

Bronchopulmonary Dysplasia Frequency and Risk Factors in Very Low Birth Weight Infants: A 3-Year Retrospective Study

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ABSTRACT

OBJECTIVE: In this study the relationship between the frequency of bronchopulmonary dysplasia and perinatal risk factors and other prematurity comorbidities was evaluated in very low birth weight infants.

METHODS: A total of 872 very low birth weight infants files were retrospectively reviewed. The effects of the clinical parameters such as type of birth, small for gestational age, gender, antenatal steroids, early membrane rupture, chorioamnionitis, surfactant administration, respiratory distress syndrome, patent ductus arteriosus, apnea, early and late sepsis on the frequency of bronchopulmonary dysplasia were evaluated by binary logistic regression analysis

RESULTS: The overall mortality rate was 20.9%. After the first 28-day mortality reduction, the total bronchopulmonary dysplasia frequency was found to be 20.1%. The odds ratio and 95% confidence intervals of the factors affecting the development of bronchopulmonary dysplasia were found to be as follows respectively; respiratory distress syndrome (OR 6.2, 95%CI 3.6-10.6, $p < 0.01$), patent ductus arteriosus (OR 4.9, %95CI 2.4-9.9, $p < 0.01$), apnea (OR 4.1, %95CI 2.5-6.9, $p < 0.01$), late sepsis (OR 2.7, 95%CI 1.6-4.5, $p < 0.01$), early membrane rupture (OR 2.6, 95%CI 1.2-5.5, $p < 0.01$), and male gender (OR 1.6, 95%CI 1.0-2.7, $p < 0.04$) was found. However, there was no effect of chorioamnionitis, antenatal steroids, small for gestational age, early sepsis and type of birth on bronchopulmonary dysplasia.

CONCLUSION: Differently from the usual factors which are low birth weight and gestational week there was a significant but non-linear risk relationship between respiratory distress syndrome, patent ductus arteriosus, late sepsis, apnea, early membrane rupture, male gender and bronchopulmonary dysplasia.

Keywords: Bronchopulmonary dysplasia; premature infant.

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Bronchopulmonary dysplasia (BPD) is a chronic lung disease requiring long-term oxygen support with $\geq 21\%$ concentration with a variety of modalities in premature infants. Until the 2000's diagnosis was made based on whether oxygen requirements continued up to the postnatal 28th day. However, after this date, diagnosis began to be made based on the severity of the disease as mild, moderate and severe according to gestational week (GW) [1, 2]. Low birth weight (WB) and GW are usual risk factors for BPD and there is an inverse linear relationship between them. Perinatal risk factors

like cesarean section, male gender, antenatal corticosteroids, EMR, chorioamnionitis, SGA, postnatal surfactant, RDS, early and late onset sepsis, PDA and apnea are reported to be associated with BPD [3]. According to centers, the incidence of BPD in < 32 GW premature infants was reported to be 30% in United States, 12% in Canada and 14% in Japan [4, 5]. In this study the relationship of BPD frequency, perinatal risk factors and other prematurity comorbidities was assessed for very low birth weight (VLBW) infants.

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MATERIALS AND METHODS

Medical files of 872 VLBW infants between January 1, 2006 and December 31, 2008 were retrospectively reviewed. Ethical approval was granted by the hospital's ethics committee (Date: 29/04/2009 and decision number: 220) was obtained before infants were enrolled in the study. Infants with multiple system anomalies or chromosomal anomalies were excluded from the study. Mortality rates for the first 28 days were determined according to BW and GW. Regardless of GW, diagnosed with BPD if there is an infant with continuing $\geq 21\%$ concentration oxygen support for postnatal 28 days or longer. After removing the first 28 day mortalities, the remainder were separated into 2 groups as BPD (+) and (-). All babies had BW, GW, type of birth (vaginal or cesarean), whether they had small for gestational age (SGA), gender, antenatal corticosteroids, early membrane rupture (EMR), chorioamnionitis, postnatal surfactant administration, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), apnea, early and late onset sepsis, periventricular leukomalacia (PVL) and total hospitalization recorded.

Statistical Analysis

Statistical analyses were performed on SPSS (SPSS Inc. Chicago, IL, USA) version 15 for Windows software. Comparisons between the groups used the Pearson chi-square test and independent groups t test or Mann Whitney U test based on type and distribution of variables. The effects of independent variables on BPD were calculated with the binary logistic regression (backward conditional model) analysis after removing those mortality within the first 28 days. For validity of the regression model, the Hosmer-Lemeshow test $p > 0.05$ condition was ensured. To determine risk levels, the odds ratios (OR) and the 95% confidence interval (CI) were used. For all calculations, $p < 0.05$ was accepted as significant.

RESULTS

The mortality rates according to BW and GW are presented in **Figure 1**. According to this figure, total mortality was 20.9% (182/872) and it appeared mortality increased in inverse linear ratio to the BW and GW. After removing mortalities in the first 28 days, total BPD incidence was 20.1% (139/690) and, similar to mortality, the incidence of BPD increased in inverse linear ratio to the BW and GW (**Fig. 2**).

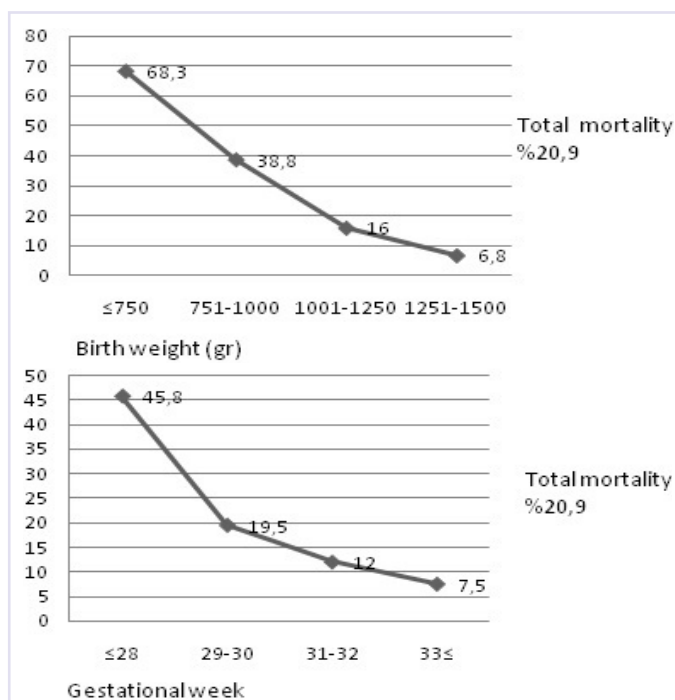


FIGURE 1. Mortality rates according to birth weight (a) and gestational week (b).

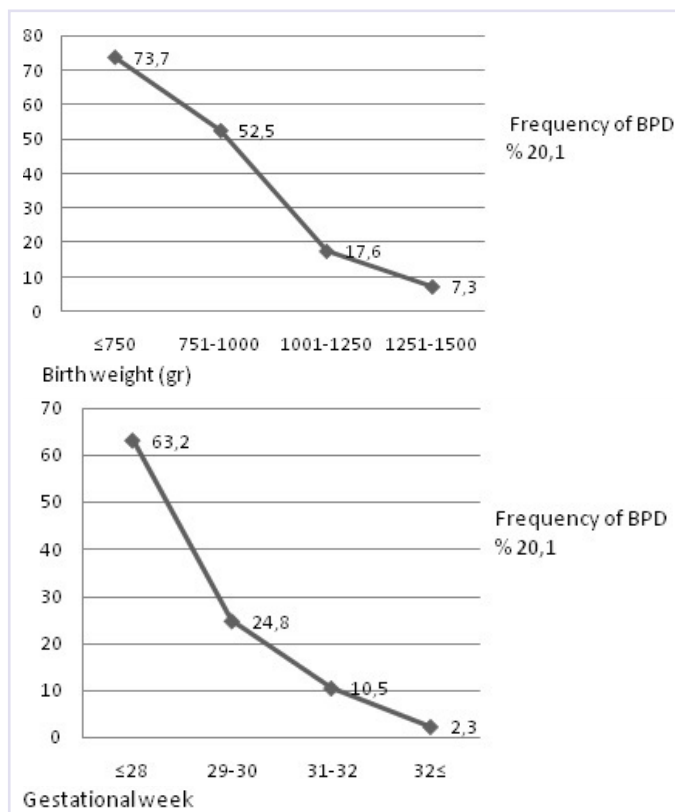


FIGURE 2. Frequency of bronchopulmonary dysplasia (BPD) according to birth weight (a) and gestational weeks (b).

The mean BW and GW were found to be significantly different between the BPD (+) and (-) groups. Cesarean section, male gender, antenatal corticosteroids, chorioamnionitis, postnatal surfactant administration, RDS, PDA, apnea and late onset sepsis were significantly high in the BPD (+) group except EMR, SGA and early onset sepsis. The significant prematurity comorbidities like PVL and total hospitalization were elevated significantly in the BPD (+) group ($p < 0.01$, Table 1).

TABLE 1. Comparison of perinatal risk factors and comorbidities between BPD (+) and (-) groups

	BPD (+) (n=139)	BPD (-) (n=551)	p
Birth weight (gr)	1014±217	1262±177	<0.01‡
Gestational week	28.3±2.3	31.8±2.2	<0.01‡
Caesarean section	66.2% (n=92)	78.2% (n=430)	0.03*
SGA	14.4% (n=20)	18.7% (n=103)	0.23*
Male gender	59.0% (n=82)	40.3% (n=222)	<0.01*
Antenatal corticosteroid	14.4% (n=20)	3.3% (n=18)	<0.01*
EMR	18.0% (n=25)	12.0% (n=66)	0.06*
Chorioamnionitis	5.8% (n=8)	0.9% (n=5)	0.01*
Postnatal surfactant	68.3% (n=95)	15.8% (n=87)	<0.01*
RDS	77.7% (n=108)	22.4% (n=123)	<0.01*
PDA	29.4% (n=41)	4.6% (n=25)	<0.01*
Apnea	69.8% (n=97)	18.7% (n=103)	0.01*
Early onset sepsis	10.8% (n=15)	11.0% (n=61)	0.92
Late onset sepsis	64.0% (n=87)	17.8% (n=98)	<0.01*
PVL	9.4% (n=13)	1.6% (n=9)	<0.01*
Total hospitalization (days)	64.4±22.2	26.7±16.5	<0.01μ

BPD: bronchopulmonary dysplasia; SGA: small for gestational age; EMR: early membrane rupture; RDS: respiratory distress syndrome; PDA: patent ductus arteriosus; PVL: periventricular leukomalacia; *Pearson Chi-square test; †independent t test; μ Mann Whitney U test.

The effect of categorical independent variables of type of birth (cesarean section), SGA, male gender, antenatal corticosteroids, EMR, chorioamnionitis, postnatal surfactant administration, RDS, PDA, apnea and early and late onset sepsis on BPD incidence was assessed with binary logistic regression analysis (Table 2). Due to the very close correlation of postnatal surfactant and RDS frequencies, calculations only included RDS in the model as a variable. RDS, PDA, apnea, late onset sepsis, EMR and male gender were observed to be risk factors increasing the development of BPD. Contrary to this, chorioamnionitis and administration or not of antenatal corticosteroid were understood not to form a risk for BPD. In this analysis, SGA did not have significant contribution in the second step, early onset sepsis in the third step and type of birth in the fourth step so they were removed from the calculations of the regression model.

DISCUSSION

Bronchopulmonary dysplasia incidence is reported in the United States of America as 52% for 501-750 g BW, 34% for 751-1000 g, 15% for 1001-1250 g and 7% for 1251-1500 g [6]. In Switzerland, it was found to be 16.7% for infants <1500 g in 1996 and 13.2% in 2000 [7]. It is reported as 18% in Denmark, 15% in France, 40% of <26 GW premature infants and 29% for <32 GW premature infants in Germany [8-10]. In our study the incidence of BPD was 73.7% for ≤750 g infants, 52.5% for 751-1000 g infants, 17.6% for 1001-1250 g infants and 7.3%

TABLE 2. The possible effects of perinatal risk factors on BPD development

Risk factors	OR	%95 CI	p
RDS	6.2	3.6-10.6	<0.01
PDA	4.9	2.4-9.9	<0.01
Apnea	4.1	2.5-6.9	<0.01
Late onset sepsis	2.7	1.6-4.5	<0.01
EMR	2.6	1.2-5.5	0.01
Male gender	1.6	1.0-2.7	0.04
Chorioamnionitis	3.7	0.8-16.1	0.07
Antenatal corticosteroid	0.42	0.1-1.0	0.05

BPD: bronchopulmonary dysplasia; OR:Odds ratio; CI:confidence interval; RDS:respiratory distress syndrome; PDA: patent ductus arteriosus; EMR: early membrane rupture.

for 1251-1500 g infants with total incidence of 20.1%. According to GW, BPD was present in 63.2% of ≤ 28 GW infants, 24.8% of 29-30 GW infants, 10.5% of 31-32 GW infants and 2.3% of $33 \leq$ GW infants (Fig. 2).

In calculations with postnatal surfactant included in the regression model as a risk factor, the preventive effect on BPD was significant; however, the power was low (OR 0.42, 95% CI 0.20-0.91, p 0.029). Due to the close correlation between postnatal surfactant and RDS, postnatal surfactant not included in the model. RDS was determined to be the strongest risk factor for BPD in regression model (OR 6.2, 95% CI 3.6-10.6, $p < 0.01$, Table 2). In the process of developing BPD, the majority of infants initially experience RDS and many have postnatal surfactant administered. As a result, a secondary triggering factor for BPD after prematurity may be said to be RDS [11].

When we examine PDA, this study revealed it was the second effective risk factor for BPD (OR 4.9, 95% CI 2.4-9.9, $p < 0.01$, Table 2). However, in the current literature there is controversy as to whether it is a risk factor for BPD or not. The results of prophylactic PDA closure studies with surgery or medication like indomethacin have shown no effect on BPD and mortality outcomes [12-14]. However, the volutrauma effect of PDA on premature lungs cannot be ignored and it is clear this mechanical trauma increases the severity of RDS and as a result may cause BPD [15].

There is strong evidence that sepsis and systemic inflammation disrupts the vascular permeability of the lungs causing structural injury and long-term alveolarization disorder [16, 17]. As a result, sepsis alone is accepted as an independent risk factor for BPD [18]. A study by Lahra et al. (2009) reported the development of postnatal sepsis increased the incidence of BPD and emphasized postnatal inflammation rather than antenatal [19]. A study by Eriksson et al. (2014) partly supports this by showing that inflammatory diseases before pregnancy do not affect the incidence of BPD [20]. Studies related to early onset sepsis reported BPD and other premature comorbidities significantly increased [21, 22]. In our study, there was no risk correlation identified between early onset sepsis and BPD; however, a significant correlation was shown for late onset sepsis (OR 2.7, 95% CI 1.6-4.5, $p < 0.01$, Table 2).

Intermittent hypoxic episodes and a variety of forms of apnea are commonly observed in preterms and excess free radicals occur during these attacks especially

in the lungs [23]. Weakness of central and peripheral chemosensitive respiratory control mechanisms or airway and pulmonary compliance disorders may cause hypoxic attacks in BPD [24]. As a result, apnea may be both a cause and a result of BPD. In our study, a link between apnea and BPD was identified and it was understood to be an effective risk factor (OR 4.1, 95% CI 2.5-6.9, $p < 0.01$, Table 2).

Early membrane rupture is responsible for nearly 1/3 of preterm births and the etiology is multifactorial [25]. EMR begins with local inflammation and ascendant bacterial colonization due to stretching of the membranes in the early period [26]. The possible fetal effects of EMR are not clearly understood because mild perinatal inflammation is reported to have possible positive effects on fetal immune system maturation [27]. Comprehensive research published by the German Neonatal Group in 2015 revealed that EMR was only a risk factor for BPD in the chronic period (OR 1.25, 95% CI 1.02-1.55, p 0.03) [28]. In our study, this risk level was found to be higher (OR 2.6, 95% CI 1.2-5.5, p 0.01, Table 2).

Some studies have reported cesarean birth increases the risk of BPD [29, 30]. In this study, the cesarean birth rate was identified to be high in the BPD (+) group; however, no risk correlation was identified with regression analysis ($p > 0.05$). Here the noteworthy situation is that the cesarean birth rate for preterm infants has increased through the years independently of BPD. BPD tends to occur with the male gender and it is reported to be observed 2-5 times more frequently in male infants [31, 32]. In our study, this possible risk was identified at low levels (OR 1.6, 95% CI 1.0-2.7, p 0.04, Table 2).

Though postnatal infections like pneumonia and sepsis are accepted as risk factors for development of BPD, the situation for prenatal infections like chorioamnionitis is not clear [33]. Chronic fetal inflammation linked to chorioamnionitis may affect the pulmonary development of the infant in very bad or good ways [34]. Some studies published recently have shown EMR and chorioamnionitis as the most common causes of preterm births, but emphasize that chorioamnionitis does not increase the BPD risk for VLBW infants [35, 36]. In this study, chorioamnionitis was not determined to be a risk factor for BPD (p 0.07, Table 2).

Antenatal corticosteroids reduce the severity of RDS and as a result reduce the incidence of BPD [37]. However, different studies have shown, contrarily, that administration does not affect BPD incidence [38-40]. In

developed countries, antenatal corticosteroids administration is reported at levels of 60-70% [6, 29, 41]. In our study, antenatal corticosteroids were administered to 14.4% in the BPD (+) group and 3.3% in the BPD (-) group ($p < 0.01$, Table 1). Although very different rates of administration have been found among the groups, antenatal steroid administration is not a significant risk factor for BPD ($p > 0.05$).

In SGA infants, pulmonary maturation occurs earlier due to chronic stress exposure and linked to this effect the incidence and severity of RDS reduces [42]. Some studies have reported the protective effect of SGA in premature infants later than 32 GW reduces the incidence of RDS, while it does not change or possibly increases the incidence of RDS for those below 32 GW [43-47]. Many studies have revealed that BPD and late-period pulmonary complications are observed more often in SGA preterm [48, 49]. In our study, the SGA preterm rate was 14.4% in the BPD (+) group and 18.7% in the BPD (-) group; however, there was no significant difference between the groups ($p = 0.23$, Table 1). The regression model revealed that SGA was not a possible risk factor for BPD ($p > 0.05$). This situation may be explained by embryological development stages of the fetal lungs and postmortem pathologic findings. Postmortem investigations have reported that though BPD infants have acinar development and alveolar stage completion in fetal lungs the saccular development stage is stopped [50]. In our study, the majority of BPD infants were preterm below 32 GW and according to Figure 2, the incidence of BPD rapidly reduces above 32 GW. According to our findings, SGA is understood not to be a possible risk factor affecting BPD.

RDS in BPD (+) and (-) groups in very different frequencies of this study (Table 1), rather than birth weight, based on the opinion of gestation week brings the idea of design. The concept of VLBW in the literature has some problems in evaluating fetal lung development. Because as the birth weight increases to 1500 grams, gestation week approaches 32 weeks and this period is critical for fetal lung maturation and BPD decreases rapidly after this period. Also, the fact that there is no risk relation between SGA and BPD partially supports this observation.

The new BPD defined in recent years, is characterized by dysmorphic vascularization with fewer and larger alveolar structure due to abnormal postnatal lung development in very preterm and ELBW infants. Factors associated with mechanical ventilation such as oxygen toxicity, barotrauma, and volutrauma are known to play

a role in the etiology of BPD [51]. Therefore, lung protective mechanical ventilation strategies have been developed in recent years to reduce the incidence of BPD.

In our study, having oxygen supplementation in postnatal 28th day and over was used for the diagnostic criterion of BPD regardless of GW. Since postnatal 36th-week oxygen support levels were not known, the classification of according new BPD criteria could not be classified. Also, the use of conventional mechanical ventilation methods during the study period made it difficult to evaluate the effects of invasive oxygen treatment modalities on BPD. These two conditions are important limitations of this study and obstructed the subgroup classification and analysis of related risk factors of new BPD.

Another limitation is that the study findings are not supported by laboratory findings such as inflammatory markers (CRP, procalcitonin, IL-1 and 6) or free radical levels. These laboratory findings may provide insight into the mechanism of inflammatory factors like sepsis, EMR and chorioamnionitis in the pathophysiology of BPD.

In this study the low antenatal corticosteroid administration rate (5.9% of VLBW infants) may be explained by pregnant women monitored at external centers being rapidly sent to our center, which is the largest and most well-known maternity hospital in the region, due to early labor. This situation usually causes the accumulation of a special group instead of a random group in terms of statistics. However, in spite of this asymmetric case accumulation, regression analysis showed antenatal corticosteroids administration or lack of administration had no effect on BPD ($p > 0.05$, Table 2). As a result, in developing countries such as ours, the low antenatal steroid administration rate is an expected situation. In spite of the low antenatal corticosteroids administration rate, it is noteworthy that the incidence of BPD in developing countries is close to that of developed countries.

To conclude RDS, PDA, apnea, late onset sepsis, EMR, and male gender was associated with the risk of BPD in preterm infants. There was no relationship between BPD and chorioamnionitis, antenatal corticosteroids, cesarean birth, early onset sepsis, and SGA. Further large studies are needed to understand the real effects of these factors that cannot be related to BPD.

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