Diabetes	7.46%	0.00%	0.00%	0.0297	0.9417
DART	20.15%	21.67%	43.33%	0.0238	0.0411
NAVA	3.73%	5.00%	16.67%	0.0224	0.0294
Tracheostomy	0.75%	8.33%	30.00%	< 0,0001	< 0,0001
Sildenafil	2.24%	3.33%	16.67%	0.0022	0.0068
BPD at 36 weeks	9.70%	6.67%	46.67%	< 0,0001	0.0003
Resp support at 36 wks cGA	9.70%	8.33%	46.67%	< 0,0001	0.0002
Resp support at discharge (O_2/NIV/ MV+trahe)	64.18%; 13.43%; 2.99%	66.67%; 6.67%; 6.67%	30.00%; 16.67%; 43.33%	< 0,0001	< 0,0001
Observation PH	5.97%	13.33%	23.33%	0.0119	0.0045

Table 4. Kruskal - Wallis's test of respiratory outcomes.

Variable	No admissions	RESP admissions	PICU admissions	p Kruskall-Wallis
BGA	26.34±1.96	26.24±2.28	25.56±2.00	0.0946
cGA at d/c (wks)	43.12±5.27	45.51±9.33	52.45±9.24	<0.0001
BW (g)	808.07±256.38	791.33±302.98	725.03±162.01	0.1578
Resp support (d)	84.57±45.77	90.18±66.78	149.33±78.38	0.0001
n/c O2 (days)	22.02±17.64	29.02±21.02	20.40±28.60	0.0110

Neurodevelopmental assessment

Of the 23 patients from the PH subgroup, 23 (82.6%) underwent Bayley's assessment at 2 years corrected gestational age, with 5 infants that were lost to follow up. Up to 57.89% (11 infants) had moderate to severe impairment, whilst 8 patients (42.10%) scored a normal assessment.

From the non-PH subgroup (201 infants), less than 10% (19 infants) were lost to follow up. 57.69% (105 cases) had a normal neurodevelopmental assessment by 2 years of cGA, whilst 25.82% (47 cases) had severe disability.

Clinical characteristic and associated co-morbidities of infants are described in Table 5, based on the presence or the absence of PH in infants diagnosed with MSBPD, which permitted to identify the effects of PH.

Table 5. Data analysis of Bayley assessment - qualitative variables.

Variable	Normal assessment (n=113)	Moderate disability (n=36)	Severe disability (n=52)	p Value Chi^2	p value univariate logistic regression
Ethnicity	41.59%	52.78%	61.54%	0.0493	0.0152
Chorioamnionitis	24.78%	30.56%	44.23%	0.0425	0.0161
Tracheostomy	0.00%	2.78%	25.00%	<0.0001	0.0002
PDA treatment	23.89%	50%	38.46%	0.0078	0.0181
BPD at 36 weeks (severe)	4.42%	22.22%	23.08%	0.0005	0.0004
Resp support at 36 wks cGA	5.31%	22.22%	23.08%	0.0013	0.0008
Resp support at discharge (O_2/NIV/ MV+trahe)	66.37%; 10.62%; 0.00%	63.89%; 13.89%; 11.11%	46.15%; 9.62%; 30.77%	<0.0001	<0,0001
2-years readmissions	28.32%	47.22%	59.62%	0.0004	< 0,0001
Observation PH	7.08%	16.67%	9.62%	0.2306	0.3661

According to the univariate analysis conducted on qualitative variables, ethnicity (p=0.0493), chorioamnionitis (p=0.0425), presence of tracheostomy (p<0.0001), need for patent ductus arteriosus treatment (p=0.0078) and need for respiratory support at 36 weeks cGA (p=0.0039) as well as on discharge (p<0.0001), were the clinical characteristics that were statistically significant for poorer neurodevelopmental outcomes.

In contrast to current published literature, within our study group, the presence of pulmonary hypertension was not independently associated with cognitive, language or motor disability (OR: 1.87; 95% CI: 0.72 to 4.88; p value=0.1925). Nevertheless, the presence of moderate-to-severe bronchopulmonary dysplasia at 36 weeks post menstrual age is independently associated with poorer neurodevelopmental outcomes (p=0.0005).

Further analysis was done to find the independent association between quantitative variables and Bayley assessment. We can safely conclude that BGA, cGA at discharge, BW, respiratory support (days) and nasal canulae oxygen (days) have a negative impact with poorer neurodevelopmental outcomes within the PH group (Table 6).

Table 6. Kruskal - Wallis's test of Bayley assessment.

Variable	Normal assessment	Moderate disability	Severe disability	p Kruskall-Wallis
BGA	26.37± 2.00	26.52±2.40	25.43±1.62	0.0122
cGA at d/c (wks)	42.47±5.63	45.18±7.36	50.10±9.45	<0.0001
BW (g)	819.28±264.38	795.94±302.87	742.79±227.35	0.0980
Resp support (d)	75.00±40.83	93.47±67.44	140.44±76.95	< 0.0001
n/c O2 (days)	26.27±17.08	22.14±19.52	18.31±20.26	0.0028

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Logistic regression models for risk of readmission and neurodevelopmental disability

Because the numerical variables were strongly correlated, and "Respiratory support (days)" had the best correlations with all other variables (Table 7), we decided to use only this variable in the logistic regression models we proposed.

Table 7. Correlation matrix (Spearman): for the used numerical variables.

Variables	BGA	cGA at d/c (weeks)	BW(g)	Respiratory support (days)	n/c O2 (days)
BGA		**-0.2104**	**0.5451**	**-0.4849**	**0.2136**
cGA at d/c (weeks)	**-0.2104**		**-0.3258**	**0.6470**	-0.0756
BW(g)	**0.5451**	**-0.3258**		**-0.4096**	**0.1618**
Resp support (days)	**-0.4849**	**0.6470**	**-0.4096**		**-0.4316**
n/c O2 (days)	**0.2136**	-0.0756	**0.1618**	**-0.4316**	

To start with two-years readmissions risk assessment, we used the significant variables in the univariate analysis, and we proposed a model, for which variables had the following levels of significance (Table 8). The accuracy of the first model was 48.26%.

Table 8. Logistic regression variables for two-year readmission, and corresponding significance levels.

Source	DF	Chi-square (Wald)	p Wald
Resp support (days)	1	0.0978	0.7544
DART	1	0.0809	0.7760
NAVA	1	0.2329	0.6294
Tracheostomy	1	6.2096	0.0127
BPD at 36 weeks	1	0.4938	0.4822
Sildenafil	1	4.0068	0.0453
Respiratory support at 36 weeks	1	0.1165	0.7328
Respiratory support at d/c	3	1.9722	0.5782
Observation PH	1	1.8762	0.1708

Since many numerical variables used in the logistic regression model showed p-values grater that 0.05, we decided to remove the ones that are strongly correlated, and we proposed the following model (Table 9).

Table 9. Logistic regression variables, version 2, and corresponding significance levels.

Source	DF	Chi-square (Wald)	P Wald
Resp support (days)	1	1.0457	0.3065
Tracheostomy	1	13.9424	0.0002
Sildenafil	1	5.9261	0.0149
Observation PH	1	2.8397	0.0920

Because this model's accuracy was lower than the original one (46.23%), we decided to take into consideration the possible interactions between the used factors (Table 10), and thus resulting in an improved model, with an accuracy of 49.43%.

Table 10. Logistic regression variables and variable interactions for two-year readmission.

Source	DF	Chi-square (Wald)	P Wald
Resp support (days)	1	0.2566	0.6124
Tracheostomy	1	0.0879	0.7669
Sildenafil	1	0.2315	0.6303
Observation PH	1	0.3768	0.5393
Resp support (days)* Tracheostomy	1	0.2849	0.5934
Resp support (days)*Sildenafil	1	1.4945	0.2215
Resp support (days)*Observation PH	1	0.0113	0.9150
Tracheostomy *Observation PH	1	2.2344	0.1350
Sildenafil*Observation PH	1	0.5117	0.4744

We did a very similar approach for predicting Bayley categories-and used all significant variable in the univariate analysis (Table 11).

The accuracy of the proposed model was 47.24%.

Table 11. Logistic regression variables for Bayley assessment, and corresponding significance levels.

Source	DF	Chi-square (Wald)	p Wald
Resp support (days)	1	3.4446	0.0635
Ethnicity	1	2.2989	0.1295
Chorioamnionitis	1	1.9087	0.1671
Tracheostomy	1	1.4260	0.2324
PDA Tx	3	0.9780	0.8066
BPD at 36 weeks	1	0.00067	0.9793
Respiratory support at 36 weeks	1	0.00069	0.9790
Respiratory support at d/c	3	0.8105	0.8469
PICU&RESP	2	8.4308	0.0148

As it can be seen, many variables that showed significant p-values in the univariate model had much higher p-values in the multivariable model.

As such, because tracheostomy was also included in type of Respiratory support at discharge, and BPD at 36 weeks and Respiratory support at 36 weeks were very similar and almost entirely included in the categories found in Respiratory support at discharge, we decided to exclude those variables in a refined model. The new model had an improved accuracy of 47.88%, and the employed variables had the levels of significance presented in Table 12.

Table 12. Logistic regression variables for Bayley assessment, version 2, and corresponding significance levels.

Source	DF	Chi-square (Wald)	p Wald
Resp support (days)	1	4.2425	0.0394
Ethnicity	1	3.3928	0.0655
Chorioamnionitis	1	1.6570	0.1980
PDA Tx	3	0.6113	0.8938
Respiratory support at d/c	3	3.0126	0.3897
PICU&RESP	2	9.7298	0.0077

Excluding the variables with a p>0,1 and keeping only Respiratory support (days), Ethnicity and Readmission (N/A, RESP/PICU) did not improve the model, resulting in an accuracy of only 46.36%, while taking into consideration all factor interactions created a model with 54.94% accuracy, but too complicated for everyday use.

Discussions

The main finding of our study was that presence of pulmonary hypertension carried an additional negative impact on the short-term prognosis of extreme infants diagnosed with moderate-to-severe bronchopulmonary dysplasia at 36 weeks post menstrual age, and increased risk of hospital re-admissions for escalating need of respiratory care.

In contrast to known literature, in our study, PH status had no negative impact for delayed neurodevelopmental outcome. This may suggest that individual clinical practice within our unit consistent of echocardiographic screening at 32 weeks cGA, active and gradual wean of respiratory support, close clinical monitoring, and multidisciplinary nutritional & respiratory care, may lead to better outcomes within the PH subgroup. Few other studies demonstrated that intra-uterine growth restriction (IUGR) and small for gestational age preterm infants may be at higher risk to develop pulmonary hypertension [16].

Our result lies in contrast with several other published studies. We cannot stipulate on the absence of correlation between IUGR and BPD-PH.

Clinical severity of BPD is well known to be independently associated with increased disability; therefore, would be safe to conclude that the poor neurodevelopmental outcome noticed within our study group is directly linked to the severity of BPD. Furthermore, univariate subgroup analysis demonstrated that severe BPD carries worse outcome in terms of disability (p=0.0033). Within the perinatal factors studied in our population, need for patent ductus arteriosus treatment was independently associated with poorer neurodevelopmental outcomes, suggesting that it may be necessary to select treatment strategies early on.

Our study has limitations. Perhaps the main one is that it was a retrospective study performed in a single centre. Although, other perinatal co-morbidities such as necrotising enterocolitis, sepsis and moderate-to-severe intra ventricular haemorrhage were not identified as additional risk factors for worse outcomes within the PH subgroup, we cannot exclude the role of these factors due to sample size. Overall lost to follow up rate within our study was low (7.8%), although 4 out of 23 patients within the PH group did not have a Bayley's assessment documented, with a higher rate up to 17.4%. This is explained by the independent challenges brought by the SARS-CoV2 pandemics with delays in formal assessments, as well as changes in family dynamics with few cases that were relocated overseas and out of area, leading to missed appointments.

Conclusions

Our study demonstrated that extremely preterm infants suffering from pulmonary hypertension associated with moderate-to-severe bronchopulmonary dysplasia are 3 times more likely to need hospital re-admissions with escalation of care. Ethnicity, chorioamnionitis and need for ductus arteriosus treatment are independently associated with poor neurodevelopmental outcomes regardless of the pulmonary hypertension status. Further prospective studies may illustrate the association between different co-morbidities and adverse neurological outcomes. There is an acute need to design a robust prediction model based on solid risk factors, aiming to predict the development of

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pulmonary hypertension associated with moderate-to-severe bronchopulmonary dysplasia that depicts with accurate sensitivity and specificity value in order to guide critical interventions and thus minimising this new entity's risk. Additional research from multiple centres is required.

Conflict of interest

None to declare

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