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RESEARCH ARTICLE

Predictors of Bronchopulmonary Dysplasia in Saudi Preterm Infants

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Abstract

Introduction: Bronchopulmonary dysplasia (BPD) is a major cause of morbidity and mortality among preterm infants.

Objective: To determine BPD prevalence and to identify factors that predict the development of BPD.

Patients and Methods: We performed a retrospective cohort study of all neonates admitted to the neonatal intensive care unit (NICU) between 2009 and 2019 with gestational age (GA) less than 32 weeks and birth weight (BW) less than 1500 g.

Results: A total of 637 preterm infants included in the study, of whom 194 (30.5%) infants developed BPD. Of the 194 preterm infants who developed BPD 89 (45.9 %) had mild, 59 (30.4%) had moderate and 46 (23.7%) had severe BPD. Multivariate analysis revealed that low GA (odds ratio [OR]: 0.62; 95% confidence interval [CI]: 0.43-0.98), low BW (OR: 20.6; 95% CI: 17.1-29.3), use of mechanical ventilation (OR: 1.07; 95% CI: 0.87-1.54), higher peak inspiratory pressure (PIP) (OR: 1.48; 95% CI: 1.44-1.91), higher fraction of inspired oxygen (FiO_2) use (OR: 0.11; 95% CI: 0.05-0.19), duration of mechanical ventilation (OR: 3.56; 95% CI: 4.28-3.75) and frequent blood transfusion (OR: 0.65; 95% CI: 0.53-0.87) were identified as the principal risk factors for BPD.

Conclusions: The prevalence of BPD among Saudi preterm infants was 30.5%. The most relevant predictors of BPD were GA, BW, mechanical ventilation, higher PIP, higher FiO_2 use, duration of mechanical ventilation and frequent blood transfusion.

Keywords: Bronchopulmonary dysplasia, predictors, preterm infants.

Introduction

Despite advances in perinatal care over the past decades, preterm infants remain at high risk for significant respiratory morbidities owing to the development of bronchopulmonary dysplasia (BPD) [1]. BPD is the most common chronic respiratory disease that results from complications related to the lung injury during the treatment of respiratory distress syndrome (RDS), or develops in older infants when abnormal lung growth occurs [2]. The incidence of BPD ranges from 4.6 % to 72 %. This broad range may be explained by heterogeneity of the studied populations, of management practices or of disease definition [3]. New therapies introduced during the past decade have reduced mortality of extreme preterm infants, but their influences in reducing the occurrence of BPD remains controversial [4]. The incidence of BPD has not changed over the past few decades, reflecting improved survival of extremely preterm infants who are at highest risk for BPD [5].

The etiology of BPD is multifactorial involving genetic predispositions in combination with prenatal and postnatal environmental influences [6]. Some of the most commonly known risk factors include lower birth weight (BW), younger gestational age (GA), male sex, fetal growth restriction, and prolonged ventilator-induced injury [7].

Because survivors with BPD have significant pulmonary and extrapulmonary morbidities, including cerebral palsy, and growth, developmental, and academic difficulties, it is imperative to optimize health care delivery systems. Identification of risk factors would possibly allow for direct therapies toward reducing the likelihood or the severity of BPD to improve long term outcomes [8-11].

There is little information about trends in the epidemiology and pathogenesis of BPD in developing countries [12]. This study was conducted to determine BPD prevalence and to identify factors that may predict the development of BPD in Saudi preterm infants in order to develop better practices in the management of these newborns in the future

Patients and Methods

Study design

A retrospective study was conducted by reviewing clinical data collected through medical records of preterm infants admitted to neonatal intensive care unit (NICU) of Abha Private Hospital, Abha, Saudi Arabia. All preterm infants with GA < 32 weeks and very low birth weight (VLBW, < 1500 g) during a 10-year period between July 2009 and June 2019 were included in the study. The exclusion criteria were diaphragmatic hernia, congenital pulmonary malformations, congenital infections, chromosomal syndromes, congenital malformations or other known explanation for prolonged need of oxygen. Furthermore, infants who died before reaching a post-conceptional age of 36 weeks were excluded.

Data collection

Antenatal data were obtained from maternal records. Relevant neonatal data were obtained from the infant's records in which gender, GA, BW, Apgar score, antenaral and postnatal corticosteroids administration, oxygen supplementation (O_2), nasal continuous positive airway pressure (CPAP), ventilator support, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), pulmonary hypertension (PHN), frequent blood transfusion ($\geq$ 3 times) and patient census included total admission, BPD occurrences and deaths were registered.

Definition of BPD

The definition and severity of BPD (non, mild, moderate, or severe) among survivors were based on The National Institute of Child Health and Human Development consensus definition and grading (2000) [13]. BPD was defined as follows: no BPD as not receiving O_2 for 28 days or at 36 weeks postconceptional age; mild BPD as receiving O_2 for greater than or equal to 28 days but not at 36 weeks postconceptional age; moderate BPD as receiving O_2 for greater than or equal to 28 days plus treatment with less than 30 % O_2 at 36 weeks postconceptional age; and

severe BPD as receiving O_2 for greater than or equal to 28 days plus treatment with greater than or equal to 30 % O_2 or positive pressure at 36 weeks postconceptional age. For infants transferred between 28 days and 36 weeks postconceptional age, we defined BPD using O_2 at the time of transfer.

Clinical practice

In 2007, we implemented less invasive practice in the delivery room and NICU, including the use of early nasal CPAP, avoiding excessive oxygen and ventilation targeting O_2 saturation between 88 % and 92 %. We began to use a selective intubation policy in the delivery room for infants at $\leq$ 29 weeks of gestation.

Statistical analysis

Quantitative data were presented as mean$\pm$ standard deviation (SD), while qualitative data were demonstrated as frequency and percent (%). The significance of comparison between mean values of two groups was evaluated by Student's *t*-test for continuous normally distributed variables. Categorical data were assessed by chi-square test. The significance of comparison between more than two groups was performed by analysis of variance for parametric continuous variables. To explore associations between studied variables and BPD, crude and adjusted odds ratio (OR) with 95 % confidence intervals (95 % CIs) were estimated in bivariate analysis, followed by multivariate regression analysis. Significant differences were denoted by $p < 0.05$. Statistical analysis was performed using the Statistical Software Package SPSS 19 (SPSS, Inc., Chicago, IL).

Results

During the study period, 723 preterm (< 32 weeks) with BW of (<1500 g) were admitted to the NICU. Eighty-six infants were excluded from the analysis (48 had congenital malformations, 25 died before 36 weeks postmenstrual age and 13 missing data). The rest of preterm infants (637) fulfilled the criteria for inclusion, of whom 194 (30.5%) infants developed BPD as shown in figure 1.

Tables 1,2 and 3 demonstrate the perinatal, neonatal demographic, clinical characteristics and respiratory management. GA, BW, and Apgar score at 1 minute were significantly lower in patients with BPD than in those without BPD. Regarding maternal infection, the incidence of chorioamnionitis was significantly higher in infants who developed BPD (p = 0.03). Among infants who developed BPD, 88.6 % had RDS, 76.3 % were on invasive mechanical ventilation and 42.3 % were on noninvasive ventilation CPAP. The mean days on mechanical ventilation and supplemental oxygen were 19.2 and 45.7 days, respectively which were significantly longer than the mean days in those supportive measures for neonates who had not developed BPD. The common complications of preterm birth were more frequent in the BPD group, who was also more premature and lower BW. From the associated co-morbidities, we looked for [sepsis, patent PDA, PHN, IVH, ROP and NEC, only IVH and frequent blood transfusion were significantly associated with BPD [p=0.03, OR = 2.1, CI = 1.06-3.95; p <0.001, OR= 0.44, CI =0.40-0.57, respectively].

Of the 194 preterm infants who developed BPD 89 (45.9 %) had mild, 59 (30.4%) had moderate and 46 (23.7%) had severe BPD. When GA was lower, the BW was lower, the duration of mechanical ventilation, oxygen therapy were longer and Maximum peak inspiratory pressure (PIP) was higher as the BPD severity increased (table 4).

The Univariate analysis indicated that low GA, low BW, presence of chorioamnionitis, low Apgar score at 1 minute, presence of pneumothorax, IVH, the use of mechanical ventilation with high level of PIP, longer duration of invasive mechanical ventilation, duration of oxygen therapy and blood transfusion were significantly associated with increased risk of BPD (table 5). Table 6 demonstrates the results of combined analysis of variables using multivariate logistic regression analysis. GA, BW, mechanical ventilation,

higher PIP, higher fraction of inspired oxygen (FiO_2) use, duration of mechanical ventilation and frequent blood transfusion were identified as the principal risk factors for BPD.

Discussion

Advances in perinatal care over the past decades have improved the survival of preterm infants. However, long-term morbidity is frequent and BPD is one of the most important chronic complications in these infants [5]. The BPD incidence observed in our study was 30.5% which is in accordance with that reported by Alshehri [12] and Mohamed et al [14] in the same region. However, the incidence of BPD was lower (17.7%) in infants admitted to NICU at lower altitude (Riyadh city, Saudi Arabia). These findings suggest that high altitude may increase the risk of BPD development among preterm infants Alshehri [12]

Our study confirmed a number of previously described neonatal risk factors for of BPD including GA, BW, and low one-minute Apgar score [15-17]. Our findings demonstrated that lower GA, lower BW were risk factors strongly related to the development of BPD. The incidence of BPD in preterm infants is inversely proportional to GA and BW. These data emphasize the fact that BPD continues to be a significant public health concern that is linked to the improved survival of extremely preterm neonates. Prematurity remains the primary determinant of an infant's risk of developing BPD [18,19]. The secular stage of development occurs from 23 to week 32 of gestation. At this stage, the premature lung has poorly developed airway supporting structures, there is surfactant deficiency, decreased compliance and inadequate fluid clearance. The lung appears to be most susceptible to damage if birth occurs during this stage of development. Growth restriction may have a significant effect on the vulnerability of lung injury [20].

Previously described risk factors for BPD not significant in our study included male gender, prolonged rupture of membranes and antenatal corticosteroids use [21]. However, our data

demonstrated that maternal chorioamnionitis was significantly associated increased odds of development of BPD. Chorioamnionitis has been postulated to play a role in the development of BPD by inflammatory processes and disturbance of lung maturation [22].

In contrast to other studies [23-25], we did not find relationship between co-morbidities as sepsis, PDA, PHN, ROP NEC and BPD. However, IVH and frequent blood transfusion were significantly associated with BPD in the present study. Infants with BPD were of lower GA and remained on ventilator support for a longer time, therefore requiring more blood sampling, causing iatrogenic anemia. The increase in circulatory blood volume could also increase pulmonary blood flow, and the increase in free iron load could lead to higher formation of toxic hydroxyl radical. This oxidative stress can trigger cellular and molecular changes that may lead to permanent changes in the lung, resulting in BPD [26].

In term of respiratory management of preterm infants, the present study demonstrated that the use of mechanical ventilation, higher PIP, longer duration of assisted ventilation, use of higher FiO_2, longer duration of oxygen therapy, less use of nasal CPAP and the less administration of caffeine were significantly associated with the development and severity of BPD. This is in agreement with previous publications [23-25]. Northway et al [27] in an initial description of BPD, speculated that the disease was mainly due to oxygen toxicity and barotraumas. The hypothesis of barotrauma in the pathogenesis of BPD is biological plausible due to the fact that the functional residual capacity of the lungs of preterm infants is small and PIP needed to inflate the surfactant-deficient lung may be five-fold greater than the physiologic inflation pressures of normal lung [28]. The use of high pressure to ventilate low compliance areas may produce stress and alveolar rupture in other non-compromised areas, pneumothorax, increased production of

pro-inflammatory mediators causing pulmonary damage that lead to the development of BPD [23]. Our study supports this hypothesis by the previous data. Early initiation of nasal CPAP has been shown to reduce the need for intubation and mechanical ventilation. Since the need for mechanical ventilation is one of the major risk factors for BPD, use of early CPAP should logically reduce its incidence [29]. Caffeine therapy is effective in reducing the number of apneic attacks and the use of mechanical ventilation therefore, reduces the rate of BPD [30].

In this study, multivariate logistic regression analysis demonstrated that, GA, BW, mechanical ventilation, higher PIP, higher FiO_2 use, duration of mechanical ventilation and frequent blood transfusion were associated with increased risk of BPD. A limitation of the present study is its retrospective design; therefore, further randomized clinical trials should be undertaken.

In conclusion, the prevalence of BPD in Saudi preterm infants was 30.5%. The most relevant predictors of BPD were GA, BW, mechanical ventilation, higher PIP, higher FiO_2 use, duration of mechanical ventilation and frequent blood transfusion. This study may provide useful information in the design of effective preventive perinatal strategies and /or interventions that will impact the outcome of extreme preterm survivors.

Conflict of interest No Conflict of interest

Author's contributions M A Carried out the study design, MA coordinated the implementation, MAR A helped to perform the statistical analysis, drafted the manuscript (All authors), RA, MAR A AND MA collected the data, MAR A performed the statistical analyses, revision of the manuscript (All authors), read and approved the final manuscript (All authors).

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Table 1. Perinatal characteristics of preterm infants with or without bronchopulmonary dysplasia (BPD)

Variables **Perinatal characteristics**	**BPD** **(n=194)**	**No BPD** **(n=443)**	***P* value**
GA (wk)[a]	28.2 ± 0.8	29.1 ± 1.7	0.001**
BW (g)[a]	1012 ± 93	1052 ± 104	0.001**
Male gender[b]	102 (52.6)	228 (51.5)	0.78
Maternal age (y)[a]	26.2 ± 2.4	26.0 ± 3.6	0.47
Twin or multiple births[b]	9 (4.6)	21 (4.7)	0.90
Antenatal steroids[b]	154 (79.4)	366 (82.6)	0.66
PROM[b]	30 (15.5)	74 (16.7)	0.69
Chorioamnionitis[b]	26 (13.4)	35 (7.9)	0.03
Caesarian section[b]	52 (26.8)	112 (25.3)	0.69
Apgar score at 1 min[a]	4.7 ± 0.6	4.9 ± 0.8	0.001**
Apgar score at 5 min[a]	6.5 ± 0.7	6.6 ± 0.9	0.17

[a]*Values are mean±SD*
[b]*Number (percent)*
GA; gestational age, BW; birth weight, PROM; prolonged rupture of membranes >18 hr
**Highly significant*

Table 2. Neonatal diseases and co-morbidities in accordance to the presence of BPD

Variables	BPD (n=194)	No BPD (n=443)	*P* value
RDS[a]	172 (88.6)	388 (87.6)	0.72
Pneumothorax[a]	20 (10.3)	24 (5.4)	0.03*
Pneumonia[a]	31 (15.9)	73 (16.5)	0.87
Sepsis[a]	58 (29.9)	138 (31.2)	0.70
PDA[a]	17 (8.8)	22 (4.9)	0.06
PHN[a]	16 (8.2)	20 (4.5)	0.06
IVH[a]	18 (9.3)	21 (4.7)	0.03*
ROP[a]	9 (4.6)	14 (3.2)	0.38
NEC[a]	24 (12.4)	39 (8.8)	0.16
Frequent blood transfusion[b]	3.2 ± 1.1	2.8 ± 0.9	0.000**
Duration of hospitalization[b]	64.3 ± 3.1	46.1 ± 3.8	0.001**
Mortaltity[a]	7 (3.6)	11 (2.5)	0.35

[a]*Number (percent)*
[b]*Values are mean±SD*
Respiratory distress syndrome; RDS, PDA; patent ductus areriosus, PHN; pulmonary hypertension, IVH; intraventricular hemorrhage, ROP; retinopathy of prematurity, NEC; necrotizing enterocolitis
**Significant, ***Highly significan*

Table 3. Respiratory management characteristics of the study population

Variables	BPD (n=194)	No BPD (n=443)	*P* value
Surfactant therapy[a]	158 (81.4)	357 (80.6)	0.81
CPAP[a]	82 (42.3)	227 (51.2)	0.04*
Duration of CPAP (d)[b]	5.2 ± 0.8	5.4 ± 1.5	0.08
Mechanical ventilation[a]	148 (76.3)	291 (65.7)	0.008**
Maximum PIP[b]	22.7 ± 1.6	20.1 ± 0.9	0.001**
Duration of mechanical ventilation (d)[b]	19.2 ± 0.9	13.2 ± 1.1	0.001**
Duration of oxygen therapy (d)[b]	45.7 ± 9.2	19.8 ± 1.3	0.001**
Maximum FiO_2[a]**:**			
< 0.60	13 (6.7)	139 (31.4)	
≥0.60	181 (93.3)	304 (68.6)	0.0001**
Caffeine[a]	89 (45.9)	244 (55.1)	0.03*

[a]*Number (percent)*
[b]*Values are mean±SD*
CPAP; continuous positive airway pressure, PIP; peak inspiratory pressure, FiO_2; fraction of inspired oxygen
**Significant, ***Highly significant*

Table 4. Demographic and clinical characteristics of preterm survivors according to the severity of BPD

Characteristics	Mild BPD (n=89)	Moderate BPD (n=56)	Severe BPD (n=42)	*P* 1	*P* 2	*P* 3
GA (wk)[a]	28.0 ± 0.1	27.9 ± 1.9	27.4 ± 0.6	0.001**	0.001**	0.001**
BW (g)[a]	954 ± 112	917 ± 125	901 ± 107	0.06	0.50	0.01
Maximum PIP[a]	21.8 ± 1.1	22.1 ± 0.9	22.7 ± 0.7	0.08	0.001**	0.001**
Duration of MV(d)[a]	18.2 ± 0.7	19.1 ± 0.9	19.5 ± 0.6	0.001**	0.01*	0.001**
Duration of oxygen therapy (d)[a]	44.8 ± 5.2	45.1 ± 6.1	45.3 ± 4.9	0.75	0.86	0.60

[a]*Values are mean±SD*
GA; gestational age, BW; birth weight, PIP; peak inspiratory pressure
p 1: between mild and moderate, p 2: between moderate and severe, p 3: between mild and Severe.
**Significant, **Highly significant*

Table 5. Univariate analysis: variables significantly associated with bronchopulmonary dysplasia

Variables	OR (95% CI)	*P* value
GA	0.81 (0.64-1.15)	0.01*
BW	31.9 (22.9-57.0)	0.01*
Chorioamnionitis	1.8 (1.05-3.09)	0.03*
Apgar score at 1 min	0.31 (0.07-0.32)	0.001**
Pneumothorax	2.0 (1.08-3.72)	0.03*
IVH	2.1 (1.06-3.95)	0.03*
CPAP	0.69 (0.49-0.97)	0.04*
Mechanical ventilation	1.68 (1.14-2.46)	0.01*
Maximum PIP	2.3 (2.79-2.4)	0.01*
Duration of mechanical ventilation (d)	5.3 (6.17-5.82)	0.001**
Duration of oxygen therapy (d)	30.5 (35.3-33.4)	0.001**
Maximum FiO_2		
≥0.60	0.15 (0.08-0.28)	0.001**
Caffeine		
Frequent blood transfusion	0.69 (0.49-0.97)	0.03*
	0.44 (0.40-0.57)	0.001**

GA; gestational age, BW; birth weight, IVH; intraventricular hemorrhage, CPAP; continuous positive airway pressure, PIP; peak inspiratory pressure, FiO_2; fraction of inspired oxygen
**Significant, **Highly significant*

Table 6. Multivariate (logistic) regression analysis for predictors of bronchopulmonary dysplasia

Variables	OR (95% CI)	*P* value
GA	0.62 (0.43-0.98)	0.01*
BW	20.6 (17.1-29.3)	0.04*
Mechanical ventilation	1.07 (0.87-1.54)	0.02*
Maximum PIP	1.48 (1.44-1.91)	0.01*
Duration of mechanical ventilation (d)	3.56 (4.28-3.75)	0.001**
Maximum FiO_2		
≥0.60	0.11 (0.05-0.19)	0.001**
Frequent blood transfusion	0.64 (0.53-0.87)	0.01*

GA; gestational age, BW; birth weight, PIP; peak inspiratory pressure, FiO_2; fraction of inspired oxygen

**Significant, **Highly significant*

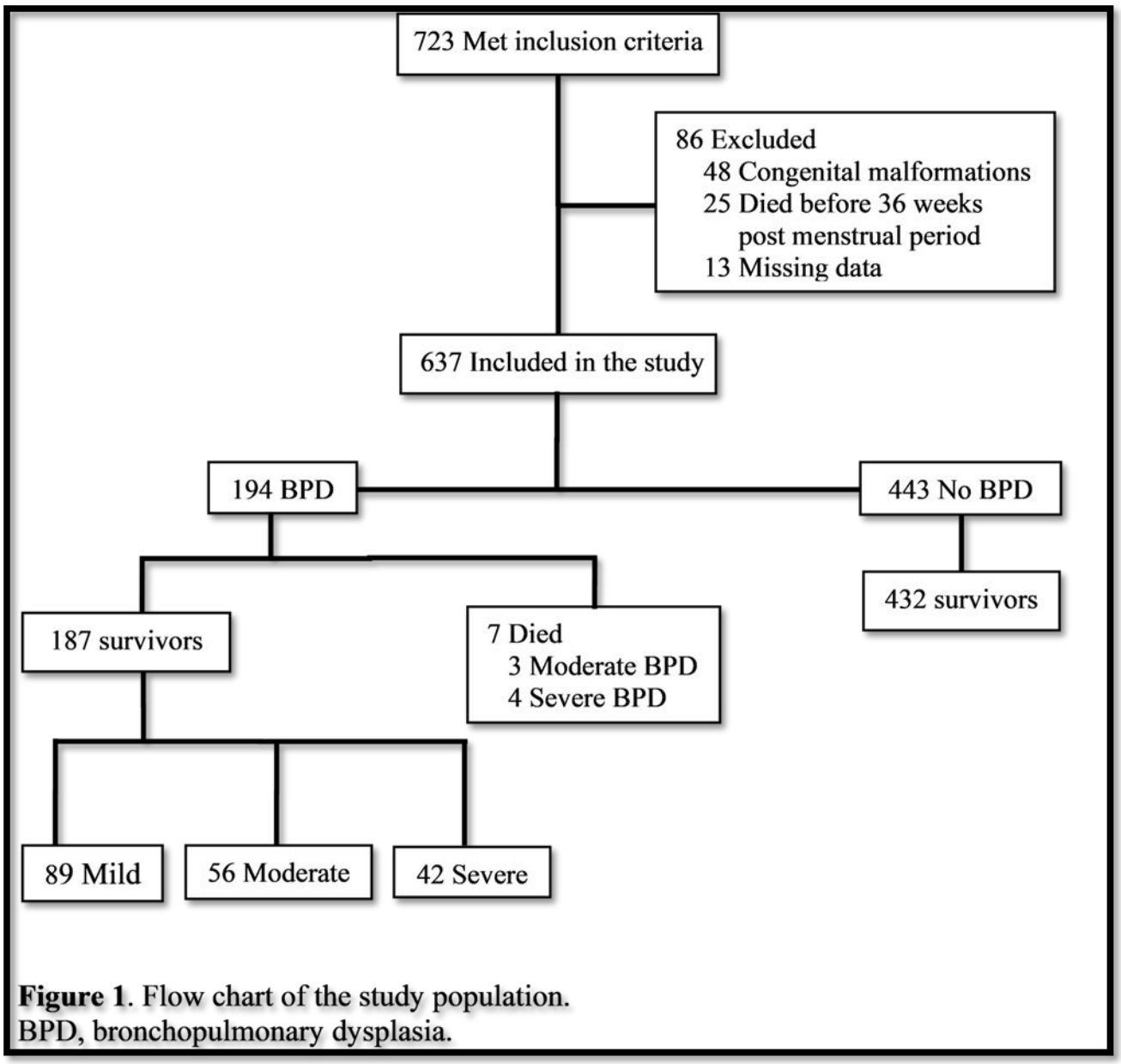

Figure 1 Flow chart of the study population. BPD, bronchopulmonary dysplasia

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