J Bras Pneumol. 2021;47(5):e20210125
https://dx.doi.org/10.36416/1806-3756/e20210125

The high-risk factors of different severities of bronchopulmonary dysplasia (BPD) based on the national institute of child health and human development (NICHD) diagnosis criteria in 2018

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Submitted: 28 April 2021.
Accepted: 19 July 2021.

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ABSTRACT

Objective: To investigate the clinical characteristics of preterm infants with different severities of bronchopulmonary dysplasia (BPD) and disclose the high-risk factors of exacerbating BPD. **Methods:** Collection of clinical data of 91 preterm infants admitted to the NICU and diagnosed with BPD, categorized in groups according to the disease severity: 41 mild cases,, 24 moderate cases, and 26 severe cases. Comparison and analysis of perinatal risk factors, treatment, complications and prognosis of the infants with different severity degrees. **Results:** The severe group had a higher proportion of infants with congenital heart disease (CHD) higher than the moderate group ($P < 0.05$), and a higher ratio of pneumonia and mechanical ventilation (MV) ≥ seven days than the mild group ($P < 0.05$). The severe group also presented higher reintubation incidence than both the mild and moderate groups ($P < 0.05$). The groups presented different ($P < 0.05$) incidence rates of hemodynamically significant patent ductus arteriosus (hsPDA) . Ridit analysis suggested that the premature infants (PIs) with hsPDA, multiple microbial pulmonary infections, or *Klebsiella pneumoniae* pneumonia had more severe illness. **Conclusion:** CHD, hsPDA, MV ≥ seven days, reintubation, pneumonia, especially multiple microbial pulmonary infections, and *Klebsiella pneumoniae* pneumonia are correlated with the severity of BPD and can be used as BPD progression predictor.

Keywords: BPD; Preterm infant; CHD; hsPDA;, Pneumonia; Mechanical ventilation.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most common complication in premature infants (PIs), especially in situations of very or extremely low birth weight (VLBW/ELBW) babies. However, the pathogenesis of BPD is still unclear and involves multiple factors, including genetic susceptibility, intrauterine factors, postnatal shock, mechanical ventilation, oxygen poisoning, pulmonary edema, infection etc. A long-term study monitoring PI lung development found significantly lower FEV1/FVC (First second forced expiratory volume accounts for the percentage of forced vital capacity) in adult BPD patients with a tendency towards airway obstruction compared with individuals without BPD in lung function tests.[1] Infants with BPD also have an increased risk of developing lower respiratory illnesses and allergic respiratory tract diseases in the future.[2] The incidence of congenital heart disease (CHD) in newborns is 5-8/1000,[3] and the incidence is higher in premature infants, especially in children with low gestational age (SGA).[4] CHD with a left-to-right shunt can aggravate pulmonary circulation pressure, and the shear force of the change will damage the vascular endothelium cells (ECs).[5] A series of changes, such as pulmonary inflammation, blood coagulation, oxidative stress, vascular proliferation, and the accumulation of inflammatory cells and fibroblasts, result from the damaged ECs.[6,7] It can increase lung injury and accelerate pulmonary vascular remodeling, eventually leading to pulmonary hypertension (PH). PH is also among the serious complications of BPD.[8,9] Since the relationship between CHD and BPD is still unclear, it is indispensable to identify the risk factors to prevent and treat BPD and meliorate the prognosis of a child patient. This study retrospectively analyzed the clinical data of children with different BPD degrees, followed by their subsequent hospitalization, in addition to exploring the risk factors for BPD severity to provide a basis for the prevention and treatment of BPD.

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Financial support: This work was supported by National Key R&D Program of China (2018YFC1002603).

METHODS

Study design and participants

We conducted a retrospective study by obtaining the predefined data set from the Guangdong provincial people's Hospital, Guangdong, China. The hospital admitted more than 1300 newborns every year during 2016 to 2020, specifically for this study, we screened the neonates discharged from the hospital between January 2016 and June 2020, in addition to and all related cases included in the 2018 NICHD diagnostic criteria for BPD.

Exclusion criteria:[1] congenital pulmonary dysplasia,[2] genetic metabolic diseases, and[3] chromosome diseases. In this study, infants with BPD were diagnosed and graded according to the criteria modified by the NICHD in 2018,[10] if a premature infant (< 32 weeks' gestational age GA) with BPD had persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks post menstrual age (PMA) required one of the following FiO_2 ranges, oxygen levels, or O_2 concentrations for ≥ three consecutive days to maintain arterial oxygen saturation in the 90-95% range, shown in Table 1 and Figure 1.

According to the BPD grades in the criteria modified by the NICHD in 2018, BPD is classified into the following three levels: grade I – identified as mild in the text, grade II – referenced as moderate, and grades III and IIIA – categorized as severe, according to Table 1.

We extracted the following variables from the electronic medical record system of our hospital: maternal age (years), pre-eclampsia (yes/no), intrauterine infection (yes/no), administration of antenatal steroids (yes/no), gestational age at birth (weeks), birth weight (kg), Apgar score at one minute, sex (male/female), surfactant administration (in/out 30mins after birth), CHD (yes/no), hsPDA (with a ratio of arterial duct diameter to body weight (mm/kg) ≥ 1.4[11]), duration of invasive ventilation (days), reintubation (yes/no), pneumonia (yes/no), septicemia (yes/no), neurological complications (yes/no; including either hypoxic-ischemic brain damage, ventricular hemorrhage, or leukomalacia), retinopathy of prematurity (ROP, yes/no), death before discharge from neonatal care (yes/no), duration of hospitalization (days), family oxygen use (yes/no), weight at discharge (kg), and re-hospitalization (yes/no). CHD included at least one of the following illnesses: patent ductus arteriosus (PDA), ventricular septal defect (VSD), aortic/nonarterial stenosis, valve stenosis/insufficiency, and pulmonary hypertension.

Statistical analysis

Variables of normal distribution were shown as $\chi \pm s$. We applied one-way Analysis of Variance (ANOVA) test to compare the groups. Means and quantiles were used to describe the skewness distribution, while the groups were compared through a rank-sum test. We applied X^2, an independent sample Kruskal-Wallis test, and ridit analysis to compare the enumeration data. Multivariate analysis was performed through unconditional logistic regression analysis. $P < 0.05$ indicates that the difference is statistically significant. Statistical analysis was performed on the SPSS V.23.0 software.

This study used ridit analysis, which can convert the grade data into count data.[12] This algorithm created statistics using 1, 2, 3..., respectively, to represent the different severities of illness: the higher the value the more significant the illness. The mean value of ridit (0.5) is the cut-off point, so it can be concluded that the higher the ridit value the more serious the disease in this group. In this study, the grouping basis of Ridit analysis differed from the Chi-square test. We grouped the cases according to the existence of high-risk events and studied their average case severity. It can directly reflect the direction and degree of influence of risk factors on the disease. $P<0.05$ indicates statistically significant difference.

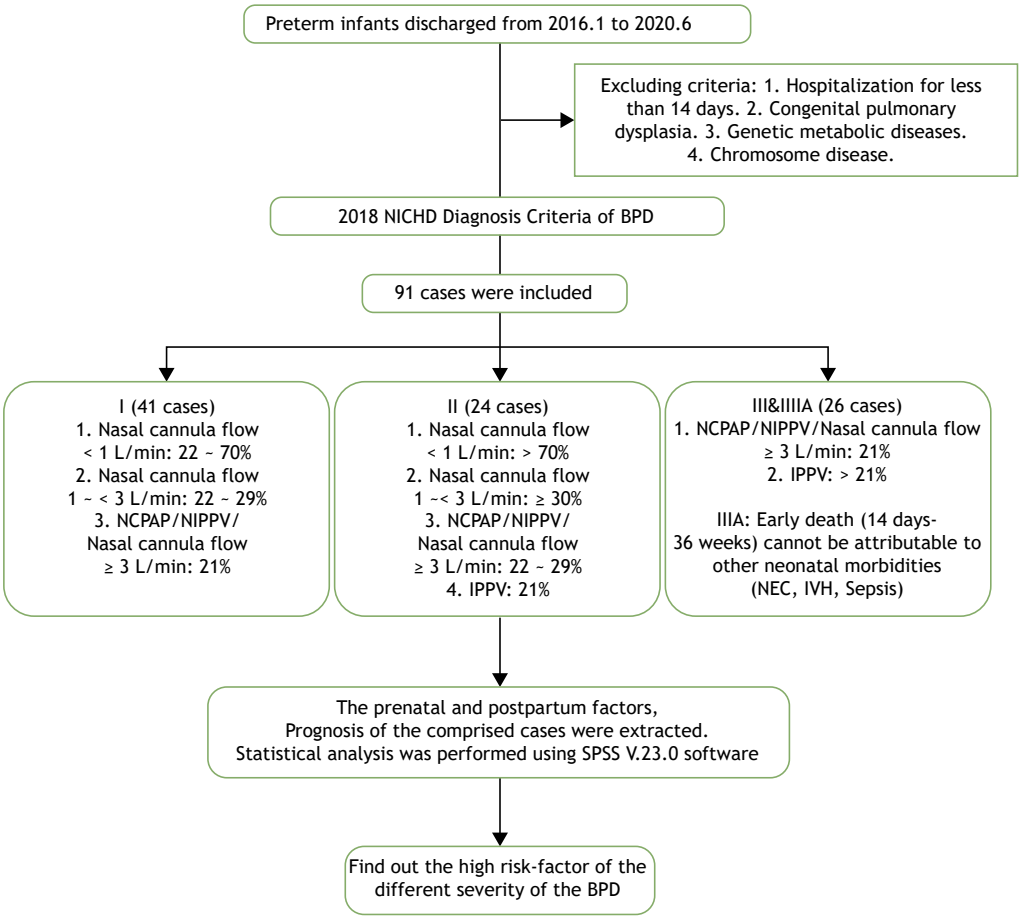
RESULTS

A total of 91 eligible infants participated in this study, including nine deaths. There were 41 cases in grade I BPD, 24 cases in grade II, and 26 cases in grades III and IIIA. Nine of the individuals died, including 1 person in grade I, who developed severe sepsis during

Table 1. BPD grades of the criteria modified by the NICHD in 2018.

Grades	Invasive IPPV*	N-CPAP, NIPPV, or nasal cannula ≥ 3 L/min	Nasal cannula flow of 1-<3 L/min	Hood O_2	Nasal cannula flow of <1 L/min
I	–	21	22-29	22-29	22-70
II	21	22-29	≥30	≥30	>70
III	>21	≥30			
III(A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular hemorrhage, redirection of care, episodes of sepsis, etc).				

*Excluding infants ventilated for primary airway disease or central respiratory control conditions. Values are percents. CPAP, continuous positive airway pressure; IPPV, intermittent positive pressure ventilation; N-CPAP, nasal continuous positive airway pressure; NIPPV, noninvasive positive pressure ventilation.



* The number following the different modes of pulmonary support reffers to FiO_2

Figure 1. The schematic illustration for the study.

hospitalization; 3 in grade II, with CHD or multiple lung infections; 2 in grade III, with one dying of severe lung infection and the other developing severe NEC, and the remaining 3 in the IIIA. Related complications and genetic diseases were excluded. The minimum and maximum gestational ages (GA) were 25.43 weeks and 31.86 weeks, respectively, with an average of 28.88 ± 1.63 weeks. The participants had a median birth weight of 1.100 kg (0.920-1.290 kg). No significant differences were found in GA, birth weight, sex ratio, or small for gestational age (SGA) ratio among the three groups (P > 0.05), shown in Table 2.

Significant differences appeared in the proportion of CHD and pneumonia among the three groups (PCHD = 0.028, P pneumonia = 0.012, P < 0.05). Further pairwise comparison between groups showed a higher CHD proportion in the severe group than in the moderate one (P = 0.025), while the general difference in the hsPDA proportion among the three groups was significant as well (P = 0.04). The severe group had a higher pneumonia ratio than the mild group (P = 0.006), while the comparison between the other groups was not statistically significant (P > 0.05). This study also conducted a further investigation on the pulmonary infections of the selected children and found statistically significant differences (P = 0.033) in the proportion of *Klebsiella pneumoniae* pneumonia among the groups, while the incidence of multiple microbial pulmonary infections and sepsis among the infants with pneumonia did not show any inter-group differences. The study showed no statistically significant differences in the administration of antenatal steroids, maternal factors (age, pre-eclampsia), low Apgar one minute score (less than or equal to seven), intrauterine infection, or sepsis among the three groups (P > 0.05), as shown in Table 2 and Figure 2.

The three groups showed statistically significant (P = 0.003) proportion of reintubation, with the severe group with the highest value (P < 0.05). There was no significant difference in the number

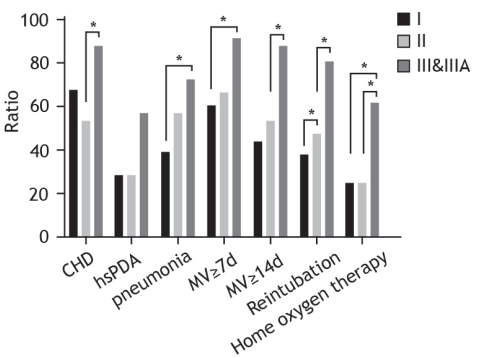
Table 2. Comparison of risk factors, treatment and prognosis of different severity of BPD.

		I N = 41	II N = 24	III/IIIA N = 26	F/X²/Z	P
GA (weeks)		28.8±1.49	28.81±1.55	29.06±1.9	0.217	0.806
Birth weight (kg) M (P25, P75)		1.100 (0.940,1.247)	1.180 (0.942,1.331)	1.070 (0.847,1.385)	1.148	0.563
SGA(%)		4 (9.8)	6 (25)	8 (30.8)	4.987	0.083
Antenatal corticosteroids (%)		18 (48.6)	11 (47.8)	7 (30.4)	2.173	0.337
pre-eclampsia (%)		4 (9.8)	5 (20.8)	3 (11.5)	1.709	0.425
CHD (%)		28 (68.3)	13 (54.2)	23 (88.5)	7.183	0.028
PDA (%)		18 (48.9)	9 (37.5)	17 (65.4)	4.477	0.107
HsPDA(%)		12(29.3)	7(29.1)	15(57.7)	6.428	0.040
Maternal age≥35(%)		12 (35.3)	8 (44.4)	7 (35)	0.494	0.781
Lung infection	Pneumonia(%)	14 (34.1)	14 (58.3)	19 (73.1)	10.239	0.006
	Multiple microbial pulmonary infection (%)	4(28.6)	3(21.4)	11(77.9)	5.334	0.069
	Pneumonia-sepsis (%)	6(42.9)	4(28.6)	3(15.8)	2.51	0.285
	Klebsiella pneumoniae pneumonia (%)	3(21.4)	2(14.3)	10(52.6)	6.802	0.033
Septicemia (%)		17 (41.5)	8 (33.3)	7(26.9)	1.523	0.467
intrauterine infection (%)		10 (24.4)	10 (41.7)	7(26.9)	2.297	0.317
MV≥3d		30 (73.1)	19 (79.2)	25 (96.2)	5.632	0.06
MV≥7d		25 (61.0)	16 (66.7)	24 (92.3)	8.016	0.018
MV≥14d		18 (43.9)	13 (54.2)	23 (88.5)	13.455	0.001
Apgar score at 1 min≤7		22 (59.5)	11 (52.4)	15(65.2)	0.75	0.687
Surfactant administration ≤30min (%)		6 (15.8)	6 (25)	4 (16.7)	0.907	0.638
Reintubation (%)		15 (37.5)	11 (47.8)	18 (81.8)	11.361	0.003
Neurological complications (%)		15 (36.6)	10 (41.7)	10 (38.5)	0.165	0.921
ROP (%)		25 (61)	10 (41.7)	12 (46.2)	2.7	0.259
Home oxygen therapy (%)		10 (25)	5 (25)	13 (61.9)	9.367	0.009
Weight growth (kg/weeks)		0.110±0.033	0.112±0.423	0.120±0.090	0.257	0.774
re-hospitalization (%)		14(35)	4(20)	7(36.8)	1.699	0.428
Death (%)		1 (2.4)	3(12.5)	5(19.2)	5.283	0.071

The deaths and those discontinued treatment were excluded from the readmission analysis.

of patients who had mechanical ventilation (MV) for more than three days among the three groups ($P > 0.05$). Statistically significant difference (P 7d = 0.018, P 14d = 0.001) occurred when invasive ventilation extended from 7 to 14 days. The severe group presented a higher ratio ($P < 0.05$), but no difference was shown between the mild and moderate groups. In addition, there was no significant difference in the number of patients treated with pulmonary surfactant (PS) within 30 minutes after birth among the three groups ($P > 0.05$), as indicated in Table 2 and Figure 2.

The study found a significantly different ($P = 0.009$) proportion of PIs with different degrees of BPD treated with home oxygen therapy, in addition to



*represents P< 0.05 for comparison between the tow groups.

Figure 2. Pairwise comparison of risk factors and prognosis between groups.

much higher values in the severe groupthan in the mild and moderate groups (P < 0.05). The incidence of neurological complications and ROP, mortality, weight growth rate in NICU and the re-hospitalization rate were not significantly different among the three groups (P > 0.05). The ratio of home oxygen therapy in BPD children with different severities was statistically significant (P = 0.009). Notably, the cases of death and individuals who discontinued treatments were excluded from the readmission analysis, as shown in Table 2 and Figure 2.

Our study also conducted a ridit analysis, which found significantly more serious values of hsPDA-PIs (ridit = 0.619, P < 0.05), as well as no difference between PIs with mild to moderate PDA. The group experiencing recurrent intubation or pneumonia had a more severe condition (ridit > 0.5, P < 0.001). We account for the duration of invasive ventilation and performed a ridit analysis considering whether the MV duration was longer than seven or 14 days. The result showed that more than seven days of invasive ventilation could aggravate the BPD (ridit > 0.5 P < 0.001). The following three factors were analyzed in pneumonia-PIs enrolled in the study. The condition of BPD-PIs with multiple pulmonary infections is more serious than single pathogen infection (ridit = 0.654,P < 0.05) and BPD-pneumonia-PIs with *Klebsiella pneumoniae* infection is more severe than infection with other pathogens (ridit = 0.678, P < 0.05). The presence of sepsis did not affect the severity of BPD-pneumonia-PIs (P > 0.05), as indicated in Table 3.

BPD severity was the dependent variable and the factors of MV ≥ seven days, pneumonia, reintubation and CHD were included in multiple regression analyses. The model proved significant (P = 0.001). R^2 was 0.262, which means that the model could explain a 26.2% variation in BPD severity. The results suggested that pneumonia and reintubation were the risk factors for BPD progression from mild to moderate. P pneumonia = 0.025, OD = 3.769, 95% CI(1.181,12.027);P reintubation = 0.037, OD = 4.71, 95% CI(1.098,20.211). In addition, the CHD was significantly associated with severe BPD. P CHD = 0.025, OD = 5.267, 95% CI(1.177,23.557), as shown in Table 4.

DISCUSSION

Currently, SGA is widely believed to be a risk factor related to BPD severity. In recent years, most NICUs in China have adopted the Fenton 2013 or INTERGROWTH-21st standards to define newborns' growth. However, detecting SGAs always differs due to racial variations. Therefore, in this study, we divided the included cases according to the curves released by Capital Children's Research Institute in 2020 of neonatal weight at different GAs in China. [13] The results were contradictory to the dominant opinion. This curve could reflect GAs distribution and birth weight of PIs with BPD in China more accurately. Although a statistical error due to insufficient samples should not be ruled out, the result was likely to reflect a trend of disease characteristics related to lower birth

Table3. The RIDIT analysis for the high risk factors of different severity of BPD.

Factors	Average Ridit	T	P
Pneumonia	0.680	4.773	<0.001
Reintubation	0.698	4.973	<0.001
MV≥7d	0.663	4.485	<0.001
MV≥14d	0.698	5.078	<0.001
Mild to Moderate PDA	0.457	-0.468	0.651
HsPDA	0.619	2.335	0.026
Multiple microbial pulmonary infection	0.654	2.243	0.039
Pneumonia-sepsis	0.348	-2.061	0.062
Klebsiella pneumoniae pneumonia	0.678	2.417	0.030

Multiple microbial pulmonary infection, Pneumonia-sepsis, Klebsiella pneumoniae pneumonia were analyzed among the pneumonia-PIs enrolled in the study.

Table 4. Multivariate logistic-regression analysis of risk factors for different severity of BPD.

Severity of BPD	Risk factors	P	OD	Exp(B) 95% CI	
I-II	CHD	9.277	2.321	9.509	10.581
	Reintubation	0.037	4.710	1.098	20.211
	Pneumonia	0.025	3.769	1.181	12.027
	MV≥7d	0.443	2.086	0.319	13.643
	constant	0.021			
II-III(A)	CHD	0.030	5.267	1.177	23.557
	Reintubation	0.177	3.033	0.607	15.159
	Pneumonia	0.666	1.334	0.360	4.940
	MV≥7d	0.413	2.321	0.309	17.411
	constant	0.016			

CHD, congenital heart disease; MV, mechanical ventilation.

weight in a moment where prenatal steroid treatment is becoming more sophisticated.

CHD is associated with increased mortality of premature infants and incidence of some diseases, including ventricular hemorrhage, pulmonary hemorrhage, necrotizing enterocolitis etc.[14] We statistically analyzed the incidence of CHD among the participating cases. CHD turned out to have been significantly associated with severe BPD (OD = 5.267, P = 0.03). However, Pappas et al.[15] reported no relationship between CHD and BPD in infants with a VLBW of less than 1000g. There was still much debate about the relationship between CHD and BPD. Newborns with CHD have impaired cardiac function and required extensive respiratory support after surgery, in addition to being often diagnosed with BPD at the time of discharge. It is the reason why the effect of CHD on BPD has been consistently underestimated.

In this study, the incidence of hsPDA in enrolled cases was also statistically analyzed. The ridit analysis revealed that the condition of PIs with hsPDA was significantly more serious (ridit = 0.619, P < 0.05), no difference appeared between mild to moderate PDA and healthy children. Changes in hemodynamics caused by these specific heart malformations were likely to be the leading cause of BPD exacerbation. In the past, the blood shunt caused by atrial septal defect (ASD) was considered harmless in pediatrics, but it was only suitable to infants with well-developed lungs, a theory that disregarded the size of the ASD. Lung development in PIs, especially extremely premature infants, is already imperfect. For infants with lung injury, any factor leading to increased pulmonary circulation burden aggravates the condition.[16]

Compared with full-term infants, preterm infants with GA <32w have higher blood pressure in adolescence, while the left ventricle and aorta shrink.[17] Whether their lungs were over circulated or not, infants with CHD would have impaired pulmonary vascular development and alveolar II cell secretion of pulmonary surfactant to a certain extent. Therefore, while studying the PIs with CHD, the influence of hemodynamics deserves more attention. Different types of heart malformations should be analyzed according to the condition of the disease to obtain more accurate results and provide a reference for clinical diagnosis and treatment. Recently, in a follow-up study of almost 100 children with allergic respiratory diseases, our team found that CHD-children had high airway reactivity after surgery, in addition, asthma incidence was higher than in healthy children.

Prolonged use of invasive ventilation can cause severe lung damage and affect newborns' development throughout life. Studies have shown increased risk of BPD in PIs with a GA less than 28 who had an MV duration longer than three to five days.[18] When investigating 200 infants, Amit Sharma concluded that along with the diagnostic criteria established in 2001, the cumulative MV for ≥ seven days in the first 21 days after birth predicted moderate to severe BPD.[19] Although early extubation is the most direct manner to alleviate lung injury caused by MV,[20] it often fails due to improper timing. Reintubation is a significant risk factor for BPD.[21] In this study, the further ridit and regression analyses performed revealed that those who experienced reintubation represented more serious cases. Considering that tn recent years, the characteristics of BPD have changed, to redetermine the impact of invasive ventilation duration on BPD-PIs and explore better timing for extubation, our analyses followed the new diagnostic criteria in 2018. Our results suggested that BPD-PIs with MV ≥ seven days were more serious, but proved insignificant in multiple logistic regression analysis. The final diagnosis of moderate and severe BPD in individuals with reintubation was about five times as likely as mild BPD (OD = 4.71), suggesting that it is questionable whether to shorten the duration of invasive ventilation as much as possible.

Ventilator-associated pneumonia (VAP) is one of the critical factors leading to prolonged respiratory support in neonates and a risk factor for BPD in PIs.[22] On this basis, this study concluded that pneumonia was also associated with the severity of BPD (OD = 3.769), which was a significant factor aggravating the diseases. We further analyzed the pulmonary infection of different BPD-PIs severity. The cases of babies with multiple pulmonary infections and *Klebsiella pneumoniae* pneumonia were more serious than those with a single pathogen or non-*Klebsiella pneumoniae* infection (ridit > 0.5, P < 0.05). Such result was likely related to severe BPD, but the chance of lung infection (multiple pathogens/common hospital pathogens) caused by the prolonged respiratory support should not be ruled out. In addition, due to the insufficient number of cases or the high vigilance of our center for sepsis, the influence of pneumonia combined with sepsis on the condition of BPD was insignificant. High neutrophil-to-lymphocyte ratio at 72 hours has been reported as an early predictor of BPD.[23] Therefore, for a better knowledge on the relationship between pneumonia and BPD, the infection time should be considered.

Respiratory support and nursing care after extubation also play a decisive role in extubation outcomes. Safer alternatives are urgently needed to reduce the lung damage caused by prolonged MV. Comparing with CPAP, noninvasive mechanical ventilation (NIMV) reduced the failure rate of extubation[24]and reduced the incidence of BPD. Heated-Humidified High Flow Nasal Cannula (HFNV) can also minimize re-intubation and accelerate CO2 removal.[25-28]

BPD has a long-term influence on respiratory growth. A statistical analysis of extremely premature infants between 2016 and 2018 conducted in the UK found that 68% of the PIs who still needed home oxygen therapy after discharge, had BPD,[29] while 49% needed another hospitalization within one year after birth.[30,31] Our study analyzed the prognosis of the comprised infants and found a positive correlation of the probability of discharge with oxygen and BPD

severity. Simultaneously, there was no difference in the incidence of neurological complications, ROP, and re-hospitalization among babies with different severities. Consistent with the results of previous studies, the three groups showed little difference in the rate of weight gain during hospitalization, possibly due to the comprehensive and continuous monitoring of the infants' development and health in the hospital.[32] A more detailed and lasting follow-up plan is required for a further understanding on the long-term effects of BPD on children's development, such as cognition, language, and lung development.

In this study, ridit analysis was introduced to convert grade data into measurement data, which could intuitively reflect the influence direction and degree of different disease factors. However, it could not avoid the reliance on medical record information, selection bias, or the absence of unmeasured variables in the retrospective study. Data bias was attenuated by clear inclusion and exclusion criteria and detailed perinatal and postpartum cohort study designs.

In conclusion, CHD, hsPDA, MV ≥ seven days, reintubation, pneumonia, especially the multiple microbial pulmonary infections, and *Klebsiella pneumoniae* pneumonia are significantly associated with BPD severity of and can be regarded as predictive events for moderate and severe BPD. The probability of home oxygen therapy is positively correlated with the condition of BPD. The specific effect of CHD on the long-term lung development of children with BPD will be our team's primary direction.

AUTHOR CONTRIBUTIONS

Contribution statement: (I) Conception and design: Minqiao Jian, Shaoru He; (II) Administrative support: Yumei Liu; (III) Provision of study materials or patients: Bowen Feng, Juan Gui, Manli Zheng; (IV) Collection and assembly of data: Minqiao Jian, Caisheng Liu,Xiaohui Zhang; (V) Data analysis and interpretation: Minqiao Jian, Xiaoqing Liu, Manli Zheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All author.

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