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# Respiratory support strategies in the prevention and treatment of bronchopulmonary dysplasia

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# Respiratory support strategies in the prevention and treatment of bronchopulmonary dysplasia

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# Editorial: Respiratory support strategies in the prevention and treatment of BPD: many questions, few answers

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KEYWORDS

bronchopulmonary dysplasia, pulmonary hypertension (PAH), chronic mechanical ventilation, non-invasive respiratory support (NIRS), chronic lung disease of prematurity

Editorial on the Research Topic
Respiratory support strategies in the prevention and treatment of bronchopulmonary dysplasia

With increased survival of premature infants, bronchopulmonary dysplasia (BPD), has become the major cause of chronic lung disease in children. It confers significant morbidity, such as chronic cardiopulmonary insufficiency, growth failure and neurodevelopmental delay, and an increased burden on the health care system and society. Since its first description by Northway and colleagues in 1967 (1), understanding the pathophysiology has allowed us to develop management techniques that should mitigate the development of BPD, but despite this the incidence of BPD has not changed for decades (2). As a mainstay therapy for preterm infants with respiratory insufficiency, there have been a series of advancements in the respiratory management of preterm infants. However, much more needs to be learned about how to apply these therapies to prevent the development of BPD and/or treat infants with established BPD. With this realization, we proposed this research topic and gathered a team of neonatal and pediatric specialists to examine ways to predict, prevent, and manage BPD once developed.

## Can we reliably predict the risk of BPD or BPD-associated pulmonary hypertension?

Given that BPD carries with it significant morbidity in survivors, early recognition allows the clinician opportunity to council families. Many risk factors for the development of BPD have been discovered and explored, some more pertinent than others. Some variables such as small for gestational age (SGA) and birth weight are well known, but they are not the only contributing factors. It is important to take the larger clinical picture into account which, given the number of possible variables, is overwhelming at the bedside. To simplify things for the clinician, Yin et al. provide a predictive model based off seven variables that can be used to calculate the risk of BPD at day 14 of life (Yin et al.). Such models are

useful not only for counseling parents, but also for designing studies to see if early interventions focused on identified risk factors can prevent BPD. In addition to predicting the risk of developing BPD, some morbidities such as BPD associated pulmonary hypertension (BPD-PH), carry a particularly high rate of mortality. Predicting which infants are at high risk of developing BPD-PH is an active area of research, asking such questions as who is at risk of developing BPD-PH, and when and how often should we screen infants at risk of BPD? Local practices and small sample sizes at individual centers make teasing out which variables are important difficult as demonstrated by two of the articles published in this research topic; one which demonstrates the presence of a hemodynamically significant PDA longer than 28 days is a risk factor and another article which showed that surgical closure of a PDA is also a risk (Wang et al., Chang et al.). At first glance these appear to be opposite conclusions surrounding the management of PDAs, but may represent the uncertainty regarding the optimal time for closure of a PDA and are indicative of the challenges facing both bedside clinicians and researchers. Further, most of the research that has been conducted is retrospective in nature and focused on BPD prevention with significantly fewer studies examining what to do once BPD has developed. However, with advancement in chest imaging techniques, combining imaging with clinical characteristics might be helpful in predicting and/or guiding management of infants developing BPD-PH as demonstrated by Yao et al.

## Do we know the best mode of non-invasive respiratory support for BPD prevention?

Mechanical ventilation is a known risk factor for the development of BPD where non-invasive ventilation has been shown to be protective. But beyond these broad categories is there any technique that leads to better outcomes? Is there an ideal mode of non-invasive ventilation in the prevention of BPD? Neither Wu nor Alvila-Alvarez with vastly different studies were able to show that one modality of non-invasive ventilation influenced the development of BPD over another (Avila-Alvarez et al., Song et al.). However, Hysinger and Ahlfeld pointed out in their review that prolonged constant distending pressure might be helpful, especially in extremely preterm infants (Hysinger and Ahlfeld). Given the heterogeneity within patients and multiple risk factors identified, might there be subsets of patients that would respond to different interventions? Close examination of risk factors will inform the design of future studies that will help answer these questions.

## What are the ideal mechanical ventilation strategies for BPD prevention and/or management?

What about infants in whom mechanical ventilation cannot be avoided after birth? In their review, Hysinger and Ahlfeld emphasized the utility of open lung ventilation in avoiding both atelectotrauma and volutrauma with a goal of supporting the cardiopulmonary needs of the extremely preterm infants while minimizing lung injury (Hysinger and Ahlfeld). In addition to existing literature demonstrating the benefit of volume targeted ventilation (3), two newer studies published in this research topic further supported the use of open lung ventilation in BPD prevention. In a retrospective cohort study, Guaman et al. found that the use of volume guarantee ventilation (VGV) is associated with a decreased risk of BPD when compared with pressure-limited ventilation (PLV) (Guaman et al.). In the other retrospective observational study, proactive ventilator adjustment was performed in infants at high risk for death and BPD (Sammour et al.). Through providing adequate PEEP and tidal volume, the team attempted to provide adequate respiratory support so that patient-ventilator synchrony is improved, and air trapping was avoided. This early intervention strategy resulted in a decreased need for tracheostomy and decreased length of stay in their unit. Although retrospective and single center in nature with small sample sizes, the investigators of these studies attempted to address an important topic, that is, how to best handle infants on a ventilator who are "developing" BPD. These investigators also brought up the importance of lung mechanics-based precision ventilator management. Further, Stockard et al. reinforced the concept of precision medicine by demonstrating that pharmacometabolomic profiling may help differentiate infants who may respond to dexamethasone therapy from those who may not (Stockard et al.).

Unfortunately, there are even less high-quality evidence to guide the respiratory management of infants who have already developed BPD. In this research topic, several review articles provided comprehensive reviews of currently available evidence (Hysinger and Ahlfeld, Miller et al., Logan et al.). The authors advocated for a pathophysiological-based ventilator management approach and emphasized that "the consistent provision of adequate support is fundamental" to the management of infants with established and longstanding BPD. Further, Akangire and Manimtim made an effort to address the questions of the indication and timing of tracheostomy placement, timing of liberation and outcomes in infants with severe BPD (Akangire and Manimtim). Their review highlighted significant center variability in both intensive care and out-patient follow-up due to the lack of high-quality evidence.

In summary, many questions remain to be answered and multicenter prospective studies focusing on respiratory support strategies in the prevention and treatment of BPD are needed to guide clinical care and decrease variation in the care of these infants.

## Author contributions

Both HZ and RM edited the manuscripts published in this research topic. They jointly wrote this editorial and both approved the final version of this manuscript.

All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Nasal Intermittent Positive Pressure Ventilation and Bronchopulmonary Dysplasia Among Very Preterm Infants Never Intubated During the First Neonatal Admission: A Multicenter Cohort Study

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**Introduction:** While non-invasive positive-pressure ventilation (NIPPV) is increasingly used as a mode of respiratory support for preterm infants, it remains unclear whether this technique translates into improved respiratory outcomes. We assessed the association between NIPPV use and bronchopulmonary dysplasia (BPD)-free survival in never intubated very preterm infants.

**Methods:** This multicenter cohort study analyzed data from the Spanish Neonatal Network SEN1500 corresponding to preterm infants born at <32 weeks gestational age and <1,500 g and not intubated during first admission. The exposure of interest was use of NIPPV at any time and the main study outcome was survival without moderate-to-severe BPD. Analyses were performed both by patients and by units. Primary and secondary outcomes were compared using multilevel logistic-regression models. The standardized observed-to-expected (O/E) ratio was calculated to classify units by NIPPV utilization and outcome rates were compared among groups.

**Results:** Of the 6,735 infants included, 1,776 (26.4%) received NIPPV during admission and 6,441 (95.6%) survived without moderate-to-severe BPD. After adjusting for confounding variables, NIPPV was not associated with survival without moderate-to-severe BPD (OR 0.84; 95%CI 0.62–1.14). A higher incidence of moderate-to-severe

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BPD-free survival was observed in high- vs. very low-utilization units, but no consistent association was observed between O/E ratio and either primary or secondary outcomes.

**Conclusion:** NIPPV use did not appear to decisively influence the incidence of survival without moderate-to-severe BPD in patients managed exclusively with non-invasive ventilation.

**Keywords: very preterm infants, bronchopulmonary dysplasia, non-invasive ventilation, preterm outcomes, nasal intermittent positive pressure ventilation**

# INTRODUCTION

Avoidance of invasive mechanical ventilation (IMV) is among the highest priorities of modern neonatal care and, globally, infants are managed less-invasively now than decades ago (1, 2). The mainstay of this non-invasive approach is prioritization of initial stabilization with continuous positive airway pressure (CPAP) rather than prophylactic intubation. However, this strategy still fails in a significant proportion of infants and emerging evidence suggests that its incorporation into clinical practice has not significantly improved rates of bronchopulmonary dysplasia (BPD) (2–6).

Efforts to reduce CPAP failure and potentially decrease the incidence of BPD prompted the incorporation of other modes of non-invasive ventilation (NIV). Nasal intermittent positive-pressure ventilation (NIPPV) is a type of NIV that combines intermittent ventilator inflations with CPAP throughout the respiratory cycle. NIPPV can be provided by conventional ventilators or bi-level CPAP devices, and the intermittent inflations may or may not be synchronized with the infant's spontaneous breathing (7). This technique has become popular in some countries and is widely used with different indications (8–11).

Available evidence suggests that the incidence of respiratory failure and the need for intubation is reduced significantly by NIPPV vs. CPAP when used for primary respiratory support (12–15). Whether this translates into improved in-hospital respiratory outcomes is less clear, since the majority of individual studies and meta-analyses report little or no effect on BPD rates (13, 16). Most studies comparing CPAP and NIPPV include infants who were intubated at some point during neonatal admission (before, after, or in between periods of NIV). Those periods of IMV may have modified the risk of chronic respiratory morbidity. However, in current neonatal medicine many preterm babies are stabilized with NIV and are never intubated, or are only briefly intubated for surfactant administration (1).

The present study investigated the association between the use of NIPPV and BPD-free survival in very preterm infants managed non-invasively. We hypothesized that the use of NIPPV would increase the probability of BPD-free survival.

# MATERIALS AND METHODS

## Study Design and Population

This multicenter cohort study is a retrospective analysis of data collected prospectively from infants who were born with a birth weight <1,500 g and/or at <32 weeks gestational age (GA), and were admitted to centers of the SEN1500 network. For this study, we selected patients born between $23^{0/7}$ and $31^{6/7}$ weeks GA who were managed exclusively with NIV. Outborn patients, infants who died in the delivery room (DR), and those with major congenital anomalies, as well as infants from units with intermittent data input, were excluded from the analysis, as were patients who did not receive any type of respiratory support. The study period was from January 2010 to December 2019.

## Outcome Variables and Definitions

The exposure of interest was NIPPV (synchronized and non-synchronized, bilevel and ventilator-delivered) at any time during the neonatal intensive care unit (NICU) stay. Infants were classified into two groups: the study group comprised patients who received NIPPV at any time during admission, while the control group consisted of patients managed only with CPAP and/or high flow nasal cannula (HFNC).

The primary outcome was survival without moderate-to-severe BPD until discharge from hospital. Secondary outcomes were survival without BPD, survival, BPD, gastrointestinal perforation, necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), pneumothorax, intraventricular hemorrhage (IVH), and home oxygen. BPD was defined as the need for supplementary oxygen for at least 28 days and classified as moderate or severe depending on oxygen requirements and ventilator support at 36 weeks postmenstrual age (17, 18).

## Statistical Analysis

Data are presented as the mean ± standard deviation or n (%). Basal and demographic characteristics, as well as interventions and predefined outcomes, were compared between the study and control group. For univariate analyses the Student *t*-test and Mann-Whitney *U* test were used for continuous variables and the Chi-squared test or Fisher exact test for categorical variables, as appropriate.

The odds ratio (OR) for the primary and secondary outcomes were then compared between groups by two different multilevel logistic-regression models, one adjusted only for GA (model 1) and another adjusted for pre-defined confounding variables: GA, sex, small for GA (SGA), prenatal steroids, multiple gestation, and surfactant (model 2). A multilevel approach, including hospital identifier as a random effect, was considered to account for clustering of patients within hospitals. The adjusted OR with corresponding 95% confidence interval (CI) were calculated.

In addition to the analysis by individual patients, an analysis by units was performed. To this end, unadjusted rates of NIPPV use were calculated per unit (i.e., proportion of patients that received NIPPV at some point). Given that units assist children with different demographic and perinatal characteristics, and clinical management also differs between units, an expected rate of NIPPV utilization was calculated for each hospital by a logistic regression analysis adjusting for confounding variables. The results from this model were used to calculate the probability of receiving NIPPV for each newborn. The expected rate of NIPPV utilization for each hospital was then computed by averaging the predicted probability for each individual newborn within that hospital. Subsequently, for each unit, the standardized observed-to-expected ratio (O/E) was calculated. Ratios >1 indicate higher-than-average use, while ratios <1 indicate hospitals with lower NIPPV use.

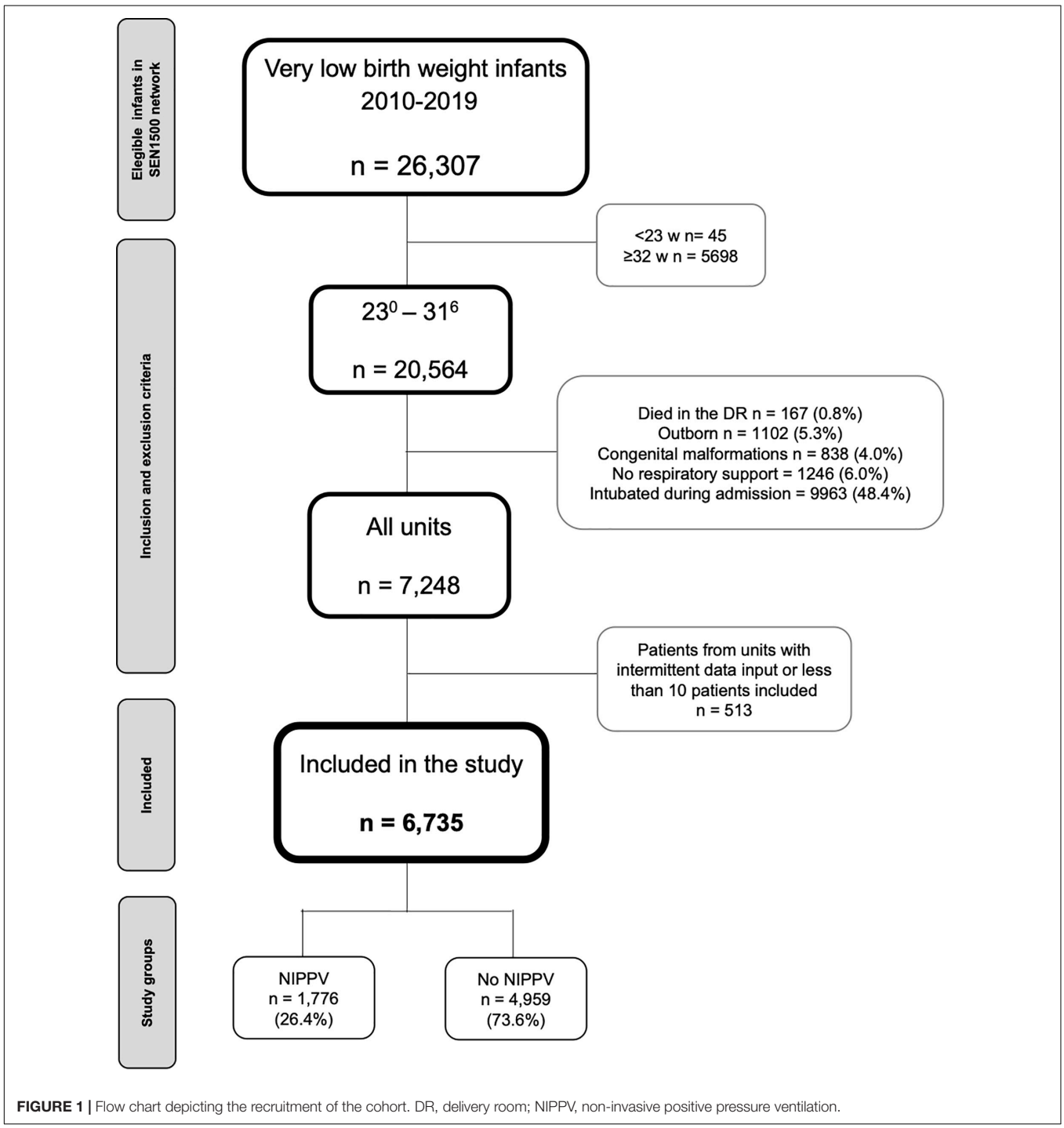


**FIGURE 1 |** Flow chart depicting the recruitment of the cohort. DR, delivery room; NIPPV, non-invasive positive pressure ventilation.

NICUs were classified as very low-, low-, medium- or high-utilization units based on the quartiles of the O/E ratio of NIPPV use, and outcome rates were compared among these groups. To further analyze the relationship between the standardized O/E ratio of NIPPV use and the different outcomes, we applied a flexible simple regression approach. Each of the outcomes was considered as the dependent variable, including the O/E ratio as a continuous independent covariate. To avoid the linearity assumption, the ratio was modeled using cubic b-splines with three degrees of freedom. Finally, a multilevel logistic regression model was established, including the quartiles of the O/E ratio of NIPPV use as an independent factor, adjusting for the same pre-defined confounding variables.

*P*-values $< 0.05$ were considered statistically significant. Statistical analysis was performed with Stata 13.1 (StataCorp, College Station, TX, United States) and R 4.0 statistical software with the libraries *splines* and *lme4* added.

## RESULTS

A total of 26,307 VLBW infants were admitted to participating units during the study period. Of these, 6,735 infants were ultimately included in the analysis after applying exclusion criteria (shown in **Figure 1**). The mean GA and birthweight of the study sample were 29.6 ± 1.5 weeks and 1,175.8 ± 222.9 g, respectively.

In total, 1,776 patients (26.4%) received NIPPV during NICU admission and were designated as the NIPPV group. The remaining patients ($n$ = 4,959, 73.6%) were assigned to the control group. Infants in the NIPPV group had a lower GA and birthweight, and more frequently received supplemental oxygen, CPAP, or NIPPV in DR, and surfactant, HFNC, and steroids during admission (**Table 1**). There were no other significant differences between groups.

In the unadjusted analysis the NIPPV group showed a lower frequency of survival without moderate-to-severe BPD (94.5 vs. 96.0%; $p < 0.001$) and BPD-free survival (81.9 vs. 86.4%; $p < 0.001$) than the control group. Moreover, the incidence of BPD, moderate-to-severe BPD, severe IVH, medically treated PDA, and domiciliary oxygen were higher in the NIPPV than the control group. No significant differences in other secondary outcomes were observed (**Table 2**).

After adjusting for GA (model 1) survival without moderate-to-severe BPD remained inversely associated with NIPPV use (OR 0.68; 95%CI 0.51–0.92). However, after adjusting for prespecified confounding variables (model 2) this association disappeared (OR 0.84; 95%CI 0.62–1.14). Significant associations persisted for other secondary outcomes, such as BPD-free survival, home oxygen, and severe IVH (**Table 2**). These results remained unchanged when focusing in the specific population of infants under 30 weeks GA (**Supplementary Tables 1, 2**).

In the analysis by units, mean observed NIPPV use was 27.7 ± 20.4% (range, 0–89.7%). After applying a logistic regression model and adjusting for potential confounding variables, expected NIPPV rates by unit ranged from 21.8 to 37.9%. Accordingly, the mean O/E ratio was 0.8 ± 0.8 (range, 0–3.5). We observed no significant and consistent association between O/E ratio by units and either primary or secondary outcomes, except for a higher incidence of survival without moderate-to-severe BPD in high-utilization vs. very-low-utilization units (shown in **Table 3** and **Figure 2**).

## DISCUSSION

In this large, retrospective, multicenter, national cohort study we used patient and unit-based approaches to explore the relationship between NIPPV use and BPD among preterm infants that were successfully managed without IMV throughout admission. Our findings show that the use of NIPPV does not appear to decisively improve the probability of survival without BPD.

Non-invasive positive-pressure ventilation is widely used in adults and children with respiratory insufficiency (19, 20). It was first used in neonatology in the 1980s, but the last decade has seen renewed interest in NIPPV in an effort to reduce the frequency of

**TABLE 1 |** Demographic and perinatal characteristics and interventions performed in the delivery room and during the NICU admission in the two study groups.

| | NIPPV $n$ = 1,776 | No NIPPV $n$ = 4,959 | $p$-value |
|---|---|---|---|
| Gestational age (weeks) | 29.1 ± 1.6 | 29.7 ± 1.4 | **<0.001** |
| Distribution by gestational age | | | **<0.001** |
| $23^0$–$25^6$ | 64 (3.6) | 41 (0.8) | |
| $26^0$–$28^6$ | 664 (37.4) | 1,270 (25.6) | |
| $29^0$–$31^6$ | 1,048 (59.0) | 3,648 (73.6) | |
| Birth weight (g) | 1,127.9 ± 235.0 | 1,192.9 ± 215.9 | **<0.001** |
| Female | 871 (49.1) | 2,543 (51.3) | 0.106 |
| Cesarean section | 1,259 (70.9) | 3,511 (70.8) | 0.944 |
| Chorioamnionitis | 346 (19.5) | 820 (16.5) | **0.005** |
| CRIB score | **1.7 (1.9)** | **1.3 (1.4)** | **<0.001** |
| Maternal arterial hypertension | 356 (20.0) | 1,037 (20.9) | 0.439 |
| Multiple birth | 591 (33.3) | 1,727 (34.8) | 0.239 |
| IVF | 424 (23.9) | 1,021 (20.6) | 0.004 |
| SGA | 232 (13.1) | 661 (13.3) | 0.776 |
| Antenatal steroids (at least one dose) | 1,713 (96.7) | 4,720 (95.6) | 0.051 |
| Supplemental oxygen in the DR | 1,307 (73.6) | 3,163 (63.8) | **<0.001** |
| CPAP in the DR | 1,463 (82.4) | 3,688 (74.4) | **<0.001** |
| NIPPV in the DR | 1,016 (57.2) | 2,370 (47.8) | **<0.001** |
| Surfactant (any time) | 524 (29.5) | 736 (14.8) | **<0.001** |
| CPAP during admission | 1,705 (96.0) | 4,884 (98.5) | **<0.001** |
| HFNC during admission | 772 (43.5) | 1,481 (29.9) | **<0.001** |
| Steroids for BPD | 44 (2.5) | 67 (1.4) | **0.001** |
| Steroids for BPD, day of life | 31.8 ± 19.7 | 32.6 ± 15.3 | 0.824 |

*BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; CRIB, clinical risk index for babies; DR, delivery room; HFNC, high flow nasal cannula; IVF, in vitro fertilization; NIPPV, non-invasive positive pressure ventilation; SGA, small for gestational age. Data expressed as the mean ± standard deviation for quantitative variables and n (%) for qualitative variables. Bold indicates statistical significance.*

**TABLE 2 |** Primary and secondary outcomes according to the use of non-invasive positive pressure ventilation (NIPPV).

| | No NIPPV | | NIPPV | | Unadjusted analysis | | Adjusted analysis[a] | | Adjusted analysis[b] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) |
| **Primary outcome:** | | | | | | | | | | |
| Moderate-to-severe BPD-free survival | 4,762 | 96.0% | 1,679 | 94.5% | <0.001 | 0.48 (0.36–0.65) | 0.013 | 0.68 (0.51–0.92) | 0.263 | 0.84 (0.62–1.14) |
| **Secondary outcomes:** | | | | | | | | | | |
| BPD-free survival | 4,286 | 86.4% | 1,454 | 81.9% | <0.001 | 0.42 (0.35–0.50) | <0.001 | 0.67 (0.55–0.81) | 0.049 | 0.81 (0.66–0.99) |
| Survival | 4,933 | 99.5% | 1,769 | 99.6% | 0.500 | 1.33 (0.58–3.07) | 0.077 | 2.17 (0.92–5.12) | 0.046 | 2.40 (1.01–5.68) |
| BPD | 636 | 12.9% | 306 | 17.3% | <0.001 | 2.41 (2.01–2.90) | <0.001 | 1.50 (1.23–1.83) | 0.047 | 1.23 (1.00–1.52) |
| Moderate-to-severe BPD | 172 | 3.5% | 90 | 5.1% | <0.001 | 2.28 (1.68–3.10) | <0.001 | 1.66 (1.21–2.27) | 0.072 | 1.34 (0.97–1.85) |
| Pneumothorax | 30 | 0.6% | 19 | 1.1% | 0.086 | 1.70 (0.93–3.11) | 0.075 | 1.75 (0.95–3.23) | 0.514 | 1.23 (0.66–2.31) |
| Discharged home on oxygen | 65 | 1.3% | 44 | 2.5% | <0.001 | 3.03 (1.92–4.78) | 0.001 | 2.15 (1.35–3.44) | 0.009 | 1.90 (1.18–3.07) |
| Medically treated PDA | 442 | 8.9% | 242 | 13.6% | <0.001 | 1.94 (1.59–2.36) | <0.001 | 1.46 (1.19–1.79) | 0.092 | 1.20 (0.97–1.48) |
| SIP | 20 | 0.4% | 5 | 0.3% | 0.474 | 0.69 (0.25–1.90) | 0.203 | 0.52 (0.19–1.43) | 0.127 | 0.45 (0.16–1.25) |
| Necrotizing enterocolitis | 142 | 2.9% | 63 | 3.5% | 0.213 | 1.24 (0.88–1.75) | 0.547 | 1.11 (0.79–1.58) | 0.812 | 1.04 (0.73–1.49) |
| Intraventricular hemorrhage > II | 77 | 1.6% | 45 | 2.5% | <0.001 | 2.69 (1.73–4.19) | 0.002 | 2.05 (1.30–3.23) | 0.009 | 1.85 (1.17–2.94) |

*Unadjusted and adjusted odds ratios and 95% confidence interval from multilevel logistic regression analysis.*
*CI, confidence interval; OR, odds ratio; NIPPV, non-invasive positive pressure ventilation; SIP, Spontaneous intestinal perforation.*
[a]*Adjusted for gestational age.*
[b]*Adjusted for gestational age, sex, small for gestational age, prenatal steroids, multiple gestation, chorioamnionitis, and surfactant.*

**TABLE 3 |** Primary and secondary outcomes according to the hospital rate of non-invasive positive pressure ventilation (NIPPV).

| | Quartiles of O/E ratio of NIPPV use | | | |
|---|---|---|---|---|
| | Very low-utilization NICUs (O/E ratio ≤ 0.22) | Low-utilization NICUs (O/E ratio 0.23–0.63) | Medium-utilization NICUs (O/E ratio 0.64–1.18) | High-utilization NICUs (O/E ratio ≥ 1.19) |
| No. units | 16 | 16 | 16 | 16 |
| No. patients (%) | 1,404 (20.8%) | 1,437 (21.3%) | 1,713 (25.4%) | 2,181 (32.4%) |
| Observed NIPPV use rate (min-max) | 0–5.4% | 5.6–18.9% | 16.9–29.1% | 30.7–89.7% |
| | OR (95% CI)[a] | OR (95% CI)[a] | OR (95% CI)[a] | OR (95% CI)[a] |
| **Primary outcome:** | | | | |
| Moderate-to-severe BPD free survival | 1 | 1.01 (0.55–1.83) | 1.14 (0.63–2.05) | 2.13 (1.15–3.94) |
| **Secondary outcomes:** | | | | |
| BPD-free survival | 1 | 0.95 (0.50–1.83) | 1.21 (0.64–2.30) | 1.76 (0.92–3.35) |
| Survival | 1 | 1.06 (0.40–2.82) | 1.35 (0.51–3.57) | 2.02 (0.72–5.62) |
| BPD | 1 | 1.06 (0.54–2.07) | 0.83 (0.43–1.61) | 0.57 (0.29–1.10) |
| Moderate-to-severe BPD | 1 | 0.98 (0.49–1.95) | 0.90 (0.46–1.76) | 0.45 (0.22–0.91) |
| Pneumothorax | 1 | 1.77 (0.64–4.92) | 1.63 (0.58–4.60) | 1.68 (0.64–4.45) |
| Discharged home on oxygen | 1 | 0.89 (0.24–3.30) | 0.91 (0.26–3.23) | 0.31 (0.08–1.25) |
| Medically treated PDA | 1 | 0.92 (0.54–1.55) | 0.97 (0.58–1.64) | 0.70 (0.41–1.18) |
| Spontaneous intestinal perforation | 1 | 1.04 (0.31–3.46) | 0.72 (0.20–2.54) | 0.54 (0.14–1.99) |
| Necrotizing enterocolitis | 1 | 0.88 (0.67–1.15) | 0.80 (0.61–1.04) | 0.83 (0.63–1.10) |
| Intraventricular hemorrhage > II | 1 | 1.94 (0.65–5.75) | 1.41 (0.47–4.21) | 1.53 (0.52–4.50) |

*Data represent the adjusted odds ratios and 95% confidence interval from multilevel logistic regression analysis.*
*NICU, neonatal intensive care unit; CI, confidence interval; O/E, observed rate to expected ratio of NIPPV use; OR, odds ratio; NIPPV, non-invasive positive pressure ventilation.*
[a]*Adjusted for gestational age, sex, small for gestational age, prenatal steroids, multiple gestation, chorioamnionitis, and surfactant.*

CPAP failure. A survey of practice in 2008 found that NIPPV was used by 44 of 91 (48%) English neonatal units, with considerable variability (11) and we recently reported increasing use of NIPPV in very preterm infants in Spain (3).

Differences in mode and device terminology, as well as study designs, complicate the interpretation of published evidence on the relationship between NIPPV and BPD. The most relevant data come from trials comparing the efficacy of NIPPV vs. the standard of treatment (i.e., CPAP) in heterogeneous preterm infant populations. The largest randomized controlled trial (RCT) was published in 2013 by Kirpalani et al. (21). The authors randomized 1,009 infants <1,000 g and <30 weeks GA to either

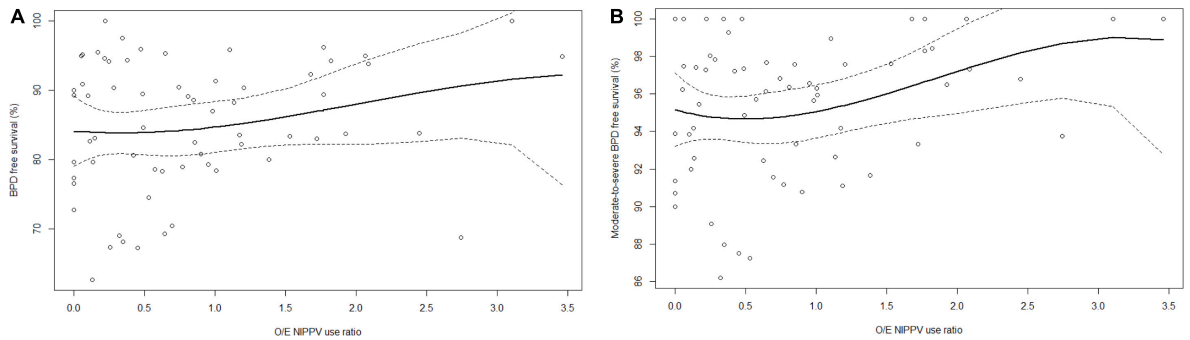


**FIGURE 2 |** Relationships between O/E ratio of NIPPV use and **(A)** BPD and **(B)** survival without moderate-to-severe BPD. Solid line represents fitted flexible regression curve using a cubic b-splines basis with three degrees of freedom. Dashed lines represent 95% confidence intervals.

NIPPV or CPAP whenever NIV was going to be used for the first time. In line with our findings, NIPPV was not associated with a significant reduction in death or BPD.

Since the first trials comparing CPAP and NIPPV and showing promising results (22, 23), some 15 RCTs and several observational studies have specifically evaluated NIPPV as primary respiratory support. While some of these studies reported short-term benefits associated with NIPPV (mainly a reduction in the need for IMV), few differences were observed in the rates of BPD or other relevant outcomes (16, 22–27).

A Cochrane review that included many of the aforementioned RCTs found that, compared with CPAP as a primary mode, NIPPV was associated with a reduced need for intubation, with a relative risk (RR) of 0.78 (95%CI 0.64–0.94) (13), but observed no reduction in BPD risk (RR 0.78, 95%CI 0.58–1.06). As in the present study, that meta-analysis included NIPPV delivered by a ventilator or by bilevel devices, as well as synchronized and non-synchronized modes.

The aforementioned Cochrane review was followed by at least three other meta-analyses. Ekhaguere et al. pooled data from 16 trials and reported findings similar to those of the Cochrane review (14). More recently, a comprehensive network meta-analysis compared the efficacy of four different non-invasive respiratory support modes used as the primary method in preterm infants (12). The authors reported that NIPPV was more effective than CPAP in decreasing the requirement for IMV (RR 0.60; CI 95% 0.44–0.77) and resulted in a slightly lower incidence of BPD or mortality (RR 0.74; CI 95% 0.52–0.98).

The most recent meta-analysis is that of Rüegger et al. which analyzed 18 trials with a total of 1,900 infants, and included data from 8 newly published trials not included in the Cochrane study. Pooled data demonstrated a 37% relative reduction in the risk of respiratory failure and a 28% reduction in BPD at 36 weeks, with no differences in mortality. However, this difference in BPD risk was fully attributable to the studies using ventilator-generating synchronized systems (28).

All these trials included infants that received IMV at some point during their clinical course. Hence, we speculate that the conclusions of those studies may not be generalizable to intubation-naïve infants. To the best of our knowledge, no RCTs have focused specifically on the subset of infants managed only with NIV and never intubated, which constitutes an increasingly common profile in neonatal units (3).

Given the overall uncertainty surrounding published findings on the long-term efficacy of NIPPV, European consensus guidelines stated that there is insufficient evidence to recommend NIPPV as a primary mode of respiratory support for preterm infants (1). Notably, the mechanism of action of NIPPV itself is not yet completely understood and there is little information available to help clinicians optimize NIPPV settings. Some of the benefits seen in adult and children populations (19, 20) may not be replicated in neonatal patients due to anatomical differences, distinct pathophysiological pathways, or the use of different interfaces.

The most likely mechanism accounting for the greater reduction in BPD observed with NIPPV vs. CPAP is avoidance of IMV. However, the pathogenesis of BPD is complex and a single intervention is unlikely to significantly alter its incidence. Our study population did not include patients who failed CPAP and required intubation during admission, and even though we adjusted for the main confounding variables, this may have biased our sample selection by underestimating the BPD rate in the CPAP group. Moreover, infants in the NIPPV group were significantly smaller and probably sicker, which might translate into higher basal risk for BPD. Encouragingly, we observed no significant differences in the incidence of previously reported NIPPV-associated complications, such as gastrointestinal perforation (9). The observed association between NIPPV and both severe intraventricular hemorrhage and domiciliary oxygen in the multivariate analysis are worrisome findings that warrant further study.

The present study has some limitations. The database used did not record data on NIPPV indication, timing, duration, the devices used, synchronization, interfaces, or settings, nor were these parameters standardized in the participating centers. The combination of different devices and techniques in our series could have contributed to the apparent absence of a beneficial effect of NIPPV. However, a previous meta-analysis (13) and a large RCT (21) both used a similarly broad definition of NIPPV technique and indications, an approach that the respective authors considered pragmatic. Limitations inherent

to population-based cohorts, such as inaccuracy in some data, cannot be excluded in this analysis. Strengths of our study include the large size of the sample of non-invasively managed infants, its multicenter nature, and the detailed evaluation of multiple clinical outcomes.

In conclusion, in this large, national-based cohort the use of NIPPV appeared not to decisively influence the incidence of survival without moderate-to-severe BPD in patients managed exclusively with NIV. Differences in the basal risk for BPD between groups and the better outcomes in high NIPPV-utilization units may show that NIPPV could in fact be protective. Uncertainty thus remains as to NIPPV efficacy in the context of longer-term outcomes. In our opinion, more data on the indications, settings, and physiological basis for NIPPV are needed before this approach can be considered as standard of treatment.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by A Coruña-Ferrol Research Ethics Committee (Ref 2017/360, first author institution). Primary data collection was approved by the local ethics research committees of the participating centers when they joined the SEN1500 Network. This study protocol has no specific ethical approval as it only gathers anonymized data. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

AA-A developed the research idea. AA-A, FG-MR, and CZ designed the protocol and requested the data. AA-A and SP-D analyzed the data. AA-A wrote the initial draft of the manuscript, which was critically revised by FG-MR, CZ, MSL, SP-D, DE, GS-G, and MI-S. All authors contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.896331/full#supplementary-material

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# Pharmacometabolomics Profiling of Preterm Infants Validates Patterns of Metabolism Associated With Response to Dexamethasone Treatment for Bronchopulmonary Dysplasia

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Bronchopulmonary dysplasia (BPD) is one of the most common health complications of premature birth. Corticosteroids are commonly used for treatment of BPD, but their use is challenging due to variability in treatment response. Previous pharmacometabolomics study has established patterns of metabolite levels with response to dexamethasone. We obtained additional patient samples for metabolomics analysis to find associations between the metabolome and dexamethasone response in a validation cohort. A total of 14 infants provided 15 plasma and 12 urine samples. The measure of treatment response was the calculated change in respiratory severity score (deltaRSS) from pre-to-post treatment. Each metabolite was assessed with paired analysis of pre and post-treatment samples using Wilcoxon signed rank test. Correlation analysis was conducted between deltaRSS and pre-to-post change in metabolite level. Paired association analysis identified 20 plasma and 26 urine metabolites with significant level difference comparing pre to post treatment samples ($p < 0.05$). 4 plasma and 4 urine metabolites were also significant in the original study. Pre-to-post treatment change in metabolite analysis identified 4 plasma and 8 urine metabolites significantly associated with deltaRSS ($p < 0.05$). Change in urine citrulline levels showed a similar correlation pattern with deltaRSS in the first study, with increasing level associated with improved drug response. These results help validate the first major findings from pharmacometabolomics of BPD including key metabolites within the urea cycle and trans-4-hydroxyproline as a potential marker for lung injury. Ultimately, this study furthers our understanding of the mechanisms of steroid response in BPD patients and helps to design future targeted metabolomics studies in this patient population.

**Keywords: pharmacometabolomics, neonatology, pulmonology, dexamethasone, pharmacology**

## INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a lung disease occurring in preterm infants resulting from lung structure immaturity, ventilator-associated lung injury and inflammation. In the US, BPD is one of the most common complications of premature birth with approximately 18,000 infants impacted annually (1). This accounts for approximately 25% of infants with birth weight lower than 1,500 g (2–4). Despite the high rate of occurrence in the preterm infant population, there is no FDA approved treatment indicated for BPD. Corticosteroids are commonly used for prevention or management of BPD symptoms. Dexamethasone is a glucocorticoid that is used primarily for its anti-inflammatory and immunosuppressant effects. In cases of bronchopulmonary dysplasia, dexamethasone helps facilitate weaning from the ventilator. Common side effects of dexamethasone in pre-term infants can include hyperglycemia, hypertension, and GI bleeding/perforation. Unfortunately, there are a number of difficulties associated with corticosteroid use in preterm infants. This can include interpatient variability in treatment response and clinical effects. Compounding this variability in treatment response, there are no predictive factors that can help determine which patients will respond to treatment.

The growing field of pharmacometabolomics has emerged as a powerful method for furthering the understanding of mechanisms contributing to variability in drug response for many different fields of medicine. The patient metabolome can be measured at both pretreatment and post-treatment periods of care. Ideally, the metabolome measured pretreatment and a difference in the metabolome measured post-treatment, can help illustrate the metabolic mechanisms of variable drug response. These metabolome baseline measurements and changes could potentially serve as signatures for predicting drug response and be used clinically to help determine the likelihood of drug response prior to treatment or early in the treatment course. Furthermore, if these metabolome changes can be replicated in multiple studies, the evidence for a mechanistic relationship between metabolism and drug response is strengthened, and the potential for a predictive metabolic signature of drug response is further supported.

We previously conducted a pharmacometabolomics study on a pilot cohort of preterm infants less than 32 weeks gestation at birth who received dexamethasone treatment for BPD (5). Our results showed metabolites with a significant difference in abundance when comparing pretreatment to post-treatment metabolite levels. In order to validate the

**TABLE 1 |** Demographics and respiratory data.

| **Discovery cohort data** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Patient #** | **GA (weeks)** | **BW (g)** | **Race** | **DOL steroid started** | **Pre-RSS** | **Post-RSS** | **deltaRSS** | **Plasma sample** | **Urine sample** |
| Median | 25 0/7 | 663 | – | 36 | 6.48 | 2.6 | –2.3 | – | – |
| IQR | 24 2/7-26 0/7 | 465–790 | – | 27–115 | 4.29–9.02 | 1.86–3.21 | –5.32 to –1.79 | – | – |
| **Replication cohort data** | | | | | | | | | |
| **Patient #** | **GA (weeks)** | **BW (g)** | **Race** | **DOL steroid started** | **Pre-RSS** | **Post-RSS** | **deltaRSS** | **Plasma sample** | **Urine sample** |
| 11 | 25 3/7 | 704 | AA | 17 | 10.32 | 2.84 | –7.48 | X | – |
| 12 | 24 3/7 | 1,000 | WH | 18 | 6.02 | 3.66 | –2.36 | X | X |
| 13 | 29 3/7 | 1,330 | WH | 27 | 10.8 | 11.5 | 0.7 | X | X |
| 14 | 24 1/7 | 510 | WH | 49 | 15 | 3.7 | –11.3 | X | U |
| 15 | 25 3/7 | 840 | AA | 158 | 5.7 | 3.37 | –2.33 | X | X |
| 16 | 25 3/7 | 510 | AA | 40 | 14.08 | 3.69 | –11.11 | X | X |
| 17 | 25 0/7 | 820 | O | 29 | 11.76 | 2.76 | –9 | X | X |
| 17-2 | 25 0/7 | 820 | O | 61 | 7.7 | 2.1 | –5.6 | X | U |
| 18 | 25 2/7 | 879 | WH | 25 | 5.17 | 2.5 | –2.67 | X | X |
| 20 | 23 1/7 | 580 | AA | 15 | 5.28 | 6.54 | 1.26 | – | X |
| 21 | 24 6/7 | 660 | WH | 24 | 7.56 | 5.27 | –2.29 | X | – |
| 22 | 24 6/7 | 970 | WH | 41 | 6.6 | 2.8 | –3.8 | X | X |
| 23 | 24 2/7 | 765 | WH | 30 | 6.24 | 7.16 | 0.92 | X | X |
| 23-2 | 24 2/7 | 765 | WH | 104 | 5.48 | 8.54 | 3.06 | X | X |
| 24 | 24 1/7 | 680 | AA | 29 | 7.95 | 3.29 | –4.66 | X | X |
| 25 | 26 2/7 | 1,090 | WH | 88 | 3.57 | 0.5 (NC) | –3.07 | X | X |
| ***T*-test** | | | | | | | | | |
| *p*-value | 0.7027 | 0.3512 | – | 0.3441 | 0.2572 | 0.1580 | 0.9837 | – | – |

*AA, African American; BW, birthweight; DOL steroid, day of life (age) when infant started steroids; GA, gestational age at birth; IQR, interquartile range; NC, Nasal Canula; O, Other; RSS, Respiratory Severity Score; U, Post treatment samples unavailable; WH, white. Negative deltaRSS indicates improved lung function.*
**T-test comparing demographics and baseline data between discovery and validation cohorts.*

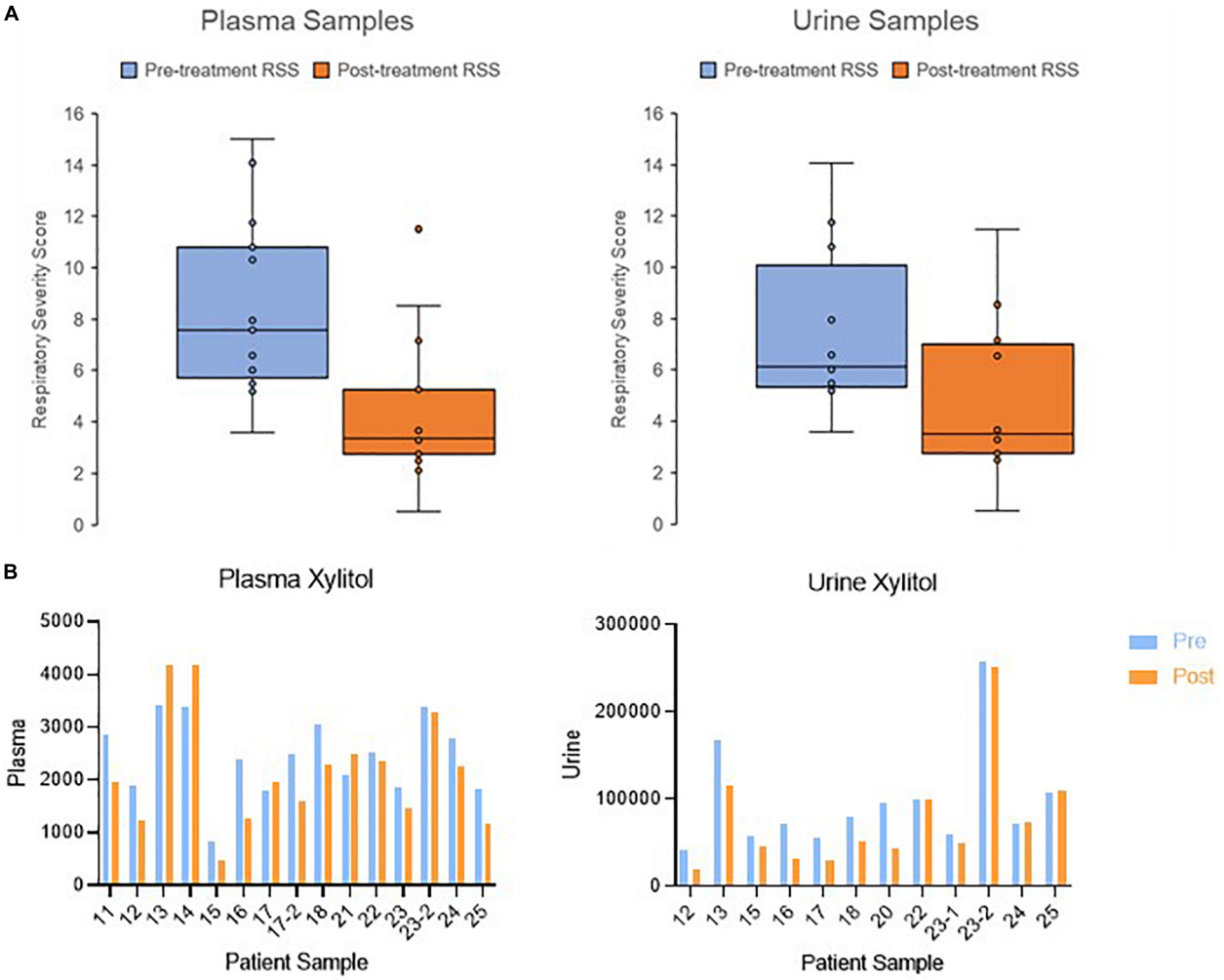


**FIGURE 1 |** Change in clinical outcome and metabolite abundance from pretreatment to post-treatment. **(A)** Boxplots showing the change in respiratory severity score in patients with collected plasma and urine samples. **(B)** Bar graph showing the change in xylitol as an example metabolite. Metabolite abundance is displayed with arbitrary units of measurement.

initial findings and confirm metabolites for future targeted analyses in larger cohorts, we obtained additional patient samples for pharmacometabolomics analysis. Our goal with this analysis is to conduct a replication cohort dexamethasone pharmacometabolomics study on preterm infant urine and plasma samples in order to identify and confirm metabolic changes associated with drug response.

## MATERIALS AND METHODS

### Subjects and Study Design

Subject enrollment and study design followed the protocol described previously (5). To summarize, this replication cohort study was conducted under the approval by the Children's Mercy Hospital institutional review board (IRB) prior to patient enrollment. Parental consent was obtained in accordance with IRB regulations. Starting in October 2016, all preterm infants less than 32 weeks gestation at birth and treated with systemic dexamethasone per clinical care were eligible for enrollment. Essentially all infants were requiring substantial ventilatory support, either intubated or via non-invasive assisted ventilation. Exclusion criteria included any patients with an active infection (the DART (Dexamethasone: A Randomized Trial) course was deferred until infection was resolved), coexisting significant structural heart disease, non-prematurity related cause of their pulmonary disease, complex structural, or known genomic differences, and congenital difference in lung or airways development. Patient demographics and clinical data were obtained from the clinical chart and by speaking with bedside clinicians. For this analysis, we used data from the first course of systemic dexamethasone for each child, as well as data from the second course of dexamethasone from two patients.

The DART course was used at our institution to standardize dexamethasone dosing for BPD. The course consisted of

**TABLE 2 |** List of metabolites significantly associated with pre-post dexamethasone treatment comparison.

| Metabolites | Fold change | Direction | *P-value*[a] |
|---|---|---|---|
| ***Plasma*** | | | |
| **Xylitol** | 0.73647 | Down | 0.0002 |
| Kynurenine | 0.62206 | Down | 0.0006 |
| Hypoxanthine | 4.0073 | Up | 0.0009 |
| Urea | 1.451 | Up | 0.0015 |
| 5-Hydroxymethyl-2-furoic acid | 0.55663 | Down | 0.0043 |
| Pseudo uridine | 0.79005 | Down | 0.0054 |
| **P-Hydroxylphenyllactic Acid** | 0.64733 | Down | 0.0067 |
| **Gluconic acid lactone*** | 0.45612 | Down | 0.0103 |
| Ribitol | 0.81318 | Down | 0.0103 |
| Uracil | 0.86725 | Down | 0.0103 |
| Xylulose | 0.71414 | Down | 0.0103 |
| Uric acid | 1.2145 | Up | 0.0151 |
| Uridine | 1.3129 | Up | 0.0151 |
| Xylose | 0.85594 | Down | 0.0151 |
| Ethanolamine | 0.66029 | Down | 0.0181 |
| Threonine | 0.73213 | Down | 0.0181 |
| Inosine | 3.3745 | Up | 0.0215 |
| Serine | 0.8359 | Down | 0.0256 |
| **Trans-4-hydroxyproline** | 0.6678 | Down | 0.0256 |
| Butane-2,3-Diol | 1.7161 | Up | 0.0413 |
| ***Urine*** | | | |
| P-hydroxylphenyllactic acid | 0.46969 | Down | 0.0005 |
| Oleic acid | 1.4567 | Up | 0.0010 |
| Xylitol | 0.69276 | Down | 0.0010 |
| Glycyl-proline | 0.56812 | Down | 0.0010 |
| Proline | 0.34309 | Down | 0.0015 |
| Palmitic acid | 1.328 | Up | 0.0024 |
| Aminomalonate | 0.47598 | Down | 0.0024 |
| Phthalic acid | 0.66116 | Down | 0.0049 |
| Creatinine | 0.57385 | Down | 0.0049 |
| Phenol | 1.9054 | Up | 0.0068 |
| Orotic acid | 0.85041 | Down | 0.0068 |
| 3-Hydroxypropionic acid | 0.68286 | Down | 0.0068 |
| Threonine | 0.39941 | Down | 0.0068 |
| **5-Hydroxymethyl-2-furoic acid** | 0.51825 | Down | 0.0093 |
| Citric acid | 0.64898 | Down | 0.0161 |
| Stearic acid | 1.3958 | Up | 0.0210 |
| Glycine | 0.55962 | Down | 0.0210 |
| **Pipecolinic acid** | 0.47561 | Down | 0.0210 |
| Aspartic acid | 0.47046 | Down | 0.0210 |
| Methionine | 0.70898 | Down | 0.0269 |
| Thymine | 0.68841 | Down | 0.0269 |
| **Kynurenine** | 0.5464 | Down | 0.0269 |
| Threitol | 1.1266 | Up | 0.0342 |
| **1-Methylinosine** | 0.82274 | Down | 0.0342 |
| Phenylalanine | 0.73404 | Down | 0.0342 |
| Citramalic acid | 1.2848 | Up | 0.0425 |

*Bold, Metabolite found significant in pre-post comparison for both discovery and replication cohorts.*

[a]*P-value included in the table is unadjusted for multiple comparisons.*

**Discovery cohort showed significant association with free gluconic acid form in serum and lactone form in urine.*

0.15 mg/kg/daily for 3 days, then 0.1 mg/kg/day for 3 days, then 0.05 mg/kg/day for 2 days, then 0.02 mg/kg/day for 2 days. The total dose was 0.89 mg/kg. Clinical outcome was measured as short-term phenotypic response to dexamethasone. The Respiratory Severity Score (RSS = mean airway pressures x FiO2) was calculated prior to treatment (baseline) and on day 7 of treatment (drug response). In order to account for intraindividual variability, the average RSS for a 24-h period was collected. RSS was calculated as the mean airway pressure × fraction of inspired oxygen (FiO2) (ranging from 21 to 100%).

Blood and urine samples were collected two times, once in the 24 h prior to starting systemic dexamethasone (pre-treatment) and again at day 3–6 after starting systemic dexamethasone (post-treatment). Post-treatment blood and urine sample collection timing was conducted during the steroid course and determined by and paired with scheduled blood draws for clinical labs within the target window. Samples were collected in the NICU and then either briefly refrigerated or immediately processed. Urine and plasma samples were aliquoted and stored at −80°C until metabolomic assay.

## Untargeted Metabolic Assessment

Methods for metabolomics analysis were described previously (5). Briefly, plasma and urine samples were submitted for untargeted metabolomics analysis to the West Coast Metabolomics Center at UC Davis. Untargeted metabolomics profiling was performed using an Agilent 7890A gas chromatograph and a Leco Pegasus IV time-of-flight mass spectrometer. BinBase database was used to identify metabolites by retention index, align mass spectra, and perform gap filling. Data was reported as mass spectral peak height.

## Statistical Analysis

Peak height values were subjected to data preprocessing prior to analysis. Missing value estimation was performed by removing metabolites with more than 30% of values missing among the patient samples. Any remaining missing values were replaced with a calculated small value (half of the minimum positive value for that metabolite reported in the raw data). Further data processing also included normalization by sum peak intensity of all known metabolites as well as log transformation. Categorical statistical analysis was performed on the MetaboAnalyst 5.0 platform (6). Patient pretreatment and post-treatment samples were paired for categorical analysis. The difference in metabolite abundance pre and post-treatment was tested using Wilcoxon signed rank test. Boxplots created from the data analysis featured quartiles 1 and 3 at the bottom and top of the box, respectively. Boxplot features included a horizontal line representing the median, an upper whisker of Q3 + 1.5*IQR and a lower whisker of Q1 − 1.5*IQR. Significance threshold was set at $p$-value $< 0.05$. Adjustment for multiple comparisons was done using Benjamini and Hochberg's false discovery rate method. Statistical analysis on change in metabolite level and RSS values was performed using Pearson correlation analysis. Correlation analysis was conducted to determine if changes in metabolite abundance from pretreatment to post-treatment was associated with change in

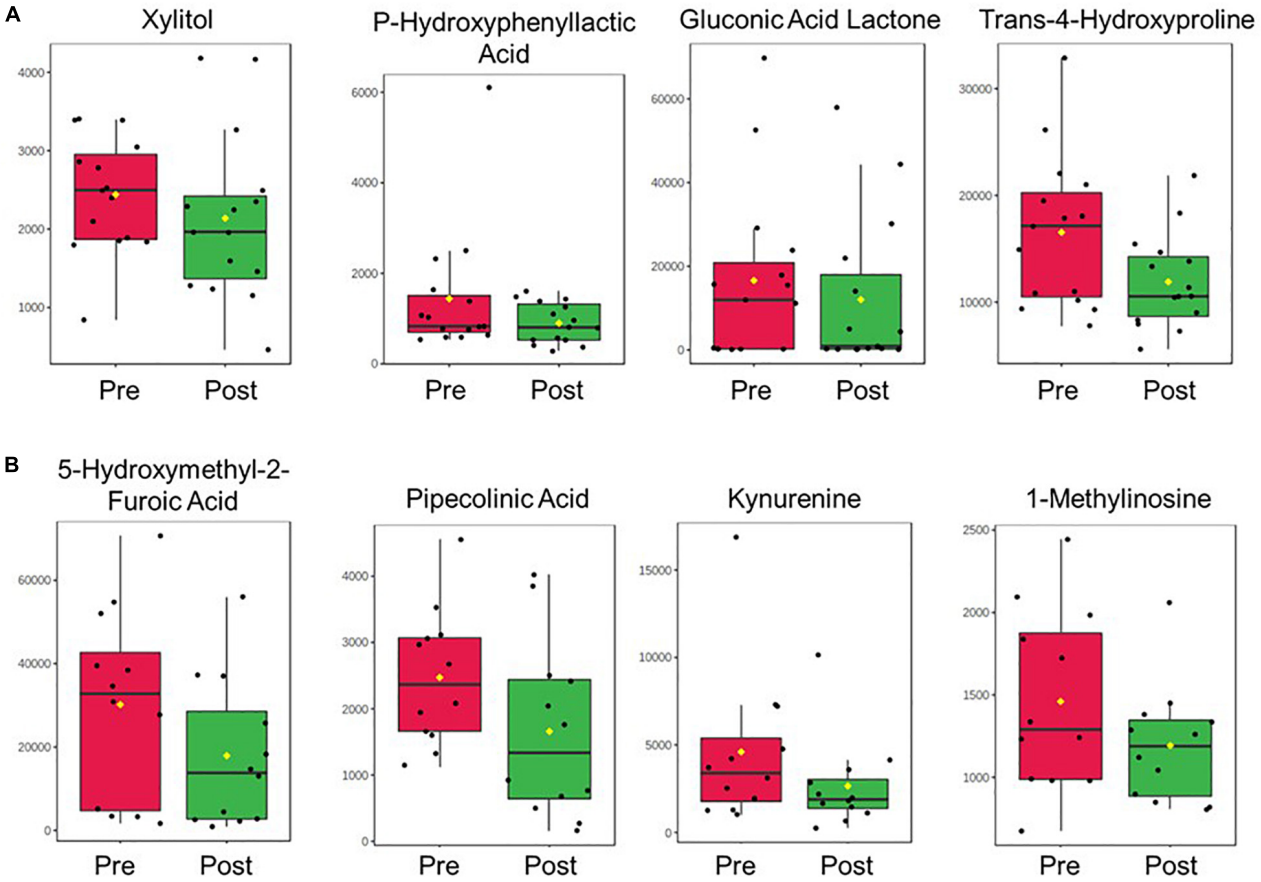


**FIGURE 2 |** Boxplots displaying the pre-to-post-treatment difference in abundance for the replicated metabolites in **(A)** plasma and **(B)** urine between the discovery and replication cohort studies. Metabolite abundance is displayed with arbitrary units of measurement. Yellow dots represent the group mean.

RSS, representing clinical response to dexamethasone therapy. Significance threshold was set at $p$-value $< 0.05$.

## RESULTS

In this replication cohort, 14 infants provided 15 matched pretreatment and post-treatment plasma samples and 12 matched pretreatment and post-treatment urine samples. Two patients, 17 and 23, provided multiple samples from both first and second rounds of treatment with dexamethasone. Detailed demographic information for the patient cohort is provided in **Table 1**. Comparison of pretreatment and post-treatment RSS values for plasma and urine samples are shown in **Figure 1**.

A total of 690 metabolites were measured in plasma and urine samples. Within this metabolite set, 135 metabolites were identified in plasma samples and 178 were identified in urine samples. Categorical analysis of pretreatment vs. post-treatment plasma samples identified 18 metabolites with statistically significant difference in abundance comparing pre and post-treatment. Among these significant metabolites, three were replicated from the same analysis in the pilot cohort. These metabolites are xylitol, trans-4-hydroxyproline, and p-hydroxyphenyllactic acid. One significant metabolite, gluconic acid lactone, was significant in the free acid form in the serum analysis of the previous study, but also significant in the lactone form in the urine sample regression analyses of deltaRSS.

In urine samples, 26 metabolites were found to be statistically significantly different between pretreatment and post-treatment samples. Among these significant metabolites, four were replicated with the results of the same analysis conducted in the discovery cohort study. These metabolites are 5-hydroxymethyl-2-furoic acid, pipecolinic acid, kynurenine, and 1-methylinosine. The significant results from both plasma and urine sample analysis are included in **Table 2**. The pre to post treatment comparison of replicated metabolite abundances are shown in **Figure 2**.

Correlation analysis was conducted to determine if change in metabolite abundance was associated with change in RSS (clinical response). Analysis of plasma samples identified four metabolites with statistically significant association. Urine sample analysis identified eight metabolites with statistically significant association. Significant results from the analysis of plasma and urine samples are shown in **Table 3**. Among these significant metabolites, change in urine levels of citrulline showed a significant association with change in RSS score

**TABLE 3 |** Metabolites with change in abundance significantly associated with change in RSS.

| Metabolites | Correlation coefficient | *p*-value |
|---|---|---|
| ***Plasma*** | | |
| Octadecanol | 0.572 | 0.026 |
| Phosphoethanolamine | 0.571 | 0.026 |
| Methionine | –0.541 | 0.037 |
| Maltotriose | 0.519 | 0.048 |
| ***Urine*** | | |
| **Citrulline** | –0.703 | 0.003 |
| 2-Picolinic acid | 0.678 | 0.005 |
| Methylmaleic acid | 0.638 | 0.010 |
| Isoleucine | 0.593 | 0.020 |
| Sorbitol | –0.559 | 0.030 |
| Indole-3-acetate | 0.557 | 0.031 |
| Aminomalonate | 0.548 | 0.035 |
| 2,4-Hexadienedioic acid | 0.540 | 0.038 |

*Bold, Metabolite found significant in correlation analysis for both discovery and replication cohorts.*

in both the original and replication cohort studies. Both association analyses also showed the same directional trend, with a positive change in RSS score (indicating poor response to therapy) associated with significantly lower levels of urine citrulline. Correlation plots of the top three most significant metabolites in plasma and urine samples are shown in **Figure 3**.

## DISCUSSION

Adequate therapy for BPD prevention or treatment continues to be a major challenge in neonatology. Response to dexamethasone therapy, a common drug used clinically, shows high interpatient variability and is highly unpredictable. As we saw in our previous study, we again observe a wide range of clinical response within our replication cohort with a group of responders and non-responders. There are a variety of proposed mechanisms for the variable response to steroids in this patient population, and many of them involve metabolic activity and pathways. Pharmacometabolomics is an emerging powerful tool for effectively capturing the differences in metabolite levels between patients that can be linked to differences in treatment response. In our previous cohort study, we showed a number of metabolites and their relevant pathways that were significantly associated with treatment outcomes in BDP patients. In this replication cohort study, we are once again able to show a substantial number of metabolites associated with treatment response, with several of these metabolites showing overlap between the pilot and replication cohorts.

Among the replicated metabolomics results between our analyses of metabolite abundance affected by dexamethasone therapy, trans-4-hydroxyproline is one the most extensively discussed and relevant to BPD pathophysiology. In the prior study and this study, trans-4-hydroxyproline was found to be decreased in serum following dexamethasone treatment. Previous studies have identified trans-4-hydroxyproline as elevated in patients with idiopathic pulmonary fibrosis,

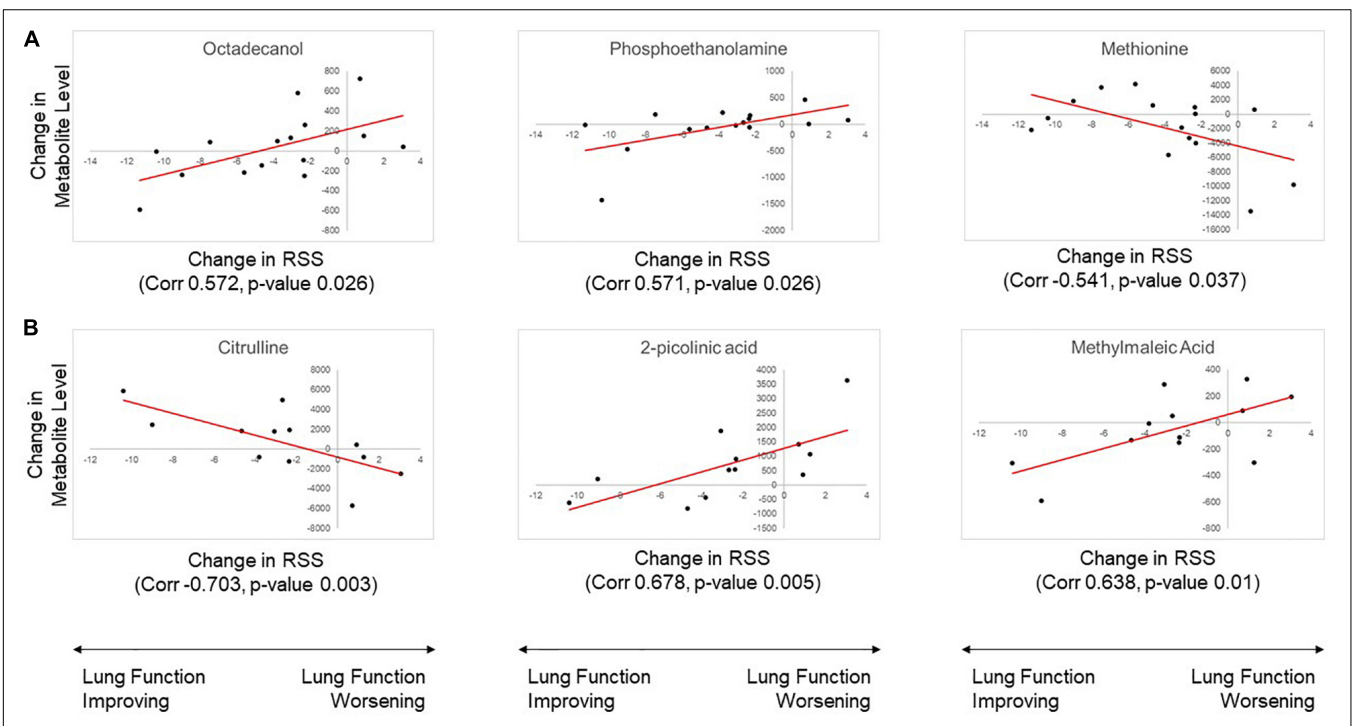


**FIGURE 3 |** Results of correlation analysis for change in metabolite level with change in Respiratory Severity Score (RSS). The three metabolites with the most significant correlation in **(A)** plasma and **(B)** urine samples are shown. Metabolite abundance is displayed with arbitrary units of measurement.

suggesting that it could serve as an indicator for lung injury and fibrosis (7). Our replication cohort study showed a consistently significant association between trans-4-hydroxyproline levels and dexamethasone treatment. The metabolite showed a fold change of 0.6678 with a downward trend following treatment, providing further evidence of the relationship between trans-4-hydroxyproline and dexamethasone therapy. Since our first metabolomics cohort study, additional articles have been published on the subject of trans-4-hydroxyproline association with pulmonary fibrosis. There are significantly elevated levels of 4-hydroxyproline in exhaled breath analysis of idiopathic pulmonary fibrosis patients as compared to control (8). Also, serum 4-hydroxyproline, along with L-arginine, could serve as an effective diagnosis biomarker for the early phase of pulmonary fibrosis. This was further supported by showing that arctiin and arctigenin can downregulate serum 4-hydroxyprogresterone levels in cases of pulmonary fibrosis associated with silicosis (9). With further evidence from our replication cohort as well as additional published articles, trans-4-hydroxyproline continues to be a promising potential marker for lung fibrosis and injury, as well as drug response, in preterm infants at risk for BPD.

Gluconic acid lactone was significantly decreased in plasma samples following dexamethasone treatment. This replicates the results from the discovery cohort study, which showed a substantial decrease of the free form of gluconic acid following steroid treatment as well as a negative correlation with RSS score in urine samples. Gluconic acid metabolism continues to be poorly understood, and its role in BPD progression is unclear. However, gluconate concentrations can influence the hexose monophosphate shunt (10, 11). This shunt contributes to the production of ribose-5-phosphate, which leads to nucleotide synthesis through the pentose phosphate pathway. Interestingly, our results also showed an association of multiple metabolites in the pentose interconversion pathway with dexamethasone therapy. These include xylulose, ribitol, and xylitol, which were also significant in the discovery cohort study. The repeat significant association of these metabolites suggest an important role for the pentose phosphate pathway in response to dexamethasone therapy. This is supported by multiple studies that have proposed a connection between increased pentose phosphate pathway (PPP) activity, pulmonary hypertension, and BPD (12, 13). A recent study explored the relationship between BPD related hyperoxia and PPP activity. The authors found that hyperoxia caused increased PPP activity, which induced abnormal endothelial cell development in neonatal mice (14). Another recent study showed that glycolysis and PPP induction by interleukin-1 beta co-occurred with induction of pro-inflammatory signaling pathways in pulmonary tissues (15).

Our results show multiple metabolites involved in the urea cycle of arginine biosynthesis significantly associated with steroid therapy across both of our analyses. The pre-post dexamethasone treatment analysis showed a significant increase in the metabolite levels of urea in plasma samples and aspartic acid in urine samples. The change in RSS correlation analysis showed significant negative correlation of citrulline levels in urine samples with RSS. Results of our discovery cohort study also showed a significant association of citrulline levels with clinical response grouping of BPD patients, with lower levels of citrulline also associated with poorer response to therapy. Citrulline is produced through arginine catabolism as a byproduct of nitric oxide synthesis catalyzed by nitric oxide synthases. Citrulline can also serve as a precursor to arginine as the reactions are bidirectional. Several studies have proposed a link between citrulline and the urea cycle with BPD and pulmonary hypertension (PH) (16, 17). One study showed that citrulline plasma levels lower than 29 μmol/L were predictive of PH secondary to BPD (18). The authors of this study, Montgomery et al. ultimately propose that citrulline could potentially serve as a therapeutic target for PH secondary to BPD in preterm infants. Another study showed that a particular arginase-1 single nucleotide polymorphism (SNP), rs2781666, protects against the development of PH secondary to BPD by increasing synthesis of nitric oxide and reducing urea synthesis (19). In summary, results in both our discovery and replication cohort studies show that urea cycle metabolites, particularly citrulline, are closely related to BPD treatment response, and they could potentially serve as predictors of BPD development and response to dexamethasone therapy with further investigation.

Our replication study shares many of the strengths and weaknesses with our discovery cohort. Once again, we recruited a group of preterm infants with an even distribution of responders and non-responders, and we were able to pair pre and post treatment samples in most patients for analysis. NICU treatment protocol was the same between studies, so mg/kg dosing of dexamethasone was the same for both cohorts. An additional strength is inherent to the nature of replication studies in that we were able to support the findings of our discovery study by replicating several of the results with equivalent analyses. Lack of reproducibility is an ongoing crisis in many fields of medical research. By reproducing several of the significant findings of our discovery cohort study, we can begin to alleviate these concerns and greatly strengthen the confidence in our conclusions. Our study did again only involve untargeted metabolomics analysis, which provides relative metabolite abundance rather than absolute quantification. However, with a set of reproducible findings of metabolites and their pathways associated with dexamethasone response, we can approach the design and selection of targeted metabolomics panels with greater confidence. We are currently recruiting a large multi-site cohort for targeted metabolomics analysis, building on the strengthened findings from this study.

Metabolomics profiling continues to develop as a powerful tool for hypothesis generation and investigation of the biological mechanisms influencing response to pharmacotherapy. Since the publication of our previous study, several additional articles have been published on the relationship between metabolic activity with BPD and its comorbidities, as referenced previously. Metabolomics have been used to investigate several other disease states relevant to the neonatal patient population as well (20–24). Our findings contribute to this growing exploration of the link between metabolism and variable treatment response in neonates as well as strengthen several of the findings we have published previously. Ultimately, pharmacometabolomics profiling has the potential to discover powerful biomarkers than can be

collected during patient care in order to predict risk of disease development and response to established pharmacotherapy for the individual patient. Furthermore, identification of relevant metabolites and their pathways can present new targets for the development of novel therapies for this patient population. The results of our study continue to expand on the investigation of pharmacometabolomics in preterm infants and the strength of reproducible results allow us to continue to narrow our focus on the relevant metabolic pathways for improving treatment outcomes in preterm infants with BPD.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Children's Mercy Hospital Institutional Review Board. We obtained written informed consent from the parents.

## AUTHOR CONTRIBUTIONS

BS, CG, WT, and TL wrote the manuscript. TL and WT designed the research. TL, CG, and WT performed the research. TL and BS processed metabolomics data and performed statistical analysis. All authors contributed to the article and approved the submitted version.

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The handling editor declared a past co-authorship with one of the authors, TL.

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# A prediction model of pulmonary hypertension in preterm infants with bronchopulmonary dysplasia

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**Objective:** Pulmonary hypertension (PH) is a severe cardiovascular complication of bronchopulmonary dysplasia (BPD) that contributes to the high mortality rates for preterm infants. The objective of this study is to establish a prediction model of BPD-associated PH (BPD-PH) by integrating multiple predictive factors for infants with BPD.

**Method:** A retrospective investigation of the perinatal clinical records and data of echocardiography in all the preterm infants with BPD was performed from January 2012 to December 2019. A prediction model of BPD-PH was established based on the univariate and multivariate logistic regression analysis of the clinical data and evaluated by using the area under the receiver operating characteristic (ROC) curve (AUC), combined with the Hosmer–Lemeshow (HL) test. Internal validation was performed with bootstrap resampling.

**Result:** A total of 268 infants with BPD were divided into the BPD-PH group and the no-PH group. Multivariate logistic regression analysis showed that the independent predictive factors of BPD-PH were moderate to severe BPD, small for gestational age, duration of hemodynamically significant patent ductus arteriosus $\geq$ 28 days, and early PH. A prediction model was established based on the β coefficients of the four predictors. The area under the ROC curve of the prediction model was 0.930. The Hosmer–Lemeshow test ($p$ = 0.976) and the calibration curve showed good calibration.

**Conclusion:** The prediction model based on the four risk factors predicts the development of BPD-PH with high sensitivity and specificity and might help clinicians to make individualized interventions to minimize the disease risk.

KEYWORDS

**preterm infant, bronchopulmonary dysplasia, pulmonary hypertension, prediction model, nomogram**

# Introduction

During the past three decades, since great progress in perinatal-neonatal medicine has been made in China, the survival of extremely premature infants has markedly increased. However, the developing lungs are susceptible to various injuries, which cause a rising incidence of bronchopulmonary dysplasia (BPD) (1). In China, based on previously published studies, the incidence of BPD in extremely premature infants with a gestational age of less than 28 weeks has increased from 19.3% in 2011 to 51.7% in 2019 (2, 3).

Survivors with BPD are at risk of cardiovascular complications because of the disruption of vascular growth and signaling (4, 5). Pulmonary hypertension (PH) is common in infants with moderate or severe BPD, with the reported incidence ranging from 8 to 38% (6–9). PH contributes significantly to high mortality and is associated with dependency on respiratory support, prolonged hospitalization, impaired neurodevelopment, and significant medical costs in infants with BPD (10, 11). In our previously published data, the mortality of BPD infants complicated with PH was 40.5% (12).

The pathogenesis of BPD-associated PH (BPD-PH) is complicated, including multiple factors, such as perinatal stress, abnormal lung development, and postnatal conditions. Therefore, identification of the risk factors is important for early prevention. However, a single predictive factor is difficult to apply in clinical practice due to its inconsistent standards, low sensitivity, and specificity. A prediction model developed by integrating multiple predictive factors may improve the accuracy of prediction. To test the hypothesis, we performed this retrospective study.

# Materials and methods

## Study population and data collection

Preterm infants admitted to the Level III neonatal intensive care unit (NICU) at Children's Hospital of Zhejiang University School of Medicine between January 2012 and December 2019 who were diagnosed with BPD were eligible for this study. We excluded infants with congenital heart diseases [except patent ductus arteriosus (PDA), atrial septal defect, or patent foramen ovale], other major congenital anomalies, incomplete data, or death before 36 weeks' postmenstrual age (PMA). This study was approved by the Ethics Committees of our hospital with a waiver of parental consent.

Clinical data were collected retrospectively from the electronic NICU database. Prenatal data included maternal demographics, oligohydramnios (defined as amniotic fluid index $\leq$ 5), prolonged rupture of membrane, pregnancy-related complications, antenatal corticosteroids use, and mode of delivery. Neonatal data included gestational age (GA), birth weight (BW), sex, the Apgar score at 1 and 5 min, small for gestational age (SGA) status, cumulative days of invasive mechanical ventilation (IMV) before 36 weeks' PMA, and co-morbidity about respiratory distress syndrome (RDS) with surfactant use, hemodynamically significant PDA (hsPDA), pneumonia with positive respiratory culture, culture proven sepsis, PDA ligation, severe intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC).

## Definitions

Pulmonary hypertension was evaluated non-invasively with echocardiography by a board-certified pediatric sonographer in cardiology and diagnosed based on either of the following criteria (7, 13, 14), including the estimated systolic pulmonary arterial pressure (sPAP) > 50% of the systemic arterial pressure, end-systolic flattened or left-deviated of the interventricular septum (IVS) with or without right ventricular dilatation, bidirectional or right-to-left shunt at the patent foramen ovale, or ductus arteriosus. When there was a tricuspid regurgitation (TR), sPAP was calculated by adding right atrial pressure (5 mmHg) to the right ventricle pressure gradient, which was estimated by the Bernoulli equation. In the absence of a measurable TR, we relied upon a PDA/patent foramen ovale gradient to estimate sPAP. Early PH was defined as having evidence of PH based on the assessment of echocardiography between 72 h and 14 days (15), while BPD-PH was defined as having evidence of PH beyond 36 weeks' PMA in preterm infants with BPD (7).

Bronchopulmonary dysplasia was diagnosed based on the 2019 criteria proposed by Jensen (16). BPD severity was categorized according to the following modes of respiratory support administered at 36 weeks PMA, grade 1, nasal cannula at flow rates $\leq$ 2 L/min; grade 2, nasal cannula at flow rates > 2 L/min or non-invasive positive airway pressure; and grade 3, IMV.

Hemodynamically significant PDA was defined as the PDA diameter exceeding 1.5 mm combined with diastolic flow reversal in the descending aorta and the ratio of the left atrium to aorta greater than 1.5, as well as the clinical findings of pulmonary overcirculation, left heart overload, and/or poor systemic perfusion (17). SGA was defined as a birth weight less than the 10th percentile for gestational age (18). NEC was defined as modified Bells' stage II criteria or greater (19). Pneumonia includes both congenital and hospital acquired pneumonia, which is defined as having chest X-ray findings with positive tracheal aspirate culture. Sepsis was defined as infants with a positive blood culture who were treated with antibiotics for at least 5 days. Severe IVH was defined as Papile's Grade III or greater (20).

## Echocardiography screening protocol for hemodynamically significant PDA and pulmonary hypertension

All the preterm infants who were admitted before 2 weeks of life were evaluated by an echocardiogram 2–3 times a week for the hemodynamic status of PDA, pulmonary hypertension, and cardiac function. After 2 weeks of age, the frequency of echocardiogram was changed to 1–2 times a week. For all the preterm infants who developed increasing oxygen or respiratory support requirements in the late stage of life (usually after 4 weeks of life), PH was screened by an echocardiogram. When PH was confirmed, a series of echocardiograms were repeated every 1 or 2 weeks to monitor the dynamic change of PH and the response to interventions. If PH resolved, the echocardiogram was repeated monthly until weaning off respiratory support for 6 months.

## Statistical analyses

Data were presented as mean ± standard deviation (SD), median [interquartile range (IQR)], or number (percentage) where appropriate. Univariate analyses were performed using an independent *t*-test or non-parametric tests for continuous variables, and the Chi-square or Fisher's exact test for categorical variables. Multivariate logistic regression was performed to identify the risk factors associated with BPD-PH. A prediction model and nomogram were established based on the multivariate logistic regression analysis of BPD-PH.

The area under the receiver operating characteristic (ROC) curve (AUC) was measured to assess the discriminative performance of the prediction model. A calibration curve was generated for the evaluation of calibration, combined with the Hosmer–Lemeshow (HL) test. An insignificant HL test statistic implies good calibration. In addition, the prediction model was subjected to 1,000 bootstrap resamples for internal validation to assess their predictive accuracies.

Statistical analysis was performed with SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, United States). The graphics of the nomogram and calibration curve were performed with R 4.0.4 (The R Foundation for Statistical Computing, Vienna, Austria) with the rms statistical packages.

# Results

During the study period, 336 preterm infants were diagnosed with BPD based on the 2019 criteria. In this study, 68 cases were excluded because of major congenital anomalies or incomplete data. A total of 268 preterm infants with BPD were enrolled, with 59 (22.0%) infants who developed BPD-PH beyond 36 weeks' PMA in the BPD-PH group and 209 (78%) infants without PH in the no-PH group (**Figure 1**). The median age at admission was 21 days of life in the BPD-PH group and 4 days of life in the no-PH group. The incidences of PH in grade 1, grade 2, and grade 3 BPD infants were 5.0% (7/139), 20.9% (19/91), and 86.8% (33/38), respectively.

1. Univariate analyses of maternal and neonatal characteristics between the two groups

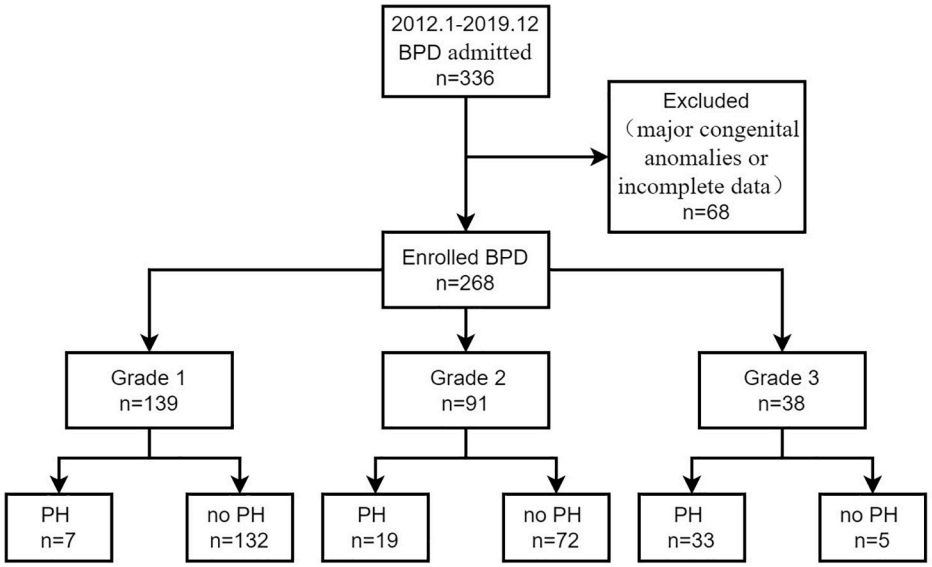


FIGURE 1
A flow diagram of study participants. BPD, bronchopulmonary dysplasia, PH, pulmonary hypertension.

TABLE 1 Maternal and neonatal characteristics between two groups.

| Variables | BPD-PH ($n$ = 59) | no-PH ($n$ = 209) | $P$ |
|---|---|---|---|
| Gestational age (weeks), mean (SD) | 27.7 ± 1.7 | 28.4 ± 1.6 | 0.009* |
| Birth weight (g), mean (SD) | 970 ± 224 | 1150 ± 250 | 0.000* |
| Male gender, $n$ (%) | 36 (61.0) | 141 (67.5) | 0.355** |
| SGA, $n$ (%) | 10 (16.9) | 10 (4.8) | 0.004** |
| Apgar score at 5 min, median (IQR) | 8 (6, 9) | 8 (6, 9) | 0.350*** |
| Delivery by C-section, $n$ (%) | 28 (47.5) | 85 (40.7) | 0.373** |
| Oligohydramnios, $n$ (%) | 4 (6.8) | 17 (8.1) | 0.732** |
| PROM > 24 h, $n$ (%) | 17 (28.8) | 49 (23.4) | 0.397** |
| pregnancy-induced hypertension, $n$ (%) | 12 (20.3) | 16 (7.7) | 0.008** |
| Antenatal corticosteroids, $n$ (%) | 13 (22.0) | 75 (35.9) | 0.059** |
| **BPD, $n$ (%)** | | | |
| Grade 1 | 7 (5.0) | 132 (95.0) | 0.000** |
| Grade 2 | 19 (20.9) | 72 (79.1) | |
| Grade 3 | 33 (86.8) | 5 (13.2) | |
| RDS and surfactant use, $n$ (%) | 53 (89.8) | 154 (73.7) | 0.008** |
| Early PH, $n$ (%) | 43 (72.9) | 63 (30.1) | 0.000** |
| **Duration of hsPDA, $n$ (%)** | | | |
| < 7 days | 8 (13.6) | 96 (45.9) | 0.000** |
| 7-13 days | 2 (3.4) | 21 (10.0) | |
| 14-27 days | 4 (6.8) | 31 (14.8) | |
| ≥ 28 days | 45 (76.3) | 61 (29.2) | |
| PDA ligation, $n$ (%) | 26 (44.1) | 34 (16.3) | 0.000** |
| pneumonia, $n$ (%) | 54 (91.5) | 135 (64.6) | 0.000** |
| NEC (II–III), $n$ (%) | 6 (10.2) | 11 (5.3) | 0.222** |
| Culture proven sepsis, $n$ (%) | 21 (35.6) | 62 (29.7) | 0.426** |
| IVH (III–IV), $n$ (%) | 8 (13.6) | 10 (4.8) | 0.034** |
| Duration of IMV before 36 weeks PMA (day), median (IQR) | 25 (9,42) | 7 (1,18) | 0.000*** |

SD, standard deviation; SGA, small for gestational age; IQR, interquartile range; PROM, premature rupture of membrane; BPD, bronchopulmonary dysplasia; RDS, neonatal respiratory distress syndrome; PH, pulmonary hypertension; hsPDA, hemodynamically significant patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; IMV, invasive mechanical ventilation. *The $t$-test for metric variable if data are normally distributed; **the Chi-square test (big sample size) and Fisher's exact test (small sample size) for categorical variables; ***the Mann–Whitney $U$-test for metric variables if data are not normally distributed.

The characteristics and related risk factors were compared between the two groups (Table 1). Infants from the BPD-PH group were born at a lower gestational age with smaller birth weights than the infants from the no-PH group ($p < 0.05$). The incidences of pregnancy-induced hypertension (PIH), grade 3 BPD, early PH, SGA, RDS with surfactant use, pneumonia, severe IVH, and PDA ligation were significantly higher in the BPD-PH group ($p < 0.05$). The duration of hsPDA and IMV before 36 weeks' PMA was much longer in infants with BPD-PH than in those without PH ($p < 0.05$).

2. Selected factors for the prediction model of BPD-PH

TABLE 2 The multivariate logistic regression analysis to estimate risk for BPD-PH.

| Variables | β | OR | 95.0% CI | $P$ |
|---|---|---|---|---|
| Constant | −4.617 | 0.010 | | |
| SGA | 1.594 | 4.924 | 1.007–24.074 | 0.013 |
| Early PH | 1.205 | 3.337 | 1.358–8.202 | 0.009 |
| BPD | | | | |
| Grade 2 | 1.201 | 3.325 | 1.237–8.935 | 0.017 |
| Grade 3 | 4.792 | 120.533 | 29.266–496.421 | 0.000 |
| Duration of hsPDA ≥ 28 days | 2.068 | 7.911 | 2.898–21.593 | 0.000 |

SGA, small for gestational age, PH, pulmonary hypertension, BPD, bronchopulmonary dysplasia, hsPDA, hemodynamically significant patent ductus arteriosus.

After univariable analysis, the variables of GA, BW, SGA, PIH, BPD, RDS with surfactant use, early PH, severe IVH, the duration of hsPDA, PDA ligation, pneumonia, and the duration of IMV before 36 weeks' PMA were entered into the multivariate logistic regression analysis.

Multivariate logistic regression analysis showed that the independent predictive factors of BPD-PH were SGA, early PH, moderate to severe BPD (Grade 2 and 3 BPD), and the duration of hsPDA ≥ 28 days (Table 2).

3. The predictive nomogram for the probability of BPD-PH

On the basis of the final regression analysis, a prediction model was established that incorporated the β coefficients of the predictors,

$$\text{logit}(p) = \ln\frac{p}{1-p} = -4.617+1.594 \times \text{SGA}+1.205 \times \text{Early PH}+1.201 \times \text{Grade 2 BPD}+4.792 \times \text{Grade 3 BPD}+2.068 \times \text{duration of hsPDA}$$

where, $p$ represented the probability of developing BPD-PH. Other values of the predictors are as follows, SGA (no = 0, yes = 1), early PH (no = 0, yes = 1), Grade 2 BPD (no = 0, yes = 1), Grade 3 BPD (no = 0, yes = 1), and the duration of hsPDA (< 28 days = 0, ≥ 28 days = 1). A nomogram was developed based on the prediction model to improve the convenience of the model in clinical practice (Figure 2).

The area under the ROC curve (AUC) of the prediction model was 0.930 (95% CI, 0.895–0.965) (Figure 3). The Hosmer–Lemeshow test revealed no statistical significance ($p$ = 0.976), suggesting a good fitting of the model. The calibration curve of the prediction model (Figure 4) demonstrated good calibration. The cutoff probability in this model is 0.173, with a sensitivity of 89.8% and a specificity of 79.4%, respectively.

## Discussion

Since PH is serious comorbidity of BPD with high mortality (31) and a lack of evidence-based therapies, it is of

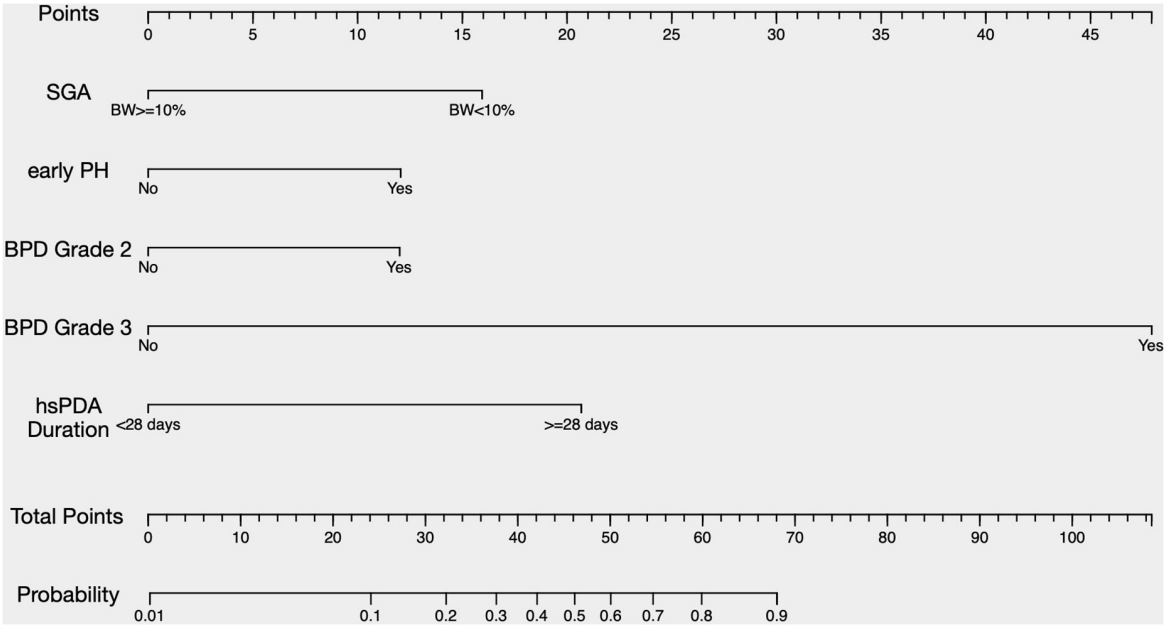


FIGURE 2
A nomogram predicting the risk of BPD-PH. The value of each of variable was given a score on the point scale axis. A total score could be easily calculated by adding each single score and, by projecting the total score to the lower total point scale, we were able to estimate the probability of BPD-PH. SGA, small for gestational age; PH, pulmonary hypertension; BPD, bronchopulmonary dysplasia; hsPDA, hemodynamically significant patent ductus arteriosus.

great importance to identify the risk factors and start early interventions to improve the long-term outcome. In this study, we established and assessed a prediction model for individually predicting patients with BPD who are likely to develop BPD-PH. The prediction model incorporated demographic and clinical characteristics and showed good discrimination and calibration performance. We further developed a nomogram, thus making it a convenient and valuable tool for clinical practice.

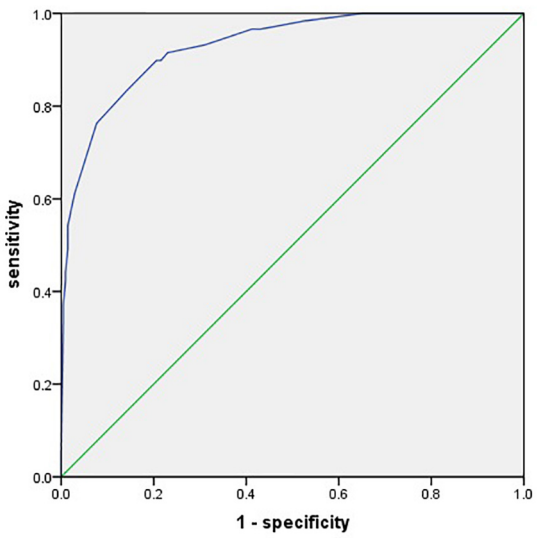


FIGURE 3
A receiver operating characteristic (ROC) curve for evaluating the prediction model's discrimination performance [area under the ROC curve (AUC) = 0.930].

Several published studies have examined a wide variety of risk factors for the development of pulmonary hypertension in infants with BPD (6, 8, 21). Nagiub et al. (22) performed a meta-analysis to further analyze the effect size of risk factors for BPD-PH and showed that the duration of mechanical ventilation, prolonged NICU stay, oligohydramnios, the use of high frequency ventilation, SGA, sepsis, and severity of BPD were significant risk factors; while birth weight and gestational age were inversely related.

However, it is difficult to quantify the risk of developing BPD-PH according to one single predictive factor due to its low sensitivity and specificity. More importantly, PH that complicates BPD is frequently multifactorial, including perinatal stress, abnormal lung development, and postnatal diseases. Thus, how to transform these risk factors into a risk-based scoring system could help develop an evidence-based screening strategy for infants at high risk.

Prediction models by integrating multiple predictive factors have been used frequently in other conditions, whereas, there are few studies about prediction models for developing PH in infants with BPD. In the study by Trittmann et al. (23), they created a predictive model by combining both clinical and

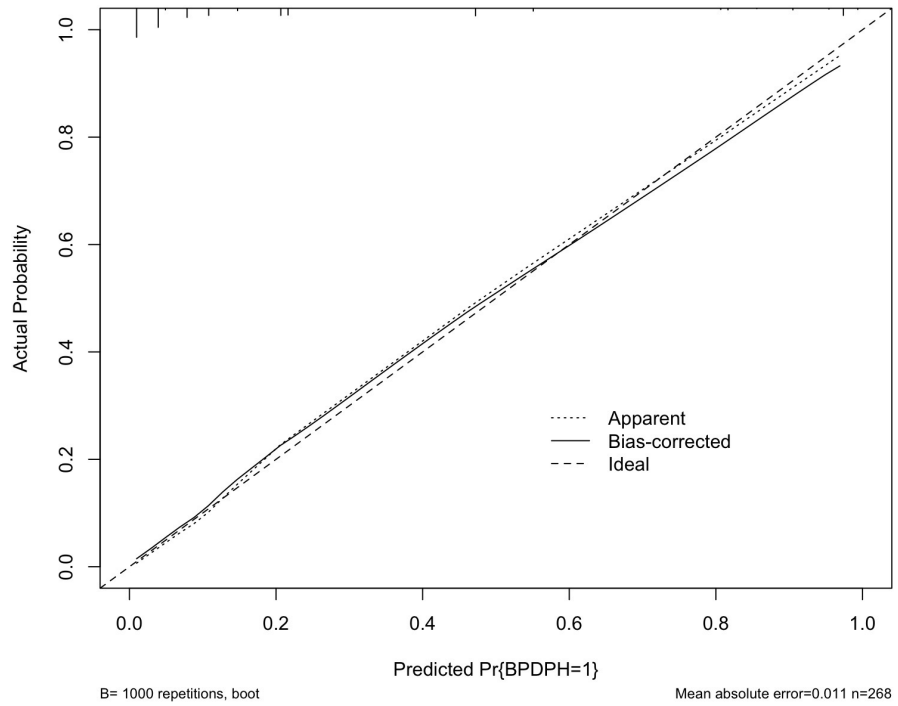


FIGURE 4
A calibration curve of the prediction model. The *x*- and *y*-axes represent the predicted risk and actual outcome, respectively. The dashed line indicates perfect prediction by an ideal model. The solid line depicts the model's performance.

genetic data to predict the development of PH in patients with BPD. An ROC analysis showed the AUC of the prediction model of clinical data only, clinical and genetic data combined were 0.65 and 0.73, respectively. Due to the small cohort size of 20 cases of BPD-PH and 59 cases of BPD, the application of their model is limited and further validation in a larger independent prospective BPD cohort is needed. Compared with this study, our prediction model has relatively higher discrimination, with an AUC of 0.930.

In our prediction model, grade 3 BPD is the greatest contributor to the risk of BPD-PH, followed by the duration of hsPDA exposure, SGA, and early PH. The impact of the severity of BPD on BPD-PH was variable in previous studies. A few studies could not find an association between PH and the severity of BPD (24). In contrast, Arjaans et al. (25) revealed that infants with severe BPD were most at risk of developing PH, with a relative risk (*RR*) doubled (*RR* 2.7, 95% CI 1.7, 4.2). Our study reconfirms severe BPD as a strong risk factor for the development of PH, compared with mild or moderate BPD.

As a provincial referral center, all the cases were transferred from the maternal hospital or local hospital. Prolonged mechanical ventilation requirement and hsPDA unresponsive to pharmacologic therapy were common reasons for transport. The longer duration of hsPDA exposure is associated with the increasing risk of BPD in extremely preterm infants (26), which elucidates that hsPDA may delay lung disease recovery. Whether continued hsPDA exposure in infants with severe BPD may exacerbate BPD-PH is uncertain. Some studies reported no relationship between hsPDA and the development of BPD-PH (8, 9). However, in these reports, hsPDA was considered a categorical variable (present or absent) with no consideration of its duration. In our study, we found infants in the BPD-PH group were transferred to our unit much later than infants in the no-PH group, which means infants with BPD-PH had longer exposure to hsPDA. This also explained why univariable analysis showed the PDA ligation rate was much higher in the BPD-PH group than in the no-PH group because 76.3% of infants in the BPD-PH group had hsPDA exposure for $\geq$ 28 days.

Small for gestational age (SGA) has been identified to be a significant risk factor across some studies. Check et al. (21) further evaluated the associations between birth weight percentile and pulmonary hypertension at 36 weeks PMA in infants with moderate or severe BPD. In this study, infants with birth weights below the 25th percentile cutoff were at a higher risk of developing BPD-PH.

An early injury to the developing lung can impair angiogenesis and alveolarization, which results in the simplification of distal lung airspace and the clinical manifestations of BPD and PH. Previous prospective and retrospective studies in preterm infants have revealed that early PH is strongly associated with a high risk for the subsequent development of BPD at 36 weeks PMA (7, 27), but the results

were conflicting on the association between early PH and the development of late PH (15, 28). However, evidence about the relationship between early PH and late BPD-PH is limited. In our cohort, early PH within 14 days of life is identified to be the independent risk factor of BPD-PH, which might improve the earlier detection and management of patients with BPD-PH.

Antenatal corticosteroids are well-known interventions that decrease the severity of RDS; however, the recent meta-analysis of the Cochrane Database shows that it is unclear if antenatal corticosteroids have any effect on the risk of BPD compared with placebo or no treatment (29). Neither of the two meta-analyses by Nagiub et al. (22) and Arjaans et al. (25) showed any effect of antenatal corticosteroids on BPD-PH. In our study, though infants with BPD-PH had received less antenatal corticosteroids, the *p*-value was above 0.05, we did not apply antenatal corticosteroids to the multivariate logistic regression analysis.

Presentations of BPD-PH are usually non-specific and easy to be neglected. Hence, active screening and treatment are recommended to minimize morbidity and mortality. Consensus recommendations for PH screening in infants with BPD have been developed by the Pediatric Pulmonary Hypertension Network (PPHNet), a multidisciplinary panel of PH experts (30). However, with the prediction model, it is possible to estimate the risk of BPD-PH precisely and optimize the utilization of medical resources. For patients with high risk, early and frequent screenings for PH may be considered individually. In addition, risk factors should be controlled more actively, such as the prompt treatment of hsPDA and optimization of respiratory support for those infants.

There are several limitations to our study. First, there might be selection bias in this retrospective study because we excluded infants without complete data or died before 36 weeks' PMA. Echocardiograms were performed to evaluate the hemodynamic status of PDA every 2 or 3 days for very premature infants until PDA became hemodynamically insignificant. HsPDA exposure is a continuous variable, but we had to divide the cohort into four subgroups because of our inability to precisely calculate the duration of hsPDA (days). Second, only internal validation was performed because of the single-center study, in which the differences in epidemiology and clinical behavior that exist between different centers were not considered. Furthermore, genomic characteristics were not considered in our study. Genetic data combining clinical characteristics may improve the prediction model performance.

In conclusion, the prediction model based on the four risk factors predicts the development of BPD-PH with high sensitivity and specificity. External validation through multicenter prospective studies is necessary to further assess the generalizability of the prediction model.

## Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

CW had primary responsibility for protocol development, preliminary data analysis, and writing of the manuscript. CW and YX participated in patient screening, enrollment, and data collection. ZC and LS participated in the design of the protocol and data analyses. XM supervised the design and execution of the study and contributed to the revision of the manuscript. LD supervised the design and performed the final data analyses. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Relationship between bronchopulmonary dysplasia phenotypes with high-resolution computed tomography score in early preterm infants

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**Objective:** To assess the relationship between high-resolution computed tomography (HRCT) abnormalities and clinical phenotypes of bronchopulmonary dysplasia (BPD).

**Methods:** A retrospective, single-center study was carried out at the Children's Hospital of Fudan University between 2013 and 2020. Preterm infants born at ≤ 32 weeks' gestation who were diagnosed with BPD and had HRCT between 40 and 50 weeks postmenstrual age (PMA)were included in the study. HRCT images from six pulmonary lobes were scored based on seven types of pulmonary lesions from two categories: hyperaeration lesions and parenchymal lesions. The hyperaeration score (HS) included scores of decreased attenuation, mosaic attenuation, and bulla/bleb, while the parenchymal score (PS) included those of linear lesion, consolidation, bronchial wall thickening, and bronchiectasis. All seven scores were summed up to create the total score (TS). One-way ANOVA testing or Kruskal-Wallis testing was adopted for the comparison of HRCT scores with BPD severity and clinical phenotypes. The correlation between HRCT scores and clinical phenotypes was evaluated by Spearman's correlation analysis.

**Results:** A total of 81 cases were included in the study. Cases with more severe BPD had a higher TS ($p$ = 0.01), HS ($p$ = 0.02), PS ($p$ = 0.02), mosaic attenuation score ($p$ = 0.03), bulla/Bleb score ($p$ = 0.03), and linear density score ($p$ = 0.01). TS ($r$ = 0.28), PS ($r$ = 0.35), linear density ($r$ = 0.34), and consolidation ($r$ = 0.24) were correlated with pulmonary hypertension (PH). However, no HRCT score was significantly different between the patients with

or without tracheobronchomalacia (TBM). BPD patients with a combination of lung parenchymal disease, PH, and TBM had the highest TS and HS.

**Conclusion:** HRCT scores correlated with BPD severity and PH in our study. HS might be a useful tool in the assessment of BPD severity while linear densities and consolidation might be helpful in predicting PH.

KEYWORDS

**bronchopulmonary dysplasia, preterm infants, pulmonary hypertension, computed tomography, tracheobronchomalacia**

# Introduction

Bronchopulmonary dysplasia (BPD) is a respiratory complication frequently present in preterm infants (1). In China, the incidence of BPD in preterm infants with gestational age (GA) $\leq$ 28 weeks reached up to 47.8% in 2019 (2). With the application of improved respiratory support strategies, antenatal steroids, surfactant therapy, and other advanced clinical technologies, an increasing number of preterm infants have survived, and the pathological process of BPD, therefore, has changed. There is growing interest in the underlying cardiopulmonary disorders and large airway complications (3–5). BPD patients are prone to pulmonary hypertension (PH) due to impaired angiogenesis and alveolarization. PH has a major impact on the prognosis and survival rate of BPD patients (6). Positive pressure respiratory support and endotracheal intubation may deform the immature airway, and thereby bring about large airway lesions, such as tracheobronchomalacia (TBM) (7). Although the current BPD definitions still define BPD and its severity based on the level of respiratory support at 36 weeks' postmenstrual age (PMA) (8, 9), classification of BPD infants into clinical phenotypes according to their predominant clinical features may facilitate better risk stratification (3).

Chest radiographs, high-resolution computed tomography (HRCT), and magnetic resonance imaging were used to assess the BPD-associated lung abnormalities in previous studies (10–12). Of these methods, HRCT has high accuracy and sensitivity. Numerous researchers have used HRCT to semi-quantify pulmonary structural abnormalities and to predict long-term outcomes of BPD patients (12). However, the relations between HRCT and clinical phenotypes of BPD patients are still unclarified. Existing data suggest that HRCT may be useful in the phenotypic classification of BPD patients and therefore may contribute to clinical decision-making and more accurate follow-ups of these patients. The purpose of this study is to explore the associations between HRCT abnormalities and clinical phenotypes in preterm infants with BPD.

# Materials and methods

## Subjects' clinical data

A retrospective, single-center study was carried out at the Children's Hospital of Fudan University between 2013 and 2020. Preterm infants born at $\leq$ 32 weeks' gestation who were diagnosed with BPD and had HRCT between 40 and 50 weeks PMA were included in the study. Those with poor HRCT images, congenital pulmonary deformities, serious pulmonary infections, and severe congenital cardiac disease were excluded from the study. Clinical information of the included patients was reviewed *via* the medical records system, including GA, body weight (BW), the duration of respiratory support in the hospital, and the existence of PH and large airway lesions. Other parameters that could affect the development of BPD, such as 1-min and 5-min Apgar scores, the use of surfactant therapy and antenatal steroids, presence of histological chorioamnionitis, and patent ductus arteriosus, were also examined. BPD was defined and its severity was graded by the NHLBI 2018 revision (8).

In this study, HRCT scores, as a representation of the severity of lung parenchymal disease, were assessed in infants with or without clinical phenotypes of PH and large airway disease of TBM. Specifically, the patient is diagnosed with PH if the pulmonary arterial pressure is estimated to be $>$ 35 mmHg by the tricuspid valve jet velocity on echocardiogram (13). TBM is defined as more than 50% of the airway lumen narrowing during expiration under bronchoscopy (14). If HRCT suggested tracheobronchial stenosis, bronchoscopy would be performed to confirm the disease. This study was approved by the Institutional Review Board and consent was obtained from the parents of each patient.

## High-resolution computed tomography protocol

High-resolution computed tomography was conducted using a 64-detector scanner (GE Healthcare, Princeton, NJ, United States) with a tube voltage of 80 kV, a tube current of 60 mAs, and a matrix of 512 × 512. The images were acquired at end-inspiration from the apex of the chest to the diaphragm. All HRCT scans had a reconstruction slice thickness of 0.625 mm. Infants were either sedated with oral chloral hydrate (25 mg/kg) or asleep after feeding. The scanning time of HRCT was 3.5∼5 s.

## High-resolution computed tomography scoring protocol

For HRCT scoring, we adopted an HRCT scoring system for BPD by Sung et al., which was modified on the basis of the HRCT scoring systems used in the recent 10 years (10, 15–17). We evaluated six pulmonary lobes (left upper lobe, left lingual segment, left lower lobe, right upper lobe, right middle lobe, and right lower lobe) and examined seven types of lesions in each lobe to identify the presence of pulmonary abnormalities. Seven types of pulmonary lesions were categorized into two types: hyperaeration and parenchymal lesions. Hyperaeration lesions included decreased attenuation, mosaic attenuation, and bulla/bleb, while parenchymal lesions included linear lesion, consolidation, bronchial wall thickening, and bronchiectasis. The radiographic definitions were defined by the Fleischner Society nomenclature (18). Decreased attenuation was defined as an area of reduced lung attenuation and mosaic attenuation was a non-homogeneous lesion that exhibited various attenuations. Bulla ($\geq$ 1 cm) or bleb ($\leq$ 1 cm) are referred to as round local lesions with reduced attenuation. Consolidation represented a homogeneous increase in parenchymal attenuation with blurred blood vessel and bronchial wall boundaries, linear lesion marked a thin and extended lesion along with soft tissue attenuation, and bronchiectasis stood for a widened airway compared to the accompanying pulmonary blood vessels.

For each lobe, one point was given for the presence of an abnormal lesion of the seven parameters, and 0 points were given if the lesions were not present. The maximum score for each lobe was seven points. The total HRCT score of six lobes was summed, including the hyperaeration score (HS), the parenchymal score (PS), and the total score (TS). Hence, a higher score reflected more severe pulmonary disease.

High-resolution computed tomography images were analyzed independently by two radiologists with more than 5 years of experience in pediatric pulmonary imaging and the scores were averaged for analysis. TS, HS, and PS were compared for inter-observer agreement evaluation. The scans were reviewed by the same observer (Dr. Yao) 1 month later to measure intra-observer agreement.

## Data analysis

Statistical analysis was carried out with SPSS (version 26.0, IBM, Armonk, NY, United States). Continuous parameters were expressed as the mean ± standard deviation or minimum-maximum range. Categorical parameters were expressed as numbers or percentages, as appropriate. For comparisons of HRCT scores among different clinical phenotypes, one-way ANOVA testing or the Kruskal-Wallis test was adopted, as appropriate. The correlations between HRCT scores and phenotypes were evaluated by Spearman's correlation analysis. The intra- and inter-observer agreement of HRCT scores was evaluated with Cronbach's α coefficient. If the value was higher than 0.8, the reliability was high. If the value was between 0.7 and 0.8, the reliability was good. If the value was between 0.6 and 0.7, the reliability was acceptable. If the value was less than 0.6, the reliability was poor. When the $p$-value was $< 0.05$, a statistical significance difference was achieved.

# Results

## Clinical characteristics of bronchopulmonary dysplasia infants

The clinical data are listed in **Table 1**. The clinical data of 376 cases diagnosed with BPD in the past 7 years were reviewed, and 107 infants with chest HRCT were preliminarily selected through the medical system. Of the 107 patients, 5 neonates were excluded due to the poor quality of images. Ten infants with severe pulmonary infections and congenital heart disease were also eliminated. Then, another 11 neonates were removed because their HRCT was performed after a PMA of 50 weeks. Finally, 81 infants (56 males and 25 females; GA: 28.93 ± 2.25 weeks; BW: 1335.86 ± 456.80 g) were enrolled in this study.

Chest HRCT was conducted at 42.19 ± 4.82 weeks (range: 36.14–50.86 weeks) PMA. The diagnosis of PH and TBM were made at 41.72 ± 4.83 weeks (range: 34.20–50.00 weeks) PMA and 40.90 ± 4.76 weeks (range: 36.14–50.00 weeks) PMA, respectively. There was a 4.56 ± 2.82 weeks (range: 0.14–9.57 weeks) gap between the assessment of the severity of BPD and the HRCT scanning because HRCT was postponed until the conditions of the patients were stable for the examination. The time interval between HRCT and PH diagnosis was 0.48 ± 0.28 weeks. The time interval between HRCT and TBM diagnosis was 1.01 ± 0.59 weeks. The volume of the CT dose index ($CTDI_{vol}$) and dose-length product (DLP) averaged 0.89 ± 0.22 mGy and 15.40 ± 5.09 mGy/cm, respectively.

TABLE 1 Clinical data of 81 BPD patients.

| Characteristic | |
|---|---|
| GA (w) | 28.93 ± 2.25 |
| >28 w | 40/81 |
| ≤28 w | 41/81 |
| BW (g) | 1335.86 ± 456.80 |
| **Sex** | |
| Male | 56/81 (69.14%) |
| Female | 25/81 (30.86%) |
| Surfactant | 78/81 (96.3%) |
| Antenatal steroids | 35/81 (43.21%) |
| Histological chorioamnionitis | 10/81 (12.35%) |

BPD, bronchopulmonary dysplasia; BW, body weight; GA, gestational age.

## Correlation of high-resolution computed tomography scores and severity of bronchopulmonary dysplasia

A total of 17 (20.99%) infants were classified as mild BPD, 31 (38.27%) as moderate BPD, and 33 (40.74%) as severe BPD. As shown in **Table 2**, there were no statistical differences in GA, BW, and duration of respiratory support among the three groups. However, infants with severe BPD had significantly higher TS ($p = 0.01$), HS ($p = 0.02$), and PS ($p = 0.02$). Mosaic attenuation ($p = 0.03$), bulla/Bleb ($p = 0.03$), and linear densities ($p = 0.01$) also demonstrated higher scores in more severe BPD group with significant difference. By Spearman's correlation analysis, TS ($r = 0.49$, $p < 0.01$), HS ($r = 0.31$, $p < 0.01$), and PS ($r = 0.30$, $p = 0.01$) were correlated with the clinical severity of BPD. Decreased attenuation ($r = 0.21$, $p = 0.04$), mosaic attenuation ($r = 0.31$, $p = 0.01$), bulla/Bleb ($r = 0.27$, $p = 0.02$), and linear densities ($r = 0.55$, $p < 0.01$) also demonstrated a correlation with BPD severity.

## Correlation of high-resolution computed tomography scores and the diagnosis of pulmonary hypertension or tracheobronchomalacia

All the data were listed in **Table 2**. In total, 40 (49.38%) infants had PH, 8 in mild BPD, 13 in moderate BPD, and 19 in severe BPD. PH (+) group were born at significantly lower GA as compared to those without PH ($p = 0.02$). Higher TS ($r = 0.28$, $p = 0.01$) and PS ($r = 0.35$, $p < 0.01$) correlated with the diagnosis of PH. Among the PSs, higher scores of linear densities ($r = 0.34$, $p < 0.01$) and consolidation ($r = 0.24$, $p = 0.03$) were associated with the diagnosis of PH.

A total of 20 (24.69%) patients had TBM, 3 with mild BPD, 7 with moderate BPD, and 10 with severe BPD. Subglottic stenosis, tracheobronchial stenosis, and other large airway lesions were not found in this study. There was no significant difference in the GA, BW, and duration of respiratory support in hospitals between the two groups. In addition, there was no difference in any of the HRCT scores between the patients with or without TBM.

## High-resolution computed tomography scores among the different combinations of phenotypes

All the patients were subdivided into four groups: parenchymal disease (Group 1 = 39), parenchymal disease + PH (Group 2 = 22), parenchymal disease + TBM (Group 3 = 9), and parenchymal disease + PH + TBM (Group 4 = 11). Group 4 had the highest TS and HS, and Group 2 got the highest PS. All the values did not have a significant difference (**Figure 1**).

## Intra- and inter-observer agreement

In this research, intra-observer agreement was high for HS (Cronbach's $\alpha = 0.85$), PS (Cronbach's $\alpha = 0.90$), and TS (Cronbach's $\alpha = 0.88$). Inter-observer agreement was high for HS (Cronbach's $\alpha = 0.85$), PS (Cronbach's $\alpha = 0.86$), and TS (Cronbach's $\alpha = 0.86$).

# Discussion

Bronchopulmonary dysplasia (BPD) is a heterogenous lung disease that may affect the airways and pulmonary vasculature in addition to causing lung parenchymal disease. Based on main clinical presentations, three main clinical phenotypes of BPD have been reported, namely lung parenchymal disease, pulmonary vascular disease, and airway disease (3). Classification of BPD into these clinical phenotypes may facilitate clinical management and better risk stratification of BPD (3, 19). Although HRCT is frequently used to evaluate infants with BPD, to our knowledge, this study is the first study attempting to explore the association of HRCT findings with these BPD clinical phenotypes.

Several studies have demonstrated a correlation between HRCT scores and the severity of BPD (10, 16, 20). Most researchers have categorized pulmonary abnormalities into two types: hyperaeration and parenchyma lesions. In our study, we found TS, PS, and HS were all associated with the severity of BPD. Previous studies have reported that hyperaeration lesions are the most commonly found features in infants with BPD and suggested that they represent the most sensitive structural abnormalities associated with BPD severity (15, 21). Consistent with previous data, our study

TABLE 2 High-resolution computed tomography (HRCT) scores of subgroups with different phenotypes.

| BPD | Total ($n = 81$) | Mild ($n = 17$) | Moderate ($n = 31$) | Severe ($n = 33$) | *P*-value | PH (+) ($n = 40$) | PH (−) ($n = 41$) | *P*-value | TBM (+) ($n = 20$) | TBM (−) ($n = 61$) | *P*-value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| GA (w) | 28.93 ± 2.25 | 29.59 ± 2.87 | 29.16 ± 2.33 | 28.36 ± 2.95 | 0.27 | 28.23 ± 2.57 | 29.61 ± 2.72 | 0.02☆ | 29.15 ± 3.47 | 28.85 ± 2.46 | 0.67 |
| BW (g) | 1335.86 ± 456.80 | 1454.41 ± 473.97 | 1385.65 ± 404.51 | 1228.03 ± 483.83 | 0.19 | 1267.5 ± 500.1 | 1402.56 ± 405.29 | 0.19 | 1390.75 ± 541.59 | 1317.87 ± 428.96 | 0.54 |
| Duration of respiratory support in hospital (d) | 113.36 ± 78.28 | 105.59 ± 69.06 | 104.13 ± 98.01 | 126.03 ± 60.42 | 0.49 | 123.5 ± 64.18 | 103.46 ± 89.65 | 0.25 | 114.2 ± 96.01 | 113.08 ± 72.47 | 0.96 |
| **HRCT scores** | | | | | | | | | | | |
| TS | 18.23 ± 5.76 | 14.47 ± 4.95 | 16.94 ± 5.6 | 21.39 ± 4.68 | <0.01☆ | 19.9 ± 5.02 | 16.61 ± 6.03 | 0.01☆ | 11.3 ± 5.04 | 9.98 ± 5.46 | 0.19 |
| HS | 10.31 ± 5.36 | 7.88 ± 3.48 | 9.68 ± 5.27 | 12.15 ± 5.72 | 0.02☆ | 10.65 ± 5.74 | 9.98 ± 5.01 | 0.57 | 8.4 ± 3.69 | 7.77 ± 3.56 | 0.34 |
| PS | 7.93 ± 3.58 | 6.59 ± 2.9 | 7.26 ± 4.02 | 9.24 ± 3.08 | 0.02☆ | 9.25 ± 3.11 | 6.63 ± 3.56 | <0.01☆ | 19.7 ± 5.8 | 17.75 ± 5.72 | 0.50 |
| Decreased attenuation | 4.12 ± 1.98 | 3.82 ± 1.91 | 3.81 ± 1.91 | 4.58 ± 2.06 | 0.24 | 4.2 ± 2.05 | 4.05 ± 1.94 | 0.73 | 4.65 ± 1.81 | 3.95 ± 2.02 | 0.17 |
| Mosaic attenuation | 3.05 ± 2.38 | 2.18 ± 2.22 | 2.65 ± 2.26 | 3.88 ± 2.38 | 0.03☆ | 3.15 ± 2.36 | 2.95 ± 2.43 | 0.71 | 3.5 ± 2.37 | 2.9 ± 2.39 | 0.33 |
| Bulla/Bleb | 3.14 ± 2.35 | 1.88 ± 1.93 | 3.23 ± 2.09 | 3.7 ± 2.58 | 0.03☆ | 3.3 ± 2.33 | 2.98 ± 2.38 | 0.54 | 3.15 ± 2.54 | 3.13 ± 2.31 | 0.98 |
| Linear densities | 4.35 ± 1.83 | 3.18 ± 1.74 | 3.84 ± 1.9 | 5.42 ± 1.15 | <0.01☆ | 5.05 ± 1.22 | 3.66 ± 2.07 | <0.01☆ | 4.7 ± 1.84 | 4.23 ± 1.83 | 0.32 |
| Consolidation | 2.7 ± 2.32 | 2.35 ± 1.94 | 2.55 ± 2.32 | 3.03 ± 2.51 | 0.56 | 3.25 ± 2.45 | 2.17 ± 2.07 | 0.04☆ | 2.95 ± 2.33 | 2.62 ± 2.32 | 0.59 |
| Bronchial wall thickening | 0.15 ± 0.55 | 0.29 ± 0.77 | 0.13 ± 0.43 | 0.09 ± 0.52 | 0.46 | 0.15 ± 0.66 | 0.15 ± 0.42 | 0.98 | 0 ± 0 | 0.2 ± 0.63 | 0.17 |
| Bronchiectasis | 0.7 ± 1.41 | 0.76 ± 1.35 | 0.74 ± 1.41 | 0.64 ± 1.48 | 0.94 | 0.75 ± 1.51 | 0.66 ± 1.32 | 0.77 | 0.75 ± 1.65 | 0.69 ± 1.34 | 0.87 |

BPD, bronchopulmonary dysplasia; BW, body weight; GA, gestational age; HS, hyperaeration score; PH, pulmonary hypertension; PS, parenchyma score; TBM, tracheobronchomalacia; TS, total score, ☆presenting the $p < 0.05$.



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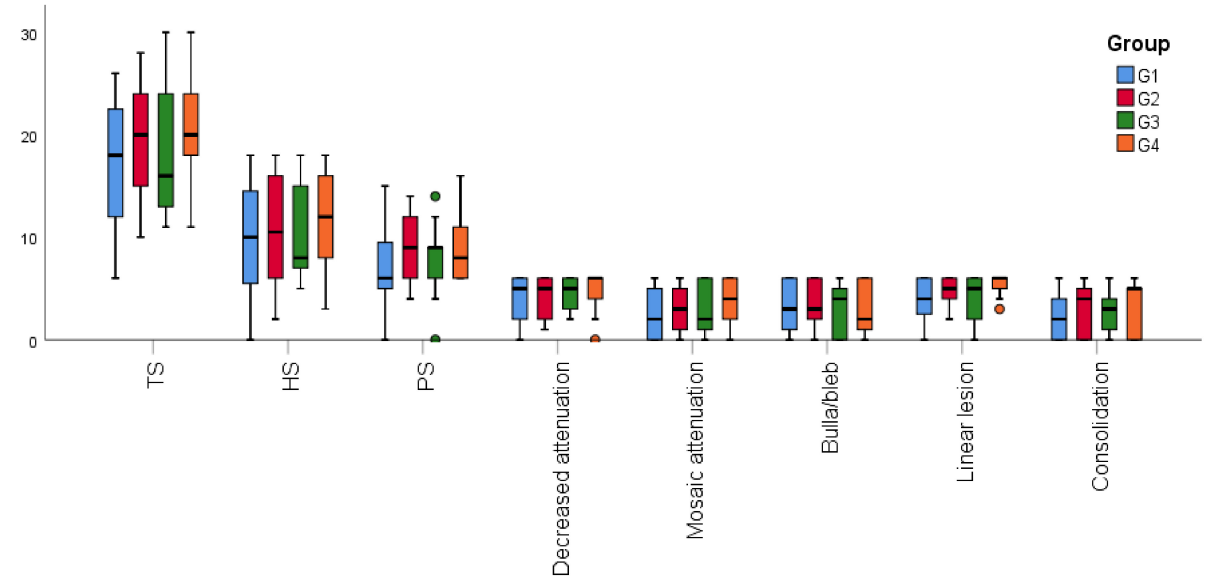


FIGURE 1
High-resolution computed tomography (HRCT) scores among the different combinations of phenotypes. G1, parenchymal disease; G2, parenchymal disease + PH; G3, parenchymal disease + TBM; G4, parenchymal disease + PH + TBM; HS, hyperaeration score; PS, parenchyma score; TS, total score.

found that all three subcategory scores of hyperaeration lesions (decrease attenuation, mosaic attenuation, and bulla/bleb) correlated with BPD severity. Previous studies have suggested that the severity of hyperaeration lesions is associated with obstructive lung disease and quantification of volume fraction of low attenuation regions has been used to predict impaired lung function in a patient with cystic fibrosis (22, 23). We speculate that HS may be a useful tool to predict lung function impairments and the development of obstructive lung disease in infants with BPD. Longer-term studies with pulmonary function testing will be needed to study this.

Current data suggest that pulmonary vascular disease may impact 16–25% of infants with BPD and increases the risk of mortality in these patients (3, 14, 24–28). Almost half of the patients enrolled in this study had PH, and a majority of them belonged to the severe BPD group. In our study, both TS and PS correlated with the diagnosis of PH. Among the PS scores, linear opacities were frequently observed in previous studies and are probably the most common features on HRCT images of BPD patients (20, 23). Linear opacities may be suggestive of alveolar septal fibrosis, obstructive ventilation impairment, and PH (29). In longitudinal studies, linear opacities did not change over time and might be considered irreversible damage in late BPD (22). We found in our study that linear opacity correlated with both the severity of BPD and PH. In addition, consolidation is another prominent feature in our patients and is also correlated with the diagnosis of PH. Our result suggests that taken together, linear opacities and consolidation might be useful parenchymal CT scores that might be used in the prediction of BPD severity and PH. However, further studies are needed to confirm this.

Clinical manifestations of large airway diseases in BPD patients are mainly bronchomalacia or tracheomalacia, either localized or generalized. The incidence of large airway diseases in BPD patients varies from 10 to 46% and contributes to air trapping, increased risk of respiratory infections, and prolonged positive pressure ventilation (3, 30, 31). Surprisingly, none of the HRCT findings was associated with the diagnosis of TBM. This could be possibly due to the small sample size since only 20 patients with TBM were included in this study. We did see a consistent trend of higher HS in all three sub-categories. Further studies with a larger sample size are needed to further explore the association of HRCT scores with TBM.

Chest radiography is the most commonly used imaging modality worldwide to assess the severity of lung disease in patients with BPD. However, compared with HRCT, chest radiography cannot reflect the abnormalities in the pulmonary parenchyma in detail. Therefore, it fails to accurately predict the clinical severity of BPD (15). HRCT can provide BPD patients with more objective and detailed information about pulmonary structural damages, and it has the potential to predict later symptoms and impairments. Considerable CT scoring methods have been adopted over the last 30 years to semi-quantify the structural abnormalities in BPD (12, 20). All of the methods proved abnormal CT findings in patients with BPD. However, no approach has been validated to be superior to other methods and there is no universally accepted CT scoring system now (20). In this study, the HRCT scoring system is a modified version

of the widely used models in the past 10 years (10, 15–17). Compared with the Ochiai scoring system, the system developed by Sung et al. is more applicable to clinical work as it calculates the scores of each lobe, not each segment. This scoring system covers the most distinguishing features of BPD. Besides, it also presents good inter-observer and intra-observer reproducibility as shown in previous studies and also seen in our study (15, 21). We, therefore, feel that this scoring system is a good objective tool to use in the research settings.

The present study has some limitations. First, the mild BPD patients without HRCT results were excluded, which would induce selection bias. Thus, the number of abnormalities might be overestimated. Second, the sample size of this study was relatively small. In the future, multicenter research with a larger sample size should be conducted to testify to the results of this study. Third, as the tricuspid regurgitant jet is undetectable in many infants, additional echocardiographic parameters are suggested to help reflect the increased pulmonary pressure, e.g., intraventricular septum flattening, right ventricular dilation and/or hypertrophy, and right ventricular dysfunction. However, these parameters were not used in our hospitals which might underestimate the incidence of PH in this research. Fourth, the association between HRCT scores and clinical outcomes was not analyzed. Hence, this study cannot provide sufficient guidance and prognostic data for the clinical management of BPD. At last, the radiation dose of the current study is relatively high, and images were only taken at the end of expiration without angiography. Further work to reduce the radiation dose of HRCT or further exploration of the utility of ultra-low dose-controlled CT angiogram protocols is needed.

## Conclusion

High-resolution computed tomography scores are correlated with the BPD severity and PH. HS might be a useful tool in the assessment of BPD severity while linear densities and consolidation might be helpful in predicting PH.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## Author contributions

QY: concept and design and acquisition of data. Q-LS: analysis and interpretation of data. QY and Q-LS: drafting the manuscript. X-HH and G-YH: revising the manuscript and final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Mechanical ventilation characteristics and their prediction performance for the risk of moderate and severe bronchopulmonary dysplasia in infants with gestational age <30 weeks and birth weight <1,500 g

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**Introduction:** Moderate and severe bronchopulmonary dysplasia (BPD) is a common pulmonary complication in premature infants, which seriously affects their survival rate and quality of life. This study aimed to describe the mechanical ventilation characteristics and evaluate their prediction performance for the risk of moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14.

**Methods:** In this retrospective cohort study, 412 infants with gestational age <30 weeks and birth weight <1,500 g were included in the analysis, including 104 infants with moderate and severe BPD and 308 infants without moderate and severe BPD (as controls). LASSO regression was used to optimize variable selection, and Logistic regression was applied to build a predictive model. Nomograms were developed visually using the selected variables. To validate the model, receiver operating characteristic (ROC) curve, calibration plot, and clinical impact curve were used.

**Results:** From the original 28 variables studied, six predictors, namely birth weight, 5 min apgar score, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, duration of invasive mechanical ventilation (IMV) and maximum of $FiO_2$ (fraction of inspiration $O_2$) were identified by LASSO regression analysis. The model constructed using these six predictors and a proven risk factor (gestational age) displayed good prediction performance for moderate and severe BPD, with an area under the ROC of 0.917 (sensitivity = 0.897, specificity = 0.797) in the training set and 0.931 (sensitivity = 0.885, specificity = 0.844) in the validation set, and was well calibrated ($P_{\text{Hosmer-Lemeshow test}} = 0.727$ and 0.809 for the training and validation set, respectively).

**Conclusion:** The model included gestational age, birth weight, 5 min apgar score, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, duration of IMV and maximum of $FiO_2$ had good prediction performance for predicting moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14.

KEYWORDS
mechanical ventilation, bronchopulmonary dysplasia, preterm infants, predictive model, newborn

# Introduction

In preterm infants, bronchopulmonary dysplasia (BPD) is one of the most common and serious pulmonary complications, seriously affecting the quality of their lives. The definition of BPD is oxygen support as needed for at least 28 days (1). According to their required fraction of inspired oxygen ($FiO_2$) at 36 weeks of corrected gestational age, infants with gestational age <32 weeks were categorized as mild (no oxygen requirement), moderate (21%–30%) or severe BPD (over 30% or positive pressure assistance) (1). With the improvement of the treatment success rate of very low birth weight infants (VLBWI, birth weight <1,500 g) and extremely low birth weight infants (ELBWI, birth weight <1,000 g), the incidence of BPD is also increasing. According to the studies from many countries, BPD's incidence varies from 11 to 50%, due to the different diagnostic and treatment criteria (2). BPD incidence increases as the gestational age or birth weight decreases. Previous studies have reported that about 30% of VLBWI suffer from BPD (3), the incidence rate of BPD fluctuated between 12.9% and 41% in infants with gestational age <32 weeks, and the incidence rate can reach 80% in infants with gestational age <25 weeks (4). The quality of life for preterm infants with BPD is reduced due to a higher mortality rate and a higher incidence of pulmonary, cardiovascular, and neurodevelopmental disorders (5, 6). Moreover, preterm infants with moderate and severe BPD are more likely to suffer complications and comorbidities, including longer hospital stays, respiratory support after discharge and higher death risk (7, 8). Therefore, clarifying the predictors of moderate and severe BPD, early screening and prevention of moderate and severe BPD is of great significance not only for clinical control of moderate and severe BPD, but also for improving the prognosis of preterm infants.

Many clinical risk factors for BPD have been reported in infants with gestational age <32 weeks over the past few decades (9). To our knowledge, smaller gestational age and lower birth weight are proven risk factors for BPD (9). Other perinatal and postpartum factors can increase the risk of BPD, such as chorioamnionitis, patent ductus arteriosus (PDA), neonatal pneumonia, neonatal respiratory distress syndrome (10). Moreover, supportive care with mechanical ventilation is an essential strategy for managing severe neonatal respiratory failure. It is well known that the ventilator-induced lung injury is an important risk factor for BPD (11). In a study involving 17 centers, the authors developed and validated models for BPD risk at 6 postnatal ages using gestational age, birth weight, race and ethnicity, sex, respiratory support, and $FiO_2$, and found that gestational age conveyed the most predictive information for BPD risk on Postnatal Days 1 and 3, and respiratory support on Days 7, 14, 21, and 28 (12). Although previous predictive models for BPD have been described (12–14), studies focused on the risk factors and prediction models for moderate and severe BPD are few, especially in infants with gestational age <30 weeks and birth weight <1,500 g. In the current study, based on the clinical characteristics and the different types of mechanical ventilation up to postnatal Day 14, we analysed and identified risk factors affecting moderate and severe BPD, and developed a meaningful risk prediction model for paediatricians and neonatologists to perform early screening of moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14. The prediction model could be used to target VLBWI at the highest risk of moderate and severe BPD, to tailor follow-up and preventive measures for VLBWI.

# Methods

## Participants and data collection

This was a retrospective study based on electronic medical records from NingBX neonatal perinatal network (http://www.ningbx.com). Infants with gestational age <30 weeks and birth weight <1,500 g were recruited at the Department of Pediatrics, Nanjing Maternity and Child Health Care Hospital from January 2018 to December 2021. This study was approved by the Ethics Committee of Nanjing Maternity and Child Health Care Hospital, and either a legal guardian or parent provided informed consent. Moderate and severe BPD is defined as oxygen requirement ($FiO_2 > 21\%$) for at least 28 days, and the need for any type of respiratory support at 36 weeks post-menstrual age (1, 15). The preterm infants with moderate and severe BPD were assigned to the case group, while preterm infants without moderate and severe BPD were assigned to the control group. Inclusion criteria were: (1) gestational age at birth <30 weeks and birth weight <1,500 g; (2) infants hospitalized within 1 day after birth. Whereas exclusion criteria were: (1) infants hospitalized for less than 28 days and lost to follow-up after discharge, who still required continued oxygen inhalation and hospitalization; (2) infants with severe congenital malformation; (3) infants with pneumothorax or pleural effusion; (4) infants undergoing surgery; (5) infants who died less than 28 days after birth;

(6) incomplete data. At last, 412 infants with gestational age <30 weeks and birth weight <1,500 g were included in the analysis, including 104 infants with moderate and severe BPD and 308 controls.

We also collected multiple maternal and neonatal data according to electronic medical records up to postnatal Day 14, including maternal characteristics, medication use, neonatal characteristics, mechanical ventilation and oxygen requirement (**Table 1**). The maternal characteristics included gestational diabetes mellitus, maternal hypertension and chorioamnionitis. Medication use included prenatal use of glucocorticoids and magnesium sulfate. The neonatal characteristics included infant gender, gestational age at birth (weeks), birth weight (g), delivery mode, 1 min and 5 min apgar score, neonatal asphyxia, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, patent ductus arteriosus (PDA), PDA size (mm), PDA treatment, PDA and ventricular septal defect, intraventricular hemorrhage (IVH III/IV), sepsis, and necrotizing enterocolitis (NEC ≥ Stage II). Neonatal asphyxia is defined as the inability of neonates to initiate and maintain breathing at birth, followed by impaired gas exchange, resulting in progressive hypoxemia, hypercapnia, and severe metabolic acidosis. Mild asphyxia is diagnosed by 1 min apgar score ≤7, or 5 min apgar score ≤7 and umbilical cord arterial pH <7.2; whereas severe asphyxia is diagnosed by 1 min apgar score ≤3, or 5 min apgar score ≤5 and umbilical cord arterial pH <7.0.

The characteristics of mechanical ventilation and oxygen requirement included conventional mechanical ventilation (CMV), duration of CMV (days), high frequency ventilation (HFV), duration of HFV (days), continuous positive airway pressure (CPAP), duration of CPAP (days), high-flow nasal cannula (HFNC), duration of HFNC (days), Bi-level positive airway pressure (BiPAP), duration of BiPAP (days), nasal intermittent positive pressure ventilation (NIPPV), duration of NIPPV (days), invasive mechanical ventilation (IMV), duration of IMV (days), noninvasive mechanical ventilation (NIMV), duration of NIMV (days), duration of $FiO_2 > 21\%$ (days), and maximum of $FiO_2$ (%). IMV includes CMV and HFV, and NIMV includes CPAP, HFNC, BiPAP and NIPPV.

## Statistical analyses

Statistical analyses were conducted by applying R (v4.1.3) software. Normally distributed continuous variables were displayed as mean (SD) and skewed distributed variables as median (25th, 75th), and Student's *t*-test or Mann-Whitney test were used to compare the two study groups. For categorical variables, frequency (percentage) was displayed and compared using $\chi^2$ test or Fisher exact test.

Based on the significantly different clinical characteristics ($P < 0.05$), we sought to build predictive model for moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14. First, conforming to a ratio of 3 : 1, we randomly divided the 412 preterm infants into a training set with 309 infants and a validation set with 103 infants. To identify the best predictors of current risk factors, LASSO (least absolute shrinkage and selection operator) regression was performed in the training set using R *glmnet* package (16). As the dependent variable is whether moderate and severe BPD is present or not, we set family = "binomial" and set type.measure = "deviance". Based on the binomial family and the type measure of deviance, the LASSO regression analysis runs a ten-fold cross-validation for centralizing and normalizing the variables included, and then the best lambda value was picked. In terms of performance, *Lambda.1se* gives the best results, but with the fewest independent variables. Then the R *rms* package was used to run logistic regression to construct a prediction model for moderate and severe BPD by introducing the factors selected in the LASSO regression and the proven risk factors for moderate and severe BPD. All of the selected factors were applied to construct nomogram prediction model. In order to easily approximate the individual-specific risk of moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14, a graphical nomogram was also created (17).

Additionally, the accuracy of the model was estimated using several validation methods using the data of training set and validation set, respectively (16, 18). Receiver-operator characteristic (ROC) curve was constructed with the R *pROC* package, and the area under the ROC curve (AUC) provided good discrimination between true positives and false positives for the quality of the risk nomogram. Using the "best threshold" criteria of the ROC curve, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated to illustrate the model effects. To evaluate the calibration of the moderate and severe BPD risk nomogram, along with the Hosmer-Lemeshow test, the R *rms* package was used to draw the calibration curves. As well, clinical impact curves were drawn using the R *rmda* package to determine whether the nomogram is clinically practicable for predicting moderate and severe BPD. All statistical significance levels reported were two-sided, and $P < 0.05$ was considered to be significant.

# Results

## Clinical characteristics and treatment

In total, 519 infants with gestational age <30 weeks and birth weight <1,500 g were recruited in Nanjing Maternity and Child Health Care Hospital from 2018 to 2021. We

TABLE 1 Characteristics of the 412 preterm infants with gestational age <30 weeks and birth weight <1,500 g enrolled in the study according to presence/absence of moderate and severe bronchopulmonary dysplasia (BPD) and randomization to training set and validation set.

| Items | Total infant cohort ($n = 412$) | Infants with moderate and severe BPD ($n = 104$) | Infants without moderate and severe BPD ($n = 308$) | Training set ($n = 309$) | Validation set ($n = 103$) | *P* value |
|---|---|---|---|---|---|---|
| Boy | 236 (57.3%) | 60 (57.7%) | 176 (57.1%) | 134 (43.4%) | 42 (40.8%) | 0.922 |
| Gestational age (weeks) | 28.3 (27.1, 29.1) | 27.1 (26.0, 28.1) | 28.6 (27.9, 29.3) | 28.3 (27.1, 29.0) | 28.7 (27.4, 29.3) | <0.001 |
| Birth weight (g) | 1109.0 ± 200.9 | 961.7 ± 191.3 | 1158.8 ± 178.7 | 1098.4 ± 195.8 | 1140.9 ± 213.6 | <0.001 |
| Cesarean delivery | 187 (45.4%) | 27 (26.0%) | 160 (51.9%) | 137 (44.3%) | 50 (48.5%) | <0.001 |
| 1 min apgar score | 8 (6, 10) | 6 (3.3, 8) | 9 (7, 10) | 8 (6, 10) | 8 (6, 9) | <0.001 |
| 5 min apgar score | 9 (8, 10) | 8 (7.3, 9) | 10 (9, 10) | 9 (8, 10) | 9 (8, 10) | <0.001 |
| Gestational diabetes mellitus | 86 (20.9%) | 20 (19.2%) | 66 (21.4%) | 70 (22.7%) | 16 (15.5%) | 0.633 |
| Maternal hypertension | 32 (7.8%) | 6 (5.8%) | 26 (8.4%) | 27 (8.7%) | 5 (4.9%) | 0.379 |
| Chorioamnionitis | 151 (36.7%) | 31 (29.8%) | 120 (39.0%) | 119 (38.5%) | 32 (31.1%) | 0.094 |
| Prenatal use of glucocorticoids | 380 (92.2%) | 94 (90.4%) | 286 (92.9%) | 291 (94.2%) | 89 (86.4%) | 0.415 |
| Prenatal use of magnesium sulfate | 270 (65.5%) | 73 (70.2%) | 197 (64.0%) | 198 (64.1%) | 72 (69.9%) | 0.248 |
| Neonatal asphyxia | 144 (35.0%) | 64 (61.5%) | 80 (26.0%) | 111 (35.9%) | 33 (32.0%) | <0.001 |
| Neonatal respiratory distress syndrome (≥Class II) | 49 (11.9%) | 25 (24.0%) | 24 (7.8%) | 35 (11.3%) | 14 (13.6%) | <0.001 |
| Neonatal pneumonia | 159 (38.6%) | 77 (74.0%) | 82 (26.6%) | 120 (38.8%) | 39 (37.9%) | <0.001 |
| Patent ductus arteriosus (PDA) | 297 (72.1%) | 84 (80.8%) | 213 (69.2%) | 234 (75.7%) | 63 (61.2%) | 0.022 |
| PDA size (mm) | 1.7 (0, 2.3) | 2.0 (0, 2.6) | 1.5 (0, 2.2) | 1.7 (0.4, 2.3) | 1.3 (0, 2.3) | 0.002 |
| PDA treatment | 99 (24.0%) | 55 (52.9%) | 44 (14.3%) | 74 (23.9%) | 25 (24.3%) | <0.001 |
| PDA and ventricular septal defect | 6 (1.5%) | 2 (1.9%) | 4 (1.3%) | 5 (1.6%) | 1 (1.0%) | 0.645 |
| Intraventricular hemorrhage (IVH III/IV) | 72 (17.5%) | 35 (33.7%) | 37 (12.0%) | 57 (18.4%) | 15 (14.6%) | <0.001 |
| Sepsis | 130 (31.6%) | 46 (44.2%) | 84 (27.3%) | 102 (33.0%) | 28 (27.2%) | 0.001 |
| Necrotizing enterocolitis (NEC ≥ Stage II) | 25 (6.1%) | 11 (10.6%) | 14 (4.5%) | 23 (7.4%) | 2 (1.9%) | 0.026 |
| Conventional mechanical ventilation (CMV) | 141 (34.2%) | 69 (66.3%) | 72 (23.4%) | 112 (36.2%) | 29 (28.2%) | <0.001 |
| Duration of CMV (days) | 0 (0, 3) | 5 (0, 10) | 0 (0, 0) | 0 (0, 4) | 0 (0, 1) | <0.001 |
| High frequency ventilation (HFV) | 36 (8.7%) | 30 (28.8%) | 6 (1.9%) | 28 (9.1%) | 8 (7.8%) | <0.001 |
| Duration of HFV (days) | 0 (0, 0) | 0 (0, 1) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | <0.001 |
| Continuous positive airway pressure (CPAP) | 315 (76.5%) | 45 (43.3%) | 270 (87.7%) | 240 (77.7%) | 75 (72.8%) | <0.001 |
| Duration of CPAP (days) | 6 (1, 10) | 0 (0, 4) | 7.5 (4, 11) | 6 (1, 11) | 5 (0, 9) | <0.001 |
| High-flow nasal cannula (HFNC) | 161 (39.1%) | 5 (4.8%) | 156 (50.6%) | 124 (40.1%) | 37 (35.9%) | <0.001 |
| Duration of HFNC (days) | 0 (0, 3) | 0 (0, 0) | 1 (0, 4) | 0 (0, 4) | 0 (0, 3) | <0.001 |
| Bi-level positive airway pressure (BiPAP) | 29 (7.0%) | 8 (7.7%) | 21 (6.8%) | 20 (6.5%) | 9 (8.7%) | 0.763 |
| Duration of BIPAP (days) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0.792 |
| Nasal intermittent positive pressure ventilation (NIPPV) | 170 (41.3%) | 58 (55.8%) | 112 (36.4%) | 116 (37.5%) | 54 (52.4%) | 0.001 |
| Duration of NIPPV (days) | 0 (0, 5) | 2 (0, 6.8) | 0 (0, 4) | 0 (0, 4) | 1 (0, 7) | 0.002 |
| Invasive mechanical ventilation (IMV) | 148 (35.9%) | 76 (73.1%) | 72 (23.4%) | 114 (36.9%) | 34 (33.0%) | <0.001 |

(*continued*)

TABLE 1 Continued

| Items | Total infant cohort ($n = 412$) | Infants with moderate and severe BPD ($n = 104$) | Infants without moderate and severe BPD ($n = 308$) | Training set ($n = 309$) | Validation set ($n = 103$) | *P* value |
|---|---|---|---|---|---|---|
| Duration of IMV (days) | 0 (0, 4) | 7 (0, 13) | 0 (0, 0) | 0 (0, 4.5) | 0 (0, 3) | <0.001 |
| Noninvasive mechanical ventilation (NIMV) | 382 (92.7%) | 79 (76.0%) | 303 (98.4%) | 285 (92.2%) | 97 (94.2%) | <0.001 |
| Duration of NIMV (days) | 14 (10, 14) | 7 (1, 14) | 14 (12, 14) | 14 (9, 14) | 14 (11, 14) | <0.001 |
| Duration of $FiO_2 > 21\%$ (days) | 14 (14, 14) | 14 (14, 14) | 14 (14, 14) | 14 (14, 14) | 14 (14, 14) | 0.019 |
| Maximum of $FiO_2$ (%) | 30 (30, 45) | 50 (40, 80) | 30 (25, 40) | 30 (30, 45) | 35 (30, 40) | <0.001 |

Note: *P* value for comparison between infants with and without moderate and severe BPD.

excluded 79 uncured infants hospitalized for less than 28 days and lost to follow-up after discharge; 3 infants with severe congenital malformation; 7 infants with pneumothorax or pleural effusion; 13 infants undergoing surgery; and 5 infants who died less than 28 days after birth. At last, 412 infants were included in the analysis (Figure 1), including 104 infants with moderate and severe BPD and 308 infants without moderate and severe BPD (as controls). These infants were randomly divided into a training set with 309 infants and a validation set with 103 infants for external validation.

The maternal characteristics, medication use, neonatal characteristics, mechanical ventilation and oxygen requirement up to postnatal Day 14 are shown in Table 1. In terms of maternal characteristics and medication use, the rates of gestational diabetes mellitus, hypertension, chorioamnionitis, prenatal use of glucocorticoids and magnesium sulfate were similar between the two study groups. In terms of neonatal characteristics, the gestational age, birth weight, cesarean delivery rate, 1 min and 5 min apgar score were significantly lower in infants with moderate and severe BPD than those in control group (all $P < 0.001$). Whereas the rates of neonatal asphyxia, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, PDA, PDA treatment, IVH III/IV, sepsis, and NEC (≥Stage II) were significantly higher in infants with moderate and severe BPD (all $P < 0.05$), and the PDA size was also larger in infants with moderate and severe BPD ($P = 0.002$).

We then focused on the characteristics of mechanical ventilation and oxygen requirement up to postnatal Day 14 between the two study groups. In infants with moderate and severe BPD, the rates of CMV, HFV, NIPPV and IMV, and the duration of CMV, HFV, NIPPV and IMV were significantly higher than those in control group (all $P < 0.01$), whereas the rates of CPAP, HFNC and NIMV, and the duration of CPAP, HFNC and NIMV were significantly lower than that in control group ($P < 0.001$). For oxygen requirement, the maximum of $FiO_2$ was significantly higher in infants with moderate and severe BPD ($P < 0.001$).

## Construction of predictive model

The significant items in Table 1 were selected for predictive variables using LASSO regression analysis. As a result, 6 of the original 28 variables were considered in the predictive model, including birth weight, 5 min apgar score, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, duration of IMV and maximum of $FiO_2$ (Figure 2). In the LASSO regression model, these 6 variables had non-zero coefficients. As smaller gestational age is proven risk factors for moderate and severe BPD, we also introduced this variable into the predictive model. In Table 2, we present the results of the logistic regression analysis for these 7 variables. Based on the predictive model, a nomogram was used to quantitatively predict the risk probability of moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14 (Figure 3A). As an example, an infant with gestational age of 25.7 weeks, birth weight of 780 g, 5 min apgar score of 9, without neonatal respiratory distress syndrome (≥Class II), with neonatal pneumonia, a duration of IMV for 13 days, and maximum of $FiO_2$ of 55%, has an estimated probability of moderate and severe BPD of 0.879 (Figure 3B).

## Validation of predictive model

In order to evaluate the predictive model's discriminatory capacity, the ROC curve was used. The pooled AUC of the predictive model is 0.917 (sensitivity = 0.897, specificity = 0.797) in the training set and 0.931 (sensitivity = 0.885, specificity = 0.844) in the validation set, which indicates good performance (Figure 4). We also conducted a sensitivity analysis for severe BPD alone, with the pooled AUC of 0.933 (sensitivity = 0.900, specificity = 0.847) in the total data set. Afterwards, the predictive model was calibrated using a calibration plot and Hosmer–Lemeshow test. According to the

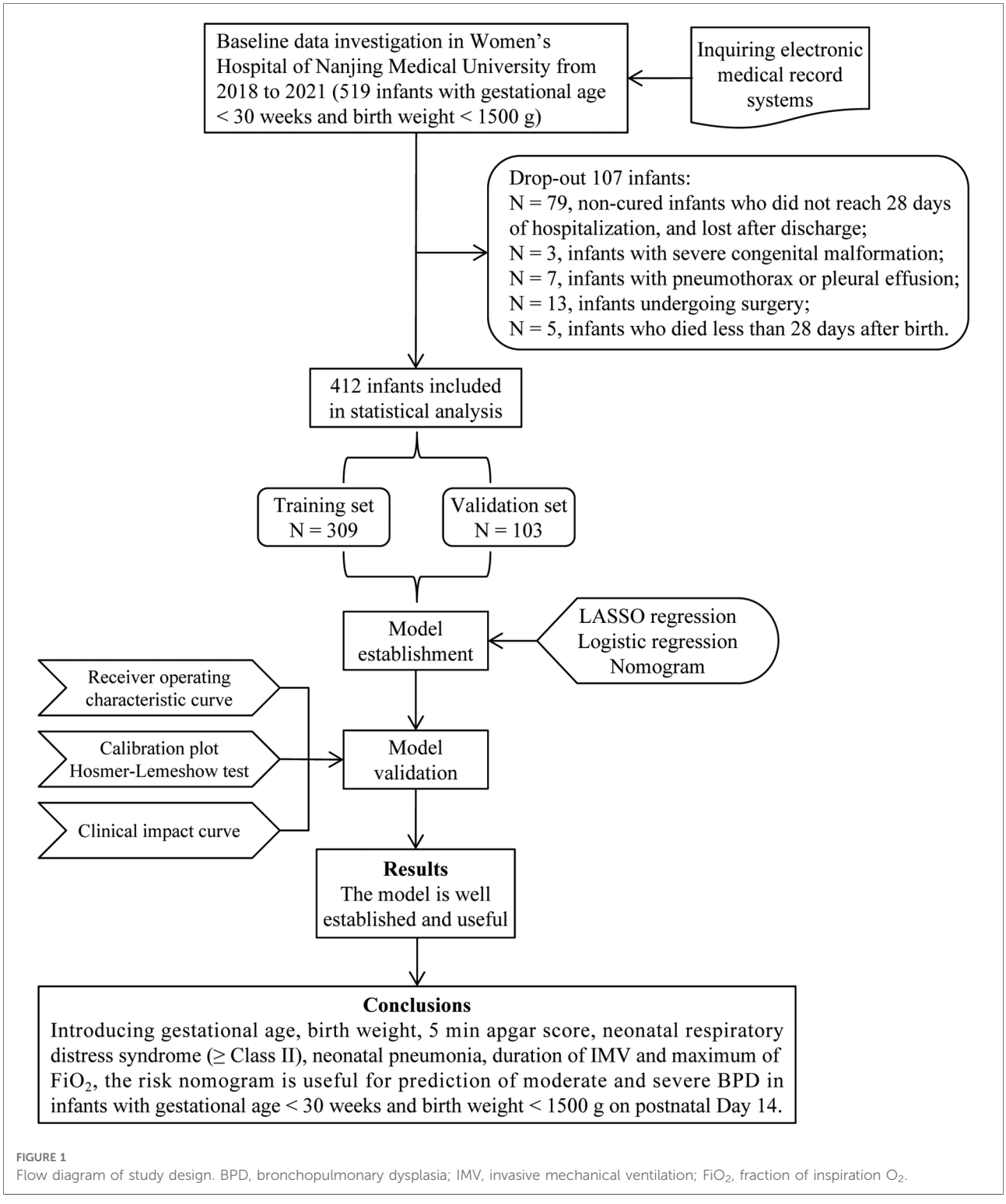


FIGURE 1
Flow diagram of study design. BPD, bronchopulmonary dysplasia; IMV, invasive mechanical ventilation; $FiO_2$, fraction of inspiration $O_2$.

calibration curves, the predictive model fit the data very well (Figure 5). Moreover, the Hosmer–Lemeshow test showed high consistency between actual and predicted probabilities ($P = 0.727$ for training set, $P = 0.809$ for validation set).

Figure 6 shows the predictive model's clinical impact curves. The red solid line shows the total number of patients deemed high risk at each risk threshold out of 1,000. The blue dashed line indicates how many of those were true positives.

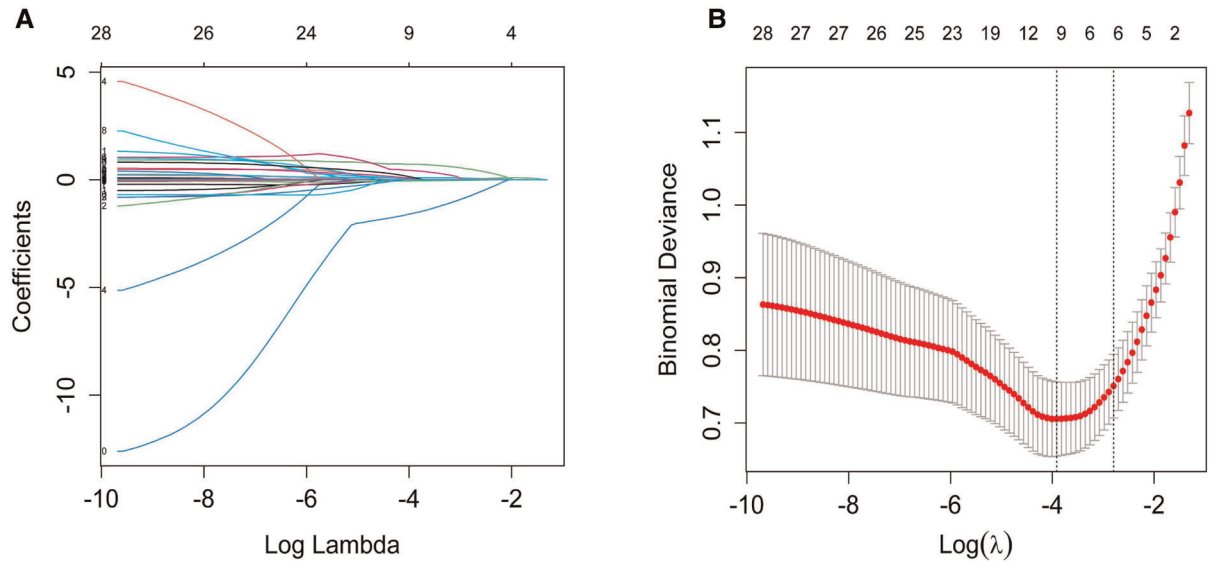


FIGURE 2
Variable selection by the LASSO binary logistic regression model. (A) A coefficient profile plot was constructed against the log(lambda) sequence. Twenty-eight variables with nonzero coefficients were selected by deriving the optimal lambda. (B) Following verification of the optimal lambda in the LASSO model, we plotted the binomial deviance curve versus log(lambda) and drew dotted vertical lines based on 1 standard error criteria. LASSO, Least absolute shrinkage and selection operator.

**TABLE 2** Logistic regression analysis of the predictors for the risk of moderate and severe bronchopulmonary dysplasia (BPD) in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14.

| Intercept and variables | Estimate | Standard error | *z* value | *P* value | Odds ratio | Confidence interval (2.5%) | Confidence interval (97.5%) |
|---|---|---|---|---|---|---|---|
| Intercept | 1.843 | 3.646 | 0.506 | 0.613 | 6.316 | – | – |
| Gestational age (weeks) | 0.002 | 0.147 | 0.010 | 0.992 | 1.002 | 0.750 | 1.337 |
| Birth weight (g) | −0.003 | 0.001 | −2.817 | 0.005 | 0.997 | 0.995 | 0.999 |
| 5 min apgar score | −0.217 | 0.107 | −2.034 | 0.042 | 0.805 | 0.653 | 0.992 |
| Neonatal respiratory distress syndrome (≥Class II) | 1.224 | 0.405 | 3.018 | 0.003 | 3.400 | 1.536 | 7.527 |
| Neonatal pneumonia | 1.325 | 0.324 | 4.093 | <0.001 | 3.762 | 1.995 | 7.097 |
| Duration of IMV (days) | 0.116 | 0.042 | 2.728 | 0.006 | 1.123 | 1.033 | 1.22 |
| Maximum of $FiO_2$ (%) | 0.020 | 0.009 | 2.302 | 0.021 | 1.020 | 1.003 | 1.038 |

Note: IMV, invasive mechanical ventilation; $FiO_2$, fraction of inspiration $O_2$.

## Discussion

In the prediction model we constructed for moderate and severe BPD, seven variables, namely gestational age, birth weight, 5 min apgar score, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, duration of IMV and maximum of $FiO_2$, are important predictors for moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14. Using these 7 predictors, the constructed model displayed good prediction performance for moderate and severe BPD, with an AUC of 0.917 in the training set and 0.931 in the validation set, and was well calibrated. Further sensitivity analysis for severe BPD alone showed the pooled AUC of the model is 0.933 in the total data set. Previously identified risk factors for BPD include gestational age, birth weight, oxygen therapy, mechanical ventilation, and duration of assisted ventilation (12). These factors measured up to postnatal Day 14 were included in our model. Besides, we added 5 min apgar score, neonatal respiratory distress syndrome (≥Class II) and neonatal pneumonia into our model, which have improved the prediction performance for the risk of moderate and severe BPD. Risk factors that were reported to be significant in previous studies but that were

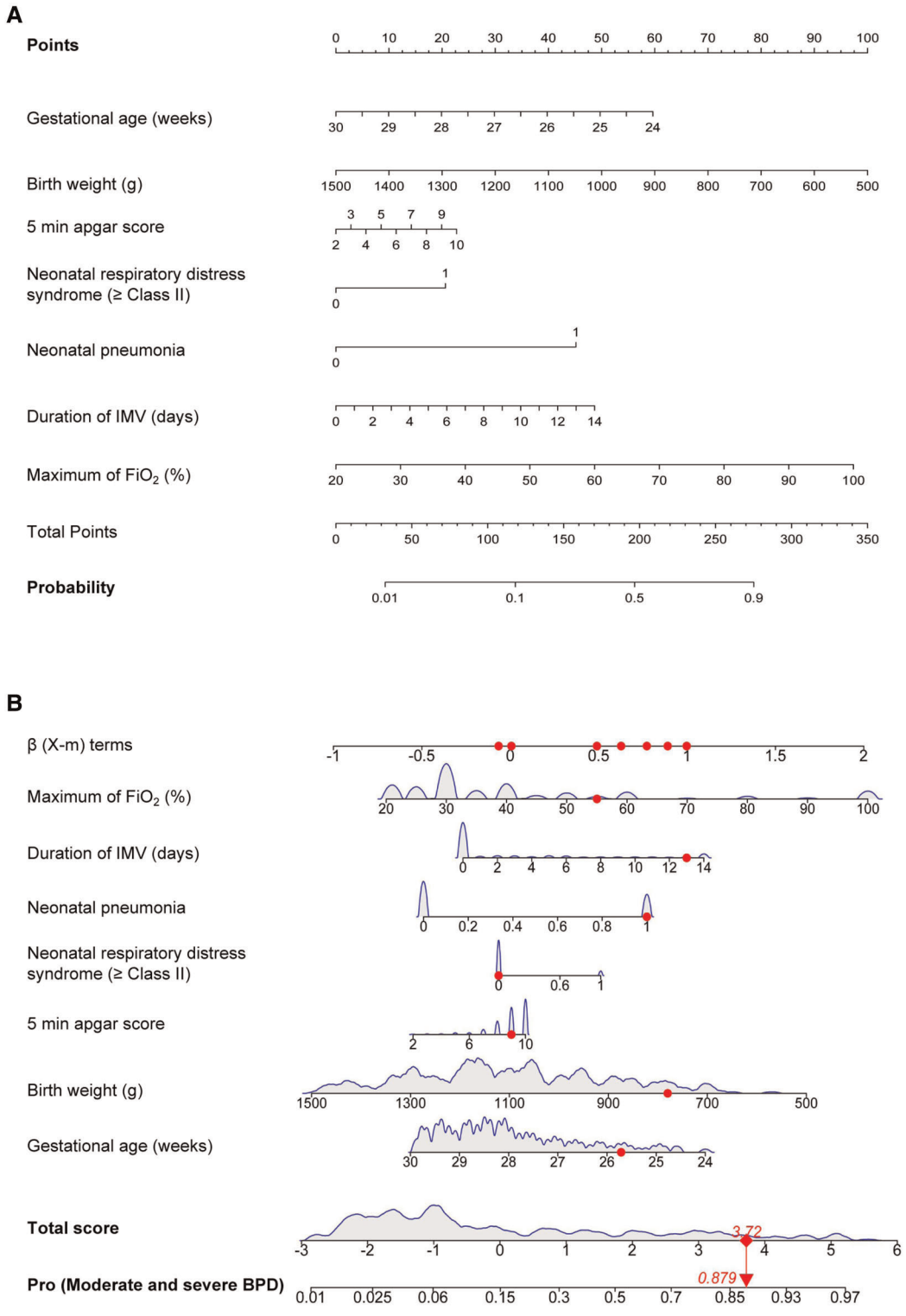


FIGURE 3
Moderate and severe BPD risk nomogram prediction model. (A) Risk factors of gestational age, birth weight, 5 min apgar score, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, duration of IMV and maximum of $FiO_2$ for nomogram prediction model. (B) Dynamic nomogram used as an example. BPD, bronchopulmonary dysplasia; IMV, invasive mechanical ventilation; $FiO_2$, fraction of inspiration $O_2$.

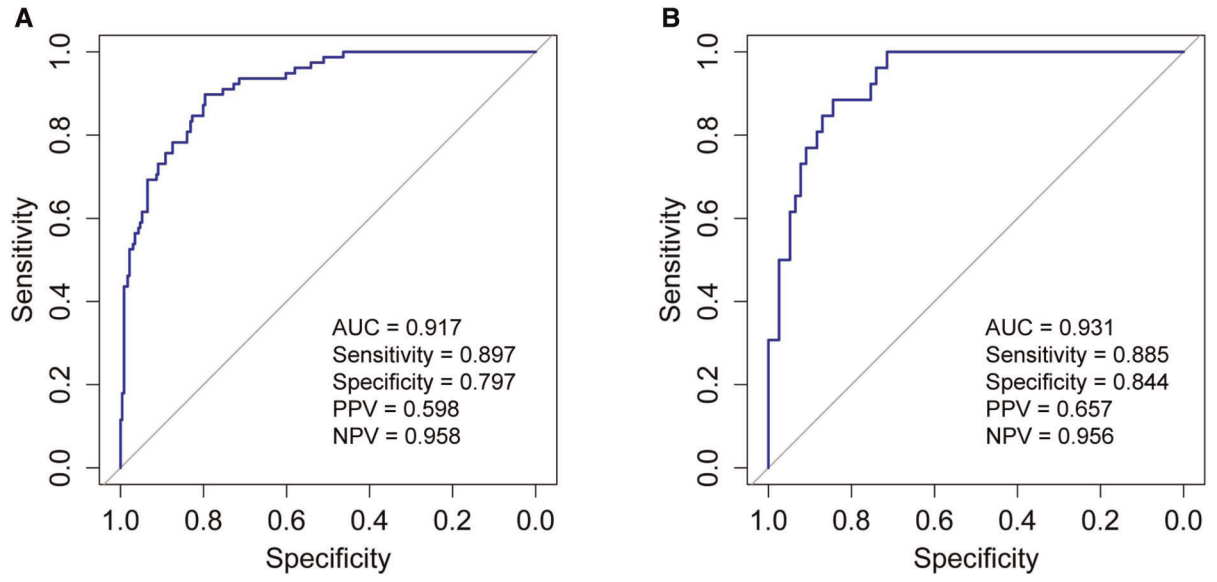


FIGURE 4
Receiver operating characteristic curve (ROC) validation of the moderate and severe BPD risk nomogram prediction. The *y*-axis represents the true positive rate of the risk prediction, the *x*-axis represents the false positive rate of the risk prediction. (A) The performance in the training set; (B) the performance in the validation set. BPD, bronchopulmonary dysplasia; AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value.

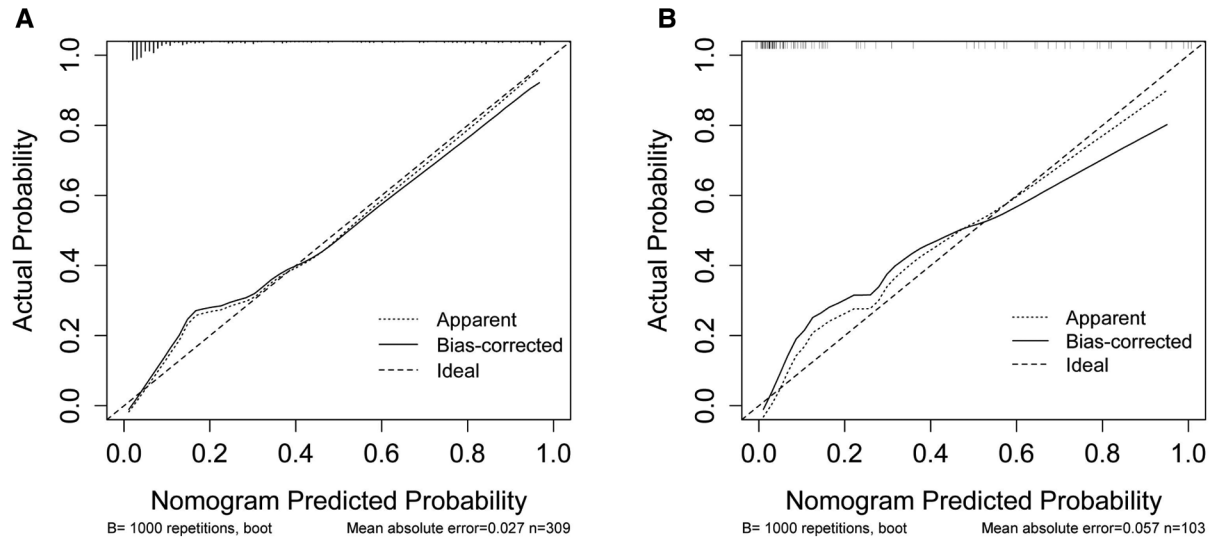


FIGURE 5
Calibration curves of the moderate and severe BPD risk nomogram. The *y*-axis represents actual diagnosed cases of moderate and severe BPD, the *x*-axis represents the predicted risk of moderate and severe BPD. The diagonal dotted line represents a perfect prediction by an ideal model, the solid line represents the performance of the moderate and severe BPD risk nomogram in the training set (A) and validation set (B), with the results indicating that a closer fit to the diagonal dotted line represents a better prediction. BPD, bronchopulmonary dysplasia.

not included in our final model include male sex, PDA, NEC, and sepsis (12). These factors were considered in this study and were significantly different between the two study groups, but were not selected by further LASSO regression. Medical resource and management practices for preterm infants, as well as risk factors for BPD, vary from region to region, which may partly explain the differences between models.

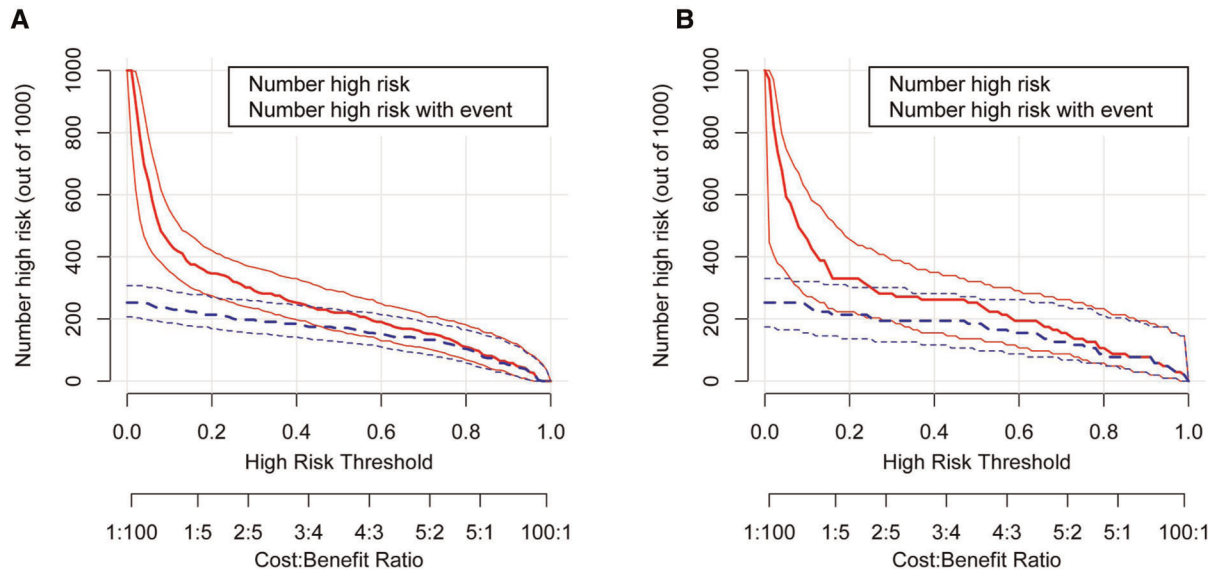


FIGURE 6
The clinical impact curve for the moderate and severe BPD predictive model. Of 1,000 patients, the red solid line shows the total number who would be deemed high risk for each risk threshold. The blue dashed line shows how many of those would be true positives (cases). (A) From the training set; (B) from the validation set. BPD, bronchopulmonary dysplasia.

In this study, a novel statistical method (LASSO regression) was used to identify the predictors for moderate and severe BPD. LASSO regression analysis minimizes the prediction error of quantitative response variables by imposing constraints on model parameters and reducing the regression coefficients of some variables to zero (16), thus providing more accurate results. A graphical nomogram was produced for obstetricians to easily use the constructed model to quantitatively predict the risk probability of moderate and severe BPD in preterm infants. Moreover, ROC, calibration and clinical impact curves were constructed to verify the model's stability and accuracy. However, the limitations of this study need to be acknowledged. Firstly, this is a retrospective study. Secondly, due to the limited infants with gestational age <30 weeks and birth weight <1,500 g, the sample size of the training set and validation set was relatively small. Researchers will investigate more thoroughly in the future by involving a larger sample of preterm infants and assessing a broader range of risk factors.

In the comparison of mechanical ventilation characteristics and oxygen requirement between the two study groups, we found that duration of IMV, duration of $FiO_2 > 21\%$, and maximum of $FiO_2$ in the infants with moderate and severe BPD were significantly higher than those in the control group, which was consistent with most studies (19, 20). Mechanical ventilation and high concentration of oxygen can cause increased reactive oxygen species and alveolar hyper-expansion, resulting in local oxidative stress injury, pressure and volume injury (20, 21). Interestingly, only duration of IMV and maximum of $FiO_2$ were identified in further LASSO regression analysis. It is estimated that 65% of the preterm infants with birth weight <1,500 g received IMV support in the delivery room and/or during their admission (22). Although IMV can be lifesaving and improve the preterm infants' respiratory status, it is related with increased risks of BPD, air leak syndrome and neurodevelopmental impairment, and may result in long-lasting consequences (20, 23). To reduce these adverse effects of IMV, preterm infants are increasingly received non-invasive respiratory support, often beginning in the delivery room (22). In general, NIMV refers to any ventilator support technique that does not require tracheal intubation but uses constant or variable pressure. In modern neonatal ventilators, improvements in the measurement of flow and volume have led to a variety of alternative NIMV procedures, such as CPAP, HFNC, BiPAP and NIPPV. In clinical practice, restricting IMV usage has been shown to be feasible and reduce the incidence of BPD and neurodevelopmental impairments (19, 24, 25). In addition, risk for respiratory disease has often been quantified by duration and concentration of supplemental oxygen, both of which could contribute to oxygen toxicity and serve as a marker for severity of disease (21, 26). Cumulative supplemental oxygen has been shown to be independently associated with BPD or death (21). In this study, based on the clinical characteristics and the different types of mechanical ventilation, we developed a meaningful risk prediction model for paediatricians and neonatologists to perform early screening of moderate and severe BPD in infants with

gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14. The prediction model could be used to target VLBWI at the highest risk of moderate and severe BPD, to tailor follow-up and preventive measures for VLBWI.

## Conclusions

The 7 predictors verified by nomogram, including gestational age, birth weight, 5 min apgar score, neonatal respiratory distress syndrome (≥Class II), neonatal pneumonia, duration of IMV and maximum of $FiO_2$, are very meaningful in identifying risk of moderate and severe BPD in infants with gestational age <30 weeks and birth weight <1,500 g on postnatal Day 14. Also, these indicators are helpful for early screening of moderate and severe BPD and provide prognostic information for families and clinicians.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Nanjing Maternity and Child Health Care Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

## Author contributions

XC and SH initiated, conceived and supervised the study. JY, LL and HL did data collection and performed the data analysis. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Respiratory support strategies in the management of severe, longstanding bronchopulmonary dysplasia

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Despite efforts to minimize ventilator-induced lung injury, some preterm infants require positive pressure support after 36 weeks' post-menstrual age. Infants with severe BPD typically experience progressive mismatch of ventilation and perfusion, which manifests as respiratory distress, hypoxemia in room air, hypercarbia, and growth failure. Lung compliance varies, but lung resistance generally increases with prolonged exposure to positive pressure ventilation and other sources of inflammation. Serial lung radiographs reveal a heterogeneous pattern, with areas of both hyperinflation and atelectasis; in extreme cases, macrocystic changes may be noted. Efforts to wean the respiratory support are often unsuccessful, and trials of high frequency ventilation, exogenous corticosteroids, and diuretics are common. The incidence of pulmonary hypertension increases with the severity of BPD, as does the mortality rate. Therefore, periodic screening and efforts to mitigate the risk of PH is fundamental to the management of longstanding BPD. Failure of conventional, lung-protective strategies (e.g., high rate/low tidal-volume and/or high frequency ventilation) warrants consideration of ventilatory strategies individualized to the disease physiology. Non-invasive modes of respiratory support may be successful in infants with mild to moderate BPD phenotypes. However, infants with moderate to severe BPD phenotypes often require invasive respiratory support, and pressure-limited or volume-targeted conventional ventilation may be better suited to the physiology than high-frequency ventilation. The consistent provision of adequate support is fundamental to the management of longstanding BPD and is best achieved with a stepwise increase in ventilator support until comfortable spontaneous respirations are achieved. Adequately supported infants typically experience improvements in both oxygenation and ventilation, which, if sustained, may arrest and generally reverses the course of a potentially lethal lung disease. Care should be individualized to address the most likely pulmonary mechanics, including variable lung compliance, elevated airway resistance, and variable airway obstruction.

KEYWORDS

bronchopulmonary dysplasia, respiratory, hypoxemia, hypercarbia, lung resistance

## Introduction

The pathophysiology of bronchopulmonary dysplasia (BPD) is complex. While the phenotype evolves principally from the gestational age at birth, the postnatal course and outcome are influenced by the net sum of exposures and events arising before, during, and after delivery. Factors already present at birth, such as intra-uterine growth status, antenatal steroid exposure, and genetic pre-disposition contribute significantly to the evolution of BPD. As the immature lung transitions from a fluid-filled organ appropriate for *in utero* lung development to an air-filled organ appropriate for gas exchange, mechanical and biological forces, exerted over time, modify and damage the structural scaffolding, airways, and pulmonary vascular bed (1). Positive pressure ventilation compresses the interstitium, disrupting the immature collagen network, and preventing normal septation (1). The density of collagen deposition increases with disease severity, the saccules become more disorganized, and V/Q mismatch becomes increasingly apparent (1). Diffusion capacity (relative to lung volume) is decreased among infants with BPD, suggesting that decreased surface area is a mechanism by which gas exchange is impaired (2).

Despite efforts to avoid intubation, about one-half of extremely preterm infants require ongoing cycled positive pressure ventilation at age 7 days. Some later fail extubation despite the use of exogenous surfactant and lung-protective strategies, including early extubation, high-frequency ventilation, and fluid restriction (3–5). Unfortunately, the lungs and airways of preterm infants are vulnerable to other postnatal exposures as well (6). For example, early onset sepsis, necrotizing enterocolitis, and other processes that produce a systemic inflammatory response contribute to the evolution of BPD (7). **Figure 1** illustrates the complex pathophysiology of BPD, illustrating the interaction of the birth phenotype, which varies significantly, even among infants of the same gestational age, with prenatal, perinatal, and postnatal exposures.

Researchers have identified several phenotypes based on risk factors and the clinical course in the neonatal intensive care unit (NICU) (8). In one study, three distinct disease elements were examined with regard to their contribution to the composite outcome, death before hospital discharge, tracheostomy, or home pulmonary vasodilator therapy. Parenchymal lung disease, pulmonary hypertension (PH), and large airway disease (tracheobronchomalacia) were significantly associated with an increased risk of the composite outcome, and the risk of the primary outcome increased with the number of disease elements documented (8).

## Natural history of BPD: care along the continuum

In the acute phase of respiratory distress syndrome (RDS), the lungs are stiff and non-compliant. Clinical factors such as surfactant administration, fluid balance, and the presence of extrapulmonary shunts, all contribute to changes in compliance. Lung resistance, however, is relatively low in the acute phase of RDS, and typically remains low for days to weeks. Early serial chest radiographs reveal homogeneous, hazy opacities, low lung volumes, and air bronchograms. With the development of less invasive surfactant administration (LISA) and minimally invasive surfactant therapy (MIST)

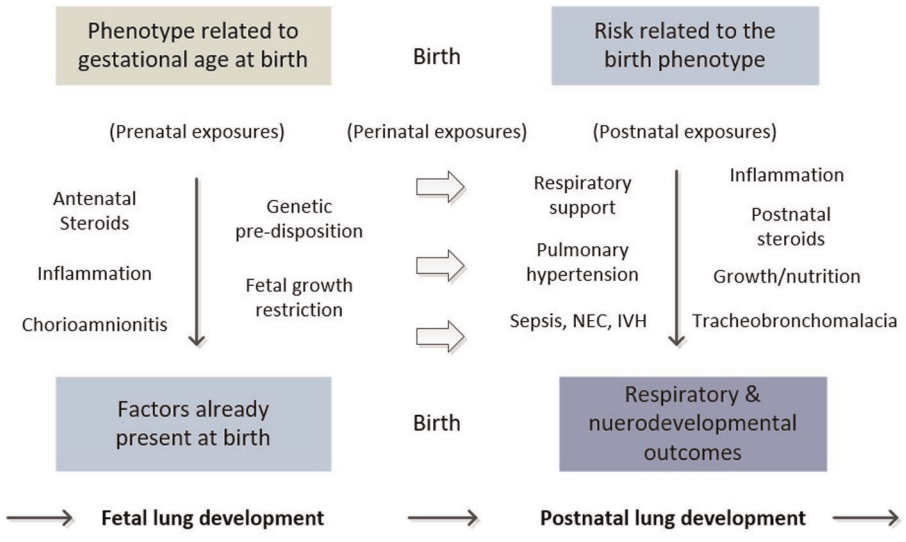


FIGURE 1
Natural history of bronchopulmonary dysplasia.

methods, infants requiring surfactant may be stabilized on non-invasive respiratory support, such as nasal CPAP, non-invasive positive pressure ventilation (NIPPV), and rarely, high-flow nasal cannula (HFNC). A lung-protective strategy utilizing short inspiratory times (≤0.35 s), lower tidal volumes (4–6 ml/kg) and higher respiratory rates (30–40 breaths/min) is generally sufficient to achieve respiratory stability in infants who require cycled positive pressure ventilation. This strategy targets low pulmonary resistance and compliance, and improvements are often noted within hours of delivery (9). Extubation success is more likely among infants requiring low concentrations of supplemental oxygen and low levels of non-invasive support, especially those born in high-volume centers with active golden hour protocols (10, 11).

Infants with a more severe BPD phenotype, however, often fail to achieve respiratory stability with non-invasive modes of support. Despite the use of caffeine, rigorous attention to the respiratory support interface, and judicious fluid management, V/Q mismatch progresses with time. Although lung compliance may normalize within days to weeks, lung resistance generally increases with prolonged exposure to positive pressure support. As the lung resistance increases, so does the degree of V/Q mismatch, hypoxemia, and hypercapnia. In time, serial radiographs reveal a more heterogeneous pattern, with areas of both hyperinflation and atelectasis, and, in extreme cases, macrocystic changes may be noted (12). This clinical pattern is sometimes described as "unstable BPD", and efforts to wean the respiratory support in this phase of care are usually unsuccessful (13). Despite trials of high frequency ventilation, aggressive diuresis, and repeated courses of exogenous corticosteroids, hypoxemia and hypercarbia progress, and growth failure is common.

## Invasive vs. non-invasive respiratory support

Infants requiring mechanical ventilation after 28 days of life are generally considered to have severe, type 1 BPD, even if they are subsequently weaned from mechanical ventilation (14). Infants who require mechanical ventilation at 36 weeks' post-menstrual age are said to have severe, type 2 BPD (14). The vast majority of infants with severe BPD have a significant diffusion defect requiring high mean airway pressures and/or inspired oxygen concentrations to maintain target oxygen saturations and achieve respiratory stability. The diffusion defect varies with the severity of BPD, but airway obstruction and airway malacia are variable (15). Infants with a more severe BPD phenotype are more likely to have airway malacia requiring higher levels of positive end-expiratory pressure, and despite theoretical concerns about the use of bronchodilators some have airway obstruction responsive to bronchodilators (8, 15). In one study, 51% patients had obstructive, 40% had mixed (obstructive and restrictive), and 9% had restrictive phenotypes (15). Bronchodilator response was seen in 74% of infants with an obstructive phenotype, 63% of infants with a mixed phenotype, and 25% of those with a pure restrictive phenotype. Regardless of the clinical phenotype, the treatment strategy should match the disease physiology, and clinicians should strive to individualize the goals of care.

While randomized trials and meta-analyses have documented the benefits of volume-targeted ventilation in the management of acute respiratory distress syndrome (RDS), we await randomized trials to determine the most appropriate mode for management of infants with severe phenotype BPD (16). The provision of adequate respiratory support is imperative, but non-invasive support should be utilized only if it serves to eliminate air hunger, achieve target oxygen saturations on relatively low inspired oxygen, and mitigate the development or evolution of PH. The need for high inspired oxygen concentration or worsening of PH suggests that invasive mechanical ventilation may be necessary. Although there is no universally accepted threshold at which to escalate support, a fraction of inspired oxygen concentration ≥0.65, increased work of breathing, worsening hypercarbia, and/or growth failure suggest that non-invasive support is likely inadequate to arrest or reverse the clinical trajectory. Most worrisome is the development or progression of PH, which is among the most important co-morbidities of BPD, occurring in as many as 50% of infants with severe BPD (17, 18).

## BPD-related pulmonary hypertension

PH contributes significantly to the severity of BPD and, when severe, is associated with a high rate of mortality (19, 20). Unfortunately, the pathophysiology of PH is as complex as that of BPD. Researchers have classified preterm infants into phenotypes based on the onset of PH: early PH (first two weeks after birth), late PH (weeks to months), and chronic/persistent PH (months to years) (20). While the early phenotype may be related to intrinsic/antenatal factors or factors related to intrauterine lung growth and development, the late and chronic phenotypes often reflect the modulating effect of postnatal events and exposures, such as prolonged mechanical ventilation and other biologic/inflammatory exposures (**Figure 1**).

In the setting of severe parenchymal lung disease, several mechanisms are likely to contribute to the development of PH (17). Air-trapping and hyper-inflation compress or stretch regional pulmonary arteries, thus increasing pulmonary vascular resistance, V/Q mismatch, and hypoxemia. Likewise, regional atelectasis compresses pulmonary blood vessels, limiting pulmonary blood flow and worsening V/Q mismatch and hypoxemia (17). Hypoxemia, in turn, results in acute

pulmonary vasoconstriction, and if prolonged, induces pulmonary vascular remodeling characterized by hyperplasia and hypertrophy of vascular smooth muscle. Expert opinion and experience from high-volume centers suggests that optimizing gas exchange is an important component of the treatment plan (17, 18).

Another potentially important mechanism of PH is the presence of extrapulmonary shunts, which can have both short- and long-term effects on the pulmonary vascular bed. Excessive left-to-right shunt (i.e., shunt from the systemic circulation toward the lungs) increases pulmonary vascular resistance and, in time, promotes pulmonary vascular remodeling (17). Unfortunately, the echocardiogram does not easily quantify the magnitude of extra pulmonary shunt, and cardiac catheterization may be needed to characterize the impact of the shunt on pulmonary hemodynamics (18). Over time, large left-to-right shunts progressively impair right ventricular function, which has important management implications. While the provision of adequate respiratory support is the principal treatment of BPD-related PH, pulmonary vasodilators are frequently used as adjuncts, and are best utilized in the context of an inter-disciplinary team that includes pediatric cardiology support (18). Until randomized controlled trials are available, expert opinion and single center case series support a management approach anchored in several concepts: the provision of respiratory support sufficient to minimize work of breathing, maintenance of oxygen saturations within a safe target range, and the employment of pulmonary vasodilators on a selective basis (18).

## Clinical recognition of longstanding BPD: when to consider an alternative approach?

There are currently no multicenter randomized controlled trials addressing the most appropriate timing or alternative approaches to the lung protective strategies used to prevent BPD. Consensus among collaborating BPD centers has highlighted the importance of interdisciplinary teams, especially with regard to optimizing respiratory support and nutrition, and mitigating the development or evolution of PH, but also to improve the quality and consistency of care (21). Clinical indicators for an alternative respiratory strategy includes: sustained respiratory distress, recurrent cyanotic or bradycardic episodes, intolerance of physical therapy and handling, poor growth, and repeated courses of systemic corticosteroids—without benefit (21). Unfortunately, no single respiratory support strategy has been shown to improve the outcomes of infants with severe, longstanding BPD. For now, the best available evidence derives from consensus recommendations and small, single center series with extensive experience and favorable outcomes (21–23).

In a study of ventilator-dependent infants who underwent tracheostomy in Denver, CO, the authors compared survival from two eras of care that employed two very different respiratory support strategies (23). In the first era, clinicians used a standard approach. In the second, an individualized care program utilized patient-specific ventilator settings, optimized lung volumes, and higher positive end-expiratory pressure (PEEP) for infants with airway malacia. The care protocol included a focus on meticulous clearance of airway secretions, universal periodic screening for PH, and prompt treatment of factors contributing to parenchymal lung injury. Survival increased from 50% in the first era to 85% in the second (23).

In a study of 71 BPD patients in Columbus, OH, infants with longstanding BPD were referred at a median PMA of 47 weeks (IQR, 42, 53) and had a median respiratory severity score (RSS) of 8.1 (IQR 4.5, 11.0) on admission (22). A dedicated multi-disciplinary team used a patient-specific ventilator strategy tailored to the most likely physiology, with an emphasis on achieving a pro-growth, pro-development state. Despite initiating this management late in the course, when infants had already developed severe disease, over 92% of patients survived to hospital discharge with improvement in comorbidities (22).

Increasing oxygen requirements, persistent hypercarbia, multiple failed attempts at extubation, and recurrent courses of postnatal steroids are all clinical markers of severe BPD. Therefore, we recommend consideration of an alternative respiratory support strategy when acute, lung-protective strategies have failed and adjunctive therapies have been exhausted, including the treatment of persistent, hemodynamically significant PDA. Objective signs of failure of lung-protective strategies include severe V/Q mismatch (hypoxemia and hypercapnia), a heterogeneous pattern on serial radiographs, and failure to benefit from high frequency ventilation, diuretics, and corticosteroids. Every effort should be made to use a lung protective strategy, and an alternative approach should be considered only when these efforts have failed.

Premature utilization of a modified/chronic approach may lead to unintentional lung injury, further complicating respiratory management. One such example is the presence of a persistent PDA. The clinical markers of a hemodynamically significant PDA include left atrial enlargement, left ventricular enlargement (suggesting over-circulation), and a rising creatinine, with or without acidosis. This scenario is common, but potentially reversible. Corrective interventions should be explored before considering an alternative respiratory support strategy. In recent years, non-invasive techniques for PDA closure have been introduced with very promising results (24–26). Potentially modifiable and/or acute respiratory maladies should be treated before moving to a chronic phase treatment strategy.

The radiographic pattern can be helpful in determining if or when to modify the management strategy. Some centers utilize high-resolution CT imaging for phenotyping, whereas others use a combination of radiographs and clinical experience (8, 23). The radiographic pattern is generally predictable, with regions of scattered, multi-focal atelectasis superimposed on regions of hyperinflation. This radiographic pattern suggests that some areas of the lung are engaged in respiration, while others are not. As the severity of BPD evolves, so too does the radiographic pattern, and in extreme cases, small and large pneumatoceles can signify a more severe BPD phenotype. In time, the mechanics of respiration evolve, and infants with severe disease will have regional variations in lung compliance and resistance within the lung compartment.

Bedside measures of lung function are generally unreliable, providing only a snapshot of the compliance and resistance of the respiratory system. Nonetheless, the time constant for acute lung diseases (e.g., RDS) is relatively short. This contrasts with the respiratory mechanics of longstanding BPD, where regional differences in lung compliance and resistance are common and where the overall resistance is much higher than that of infants with RDS. Stated differently, in severe, longstanding BPD some regions of the lung compartment have high resistance correlating with longer time constants (the slow compartment), while other regions of the lung compartment have low resistance and shorter time constants (the fast compartment). Theoretically, the slow compartment dominates the physiology of infants with severe, longstanding BPD, so the respiratory support strategy should target the slow compartment.

## An alternative respiratory support strategy for infants with severe, longstanding BPD

Use of an acute, lung-protective strategy (high rate, low tidal volume) in infants with severe longstanding BPD typically results in failure to ventilate a large portion of the lungs during the respiratory cycle, which results in worsening of V/Q mismatch, air hunger, and air-trapping (12). Air-trapping, in turn, results in dynamic collapse of regional airways, which by compressing the pulmonary vascular bed, only worsens V/Q mismatch (diffusion defect) and its downstream effects.

Because high lung resistance and airway obstruction dominate the physiology, the respiratory strategy must target the disease physiology—variable lung compliance, high lung resistance, and airway obstruction for the vast majority of patients. In order to adequately engage the slow compartment (high lung resistance), longer inspiratory times and larger tidal volumes are required to improve V/Q matching (13). In extreme cases, inspiratory times as long as 0.6–0.8 s and tidal volumes as high as 10–15 ml/kg may be needed. Elastic recoil is significantly impaired in severe BPD, which manifests clinically as airway obstruction (15). Therefore, lower ventilator rates are needed to facilitate passive emptying of the lungs. Ventilator rates as low as 12–16 breaths/min and I:E ratios ≥1 to 3.5 may be needed to facilitate carbon dioxide clearance. Over 70% of infants with severe BPD demonstrate airway obstruction responsive to bronchodilators, including infants with a mixed obstructive/restrictive phenotype (15). As such, the use of inhaled beta-agonists can facilitate carbon dioxide clearance, and ventilator graphics can be used to estimate the end of each exhalation cycle (15, 27).

Despite consensus recommendations from collaborating centers, significant variations in care have been documented (21). In a recent publication from the Children's Hospital Neonatal Consortium (CHNC), researchers found significant differences in ventilator modes and practices; 51% were treated with volume-control or volume guarantee, 43% with pressure-control, and 6% with neurally adjusted ventilatory assist (NAVA) (28). The use of non-invasive modes was equally variable; 41% were treated with high-flow nasal cannula (HFNC), 28% with low-flow nasal cannula (LFNC), 26% with continuous positive airway pressure (CPAP), and 5% with other modes (28). Likewise, in a study of 700 infants with BPD, published in 2015, marked differences were noted in the use of mechanical ventilation, diuretics, inhaled corticosteroids, and inhaled beta-agonists (29). The timing and prevalence of tracheostomy insertion are also variable, especially among infants with BPD-related PH and those born small for gestational age (SGA) (30, 31).

Consistent care and enhanced team communication are marks of exemplary BPD care that translate into improvements in respiratory outcomes and survival (23, 32, 33). Data on long-term respiratory outcomes suggests that infants with severe BPD are at greater risk for airway obstruction and hospital re-admission extending into adolescence and adulthood (27, 34). However, data from population based studies is sparse and lacks the granularity needed to correlate clinical strategies with outcomes (35–37). Nonetheless, use of a ventilatory approach that is tailored to the most likely physiology, together with the use of inter-disciplinary teams and guidelines has been shown to improve both care and outcomes (21, 33).

## Goals of respiratory management for severe, longstanding BPD

The goals of management for severe, longstanding BPD are different from those related to the prevention of BPD. Whereas lung-protective strategies are designed to minimize exposure to positive pressure ventilation, the goals of management for severe longstanding BPD center around the three major aims: (1) providing ventilatory support sufficient to achieve comfortable

work of breathing, (2) minimizing exposures that interfere with lung growth, and (3) furnishing an environment that optimizes both lung and brain development (12, 38). Performing a comprehensive physical exam is fundamental to the first goal, as it is important to match the respiratory support strategy with the infant's respiratory and metabolic needs. Specifically, the respiratory support settings should be increased, incrementally, until the infant has achieved comfortable respirations, both at rest and during age-appropriate cares and activities.

Conventional ventilation modes (pressure or volume regulated) are recommended for infants who require positive pressure ventilation. In general, higher peak inspiratory pressures (and/or tidal volumes) are needed to alleviate air-hunger and respiratory distress. Once the air hunger/distress has been alleviated, the respiratory support should be maintained at a level sufficient to maintain stable oxygen saturations, comfortable work of breathing, and adequate growth. Increased work of breathing interferes with lung growth by expending nutritional reserves that promote growth. Once the patient is adequately supported, the oxygen saturation has been stabilized within an accepted target range (e.g., ≥94%), and linear growth has been documented, the FiO2 can be reduced in small increments. While great care should be exercised to avoid wide swings in oxygen saturation, the ability to reduce the FiO2 sequentially is an important marker of clinical improvement.

Care should be individualized and modified in consideration of disease severity. Decreasing the level of support should be avoided until substantial gains in respiratory reserve and linear growth have been achieved (22, 38). Premature reduction of the level of support could result in respiratory failure, growth failure, and/or pulmonary hypertension. Specifically, efforts to reduce the respiratory support should be avoided until the oxygen requirement is consistently less than 40% or until consistent hypocapnia (e.g., PCO2 < 35) mandates a reduction in tidal ventilation. Hypercarbia is common among infants with BPD, especially among those with severe phenotype BPD. Carbon dioxide retention is better assessed with serial (weekly) bicarbonate levels than with serial blood gases, so once the patient has reached a chronic/stable phase of BPD, the frequency of blood gases can be reduced or reserved for acute clinical deteriorations (12).

Another important marker of clinical improvement is the infant's tolerance for age-appropriate developmental challenges (e.g., age-appropriate play, upright positioning, and social interactions with nurses and parents). Once the patient has achieved clinical stability, demonstrated by tolerance for age-appropriate activities, and has reached a sustained pro-growth state, then a cautious, stepwise reduction of the respiratory support apparatus should be considered (13). For infants with severe, longstanding BPD, this may not occur until weeks to months after the initial stabilization. The most appropriate interval for weaning the support apparatus depends on the phenotype, disease severity, the level of stability achieved, and progress toward goals.

## Conclusion

Until results of adequately powered randomized trials are available, the respiratory support strategy of infants with severe, longstanding BPD should target the most likely physiology. We advocate an approach taken by centers documenting improvements in both lung function and survival (15, 21–23). Severe, established BPD is characterized by high respiratory system resistance, which correlates with longer time constants and variable airway obstruction. For infants who require mechanical ventilation, longer inspiratory times and higher tidal volumes are needed to overcome V/Q mismatch (12). Likewise, infants with severe, longstanding BPD typically have impaired elastic recoil and airway obstruction, and generally benefit from lower ventilator rates to facilitate passive emptying of the lungs. Continuous provision of adequate respiratory support anchors the approach to both the prevention and treatment of BPD-related PH. Expert opinion supports the maintenance of oxygen saturations within a safe target range and the use of pulmonary vasodilators as an adjunctive PH therapy in collaboration with a pediatric cardiologist (26). Finally, an inter-disciplinary team approach is key to tracking progress toward respiratory goals, cardiac function and hemodynamics, somatic, linear, and end-organ growth, and overall progress toward the goal of successful discharge (21).

## Author contributions

The primary author (JWL) prepared the initial draft of the manuscript, presented it to the co-authors for general acceptance, provided the content and organization of the draft, and approved the final draft. Secondary authors (PDN, SDS, SN) agreed with the content, provided editorial improvements during each of several iterations, and approved the final draft. The senior author (MH) agreed with the content and organization of the draft, provided meaningful improvements during several editorial revisions, and approved the final draft. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the literature review and manuscript were conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Optimizing ventilator support in severe bronchopulmonary dysplasia in the absence of conclusive evidence

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## Introduction

Bronchopulmonary dysplasia (BPD) remains the most common late morbidity of infants born preterm (1–3). BPD occurs along a spectrum of disease severity, and we will refer to severe BPD as the need for invasive mechanical ventilation at 36 weeks post-menstrual age (PMA), which in a contemporary definition of BPD is classified as grade 3 BPD (1). Infants with severe BPD are at higher risk for mortality, significant morbidities, neurodevelopmental impairment, total ventilator days, medication usage, and rates of procedures (tracheostomy and gastrostomy tube) compared to infants with less severe forms of BPD (1, 2, 4–6).

Given the lack of high-level evidence regarding the optimal management of infants with established severe BPD, care is highly variable across centers and regions (7). It is acknowledged that ventilator approach, settings, and weaning methods for the infant with established severe BPD vary widely between both providers and centers (6, 8). There remain no prospective, randomized controlled trials that support widespread application of any given respiratory approach. One multi-center point prevalence study evaluated ventilator modes and settings in infants with severe BPD, and as expected significant variation in ventilation setting and mode selection was reported (9). This variation was noted among sites in the BPD Collaborative, a collective of hospitals with interdisciplinary BPD programs, and is illustrated in **Figure 1** (9).

Furthermore, it has been reported that there is also large variation in the rates of death or tracheostomy in infants with severe BPD. Murthy et al. (7) found in a large, multi-center cohort of infants with severe BPD, the center itself was an independent risk factor for death or tracheostomy, suggesting marked practice variation among clinicians, particularly with regards to tracheostomy. There is currently no uniformly accepted guidance

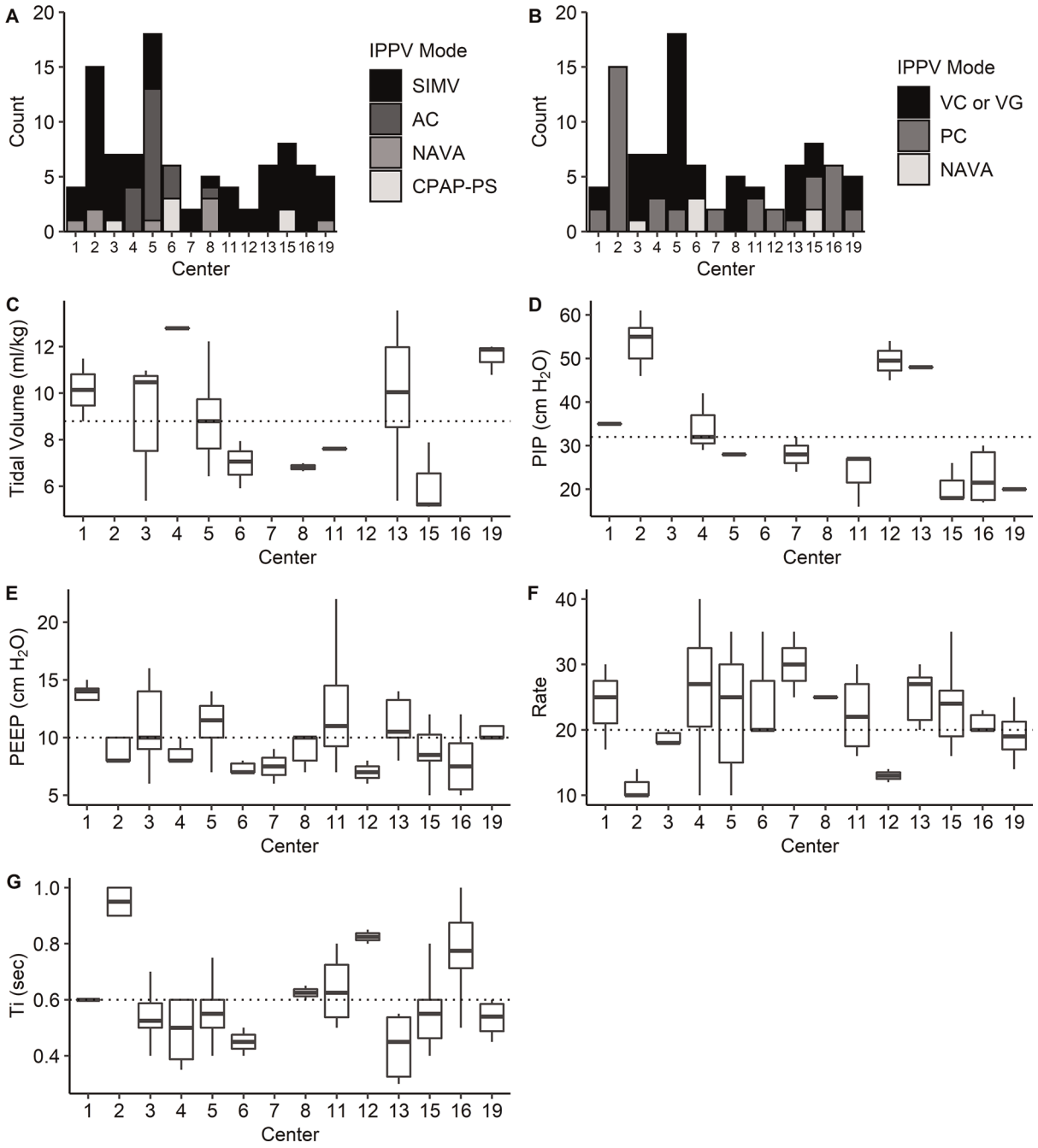


FIGURE 1
The distribution of IPPV modes and settings stratified by center. (**A**) Mode selection varied significantly by center when comparing the use of AC, SIMV, NAVA, and CPAP-PS ($P < 0.0001$, $\chi^2$ test). (**B**) Mode selection varied by center when comparing VC/VG, PC, and NAVA modes ($P < 0.0001$, $\chi^2$ test). (**C**,**D**) Among centers, $V_T$ (ml/kg) did not differ significantly for patients on VC/VG ventilation ($n = 49$; $P = 0.09$) (**C**); however, PIP differed significantly for patients on PC ventilation ($n = 40$; $P = 0.002$) (**D**). (**E**,**F**), PEEP differed significantly for subjects receiving IPPV ($n = 91$; $P = 0.001$ (**E**), as did rate ($n = 83$; $P = 0.001$) (**F**). (**G**) Ti differed significantly for patients receiving time-cycled ventilation ($n = 83$; $P < 0.0001$). The median for study population is represented by the dotted line for each setting. PS, pressure support. Reprinted from McKinney et al. (9).

regarding tracheostomy indications or timing, or more importantly evidence on how tracheostomy, or timing of tracheostomy, influence respiratory and neurodevelopmental outcomes (7, 10).

In the absence of high-quality evidence, therapeutic and ventilation strategies should be based on the information available related to respiratory physiology and minimizing complications.

# Available information

## Natural history of disease

BPD is a chronic disease that develops and then evolves over time. The precise pathogenic mechanisms that lead to the development of BPD, and the disease course, remain uncertain. There are several risk factors that predispose infants to the development of BPD, including lower gestational age at birth, sepsis, surgical necrotizing enterocolitis, and the need for mechanical ventilation (11). The pathophysiology of BPD is influenced by lung development, lung injury, and repair mechanisms that together ultimately lead to a heterogeneous disease with significant variability across the lung (12). This heterogeneous lung disease includes alveolar simplification, macrocystic disease, hyperinflation, microcystic disease, fibrosis, pulmonary vascular disease, and/or atelectasis (12). Infants with severe BPD can have significant parenchymal lung disease, large airway disease, and/or pulmonary hypertension, often with more than one of these disease components (13).

## Respiratory physiology

The respiratory physiology observed in severe BPD is markedly different than that seen in the preterm infant with respiratory distress syndrome, which is a homogeneous lung disease. Infants with severe BPD as described above have a heterogeneous lung disease with areas of very different lung physiology (14). There are regions of the lung in severe BPD with a relatively normal compliance and resistance, and therefore a relatively normal (or in comparison to other lung regions a relatively short) time-constant (time constant = resistance × compliance). These regions of the lung are often in the minority in patients with severe BPD (15). The majority of the lung in these patients is characterized by regions with relatively high airway resistance and normal or high compliance, resulting in very long time-constants. These areas of lung are characterized by hyperinflation, airway obstruction, air trapping, and ventilation perfusion (V/Q) mismatch (16–18). The majority of infants with severe BPD demonstrate this element of obstruction, with 91 percent of infants with severe BPD in one cohort demonstrating evidence of airflow obstruction on pulmonary function testing (14).

The respiratory mechanics of severe BPD suggest that the ventilation strategy used acutely in preterm infants aimed towards prevention of BPD, which is characterized by small tidal volumes (Vt), fast rates, and short inspiratory times (Ti) will no longer be effective for patients with severe BPD. This "lung protective" strategy preferentially ventilates the relatively healthy lung regions, which make up the minority of cross-sectional area available for gas exchange. This happens at the expense of the diseased lung regions, which make up the majority of cross-sectional area available for gas exchange. Infants with severe BPD ventilated with this "lung protective" strategy therefore usually manifest signs of being under supported including increased work of breathing, hypoxemia, desaturation events or "spells", and/or severe V/Q mismatch as manifest by a requirement for a very high fraction of inspired oxygen ($FiO_2$) (11).

A "chronic" ventilator approach using a relatively slow-rate, high Vt, and long Ti, improves ventilation of the diseased lung regions, which make up the majority of the available gas exchange area and are characterized by a very slow time constant. By improving ventilation to the diseased regions of the lung, V/Q matching is improved, which is evidenced by the ability to wean the $FiO_2$. Furthermore, the slow rate allows for a prolonged expiratory time to facilitate lung emptying and improve hyperinflation, which will not only increase Vt but also result in further improvement in V/Q matching (16). This strategy allows for improved gas exchange, reduced atelectasis, and decreased dead space ventilation in the majority of patients with severe BPD (11). While this strategy is not based on high-quality evidence, it is guided by the respiratory physiology seen in severe BPD, and is supported by clinical experience (15–18).

## Complications

Infants with severe BPD are at risk of in-hospital mortality (6). Pulmonary hypertension (BPD-PH) is seen in up to 25% of patients with severe BPD and is associated with increased risk for mortality (19). The risk of death after discharge in patients with severe BPD is likely highest in patients with tracheostomies and a history of BPD-PH (20, 21). Infection is also an important cause of both in-hospital and post-discharge mortality in this population (9).

Infants with severe BPD often have significant co-morbidities. These infants are at risk for growth failure, which is likely multifactorial and secondary to the level of nutritional support, medical management practices that suppress growth, chronic stress, and/or inflammation (22). Infants with severe BPD often require supplemental oxygen after discharge (23). Infants with BPD are at higher risk for re-hospitalizations compared to patients without BPD, often secondary to respiratory illnesses, with one study demonstrating 49% of infants with BPD required re-hospitalization in the first year of life (24). Infants with severe BPD are also at risk for developing blindness and hearing loss (25).

BPD is a known risk factor for long-term neurodevelopmental impairment (26). BPD has been independently associated with cerebral palsy in infants that require mechanical ventilation at 36 weeks PMA compared to

infants with BPD not requiring mechanical ventilation at that time (27). Additional studies have shown that BPD patients are more likely to have microcephaly, behavioral, motor, and postural disturbances compared to controls (28).

Infants with severe BPD are also often subjected to treatment practices and therapeutics that have known risks for neurodevelopmental impairments. The use of analgesics and sedatives may have a detrimental effect on the developing brain as suggested by animal and clinical studies (29). Opioids may induce apoptosis in human microglial cells and neurons, and lead to long-term changes in brain function and memory (29). Exposure to midazolam has been shown to affect hippocampal development and long-term learning memory in survivors of neonatal illness (29).

In infants, touch is an important part of sensory-cognitive development, and the response to light touch is positively impacted by the number of supportive experiences and negatively impacted by the number of painful experiences (30). Preterm infants with a higher number of skin-breaking procedures (i.e., lab draws) from birth to term had lower cognitive and motor development at 8 and 18 months corrected age (31). This implies that repetitive pain-related stress and procedures are associated with worse neurodevelopment in the first 2 years of life (31). This evidence suggests that routine blood gas sampling may be associated with long-term harm in patients with severe BPD.

A respiratory support strategy that does not allow for patient comfort or ease of breathing leads to an inability to engage with the environment and make developmental progress. A chronic care model that focuses on adequate respiratory support with positive touch experiences, avoidance of noxious stimuli, early intervention programs, and a reduction in medications is key in positively impacting neurodevelopment in these high-risk infants. One study demonstrated that 56% of infants in a cohort of patients with moderate to severe BPD had no neurodevelopmental impairment using this type of chronic care model (32).

## Acute to chronic care transition

Patients with severe BPD are often cared for in acute care settings (11). Within the practice of acute critical care, the fundamental goal is often to wean respiratory support based on the rationale that a shorter duration of support is associated with a shorter length of stay, fewer complications, and better overall care. In this acute care setting, the goal for patients with severe BPD is often to decrease ventilator settings and extubate to non-invasive support as soon as possible. Additionally, escalation of support may be viewed as a failure of care. For very preterm infants early on in life, this acute care approach and lung protective ventilation strategy aimed towards prevention of BPD are appropriate (18). However, those infants who cannot be weaned from invasive respiratory support will require chronic ventilation. Continued efforts using an acute care approach of trying to wean support in these infants may result in atelectasis, worsening gas exchange, escalating $FiO_2$ requirements, and increased work of breathing.

Additionally, an assumption in critical care is that we can use discrete and objective data to reassure providers that current care goals are being met, or redirect providers to change the care plan. This leads to the thought process that more data is better (blood gases, lab monitoring, imaging), and often leads to more acute clinical changes. These data are helpful in the acute setting where the goal is BPD prevention. However, in patients with established severe BPD, respiratory stability may be better reflected in clinical variables that can be measured non-invasively at the bedside, such as $FiO_2$ needs, work of breathing, growth, parental reports of comfort, and ability to tolerate cares and developmental therapies.

There is no definitive evidence upon which to base the decision of optimal timing to transition from acute models of respiratory support to chronic phase ventilation (CPV). However, there is evidence that resistance increases in chronically ventilated premature infants (16). Therefore, we believe that transition to CPV should occur when clinical indicators suggest that premature infants are no longer responding well to standard lung protective ventilator strategies. This is frequently described as clinical instability, worsening hypoxia despite increased mean airway pressure, and frequent desaturations or "spells." In addition, other signs of increased resistance include hyperinflation on chest radiography, positive response to bronchodilators and/or corticosteroids, and worsening status on "gentle ventilation" modes like HFOV, or high-rate, low tidal volume ventilation. This may occur relatively early in the disease progression (near the first month of life), or it may occur as late as 32–36 weeks PMA.

Thus, infants with severe BPD require transition from an acute care model to a chronic care model. Provision of adequate respiratory support without rapid weaning becomes critical, and allows for adequate gas exchange, reduced work of breathing, and improved overall growth and development.

## Principles of respiratory care of infants with severe BPD

Given that there is no conclusive evidence for how to manage infants with severe BPD we have based our approach on the best available information relating to the respiratory physiology and expected natural history of the disease process.

### Ventilator management

The best available evidence suggests that severe BPD is a heterogeneous lung disease that can be adequately described

using two functionally distinct compartments. The first lung compartment is relatively healthy with normal compliance and resistance. The second, and predominant, compartment is damaged and has high resistance with relatively normal compliance. As a result, the time constant for the second or "slow" compartment is very long leading to prolonged exhalation and air-trapping. Because of this heterogeneity, ventilator management is difficult and does not follow the typical algorithms used in the "lung protective strategies" discussed above.

There is wide provider variability regarding ventilator mode selection for patients with BPD, even among centers in the BPD Collaborative (9). Our preference is a pressure synchronized intermittent mandatory ventilation (SIMV) with pressure support mode. We find that pressure control allows us to adequately ventilate in the setting of large air leaks around the endotracheal tube affecting reliable Vt delivery, which is common in this population. However, the underlying principles of CPV work regardless of which mode is selected, and would apply to centers using volume based ventilation.

The diseased lung compartment, with a slow time constant, is managed by allowing full exhalation with each set ventilator breath. Specifically, the ventilator rate must be set to allow five exhalatory time constants between breaths. In practical terms, this requires a ventilator rate of somewhere between 10 and 16 breaths per minute for infants with the most severe forms of BPD. Such rates allow 3–5 s of exhalation which in most cases will be adequate to achieve full exhalation. As a result, to achieve adequate minute ventilation, the tidal volume given with each ventilator breath must be high. Pressure settings to achieve adequate minute ventilation (tidal volume × rate) in this very ill population often are greater than 40 cm $H_2O$.

For centers that utilize volume based ventilation, a target Vt within the range of 10–15 ml/kg is often needed, although this may be higher in infants with the most severe forms of disease. A good indication of adequate Vt in this population is good chest rise with ventilator breaths and comfortable work of breathing. Targeting these tidal volumes often leads to the need to set a higher peak pressure limit, as higher pressures (even exceeding 40 cm $H_2O$) may be needed.

The appropriate level of positive end-expiratory pressure (PEEP) needed for patients with severe BPD remains to be determined, and a wide practice variation exists among centers (9). Even in the setting of hyperinflation, the set PEEP should be high (≥8 cm $H_2O$) to maintain functional residual capacity, avoid atelectasis, and improve gas exchange (11). Some patients may require an even higher PEEP in the setting of tracheomalacia, bronchomalacia, or small airway malacia. Some patients may benefit from brief periods of higher PEEP to mitigate airway collapse, often in the setting of agitation or passing of stools (12). Intrinsic PEEP may contribute to patient/ventilator dyssynchrony, which may be improved by increasing the set PEEP (33).

Pressure support breaths where the patient sets their own Ti, additionally allows for ventilation of the healthy lung compartment. This combination of addressing the diseased and healthy lung compartments allows for more equal distribution of ventilation and thereby significantly improves V/Q matching. Please see **Table 1** for typical CPV settings in this population.

## Ventilator weaning

Severe BPD is a disease with a protracted course which improves over time and successful weaning usually occurs with improvements in the rate of linear growth. Linear growth reflects overall nutritional status (34), is associated with successful respiratory support weaning (35), and is associated with improvement of lung function (36). Thus, weaning should be done slowly and cautiously. Our approach is to escalate ventilator support until the infant is comfortable, interactive, well saturated, and able to make developmental progress. Once we have achieved these settings, we focus on weaning oxygen until we achieve good length growth on a $FiO_2$ of 0.4 or less. We do not believe that high ventilator peak inspiratory pressures (PIP) preclude an attempted extubation, and therefore do not routinely wean PIP prior to an extubation attempt. However if PIP weaning is attempted prior to extubation, a slow approach with changes only every 1–2 weeks is usually needed. On the other hand, we have found success with weaning the PEEP to 8 cm $H_2O$ prior to an attempted extubation to nCPAP. Our practice is to extubate to nCPAP at a level of 8 cm $H_2O$, although we recommend extubating to the non-invasive device most successfully used in each center, which may include non-invasive positive pressure ventilation and/or high flow nasal cannula.

## Weaning from non-invasive support

Convalescence on non-invasive support typically occurs at about the same rate as improvement on the ventilator, and therefore prolonged periods of non-invasive support may be necessary. Our practice is to maintain nCPAP until we achieve steady linear growth and good developmental interactions on a $FiO_2$ less than 0.3, at which point an attempt at low flow nasal cannula oxygen may be appropriate. We transition from nCPAP of 8 cm $H_2O$ directly to nasal cannula, without prior

**TABLE 1** Example of chronic phase ventilation settings for the most severe forms of BPD.

| | |
|---|---|
| Respiratory rate | 10–16 breaths per minute |
| Inspiratory time | 0.7–1.0 s |
| Peak inspiratory pressure | As needed, often 40–45 cm $H_2O$ or higher |
| Positive end-expiratory pressure | As needed, often 8–12 cm $H_2O$ or higher |
| Tidal volume | 10–15 ml/kg or occasionally higher in the very worst forms of disease |

weaning of the nCPAP level. However, other centers may take a step wise approach to weaning nCPAP and/or change to high flow nasal cannula before reaching low flow nasal cannula. Regardless of the approach, the goal while weaning non-invasive support should again focus on continued developmental advancement and good linear growth.

### Respiratory assessment

While there is no evidence on the optimal way to assess chronic respiratory status, there is evidence that the quantity of skin breaking procedures done during neonatal hospitalization is directly correlated with worse neurodevelopmental outcomes. Given that there is also evidence that capillary blood gases may not be an accurate reflection of steady state respiratory status, we no longer believe that there is a positive risk:benefit ratio favoring obtaining routine capillary blood gases in infants with severe BPD. Therefore, we rely almost entirely on clinical assessments of overall respiratory status, including steady state oxygenation, serial physical exams, and repeated assessments by bedside staff.

### Timing of tracheostomy

A fraction of infants with severe BPD will require tracheostomy to maintain a stable airway. There is no consensus on the optimal timing for tracheostomy and long-term outcomes are uncertain. Tracheostomy and chronic home ventilation have significant risks and are resource intensive. Therefore, we believe that it is imperative to take a systematic approach with an emphasis on avoiding tracheostomy placement if possible. Consequently, we generally recommend tracheostomy placement after an infant reaches 50–52 weeks PMA and has failed repeated extubation attempts after 40 weeks PMA.

### Additional considerations

There are a number of additional controversies in the management of severe BPD, including the optimal use of diuretics, bronchodilators, inhaled steroids, systemic steroids, and the most effective means of providing enteral nutrition. While these are beyond the scope of this review, given the chronic nature of BPD it is critical to continue to use and create consistent guidelines in order to decrease unintended variability among providers and to facilitate learning and analysis (37, 38). Additionally, this described physiology and management approach is specific to infants with severe BPD, and may or may not apply to infants with other chronic respiratory disease, such as congenital diaphragmatic hernia, pulmonary hypoplasia, or other interstitial lung disease.

## Conclusion

The goal of chronic respiratory care in severe BPD is to provide an optimal platform of respiratory stability and growth to improve long-term pulmonary and neurodevelopmental outcomes. Factors that contribute to improving outcomes should be done aggressively, and factors that impair outcomes should be eliminated if possible. A lack of weaning respiratory support should not be viewed as failure, but as an opportunity to achieve success while promoting growth, neurodevelopment, and long-term outcomes.

## Author contributions

ES contributed to conception and design of the paper. AM and ES wrote the first draft of the manuscript. All authors contributed significantly to manuscript revision, read, and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Volume-guarantee vs. pressure-limited ventilation in evolving bronchopulmonary dysplasia

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**Introduction:** Extremely premature infants are at high risk for developing bronchopulmonary dysplasia (BPD). While noninvasive support is preferred, they may require ventilator support. Although volume-targeted ventilation (VTV) has been shown to be beneficial in preventing BPD, no data exists to guide ventilator management of infants with evolving BPD. Thus, clinicians employ a host of ventilator strategies, traditionally time-cycled pressure-limited ventilation (PLV) and more recently volume-guarantee ventilation (VGV) (a form of VTV). In this study, we sought to test the hypothesis that use of VGV in evolving BPD is associated with improved clinical and pulmonary outcomes when compared with PLV.

**Design:** Single-center, retrospective cohort review of premature infants born less than 28 weeks inborn to a Level 4 NICU from January 2015 to December 2020. Data abstracted included demographics, maternal and birth data, and ventilator data until death or discharge. Exposure to either VGV or PLV was also examined, including ventilator "dose" (number of time points from DOL 14, 21 and 28 the patient was on that particular ventilator) during the period of evolving BPD.

**Results:** Of a total of 471 patients with ventilation data available on DOL 14, 268 were not ventilated and 203 were ventilated. PLV at DOL 21 and 28 was associated with significantly higher risk of BPD and the composite outcome of BPD or death before 36 weeks compared to VGV. Both increasing VGV and PLV doses were significantly associated with higher odds of BPD and the composite outcome. For each additional time point of VGV and PLV exposure, the predicted length of stay (LOS) increased by 15.3 days ($p < 0.001$) and 28.8 days ($p < 0.001$), respectively.

**Discussion:** Our study demonstrates the association of use of VGV at DOL 21 and 28 with decreased risk of BPD compared to use of PLV. Prospective trials are needed to further delineate the most effective ventilatory modality for this population with "evolving" BPD.

KEYWORDS

BPD (bronchopulmonary dysplasia), ventilaion, volume-guaranteed ventilation, pressure-limited ventilation, premature

## Introduction

Extremely premature infants (< 28 weeks gestation at birth, EPIs) are at high risk for developing a chronic lung disease termed bronchopulmonary dysplasia (BPD) (1–4). Despite numerous technological advances, the incidence, clinical course, and management of infants with BPD remain poorly defined and extremely variable (5–8). To standardize care for this high-risk group of infants, in 2001, the National Institute of Child Health and Human Development (NICHD) workshop proposed a definition of BPD defining BPD by the treatment received at 28 days of life (DOL) and 36 weeks postmenstrual age (PMA) (2, 9–11). This definition has been validated in multiple studies and is useful in predicting long-term pulmonary outcomes (12). Recently Jensen et al. have updated this definition (8). While standardizing terminology and definitions used in the management of patients with BPD is important, it is only the first step in improving care (10, 13, 14). A necessary next step to improving clinical outcomes and preventing BPD is understanding the pathophysiological mechanisms that cause BPD in the high-risk EPI population, as not all EPIs develop BPD. This understanding will lead us to treat EPIs differently to address their underlying susceptibilities, which could decrease the incidence of the disease. Management strategies to address such underlying susceptibilities before an infant's birth include treating maternal uterine infections, antenatal steroids, and tocolytics (15–18). Regarding ventilatory strategies to prevent BPD, only using volume-targeted ventilation (VTV) when invasive respiratory support is unavoidable has been suggested (19, 20).

Ventilator management of the EPI has been described extensively, with the acknowledged best strategy being avoiding invasive ventilation altogether (21–23). However, in a subset of EPIs, invasive ventilation is unavoidable and/or attempts at extubation fail, and these infants subsequently may develop BPD (5, 24, 25). Currently, there are no optimal methods to screen for or guide the management of this vulnerable cohort, especially with regards to ventilator management (26, 27). Not surprisingly, clinicians employ a host of ventilator strategies, traditionally time-cycled pressure-limited ventilation (PLV) and VTV (19, 28). When used in the immediate postnatal period, VTV has been shown to decrease the incidence of BPD in EPIs (20, 29, 30), however, the utility of VTV in EPIs with evolving and/or established BPD has not yet been investigated. To address this knowledge gap, in this study, we sought to investigate the clinical and pulmonary outcomes of EPIs with evolving BPD treated with either VTV or PLV. Specifically, in this retrospective study, we tested the hypothesis that use of volume-guarantee ventilation (VGV - a form of VTV) would result in improved clinical and pulmonary outcomes when compared with use of PLV in a high-risk cohort of EPIs.

## Materials and methods

Data Extraction and Patient Selection: We identified all infants born at less than 28 weeks gestation who were admitted to the Pavilion for Women at Texas Children's Hospital from January 2015 to December 2020 using the institutional database that is submitted to the Vermont Oxford Network (VON). All patient information in this registry is de-identified. The definition we utilize for BPD is the one described in the NICHD workshop in 2001 at 36 weeks PMA. At our institution, if EPIs need ventilation at birth, our primary mode of ventilation is Assist-Control/Volume-Guarantee (AC-VG) with an attempt to extubate babies to nasal continuous positive airway pressure (NCPAP) in the first week of life or as soon as possible. Infants who fail to be extubated stay on AC-VG with continued attempts to extubate them. If they continue to fail, often somewhere in the 3rd or 4th week of life, alternative modes of ventilatory support may be considered, depending on the biases of the clinician on service and their management of the infant at the time. The usual rotation of an attending in the NICU is between 2 and 4 weeks but, to minimize the variability in care delivered, these infants are usually cared for in a small baby unit with a subset of neonatologists and other dedicated personnel. Ventilator management and non-invasive respiratory support provided to this population followed evidence-informed consensus-based guidelines that are reviewed annually, however the use of postnatal steroids for ventilator-dependent EPIs is variable and practitioner-dependent.

We subsequently conducted a chart review *via* an EPIC data extract to retrieve clinically relevant information, including demographic and respiratory support/ventilator data, using a standardized clinical data collection form for each patient weekly between birth and 36 weeks PMA and/or discharge date or death, if earlier. All data were collated in a de-identified datasheet for analyses.

Inclusion Criteria: Infants with gestational age (GA) less than 28 weeks at birth with mechanical ventilation data available at DOL 14, from January 2015 to December 2020.

Exclusion Criteria: Infants with GA 28 weeks or greater at birth, infants with major congenital or genetic anomalies, including congenital diaphragmatic hernia, congenital heart disease, myelomeningocele, or trisomies.

Data Analyses: The analytic cohort was restricted to patients with ventilator status data (PLV, VGV, Other) available for DOL 14. These patients' ventilator status at DOL 21 and 28 was also ascertained when data was available. A "VGV dose" variable was created for each patient that was calculated as the number of VGV ventilations across the three time points (DOL 14, 21 and 28), so the VGV dose could range from a score of 0 to 3 across these three time points. A "PLV dose" variable was computed in the same way. To control for

differences in severity of lung disease, we used a previously validated respiratory severity score (RSS) (31). In addition to the unadjusted analyses, logistic regression analysis was used to compare odds of BPD, death before 36 weeks PMA and the composite of these two outcomes for patients on PLV vs. VGV at DOL 14, 21 and 28, after controlling for time period (2015–2017 vs. 2018–2020) and RSS at the corresponding DOL. Similarly, logistic regression was used to examine the associations of PLV and VGV dose exposures both before and after controlling for RSS at DOL 14 and time period (2015–2017 vs. 2018–2020).

Quantitative variables were assessed for normality using the Shapiro-Wilk test. Variables that were not normally distributed were compared between groups using the Wilcoxon rank sum test while normally distributed variables were compared using the two-sample t-test. Categorical variables were compared using Fisher's exact test. Logistic regression was used to examine associations of ventilator dose with binary outcomes and linear regression was used for continuous outcomes. The Cochran-Armitage trend test was used to test for a temporal relationship with ventilator modes. SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) was used for data analysis. A 5% significance level was used for all hypothesis tests.

## Results

There were 471 patients with mechanical ventilation data available at DOL 14. Of the 471 patients analyzed, 203 (43.1%) were on mechanical ventilation at DOL 14 and 268 (56.9%) were not. Patients who were on mechanical ventilation at DOL 14 had a significantly lower birthweight, lower GA, lower Apgar scores at 1 min and 5 min, as well as a significantly longer length of stay (LOS) (**Table 1**). RSS at DOL 14 were significantly ($p < 0.01$) higher for the 67 patients on PLV (median = 3.3, IQR: 2.7–4.8) compared to the 113 patients on VGV (median = 2.8, IQR: 2.1–3.4, **Figure 1**).

When comparing patients mechanically ventilated that were on VGV vs. PLV at DOL 14, there was no significant difference between BPD and the composite outcome of BPD or death before 36 weeks. Notably, PLV at DOL 21 was associated with significantly higher risk of BPD and the composite outcome of BPD or death before 36 weeks compared to VGV. Similarly, at DOL 28, PLV was associated with significantly higher risk of BPD and the composite BPD or death before 36 weeks outcome compared to VGV. After controlling for time period (2015–2017 vs. 2018–2020) and RSS at the corresponding DOL, odds of BPD and the composite outcome remained higher at DOL 21 and 28 for patients on PLV (**Table 2**). Examining the 180 patients on VGV or PLV at DOL 14, there was a significant ($p < 0.01$) increasing trend in the relative proportion of patients who were on VGV over the 6-year study period (**Table 3**).

TABLE 1 Comparison of patients who were vs. were not on a ventilator at day of life 14.

| Characteristic | Not on Ventilator at 14 Days of Life ($n = 268$) | On Ventilator (VGV, PLV or Other) at Day of Life 14 ($n = 203$) | $p$-value |
|---|---|---|---|
| Gender[a] | | | 0.10 |
| Female | 145 (54.1) | 94 (46.3) | |
| Male | 123 (45.9) | 109 (53.7) | |
| Maternal race[a] | | | 0.40 |
| Black | 89 (33.2) | 66 (32.5) | |
| White | 161 (60.1) | 118 (58.1) | |
| Asian | 18 (6.7) | 17 (8.4) | |
| American Indian | 0 (0) | 2 (1.0) | |
| Hispanic ethnicity[a] | 90 (33.6) | 59 (29.1) | 0.32 |
| Birthweight (g)[b] | 890.0 (752.5, 1007.5) | 675.0 (585.0, 794.0) | <0.01 |
| GA at birth (weeks)[b] | 26.7 (25.7, 27.3) | 24.9 (24.0, 25.9) | <0.01 |
| Apgar score at 1 min[b] | 4 (2, 6) | 3 (1, 5) | <0.01 |
| Apgar score at 5 min[b] | 7 (6, 8) | 7 (5, 8) | <0.01 |
| Antenatal steroids[a] | 255 (95.2) | 190 (93.6) | 0.54 |
| Chorioamnionitis[a] | 32 (11.9) | 24 (11.8) | 1.00 |
| Maternal hypertension[a] | 84 (31.3) | 72 (35.5) | 0.37 |
| Multiple gestation[a] | 71 (26.5) | 68 (33.5) | 0.10 |
| LOS (days) | 93.0 (78.0, 113.0) | 143.5 (119.0, 208.0) | <0.01 |

[a]Frequency (%), Fisher's exact test $p$-value.
[b]Median (inter-quartile range), Wilcoxon rank sum test $p$-value.

Among the 471 patients with ventilator status data available at DOL 14, both increasing VGV dose and increasing PLV dose were associated with significantly increased odds of BPD, death before 36 weeks PMA, and the composite outcome of BPD or death before 36 weeks PMA (**Table 4**). After controlling for time period (2015–2017 vs. 2018–2020) and RSS at DOL 14, VGV dose was no longer significantly associated with BPD or the composite outcome, but increasing PLV dose was still associated with increased odds of these two outcomes. Neither VGV nor PLV dose was significantly associated with death before 36 weeks PMA after controlling for time period (2015–2017 vs. 2018–2020) and RSS at DOL 14 (**Table 4**).

For every additional week of VGV, the predicted LOS increased by 15.3 days ($p < 0.01$, **Figure 2**). For every

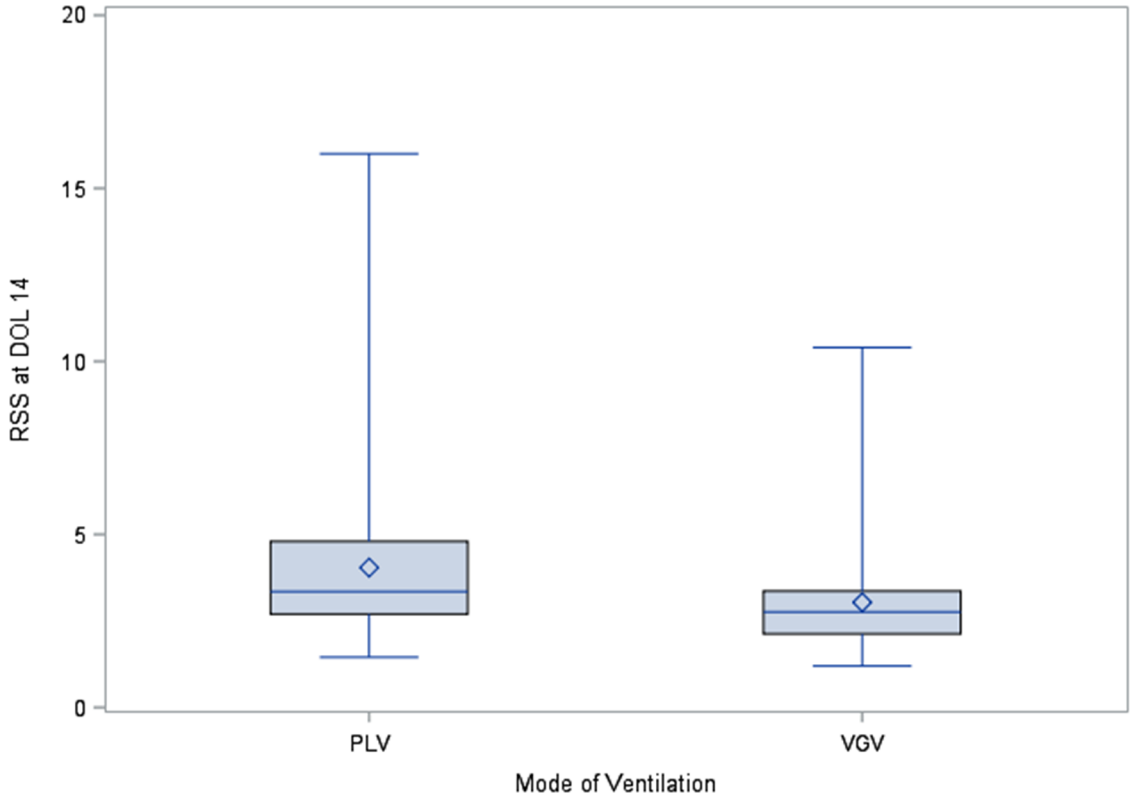


FIGURE 1
Boxplots of RSS at DOL 14 for patients on PLV and VGV.

TABLE 2 Risk of outcomes for VGV vs. PLV.

| | On PLV | On VGV | *p*-value | Adjusted *p*-value[a] |
|---|---|---|---|---|
| At 14 days of life | (*n* = 67) | (*n* = 113) | | |
| BPD | 48 (71.6%) | 85 (75.2%) | 0.603 | 0.18 |
| Death before 36 weeks PMA | 9 (13.4%) | 8 (7.1%) | 0.191 | 0.13 |
| Death before 36 weeks PMA or BPD composite | 57 (85.1%) | 93 (82.3%) | 0.684 | 0.64 |
| At 21 days of life | (*n* = 101) | (*n* = 93) | | |
| BPD | 87 (86.1%) | 62 (66.7%) | 0.002 | 0.04 |
| Death before 36 weeks PMA | 6 (5.9%) | 7 (7.5%) | 0.777 | 1.00 |
| Death before 36 weeks PMA or BPD composite | 93 (92.1%) | 69 (74.2%) | 0.001 | 0.02 |
| At 28 days of life | (*n* = 105) | (*n* = 75) | | |
| BPD | 92 (87.6%) | 52 (69.3%) | 0.004 | 0.04 |
| Death before 36 weeks PMA | 5 (4.8%) | 5 (6.7%) | 0.744 | 0.68 |
| Death before 36 weeks PMA or BPD composite | 97 (92.4%) | 57 (76.0%) | 0.003 | 0.02 |

[a]Adjusted for time period (2015–2017 vs. 2018–2020) and RSS at corresponding DOL.

additional week of PLV, the predicted LOS increased by 28.8 days ($p < 0.01$, Figure 2).

## Discussion

This is a retrospective chart review of the medical records of EPIs admitted to a tertiary-care Level 4 NICU over a 6-year period who were ventilated during the first month of life. In this study, we found that EPIs ventilated at DOL14 were more likely to develop BPD, and at DOL 21 and 28, those treated with PLV had significantly higher incidence of BPD compared to those treated with VGV.

Recent trends in neonatal care show increased survival among infants born at lower GA (23–24 weeks), and underscores a need to focus on intervention strategies for the most immature infants (32, 33). Our findings highlight the fact that infants born at the lower extremes of birth weight and GA remain at increased risk for prolonged hospitalization and significant pulmonary morbidities. Due to this, there is a continued need to better understand the factors that might adversely impact outcomes.

As prior studies have focused on prevention of BPD and management strategies in established BPD, in our study, we chose to evaluate a unique time period in the hospitalization of EPIs, where the risk of mortality may have diminished but the risk of significant morbidity still remains (34, 35). Given that many infants of low birth weight and gestation may die before DOL 14, we chose to examine the 3rd and 4th week of life to focus on EPIs with "evolving BPD". While the diagnosis of BPD has historically been assessed at 36 weeks PMA (8, 12, 36, 37), the optimal timing to transition management strategies from disease prevention to providing optimal long-term care of those with established BPD remains unknown. This is particularly true for the subset of infants with severe BPD (sBPD) as described in the literature (1, 38). As lung pathophysiology changes from that of respiratory distress syndrome to "evolving BPD", ventilator management needs to change to match an infant's needs (5, 7, 39). Further research is however needed to determine what the optimal strategies are and when they should be implemented to minimize further lung injury and improve outcomes.

In our cohort, EPIs receiving mechanical ventilation at DOL 14, 21 and 28 had significantly higher probability of BPD, death before 36 weeks PMA, and composite outcome of BPD or death prior to 36 weeks. After controlling for RSS at DOL 14, increasing PLV dose, but not VGV dose, was still associated with significantly increased odds of BPD and the composite outcome. Neither VGV nor PLV dose was associated with death before 36 weeks PMA after controlling for RSS at DOL 14. This association implies that the pathophysiologic mechanisms underpinning the need for PLV persist in this subpopulation and/or PLV itself could incite lung injury that

TABLE 3 Frequency (%) of patients on PLV and VGV by year among the 180 patients on PLV or VGV at DOL 14.

| Year | On PLV | On VGV |
|---|---|---|
| 2015 | 23 (74.2%) | 8 (25.8%) |
| 2016 | 26 (55.3%) | 21 (44.7%) |
| 2017 | 4 (15.4%) | 22 (84.6%) |
| 2018 | 2 (7.1%) | 26 (92.9%) |
| 2019 | 3 (15.0%) | 17 (85.0%) |
| 2020 | 9 (32.1%) | 19 (67.9%) |
| Total | 67 (37.2%) | 113 (62.8%) |

TABLE 4 Association with outcomes of each additional week of exposure to VGV and PLV between DOL 14 and 28.

| Exposure and Outcome | Ventilator Dose Exposure Odds Ratio (95% CI) | *p*-value | Adjusted Odds Ratio (95% CI)[a] | Adjusted *p*-value[a] |
|---|---|---|---|---|
| **VGV exposure** | | | | |
| BPD | 1.66 (1.30–2.12) | <0.01 | 0.891 (0.647–1.228) | 0.48 |
| Death before 36 weeks PMA | 2.03 (1.10–3.76) | 0.02 | 0.936 (0.419–2.090) | 0.87 |
| BPD or Death before 36 weeks PMA | 1.74 (1.38–2.20) | <0.01 | 0.887 (0.650–1.209) | 0.45 |
| **PLV exposure** | | | | |
| BPD | 3.41 (2.62–4.43) | <0.01 | 1.911 (1.392–2.625) | <0.01 |
| Death before 36 weeks PMA | 1.93 (1.08–3.46) | 0.03 | 1.665 (0.767–3.612) | 0.20 |
| BPD or Death before 36 weeks PMA | 3.44 (2.66–4.44) | <0.01 | 2.008 (1.463–2.755) | <0.01 |

[a]Adjusted for time period (2015–2017 vs. 2018–2020) and RSS at DOL 14.

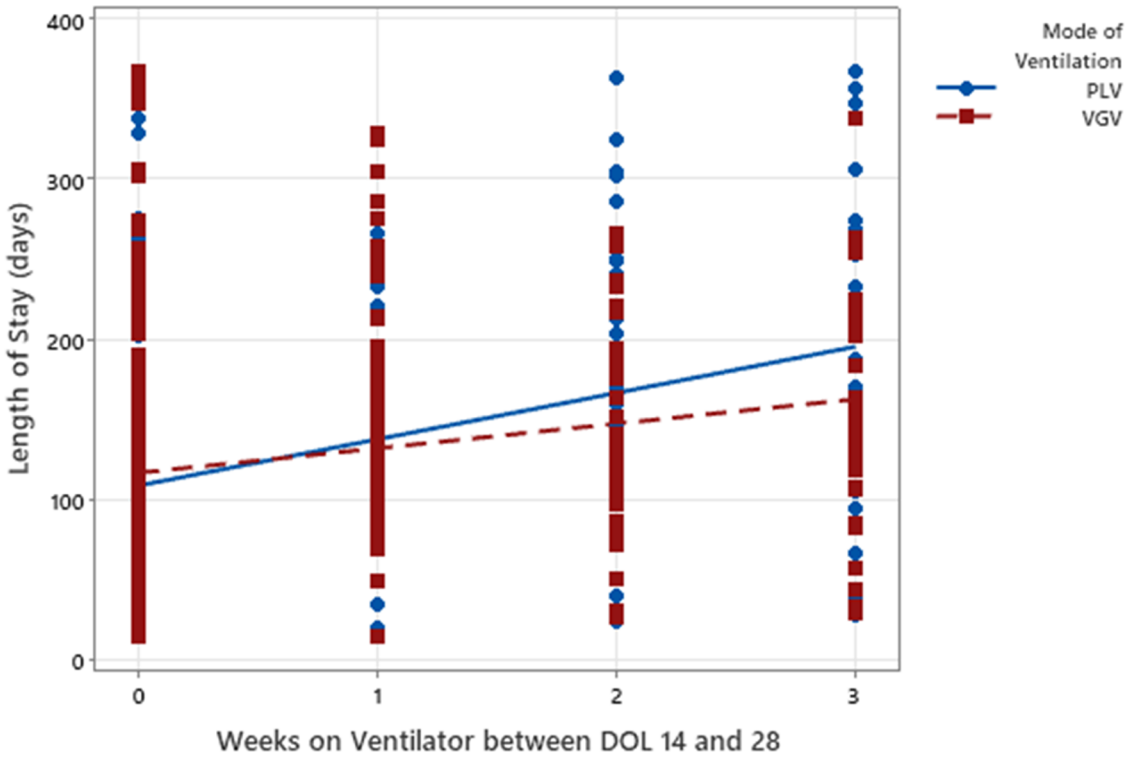


FIGURE 2
Scatterplot of weeks on VGV or PLV vs. LOS with linear regression line superimposed.

prolongs the need for ventilation. Recognizing this association is important because EPIs who require protracted mechanical ventilation are known to have significant increased morbidity and mortality over time, whether they remained on positive pressure ventilation at initial hospital discharge or not (40, 41). It is also important to note that more premature babies (23–25 wk GA) are more likely to be ventilated on DOL 14 than less premature babies (26–28 wk GA); this can affect BPD, BPD/death, or hospital LOS as a confounding variable. The likelihood of death or BPD in this cohort has been modeled using RSS at DOL 14, 21 and 28 (42). In light of this, attempts to ameliorate further lung injury are both warranted and should be attempted wherever possible.

While newborn premature infants ventilated at birth using VTV modes have been reported to have reduced rates of death, BPD, pneumothoraces, and duration of ventilation when compared with infants ventilated using PLV modes, the optimal ventilator strategy for infants with evolving or established BPD has not yet been determined (20, 29, 30). In our cohort, the number of babies on VGV on DOL 21 and DOL 28 were lower than on DOL14 whereas the number of babies on PLV was higher on DOL 21 and DOL 28 than on DOL14, although the relative proportion of infants ventilated with VGV increased over the 6-year period. One interpretation for this finding is that clinicians who did not find that VGV worked sufficiently well for their patients changed from VGV to PLV (5, 24, 38). In comparing patients mechanically ventilated on VGV vs. PLV, PLV at DOL 21 and 28 was associated with significantly higher risk of BPD and the composite BPD or death before 36 weeks compared to VGV. This is consistent with other reports of VTV reducing death or BPD (20). Infants requiring prolonged ventilation have a diverse airway and parenchymal and vascular phenotypes that may contribute to the need for PLV as a mode for effective ventilation. As such, as there are currently no standardized ventilator management guidelines for established BPD, the decision to use PLV or VGV is at the discretion of the clinician. In our cohort, we found a temporal shift over the 6-year period in practitioners' use of VGV over PLV from 26% in 2015 to 63% VGV by 2020 (**Table 4**). Additional studies are required to evaluate patient- and provider-specific clinical factors related to the use of VGV vs. PLV. Prospective trials are also needed to determine which invasive positive pressure ventilation (IPPV) or non-invasive support strategies are most effective in supporting infants with established BPD (6, 14, 43).

Although necessary for some patients, the use of PLV carries a theoretical risk of continuing volutrauma in lung units with greater compliance than others, as well as the risk of prolonging need for ventilator support. Indeed, while we found that increased duration of exposure to both VGV and PLV were associated with significantly increased odds of BPD,

death before 36 weeks PMA, and the composite outcome, for each additional week of exposure, infants treated with PLV had almost twice the predicted increase in LOS compared to infants treated with VGV. While increased exposure to invasive ventilation is known to be associated with poor long-term outcomes (8, 43–45), whether and what part of this association is the result of ventilator-induced lung injury is yet to be determined (46–51).

We acknowledge some limitations in our study. As a single-center study, we lack data from other institutions and our patient demographics may be different compared to other NICUs, potentially limiting the generalizability of our observations. As a retrospective cohort study, our study also lacks randomization due to the observational nature. The initial analysis compared two groups: infants at DOL 14 who did not require ventilator support and infants who continued requiring mechanical ventilation, receiving either VGV, PLV or another ventilator strategy. Also due to the nature of our study and the hypothesis proposed, infants not requiring mechanical ventilation at DOL 14 were utilized as our control group. The VGV and PLV dose variables only quantify the number of time points among DOL 14, 21 and 28 that the patient was on that particular ventilation mode, which does not guarantee the patient was on that same type of ventilation mode for the entire week. In addition, it did not quantify the level of VGV and PLV support since the details of ventilator support such as mean airway pressure and achieved TV were not collected as well as not including other morbidities as PDA or sepsis. Furthermore, our results do not identify cause-effect and are reported as associations. Nevertheless, our study has some important strengths, including a large cohort of preterm patients with respiratory distress syndrome and protracted ventilation and data abstracted by a dedicated data team using standardized VON definitions. To our knowledge, our study is unique in examining the use of VGV vs. PLV in EPIs with "evolving BPD" and in demonstrating the association of use of VGV with decreased risk of BPD at DOL 21 and 28, compared to PLV.

Our findings suggest that the use of VGV rather than PLV for intubated EPIs during evolving BPD may lead to better clinical outcomes. We caution however, that our observed association of PLV with increased risk of adverse outcome in our cohort does not axiomatically imply a causal relationship. Prospective randomized trials are unquestionably needed to further delineate the most effective ventilatory modality for EPIs with "evolving" BPD.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

All authors are responsible for reported research and have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and that they have approved the manuscript as submitted. The manuscript does not have or use similar data contained in previously published articles. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Adjusting ventilator settings to avoid air trapping in extremely premature infants reduces the need for tracheostomy and length of stay

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Despite the improving understanding of how lung mechanics and tidal volume requirements evolve during the evolution of bronchopulmonary dysplasia (BPD), clinical management continues to be heterogeneous and inconsistent at many institutions. Recent reports have examined the use of high tidal-volume low respiratory rate strategies in these patients once disease has been well established to help facilitate their eventual extubation and improve their long-term neurodevelopmental outcomes. In this retrospective observational research study, we describe how intentional adjustment of ventilator settings based on patient lung mechanics by an interdisciplinary BPD team improved the care of the at-risk population of infants, reduced the need for tracheostomies, as well as length of stay over a period of over 3 years. The team aimed to establish consistency in the management of these children using a high tidal volume, low-rate approach, and titrating PEEP to address the autoPEEP and bronchomalacia that is frequently observed in this patient population.

KEYWORDS

bronchopulmonary dysplasia, BPD, ventilator, interdisciplinary, team, tracheostomy, length of stay, outcome

## Introduction

In an effort to reduce the incidence and severity of BPD, lung protective strategies have been employed to stem the development of ventilator induced lung injury; a major contributor to the development of BPD (1–8). These early interventions, along with postnatal corticosteroid use and early extubation to CPAP have impacted the development of chronic lung disease in animal models and clinically in premature infants (9–13).

As lung architecture changes under the influence of prematurity, oxygen exposure, and inflammatory mediators that could be incited by sepsis, necrotizing enterocolitis, or ventilator induced lung injury, lung mechanics change significantly. While initial tidal volume targets of 4.5–6 ml/kg (14) are used by many Neonatal Intensive Care

Units (NICU), it is known that anatomical dead space increases significantly with prolonged ventilation, this is likely contributed to by the development of tracheomegaly (15–18). This increase in dead space is often accompanied by rising lung compliance as the alveoli lose elastic recoil from alveolar simplification, and increasing airway resistance as the airways develop epithelial lesions and bronchomalacia. These changes lead to a rise in tidal volume requirements to maintain ventilation and avoid atelectasis, along with prolongation in the inspiratory and expiratory time constants of the lung. Continued use of a high ventilator rate in the setting of prolonged expiratory time constants leads to air trapping, causing hyperinflation of the lung and volutrauma despite smaller tidal volumes (4, 19, 20). If air trapping is not addressed by altering ventilator strategies, patients develop severe hyperinflation often leading to inability to wean from invasive mechanical ventilation.

The use of an open lung strategy, providing adequate tidal volume and addressing lung mechanics has been shown to reduce inflammatory mediators in animal studies, and resulted in lower pressure and oxygen requirements in clinical studies (6, 21–24). As lung disease is established and obstructive lung mechanics are more prominent, some patients develop hyper-inflation with increasing lung volumes which can lead to challenges for providing respiratory support (25).

Interdisciplinary programs lead by physicians who understand the changing mechanics and the complex care these infants require may improve outcomes. A hallmark of ventilator management in this group is the use of higher-tidal volumes, lower ventilator rates, and enough PEEP to address triggering and bronchomalacia that children with severe bronchopulmonary dysplasia experience (26–28). Our institution's rate of tracheosomy in preterm infants was higher than the 5% found by Padula et al. from data from the Childrens's Hospital Neonatal Consortium (29), but within the wide range of rates reported by Guaman et.al, from the BPD collaborative. Infants discharged from our hospital with tracheostomy and prolonged mechanical ventilation have an average of 2 hospital admissions and 16% mortality in the first year after initial discharge (30). Thus we aimed to decrease the rate of tracheostomy and prolonged mechanical ventilation in our patients at high risk of severe BPD or death.

This report describes the effect of an interdisciplinary BPD team utilizing individualized ventilator management directed at ventilating all of the lung while avoiding air trapping on the proportion of inborn premature infants at high risk for severe BPD or death who required tracheostomy.

## Methods

Our NICU is a level IV referral NICU offering subspecialty surgical care, and Extra Corporeal Life Support. Approximately one third of our patients are inborn at our level IV maternity center with most of the remaining patients coming from other level III NICUs around the state. We attempt to limit invasive mechanical ventilation in our preterm infants as much as possible while still providing adequate oxygenation and ventilation and supporting optimum growth. Despite these efforts, many patients remain on invasive mechanical ventilation at 28 days of age.

We use the Hamilton-G5© (Hamilton Medical, Switzerland) in the neonatal mode for conventional ventilation in our NICU. The standard in our NICU is to use uncuffed endotracheal tubes (ETT) for the majority of patients on invasive mechanical ventilation, using the weight ranges recommended by NRP. However, chronically ventilated patients develop leaks around their ETTs with growth and stretching of the airway from the positive pressure of the ventilator. When a leak around the ETT is greater than 35% and interfering with patient/ventilator synchronicity, we consider upsizing the ETT if the patient's estimated dry weight is within 100 grams of the weight for the next size ETT. If the patient's estimated dry weight is within 500 grams but not 100 grams of the next larger ETT, we discuss the use of a cuffed ETT with the neonatal team. We only use cuffed tubes that have a Murphy eye, due to concern for acute obstruction when a Murphy eye is not present, thus the smallest cuffed tube we use is a 3.0 ID ETT. Patients with <35% leak around the ETT are generally placed in the volume targeted pressure control mode. Patients with >35% leak who are too small for a larger size or cuffed ETT are placed in conventional pressure control mode. We prefer assist control (CMV on the G5) for most patients to maximize ventilator synchrony and support growth by fully supporting every breath. Some patient are switched to SIMV plus pressure support during weaning or physician preference.

In our NICU, patients at high risk for BPD or death may have any of twenty-six neonatologists as the leader of their primary care team. At the initiation of this project, the primary neonatologist changed every 3 weeks, and in the middle of the project, staffing models changed and the primary neonatologist now changes every 2 weeks. Patients with long lengths of stay may have up to six different primary neonatologists. Frequently, ventilator strategies changed with each change of primary neonatologist. Before the development of the BPD team the pulmonologists were only consulted if the primary team felt the patient required investigation of airway disease with dynamic bronchoscopy, needed testing for pulmonary interstitial disease, needed a tracheostomy, or was diagnosed with pulmonary hypertension. Most patients were continued on the lower tidal volume higher rate strategy on the ventilator until extubated or transferred to the Pediatric Intensive Care (PICU) for transition to home ventilator after tracheostomy. Decision to place tracheostomy was made by the current attending neonatologist but was generally discussed with the parents when a patient over 40 weeks

TABLE 1 Process for ventilator assessment.

**Process for Bedside Ventilator Assessment**

| Assessment | Action |
|---|---|
| Ensure patient is in a calm state | If unable to achieve calm state, discuss best time to return for assessment with the bedside nurse and neonatology providers |
| Evaluate dynamic pressure-volume loops and flow-volume loops for increased inspiratory and expiratory flow resistance. | Take picture in HIPPA compliant mobile phone application and upload into patient chart as pre assessment loops |
| Observe resting respiratory rate, if >30 bpm, gradually increase tidal volume until <30 bpm | If resting respiratory rate is >30 bpm, gradually increase tidal volume until <30 bpm over 5–15 min. Do not increase by more than 25%.[a] |
| Evaluate flow scalers to ensure a brief expiratory pause before next attempted breath. | If no expiratory pause, gradually increase tidal volume until this is achieved |
| Check patient trigger sensitivity | If too high, set to appropriate level (generally 0.1–0.3 lpm in flow trigger mode) |
| Evaluate for patient trigger efforts not resulting in a ventilator supported breath (when triggering sensitivity is set appropriately) | This is frequently caused by autoPEEP, address this by gradually increasing PEEP until all patient efforts result in a patient breath.[b] |
| Re-evaluate Pressure-Volume loops, Flow-Volume loops, and flow scaler for improvement in obstructive patterns | If still concerning for autoPEEP, perform expiratory hold maneuver without neuromuscular blockade. If concerning for autoPEEP increase PEEP until improved.[b] |
| Examine Flow scalars for adequacy of I-time | If there is no inspiratory pause and end-inspiratory flow is still significantly positive with CXR findings of heterogenous disease, increase the I-time by 0.05–0.1 s |
| Assessment Complete | Take picture in HIPPA compliant mobile phone application and upload into patient chart as post assessment loops |

[a]Most patients are in assist control with the rate set lower than their resting respiratory rate to allow for best synchronization of the ventilator with patient efforts.
[b]If PEEP is increased by 3 more than before the assessment and there is still concern for autoPEEP, maintain there and recommend dynamic bronchoscopy through the ETT for PEEP titration.

PMA was unable to be weaned on the ventilator and successfully transitioned to non-invasive respiratory support.

Our interdisciplinary BPD team was established to reduce variation in care both between patients and within the same patient throughout a long length of stay, improve transitions to our PICU and to the outpatient BPD clinic, decrease the number of patients requiring tracheostomy, and decrease hospital length of stay (LOS). An integral part of achieving these goals is the early collaboration between neonatologists and pulmonologists committed to improving the care of patients with BPD. This manuscript describes one focus of the BPD team to ameliorate progression of disease in the patients at highest risk for death or severe BPD. The inclusion criteria for a BPD team consult are that patients are born at <32 weeks estimated gestational age (EGA), and still require invasive mechanical ventilation at 28 days of life. Patients are seen by the BPD team as soon as they meet the inclusion criteria, which can be as early as 27 weeks post menstrual age (PMA). The team meets weekly along with the primary neonatologist caring for the patients. Patients are seen at least every other week, and weekly when not improving with interventions. Team members are available for questions from the primary team on request. Decisions about tracheostomy are discussed during BPD rounds, but the indications for pursuing tracheostomy have not changed.

During BPD rounds, clinical course, current chest imaging, trends in ventilator settings, $FiO_2$, and respiratory rate are reviewed. Neonatologists and pulmonologists combine their expertise to develop and discuss recommendations for ventilator settings with the primary team. The goal of these recommendations is to avoid air trapping by ensuring adequate PEEP, avoid excessive respiratory rates, and ensure complete exhalation. Patients with signs of air trapping on chest x-ray (CXR) or requiring >70% $FiO_2$ despite moderate to high ventilator settings get a patient-ventilator bedside assessment. Goals of this assessment are to ensure optimized PEEP setting and ensure adequate minute ventilation without relative tachypnea.

Our neonatologists on the BPD team, with input from the pulmonologists, developed a process for ventilator assessment (Table 1). At the bedside, with the patient in a calm state, dynamic pressure-volume loops and flow-volume loops are evaluated for increased inspiratory and expiratory flow resistance. Flow scalars are evaluated to ensure that full exhalation occurs with a brief period of expiratory pause before the next inhalation breath. If the resting respiratory rate exceeds 30 bpm, tidal volume target or set pressure control is gradually increased until a resting respiratory rate <30 bpm is achieved. Careful observation to ensure that all patient trigger efforts are detected by the ventilator is assessed by examining patient/ventilator interactions. If missed triggers are noted, and trigger sensitivity is appropriately set, it is likely that autoPEEP is interfering with the sensor's ability to detect the patient's attempts to breathe. To minimize autoPEEP, the PEEP is increased until patient ventilator synchronicity is reestablished (31, 32). Pressure-Volume loops

and Flow-Volume loops are then assessed for improvement in obstructive patterns. Frequently, improvements in oxygen saturation will occur during these changes. If there are still concerns for autoPEEP, an expiratory hold maneuver is performed without routine administration of neuromuscular blockade. If it suggests autoPEEP is occurring, PEEP will be increased until improved, or until PEEP is increased to 3 cm $H_2O$ above the previous setting. In the event there is still concern for autoPEEP and large airway malacia is suspected, dynamic bronchoscopy through the ETT for PEEP titration by our Pulmonology members is recommended. Flow scalars are examined for adequacy of I-time. If an inspiratory pause is not observed, there is no significant leak, and end-inspiratory flow is still significantly positive with CXR findings of heterogenous disease, the I-time is increased by 0.05–0.1 s to allow for either a larger tidal volume delivery in setpoint pressure control, or for lower driving pressures in adaptive volume targeted pressure control schemes. We generally limit the increase in I-time to 0.1 s but could increase farther as long as inspiratory flow does not reach zero, and the respiratory rate is low enough that the increased I-time does not compromise expiratory time and full exhalation is achieved before the next breath. Of note, when an adaptive volume targeted mode is used, the pressure limit is liberalized to allow for adequate tidal volume delivery.

For this retrospective observational research study patients at high risk for severe BPD were defined as those born before 29 completed weeks of gestation, and still requiring invasive mechanical ventilation at 28 days of life for respiratory issues ($FiO_2$ >30% or parenchymal disease visible on CXR). To assess the effect of early interventions to avoid air trapping, patients were excluded from this analysis if they were admitted to our NICU after 32 weeks PMA. IRB approval for data collection to guide improvement efforts was obtained. The BPD team was implemented in September 2018. Data were collected from 1/1/2017 to 12/31/21. Patients were separated into quarters by birthdate for adequate sample sizes in each. The first 7 quarters were considered pre-intervention, "before BPD team.".

## Statistics

Control charts were created in Excel© using the QI Macros© add in. We compared the proportion of patients with BPD who went on to require a tracheostomy, measured the LOS, measured the PMA at discharge, and assessed the proportion of patients discharged home in room air before and after the BPD team was established. A two-sided *t* test using QI Macros© was used. A *p*-value of <0.05 was considered statistically significant.

TABLE 2 Characteristics of patients at high risk for severe BPD.

| | Before BPD Team | After BPD Team |
|---|---|---|
| Number of Patients | 75 | 132 |
| EGA at Birth, *mean (range)* | 24.8 (22–28) | 24.8 (22–28) |
| Age on Admission in Days, *mean (range)* | 10 (0–62) | 13 (0–61) |
| PMA at Admission, *mean (range)* | 26.7 (22–31) | 27.1 (22–31) |

## Results

During the periods evaluated, 75 subjects met the criteria before the establishment of the BPD team, and 132 afterwards, for a total of 207 subjects. The EGA, age at admission, and PMA age at admission were similar in both periods (Table 2). The control chart for proportion of high-risk patients requiring tracheostomy is shown in Figure 1. The centerline from the 7 quarters prior to the BPD team was established was 40%. There was a rapid decline in the proportion of patients requiring tracheostomy after the BPD team, with all quarters having less than 40%. The centerline after this change shifted to 13%.

The control chart of proportion of survivors requiring tracheostomy is shown in Figure 2. There is a similar decrease compared to Figure 1, with the mean decreasing from 43% to 12.5%.

Figure 3 demonstrates the control chart for length of stay. The mean LOS in the baseline period was 180 days. This decreased to 153 after the BPD team intervention but did not meet statistical significance. There is a trend towards decreased variation in LOS (Figure 3). PMA at discharge was not significantly different between the two epochs (Table 3). There was a trend towards more patients discharged home in room air, but it was not statistically significant (Table 3). We also evaluated the PMA at time of tracheostomy procedure (Table 3) as a measure of possible changes in decision making leading to tracheostomy between the two epochs. The mean PMA at the time of tracheostomy placement was not significantly different between the two epochs.

## Discussion

Despite advances in the utilization of non-invasive support modalities to reduce the need for invasive support, a significant proportion of premature neonates continue to require prolonged invasive mechanical ventilation. This is associated with ventilator induced lung injury, especially atelectotrauma and volutrauma, when the changes in tidal volume and PEEP requirements are not addressed in this vulnerable population. Previous work had shown that an interdisciplinary team can

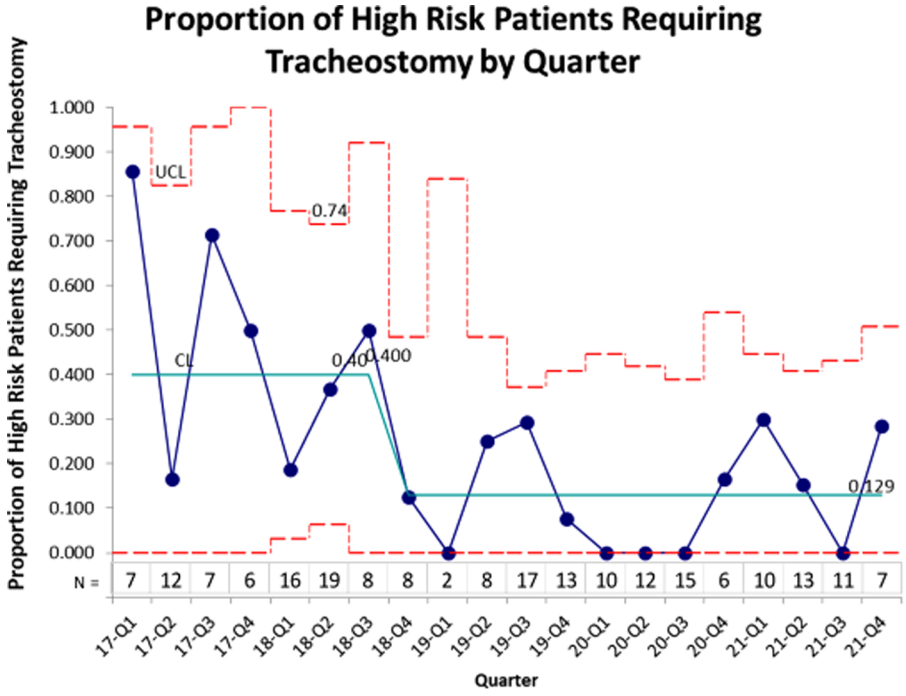


FIGURE 1
Proportion of patients at high risk for severe BPD requiring tracheostomy over time.

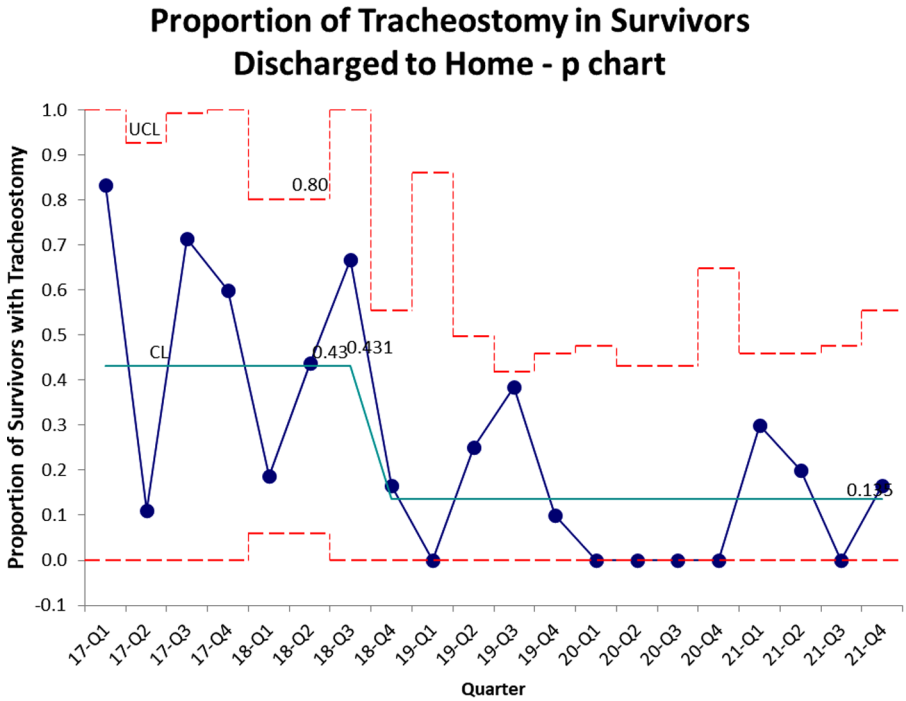


FIGURE 2
Proportion of survivors requiring tracheostomy.

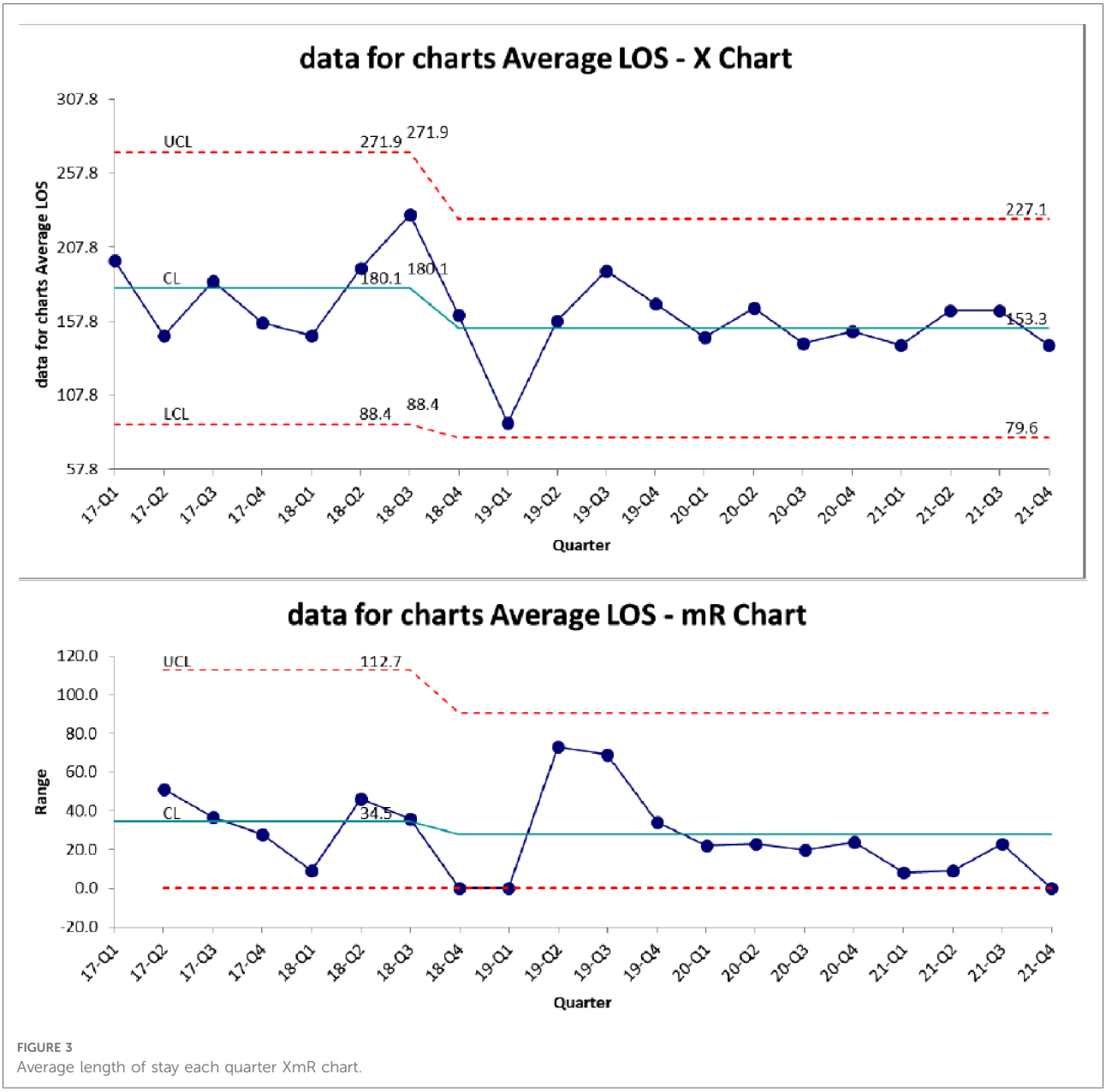


FIGURE 3
Average length of stay each quarter XmR chart.

improve long-term outcomes for these patients, however, did not address the timing of such interventions to reduce the need for tracheostomy (26, 27, 33).

TABLE 3 Characteristics of patients at discharge.

| | Before BPD Team | After BPD Team | *p*-value |
|---|---|---|---|
| PMA at Discharge (Weeks) | 51.85 | 50.53 | 0.365 |
| Percent Discharged in Room Air | 5 | 13 | 0.089 |
| Mean PMA at Time of Tracheostomy Procedure (Weeks) | 47.49 | 48.87 | 0.360 |

In this this retrospective observational research study, we describe how early intervention by an interdisciplinary team focused on an open-lung strategy, addressing lung mechanics and patient-ventilator interactions can reduce the need for tracheostomy, improve LOS, and trend towards more patients being discharged home in room air.

Our interdisciplinary BPD team consults on patients earlier than previously described in the literature with the goal of early intervention in the patients most at risk for severe BPD and death. This earlier intervention may decrease variation in ventilation strategies by having the same team involved in the care throughout the NICU stay. In addition, our approach of adjusting ventilator settings based on the patients current lung

physiology may ameliorate the progression of disease despite long term invasive ventilation. Following the initiation of the team-based intervention, we observed a significant decline in tracheostomy rates which did not come at the cost of a longer LOS or mortality. On the contrary, there was an improvement in the length of stay since the initiation of the program.

Our findings highlight the importance of addressing the changing lung mechanics and maintaining an open-lung approach in breaking the cycle of ventilator induced lung injury associated with more severe forms of bronchopulmonary dysplasia; specifically targeting atelectotrauma and abnormal patient-ventilator interactions. This requires accurate feedback from the conventional mechanical ventilator to facilitate the interpretation of the scalars, pressure-volume, and flow-volume loops. Our interdisciplinary group utilizes a bedside ventilator assessment to guide changes in ventilator parameters to minimize autoPEEP while addressing restriction to inspiratory and expiratory flow with larger tidal volumes and slower respiratory rates. These strategies have been recommended by multiple experts in the field (34, 35).

The goals of the ventilator assessment are based on the concept of addressing pathophysiologic changes in the lung utilizing information from the ventilator (32, 36). The restriction of flow during expiration often seen in BPD requires increased time for expiration before the start of the next breath. Thus the initial part of the assessment involves ensuring that the respiratory rate is slow enough to provide time for a complete expiration (26, 34). If the flow scaler depicts a brief pause in expiration before the next breath, there is less risk of autoPEEP (32, 36). The lack of a pause in expiration can be addresses by small incremental increases in tidal volume to decrease the patient initiated respiratory rate until a pause is seen.

Patient/ventilator asynchrony, demonstrated by patient efforts that do not result in a ventilator delivered breath despite appropriate trigger sensitivity, can be a sign of autoPEEP (31). When present, incremental increases in the PEEP to a level higher than the autoPEEP will improve patient/ventilator synchronicity and often decreases patient agitation. For patient safety, our practice is to only increase PEEP by 3 cm before stopping and reassessing over time, with consideration of dynamic bronchoscopy through the ETT for further PEEP titration.

Limitations of this study include a relatively small number of patients and it only represents care at one institution, with one brand of ventilator. In our NICU, as in many academic NICUs, there are several quality improvement projects and clinical research projects occurring concurrently. These concurrent projects may have influenced our results, although none of the projects were addressing this specific population. In addition, this project only addresses the short term outcomes of tracheostomy and LOS. As more patients are evaluated and managed by this interdisciplinary team on the inpatient and outpatient side, we are hoping to garner a better understanding of whether such early interventions also lead to improved long-term outcomes from a respiratory and neurodevelopmental standpoint. Finally, the consistent care plan from the interdisciplinary BPD team throughout the NICU stay may have contributed to the improvement in short term outcomes.

In summary, in our NICU, early intervention in premature infants at high risk for death or severe BPD, addressing lung mechanics and patient-ventilator interactions, with input from a dedicated BPD team, is associated with a decreased need for tracheostomy and decreased LOS. Our data support the need of a multi-center prospective study to further examine the effect of this type of ventilation approach in infants with high risk of death or severe BPD.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Indiana University School of Medicine Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

## Author contributions

All authors contributed to concept and editing. SI created initial drafts. RSR contributed graphs and statistics. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Individualized dynamic PEEP (dynPEEP) vs. positive pressure ventilation in delivery room management: A retrospective cohort study

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**Objective:** Although nasal continuous positive airway pressure (nCPAP) is recommended in delivery room (DR) management for preterm infants, the effect of delivering nCPAP at 6–8 $cmH_2O$ is not satisfactory. Therefore, we conducted this retrospective cohort study to compare the effects of individualized dynamic positive end-expiratory pressure (dynPEEP) vs. positive pressure ventilation (PPV) in the DR on clinical outcomes.

**Methods:** Preterm infants with a gestational age (GA) less than 30 weeks who received PPV (peak inspiratory pressure, PIP/PEEP 15–25/6–8 $cmH_2O$) from August 2018 to July 2020 were included as Cohort 1 (PPV group, $n = 55$), and those who received dynPEEP (nCPAP 8–15 $cmH_2O$) from June 2020 to April 2022 were included as Cohort 2 (dynPEEP group, $n = 62$). Primary outcomes included the DR intubation rate and the bronchopulmonary dysplasia (BPD) rate. The secondary outcomes included DR stabilization, transfer, admission, respiratory function, and other outcomes.

**Results:** The percentage of singleton infants was higher in the PPV group (63.6%) than in the dynPEEP group (22.6%, $p = 0.000$). The DR intubation and chest compression rates were higher in the PPV group (80.0% and 18.2%, respectively) than in the dynPEEP group (45.2%, $p = 0.000$; 3.0%, $p = 0.008$, respectively). The percentage of patients with 5-min Apgar scores $< 5$ was higher in the PPV group (9.1%) than in the dynPEEP group (0%, $p = 0.016$). The partial pressure of carbon dioxide was lower in the PPV group ($49.77 \pm 11.28$) than in the dynPEEP group ($56.44 \pm 13.17$, $p = 0.004$), and lactate levels were higher in the PPV group (3.60 (2.10, 5.90)) than in the dynPEEP group (2.25 (1.38, 3.33), $p = 0.002$). No significant differences in the BPD rate or other secondary outcomes were noted.

**Conclusions:** In this retrospective cohort study, the dynPEEP strategy reduced the need for DR intubation compared with PPV. The dynPEEP strategy is feasible and potentially represents an alternative respiratory strategy to PPV. Nevertheless, a randomized control trial is needed to evaluate the dynPEEP strategy.

KEYWORDS

dynamic PEEP, positive pressure ventilation, bronchopulmonary dysplasia, intubation, delivery room management

# 1. Background

Some preterm infants require respiratory support at birth to adequately aerate their lungs (1–5). Lung aeration plays an important role in the transition from intrauterine to extrauterine life. However, studies have demonstrated a direct relationship between exposure to intubation (and/or mechanical ventilation, MV) and an increased risk of developing bronchopulmonary dysplasia (BPD) (6, 7). Therefore, noninvasive respiratory support in the form of nasal continuous positive airway pressure (nCPAP) of 6–8 $cmH_2O$ is recommended in the international guidelines for delivery room (DR) management (8, 9). Theoretically, nCPAP could contribute to early physiological transition by facilitating alveolar recruitment and establishing functional residual capacity in preterm infants. However, although we performed nCPAP for all very preterm infants (VPI: gestational age less than 32 weeks) immediately after birth, 17% of VPIs and 36% of extremely preterm infants (EPI: gestational age less than 28 weeks) required intubation in the DR (10).

Using higher pressures up to 20–25 cm $H_2O$ for a period of approximately 10–15 s at the initiation of respiration (sustained lung inflation, SLI) has been reported as a method to avoid intubation (11). However, the Sustained Inflation of Infants Lung (SAIL) trial was suspended early because it detected higher rates of early death, possibly attributable to receiving SLI (20–25 $cmH_2O$, 10–15 s) (12). The European Guidelines on Respiratory Distress Syndrome (RDS) management recommend that SLI should only be used in clinical trials until further analysis of available data (8). Preclinical studies among premature lambs have shown that rapidly aerating the preterm lung at birth produces distinct regional injury patterns that affect subsequent tidal ventilation (13). The ongoing development and heterogeneity of the preterm lung are not conducive to rapid forced aeration (e.g., SLI) (14). On the other hand, SLI before tidal ventilation is not physiological in the preterm lung, and SLI at birth blunted the effect of surfactant on lung compliance (15).

However, to date, the ideal level of nCPAP in the DR remains unknown. Clinical studies regarding the appropriate positive end-expiratory pressure (PEEP) levels, which could be provided by nCPAP, are lacking. Te Pas et al. reported that immature rabbits required higher starting pressures and longer sustained inflation durations to achieve a set inflation volume (16). Higher PEEP levels improve lung aeration and pulmonary blood flow and reduce the need for positive pressure ventilation (PPV) (17). A retrospective study on EPIs showed that nCPAP with higher pressures (12–35 $cmH_2O$) at birth may require less oxygen and decrease intubation rates compared to pressures of 5–8 $cmH_2O$, whereas the pneumothorax rates (19 vs. 4%, $p = 0.125$) and the occurrence of spontaneous intestinal perforations (15 vs. 0%, $p = 0.125$) were increased (18). This study indicated that initial respiratory support for EPIs with high nCPAP levels might decrease intubation rates. However, the adverse event rates increased, and the optimal nCPAP pressure was not specified.

A longitudinal study indicated that after the introduction of a revised protocol to assist EPIs with a GA of 22–26 weeks, the rates of infants intubated in the DR and BPD were significantly decreased (19). In this study, the revised PEEP protocol used in the DR was between 8 and 14 cm $H_2O$, and no harmful effects were noted. Instead, the overall mortality in the revised study group was lower than that in the control group. This study may imply that using a PEEP level of 8–14 cm $H_2O$ would be beneficial for EPIs. However, the protocol includes several interventions [e.g., prenatal management and delayed cord clamping (DCC)]; thus, the beneficial outcomes are not only associated with the revised PEEP protocol.

Above all, we hypothesize that different preterm infants may have different lung development conditions; thus, the PEEP required at birth to adequately aerate their lungs is different. In addition, the intubation rate is still high in the DR, which may also indicate that the effect of delivering nCPAP of 6–8 $cmH_2O$ is not satisfactory. Therefore, an individualized dynamic PEEP (dynPEEP) is proposed. DynPEEP using an optimal PEEP strategy might be more lung protective than SLI because it adjusts the pressure required according to the vital signs of preterm infants. In preterm lambs, dynPEEP at birth with tidal ventilation and PEEP results in more uniform aeration and ventilation and less lung injury than SLI (13) and improves the surfactant response (15). We inferred that the improved surfactant response using the dynPEEP strategy, which increased functional residual capacity and improved lung compliance/homogeneity compared with SLI, would be more likely to reduce the incidence of PPV and intubation. A recent study conducted in France showed that dynPEEP combined with the SLI strategy was beneficial. However, it is difficult to explain whether the benefit is attributable to dynPEEP or SLI (20).

The dynPEEP strategy was implemented in our hospital in June 2020. We conducted this retrospective cohort study to compare the dynPEEP strategy with PPV in the DR on the clinical outcomes of preterm infants with a gestational age (GA) less than 30 weeks who did not respond to an initial CPAP at 6–8 $cmH_2O$.

# 2. Methods

## 2.1. Inclusion and exclusion criteria

All inborn infants < 30 weeks of gestation admitted to the neonatal intensive care unit (NICU) of the Women and Children's Hospital of Chongqing Medical University, which is a tertiary hospital in southwestern China, were initially included in this study. The study period was between August 2018 and April 2022.

The inclusion criteria were as follows: 1. Infants delivered at <30 weeks of gestation who did not respond to an initial CPAP at 6–8 $cmH_2O$; and 2. noninvasive respiratory support was provided immediately after birth in the DR.

The exclusion criteria were as follows: 1. Refusal of consent for the data to be analyzed; 2. there was no need for any respiratory support or only support with a PEEP of 6–8 $cmH_2O$ in the DR, but dynPEEP or PPV was not provided; 3. known major congenital anomalies or inherited metabolic diseases that might have an adverse effect on breathing or ventilation; 4. maternal factors, such as general anesthesia, placental abruption, placenta previa, and monochorionic twins; and 5. outborn infants.

## 2.2. Participants

Two cohorts of preterm infants born at < 30 weeks of gestation and observed for 4 years were compared retrospectively before (Cohort 1: PPV group) and after the renovation of respiratory support management in the DR (Cohort 2: dynPEEP group). In Cohort 1, preterm infants who received PPV (peak inspiratory pressure, PIP/PEEP 15–25/6–8 $cmH_2O$) from August 2018 to July 2020 were included (the PPV group, $n = 55$). In Cohort 2, preterm infants who received dynPEEP (nCPAP 8–15 $cmH_2O$) from June 2020 to April 2022 were included (the dynPEEP group, $n = 62$).

## 2.3. Stabilization and respiratory support in the DR

All team members were trained to deliver noninvasive respiratory support. At delivery, DCC was performed first. The obstetricians and/or midwife were the DCC providers, and they simultaneously gently rubbed the backs of the infants. The delay time of DCC was based on the recommendation made by the European Consensus Guidelines and the American Heart Association to wait for at least 30–60 s (8,9). Then, eligible infants ($23^{0/7}$ to $29^{6/7}$ weeks GA) were placed onto a radiant warmer (Giraffe Omnibed) wrapped in plastic wrap. Then, nCPAP was given *via* a face mask or nasal prong using a T-piece device (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, New Zealand) with pressure at 6–8 $cmH_2O$ and a fraction of inspired oxygen ($FiO_2$) of 21%–30% (30% for babies < 28 weeks gestation and 21%–30% for those 28–30 weeks gestation) (8). A pulse oximeter probe (L-NOPNeo; Masimo Corp, Irvine, CA) was placed on the right hand, and 3 ECG chest leads were applied on the chest. The oximeter was set to acquire data with maximum sensitivity and a 5 s average interval.

In the PPV group, if the infant was apneic (no spontaneous breathing with stimulation by rubbing the soles of the feet or the back of the chest for more than 10 s) and/or bradycardic (heart rate less than 100 bpm), PPV (peak inspiratory pressure, PIP/PEEP 25/6%–8% $cmH_2O$, 40–60/min) was administered. The $FiO_2$ was initially set at 30% and could be adjusted to 100% based on the 25th percentile of the Dawson criteria (21). Respiratory support was provided using the Neopuff TM T-piece resuscitator (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) *via* face mask or prongs.

In the dynPEEP group, if the infant was apneic and/or bradycardic (same definition as mentioned above), PEEP was increased by 2 $cmH_2O$/15–30 s to a maximum of 15 $cmH_2O$ without any PIP inflation. The $FiO_2$ was initiated at 30% and could be increased to 100% based on the 25th percentile of the Dawson criteria. The PEEP was increased prior to $FiO_2$ initiation. PEEP was allowed to be decreased if a baby improved. **Figure 1** shows the dynPEEP algorithms in DR management. To ensure that this new method would be adopted by our staff, we trained the staff first at the beginning of the implementation. It took approximately 2 months (from the beginning of May 2020 to the end of June) for all the staff to adhere to this new method. At the beginning, all the stabilization processes of preterm infants with GAs less than 30 weeks were videotaped (the first 3 weeks in May), and the resuscitation records and videos were used to check whether the dynPEEP algorithms were carried out. We were then debriefed on the stabilization process and gave feedback to the staff who were in charge, and we trained the staff repeatedly. At the end of May 2020, the video playback and debrief process were performed approximately once or twice a week with the gradual acceptance of this new intervention. At the end of June 2020, approximately 90% of the providers stabilized the infants according to the dynPEEP algorithms in the DR.

If PPV or dynPEEP was ineffective, then the infant was intubated. The DR intubation criteria were as follows: (1) heart rate less than 60 bpm after 30 s of effective respiratory support (dynPEEP or PPV; in this case, dynPEEP was interrupted at 10–12 $cmH_2O$), (2) heart rate remaining at less than 100 bpm 3 min after birth, and (3) still apneic 3 min after birth. Intubation was performed at the discretion of the neonatologist in charge.

The less invasive surfactant administration (LISA) method was used for pulmonary surfactant administration in the DR for all infants in case intubation was not needed. The LISA method was introduced in our unit in 2017 as a priority method for all preterm infants less than 1500 grams or with a GA less than 32 weeks. All the doctors who used this method were highly trained and experienced. If the infant was already intubated, then the intubation-surfactant-extubation (INSURE) procedure or intubation-surfactant (INSUR) without the extubation method was used, which were introduced in our unit in 2010. Surfactant was administered through the endotracheal tube; if the $FiO_2$ dropped to 30% in a short time without dyspnea, then extubation and noninvasive respiratory support were continued. If not, MV was implemented. Pulmonary surfactant was used in the DR or in the NICU.

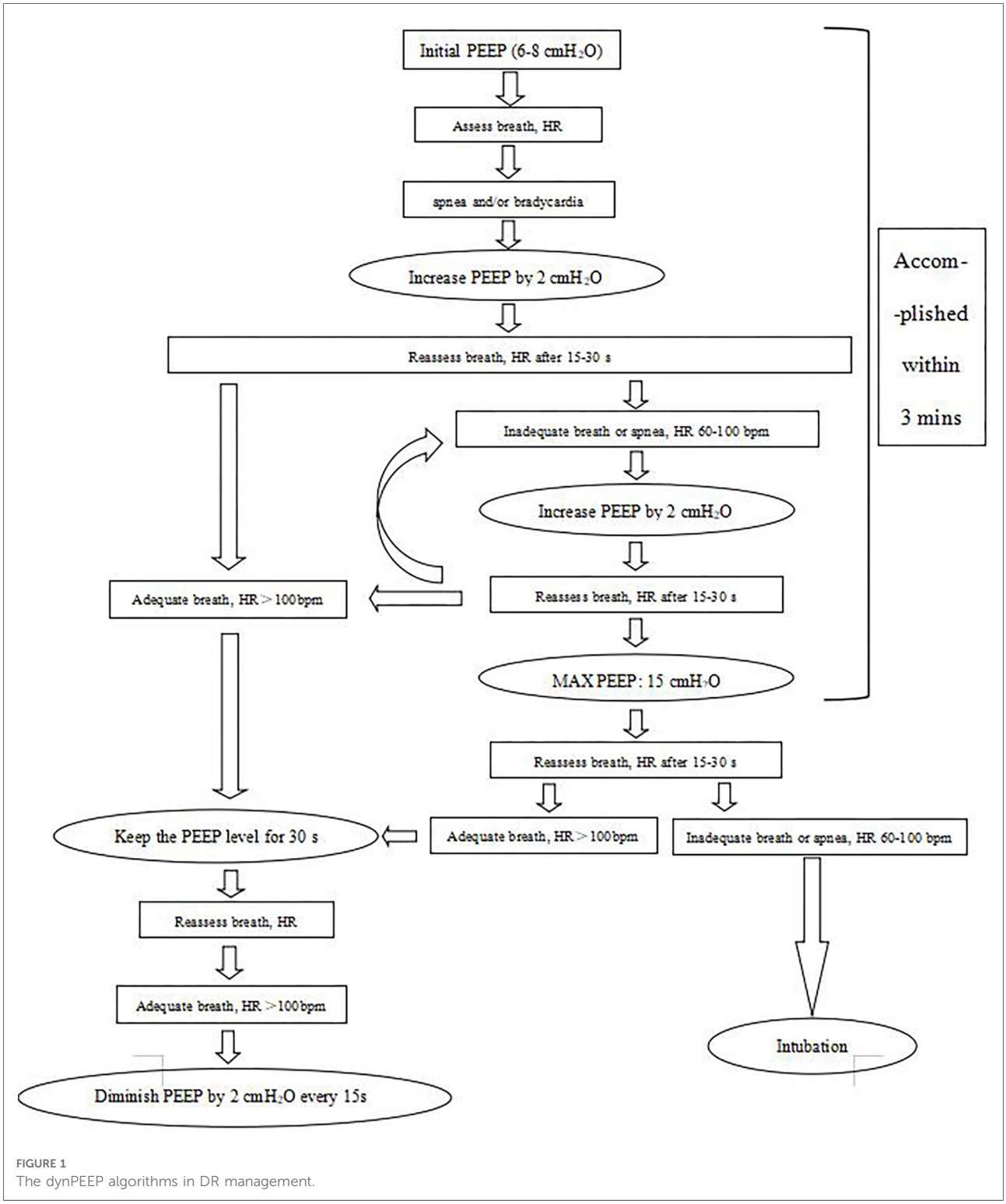


FIGURE 1
The dynPEEP algorithms in DR management.

After stabilization in the DR, the infants were transported to the NICU in incubators. We used a Hamilton ventilator (Hamilton Medical AG, Switzerland) during the transfer for both noninvasive and mechanical ventilation. If the infant was on noninvasive respiratory support (nCPAP or nasal intermittent positive pressure ventilation, NIPPV), then a binasal prong was used as the interface. The methods and settings of respiratory support during the transfer were recorded in the resuscitation records.

In the NICU, the criteria for intubation were as follows: (1) for infants <32 weeks gestation with severe apnea (defined as

recurrent apnea with >3 episodes/h associated with a heart rate < 100/min, a single episode of apnea that required PPV, or saturation of pulse oxygen ($SpO_2$) < 85% and $FiO_2$ > 0.6); (2) for infants with RDS or dyspnea that rapidly progressed and/or persisted after noninvasive ventilation and/or pulmonary surfactant treatment, and $FiO_2 \geq 40\%$, $PaO_2$ < 50–60 mmHg or $SpO_2$ < 90% (except for cyanotic heart disease), or partial pressure of carbon dioxide ($PCO_2$) > 60–65 mmHg, pH <7.25; and (3) if there was some instability in the hemodynamics of the infants. The extubation criteria were as follows: extubation was recommended within 24 h of meeting all the following criteria: $PCO_2$ of 55 mmHg or less, pH of 7.25 or greater, $FiO_2$ of 0.40 or less with oxygen saturation as measured by pulse oximetry ($SpO_2$) of 90% or greater, and mean airway pressure (MAP) of 8 $cmH_2O$ or less with hemodynamic stability. High-frequency oscillation (HFO) ventilation was recommended if one of the following criteria was met: (1) $PCO_2$ > 60–65 mmHg and pH <7.25 even when the tidal volume reached 6 ml/kg and the minute volume reached 0.3 L/min under MV, (2) excess secretion in the airway, and (3) air leakage, including pneumothorax and mediastinal emphysema. Permissive hypercapnia (pH >7.25, $pCO_2$ 50–65 mmHg) was allowed in our unit. The criteria to start systemic corticosteroids were as follows: (1) for infants with severe BPD according to the National Institute of Child Health and Human Development (NICHD) workshop definition (22), (2) for infants who required MV for more than 7–10 days since birth, and for those who had $FiO_2$ > 0.4. Systematic sedation-analgesia (fentanyl and/or midazolam) was used only for mechanically ventilated infants who were irritated. The doses of caffeine citrate were as follows: a loading dose of 20 mg/kg and a maintenance dose of 5 mg/kg q24 h or q12 h.

## 2.4. Demographic characteristics and clinical outcomes

### 2.4.1. Demographic characteristics

All data on neonatal and maternal demographics were collected *via* resuscitation and electronic medical records.

### 2.4.2. Primary outcomes

The primary outcomes were the DR intubation rate and bronchopulmonary dysplasia (BPD) rate.

The definition of BPD was as follows: A premature infant (<32 weeks gestational age) with BPD had persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and required respiratory support or oxygen mode for ≥ 3 consecutive days to maintain arterial oxygen saturation in the 90%–95% range at 36 weeks PMA (22).

### 2.4.3. Secondary outcomes

1) *DR outcomes*

The DR chest compression rate; Apgar scores at 1, 5, and 10 min; Apgar score < 1 at 1 min and < 5 at 1, 5, and 10 min; and DR maximum fraction of inspired oxygen ($FiO_2$) were the DR outcomes.

2) *Transfer outcomes: Respiratory support during the transfer to the NICU*

The methods and settings of respiratory support during the transfer were collected from the resuscitation records.

3) *Admission outcomes*

Admission arterial blood gas, including pH values, partial pressure of oxygen, partial pressure of carbon dioxide, base excess, lactate, maximum $FiO_2$, and *P*/F (formula: $PaO_2 \div FiO_2$).

4) *Respiratory outcomes*

Mortality within 48 h after birth, surfactant therapy, surfactant administration ≥ 2 times, pneumothorax rate within 72 h of age, MV within 72 h of age, MV during hospitalization, time of start on MV (hours), duration of MV (hours), duration of noninvasive respiratory support (hours), duration of oxygen therapy (days), systematic dexamethasone and treated PDA (ibuprofen), mortality and composite BPD and/or mortality rate were the respiratory outcomes.

5) *Other outcomes*

Early-onset sepsis (EOS) (23), late-onset sepsis (LOS) (23), necrotizing enterocolitis (NEC) (≥ phase 2) (24), intraventricular hemorrhage (IVH) (≥ grade 3) (25), and retinopathy of prematurity (ROP) (> phase 2) were the other outcomes (26).

All data on outcomes were collected *via* resuscitation and electronic medical records. Outcomes with missing data due to transfer or death prior to assessment were excluded. Both the number of infants with the outcome and the number assessed are shown.

## 2.5. Data analysis

Data were analyzed using IBM SPSS Statistics version 23.0 (IBM Software, Chicago, Illinois, United States, 2016). The normality test and the homogeneity of variance test were performed for continuous data. If the data were normally distributed and homogenous in variance, the data were expressed as the means ± standard deviations ($X \pm SDs$), and Student's t test was used for comparisons between the two groups. If the data were not normally distributed or the variance was not uniform, the rank-sum test (Mann–Whitney *U* test) was used, and the data were presented as the medians (interquartile ranges, IQRs). The categorical data were expressed as percentages (%), and the rates were compared between the two groups by the chi-square test or Fisher's exact probability method and are presented as counts (*n*) and

percentages (%). To control for the confounders for DR intubation, the demographic characteristics and variables with a $P$ value < 0.05 in the univariate analysis were applied to the multivariate analysis based on logistic regression. The power of the association was represented by $\chi^2$ in the logistic regression model. Furthermore, a subgroup analysis was performed for infants with a GA less than 28 weeks. $P$ values < 0.05 were considered statistically significant, and reported $P$ values were two sided. No adjustment of $P$ values was performed to account for multiple comparisons because subgroup analyses were considered exploratory.

## 2.6. Ethics

This study was approved by the Ethics Committee of Chongqing Health Center for Women and Children (No. 2021–022).

# 3. Results

Of the 377 preterm infants who were potentially eligible to participate, 117 were included in this study, and 260 did not meet our inclusion criteria. In total, 55 infants were supported with PPV, and 62 infants were supported with dynPEEP.

The flowchart shows the inclusion and exclusion criteria for the patients (Figure 2).

## 3.1. Maternal and neonatal demographics

The maternal and neonatal demographics are shown in Table 1. The percentage of singleton infants in the PPV group (63.6%) was significantly higher than that in the dynPEEP group (22.6%, $p = 0.000$). There were no significant differences in the other demographics between the two groups.

The DR maximum PEEP was significantly higher in the dynPEEP group (12, (10, 15)) than in the PPV group (6, (6, 8)) ($p = 0.000$). In the dynPEEP group, the number and percentage of cases with different PEEP levels were 21 cases (33.87%) at 9–10 $cmH_2O$, 25 cases (40.32%) at 11–14 $cmH_2O$, and 16 cases (25.81%) at 15 $cmH_2O$.

## 3.2. Primary outcomes

The DR intubation rate was higher in the PPV group (80.0%) than in the dynPEEP group (45.2%, $p = 0.000$) (Table 2). No significant difference in the BPD rate was noted between the two groups.

## 3.3. Secondary outcomes

### 3.3.1. DR, transfer, and admission outcomes

Table 3 displays the DR, transfer, and admission outcomes.

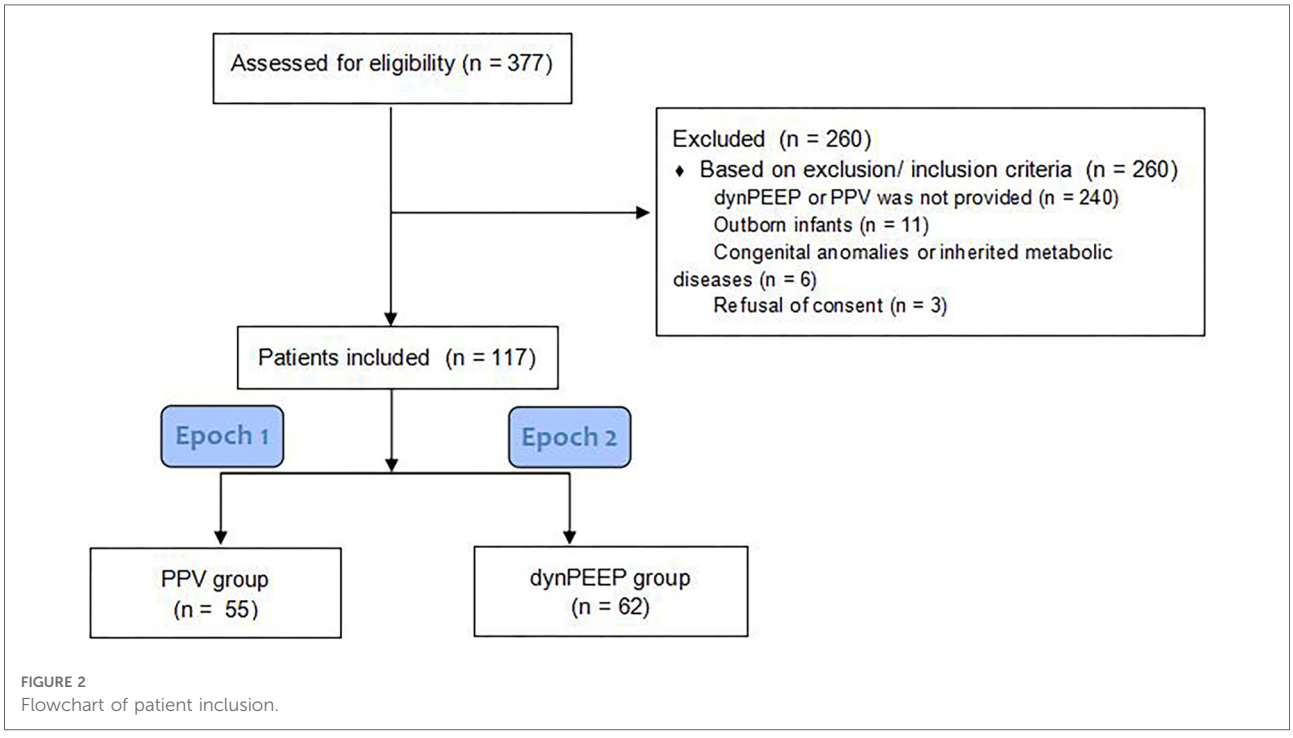


FIGURE 2
Flowchart of patient inclusion.

TABLE 1 Baseline maternal and neonatal demographic and clinical characteristics.

| | PPV ($n = 55$) | dynPEEP ($n = 62$) |
|---|---|---|
| Neonatal Demographics | | |
| Gestational age, ($x \pm$ SD) | 27.7 ± 1.6 | 27.2 ± 1.5 |
| Birthweight, ($x \pm$ SD) | 1050 ± 237 | 997 ± 239 |
| Male sex, *n* (%) | 34 (61.8%) | 30 (48.4%) |
| Singleton birth, *n* (%) | 35 (63.6%) | 14 (22.6%)* |
| Cesarean delivery, *n* (%) | 39 (70.9%) | 35 (56.5%) |
| SGA, *n* (%) | 2 (3.6%) | 1 (1.6%) |
| DCC, *n* (%) | 35 (63.6%) | 47 (75.8%) |
| Maternal Demographics | | |
| Pregnancy-induced hypertension, *n* (%) | 12 (21.8%) | 9 (14.5%) |
| GDM, *n* (%) | 14 (25.5%) | 16 (25.8%) |
| ICP, *n* (%) | 0 | 0 |
| PROM, *n* (%) | 16 (29.1%) | 19 (30.6%) |
| Chorioamnionitis, (*n*) (%) | 4 (7.3%) | 7 (11.3%) |
| Antenatal steroids (full course), *n* (%) | 29 (52.7%) | 41 (66.1%) |
| Antenatal magnesium sulfate, *n* (%) | 37 (67.3%) | 45 (72.6%) |
| Antenatal antibiotics, *n* (%) | 18 (32.7%) | 27 (43.5%) |

*: vs. PPV group, $P < 0.01$.

IQR, interquartile range; SGA, Small for gestational age; DCC, delayed cord clamping; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PROM, premature rupture of membranes; PPV, positive pressure ventilation; dynPEEP, dynamic positive end expiratory pressure.

TABLE 2 The primary outcomes of preterm infants with gestational Age less than 30 weeks who received PPV or DynPEEP in the DR.

| | PPV ($n = 55$) | dynPEEP ($n = 62$) | *P* value |
|---|---|---|---|
| **Primary Outcomes** | | | |
| DR intubation rate, *n* (%) | 44 (80.0%) | 28 (45.2%) | 0.000 |
| BPD, *n* (%) | 14/43 (32.6%) | 13/45 (28.9%) | 0.709 |
| ***Subgroup analysis (GA less than 28 weeks)*** | ($n = 26$) | ($n = 45$) | |
| DR intubation rate, *n* (%) | 22 (84.6%) | 24 (53.3%) | 0.008 |
| BPD, *n* (%) | 10/18 (55.6%) | 13/29 (44.8%) | 0.474 |

DR, delivery room; BPD, bronchopulmonary dysplasia; PPV, positive pressure ventilation; dynPEEP, dynamic positive end expiratory pressure.

Note: For the calculation of BPD, the denominator indicates the number of preterm infants who survived at 36 GA in our NICU. Those who died or were transferred to another hospital prior to assessment were excluded. Both the number of infants with the outcome and the number assessed are shown.

For the DR outcomes, the DR chest compression rate was higher in the PPV group (18.2%) than in the dynPEEP group (3.2%, $p = 0.008$), and the percentage of patients with 5 min

TABLE 3 The secondary outcomes (DR, transfer, and admission) of preterm infants with gestational Age less than 30 weeks who received PPV or DynPEEP in the DR.

| | PPV (n = 55) | dynPEEP (n = 62) | *P* value |
|---|---|---|---|
| **Secondary Outcomes** | | | |
| **DR outcomes** | | | |
| DR chest compression rate, *n* (%) | 10 (18.2%) | 2 (3.2%) | 0.008 |
| Apgar scores | | | |
| < 3 at 1 min, *n* (%) | 7 (12.7%) | 3 (4.8%) | 0.129 |
| < 5 at 1 min, *n* (%) | 19 (34.5%) | 15 (24.2%) | 0.218 |
| < 5 at 5 min, *n* (%) | 5 (9.1%) | 0 | 0.016 |
| < 5 at 10 min, *n* (%) | 2 (3.6%) | 0 | 0.132 |
| Maximum DR $FiO_2$, median (IQR) | 70 (45, 100) | 60 (45, 100) | 0.372 |
| **Transfer outcomes** | | | |
| Respiratory mode | | | |
| nCPAP, *n* (%) | 16 (29.1%) | 32 (51.6%) | 0.035 |
| NIPPV, *n* (%) | 4 (7.3%) | 5 (8.1%) | |
| MV, *n* (%) | 35 (63.6%) | 25 (40.3%) | |
| Settings | | | |
| nCPAP | | | |
| $FiO_2$ | 30 (25, 40) | 30 (26, 39) | 0.797 |
| PEEP | 6 (6, 7.5) | 8 (7, 8) | 0.003 |
| MV | | | |
| $FIO_2$ | 35 (30, 45) | 40 (30, 50) | 0.554 |
| PIP | 20 (16, 20) | 16 (15.5, 18) | 0.016 |
| PEEP | 6 (6, 6) | 6 (6, 8) | 0.025 |
| **Admission outcomes** | | | |
| pH values, ($x \pm$ SD) | 7.23 ± 0.08 | 7.20 ± 0.09 | 0.108 |
| $PaO_2$, ($x \pm$ SD) | 89.2 ± 26.5 | 89.5 ± 30.3 | 0.956 |
| $PaCO_2$, ($x \pm$ SD) | 49.8 ± 11.3 | 56.4 ± 13.2 | 0.004 |
| Base excess, ($x \pm$ SD) | −6.6 ± 4.1 | −6.4 ± 3.7 | 0.714 |
| Lactate, median (IQR) | 3.6 (2.1, 5.9) | 2.3 (1.4, 3.3) | 0.002 |
| Maximum $FiO_2$, median (IQR) | 35 (30, 45) | 35 (25, 45) | 0.954 |
| *P*/F, median (IQR) | 245 (180, 349) | 286 (200, 350) | 0.346 |

IQR, interquartile range; DR, delivery room; $FiO_2$, fraction of inspired oxygen; $PaO_2$, partial arterial oxygen pressure; $PaCO_2$, partial arterial carbon dioxide pressure; nCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; MV, mechanical ventilation; PIP, peak inspiratory pressure; PEEP, positive end expiratory pressure; PPV, positive pressure ventilation; dynPEEP, dynamic positive end expiratory pressure.

Note: *P*/F (formula: $PaO_2 \div FiO_2$).

Apgar scores < 5 at was higher in the PPV group (9.1%) than in the dynPEEP group (0%, $p = 0.016$).

With regard to the transfer outcomes, the percentage of infants with noninvasive respiratory support in the dynPEEP group was higher than that in the PPV group. The settings during the transfer also exhibited significant differences in PEEP levels (nasal or MV) and PIP levels (MV) between the two groups.

Regarding the admission outcomes, the partial pressure of carbon dioxide on admission was lower in the PPV group ($49.8 \pm 11.3$) than in the dynPEEP group ($56.4 \pm 13.2$, $p = 0.004$), and the lactate levels were higher in the PPV group (3.6 (2.1, 5.9)) than in the dynPEEP group (2.3 (1.4, 3.3), $p = 0.002$).

No significant differences in the other DR, transfer, or admission outcomes were noted.

### 3.3.2. Respiratory and other outcomes

Table 4 displays respiratory and other outcomes. The percentage of the less invasive surfactant administration (LISA) method was lower in the PPV group (25.5%) than in the dynPEEP group (50%, $p = 0.006$). No differences in other secondary respiratory or other outcomes were noted between the two groups, including mortality within 48 h after birth, mortality rate, composite BPD and/or mortality rates.

The HFO mode was used for 14 infants in the PPV group and for 16 infants in the dynPEEP group.

## 3.4. Multivariate logistic regression

We applied the demographic characteristics, dynPEEP vs. PPV and Apgar score at 1 min (variables with $P$ value < 0.05) in the univariate analysis to the multivariate analysis based on logistic regression (Table 5).

Logistic regression showed that dynPEEP was a protective factor compared with PPV. Moreover, the Apgar score at 1 min, GA, pregnancy-induced hypertension, and antenatal antibiotics were associated with DR intubation.

## 3.5. Subgroup analysis among infants with a ga less than 28 weeks

We further performed a subgroup analysis among infants with a GA less than 28 weeks. The maternal and neonatal demographics are shown in Supplementary Table S1. The percentage of singleton infants in the PPV group (57.7%) was significantly higher than that in the dynPEEP group (20.0%, $p = 0.001$). No significant differences in the other demographics were noted between the two groups.

Regarding the primary outcomes, the DR intubation rate was higher in the PPV group (84.6%) than in the dynPEEP group (53.3%, $p = 0.008$) (Table 2). No significant differences in the BPD rate were noted between the two groups.

TABLE 4 The secondary outcomes (respiratory and other) of preterm infants with gestational Age less than 30 weeks who received PPV or DynPEEP in the DR.

| | PPV ($n = 55$) | dynPEEP ($n = 62$) | $P$ value |
|---|---|---|---|
| **Secondary Outcomes** | | | |
| **Respiratory outcomes** | | | |
| Mortality within 48 h after birth, *n* (%) | 2 (3.6%) | 4 (6.5%) | 0.491 |
| Surfactant, *n* (%) | 51 (92.7%) | 58 (93.5%) | 0.861 |
| LISA method | 14 (25.5%) | 31 (50.0%) | 0.006 |
| INSURE method | 14 (25.5%) | 8 (12.9%) | 0.083 |
| Surfactant ≥ 2 times, *n* (%) | 9 (16.4%) | 15 (24.2%) | 0.295 |
| Pneumothorax within 72 h of age, *n* (%) | 2 (3.6%) | 0 | 0.130 |
| MV within 72 h of age, *n* (%) | 29 (52.7%) | 25 (40.3%) | 0.179 |
| MV during hospitalization, *n* (%) | 29 (52.7%) | 32 (51.6%) | 0.904 |
| Time start on MV (h), median (IQR) | 0.5 (0.5, 4.5) | 0.75 (0.2, 32.3) | 0.728 |
| Duration of MV (h), median (IQR) | 72 (28.5, 144.5) | 64.5 (15.9, 137.5) | 0.544 |
| Duration of non-invasive respiratory support (h), median (IQR) | 216 (120.0, 427.0) | 239 (93.3, 490.3) | 0.842 |
| Duration of oxygen therapy (d), median (IQR) | 38.7 (18.3, 51.9) | 34.6 (11.5, 59.1) | 0.816 |
| Systemic dexamethasone, *n* (%) | 4 (7.3%) | 1 (1.6%) | 0.186 |
| Treated PDA (Ibuprofen), *n* (%) | 14 (25.5%) | 19 (30.6%) | 0.533 |
| Mortality, *n* (%) | 9 (16.4%) | 9 (14.5%) | 0.782 |
| Composite BPD and/or mortality, *n* (%) | 21 (38.2%) | 22 (35.5%) | 0.763 |
| **Other outcomes** | | | |
| Early-onset sepsis, *n* (%) | 12 (21.8%) | 13 (21%) | 0.911 |
| Late-onset sepsis, *n* (%) | 10 (18.2%) | 11 (17.7%) | 0.951 |
| NEC ≥ phase 2, *n* (%) | 6 (10.9%) | 8 (12.9%) | 0.740 |
| IVH ≥ grade 3, *n* (%) | 3 (5.5%) | 3 (4.8%) | 0.88 |
| ROP ≥ phase 2, *n* (%) | 11 (26.8%) | 18 (34.6%) | 0.421 |

IQR, interquartile range; LISA, less invasive surfactant administration; INSURE, intubate-surfactant-extubate; MV, mechanical ventilation; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; PPV, positive pressure ventilation; dynPEEP, dynamic positive end expiratory pressure; DR delivery room.
Note: Two preterm infants died after they were diagnosed with BPD in the PPV group.

With regard to the secondary outcomes (Supplementary Table S2), the DR chest compression rate was higher in the PPV group (23.1%) than in the dynPEEP group (0.0%, $p = 0.000$), and the lactate levels were higher in the PPV group (3.8 (2.0, 6.0)) than in the dynPEEP group (2.3 (1.4,

TABLE 5 The multivariate analysis of the DR intubation risk based on logistic regression.

| Variables | OR (95% CI) | $\chi^2$ | *P* value |
|---|---|---|---|
| dynPEEP vs. PPV | 0.054 (0.012, 0.239) | 14.70 | 0.001 |
| Apgar score at 1 min | 0.48 (0.29, 0.81) | 7.49 | 0.0062 |
| **Neonatal Demographics** | | | |
| Gestational age | 0.34 (0.16, 0.75) | 7.15 | 0.0075 |
| Birthweight | 1.00 (0.997, 1.005) | 0.20 | 0.6532 |
| Male sex | 1.31 (0.41, 4.21) | 0.20 | 0.6520 |
| Singleton birth | 1.25 (0.35, 4.53) | 0.12 | 0.7309 |
| Cesarean delivery | 2.37 (0.61, 9.22) | 1.54 | 0.2139 |
| SGA | <0.001 (<0.001, >999.99) | 0.0003 | 0.9873 |
| DCC | 1.10 (0.29, 4.19) | 0.02 | 0.8904 |
| **Maternal Demographics** | | | |
| Pregnancy-induced hypertension | 8.29 (1.40, 49.05) | 5.44 | 0.0197 |
| GDM | 0.38 (0.10, 1.51) | 1.89 | 0.1693 |
| PROM | 1.24 (0.35, 4.36) | 0.11 | 0.7418 |
| Chorioamnionitis | 0.20 (0.03, 1.30) | 2.84 | 0.0919 |
| Antenatal steroids (full course) | 0.34 (0.07, 1.56) | 1.93 | 0.1647 |
| Antenatal magnesium sulfate | 0.48 (0.09, 2.46) | 0.78 | 0.3785 |
| Antenatal antibiotics | 10.42 (2.18, 49.77) | 8.63 | 0.0033 |

OR, odds ratio; CI, confidence interval; SGA, Small for gestational age; DCC, delayed cord clamping; GDM, gestational diabetes mellitus; ICP, intrahepatic cholestasis of pregnancy; PROM, premature rupture of membranes; PPV, positive pressure ventilation; dynPEEP, dynamic positive end expiratory pressure; DR, delivery room.
Note: The $\chi^2$ represents the power of the association in the logistic regression model.

3.3), $p = 0.013$). No significant differences in the other secondary outcomes were noted.

## 4. Discussion

Clinical data regarding the effect of dynPEEP on both DR and NICU outcomes are still lacking. We conducted this retrospective cohort study to compare dynPEEP vs. PPV. We showed in this study that the dynPEEP strategy with a PEEP level of 8–15 $cmH_2O$ decreased the DR intubation rate. However, the dynPEEP strategy showed no impact on the BPD and/or mortality rates. In addition, the dynPEEP strategy is feasible and might represent an alternative respiratory strategy to PPV in the DR.

Endotracheal intubation is an emergency treatment for some preterm infants. Intubation is associated with increased BPD and mortality rates (27). Therefore, the dynPEEP strategy could theoretically decrease the BPD rate. In contrast, the dynPEEP strategy showed no impact on the BPD and mortality rates. We hypothesize that BPD is a multifactorial condition with antenatal genetic and environmental factors; thus, respiratory support in the DR is not the only risk factor. In addition, approximately half of the included infants had a GA > 28 weeks, among whom the BPD and mortality rates were relatively lower. This finding might also explain the lack of significant differences in the outcomes. However, when we performed a subgroup analysis among infants with a GA less than 28 weeks, we still found no differences between the two groups. The twofold higher rate of multiple births in the dynPEEP group could also partially explain the lack of difference in the BPD rate between the two groups. Moreover, as the sample size was small, the statistical analysis may not have been sufficiently statistically powered to draw a conclusion. Notably, although there was no significant difference, the rate of systemic dexamethasone decreased from 15.4% in the PPV group to 2.2% in the dynPEEP group among infants with a GA less than 28 weeks (**Supplementary Table S2**), which was a sevenfold decrease. We suspected that this phenomenon might explain the lessened pulmonary morbidity during the second epoch. Nevertheless, a larger, randomized control trial (RCT) is needed to evaluate the effect of the dynPEEP strategy on BPD prevalence.

Although the dynPEEP strategy could decrease the DR intubation rate, the DR intubation rate in the PPV group was 80%, which was considerably greater than those among VPIs (17%) and EPIs (36%), as described in the Background section. These data were obtained from all the VPIs and EPIs in our hospital. Nevertheless, we excluded infants supported only with PEEP levels of 6–8 $cmH_2O$ ($n = 240$), as shown in **Figure 1**. We presumed that this group of infants might have more mature lungs than those who needed dynPEEP or PPV. Therefore, the DR intubation rate in the PPV group was much higher. Consistent with the lower DR intubation rate, the chest compression rate and the percentage of 5 min Apgar scores < 5 were also lower in the dynPEEP group. Consequently, the rate of the LISA method and the percentage of infants with noninvasive respiratory support in the dynPEEP group during the transfer from the DR to the NICU were higher. Due to higher PEEP levels in the dynPEEP group, the PIP levels were lower than those in the PPV group. Given that a $\Delta P$ was noted in the PPV group, which could lower the $CO_2$ levels, the $PaCO_2$ values were higher in the dynPEEP group. Interestingly, lower lactate levels were noted in the dynPEEP group, which might be explained by the enhanced alveolar recruitment and oxygenation in the dynPEEP group. However, the $PaO_2$ and *P*/F values were not significantly different between the two groups. This phenomenon should be considered in future studies.

There are concerns that higher PEEP levels could overexpand the lungs, thereby increasing the risk of pneumothorax and

causing lung injury (17). The SAIL trial showed that death at less than 48 h of age occurred in 16 infants (7.4%) in the SLI group vs. 3 infants (1.4%) in the PPV group. We found no significant adverse events in the dynPEEP group in our study, but the rates of deaths at less than 48 h of age were 6.5% in the dynPEEP group and 3.6% in the PPV group. As seen from the above data, there was a higher mortality rate in the PEEP group than that in the PPV group both in our study and in the SAIL trial. Given that this was a single-center retrospective study with a small sample size, it is difficult to draw a conclusion regarding the safety of the dynPEEP strategy. A well-designed prospective study is needed to evaluate the safety of the dynPEEP strategy with SLI or PPV.

The European Guidelines on RDS management suggest that routine use of positive pressure breaths should be discouraged (9, 28). However, for babies who remain apneic or bradycardic, gentle PPV may be needed. Herein, we demonstrated that the dynPEEP strategy decreased the DR intubation rate compared to the PPV strategy. Therefore, the dynPEEP strategy might represent an alternative respiratory strategy to PPV in the DR.

A randomized controlled, multinational, multicenter trial has been ongoing since May 2021 (29). This is a two-arm study comparing the dynPEEP strategy of 8–12 $cmH_2O$ with the standard PEEP strategy of 5–6 $cmH_2O$ in the DR. The aim of the POLAR trial and our study is to compare the optimal amount or level of PEEP to give at birth and its consequential outcomes. Although the POLAR trial also focuses on the effect of dynPEEP, the PEEP range in the dynPEEP group is between 8 and 12 $cmH_2O$, as mentioned above, which is different from that used in our study. One of the inclusion criteria in the POLAR trial is that infants receive respiratory intervention at birth with CPAP and/or PPV in the DR. Thus, infants in the dynPEEP group might also receive PPV, which differs from our study design. In addition, the primary outcome of the POLAR trial is the prevalence of the composite outcome of either death or BPD, as assessed by a standard oxygen reduction test, which is different from the BPD definition in our study. To date, the POLAR trial has not posted results on ClinicalTrials.gov and is currently recruiting participants. We believe that the results from the POLAR trial would be more convincing than our study because it is a prospective and multicenter RCT.

Given that this was a retrospective cohort study, some limitations should be noted. First, given the retrospective design, there may be confounding factors (twin differences, gestation, unknown, etc.) and bias, and a prospective RCT is needed to make categorical statements regarding safety or benefit. Clinicians might have been more likely to intubate the infants in the PPV group once PPV had started, which might be a potential bias. However, PPV was not allowed in the dynPEEP group because we were concerned that PPV would mask the lung protection of the dynPEEP method (13, 15, 30). Second, half of the included infants had a GA > 28 weeks; thus, the requirement for early respiratory support and the BPD and mortality rates were relatively low. This might explain the lack of significant differences in the outcomes. Although a stratified analysis among infants less than 28 weeks gestation still showed no significant difference, the small sample size might not have been sufficiently statistically powered. Furthermore, the BPD assessment had limitations due to missing data (infants were transferred to another hospital). Third, the lack of systematic assessment of compliance with dynPEEP in the DR was another limitation. Finally, the sample size was relatively small, as this was a time-based feasibility sample, and the multiple secondary statistical analyses made in this study limited the value of significant results.

## 5. Conclusions

Our study showed that the dynPEEP strategy was feasible for preterm infants with a GA < 30 weeks in the DR. Although the dynPEEP strategy with a PEEP level of 8–15 $cmH_2O$ could decrease the need for DR intubation, decreased BPD and/or mortality rates were not observed, and the corresponding measurable clinical outcomes were not approved. The dynPEEP strategy might be an alternative respiratory strategy in the DR instead of PPV. Because another RCT for preterm infants of less than 32 weeks GA in the DR was conducted in our hospital, we could not perform a dynPEEP RCT. A larger, multicenter RCT including more preterm infants with GAs less than 30 or 28 weeks is needed to evaluate the complete effects of the dynPEEP strategy. Above all, the dynPEEP strategy in the DR is worth further exploration.

## Data availability statement

The original raw data (individual de-identified subject data) can be obtained and reviewed by email correspeondence to [YW, e-mail address: bird8227@163.com] upon reasonable request.

## Ethics statement

The studies involving human participants were reviewed and approved by The Ethics Committee of Chongqing Health Center for Women and Children.. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## Author contributions

SS performed the data analyses and wrote the manuscript; YZ contributed significantly to analysis and manuscript preparation

JL helped perform the analysis with constructive discussions. HG contributed to data collection XZ participated in designing the study initiated and managed the study YW contributed to the conception of the study, writing and revision. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1007632/full#supplementary-material.

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# Tracheostomy in infants with severe bronchopulmonary dysplasia: A review

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In recent years, with increased survival of infants with severe bronchopulmonary dysplasia (BPD), long term ventilation due to severe BPD has increased and become the most common indication for tracheostomy in infants less than one year of age. Evidence shows that tracheostomy in severe BPD may improve short- and long-term respiratory and neurodevelopmental outcomes. However, there is significant variation among centers in the indication, timing, intensive care management, and follow-up care after hospital discharge of infants with severe BPD who received tracheostomy for chronic ventilation. The timing of liberation from the ventilator, odds of decannulation, rate of rehospitalization, growth, and neurodevelopment are all clinically important outcomes that can guide both clinicians and parents to make a well-informed decision when choosing tracheostomy and long-term assisted ventilation for infants with severe BPD. This review summarizes the current literature regarding the indications and timing of tracheostomy placement in infants with severe BPD, highlights center variability in both intensive care and outpatient follow-up settings, and describes outcomes of infants with severe BPD who received tracheostomy.

KEYWORDS

tracheostomy (TS), bronchopulmonary dysplasia, reshospitalization, home ventilation, airway disorders, chronic lung disease (CLD) of prematurity, neonatal outcomes

## 1. Introduction

Pediatric tracheostomy has increased significantly in recent years, particularly in children less than one year of age (1–4). Prolonged mechanical ventilation in post-prematurity infants with severe bronchopulmonary dysplasia (BPD) is now the most common indication for tracheostomy in infants (5, 6). As advanced technology in neonatal intensive care units (NICUs) becomes more routine, the survival of extremely premature infants has also increased the need for long-term mechanical ventilation (7), specifically for those infants born at the threshold of viability (≤24 weeks' gestation), who have greater odds of developing severe BPD (8, 9). Other reasons for performing tracheostomy in infants include congenital anomalies of the airway, neurological and complex cardiac anomalies, and genetic diseases with either short- or long-term survival outcome (7, 8, 10).

A recent study found that the rate of tracheostomy in infants increased from 1.9 to 3.5 per 100,000 live births between 2011 and 2017 with a corresponding increase in hospital costs (8). Murthy et al. reported that among members of the Children's Hospital Neonatal Consortium (CHNC), the incidence of tracheostomy varied between centers ranging from as low as 2% to as high as 37%, showing that the indication of tracheostomy in severe BPD infants remains uncertain (11). The timing or age when tracheostomy was performed also varied across institutions, as generally accepted guidelines do not exist. Although various authors have described management of ventilator-dependent infants with severe BPD in intensive care settings (12–15), a recent multicenter collaborative study found significant variation in the

mode of respiratory support provided to these infants (16). In an effort to standardize the care of ventilator-dependent infants and children through a tracheostomy after hospital discharge, the American Thoracic Society (ATS) has published clinical practice guidelines (17). However, significant institutional variation exists in follow-up care models and discharge destinations (18, 19). The literature on post-discharge outcomes of infants with tracheostomy is very limited. Outcomes that are ultimately important in this vulnerable population include the survival rate, liberation from the ventilator, rate of tracheostomy decannulation, growth, and neurodevelopmental trajectories.

Our goal in this review is to provide a synopsis of currently available studies that have reported the indications, rate, and timing of tracheostomy in infants with severe BPD, including the available post-hospital discharge survival, respiratory, growth and neurodevelopmental outcomes. The available knowledge about these outcomes, while limited, will help clinicians navigate the difficulty of counseling families and caregivers who may choose the path of tracheostomy and long-term assisted ventilation of infants with severe BPD.

## 1.1. Indications for tracheostomy in infants with severe BPD

In the last few decades, the most common indications for tracheostomy in children have changed from acute infections, such as epiglottitis and croup, to prolonged mechanical ventilation in infants (20). BPD, or chronic lung disease (CLD), comprises almost 50% of infants needing tracheostomy, followed by congenital or acquired airway abnormalities (vocal cord paralysis, tracheobronchomalacia (TBM), subglottic stenosis), craniofacial anomalies, and cardiac, neurologic or musculoskeletal, and genetic disorders (19, 21, 22). Recently, in addition to BPD or CLD, rare genetic anomalies in infants are increasing indications for receiving tracheostomy to sustain survival outside of intensive care settings (1, 23, 24).

Specific to infants with severe BPD, tracheostomy is performed based on several factors including center-specific practices, corrected age and clinical status of the infant, and parental preferences (5, 19). The decision to offer tracheostomy may also depend on the availability of a home ventilator follow-up program within the hospital's geographical location. Traditionally, tracheostomy is considered for infants who are unable to be weaned off from mechanical ventilation. To facilitate successful extubation, prevent reintubation, and minimize the consequences of prolonged invasive ventilation, various modes of non-invasive ventilatory (NIV) support have been used, that include non-invasive neurally adjusted ventilatory assist (NIV-NAVA), non-invasive positive pressure ventilation (NIPPV), nasal continuous positive airway pressure (CPAP) and high flow nasal cannula (HFNC). A recent study suggests that extubation to NIV-NAVA may be a more successful strategy than to either nasal CPAP or NIPPV (25, 26). The reasons for failure of extubation to NIV may include patient's asynchrony with the ventilator, or patient's inability to trigger the ventilator, or use of ineffective nasal interphase. Tracheostomy is also indicated in infants with severe BPD who have difficulty in achieving adequate growth and developmental milestones with advancing gestational age. However, high cost of tracheostomy and subsequent follow-up may limit its use in infants who require prolonged respiratory support.

Airway complications from prolonged intubation, such as subglottic stenosis or TBM that require tracheostomy, have been observed more frequently in infants with severe BPD (27). In infants with severe BPD and TBM, a continuous level of positive end-expiratory pressure (PEEP) directly applied into the airway may be needed to stent the airway open during exhalation, as described in a recent case report of severe TBM in a ventilator-dependent infant with BPD who required a combination of NAVA ventilation and a PEEP of up to 20 cm H2O during episodes of severe airway obstruction (28).

The development of BPD-associated pulmonary hypertension has been found to be independently associated with the need for tracheostomy in infants with severe BPD (24). Poor growth and delayed development may also contribute to the need for long-term mechanical ventilation through a tracheostomy in infants with severe BPD. A recent survey among 29 responders from 34 tertiary care centers participating in the Children's Hospitals Neonatal Consortium (CHNC) reported that, the most common criteria that contributed to the decision for tracheostomy in infants with severe BPD were airway and ventilation (32%), pulmonary hypertension (16%), multiple courses of corticosteroid therapy (11%), and failure to thrive on noninvasive support (11%) (5). In this same study, the ranges of clinical parameters that would prompt discussion of tracheostomy included pCO2 76–85 mmHg, FiO2 > 0.60, PEEP 9 cm–11 cm H2O, respiratory rate 61–70 breaths/min consistently, post menstrual age (PMA) > 44 weeks, and weight <10th percentile at 44 weeks PMA (5).

In our institution, the decision to place a tracheostomy in infants with severe BPD for purposes of long-term ventilation at home is arrived at after a multidisciplinary team discussion and parental acceptance. A gastrostomy tube is usually placed at the same time in anticipation that these infants will have limited ability to take feedings by mouth.

## 1.2. Timing of tracheostomy in infants with severe BPD

Currently, no consensus recommendation exists for the optimal timing of placement of tracheostomy in infants with severe BPD. Most single-center studies have reported the timing of tracheostomy as ranging between 42 and 51 weeks PMA (7, 19, 29–31). This variation in timing may be related to multiple factors but presumably indicates individual institutional practices, clinician, or parental preferences. It is also unclear whether the timing of tracheostomy has any impact on long-term respiratory, growth, and neurodevelopmental outcomes. It was reported that after placement of a tracheostomy in infants with severe BPD while in the NICU, sustained adequate growth and active participation in neurodevelopmental activities was observed, leading to improved outcomes (32). In a large multicenter study, Demauro et al. reported that the odds of death or neurodevelopmental impairment at 18–22 months of age are lower in infants who received

tracheostomies before, rather than after, 120 days of life (aOR 0.5, 95% CI 0.3–0.9) (1).

## 1.3. Post-tracheostomy management of infants with severe BPD

Immediately following tracheostomy placements, these infants are expected to be either medically paralyzed or heavily sedated in the first few days to a week until the first tracheostomy tube change is accomplished based on local institutional practices (12). Once paralysis and/or sedation medications are weaned, the ventilator settings are adjusted based on the patient's clinical parameters. Frequently, these infants may require higher ventilator settings post-tracheostomy compared to pre-tracheostomy level of respiratory support. A previous study in our institution observed that infants with evidence of pulmonary hypertension on echocardiogram were at higher risk for clinical deterioration post tracheostomy, likely related to resurgence of pulmonary hypertensive crisis (33). Respiratory infections that develop soon after tracheostomy placement may also cause respiratory deterioration in some infants (12). Often, uncontrolled pain and ongoing need for pain medications and/or sedation prevent stabilization of these infants postoperatively (12). Variation exists across institutions on the choice of cuffed or uncuffed tracheostomy tubes. In general, if tracheostomy is performed for an upper airway obstruction and if patient is not ventilator dependent, uncuffed tracheostomy tube is preferred. Patients with severe BPD are most likely ventilator dependent and some institutions including ours prefer cuffed tube to optimize the delivery of high pressures and tidal volume by allowing only minimal leak. Minimal leak point is achieved by adding water to the cuff while auscultating the airway at laryngeal level until leak is not heard during inspiration, then, some water is withdrawn until a small leak is heard. Some ventilators have the ability to provide % leak which can be utilized as well to determine minimal leak. Although gestational age is a driving factor to choose the initial tracheostomy size and length, anatomical differences play a significant role. Upsizing the tracheostomy is determined by otolaryngologists based on the bedside flexible endoscopy through tracheostomy. During this procedure it is ensured that there is enough space above carina so a longer tracheostomy would fit well. If there is significant tracheomalacia, a longer tracheostomy is preferred to bypass the proximal tracheomalacia. Large tracheostomy tubes have less chance of plugging and accidental decannulation but decrease phonation when child tries to vocalize. Otolaryngologists perform a bronchoscopy after tracheostomy and prior to hospital discharge, and the tracheostomy tube is upsized then if needed based on the findings. Tracheostomy granulomas, stoma breakdown, stoma infection, and tracheostomy tube plugging are some of the common complications. Tracheostomy granulomas are typically managed by using topical steroid and antibiotic combination cream for several days. Stoma break down is typically caused by tracheostomy tube pressing or rubbing on the skin and can be prevented by using dressings like simple gauze, tritec silver or tritec ultra for 1–2 weeks after tracheostomy placement. Stoma infection is treated with topical antibiotic cream and in some instances, systemic antibiotic is needed. Tracheostomy tube plugging can be prevented by maintaining adequate hydration status of the patient and providing adequate moisture in respiratory circuit and airway.

McKinney, et al. recently reported that, among 15 BPD Collaborative academic centers, there was a significant variation in mode and settings among centers for both invasive and noninvasive ventilation for infants with established severe BPD (16). Among those receiving invasive ventilation, 53% had tracheostomy, and synchronized intermittent mandatory ventilation (SIMV) was most frequently utilized, with volume control (VC) or volume guaranteed (VG) mode more commonly used than pressure control (PC) mode. Only a small number (6%) used neurally adjusted ventilatory assist (NAVA) mode (34). A recent multicenter experience with NAVA in infants with severe BPD concluded that NAVA can be used safely and effectively in select infants with severe BPD (16). In addition, NAVA when used as a sequel mode of ventilation in infants with evolving or established BPD showed similar respiratory outcomes compared to conventional ventilation and may decrease the need for sedation (35). Nevertheless, the variation in ventilator modes and settings among centers is likely multifactorial in nature and highlights the need for a prospective trial to determine what ventilation strategies are most effective for infants with established severe BPD based on the specific BPD phenotype.

## 1.4. Transitioning from ICU ventilator to home ventilator

The current literature is very limited on how infants with severe BPD who received tracheostomy are transitioned to portable ventilators that can be used outside of intensive care settings. Because there are technological limitations to the degree and mode of respiratory support that portable ventilators can provide at home, ventilatory support after tracheostomy placement in infants with severe BPD must be weaned to a level that can be accommodated by a portable ventilator.

Once a period of clinical stability is achieved, ventilator settings are adjusted with the goal of weaning settings to levels that can be matched on the portable home ventilator. This desired level may take several weeks to months to reach. There are several types of home ventilators available in the market that have their own specific capabilities, unique features, or single vs. double limb circuits. Most ventilators designed for home use may have a minimum weight requirement of at least 5 kg (12). Each institution may have its own preference which home ventilator to prescribe, and it depends most likely on the medical provider's own experience. Some institutions are left with the option of using whatever home ventilator is supplied by the local durable medical equipment (DME) company. There has not been any study that compared the effectiveness of the different types of home ventilators for ventilator-dependent infants with BPD. However, a quality improvement study published recently reported that using a standard protocol of transitioning from an ICU to a portable

ventilator increased the success rate and earlier transition to home ventilator (36). During transition, tidal volume on the portable ventilator is increased by 5–10 ml, PEEP and peak inspiratory pressure (PIP) may be increased based on patients' tolerance to change, work of breathing, and FiO2 change. Trigger sensitivity of portable ventilator is adjusted based on patients' needs, synchrony with triggering and type of portable ventilator provided by local DME company. Depending on the type of portable home ventilator, triggering sensitivity level can range from 0.25 L/minute to 1 L/minute and may have to be adjusted based on patients' ability to trigger ventilator supported breaths consistently. The success of transition to a home ventilator depends on multiple factors such as the severity and specific phenotype of the BPD disease, presence of co-morbidities, growth velocity and the required level of respiratory support. More generalizable clinical practice guidelines are urgently needed that can be adopted by most centers caring for infants with BPD who received tracheostomy and are being transitioned to home ventilators.

## 1.5. Discharge criteria, preparation, and destination

In 2016, the American Thoracic Society (ATS) published an official clinical practice guideline for pediatric chronic home invasive ventilation (17). Based on available evidence, this document detailed the preparation, education, and skills training for at least two caregivers in the home to be able to care safely for a child on a ventilator at home. Further, the document described the requirements for a caregiver who is always awake, the use of monitoring devices such as pulse oximeter, and the provision of all equipment by a DME company. The document also emphasized the importance of securing skilled nursing for support at home (17).

In our institution, parents and/or family caregivers of an infant with tracheostomy are required to take multiple classes as part of educational training (19) on cardiopulmonary resuscitation, which includes simulation sessions using different emergency scenarios that could happen at home. Primary caregivers are required to demonstrate competency in various skills, such as tracheostomy tube changes, tracheostomy care, airway suctioning, and respiratory medication administration. Parents are asked to conduct a stroller ride to familiarize themselves with packing supplies and portable equipment to use during travel. Following these classes, parents are asked to stay in a parent care unit where they care for their infants on their own for 48 h continuously to simulate the real home environment. Typically, private duty nursing coverage is required during the first two weeks of being home. However, due to the recent national shortage of availability of skilled home nurses (37), parents are encouraged to rely on additional caregivers including family, relatives, and friends to provide respite care. A published quality improvement project reported that using a standardized discharge process that included educational materials, a chronic ventilation road map for caregivers, electronic tracking of discharge readiness, team-based care coordination, and timely arrangement for home nursing significantly decreased the length of hospital stay and cut the cost of hospitalization without compromising the safety of ventilator-dependent children with tracheostomy discharged to home (38).

The discharge destination for children receiving invasive ventilation through a tracheostomy may vary depending on the institution's local practice model and the available resources in the geographic area where care is provided. In some states, long-term care facilities that can provide chronic respiratory and rehabilitative services are available to which infants with tracheostomy and ventilator dependence can be discharged as a bridge to going home eventually. This type of accommodation will allow parents and family caregivers to continue to learn the skills necessary to care for their technology-dependent children in a setting with much less intensive care. Although this type of arrangement facilitates earlier discharge from the ICU, it is not readily available in most cities and, where it is, the waiting period for the next available space is usually quite long. As an alternative, some children's hospitals have specialized transition or step-down units for patients with tracheostomy where they can be cared for until certain respiratory support status and set criteria are met for discharge to home. Foster care parenting is sometimes pursued legally for some of these medically complex children whose parents may have significant psychosocial issues. This situation occurs in our institution at a rate of 9%–10% among our ventilator-dependent infants with tracheostomy (19).

## 1.6. Follow-up care and home management of infants with severe BPD who received tracheostomy

According to the ATS evidence-based clinical practice guidelines for hospital discharge and management of children requiring chronic invasive ventilation at home and in the community (17), a collaborative generalist and subspecialist co-management medical home model is most likely to be successful for the care of children requiring chronic home invasive ventilation. In addition, several authors have described their center's follow-up care models after hospital discharge of this cohort of chronically ventilated children (7, 31). In our institution, the coordinated and complex multidisciplinary medical care provided to ventilator-dependent infants with severe BPD and discharged to home is unique in that it is led by the same group of dedicated neonatologists who cared for them while they were in the NICU. Additionally, these neonatologists also provide both primary and subspecialty care in the medical home clinic supported by a dedicated pulmonologist, otolaryngologists, gastroenterologist, the pulmonary hypertension team, and allied medical health providers (19). As new technologies are developed for home use, as the number of technology-dependent infants discharged from intensive care settings continues to grow, and as evidence of their outcomes becomes available, medical providers, parents, and families, and the community-at-large will be better informed about the comprehensive care needed to manage this unique subpopulation of high-risk and medically complex children in the comfort of their home.

## 1.7. Ventilator weaning, decannulation, growth, and neurodevelopmental outcomes of infants with severe BPD who received tracheostomy

### 1.7.1. Weaning from the home ventilator and tracheostomy decannulation

To date, there are no universal guidelines for weaning from the ventilator for those children who are chronically ventilated at home through a tracheostomy. Furthermore, institutions vary in the frequency of follow-up clinic visits that may preclude early and aggressive weaning of these patients from the ventilator. Some centers have incorporated telehealth visits during the COVID-19 pandemic to wean their clinically stable patients virtually from the ventilator. Nevertheless, an increasing number of single-center studies have been published describing individual centers' own method of weaning from the home ventilator and their outcomes. The first comprehensive study by Cristea et al., in 2013, reported a cohort of 102 patients with severe BPD and tracheostomy and showed that, of the infants who survived during the study period, 83% were liberated from the home ventilator, of which 97% were liberated from home ventilator by five years of age, with a median age of liberation from the ventilator of 24 months (31). Following liberation from the ventilator, a median period of 11 months elapsed between ventilator liberation and tracheostomy decannulation (31). More recent studies, including one from our center, have shown a similar median age of liberation from the ventilator and age of decannulation (7, 19, 39–41). Specific to our cohort, we found that ventilator-dependent infants with severe BPD have much greater odds of successful weaning from the ventilator and decannulation by three to four years of age, compared to those infants with other indications for tracheostomy and chronic invasive ventilation at home (19, 42). **Table 1** summarizes the respiratory outcomes to date of infants with severe BPD who were chronically ventilated at home through a tracheostomy. There are also center variations in terms of methods for weaning infants from the ventilator. Examples may include daytime first followed by nighttime weaning, performance of polysomnogram during nocturnal weaning, transition to CPAP, or overnight hospital admission to wean from the ventilator (39, 43–45).

Once these children are weaned off the ventilator and continue to improve and thrive, the introduction and demonstration of tolerance for using a speaking valve (Passy Muir) to facilitate swallowing, vocalization, and improved secretion clearance (46, 47), followed by tracheostomy tube capping during awake periods, may be prescribed. In our institution, as in many other institutions, to prepare for decannulation, we perform a routine surveillance airway bronchoscopy to look for possible airway obstructive lesions or dynamic airway collapse and a capped overnight sleep study in the sleep lab (39, 43, 45, 48–51), to ensure successful and safe decannulation. Post decannulation, otolaryngologists and pediatric pulmonologists follow these patients for the management of tracheostomy stoma, other airway complications, and long-term respiratory morbidities related to severe BPD (19).

### 1.7.2. Growth outcomes

Several studies have indicated that nutrition is a key component of lung growth, particularly for infants with severe BPD who require tracheostomy and home ventilation (52–55). These infants have high energy needs and energy consumption, manifested by increased work of breathing in an effort to mitigate ongoing lung inflammation and sustain continuous lung repair (56). The study by Luo et al. found that most of these infants were born AGA and yet were severely and disproportionately growth restricted by the time of tracheostomy suggesting that these infants suffer from postnatal growth failure in the early weeks of NICU hospitalization. The median weight z-score decreased from −0.45 at birth to −1.42, with >41% of infants had z-score <2 at the time of tracheostomy. The length *z*-score also decreased from −0.64 at birth to −3.07 with >63% of patients having *z*-score <2 at the time of tracheostomy (32). Luo also found that these infants had significant improvement in their z-scores for weight, length, weight/length ratio despite decreased caloric intake after receiving tracheostomy while in the NICU (32). On the other hand, infants who were born already small for gestational age (SGA) continue to suffer from postnatal growth failure while in the NICU and were found to be at much greater risk for worse outcomes (57). These findings underscore the role of a dedicated dietician to optimize nutritional and feeding support for all infants with severe BPD prior to and after tracheostomy while in the NICU.

There is limited literature on the post-hospitalization growth outcomes of infants with severe BPD who received tracheostomy. Typically, these infants are followed by pediatricians who work collaboratively with dietitians. Most of these infants are discharged on gastrostomy tube feeding to optimize delivery of nutrition (30, 57, 58). The unique aspect of our medical home care model for infants with severe BPD and tracheostomy renders us the ability to optimize their nutritional support and manage any coexisting feeding problems, which are very common in this patient population (19). We reported previously that ventilator-dependent infants with tracheostomy had improved z-scores for weight and weight for length at hospital discharge that remained consistent through three years of age, a testament to the dedicated dietitian's role that extends into the outpatient follow-up clinic (19). One area of research that must be explored is whether providing optimal nutrition to improve growth has an impact on weaning from ventilator support that leads to successful decannulation in infants with severe BPD who received tracheostomy.

### 1.7.3. Neurodevelopmental outcomes

Infants with severe BPD who received tracheostomy were found to have improved short-term outcomes while in the NICU. These infants were able to tolerate active participation in various developmental activities without respiratory compromise (32). In addition, they were also found to have less need for sedation medications with their potential negative effect on neurodevelopment (32). In a large multicenter study that included 304 preterm infants who received tracheostomy, Demauro et al. found that the odds of death or neurodevelopmental impairment are high (OR 3.3, 95% CI 2.4–4.6) and that tracheostomy alone cannot mitigate the significant risk associated with many complications of prematurity (1). Furthermore,

TABLE 1 Summary of respiratory outcomes of infants with severe BPD who received chronic ventilation at home through a tracheostomy.

| Authors, year of publication | Patient Population | Primary Indication for Tracheostomy | Age at Tracheostomy | Rate (%) and Age at liberation from home ventilator | Rate (%) and Age at decannulation | Survival rate (%) after hospital discharge | Follow-up period |
|---|---|---|---|---|---|---|---|
| Cristea et al., 2013 | Preterm infants born at 26 weeks ** (IQR 25, 27) ($n = 102$) | Severe BPD | Not reported | 97.1% 24 months** (IQR-19–33) | 58.8% 37.5 months** (IQR-31.5–45) | 81.4% | Up to 5–6 years of age (total of 871 person years) |
| Akangire et al., 2020 | Ventilator-dependent infants (n = 204) BPD only ($n = 82$)[#] | Severe BPD Airway Cardiac Neurologic Genetic | 4.9 months* (SD 4.6) | 100% 27.2 months*(SD 23) | 50% 41.9 months*(SD 23.3) | 80.5% | Up to 4 years of age |
| House et al., 2021 | Preterm infants born at < 33 weeks ($n = 49$) | Severe BPD | 43.3 weeks* (range 36.3-56.9) | 97.0% 27.3 months* (SD 4.1, range 7–45 months) | 79% 44.7 months* (range- 22–79) | 73.9% | Up to 5 years of age |
| Sillers et al., 2021 | Tracheostomy-dependent infants ($n = 323$) CLD/BPD only ($n = 180$)[#] | Pulmonary Anatomic Cardiac Neurologic Musculoskeletal Other | 52.3 weeks PMA** (IQR 44.3, 60.0) | Not reported | 51.3% 3.1 years** (IQR 2.4, 4.5) | 82% | Minimum of 3 years after tracheostomy placement |
| Akangire et al., 2022 | Tracheostomy dependent infants ($n = 98$) | Severe BPD | 43 weeks PMA or 4 months** (IQR 3, 5) | 100%, 24 months** (IQR 18, 29) | 52%, 32 months** (IQR 26, 39) | 99% | Up to 4 years of age |

*Mean.
**Median.
[#]Outcomes for CLD/BPD subgroup only.

Annesi et al. reported that infants with severe BPD and tracheostomy suffered from increased long-term cognitive delay beyond 24 months of age (59). On the other hand, Cammack et al. observed no difference in cognitive and language development at two years of age in infants with severe BPD who received tracheostomy compared to those without a tracheostomy (60). As more and more extremely preterm infants with severe BPD are surviving to hospital discharge with a tracheostomy for chronic invasive ventilation, the need for multicenter research to determine their long-term neurodevelopmental outcomes and identify modifiable risk factors for worst outcomes become imperative.

## 1.8. Mortality and rehospitalizations

The mortality rate after hospital discharge of infants with severe BPD who received tracheostomy ranged between 15% and 21% as reported by several authors (19, 22, 31). (**Table 1**) Cristea et al. reported no significant difference in the demographic data in their cohort between those who died and those who survived (31). Akangire et al. reported that of the 21% of their patients who died by four years of age, the median age of death occurred at 27 months (19), while Sillers et al. found a median age of death to be 17 months (22). The most common cause of death after discharge from the hospital was cardiopulmonary arrest due to accidental tracheostomy decannulation or plugging (7, 19). Interestingly, Cristea et al., in a study of 94 infants with severe BPD and tracheostomy found significantly higher mortality among economically disadvantaged families with income below the state median household income, or those who reside in poor geographic Zip codes (61).

On the other hand, the overall mortality rate including those who died after tracheostomy but before hospital discharge was about 26% (7, 22). The cause of death for these patients varied depending on the primary indication for tracheostomy (22), or prematurity-related issues, redirection of care due to poor neurologic prognosis, or respiratory failure related to severe pulmonary hypertensive crisis (7). Additionally, being born SGA was found to be a significant risk factor for death. However, the degree of respiratory support as measured by mean airway pressure and fraction of inspired oxygen at the time of tracheostomy were not found to be associated with the risk for death (7).

Information about the rehospitalization of ventilator-dependent infants with severe BPD with a tracheostomy is very limited. Several reasons may be related to the nature and geographical location of where these infants receive both their primary and subspecialty care, i.e., community-based care setting vs. academic or tertiary hospital-based clinics with availability of pediatric subspecialty support including pediatric pulmonology and otolaryngology. Akangire et al. reported respiratory viral infections specifically caused by rhino-enterovirus as the most common cause of rehospitalization. Other causes include non-infectious respiratory conditions, equipment malfunction, feeding or gastroenterology-related causes, and need for surgical procedures. In the same study, infants who were ventilator and oxygen-dependent, and on chronic use of inhaled corticosteroid were

significantly at higher risk of rehospitalization in the first two years of life (62).

## Author contributions

GA and WM conceptualized the idea. GA wrote the first draft and both GA and WM edited the manuscript. Final version was approved by GA and WM prior to submission. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Respiratory support strategies in the prevention and treatment of bronchopulmonary dysplasia

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Neonates who are born preterm frequently have inadequate lung development to support independent breathing and will need respiratory support. The underdeveloped lung is also particularly susceptible to lung injury, especially during the first weeks of life. Consequently, respiratory support strategies in the early stages of premature lung disease focus on minimizing alveolar damage. As infants grow and lung disease progresses, it becomes necessary to shift respiratory support to a strategy targeting the often severe pulmonary heterogeneity and obstructive respiratory physiology. With appropriate management, time, and growth, even those children with the most extreme prematurity and severe lung disease can be expected to wean from respiratory support.

KEYWORDS

prematurity, bronchopulmonary dysplasia, CPAP, mechanical ventilation, tracheostomy

## Introduction

Neonates who are born preterm frequently lack adequate lung development to support breathing independently and are quite prone to needing respiratory support, with increasing risk as gestational age decreases. Even during the first days and weeks of life, there are extensive changes in the respiratory system and breathing mechanics for children who are born prematurely, and ventilatory strategies must be titrated to meet each patient's evolving needs and avoid complications. Early in the disease course respiratory support should focus on limiting additional lung injury by utilizing non-invasive ventilation or "gentle" invasive mechanical ventilation with a low tidal volume, short inspiratory time, and high respiratory rate strategy. However, for those infants who go on to need chronic respiratory support, worsening obstructive lung disease requires a transition to longer inspiratory times, lower rates, and a higher tidal volume strategy to optimize ventilation. This review will describe the changes in respiratory support throughout the evolution of premature lung disease.

## Non-invasive ventilation

Although an in-depth discussion is beyond the scope of this review [which is primarily focused on invasive mechanical ventilation of infants at-risk for and with severe bronchopulmonary dysplasia (BPD)], non-invasive ventilation used as both initial support for infants with respiratory distress syndrome and/or as post-extubation support can limit lung injury, minimize exposure to mechanical ventilation, and theoretically can reduce the risk of severe BPD. Excellent, contemporary reviews have thoroughly summarized the

safety and efficacy of non-invasive modes of respiratory support (1, 2) including nasal high frequency ventilation (nHFV) (3, 4), non-invasive neurally-adjusted ventilatory assist (NI-NAVA) (5), nasal intermittent positive pressure ventilation (NIPPV) (6), and nasal continuous positive pressure ventilation (nCPAP) (7, 8). Indeed, following publication of the COIN trial in 2008 [the first multicentered, randomized controlled trial demonstrating the safety and efficacy of nCPAP as primary respiratory support for extreme preterm infants with respiratory distress syndrome (9)], from 2008 to 2018 in the United States there has been a shift toward decreased use (and duration) of mechanical ventilation and a concomitant increased use (and duration) of non-invasive ventilation (10). During the same era, however, the incidence of BPD, including severe BPD, has not improved significantly (11–13). Though supported by sound biological plausibility, meta-analysis of the major trials that relied on nCPAP to avoid mechanical ventilation resulted in only a modest (~10%) reduction in BPD (14). Especially true for infants born at the earliest gestational ages (15), despite efforts to provide non-invasive respiratory support, many infants ultimately require mechanical ventilation. For infants born at 22–28 weeks' gestation and cared for in the Neonatal Research Network between 2013 and 2018, 85% of infants required mechanical ventilation at some point in their hospitalization, and 8% of infants at 36 weeks' corrected gestational age were still ventilator-dependent (16). In the major multicenter randomized controlled trials (RCTs) comparing CPAP to intubation for prophylactic surfactant, by 5–7 days of age ~50% of extremely preterm infants experienced CPAP failure (9, 17–19). Though reduced by 50% in the recent OPTIMIST-A trial, despite avoidance of endotracheal intubation for minimally-invasive surfactant therapy in the first 6 h of age, by 72 h of age nearly 40% of MIST infants ultimately required intubation and mechanical ventilation (20). Emerging experience with synchronized NIPPV, specifically the use of NIV-NAVA, may prove most beneficial in terms of avoiding initial or subsequent need for mechanical ventilation and hold promise. However, limited options for providing synchronization have hindered wide-spread use. In summary, although questions remain concerning the impact of synchronized noninvasive positive pressure ventilation, despite now over a decade of coordinated efforts to avoid mechanical ventilation, for the majority of extremely preterm infants invasive mechanical ventilation inevitably will be required.

While the majority of infants require a period of invasive mechanical ventilation, by 36 weeks' corrected gestational age, more than 90% will have been extubated and supported non-invasively (16, 21). As stated previously, evidence comparing the efficacy of various modes of non-invasive support is emerging, but presently nCPAP comprises the bulk of available data. Since 2008, 5 large multicenter RCTs (COIN (9), SUPPORT (17), CURPAP (19), Vermont Oxford (18), and now OPTIMIST-A (20)) have enrolled over 3,000 infants born at 24–29 weeks' gestation and cared for with nCPAP and, therefore, provide a wealth of safety and efficacy data. However, despite wide-spread acceptance and use of non-invasive ventilation in both the United States (10) and United Kindom (22), nearly 50% of surviving infants continue to develop BPD (16, 21). Preclinical and clinical evidence implies that outcomes may be improved by prolonging the duration of constant distending pressure. A strategy employing prolonged, prophylactic support on nCPAP until respiratory stability is achieved and infants can be weaned directly to room air is associated with the lowest rates of BPD (23).

Supporting evidence derived from preclinical animal models demonstrates that constant distending pressure minimizes lung injury and augments lung growth. In both murine and rabbit models of hyperoxic neonatal lung injury, compared to no support, use of CPAP reduced inflammation, preserved alveolar-capillary development, and durably improved lung function (24, 25). Exposure of juvenile ferrets to 2 weeks of constant distending pressure significantly increased lung weight and DNA content and increased total lung capacity by 40% while preserving elastic recoil, thus implying CPAP induced not merely lung distension but lung growth (26). In infants with severe congenital diaphragmatic hernia, tracheal occlusion (resulting in lung fluid retention and constant distension of the developing lungs) improved survival and reduced the need for ECMO, strongly-implying improved lung function (27).

Recent clinical evidence indicates that extremely preterm infants with evolving BPD may similarly benefit from prolonged constant distending pressure. Forty-four infants born ≤32 weeks' gestation and requiring ≥24 h of bubble CPAP that had reached clinical stability (i.e., CPAP ≤5 cm $H_2O$, $fiO_2$ 21%, RR < 70, comfortable work of breathing, minimal cardiorespiratory events, and stability off CPAP for routine care) were randomized to wean directly to room air or remain on bubble CPAP for an additional 2 weeks (28). Infants were randomized at a mean of 32 weeks' corrected gestational age, and extended CPAP was well-tolerated. Despite being similar at randomization, at the end of the treatment period, infants who remained on bubble CPAP for two weeks rather than weaning immediately to room air had significantly larger (~10%) functional residual capacity (FRC), and the change in FRC was nearly double (12.6 vs. 6.4 ml). At discharge (an average of 2 weeks following discontinuation of the intervention) infants randomized to prophylactic, prolonged nCPAP continued to have a larger FRC (~20%) that had grown nearly 60% more (27.2 vs. 17.1 ml). Importantly, infants in both groups reached full oral feeds and were discharged at similar corrected gestational ages indicating that extending nCPAP did not prolong hospitalization. A follow-up study will determine the durability of benefits to lung function, but the preliminary results in combination with preclinical data and sound biological plausibility provide promise that prophylactic, prolonged nCPAP may help support and preserve lung development and function.

## Invasive mechanical ventilation

When the severity of respiratory failure requires invasive ventilation, maintaining optimal FRC with appropriate positive end expiratory pressure (PEEP) and avoiding volutrauma through volume targeted ventilation can minimize lung injury. Mechanisms of neonatal lung injury are multifactorial, but

include a combination of biotrauma, atelectotrauma, and volutrauma (the concepts for which have been nicely reviewed) (29). Whether acquired prenatally (chorioamnionitis), through vertical transmission of vaginal organisms, or postnatally through ventilator-associated pneumonia, the inflammatory cytokine milieu invoked by neonatal pulmonary infections results in biotrauma. Poor lung compliance and surfactant deficiency places the infant at risk for poor lung recruitment and alveolar instability; the sheering forces associated with the repetitive re-opening of collapsed alveoli with each breath underlie atelectotrauma. Conversely, over-distension of fragile neonatal alveoli, even for brief periods of time, stretches the alveolar walls, disrupts the underlying extracellular matrix, and incites an inflammatory cascade that results in volutrauma. The neonatal lung injury associated with biotrauma, atelectotrauma, and volutrauma, place the preterm infant at significantly increased risk of developing severe BPD.

Supporting the cardiopulmonary needs of the extremely preterm neonate while minimizing neonatal lung injury, and therefore the risk of severe BPD, can be accomplished through a comprehensive approach to neonatal mechanical ventilation. The key principles of avoiding both atelectotrauma and volutrauma are satisfied by relying on open lung ventilation. Prior to the availability of reliable neonatal volume ventilators, high frequency oscillatory ventilation (HFOV) was utilized to provide sub-physiological tidal volumes and constant distending pressure in an effort to provide lung-protective ventilation. However, metanalysis of 19 trials randomizing nearly 5,000 infants failed to show a benefit for mortality and there was only a very small, inconsistent effect to reduce BPD in survivors (30, 31). Moreover, in trials that compared modern-day conventional ventilation strategies (lower volume, higher rate) to HFOV, there was no benefit (32). Advances in neonatal ventilator microprocessor technology allowing for delivery of small tidal volumes reliably and reproducibly have led to the preferred mode of neonatal invasive ventilatory support being volume-targeted ventilation. The resulting ventilatory support allows for the benefits of a pressure-controlled mode in terms of flow while offering the lung-protective benefits of limited volume. These volume targeting/guarantee modes of ventilation utilize the lowest possible pressure to achieve a desired targeted tidal volume. Previously, during pressure-limited ventilation, rapid changes in compliance accompanying surfactant administration had the potential to translate into delivery of excessive tidal volume. The immediate response to the volutrauma that ensues is hyperventilation and air leak (pulmonary interstitial emphysema and pneumothoraces). Preclinical evidence demonstrated that even a few excessive breaths to a surfactant-deficient lung (as can happen in the delivery room or following exogenous surfactant administration) incites an enduring inflammatory cascade and lung injury (33–35). When comparing pressure-limited and volume-targeted ventilation, 20 randomized trials enrolling 1,065 infants from 1997 to 2016 demonstrated a reduction in episodes of hyperventilation, air leak [RR 0.52 (0.31–0.87)], Grade 3–4 IVH [RR 0.53 (0.37–0.77)], and BPD [RR 0.68 (0.53–0.87)] (36). Therefore, including at our institution, volume-targeted ventilation using lower tidal volumes (4–6 ml/kg), shorter inspiratory times (0.3–0.4 s), and higher rates (40–60 bpm) has become the preferred initial mode of ventilation.

To avoid both volutrauma and (as importantly) atelectotrauma, it is imperative to give judicious attention to optimizing PEEP. Maximal compliance (change in tidal volume for a given change in inspiratory pressure) occurs at optimal FRC. In the presence of inadequate PEEP, poor compliance and alveolar instability result in atelectasis. For an atelectatic distal airspace to be ventilated, the ventilator must first apply a critical opening pressure. Indeed, reaching the critical opening pressure to provide ventilation to the distal airspace utilizes a significant proportion of the inspiratory cycle and peak inspiratory pressure. Repetitive reopening of the alveolus exposes the alveolar wall to damaging shearing forces that disrupt lung structure and incite inflammation, and the expense of a significant proportion of the respiratory cycle merely to open the alveolus reduces ventilation efficacy. The impact of optimal lung inflation on oxygenation, as well as the contribution of surfactant replacement, were nicely demonstrated in 103 preterm infants (mean GA 29.4 wk) with respiratory distress syndrome requiring intubation and mechanical ventilation in the first hours of age (37). Using a step-wise titration of constant distending pressure while on high frequency ventilation, titration from closed pressure (mean 12.0 cm ± 4.0 cm $H_2O$), to a fully-recruited open pressure (mean 20.5 cm ± 4.3 cm $H_2O$), and back to an optimal constant distending pressure (mean 14.0 cm ± 4.0 cm $H_2O$) was associated with a robust and significant reduction in supplemental oxygen needs (from mean 0.7 ± 0.27–0.24 ± 0.04). Surfactant administration was associated with a significant, further reduction in optimal distending pressure (mean 9.3 cm ± 2.6 cm $H_2O$). Thus, not only does optimal recruitment protect from atelectotrauma, it also allows for a reduction in oxygen exposure.

Examination of the pressure-volume loop will demonstrate flattening of the initial portion with a sudden upward inflection when critical opening pressure is reached. Conversely, in the presence of excessive PEEP (either extrinsic or intrinsic), excessive pressure is required to force tidal volume into an already over-distended alveolus. Examination of the pressure-volume loop in this case will demonstrate "beaking" at the tip of the curve representing the excessive pressure required to force a relatively small amount of volume into a lung that at end-expiration is already near total lung capacity (**Figure 1**) (38, 39).

Clinically, the infant with atelectatic lungs will require higher fractional inspired oxygen and demonstrate oxyhemoglobin saturation (SpO2) instability due to inadequate FRC, while the infant with hyperexpanded lungs tends to require relatively lower amounts of inspired oxygen but have carbon dioxide retention and, when severe, hypotension secondary to impaired venous return. In terms of compliance, both atelectasis and over-distension require a higher change in pressure to achieve a similar change in volume when compared to an optimally-inflated lung. At optimal inflation, where atelectasis and over-distension are minimized (typically a PEEP of 4 cm–7 cm $H_2O$), not only is the smallest change in pressure required to deliver a given tidal volume, both atelectotrauma and volutrauma are minimized. Therefore, during volume-target ventilation, in addition to ensuring 8–9 rib expansion on chest xray, one can titrate to optimal PEEP by monitoring and optimizing compliance.

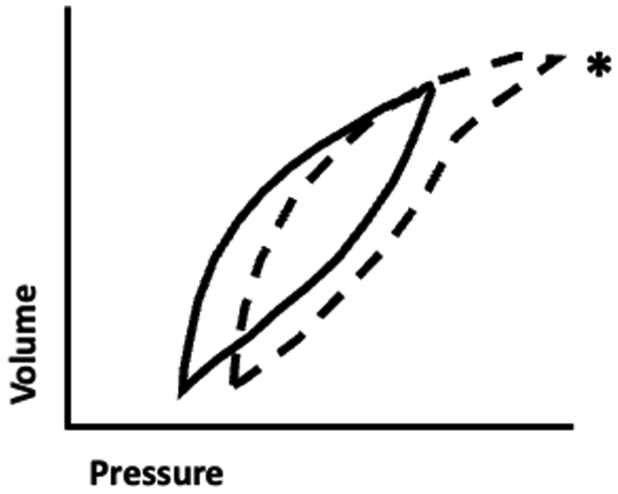


FIGURE 1
Pressure-volume loop demonstrating the phenomenon of "beaking." A typical pressure-volume loop generated from ventilation of an optimally-expanded lung (solid line) is shown for reference. Note that in the normal condition, a relatively small change in pressure results in a significant change in volume. Excessive positive end expiratory pressure can result in ventilation of a hyperinflated lung (dashed line), and as tidal volume nears total lung capacity it requires a higher change in pressure and a higher peak pressure to attain a similar change in volume. The flattening of the upper portion of the curve is referred to as "beaking" (asterix)

Although avoidance and minimization of mechanical ventilation is ideal, for a subset of infants mechanical ventilation will be prolonged (40). In infants remaining on volume-targeted ventilation beyond the first week of age, it is imperative they be monitored for tidal volume evolution. Although initial tidal volumes of 4–5 ml/kg are sufficient to support infants with early RDS (41, 42), several lines of evidence in infants requiring mechanical ventilation for the first month support the need to modestly increase tidal volumes. In a retrospective observational study of 26 infants with birthweights <800 g cared for on volume-targeted ventilation over the first three weeks of age, exhaled tidal volumes associated with target carbon dioxide (PCO2) levels were examined for evolution. Over the first 3 weeks of age, mean exhaled tidal volumes increased significantly from a mean of 5.15 ml/kg (day 1–2) to 6.07 ml/kg (day 18–21) (41). In a similar observational study of 18 infants with median GA of 25 weeks' who were ventilated for the first 28 days of age, despite carbon dioxide levels increasing significantly (from a mean PCO2 42 mmHg to 60 mmHg), mean exhaled tidal volumes steadily rose from 5.4 to 7.2 ml/kg. There was a corresponding increase in mean minute ventilation (263–368 ml/kg/min) and a modest increase in peak inspiratory pressures (18.1–22.4 cm $H_2O$) (43). The authors speculated that to maintain relative normocapnia, the increase in minute ventilation and tidal volume were required to compensate for an expansion of the anatomical dead space (*via* both distension of the upper airways as well as alveolar airspace dilation).

Anatomical dead space is relatively increased in extremely preterm infants and expands with mechanical ventilation. In an observational study of 45 premature infants (median 25 weeks' GA) ventilated for a median of 8 days compared to 11 term infants, despite similar tidal volumes (5.6 and 5.3 ml/kg, respectively) the preterm infants had significantly larger anatomical (3.7 vs. 2.4 ml/kg) and alveolar component (0.3 vs. 0.1 ml/kg) of dead space (44). The increase in dead space was accompanied by higher respiratory rates (median 71 vs. 55 breaths/min), presumably to maintain adequate alveolar ventilation. Notably, anatomical dead space in relation to body weight (ml/kg) was inversely proportional to birthweight and gestational age. Thus, likely owing to a relatively fixed endotracheal tube volume, smaller and more immature infants have a relatively higher proportion of tidal volume occupied by the anatomical dead space. Anatomical dead space is directly proportional to days of mechanical ventilation, and it is significantly higher in infants that go on to develop BPD (45).

When ventilating a preterm infant beyond the first week of age, it is imperative to account for growth of anatomical dead space and its contribution to tidal volume evolution. Ventilator algorithms that allow for volume-targeted ventilation adjust the peak inspiratory pressure based on exhaled (measured) tidal volume. Over the first 3–4 weeks of age, infants that have continuously required mechanical ventilation will demand more tidal volume to account for an increase in anatomical dead space. Unless set tidal volume is increased, as infants inspire additional tidal volume to compensate for dead space, the ventilator will attempt to maintain the set tidal volume by reducing peak inspiratory pressure. The result is the infant must assume more of the work of breathing. In an observational study of 18 ventilator-dependent infants (24–30 weeks' GA) studied at a median of 18 days of age (range 7–60 days), as tidal volume was advanced from baseline (5.8 ml/kg) to 7 ml/kg, there was significantly lower work of breathing (46). Additionally, mean respiratory rates fell as tidal volume was increased (from 54 breaths/min at baseline to a 44 breaths/min at 7 ml/kg). At all tidal volumes, minute ventilation was similar but peak inspiratory pressures increased significantly (from 19.7 cm to 24.3 cm $H_2O$). Similar results were noted by the same authors in a prior trial (47). Thus, over the first 3–4 weeks of age, it is prudent to compare exhaled to set tidal volumes. As exhaled tidal volumes exceed set tidal volumes, there will be an accompanying decrease in peak inspiratory pressures (**Figure 2**). The decrease in inspiratory pressures is often erroneously viewed as improved compliance, when in actuality it is a product of ventilator compensation. If mechanical ventilation is still required, an increase in set tidal volume (usually to 6–7 ml/kg) to match the patient's effort will often result in improved ventilation and patient comfort.

## Chronic mechanical ventilation

Although the overwhelming majority of premature infants will eventually wean from positive pressure ventilation, some will need chronic respiratory support. There is no clear timing when providers should transition to chronic ventilator strategies, and there is wide variation based on center (48). However, once it has been determined that an infant with BPD will be treated

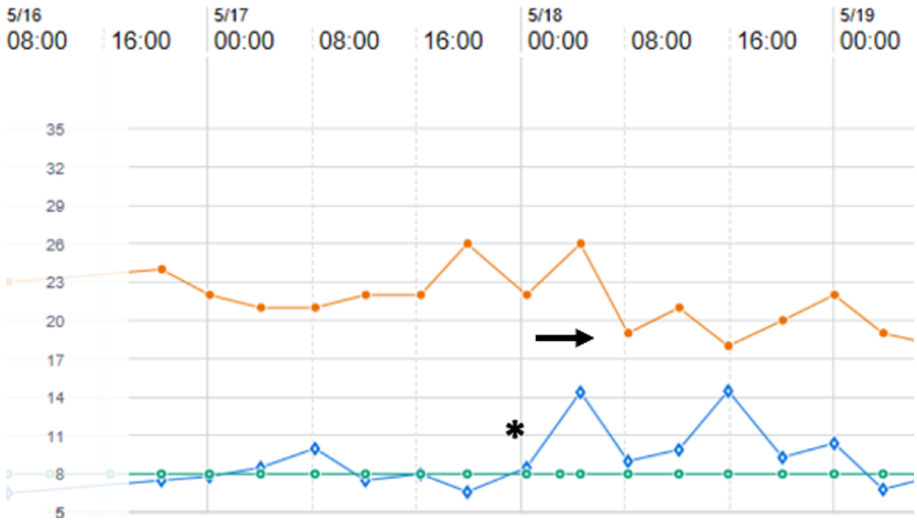


FIGURE 2
Ventilator data flowsheet encompassing 18–21 days of age for a former 27 week, 1,160 gram premature infant with evolving chronic lung disease and supported on pressure-regulated volume control ventilation. As exhaled tidal volume (open diamonds) exceeds the set tidal volume (open circles) (asterix), note that the ventilator compensates by lowering peak inspiratory pressure (closed circles) (arrow).

with chronic mechanical ventilation, the ventilation strategy should shift. While there should be continued efforts to minimize lung injury as much as possible, the primary focus transitions to providing optimal respiratory support for patient comfort, growth and development, and gas exchange, which appears to improve in neonates with BPD following placement of a tracheostomy tube and chronic mechanical ventilation (49).

Currently, there is an extreme paucity of data comparing different chronic ventilator strategies in established severe BPD; consequently, a physiologic approach to mechanical ventilation must be considered. Neonates with severe BPD have extensive pulmonary heterogeneity with areas of alveolar simplification and air-trapping as well as scarring and fibrosis (**Figure 3**) resulting in high respiratory system resistance and low respiratory system compliance (50, 51); further, small and large airway disease are also frequently encountered (52, 53). As a result of these complex interactions, neonates with severe BPD may have obstructive, mixed obstructive and restrictive, or restrictive respiratory disease, with 90% developing at least some degree of obstruction (53). Thus, ventilator strategies are typically designed

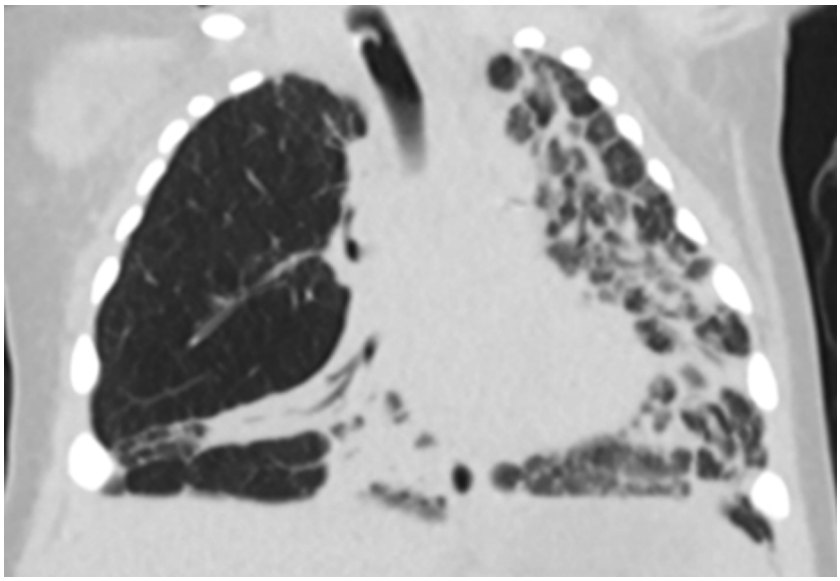

FIGURE 3
Chest computed tomography of an 8 month old former 26 week premature infant with severe BPD demonstrating dramatic pulmonary heterogeneity with alveolar simplification of the right upper lobe and diffuse fibrosis of the left lung. The patient is also severely hyperinflated with flattened diaphragms.

for obstructive respiratory disease with severe pulmonary heterogeneity.

## Trigger

Most providers will rely on a combination of time and flow triggers for chronic mechanical ventilation. A time trigger will initiate a breath based on the set respiratory rate regardless of patient effort. However, flow triggered breaths rely on the patient to generate inspiratory flow to initiate the breath. Obstructive lung disease can lead to an increase in intrinsic PEEP (PEEPi), and the baby will then have to overcome the PEEPi prior to generating the airflow needed to trigger a breath. As a result, patients with established severe BPD may have delayed triggers or failed triggers (**Figure 4A**). In one report, a majority patients with severe BPD treated with chronic mechanical ventilation experienced failed triggers, with nearly 15% of breaths resulting in a wasted effort. The inability to trigger, results in patient ventilator dysnchronization and patient discomfort. This may manifest with agitation, hypoxemic episodes, poor ventilation, and increased need for sedation (54).

If a patient is having difficulty triggering a breath, the flow trigger can be made as sensitive as possible without generating autocycling where the ventilator initiates a spontaneous breath without a patient effort. Further, increasing or decreasing PEEP to match PEEPi can improve triggering and should be considered (**Figure 4B**) (54). If optimization of respiratory mechanics does not permit adequate patient-ventilator interaction, NAVA can be used. NAVA relies on diaphragmatic activity for synchronization rather than the generation of airflow and can improve synchronization and gas exchange and reduce respiratory work and the need for sedation in patients with severe BPD (55–57). Despite the potential benefits, NAVA is only implemented in a minority of centers that care for patients with severe BPD and is not compatible with home ventilators.

## PEEP

Management of PEEP can be challenging in patients with severe BPD but is critical to prevent atelectasis and maintain FRC. Currently there are no large studies to define the optimum PEEP for patients with severe BPD requiring chronic ventilation. Titration of PEEP to match PEEPi can improve patient triggering and patient comfort as described above. PEEP can also be titrated during bronchoscopy to maintain airway lumen patency in patients with severe BPD and tracheobronchomalacia (58), which is quite common and associated with increased respiratory morbidity in neonates with severe BPD (52, 59). For these children with dynamic central airway collapse, PEEP can improve respiratory mechanics and increase expiratory flow rates (60, 61). Similarly, the titration of PEEP can help minimize dynamic collapse of smaller airways, and fairly high PEEP (>15 cm $H_2O$) may be necessary in patients with more severe disease (62). Paradoxically, higher PEEP may result in reduce rather than increase hyperinflation by preventing dynamic airway collapse. However, excessive PEEP can worsen hyperinflation and decrease respiratory system compliance as described above. Thus, PEEP must be adjusted to match the physiology of each patient.

To objectively titrate PEEP, esophageal pressure can be measured as a surrogate for pleural pressure and PEEP adjusted to

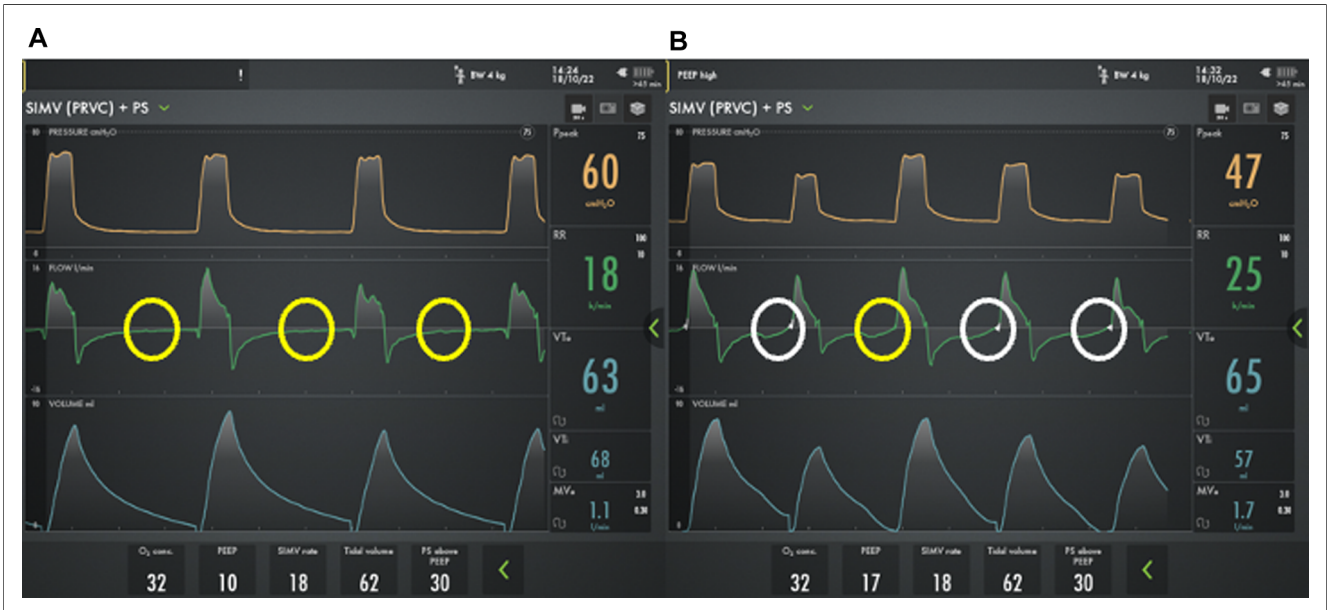


FIGURE 4
Ventilator waveforms from a 2 month old former 24 week premature infant with severe bronchopulmonary dysplasia using two different PEEP strategies. On physical exam, the child has a respiratory rate of 26 breaths/min. A) However, using a PEEP 10 cm $H_2O$, he has multiple failed triggers (yellow circles) and does not appear to breathe above the mandated rate. B) By increasing the PEEP to 17 cm $H_2O$ there is improved synchronization with the ability to trigger his spontaneous breaths, though the trigger is delayed (white circles) and one patient effort fails to trigger a breath (yellow circles).

match pleural pressure. In cases where esophageal manometry is not feasible or not available, measuring static respiratory mechanics using an expiratory hold can identify the severity of PEEPi, and an inspiratory hold at increasing leveles of PEEP, often called a "PEEP grid," can determine the PEEP that optimizes respiratory system compliance and resistance, which is generally ideal for chronic respiratory support (62, 63). Forced oscillation technique (FOT) can also be used to objectively measure respiratory system resistance and reactance in neonate with BPD and is becoming increasingly available; thus, FOT could prove useful when titrating PEEP as well as measuring response to other interventions (64).

## Tidal volume

When considering the tidal volume needed for chronic ventilatory support in children with severe BPD, it is critical to understand that the lung parenchyma is quite heterogenous, with some units having long time constants and others that have shorter time constants, and these patients have a significant increase in dead-space. As a result, it is typically necessary to implement a strategy of longer inspiratory times and lower mandatory respiratory rates to ensure all respiratory units are adequately ventilated and allowed to empty. Because emptying requires a prolonged expiratory time (and, therefore, fewer breaths per minute), maintenance of adequate minute ventilation requires a larger tidal volume strategy (65). Such a strategy is in stark contrast to that required for acute respiratory distress syndrome, which typically relies on low tidal volume, short inspiratory times, and high mandatory rates to minimize lung injury. While there is no universally agreed upon tidal volume, support should be titrated to the individual patient's need; most authors suggest a tidal volume of 8–12 ml/kg for children with severe BPD and chronic respiratory failure, and some advocate the use of up to 15 ml/kg (62, 63, 65, 66).

Because of the need for large mandatory breaths and significant heterogenous lung disease, inspiratory times of 0.6 s or more are often needed to ensure adequate filling of respiratory units, especially those with long time constant. Generally, the inspiratory time should be titrated to allow nearly complete filling as can be identified by the flow-time curve approaching zero inspiratory flow based on ventilator graphics (**Figure 5**) combined with chest auscultation. Failure to provide adequate inspiratory time will result incomplete filling and dead-space ventilation. Similarly, pressure supported breath should be supported with a low flow cycle sensitivity (typically 20%–30%) and utilize pressures that result in tidal volumes similar to those achieved during a mandatory breath (62, 63, 65, 66).

## Mandated respiratory rate

While ensuring adequate filling of respiratory units with differing time-constants using a long inspiratory time strategy, it is also critical to ensure that children with BPD have adequate time to exhale. Because children with BPD typically have obstructive respiratory disease, long expiratory times are needed to prevent incomplete exhalation and dynamic air-trapping. Thus, low mandatory respiratory rates (<20 breaths per minute) should be implemented. This combination of a low rate, large breath, long inspiratory time strategy, will provide adequate minute ventilation and maximize gas distribution to the entire lung despite the pulmonary heterogeneity, thus maintaining reasonable gas exchange.

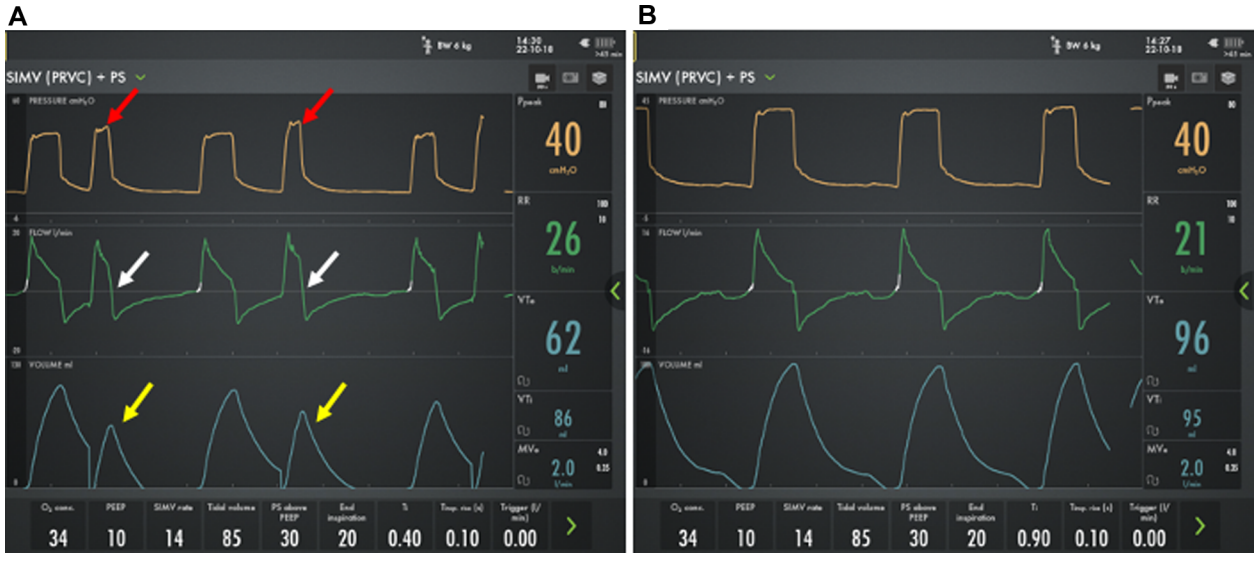


FIGURE 5
Ventilator waveforms from an 8 month old former 24 week premature infant with severe bronchopulmonary dysplasia using two different inspiratory time strategies. (**A**) Using a short (0.4 s) inspiratory time, there is incomplete filling (white arrows) with reduced tidal volume (yellow arrows), increased respiratory rate, and increased peak pressures (red arrows) compared with (**B**) a long (0.9 s) inspiratory time.

## Gas exchange

There are currently no trials that define the optimal SpO2 nor PCO2 for infants with established BPD who need chronic ventilation. Sustained hypoxemia with SpO2 below 92% during sleep time has been correlated with growth failure and should be avoided (67, 68). while targeting SpO2 > 93% may reduce the need for rehospitalization following the initial discharge (69). Further, permissive hypercapnia is generally tolerated in this patient population due to the increased dead-space; however, given the risk of pulmonary hypertension, targeting PCO2 less than 60 mm Hg and a neutral pH is likely prudent (70). Because of the limited data surrounding optimal gas exchange for chronic ventilation in children with BPD, it is more important to utilize a strategy that allows adequate growth and respiratory comfort and optimizes development and tolerance of care.

## Transition to home ventilators

Once infants are stable on chronic ventilator settings and large enough (>5 kg for most ventilators), transition to a home ventilator can be considered. While reports do exist describing methods for transition to home ventilators (71), practice patterns vary considerably by center. In general, most providers will attempt to transition to the home ventilator on settings consistent with the hospital ventilator. In some situations, it may not be possible to achieve identical settings. Trigger sensitivity is less for home ventilators, which can lead delayed or failed triggers during the transition. Further, hospital ventilators may allow a longer inspiratory time than is feasible on a home ventilator, particularly with smaller tidal volumes, which can be problematic in children who need long inspiratory times to ensure recruitment of regions with long time constants (62).

For many home ventilators, it may also be necessary to transition from an active, double-limb circuit to a passive, single-limb circuit. Passive, single-limb circuits can be particularly challenging as the ventilators rely on algorithms rather than direct measurement of tidal volume and typically underestimate the volume delivered to the patient. As a result, minute ventilation may be reduced resulting in hypercapnia and increased respiratory effort. Additionally, passive, single-limb circuits require inspiration and exhalation *via* the same tubing and rely on exhalation through a fixed leak in the circuit such as a Whisper Swivel (Respironics). As a result, there is risk of rebreathing exhaled gas. To prevent this, the ventilator delivers a continuous flow of gas to washout the dead space; however, if insufficient flow is delivered, the patient may develop hypercapnia. Active exhalation can also be used to avoid this issue (72). If available, a double-limb circuit can be used to avoid the challenges of a single-limb circuit; unfortunately some home ventilators do not provide this option.

These differences among many others may results in difficulty tolerating the home ventilator. If a child fails the initial transition to a home ventilator, most centers will wait one to two weeks prior to attempting the transition again. Once the child has successfully transitioned to a home ventilator, preparation for discharge home should commence.

## Transition to home

While transition to home is often an exciting time for families, many care givers report significant depression and anxiety surrounding discharge. Caregivers also experience reduced quality of life and increased fatigue related to the burden of care for technology dependent children at home, though this can be mitigated if home nursing support is available (73–75). Fatigue is of particular importance as in home mortality in this population exceeds 15%, and many of the events resulting in the patient's demise are preventable or treatable e.g., mucus plugs or accidental decannulation rather than progression of the underlying lung disease (76–79). Because of the risks, most programs provide extensive training for caregivers of technology dependent children that center on management of the tracheostomy, ventilator, and all other equipment that will be necessary to meet the child's needs at home. Caregivers should also be trained in cardiopulmonary resuscitation and patient transfers. These skills can be demonstrated with a combination of simulation training and independent stays prior to hospital discharge (80–86).

## Weaning chronic mechanical ventilation

Children with BPD who are discharged with home mechanical ventilation are expected to gradually wean ventilatory support over a period of months to years, and nearly all children are liberated from mechanical ventilation by 5 years of age (79). There is no specific, validated protocol for weaning mechanical ventilation in the ambulatory setting, and practices vary by both provider and institution (63). Typically, patients are allowed progressively increased periods off mechanical ventilation during the day. Once off support during the day, nocturnal support is then discontinued. This may be done at home, during a short hospital admission, or with the aid of polysomnography (87, 88).

## Weaning non-invasive support

As with weaning of mechanical ventilation, there is precious little data for the optimal strategies to wean non-invasive support following hospital discharge. In one small case series, 12/17 (71%) patients with BPD discharged using HFNC were able to successfully wean to room air after an average of about 6 months. However, 4/17 (24%) of these patients died prior to weaning from support, which is much higher than demonstrated in other cohorts of patients with severe BPD (89, 90). Because of the high rates of mortality following discharge, home HFNC should be considered with extreme

caution in neonates with BPD. The experience with non-invasive positive pressure is limited to case reports (91); thus, the safety and efficacy of home non-invasive positive pressure remains largely unknown.

## Conclusion

Ventilator strategies for children born premature evolve as the disease process progresses. While there is currently a wealth of information highlighting the use lung protective strategies with non-invasive positive pressure ventilation or invasive ventilation with small tidal volumes and high mandatory rates during the earliest phase of disease, there is a dearth of data about the timing of transition to chronic respiratory support and the optimal chronic ventilatory strategies. Ultimately, children will gradually wean from support, typically by school-age. Prospective trials that establish optimal ventilator strategies for children with severe established BPD are desperately needed, and the need for such studies continues to grow as the limit of viability is decreased and more children will need chronic mechanical ventilation.

## Author contributions

EBH and SKA: both drafted and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Outcomes of and factors associated with the development of bronchopulmonary dysplasia with pulmonary hypertension in very low birth weight infants: A retrospective study in a medical center

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**Introduction:** Bronchopulmonary dysplasia (BPD) with pulmonary hypertension (PH) leads to increased morbidity and mortality in extremely preterm infants. Recent studies have analyzed factors associated with development of PH in BPD; however, this research remains inconclusive, and controversy exists regarding the correlation between BPD and PH. This study aimed to investigate potential associated factors, clinical characteristics, and outcomes of BPD with pulmonary hypertension in very low birth weight (VLBW) preterm infants.

**Methods:** We conducted a retrospective study, reviewing the records of infants with gestational age (GA) <32 weeks and birth weight <1,500 g admitted to a tertiary neonatal intensive care unit between January 2020 and October 2021 who were diagnosed with moderate to severe BPD. Echocardiogram was performed at the postmenstrual age of 36 weeks or before discharge. The diagnosis of PH was based on the findings of echocardiogram. Prenatal and postnatal characteristics, demographic data, treatment details, and outcomes were collected and analyzed.

**Results:** A total of 139 VLBW infants with BPD were enrolled and divided into a PH group ($n = 25$) and a non-PH group ($n = 114$). The mean GA was $27.3 \pm 2.3$ weeks and the mean birth weight of infants with BPD was $927.3 \pm 293.3$ g. A multivariate logistic regression model revealed that a high positive end-expiratory pressure (PEEP) setting (OR: 2.105; 95% CI: 1.472–3.011; $p < 0.001$) in established BPD and surgical closure of patent ductus arteriosus (PDA; OR: 6.273; 95% CI: 1.574–24.977; $p = 0.009$) were associated with BPD–PH. Neonates with BPD who developed pulmonary hypertension remained hospitalized for longer ($p < 0.001$), received invasive mechanical ventilation support for longer ($p < 0.001$), had a higher incidence of retinopathy of prematurity (ROP; OR: 4.201; 95% CI: 1.561–11.304; $p = 0.003$), were more likely to require oxygen support at discharge (OR: 5.600; 95% CI: 2.175–14.416; $p < 0.001$), and were more likely to undergo tracheostomy (OR: 35.368; 95% CI: 4.03–310.43; $p < 0.001$).

**Conclusion:** PDA ligation and a higher PEEP setting were associated with BPD–PH in our cohort study. Compared with VLBW infants with BPD but without PH, infants with BPD and PH were hospitalized for longer, and also had a higher incidence of oxygen support after discharge, ROP, and tracheostomy.

KEYWORDS

bronchopulmonary dysplasia, pulmonary hypertension bronchopulmonary dysplasia, positive end-expiratory pressure, preterm infants, pulmonary hypertension, very low birth weight infants, associated factor

# 1. Introduction

Advanced care, including prenatal steroids, gentle ventilation policies, and surfactants, has improved the survival rate of infants with very low birth weight (VLBW) (1). The incidence of bronchopulmonary dysplasia (BPD) in extremely preterm infants in Asia ranges from 25% to 56% (2). BPD with pulmonary hypertension (PH) is associated with higher morbidity and mortality in premature infants. Immature lung development and postnatal oxidative damage cause vascular remodeling and pruning of the pulmonary blood vessels, leading to increased pulmonary vascular resistance (PVR) (3). Increased PVR and pulmonary arterial pressure in extremely preterm infants results in chronic respiratory morbidities, such as right ventricular (RV) failure or cor pulmonale with RV hypertrophy. The prevalence of PH associated with BPD is estimated to range from 10% to 60% (4), and the mortality rate increases from 14% to 50% in neonates with BPD (5, 6).

Many retrospective studies have analyzed the factors influencing the occurrence of BPD with PH, such as gestational diabetes mellitus (GDM), chorioamnionitis, low gestational age (GA), low birth weight, intrauterine growth restriction, prolonged ventilation support, and surgical closure of patent ductus arteriosus (PDA) (7–11). However, research on the development of PH and PH-associated complications is limited. Therefore, we aimed to investigate the associated factors, clinical characteristics, and outcomes of BPD with PH in VLBW preterm infants. Identifying these variables could help to reduce morbidity and mortality associated with BPD.

# 2. Methods

## 2.1. Patients

This retrospective study reviewed neonates with GA <32 weeks and birth weight <1,500 g who were admitted to the Linkou Chang Gung Memorial Hospital between January 2019 and October 2021. All included neonates were diagnosed with moderate to severe BPD and were divided into a PH and a non-PH group based on echocardiography performed at a postmenstrual age of 36 weeks or before discharge. Patients with congenital anomalies, congenital heart disease, or airway anomalies were excluded.

## 2.2. Data collection

Maternal characteristics, including antenatal steroid use, delivery mode, pregnancy-induced hypertension, GDM, pre-eclampsia, chorioamnionitis, and premature rupture of membranes, were reviewed using electronic medical records. Neonatal demographic data were collected and analyzed, including clinical characteristics, radiological images, treatment provided, ventilation settings, and outcomes.

## 2.3. Clinical variables

Antenatal steroid use was defined as corticosteroid use before delivery. Early-onset sepsis (EOS) was defined as blood cultures yielding bacteria within 1 week of life. In comparison, late-onset sepsis (LOS) was defined as blood cultures yielding bacteria after 1 week of life. Respiratory distress syndrome was clinically graded on the basis of radiographic findings within 1 day after birth (12), as follows: (1) grade I comprised fine homogenous and ground-glass shadowing; (2) grade II included bilateral widespread air bronchograms; (3) grade III involved confluent alveolar shadowing, and (4) grade IV comprised alveolar shadowing obscuring the cardiac border on plain radiography.

## 2.4. Definition of bronchopulmonary dysplasia

The diagnostic criteria for BPD and criteria for classification of sub-types were based on the definitions published in the summary of a workshop of the National Institute of Child Health and Human Development (NICHD) (13). BPD was classified as mild (no oxygen supplementation), moderate ($FiO_2 < 30\%$), or severe ($FiO_2 \geq 30\%$ and/or requirement for positive pressure support). The definitions of late-evolving and established BPD were based on a study by Htun et al. (14).

## 2.5. Pulmonary hypertension and echocardiographic variables

The diagnosis of PH was established *via* echocardiography performed at least 28 days after birth (over 36 weeks corrected age or before discharge). Pediatric cardiologists screened all

echocardiographic examinations. The directionality of the shunt through an atrial septal defect, patent foramen ovale, or PDA was evaluated as follows: (1) left-to-right, (2) right-to-left, or (3) bidirectional. Septal flattening, RV hypertrophy, and dilatation were recorded by pediatric cardiologists. RV systolic pressure was estimated on the basis of tricuspid regurgitant jet velocity. The criteria for PH were as follows (8): (1) RV systolic pressure >40 mmHg; (2) bidirectional or right-to-left cardiac shunt; and (3) interventricular septal flattening, right ventricular hypertrophy or dilatation present if no tricuspid regurgitation shunt was revealed on echocardiography, and absence of a residual shunt, including atrial septal defect, ventricular septal defect, or PDA.

## 2.6. Statistical analysis

The chi-squared test or Fisher's exact test was used to analyze categorical variables. Continuous variables were analyzed using the independent samples *t*-test or the Mann–Whitney *U*-test. The PH and non-PH groups were compared on maternal factors and neonatal clinical characteristics and outcomes. A multivariate logistic regression model was used to analyze certain PH-associated factors, including gender, GA, application of high-frequency oscillatory ventilation (HFOV), and inhaled nitric oxide (iNO). Other factors analyzed were positive end-expiratory pressure (PEEP) setting, mean airway pressure (MAP) setting, and duration of highest PEEP setting in late-evolving and established BPD; PDA requiring surgical closure; time of PDA ligation; and EOS or LOS. Statistical significance was defined as a *p*-value of <0.05. All statistical analyses were conducted using the IBM SPSS software package, version 24 (IBM Corp., Armonk, NY, USA).

# 3. Results

The study included 139 patients with GA < 32 weeks, birth weight <1,500 g, and a diagnosis of moderate to severe BPD. We divided the patients into a PH group ($n = 25$) and a non-PH group ($n = 114$); the prevalence of PH was 17.9% (25/139) among VLBW infants with moderate to severe BPD. There were no statistically significant differences in maternal demographic characteristics between the PH and non-PH groups (Table 1).

The mean GA was 27.3 ± 2.3 weeks, and the mean birth weight of infants with BPD was 927.3 ± 293.3 g. The PH group had shorter GAs (25.8 ± 1.7 vs. 27.6 ± 2.3, $p = 0.038$) and contained a higher proportion of male infants (80%, 20/25 vs. 56.1%, 64/114, $p = 0.027$). The PH group had a higher incidence of hemodynamically significant PDA (hsPDA; OR: 4.910; 95% CI: 1.385–17.414; $p = 0.008$), PDA ligation (OR: 6.364; 95% CI: 2.227–18.185; $p < 0.001$), later PDA ligation ($p < 0.001$), and postnatal steroid use (OR: 5.417; 95% CI: 2.145–13.679; $p < 0.001$). They were also more likely to receive HFOV (OR: 4.444; 95% CI: 1.560–12.659; $p = 0.004$) and inhaled nitric oxide (OR: 5.417; 95% CI: 2.145–13.679; $p < 0.001$), had a higher incidence of LOS (OR: 3.550; 95% CI: 1.397–9.024; $p = 0.006$), and required higher settings for PEEP ($p < 0.001$) and MAP ($p < 0.001$) in cases of established and late-evolving BPD treated with invasive or non-invasive ventilation (Table 2).

Neonates with PH stayed in the hospital for longer ($p < 0.001$), received invasive mechanical ventilation support for longer ($p < 0.001$), and had a higher incidence of retinopathy of prematurity (ROP; OR: 4.201; 95% CI: 1.561–11.304; $p = 0.003$), provision of oxygen support at discharge (OR: 5.600; 95% CI: 2.175–14.416; $p < 0.001$), and tracheostomy (OR: 35.368; 95% CI: 4.03–310.43; $p < 0.001$) (Table 3). We assessed the mortality rate within 1 year. No mortality occurred in the non-PH group; a preterm infant with a GA of 26 weeks died at a corrected age of 3 months as a result of severe cor pulmonale.

A multivariate logistic regression model revealed that higher PEEP settings with invasive or non-invasive ventilators in cases of established BPD (OR: 2.105; 95% CI: 1.472–3.011; $p < 0.001$) and PDA requiring surgical closure (OR: 6.273; 95% CI: 1.574–24.997; $p = 0.009$) were significantly associated with BPD–PH (Table 4).

# 4. Discussion

This retrospective study compared patients with BPD with and without PH in terms of the factors associated with PH, clinical characteristics, and outcomes. Most of the neonates (84%; 21/25)

TABLE 1 Maternal characteristics for preterm infants with bronchopulmonary dysplasia with and without pulmonary hypertension.

| | Total ($n = 139$) | BPD ($n = 114$) | BPD–PH ($n = 25$) | *p*-value | Odds ratio |
|---|---|---|---|---|---|
| Maternal characteristics | | | | | |
| Antenatal steroid (*n*, %) | 112 (80.1) | 90 (78.9) | 22 (88) | 0.408 | 1.956 (0.540–7.087) |
| Cesarean section (*n*, %) | 97 (70) | 83 (72.8) | 14 (56) | 0.097 | 0.475 (0.195–1.159) |
| Pregnancy-induced hypertension (*n*, %) | 30 (21.6) | 26 (22.8) | 4 (16) | 0.454 | 0.645 (0.203–2.047) |
| Gestational diabetes mellitus (*n*, %) | 7 (5) | 6 (5.3) | 1 (4) | 0.794 | 0.750 (0.086–6.521) |
| Oligohydraminos (*n*, %) | 3 (2.2) | 3 (2.6) | 0 | 0.412 | 0.816 (0.754–0.884) |
| Polyhydraminos (*n*, %) | 6 (4.3) | 5 (4.4) | 1 (4) | 0.931 | 0.908 (0.101–8.133) |
| Preeclampsia (*n*, %) | 18 (12.9) | 15 (13.2) | 3 (12) | 0.876 | 0.900 (0.240–3.379) |
| Chorioamnionitis (*n*, %) | 32 (23) | 22 (19.3) | 9 (36) | 0.069 | 2.352 (0.919–6.021) |
| pPROM (*n*, %) | 74 (53.2) | 60 (52.6) | 14 (56) | 0.760 | 1.145 (0.479–2.737) |

BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; pPROM, preterm premature rupture of membranes.

TABLE 2 Characteristics of preterm infants with bronchopulmonary dysplasia with and without pulmonary hypertension.

| | Total ($n = 139$) | BPD ($n = 114$) | BPD–PH ($n = 25$) | $p$-value | Odds ratio |
|---|---|---|---|---|---|
| Neonatal characteristics | | | | | |
| Male ($n$, %) | 84 (60.4) | 64 (56.1) | 20 (80) | 0.027* | 3.125 (1.096–8.908) |
| Gestational age (weeks), mean ± SD | 27.3 ± 2.3 | 27.6 ± 2.3 | 25.8 ± 1.7 | 0.038* | NA |
| Birth weight (g), mean ± SD | 927.3 ± 293.3 | 962.6 ± 297.3 | 766.4 ± 213.5 | 0.08 | NA |
| Small for gestational age ($n$, %) | 18 (12.9) | 15 (13.2) | 3 (12) | 0.876 | 0.900 (0.240–3.379) |
| EOS ($n$, %) | 13 (9.3) | 11 (9.6) | 2 (8) | 0.798 | 0.814 (0.169–3.925) |
| LOS ($n$, %) | 56 (40.3) | 40 (35.1) | 16 (64) | 0.006* | 3.550 (1.397–9.024) |
| Ureaplasma ($n$, %) | 16 (11.5) | 8 (7) | 8 (32) | 0.058 | 4.000 (0.920–17.396) |
| RDS grade | | | | | |
| RDS grade I–II ($n$, %) | 79 (56.8) | 64 (56.1) | 15 (60) | 0.724 | 1.172 (0.485–2.830) |
| RDS grade III–IV ($n$, %) | 60 (43.2) | 50 (43.9) | 10 (40) | 0.724 | 0.853 (0.353–2.060) |
| Pneumothorax ($n$, %) | 10 (7.2) | 8 (7) | 2 (8) | 0.863 | 1.152 (0.229–5.786) |
| hsPDA ($n$, %) | 88 (63.3) | 67 (58.8) | 21 (84) | 0.008* | 4.910 (1.385–17.414) |
| PDA ligation ($n$, %) | 63 (45.3) | 43 (37.7) | 20 (80) | <0.001* | 6.605 (2.310–18.886) |
| Time of PDA ligation (days), mean ± SD | 9 ± 14 | 7 ± 14 | 14 ± 15 | <0.001* | NA |
| HFOV ($n$, %) | 74 (53.2) | 54 (47.4) | 20 (80) | 0.004* | 4.444 (1.560–12.659) |
| iNO ($n$, %) | 32 (16.5) | 19 (16.7) | 13 (52) | <0.001* | 5.417 (2.145–13.679) |
| Postnatal steroid ($n$, %) | 34 (24.5) | 21 (18.4) | 13 (52) | <0.001* | 4.798 (1.919–11.996) |
| Ventilator setting | | | | | |
| PEEP, maximum level in evolving BPD (cm $H_2O$), mean ± SD | 6 ± 1 | 6 ± 1 | 7 ± 1 | <0.001* | NA |
| PEEP, maximum level in established BPD (cm $H_2O$), mean ± SD | 6 ± 2 | 6 ± 1 | 9 ± 2 | <0.001* | NA |
| MAP, maximum level in evolving BPD (cm $H_2O$), mean ± SD | 9.9 ± 2.8 | 9.2 ± 2.2 | 13 ± 3.5 | <0.001* | NA |
| MAP, maximum level in established BPD (cm $H_2O$), mean ± SD | 9.3 ± 3.6 | 8.4 ± 2.4 | 13.5 ± 5 | <0.001* | NA |
| Duration of maximum PEEP in established BPD (days), mean ± SD | 11 ± 9 | 11 ± 9 | 12 ± 7 | 0.34 | NA |
| BPD, median (IQR) | | | | | |
| Moderate ($n$, %) | 15 (10.8) | 13 (11.4) | 2 (8) | 0.619 | 0.676 (0.143–3.202) |
| Severe ($n$, %) | 124 (89.2) | 101 (88.6) | 23 (92) | 0.619 | 1.480 (0.312–7.016) |

RDS, respiratory distress syndrome; hsPDA, hemodynamically significant patent ductus arteriosus; PDA, patent ductus arteriosus; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; PEEP, positive end-expiratory pressure; MAP, mean airway pressure; BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; EOD, early-onset sepsis; LOS, late-onset sepsis.
*Statistically significant at $p < 0.05$.

TABLE 3 Outcomes of preterm infants with bronchopulmonary dysplasia with and without pulmonary hypertension.

| | Total ($n = 139$) | BPD ($n = 114$) | BPD–PH ($n = 25$) | $p$-value | Odds ratio |
|---|---|---|---|---|---|
| Outcome | | | | | |
| Duration of invasive mechanical ventilation (days), mean ± SD | 53.4 ± 3.8 | 42.3 ± 30.5 | 105.4 ± 70.7 | <0.001* | NA |
| Extubation age (weeks), median (IQR) | 34.4 (32.6–36.5) | 34.3 (32.3–36.3) | 35.1 (33.5–39.6) | 0.054 | NA |
| Duration of mechanical ventilation support (days), mean ± SD | 93.2 ± 47 | 82.2 ± 32.3 | 145.3 ± 67.7 | <0.001* | NA |
| IVH ($n$, %) | 43 (30.9) | 31 (27.2) | 12 (48) | 0.056 | 2.741 (1.019–5.997) |
| ROP ($n$, %) | 68 (48.9) | 49 (43) | 19 (76) | 0.003* | 4.201 (1.561–11.304) |
| NEC ($n$, %) | 14 (10.1) | 10 (8.8) | 4 (16) | 0.277 | 1.981 (0.567–6.919) |
| Oxygen support at discharge ($n$, %) | 46 (33.1) | 30 (26.3) | 16 (64) | <0.001* | 5.600 (2.175–14.416) |
| Tracheostomy ($n$, %) | 7 (5) | 1 (1) | 6 (24) | <0.001* | 35.368 (4.03–310.43) |
| Length of hospital stay (days), mean ± SD | 115.6 ± 46.8 | 93.1 ± 37.8 | 159.5 ± 63.5 | <0.001* | NA |

IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; NA, not applicable; BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension.
*Statistically significant at $p < 0.05$.

who had BPD with PH were born before 28 weeks' GA. Similar to previous reports, we found a lower average GA (27.6 ± 2.3 vs. 25.8 ± 1.7 weeks) and birth weight (962.6 ± 297.3 vs. 766.4 ± 213.5 g) in patients with BPD and PH in our study (8, 15).

Research has revealed that the factors for PH associated with BPD are multifactorial. Prenatal factors include chorioamnionitis, GDM, pregnancy-induced hypertension, preeclampsia, and oligohydramnios; postnatal factors include hsPDA, PDA requiring surgical closure, prolonged mechanical ventilation, and LOS (7, 9, 16, 17). Compared to neonates without BPD–PH, those with BPD–PH required higher PEEP settings in our cohort study. Patients with severe BPD have a higher rate of tracheobronchomalacia (18) and thus require a higher-level PEEP setting in clinical practice (19). Gentle ventilation includes a high rate, low tidal volume, and adequate PEEP through conventional mechanical ventilation or HFOV, and this approach has been regularly applied in patients with BPD (20). However, most ventilation strategies have focused on preventing BPD, thus

TABLE 4 Factors associated with BPD–PH in very low birth weight infants based on multivariate logistic analysis.

| Clinical characteristics | Odds ratio | 95% CI | *p*-value |
|---|---|---|---|
| Gender: male | 4.267 | 0.966–18.850 | 0.056 |
| Gestational age, weeks | 0.733 | 0.495–1.087 | 0.123 |
| Application of HFOV | 0.368 | 0.065–2.096 | 0.260 |
| Application of iNO | 0.559 | 0.091–3.432 | 0.530 |
| Elevated PEEP in evolving BPD | 0.549 | 0.242–1.247 | 0.152 |
| Elevated PEEP in established BPD | 2.105 | 1.472–3.011 | <0.001* |
| Elevated MAP in evolving BPD | 1.256 | 0.938–1.681 | 0.126 |
| Elevated MAP in established BPD | 1.152 | 0.820–1.617 | 0.415 |
| Surgical closure of PDA | 6.273 | 1.574–24.997 | 0.009* |
| Time of PDA ligation | 0.961 | 0.911–1.014 | 0.147 |
| LOS | 2.104 | 0.493–8.973 | 0.315 |

BPD, bronchopulmonary dysplasia; PH, pulmonary hypertension; HFOV, high-frequency oscillatory ventilation; iNO, inhaled nitric oxide; PEEP, positive end-expiratory pressure; PDA, patent ductus arteriosus; LOS, late-onset sepsis.
*Statistically significant at $p < 0.05$.

providing insufficient evidence on the best approach to ventilating infants with severe established BPD; moreover, these strategies may not be relevant for chronic lung pathophysiology (19). Several studies have also revealed the use of various types of mechanical ventilation support and medications for neonates with severely established BPD across multiple centers and regions (21, 22), which could lead to different outcomes. The optimal administration of PEEP in extremely premature neonates with established BPD remains uncertain because randomized controlled trials are rarely conducted in these populations. Some studies have assumed that an elevated PEEP setting may impair cardiopulmonary function. Studies in a Rhesus monkey model have shown that a higher setting PEEP (15 cm $H_2O$) contributes to a beneficial decrease in left ventricular preload or PVR, but decreases the cardiac index, stroke volume, and oxygen delivery (23). Polglase et al. indicated that high levels of PEEP improve oxygenation, but may also have adverse effects, such as increasing PVR and reducing pulmonary blood flow, in very premature lambs (24). Compression of the perialveolar capillaries is thought to cause high PEEP levels, increasing PVR (25). Recent studies have shown that patients who have acute respiratory distress syndrome with high PEEP have higher PVR and decreased RV contractility on echocardiography (26). Clinicians increase PEEP to recruit unventilated lung regions to improve oxygenation. However, the mean airway pressure is not even across the entire lung, and the overexpansion of localized lesions may contribute to high resistance. Reports also indicate that overdistended lesions may result in prolonged overexpansion with higher resistance, despite the high PEEP returning to low levels (24). Another factor is that a high PEEP can lead to increased RV afterload and reduced coronary arterial blood flow caused by coronary artery compression (27). The adverse effect of coronary vascular resistance can also decrease the left ventricular output, which leads to long-term degradation of cardiopulmonary function (28). Previous studies have shown that increased PVR occurs at PEEP levels >10 cm $H_2O$, but have observed no difference between PEEP of 5 cm $H_2O$ and 5–10 cm $H_2O$ (26), which is considered to be attributable to the direct impact of the compression of intra-alveolar capillaries by overexpanded alveoli (29) at PEEP levels >10 cm $H_2O$. Our study showed that patients with BPD–PH had higher PEEP (mean: 9 cm ± 2 cm $H_2O$) at the established BPD stage; this finding conforms with those of previous studies, which have indicated that higher PEEP might cause increased PVR (30, 31). Previous studies have attempted to explain the relationship between high PEEP and PVR; however, most have been observational studies providing insufficient evidence to identify the causal relationship between PEEP and PH. High-quality evidence on appropriate ventilator strategies and cardiopulmonary function in extremely premature neonates with established BPD is limited, and well-designed prospective studies are required (32).

PDA ligation is considered to be an independent associated factor in development of BPD, particularly in the case of prophylactic surgical closure (33). Collaco et al. identified surgical ligation as a component of a PH risk score in patients with BPD (11). Surgical closure of the ductus arteriosus seems not to have the same advantages of increasing the alveolar surface and alveolar water clearance as closure by indomethacin/ibuprofen (34). Injury due to surgical ligation contributes to an increase in expression of genes involving pulmonary inflammation and a decrease in the pulmonary epithelial sodium channel, which is helpful for alveolar water clearance (35). Previous studies have demonstrated that surgical closure results in poorer respiratory outcomes than medication- (36) or transcatheter-induced PDA closure (37) in extremely low birth weight infants. Pulmonary inflammation and immature alveolar growth caused by PDA ligation may lead to poor pulmonary vascular growth and promote the development of PH. In the current study, PDA ligation was performed between postnatal days 6 and 66, and most PDA ligations were completed within 4 weeks of life. PDA ligation performed at any time during the study period was associated with BPD–PH. Nevertheless, patients requiring surgical PDA treatment are usually more ill than those requiring medication-induced closure, and the severity of the illness may also contribute to pulmonary vascular changes.

Compared with the non-PH group, neonates with BPD and PH had poor respiratory outcomes, including prolonged invasive mechanical ventilation, longer hospital stays, supplemental oxygen support at home, tracheostomy, and ROP; this finding is similar to those of previous studies (9, 11). Poor neurological outcomes and long-term growth have been observed in extremely preterm infants with BPD and PH (38). BPD–PH in neonates causes additional medical costs and a higher burden on parents compared to BPD alone (39). Hence, long-term follow-up of cardiopulmonary function and early intervention are important to improve neurological outcomes in infants with BPD–PH.

The current study has several limitations. First, it was a retrospective, observational, and single-center study that could not provide a complete evaluation of the associated factors. Second, routine echocardiography at a postmenstrual age of 36 weeks or before discharge was not performed in all extremely preterm infants, which might have caused selection bias in our cohort. Third, echocardiography was performed by different

pediatric cardiologists at our institute, which might have resulted in reader bias. Fourth, we did not obtain long-term follow-up data such as growth and neurodevelopmental outcomes.

## 5. Conclusion

Higher PEEP settings and a higher incidence of surgical PDA ligation were significantly associated with BPD–PH in VLBW infants. The application of optimal PEEP in extremely preterm infants with BPD should be guided by well-designed clinical trials in the future. We hope that the identification of appropriate ventilation strategies will facilitate further research to address the care of these high-risk patients following this discussion. Compared with VLBW infants with BPD but without PH, infants with BPD and PH were hospitalized for longer, had a higher incidence of oxygen support at discharge and a higher risk of ROP, and were more likely to undergo tracheostomy. Further investigations are required to assess the long-term outcomes of PH in extremely premature infants with BPD.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved. This study was approved by the ethics committee of Chang Gung Medical Hospital, and the requirement to obtain informed consent for the collection of anonymized data was waived. Written informed consent from the participants' legal guardian/next of kin was not required for participation in this study in accordance with national legislation and the institutional requirements.

## Author contributions

H-PC conceived the study, collected the patient data, and drafted the manuscript. RL, S-MC, and J-JL provided professional guidance and revised the manuscript. M-CC conceived the study, provided professional guidance, and revised the manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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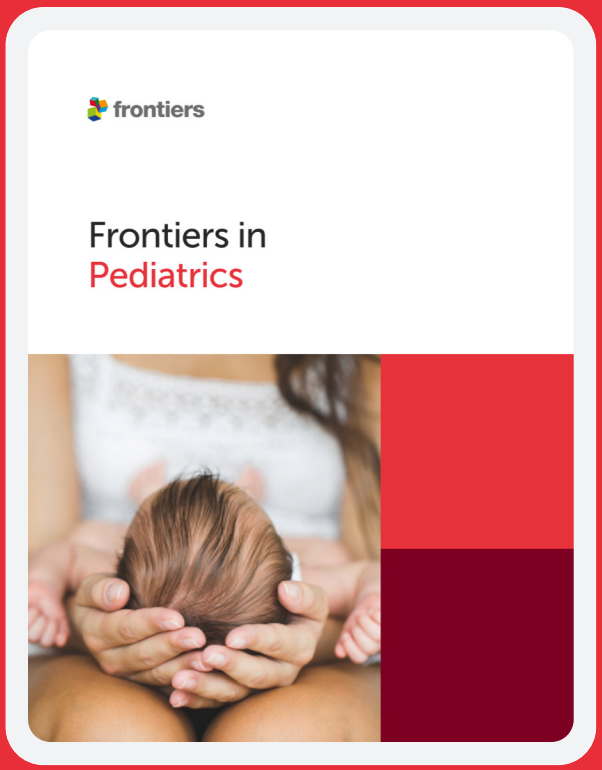


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