의학박사 학위논문

Comparisons of perinatal characteristics and neonatal outcomes between the BPD Collaborative type 1 and type 2 severe bronchopulmonary dysplasia

BPD Collaborative 분류에 따른 중증 기관지폐이형성증 환자의 주산기적 특성과 신생아기 임상 양상의 비교

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서울대학교 대학원

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Comparisons of perinatal characteristics and neonatal outcomes between the BPD Collaborative type 1 and type 2 severe bronchopulmonary dysplasia

By

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Abstract

Comparisons of perinatal characteristics and neonatal outcomes between the BPD Collaborative type 1 and type 2 severe bronchopulmonary dysplasia

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Background: Infants with severe bronchopulmonary dysplasia (BPD) have complicated clinical courses and suffer substantial life-long burdens of pulmonary and neurodevelopmental sequelae. The present study compared maternal and neonatal characteristics, comorbidities and clinical burden of preterm infants with type 1 and type 2 severe BPD Collaborative classification.

Methods: This study was a prospective cohort study of preterm (<32 weeks' gestation) very-low-birth-weight infants. Severe BPD was divided into type 1 severe BPD requiring of ≥30% oxygen and/or noninvasive ventilation at 36 weeks postmenstrual age (PMA), and type 2 severe BPD requiring invasive mechanical ventilation at 36 weeks PMA. Maternal and neonatal characteristics, comorbidities and clinical burden were compared between these two types of severe BPD.

Results: Of the 1,328 infants included, 983 (74.0%) developed type 1 severe BPD, and 345 (26.0%) developed type 2 severe BPD. Lower birth weight, small for gestational age, lesser maternal premature rupture of membrane, lower 5-min Apgar score, air leak, pulmonary hemorrhage, surgical ligation of patent ductus arteriosus, necrotizing enterocolitis, and late-onset sepsis were significantly associated with type 2 severe BPD. Compared with infants with type 1 severe BPD, infants with type 2 severe BPD had an increased risk of mortality (adjusted odds ratio (aOR) 18.64, 95% confidence interval (CI) 10.81-32.13), pulmonary hypertension (aOR 2.16, 95% CI 1.59-2.93), and tracheostomy (aOR 10.38, 95% CI 2.05-52.49).

Conclusions: Our data highlight the substantially greater mortality and clinical burden in infants with type 2 severe BPD than infants with type 1 severe BPD. A comprehensive and multidisciplinary approach is needed for infants with type 2 severe BPD.

Keywords: Preterm infants, Very low birth weight infant,

Severe bronchopulmonary dysplasia, Comorbidities of prematurity

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List of Abbreviations

AABR: automated auditory brainstem response

BPD: bronchopulmonary dysplasia

CI: confidence interval

CPAP: continuous positive airway pressure

ELBW: extremely low birth weight

EOS: early-onset sepsis

GA: gestational age

HFNC: high-flow nasal cannula

IVH: intraventricular hemorrhage

KNN: Korean Neonatal Network

LOS: late-onset sepsis

MRI: magnetic resonance imaging

NEC: necrotizing enterocolitis

NICU: neonatal intensive care unit

NIH: National Institutes of Health

OR: odds ratio

PDA: persistent ductus arteriosus

PMA: postmenstrual age

PROM: premature rupture of membrane

PVL: periventricular leukomalacia

RDS: respiratory distress syndrome

ROP: retinopathy of prematurity

SGA: small for gestational age

VLBW: very low birth weight

Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common chronic morbidities in preterm infants (1). BPD is commonly defined based on consensus recommendations from a National Institutes of Health (NIH) workshop (2). These recommendations classified BPD in preterm infants born at <32 weeks as mild, moderate, or severe, according to the amount of supplemental oxygen and the mode of respiratory support administered at 36 weeks postmenstrual age (PMA).

Infants with severe BPD have higher mortality and morbidity than infants with mild or moderate BPD (3). Infants with severe BPD have complicated clinical courses and suffer substantial life-long burdens of pulmonary and neurodevelopmental sequelae (4-8). However, large variation in the severity of the disease is noted even within the severe BPD.

To better define BPD severity, a multi-institution group dedicated to filling knowledge gaps in the care of infants with BPD called the BPD Collaborative recommended that severe BPD be further classified into two phenotypes (9). Infants receiving persistent oxygen and/or nasal continuous positive airway pressure (CPAP) or high-flow nasal cannula (HFNC) at 36 weeks PMA were defined as having type 1 severe BPD, and infants requiring invasive mechanical ventilation were defined as having type 2 severe BPD. The BPD Collaborative reported a point prevalence of severe BPD of 36.5% in preterm infants born at <32 weeks in tertiary referral neonatal intensive care units (NICUs), and 41% of these patients had type 2 severe BPD (10). Infants with type 2 severe BPD are more likely to die and have neurodevelopmental impairments (11).

However, maternal and neonatal characteristics and comorbidities associated with type

2 severe BPD remain understudied given its low incidence. Few reports have focused on perinatal factors that could affect disease severity and variation in the clinical burden within a severe BPD category.

In the present study, we identified maternal and neonatal characteristics associated with the development of type 2 severe BPD and assessed the clinical burden of type 2 severe BPD in compare to type 1 severe BPD using a large cohort of very-low-birth-weight (VLBW) infants.

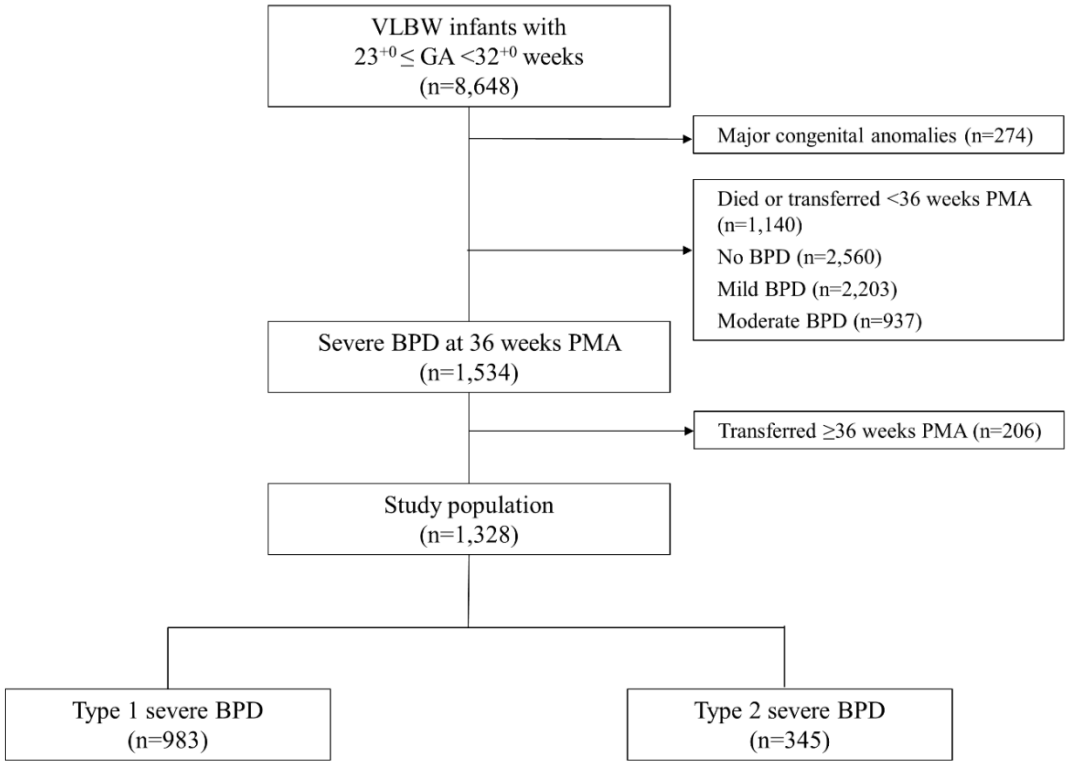
Materials and methods

Study design

We performed a cohort study using prospectively collected data from 69 NICUs participating in the Korean Neonatal Network (KNN). The KNN is a nationwide multicenter registry of VLBW infants that collects demographic and clinical data using a standardized operating procedure (12).

Information on the study population is presented in Figure 1. We enrolled 8,648 VLBW infants registered in the KNN registry who were born at 23^{+0}-31^{+6} gestational weeks between January 2013 and December 2017. Among these, 274 infants who had major congenital anomalies, 1,140 infants who died or were transferred to other hospitals before the diagnosis of BPD at 36 weeks PMA, and 2,560, 2,203, 937 infants with no, mild, moderate BPD, respectively were excluded. The remaining 1,534 infants had severe BPD, which was defined as the use of supplemental oxygen for at least 28 days plus treatment with ≥30% oxygen and/or positive pressure ventilation at 36 weeks PMA (2). Among these, 206 infants who were transferred to another hospital or ward in a hospital after 36 weeks PMA and for whom late morbidity data were unavailable were also excluded. Finally, data from 1,328 infants were analyzed. Infants with severe BPD were divided into infants with type 1 severe BPD and infants with type 2 severe BPD according to the BPD Collaborative recommendation (9). Infants with type 1 severe BPD were defined as requiring ≥30% oxygen and/or CPAP or HFNC at 36 weeks PMA, and infants with type 2 severe BPD were defined as requiring invasive mechanical ventilation at 36 weeks PMA.

Figure 1. Study population



BPD, bronchopulmonary dysplasia; GA, gestational age; PMA, postmenstrual age; VLBW, very low birth weight.

Data collection

The maternal data included hypertension, diabetes, premature rupture of membrane (PROM), histological chorioamnionitis, and the use of antenatal corticosteroids. The neonatal data included gestational age (GA), birth weight, sex, small for gestational age (SGA), multiple births, delivery mode, and Apgar scores at 1 and 5 minutes. The following clinical information was collected: respiratory distress syndrome (RDS), air leak, pulmonary hemorrhage, surgical ligation of patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), late-onset sepsis (LOS), pulmonary hypertension, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP) requiring treatment, the results of automated auditory brainstem response (AABR) before discharge, duration of invasive mechanical ventilation and noninvasive ventilation, length of NICU admission, and survival to NICU discharge or death. Because the KNN VLBW infant registry only collects data up to 12 months after birth, discharge information for infants who stayed in the NICU beyond 12 months of age were not available and not included in the analysis of discharge information. For surviving infants discharged from the NICU, we collected data on z-scores for weight, height, and head circumference at the time of discharge using Fenton 2013 growth curves (13).

The primary outcome was mortality after 36 weeks PMA during the NICU admission. Secondary outcomes were various neonatal comorbidities and clinical burden, including pulmonary hypertension, PVL, ROP requiring treatment, abnormal AABR results, duration of invasive mechanical ventilation and noninvasive ventilation, length of NICU admission, tracheostomy, the use of supplemental oxygen, and mechanical ventilation at NICU discharge.

Definitions

Maternal hypertension included pre-existing hypertension and/or pregnancy-induced hypertension (14). Antenatal corticosteroid administration was defined as the successful completion of a dexamethasone or betamethasone regimen within 7 days before delivery. SGA was defined as birth weight below the 10th percentile for GA based on Fenton 2013 growth charts (13). RDS was defined by the presence of respiratory insufficiency that manifested at or shortly after birth with a typical radiological finding and required surfactant replacement therapy. NEC was defined as stage 2 or higher NEC according to modified Bell's staging criteria (15). High-grade IVH was defined as grade III or IV IVH according to the criteria of Papile classification system, and the worst grading result during hospitalization was recorded (16). LOS was defined as a culture-proven sepsis treated with appropriate antibiotics for five or more days which occurred after 72 hours of life and prior to 36 weeks PMA (17). Pulmonary hypertension was diagnosed based on echocardiography and whether it required medical management. PVL was diagnosed based on the results of brain ultrasound or magnetic resonance imaging (MRI) findings before discharge. Invasive mechanical ventilation included conventional mechanical ventilation and high-frequency oscillatory ventilation. Noninvasive ventilation included nasal CPAP, nasal intermittent positive pressure ventilation, and HFNC.

Statistical analysis

Continuous variables are expressed as the means ± standard deviations; categorical variables are expressed as numbers and proportions. Comparisons of continuous variables between the groups were performed using Student's *t*-test for normally

distributed variables and a *Mann-Whitney U* test for variables with nonnormal distributions. Categorical variables were compared using Pearson's chi-squared test. Multivariate analysis was performed using logistic regression, and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk NY, USA). A *P* value <0.05 was considered statistically significant.

Ethical approval and informed consent

The registration of data in the KNN was approved by the institutional review board of each participating center. Informed consent was obtained from the parents of each infant prior to participation in the KNN registry.

Results

The final study population included 1,328 preterm (23^{+0}-31^{+6} weeks) VLBW infants. Maternal and neonatal characteristics of the 1,328 infants are presented in Table 1. Their mean GA was $27^{+0} \pm 2^{+0}$ weeks, and their mean birth weight was 893 ± 253 g. Of these 1,328 infants, 983 (74.0%) infants developed type 1 severe BPD, and 345 (26.0%) infants developed type 2 severe BPD.

Maternal and neonatal characteristics

The comparisons of maternal and neonatal characteristics are presented in Table 2. There were no significant differences in maternal characteristics between the type 1 and type 2 severe BPD groups, except maternal PROM, which was significantly more common in the type 1 severe BPD group than in the type 2 severe BPD group (41.0% *vs.* 34.4%, p=0.038).

Compared to infants with type 1 severe BPD, infants with type 2 severe BPD had a lower birth weight, lower 5-minute Apgar score and a higher rate of SGA. Infants who developed type 2 severe BPD also had significantly higher rates of air leak, pulmonary hemorrhage, surgical ligation of PDA, NEC, and LOS (Table 2).

Mortality, comorbidities and clinical burden

The mortality, comorbidities, and clinical burden of the type 2 severe BPD group were compared to those of the type 1 severe BPD group (Table 3). Overall, 8.2% (n=109) of the infants with severe BPD died before discharge, and 0.5% (n=7) remained in the

NICU beyond 12 months of age. Cardiorespiratory failure was the most common cause of death and accounted for 40% of all deaths. The mortality rate during the NICU admission was 1.9% in the type 1 severe BPD group and 26.1% in the type 2 severe BPD group (Table 3). After adjustment for GA, birth weight, sex, SGA and maternal PROM, the aOR for death during the NICU admission increased to 18.64 (95% CI 10.81-32.13, $p<0.001$) for infants with type 2 severe BPD compared to infants with type 1 severe BPD (Table 4 and Figure 2).

The type 2 severe BPD group had significantly higher rates of comorbidities, including pulmonary hypertension, ROP requiring treatment, PVL, and abnormal AABR results, than the type 1 severe BPD group. Infants with type 2 severe BPD had a higher clinical burden as represented by a longer duration of invasive mechanical ventilation, and NICU admission than infants with type 1 severe BPD. The type 2 severe BPD group had lower z-scores for weight, height, and head circumference at the time of NICU discharge (Table 3).

After adjustment for GA, birth weight, sex, SGA, and maternal PROM, the odds of pulmonary hypertension increased significantly in infants with type 2 severe BPD (aOR 2.16, 95% CI 1.59-2.93, $p<0.001$). The odds of PVL (aOR 1.64, 95% CI 1.17-2.29, $p=0.004$) and abnormal AABR results (aOR 1.54, 95% CI 1.10-2.15, $p=0.011$) were also significantly increased in these infants. Regarding the clinical burden, the type 2 severe BPD group was associated with a longer duration of invasive mechanical ventilation and NICU admission, and increased risks of discharge with home oxygen (aOR 2.73, 95% CI 2.03-3.68, $p<0.001$), tracheostomy (aOR 10.38, 95% CI 2.05-52.49, $p=0.005$), and mechanical ventilation (aOR 6.25, 95% CI 1.47-26.64, $p=0.013$). For somatic growth at the time of discharge, the type 2 severe BPD group was associated with lower z-scores for weight, height, and head circumference (Table 4 and Figure 2).

Table 1. Maternal and neonatal characteristics of study subject

	Study population N=1,328
Gestational age (weeks^{+days})	$27^{+0} \pm 2^{+0}$
Birth weight (g)	893 ± 253
Male (%)	715 (53.8)
SGA (%)	227 (17.1)
Caesarean section (%)	1027 (77.3)
Multiple gestation (%)	399 (30.0)
Maternal hypertension (%)	254 (19.1)
Maternal diabetes (%)	103 (7.8)
Maternal PROM (%)*	516 (38.9)
Histologic chorioamnionitis (%)**	501 (37.7)
Antenatal corticosteroids (%)	662 (49.8)
1-minute Apgar score	3.9 ± 1.8
5-minute Apgar score	6.2 ± 1.8
Respiratory distress syndrome (%)	1263 (95.1)
Air leak (%)	115 (8.7)
Pulmonary hemorrhage (%)	139 (10.5)
Surgical ligation of PDA (%)	372 (28.0)
High-grade IVH	308 (23.2)
NEC (≥stage II)	161 (12.1)
LOS before 36 weeks PMA (%)	433 (232.6)

Values are presented as means ± SDs or numbers (%). BPD, bronchopulmonary dysplasia; CI, confidence interval; IVH, intraventricular hemorrhage; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus; PMA, postmenstrual age; PROM, premature rupture of membrane; SGA, small for gestational age.

* Data were available for 1,313 infants.

** Data were available for 1,115 infants.

Table 2. Comparisons of maternal and neonatal characteristics between the type 1 severe BPD and type 2 severe BPD groups

	Type 1 severe BPD N=983	Type 2 severe BPD N=345	*p*-value	Adjusted OR* (95% CI)	Adjusted *p*-value*
Gestational age (weeks^{+days})	$27^{+1} \pm 2^{+0}$	$26^{+6} \pm 2^{+0}$	0.053		-
Birth weight (g)	909 ± 251	844 ± 253	<0.001		-
Male (%)	530 (53.9)	185 (53.6)	0.950		-
SGA (%)	144 (14.6)	83 (24.1)	<0.001		-
Caesarean section (%)	754 (76.7)	273 (79.1)	0.371		-
Multiple gestation (%)	302 (30.7)	97 (28.1)	0.376		-
Maternal hypertension (%)	192 (19.5)	62 (18.0)	0.578		-
Maternal diabetes (%)	79 (8.0)	24 (7.0)	0.560		-
Maternal PROM (%)**	400 (41.0)	116 (34.4)	0.038		-
Histologic chorioamnionitis (%)†	388 (45.8)	113 (42.2)	0.324		-
Antenatal corticosteroids (%)	490 (49.8)	172 (49.9)	0.524		-
1-minute Apgar score	4.0 ± 1.8	3.7 ± 1.8	0.014	0.943 (0.876-1.015)	0.115
5-minute Apgar score	6.3 ± 1.8	6.0 ± 1.8	0.006	0.931 (0.867-0.999)	0.048
Respiratory distress syndrome (%)	929 (94.5)	334 (96.8)	0.110	1.582 (0.802-3.122)	0.186
Air leak (%)	67 (6.8)	48 (13.9)	<0.001	2.029 (1.350-3.049)	0.001
Pulmonary hemorrhage (%)	77 (7.8)	62 (18.0)	<0.001	2.493 (1.725-3.603)	<0.001
Surgical ligation of PDA (%)	239 (24.3)	133 (38.6)	<0.001	1.872 (1.427-2.455)	<0.001
High-grade IVH	215 (21.9)	93 (27.0)	0.064	1.290 (0.963-1.728)	0.088
NEC (≥stage II)	99 (10.1)	62 (18.0)	<0.001	1.808 (1.267-2.580)	0.001
LOS before 36 weeks PMA (%)	294 (29.9)	139 (40.3)	0.001	1.535 (1.182-1.994)	0.001

Values are presented as means ± SDs or numbers (%). BPD, bronchopulmonary dysplasia; CI, confidence interval; IVH, intraventricular hemorrhage; LOS, late-onset sepsis; NEC, necrotizing enterocolitis; OR, odds ratio; PDA, patent ductus arteriosus; PMA, postmenstrual age; PROM, premature rupture of membrane; SGA, small for gestational age.

[*]The ORs and *p*-values were calculated with adjustment for gestational age, birth weight, sex, SGA and maternal premature rupture of membrane.

[**] Data were available for 976 infants in the type 1 severe BPD group and 337 infants in the type 2 severe BPD group.

[†] Data were available for 847 infants in the type 1 severe BPD group and 268 infants in the type 2 severe BPD group.

Table 3. Comparisons of comorbidities and clinical burden between the type 1 and type 2 severe BPD groups

	Type 1 severe BPD N=983	Type 2 severe BPD N=345	*p*-value
Pulmonary hypertension (%)	152 (15.5)	102 (29.6)	<0.001
PVL (%)	125 (12.7)	66 (19.1)	0.004
ROP requiring treatment (%)	292 (29.7)	128 (37.4)	0.013
Abnormal AABR results (%)*	190 (20.9)	68 (30.1)	0.004
Duration of invasive mechanical ventilation (days)	32.0 ± 27.7	83.8 ± 51.1	<0.001
Duration of noninvasive ventilation (days)	44.8 ± 24.4	26.9 ± 31.7	<0.001
Length of NICU admission (days)	109.3 ± 38.7	137.3 ± 59.0	<0.001
PMA at discharge (weeks)	$42^{+4} \pm 4^{+4}$	$46^{+3} \pm 8^{+0}$	<0.001
Death during the NICU admission (%)	19 (1.9)	90 (26.1)	<0.001
Discharge with supplemental oxygen (%)**	241 (25.1)	120 (47.6)	<0.001
Discharge with tracheostomy (%)**	2 (0.2)	6 (2.4)	0.001
Discharge with mechanical ventilator (%)**	3 (0.3)	5 (2.0)	0.012
Weight z-score at discharge**	-1.74 ± 1.45	-2.59 ± 1.66	<0.001
Length z-score at discharge**	-2.44 ± 1.71	-3.40 ± 2.16	<0.001
Head circumference z-score at discharge**	-1.47 ± 1.38	-2.60 ± 2.14	<0.001

Values are presented as means ± SDs or numbers (%). AABR, automated auditory brainstem response; BPD, bronchopulmonary dysplasia; NICU, neonatal intensive care unit; PMA, postmenstrual age; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

* Data were available for 909 infants in the type 1 severe BPD group and 225 infants in the type 2 severe BPD group.

**Calculated for survivors to NICU discharge.

Table 4. **Adjusted odds ratios and *p*-values for comorbidities and clinical burden of type 2 severe BPD compared to those of type 1 severe BPD**

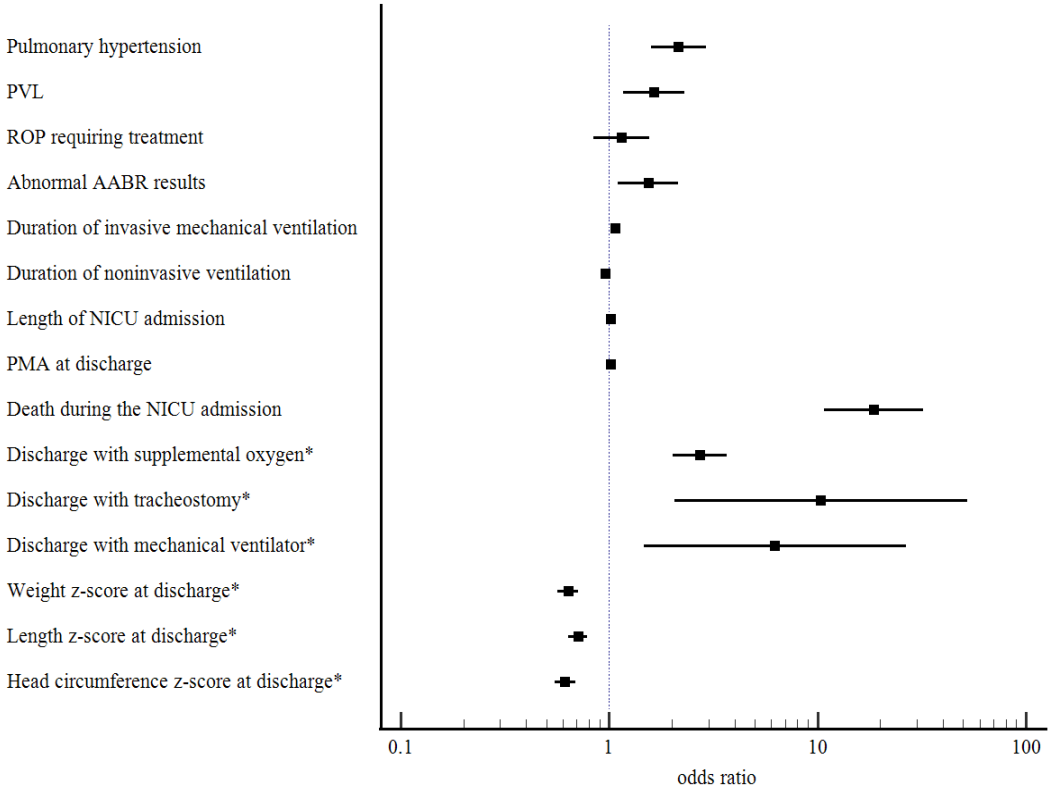
	Adjusted OR* (95% CI)	Adjusted *p*-value*
Pulmonary hypertension	2.155 (1.587-2.927)	<0.001
PVL	1.636 (1.168-2.292)	0.004
ROP requiring treatment	1.144 (0.840-1.558)	0.392
Abnormal AABR results	1.538 (1.102-2.148)	0.011
Duration of invasive mechanical ventilation	1.065 (1.057-1.073)	<0.001
Duration of noninvasive ventilation	0.962 (0.955-0.969)	<0.001
Length of NICU admission	1.014 (1.010-1.017)	<0.001
PMA at discharge	1.014 (1.010-1.017)	<0.001
Death during the NICU admission	18.635 (10.807-32.132)	<0.001
Discharge with supplemental oxygen**	2.730 (2.025-3.682)	<0.001
Discharge with tracheostomy**	10.380 (2.053-52.487)	0.005
Discharge with mechanical ventilator**	6.250 (1.467-26.639)	0.013
Weight z-score at discharge**	0.635 (0.566-0.712)	<0.001
Length z-score at discharge**	0.709 (0.640-0.787)	<0.001
Head circumference z-score at discharge**	0.615 (0.547-0.691)	<0.001

AABR, automated auditory brainstem response; BPD, bronchopulmonary dysplasia; CI, confidence interval; NICU, neonatal intensive care unit; OR, odds ratio; PMA, postmenstrual age; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

*The ORs and *p*-values were calculated using binary logistic regression analysis with adjustment for gestational age, birth weight, sex, small for gestational age, and maternal premature rupture of membrane.

**Calculated for survivors to NICU discharge

Figure 2. Adjusted odds ratios with their 95% confidence intervals for comorbidities and clinical burden of the type 2 severe BPD compared to those of the type 1 severe BPD



AABR, automated auditory brainstem response; BPD, bronchopulmonary dysplasia; NICU, neonatal intensive care unit; PMA, postmenstrual age; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

*Calculated for survivors to NICU discharge

Discussion

Our results showed that infants with the type 2 severe BPD had an 18-fold increased risk of mortality, a two-fold increased risk of pulmonary hypertension, and a 10-fold increased risk of tracheostomy and a greater clinical burden as indicated by a longer duration of invasive mechanical ventilation and NICU admission than infants with the type 1 severe BPD. Among maternal and neonatal characteristics, lower birth weight, SGA, lesser maternal PROM, lower 5-minute Apgar score, air leak, pulmonary hemorrhage, surgical ligation of PDA, NEC, and LOS were significantly associated with type 2 severe BPD. These antenatal and postnatal factors may predispose the immature lung to injuries or directly cause injury to the immature lung and contribute to impaired alveolar and pulmonary vascular development, which increases the risk of type 2 severe BPD (18). Other investigators noted similar observations that PDA, sepsis, and surgical NEC had a significant role in the development of severe BPD (19, 20). The presence of PDA has been associated with the development of BPD (21, 22). The persistence of left-to-right shunting through PDA results in pulmonary edema and endothelial injury. These alterations lead to the prolonged need for high levels of respiratory support, including invasive mechanical ventilation and high inspired oxygen concentrations. Surgical ligation of PDA may indicate the greater severity of PDA, which may lead to exacerbation of lung disease, such as type 2 severe BPD. However, in addition to being reflective of a significant left-to-right shunt, there is evidence that surgical ligation of PDA itself may contribute to lung injury directly (23). Sepsis is also related to the development of BPD (17). There is considerable evidence to support that postnatal infection exacerbates the severity of BPD (24, 25). Jung et al. recently demonstrated that LOS was a risk factor for BPD in extremely low birth weight (ELBW)

infants using the KNN database (26). Because we limited LOS to cases that occurred before 36 weeks PMA when the diagnosis of BPD was made, our results support the role of LOS as a risk factor for more severe type of BPD.

Severe BPD results in high mortality and extensive morbidities (3). More specifically, infants with severe BPD are at an increased risk of long-term serious morbidities, including late pulmonary morbidity, pulmonary hypertension, gastroesophageal reflux, feeding difficulty, ROP, systemic hypertension, and neurodevelopmental impairment (4-8). Infants with severe BPD receiving invasive mechanical ventilation at 36 weeks PMA also had an increased risk of late mortality, severe respiratory morbidities, poor growth, and neurodevelopmental impairment than infants receiving noninvasive ventilation at 36 weeks PMA (11). We found that infants with type 2 severe BPD had an 18-fold increased risk of death during the NICU admission compared to infants with type 1 severe BPD, and the mortality rate reached 26% in infants with type 2 severe BPD. Type 2 severe BPD was strongly associated with a longer duration of invasive mechanical ventilation. At NICU discharge, infants with type 2 severe BPD were associated with a 10-fold increase in tracheostomy, a three-fold increase in supplemental oxygen use, and a 6-fold increase in mechanical ventilator requirement. These results suggest that infants with type 2 severe BPD are at a high risk of having chronic respiratory support and undergoing tracheostomy. These findings may reflect the disease severity and indicate that infants with type 2 severe BPD had more severe lung parenchymal and airway diseases. In our study population, the rates of tracheostomy and mechanical ventilation at discharge were 0.5% and 0.7%, respectively, which were much lower than those of previously reported referral-based cohort (27). According to a report from Children's Hospital Neonatal Consortium on infants with severe BPD born at <32 weeks, 5% had tracheostomy and 4% required mechanical ventilation at the time

of discharge (27). The reason for this discrepancy may be due to the different study populations. Their study included preterm infants who were admitted to tertiary referral hospitals. In contrast, we excluded from the analysis 206 infants who were transferred to another hospital or unit after 36 weeks PMA. These infants were often more ill than those who stayed at their initial hospital until NICU discharge. Of the 206 infants who were transferred, 121 infants had type 1 severe BPD and 85 infants had type 2 severe BPD. Because infants with type 2 severe BPD were transferred twice as many as infants with type 1 severe BPD after 36 weeks PMA, exclusion of these infants might have led to under-reporting of the actual rates of tracheostomy and mechanical ventilator use at discharge. Similarly, exclusion of these infants might have reduced the gaps in mortality, comorbidities, and clinical burden between type 1 and type 2 severe BPD.

We also found that infants with type 2 severe BPD were subject to significant comorbidities, including pulmonary hypertension, PVL, and impaired auditory response. Pulmonary hypertension developed in 20% of severe BPD infants, which is consistent with prior reports and highlights the importance of pulmonary hypertension as a comorbidity in infants with severe BPD (28, 29). After adjusting for confounding variables, the odds of developing pulmonary hypertension were increased twofold in infants with type 2 severe BPD compared with infants with type 1 severe BPD. A diagnosis of BPD-associated pulmonary hypertension was consistently associated with 2-year mortality rates as high as 40-50% (30, 31). Pulmonary hypertension has also been linked to an increased risk of death or tracheostomy (32, 33).

Infants with BPD also have difficulty maintaining growth (34). Based on the lower z-scores of weight, height, and head circumference at the time of discharge, we found that infants with type 2 severe BPD grew more poorly. The causes of growth failure in infants with type 2 severe BPD may include increased work of breathing, chronic stress

and inflammation, and feeding problems associated with respiratory insufficiency.

The strength of our study is that we evaluated maternal and neonatal characteristics, mortality, comorbidities, and clinical burden of severe BPD based on disease severity in a large, multicenter prospective cohort. However, there are several limitations that should be mentioned. First, we limited our analysis to infants who survived to 36 weeks PMA. Infants with the most severe BPD might have not survived to 36 weeks PMA. As many as half of all deaths in very preterm infants before 36 weeks PMA are pulmonary-related (1, 35). This might have led to under-reporting of the disease severity of type 2 severe BPD. Secondly, as mentioned above, exclusion of 206 infants who were transferred after 36 weeks PMA due to unavailability of late morbidity data might have reduced the gaps in comorbidities and clinical burden between type 1 and type 2 severe BPD. Finally, we did not examine long-term outcome data beyond NICU discharge.

Conclusion

The present study identified maternal and neonatal characteristics, comorbidities, and clinical burden associated with type 2 severe BPD with a cohort of preterm VLBW infants. Type 2 severe BPD was associated with a substantially high rate of various comorbidities and an enormous clinical burden. Stratifying infants with severe BPD into subtypes based on disease severity will likely improve the care of infants with more severe BPD. Our data highlight the need for a better understanding of the specific etiologies of type 2 severe BPD and a comprehensive, multidisciplinary approach for infants with type 2 severe BPD.

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요약 (국문초록)

목적: 중증 기관지폐이형성증은 복잡한 임상 경과를 가지며 호흡기계 및 신경학적인 합병증으로 장기적으로 광범위한 영향을 받을 수 있다. 본 연구는 BPD Collaborative 분류에 따라 중증 기관지폐이형성증을 type 1과 type 2 중증 기관지폐이형성증으로 나누어 각 type의 중증 기관지폐이형성증이 가지는 주산기적 특성과 동반 질환 및 임상적 부담을 비교하고자 하였다.

방법

재태주령 32주 미만의 극소저출생체중아를 대상으로 한 전향적인 코호트 연구이며 BPD Collaborative의 분류를 이용하여 중증 기관지폐이형성증으로 진단된 환자를 type 1과 type 2 중증 기관지폐이형성증으로 세분화하였다. Type 1 중증 기관지폐이형성증은 월경 후 나이 36주에 30% 이상의 산소가 필요하거나 비침습적인 기계환기가 필요한 경우, type 2 중증 기관지폐이형성증은 월경 후 나이 36주에 기관삽관을 통한 기계 환기가 필요한 경우로 정의하였다.

결과

1,328명의 대상 환자들 중 983 (74.0%)명의 환자가 type 1 중증 기관지폐이형성증, 345 (26.0%)명의 환자가 type 2 중증 기관지폐이형성증에 해당하였다. Type 2 중증 기관지폐이형성증은 type 1 중증 기관지폐이형성증에 비하여 출생 체중이 작고 부

당경량아의 비율이 높았으며 조기 양막 파수의 비율이 낮고, 5분 아프가 점수가 낮았다. 또한 type 2 중증 기관지폐이형성증에서 type 1 중증 기관지폐이형성증에 비해 공기 누출 증후군, 대량 폐출혈, 동맥관 결찰술 시행, 괴사성 장염, 후기 패혈증의 비율이 높았다. Type 2 중증 기관지폐이형성증 환자는 type 1 중증 기관지폐이형성증 환자에 비하여 신생아중환자실 퇴원 시까지 사망률이 18.64 배 (보정 오즈비 18.64, 95% 신뢰 구간 10.81-32.13) 높았고 폐동맥 고혈압은 2.16배 (보정 오즈비 2.16, 95% 신뢰 구간 1.59-2.93) 높았으며, 기관 절개는 10.38배 (보정 오즈비 10.38, 95% 신뢰 구간 2.05-52.49) 높았다.

결론

본 연구에서 type 2 중증 기관지폐이형성증 환자는 type 1 중증 기관지폐이형성증 환자에 비하여 사망률이 높고 임상적 부담이 유의하게 컸다. Type 2 중증 기관지폐이형성증 환자에 대하여 예상되는 합병증 및 예후를 고려하여 장기적이고 다각적인 관리 및 치료가 필요하겠다.

주요어: 조산아, 극소저출생체중아, 중증 기관지폐이형성증, 조산아 합병증

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