

Predictors of Bronchopulmonary Dysplasia in 625 Neonates with Respiratory Distress Syndrome

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ABSTRACT

Objective: This study was designed to investigate the predictors of bronchopulmonary dysplasia in neonates with respiratory distress syndrome.

Methods: This was a single-center retrospective cohort study conducted between 1 January 2015 and 31 December 2020. A total of 625 neonates with respiratory distress syndrome (RDS) were enrolled. Demographic data, clinical presentations, complications and related treatment information were collected and analyzed. We used bivariate and multivariate logistic-regression analyses to determine significant predictors of bronchopulmonary dysplasia (BPD) in RDS neonates.

Results: In these 625 neonates, 102 (16.3%) of them developed BPD. Bivariate analysis and multivariate logistic-regression analyses revealed that birthweight, gestational age under 32 weeks, duration of oxygen therapy over 10 days, asphyxia, patent ductus arteriosus, transfusion of red blood cells (packed red blood cells) and surfactant use were significantly associated with the development of BPD.

Conclusion: Birthweight, gestational age <32 weeks, total duration of oxygen therapy >10 days, asphyxia, patent ductus arteriosus, need for red blood cell infusion, and the use of pulmonary surfactant were important predictors of BPD in neonates with RDS.

KEYWORDS: bronchopulmonary dysplasia, neonate, respiratory distress syndrome, risk factors

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is one of the most common and serious pulmonary complications in premature infants. BPD is associated with maternal inflammation, surfactant deficiency, mechanical ventilation and oxygen toxicity, which provoke an inflammatory response and impair lung development, along with dysregulated angiogenesis and alveolarization [1, 2]. Premature infants are often exposed to positive pressure ventilation and supplemental

oxygen, which contributes to multiple complications such as chronic respiratory and cardiovascular system illnesses, physical and neurological developmental delays, a low survival rate and diminished quality of life [3].

Since Northway *et al.* [4] first reported BPD in 1967, the definition and diagnostic criteria of BPD have undergone several revisions. Despite the variability in diagnostic criteria and diverse clinical practices, the requirement for supplemental O₂ at 28 days has

been used as the definition of BPD for over three decades [5, 6].

A retrospective study of preterm infants in the United States over the past 20 years found that the survival rate of extremely preterm infants increased from 70 to 79%, while the incidence of BPD increased from 32 to 45%. Approximately 25% of preterm infants with a birth weight <1500 g were diagnosed with BPD at 36 weeks of postmenstrual age (PMA) [7]. With the recent applications of prenatal glucocorticoids and postnatal pulmonary surfactants, as well as the implementation of protective ventilatory strategies, great changes have occurred regarding the clinical aspects of BPD.

The incidence of BPD increases due to variables available at or shortly after birth such as birthweight, gestational age, sex, growth restriction and lung function [8]. These variables relate to the fetal state of lung development or maturation at birth. Previous studies have revealed that birthweight, gestational age (GA), mechanical ventilation, pulmonary surfactant (PS), RBC transfusion, asphyxia, pneumonia and patent ductus arteriosus are all potential factors for BPD [9–15]. Although respiratory distress syndrome (RDS) is the classic primary disease in BPD, there is currently a paucity of research on the risk factors for developing BPD in children with RDS. In addition, the sample sizes delineated in the majority of studies are relatively small. Therefore, the elucidation of BPD risk factors is of utmost importance in preventing and treating BPD and improving its prognosis.

METHODS

Study design and participant selection

We performed a retrospective study and reviewed the medical records of neonates with RDS who underwent treatment as inpatients at the Children's Hospital of Soochow University during a 6-year period between 1 January 2015 and 31 December 2020. The inclusion criteria consisted of neonates with RDS, and the exclusion criteria comprised neonates with (i) congenital birth defects; (ii) showing incomplete medical records; and (iii) who were discharged from the hospital or died due to causes other than respiratory distress during the study period (Fig. 1). Neonatal RDS was defined by

respiratory distress that occurred within 24 h after birth and responded well to surfactant use (chest X-ray evidence of improvement compared with status prior to surfactant use or effective reduction of ventilatory parameters) and lung recruitment therapy [16]. Hypoalbuminemia was designated as a plasma albumin concentration less than 30 g/l [17]. Neonatal asphyxia is a condition characterized by an impairment of exchange of the respiratory gases (oxygen and carbon dioxide) and cannot establish effective spontaneous breathing within 1 min after birth with an Apgar score of ≤ 7 , including that has not established effective spontaneous breathing 5 min after birth with an Apgar score of ≤ 7 ; or the Apgar score was relative high at birth but declined to ≤ 7 , 5 min after birth; Low umbilical arterial blood pH (< 7.15); other causes of low Apgar score have been ruled out [18]. Neonatal pneumonia refers to the newborn having clinical symptoms, such as tachypnea, respiratory distress (chest retractions/grunting) and evidence of pneumonia on chest X-ray (nodular or coarse, patchy non-homogenous infiltrates, air bronchogram, lobar, multilobar or segmental consolidation) [19]. Neonatal sepsis was linked to at least two of the following four criteria (one of which had to include abnormal body temperature or leukocyte count): body temperature greater than 38.5°C or less than 36°C , tachycardia (180 beats/min) or bradycardia (< 100 beats/min), increased respiration (50 breaths/min at an age of 0–7 days; 40 breaths/min at 7–30 days) and elevated or depressed leukocyte count vis-à-vis age (not secondary to chemotherapy-induced leukopenia) or $> 10\%$ immature neutrophils [20]. Feeding intolerance referred to the occurrence of milk-digestion disorders that resulted in abdominal distention, vomiting, stomach retention or other conditions after intestinal feeding. Granulocytopenia pertained to a neutrophil number less than 1500/ml and agranulocytosis to neutrophils fewer than 500/ml [21]. Intracranial hemorrhage stipulated a head CT or MRI scan or ultrasonogram that showed intracranial hemorrhage. Pulmonary hemorrhage (PH) is lungs' angiorehesis caused by an increased pressure on the capillaries of the alveolar wall due to a variety of factors, and the blood enters the lung tissue, which is characterized by sudden onset of frothy, pink-tinged secretions or discharge of bloody fluid from the upper

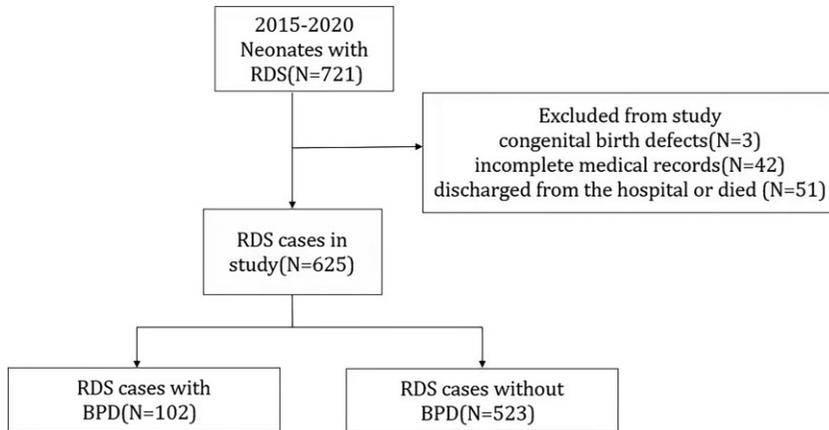


Fig. 1. The flow chart of the study.

respiratory tract or the endotracheal tube [22]. The present study protocol was approved by our Hospital Ethics Committee.

Data collection

We collected the following data: sex, birthweight, gestational age, delivery mode, Apgar scores at 1 and 5 min, amniotic fluid condition, umbilical cord and placental positions, intrauterine distress, multiple pregnancy status, postnatal disease (neonatal asphyxia, neonatal pneumonia, hypoalbuminemia, anemia, intracranial hemorrhage, patent ductus arteriosus, pneumothorax, pulmonary hemorrhage, sepsis, granulocytopenia or agranulocytosis, feeding intolerance, neonatal necrotizing enterocolitis, apnea and pulmonary arterial hypertension), the application and duration of invasive mechanical ventilation and non-invasive mechanical ventilation, the total duration of oxygen therapy, prenatal maternal use of dexamethasone and antibiotics, premature rupture of membranes and diseases during pregnancy (pregnancy-induced hypertension, gestational diabetes and gestational heart disease). These data were used to analyze the risk factors for BPD in neonates with RDS.

Neonates were followed up during hospital admission. BPD was diagnosed based upon the recommended diagnostic criteria and concerned any newborn with oxygen dependence (fraction of inspiration O_2 [FiO_2] >0.21) ≥ 28 days). Clinical grading implied that at a newborn's gestational age of less than 32 weeks, BPD was to be graded

according to the corrected gestational age of 36 weeks or to the oxygen concentration at discharge. If the gestational age was ≥ 32 weeks, BPD was graded according to the oxygen demand concentration at 56 days after birth or at discharge as follows: (1) mild, no oxygen; (2) moderate, an $FiO_2 < 0.30$; and (3) severe, an $FiO_2 \geq 0.30$ or requiring mechanical ventilation. Pulmonary X-ray findings were not used as the basis for evaluating the severity of the disease. Mild BPD referred to patients whose cumulative time of oxygen dependence was ≥ 28 days, but where oxygen therapy was halted at discharge or 36 weeks of corrected gestational age [6]. The neonates were assigned into either the BPD group or non-BPD group.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables that did not follow a normal distribution are reported as medians (P25–P75) and were analyzed by the Wilcoxon rank-sum test. Categorical variables are reported as numbers and were analyzed by the Chi-squared test, continuity corrected Chi-squared test or the Fisher exact-probability method for inter-group comparisons. Variables with significant inter-group differences ($p < 0.05$) were entered into the multivariate logistic-regression analysis to identify factors associated with BPD. The receiver operating characteristic (ROC) curve and the Hosmer–Lemeshow

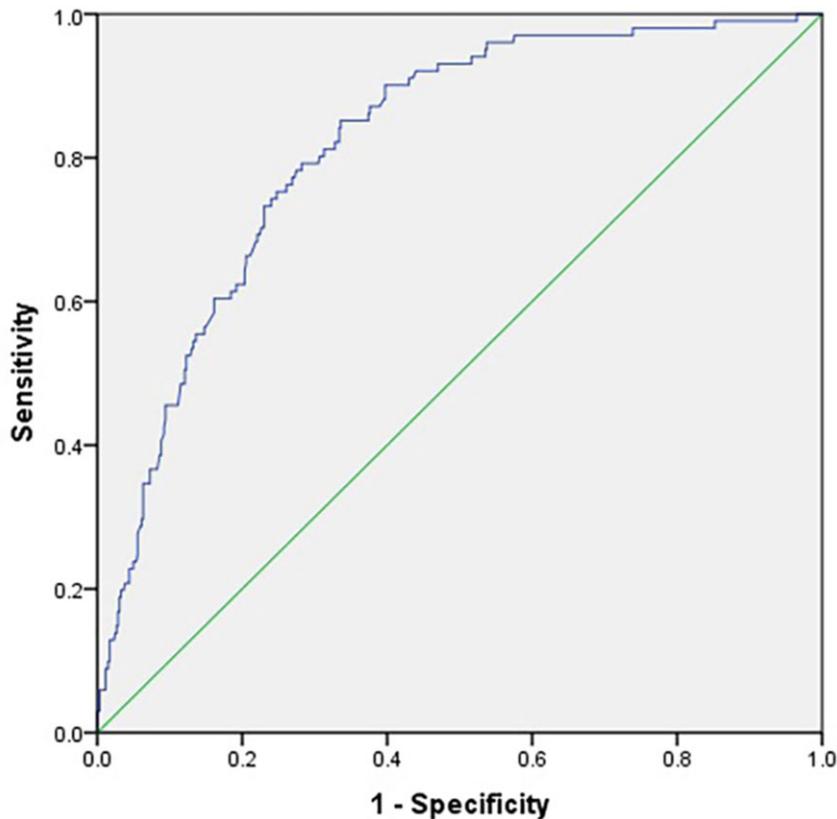


Fig. 2. Receiver operating characteristics curves for the prediction model of bronchopulmonary dysplasia in neonate with respiratory distress syndrome (AUC = 0.818).

goodness-of-fit test were used to assess the performance of the derived models. A $p < 0.05$ (two-sided) was considered statistically significant (Fig. 2).

RESULTS

Clinical characteristics of study participants

Of the 625 infants, 523 were in the non-BPD group and 102 were in the BPD group. The incidence of BPD in the RDS neonates was 16.3% (102/625). The incidences of BPD with gestational age <32 weeks and gestational age >32 weeks were 26.9% (92/342) and 3.5% (10/283), respectively.

Bivariate analysis of neonates between the BPD and non-BPD groups

There were significant differences in birthweight, gestational age <32 weeks, delivery mode, multiple

pregnancy and Apgar scores at 1 and 5 min between the BPD and non-BPD groups ($p < 0.05$, Table 1). In the BPD group, the proportion and duration of high- and normal-frequency mechanical ventilation; non-invasive continuous airway pressure (CPAP); high-, medium- and low-concentration oxygen inhalation; facemask and box oxygen inhalation; and total duration of oxygen therapy were higher than those in the non-BPD group ($p < 0.05$, Fig. 3). Compared with the neonates in the non-BPD group, the neonates in the BPD were more likely to use albumin, gamma globulin, pulmonary surfactant, respiratory stimulant and red blood cell transfusion (PRBC) ($p < 0.05$, Table 2). In addition, compared with the neonates in the non-BPD group, neonates in the BPD group were significantly more likely to have asphyxia, pneumonia, pulmonary hemorrhage, intracranial hemorrhage, patent ductus arteriosus, anemia and pneumothorax ($p < 0.05$, Table 3).

Table 1. Demographic and clinical characteristics in neonates with RDS in two groups

Characteristics	BPD	Non-BPD	<i>p</i> value
Neonatal factors			
Sex			0.527 ^a
Male	68 (66.7)	318 (60.8)	
Female	34 (33.3)	205 (39.2)	
Birthweight (g) (M [P25, P75])	1150 (1000, 1500)	1710 (1380, 2250)	0.000 ^b
Gestational age <32 W	92 (90.2)	250 (47.8)	0.001 ^a
Apgar scores at 1 min (M [P25, P75])	7 (4, 9)	9 (7, 9)	0.000 ^b
Apgar scores at 5 min (M [P25, P75])	8 (6, 9)	9 (8, 10)	0.000 ^b
Caesarean delivery	35 (34.3)	338 (64.6)	0.008 ^a
Meconium stained fluid	6 (5.9)	31 (5.9)	0.601 ^a
Cord around neck	2 (2.0)	31 (5.9)	0.084 ^c
Abnormal placenta	16 (15.7)	91 (17.4)	0.800 ^a
Premature rupture of membranes	13 (12.7)	113 (21.6)	0.904 ^a
Intrauterine distress	5 (4.9)	38 (7.3)	0.554 ^a
Maternal factors			
Pregnancy-induced hypertension	10 (9.8)	80 (15.3)	0.701 ^a
Gestational heart disease	1 (1.0)	5 (1.0)	1.000 ^c
Gestational diabetes	4 (3.9)	27 (5.2)	1.000 ^c
Multiple pregnancy	26 (25.5)	84 (16.1)	0.010 ^a
Maternal prenatal use of dexamethasone	22 (21.6)	72 (13.8)	0.151 ^a
Maternal prenatal use of antibiotics	2 (2.0)	1 (0.2)	0.175 ^c

Note: Values are presented as median (interquartile range) (M [P25, P75]) or *n* (%).

^aChi-squared test.

^bWilcoxon rank-sum test.

^cContinuity correction chi-squared.

Multivariate analysis of neonates between the BPD and non-BPD groups

Bivariate analysis showed that birthweight, gestational age <32 weeks, delivery mode, multiple pregnancies, Apgar scores at 1 and 5 min, the proportions and durations of high- and normal-frequency mechanical ventilation, non-invasive CPAP, high-, medium-, and low-concentration oxygen inhalation, facemask and box oxygen inhalation, the uses of albumin, gamma globulin, pulmonary surfactant, respiratory stimulant and transfusion with PRBCs, asphyxia, pneumonia, pulmonary hemorrhage, intracranial hemorrhage, patent ductus arteriosus, anemia and pneumothorax were associated with BPD. When we entered birthweight (odds ratios (OR) = 0.998; 95% confidence interval (CI), 0.997–0.999), gestational age less than 32 weeks (OR = 3.206; 95% CI, 1.293–7.949), total duration of oxygen therapy more than 10 days

(OR = 1.184; 95% CI, 1.105–1.269), neonatal asphyxia (OR = 14.006; 95% CI, 5.071–247.219), patent ductus arteriosus (PDA) (OR = 1.858; 95% CI, 1.073–3.220), need for RBC transfusion (PRBC) (OR = 7.557; 95% CI, 2.826–20.210), and the use of surfactant (OR = 0.425; 95% CI, 0.239–0.753) into the multivariate logistic-regression analysis model, we found that elevated birthweight and the use of surfactant were protective factors for the occurrence of BPD (Table 4) [the Hosmer–Lemeshow goodness-of-fit test showed a *p* = 0.961, and the area under the ROC curve was 0.818 (Fig. 1)].

DISCUSSION

Although BPD is one of the most common and severe complications in preterm infants, its exact pathogenesis remains unclear at present. Children with BPD can present clinically with various

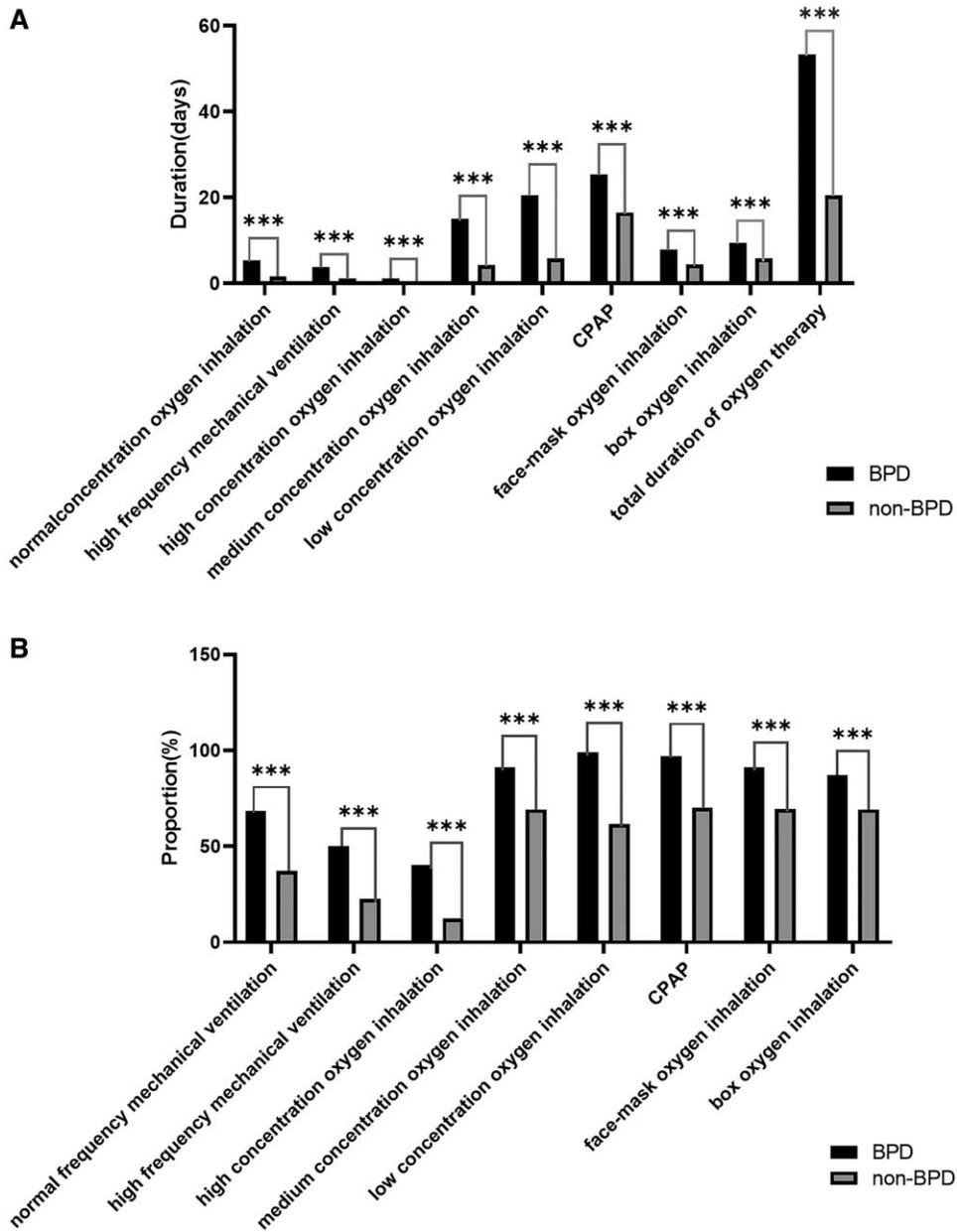


Fig. 3. Comparison of different modes of respiratory support between BPD and non-BPD group.

symptoms such as progressive dyspnea and hypoxemia; and severe cases can develop complications such as pulmonary hypertension and even cor pulmonale. This is primarily due to the pathophysiological changes secondary to the severe lung tissue damage endured by the affected children, including decreased pulmonary compliance and increased

airway resistance that generate a dysregulated ventilation/flow ratio. Children with BPD exhibit a poor long-term prognosis and are prone to recurrent respiratory infections, gasping, cardiopulmonary impairment and regressed physical development that seriously affect their quality of life [23]. A retrospective study of extremely preterm infants in the United

Table 2. Comparison of treatments during hospitalization in neonates with RDS between two groups

	BPD	Non-BPD	<i>p</i> value
Albumin	82 (80.4)	179 (34.2)	0.000
Gamma globulin	77 (75.5)	161 (30.8)	0.000
Pulmonary surfactant	91 (89.2)	355 (67.9)	0.000
Red blood cell	97 (95.1)	209 (40.0)	0.000
Respiratory stimulant	75 (73.5)	145 (27.7)	0.000

Note: Values are presented as *n* (%).

Table 3. Comparison of complications in neonates with RDS between two groups

	BPD	Non-BPD	<i>p</i> value
Hypoalbuminemia	4 (3.9)	21 (4.0)	0.496
Sepsis	6 (5.9)	31 (5.9)	0.807
Granulocytopenia or agranulocytosis	5 (4.9)	17 (3.3)	0.796
Anemia	80 (78.4)	235 (44.9)	0.000
Feeding intolerance	1 (1.0)	4 (0.8)	0.719
Neonatal necrotizing enterocolitis	4 (3.9)	15 (2.9)	0.477
Pneumothorax	1 (1.0)	35 (6.7)	0.031
Pulmonary arterial hypertension	2 (2.0)	113 (21.6)	0.797
Neonatal asphyxia	44 (43.1)	196 (37.5)	0.000
Neonatal pneumonia	54 (52.9)	400 (76.9)	0.034
Pulmonary hemorrhage	14 (13.7)	28 (5.3)	0.000
Apnea	3 (2.9)	21 (4.0)	1.000
Intracranial hemorrhage	30 (29.4)	51 (9.8)	0.000
PDA	34 (33.3)	96 (18.3)	0.001

Note: Values are presented as *n* (%).

States over the past 20 years found that the survival rate increased from 70 to 79%, while the incidence of BPD rose from 32 to 45%. Approximately 25% of preterm infants with a birthweight <1500 g were diagnosed with BPD at 36 weeks of PMA [7]. Momentous changes have thus arisen in the resulting treatments of BPD with the application of prenatal glucocorticoids, postnatal pulmonary surfactants and the implementation of protective ventilatory strategies.

Jensen and Schmidt [9] and Egreteau *et al.* [10] reported that the incidence of BPD was 5% in infants

with a birthweight of 1000–1500 g, 36% at 751–100 g, and 60% at 500–750 g. Seventy-two percent of infants born before 26 weeks of GA and 50% of infants born between 26 and 27 weeks of GA developed BPD. In contrast, BPD occurred in 28% of infants born at 28–29 weeks of GA, and in 13% of infants born at 30–31 weeks of GA—indicating that younger gestational age, lower birthweight, and less-mature lung development correlated with a higher incidence of BPD, which is consistent with our study.

In the present study, we observed a significant difference in the number of neonatal asphyxias between the BPD and non-BPD groups ($p < 0.05$), indicating that neonatal asphyxia was a high-risk factor for the occurrence of BPD. When neonatal asphyxia occurs, the lack of oxygen can affect the blood perfusion of important organs, which leads to increased pulmonary vascular resistance and decreased blood flow in the pulmonary arteries. If hypoxia and acidosis persist, this can cause pulmonary vascular reconstruction and connective tissue hyperplasia. The latter will deposit in the pulmonary vascular smooth muscle cells and eventually result in reduced vascular diastolic function and delayed pulmonary development. In addition, asphyxia can relax the fetal anal sphincter and discharge meconium. Hypoxia can simultaneously cause gasp in the fetus; both allow the meconium-contaminated amniotic fluid to go into the lungs. All of these mechanisms can ultimately cause atelectasis or emphysema, lung ventilation and exchange dysfunction, and increased lung damage. Therefore, we suspect that the damage caused by lung developmental delay and meconium inhalation after neonatal asphyxia increases the susceptibility to BPD.

The study of Stephens *et al.* [14] and Clyman *et al.* [24] revealed that persistent PDA leads to increased hydrostatic pressure in the pulmonary capillaries, increased fluid in the pulmonary interstitium, decreased osmotic pressure and excessive fluid replacement. These results can lead to pulmonary edema, pulmonary function deterioration, and reduced gas exchange in children, which ultimately increases their susceptibility to BPD. While clinical evidence indicates that pharmacological closure of the PDA leads to improved alveolarization, it is at

Table 4. Multivariate logistic-regression analysis on the factors associated with the development of BPD in neonates with RDS

Variables	β	SE	Wald	p	OR	95%CI
Birthweight	-0.002	0.035	14.852	0.000	0.998	0.997-0.999
Gestational age <32 W	1.165	0.463	6.322	0.012	3.206	1.293-7.949
Total duration of oxygen therapy (>10 days)	0.169	0.037	22.828	0.000	1.184	1.105-1.269
Neonatal asphyxia	5.869	2.166	7.341	0.007	14.006	5.071-247.219
PDA	0.620	0.280	4.884	0.027	1.858	1.073-3.220
Red blood cell transfusion	2.022	0.502	16.239	0.000	7.557	2.826-20.210
Pulmonary surfactant	-0.857	1.203	3.501	0.003	0.425	0.239-0.753

this time unclear whether the improvement associated with such closure is due to the closure of the PDA itself or due to the pharmacologic agents (i.e. indomethacin and ibuprofen) used to seal it. In addition, inflammation of the airways and lung tissue is associated with the development of BPD, and we corroborated this and further confirmed that PDA was an independent predictor of chest drainage using multivariate analysis.

We also observed an association between the duration of total oxygen use and the incidence of BPD ($p < 0.05$). As Perrone *et al.* and Laughon *et al.* suggested [25, 26], the generation and scavenging of oxygen radicals are normally in equilibrium. When premature infants are exposed to a high oxygen environment, toxic products, such as the hyperactive superoxygen radical, hydrogen peroxide, and other free radicals, are produced in large quantities. When the serious oxidative-stress reaction exceeds the normal antioxidant and scavenging capacity of premature infants, lung damage could develop. A meta-analysis of individual patient data from 10 randomized controlled trials demonstrated no benefit from high-frequency ventilation relative to conventional ventilation for BPD or for other adverse outcomes. Either approach to ventilatory support is effective, although complete avoidance of mechanical ventilation comprises the optimal strategy in theory [27].

The use of surfactant is one of the predominant measures in reducing premature infant mortality and improving BPD. Early use of surfactants allows for early extubation and mild-ventilation oxygen therapy, thereby reducing the risk for BPD [11, 28].

An association between PRBC-transfusion and BPD has been reported previously [12, 29-31].

These retrospective analyses depicted BPD as a secondary outcome while primarily focusing on the effects of transfusions and ferritin levels related to the number of blood transfusions in all analyzed infants. In a study on 98 infants with a GA of 34 weeks, Cooke *et al.* [29] reported a higher incidence of BPD in the PRBC-transfusion group. Valieva *et al.* also assessed the effects of transfusions in extremely low birth weight infants and demonstrated that the incidence of BPD was significantly associated with the number of transfusions at day 28 of life; however, this relationship disappeared by 36 weeks of PMA [31]. A recent retrospective investigation of 50 infants with very low birth weight (VLBW) exhibited an increase in neonatal morbidities (including BPD) in infants who received PRBC-transfusions [30]. The possible mechanism might be the iron produced by the breakdown of heme that is released after the destruction of transfused red blood cells, as this could promote the production of free radicals, inflammation and fibrosis. After erythrocyte destruction, the abundant heme could lead to hyperactivation of heme oxygenase and exacerbate the lung damage. In addition, transfusion-associated acute lung injury could result in lung damage through acute inflammation. It is therefore difficult to withdraw breathing machines from neonates who are chronically dependent on oxygen. The neonates in our study received transfusions with PRBCs, but whether human recombinant erythropoietin used as a means of reducing the need for blood transfusions would also reduce the risk of BPD remains to be established [32].

A large number of clinical data and experimental studies have demonstrated that intrauterine

infections such as bacterial vaginitis, chorioamnionitis and cytomegalovirus infection are critical to the pathogenesis of BPD [33, 34]. One limitation to the present study was that we did not include these influential factors. Because our hospital is an institution specializing in children, our prenatal data were incomplete and we therefore could only delete such variables during our statistical analysis.

By analyzing our clinical data, we found that a gestational age less than 32 weeks, total duration of oxygen therapy more than 10 days, neonatal asphyxia, PDA and red blood cell infusion were the risk factors for BPD; whereas a high birthweight and the use of pulmonary surfactant were protective factors against BPD. When we analyzed our ROC curves to determine the utility of predictors to assess the onset of BPD in premature infants, we were able to detect BPD with respect to the aforementioned risk factors both in infants with and without BPD with a robust AUC of 0.818.

Strengths and limitations

We herein executed a retrospective cohort study at our hospital over a 6-year period, analyzed a relatively large number of neonates ($n = 625$) with RDS, and implemented a stepwise logistic-regression analysis to assess the independent predictors of BPD in neonates with RDS.

There were several limitations to the present study. First, this study entailed a retrospective design and was thereby subject to potential selection bias. Our conclusions were also purely based on observations from a single children's center. Thus, a prospective, multicenter study is needed to further evaluate the factors that predict BPD. Finally, our hospital is a specialized children's institution, and complete prenatal information was therefore lacking.

CONCLUSIONS

Our study was designed to investigate the predictors of BPD in neonates with RDS, and we concluded that a gestational age < 32 weeks, low birthweight, total duration of oxygen therapy > 10 days, neonatal asphyxia, PDA and red blood cell transfusion were risk factors for BPD.

ETHICS APPROVAL

This study was approved by the Institutional Review Board of the Children's Hospital of Soochow University.

SUPPLEMENTARY DATA

Supplementary data are available at *Journal of Tropical Pediatrics* online.

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