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Original article

Frequency and risk factors of bronchopulmonary dysplasia in low-birth-weight infants in Saudi Arabia: a 5-year experience

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Abstract

Background: Due to improved survival of extremely low-birth-weight (ELBW) infants, the frequency of bronchopulmonary dysplasia (BPD) has remained unchanged or even increased.

Objective: To study the frequency as well as the perinatal and neonatal risk factors of moderate-to-severe BPD and its related mortality in low-birth-weight (LBW) infants in a single-center study over 5 years in the Kingdom of Saudi Arabia (KSA).

Methods: A total of 461 LBW infants' files with gestational age (GA) ≤ 32 weeks that met the inclusion criteria were retrospectively reviewed. Maternal and neonatal characteristics were evaluated. Furthermore, the hospital course of management of LBW infants and outcomes of mortality and morbidity were recorded.

Results: The overall mortality rate in LBW and ELBW infants was 19.52% and 38.62%, respectively. At 36 weeks' corrected GA, the total BPD frequency in LBW and ELBW infants was 9.87% and 32%, respectively. BPD(+) cases had a lower mean GA and birth weight than BPD(-) cases, 26 ± 2.68 weeks, 830 ± 340 grams and 29 ± 2.56 weeks, 1,395 ± 470 grams, respectively ($p < 0.0001$). The BPD(+) group had a significantly higher maternal chorioamnionitis infection rate, 8/39 (20.51%), than the BPD(-) group, 25/356 (7.02%) ($p = 0.004$), higher late-onset sepsis (11 [28.21%] and 54 [15.17%], $p = 0.04$). BPD(+) cases had a significantly higher risk

of intubation in the delivery room, more frequently more than one dose of pulmonary surfactant, more invasive ventilation on day 1 and day 7, more days on oxygen therapy, more days on invasive and non-invasive ventilatory support, more days of hospitalization (115.41 ± 92.14 days compared to 43.72 ± 27.98 days in BPD[-]; all $p < 0.0001$).

Conclusion: ELBW infants had a 2-fold higher rate of mortality and a 3-fold higher rate of BPD, compared with LBW infants. The frequency of BPD increased with low GA/birth weight and BPD(+) cases had a higher risk for intubation in the delivery room, received more frequently more than one dose of pulmonary surfactant, remained for more days on either invasive or non-invasive ventilatory support, and had longer hospital stays.

Keywords

Bronchopulmonary dysplasia, risk factors, low birth weight, extremely preterm, frequency.

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Introduction

Low birth weight (LBW) is defined as any baby delivered with a birth weight less than 2,500 grams. The incidence of LBW is estimated from 7% to 20% of total births annually [1]. LBW is considered a major health problem, especially in low- and middle-income countries [2]. LBW imposes a significant burden on the health care system, with increased mortality and disability in neonates and infants when compared to average-birth-weight infants [3]. A higher risk of death and early- and late-onset morbidity has been linked to preterm birth [4]. Complications are more common with lower gestational age (GA), especially in extremely low-birth-weight (ELBW) infants (weight < 1,000 grams) [5].

Perinatal and neonatal intensive care has improved markedly, leading to increased survival of premature infants; a parallel increase in the incidence of bronchopulmonary dysplasia (BPD) has occurred [6]. Over the last few decades, the frequency of BPD has been about 40-45% among surviving ELBW infants in the United States [7].

BPD was initially defined by Northway and colleagues in 1967 as fibrosis, scarring, and hyperinflation of the lungs as a result of pulmonary injury after mechanical ventilation (MV) and oxygen toxicity in infants who were late preterm and had a history of respiratory distress syndrome (RDS) [8]. This "old" BPD has evolved into a "new" BPD as a result of advancements in neonatal medical care, as reported by Jobe and Bancalari in 2001 [9]. The "new" BPD, which primarily affects extremely preterm infants, is characterized by an arrest in lung growth that results in alveolar simplification and pulmonary vascular dysgenesis [10].

Among the critical contributing factors to the pathogenesis of BPD caused by invasive MV exposure there are: volutrauma, which refers to lung injury caused by exposure to high tidal volume with which results in alveolar and airway overdistension and overinflation [11]; barotrauma, which refers to the lung injury caused by overstretching of the airways and alveoli from high peak inspiratory pressure (PIP) [12]; atelectrauma, which refers to repeated alveolar collapse and expansion, resulting from ventilation at low positive end-expiratory pressure (PEEP) [13]; hyperoxia, which refers to lung injury from excessive oxygen exposure [14]; biotrauma, which results from the release of inflammatory mediators (cytokines and chemokines) [15]; plus other factors as prematurity, nutrition and intestinal dysbiosis [16].

BPD imposes a major neonatal healthcare burden, with short- and long-term morbidity and higher mortality, including the need for prolonged hospitalizations, a rise in pulmonary pressure, childhood wheezing, and asthma, as well as neurodevelopmental sequelae [17, 18].

Although there are many definitions and classifications of BPD [19], to allow comparability with other studies, we decided to use the most widely used National Institutes of Health (NIH) consensus definition, which proposed a categorical definition of BPD in 2001 [9, 20] as the following: moderate BPD if receiving supplemental O_2 for 28 days and requiring < 30% oxygen at 36 weeks' GA, and severe BPD if receiving supplemental O_2 for 28 days and requiring ≥ 30% oxygen and/or needing positive pressure support at 36 weeks' GA. Patients were classified to suffer

from mild BPD with oxygen dependency for at least 28 days of life but not fulfilling any BPD criterion at 36 weeks' GA. Mild BPD cases were grouped with infants that did not have BPD in this study.

Prematurity and low birth weight are among the highest BPD risk factors. Other perinatal and neonatal risk factors, including gender, chorioamnionitis, race, smoking, and genetic risk factors, are still being studied. Therefore, the aim of this retrospective study was to evaluate the frequency, risk factors, and outcome of moderate-severe BPD and its related mortality in LBW infants in a single-center study over 5 years in the Kingdom of Saudi Arabia (KSA).

Methods

The study was conducted at Maternal Child Hospital, Al-kharj, KSA, the largest tertiary perinatal referral center level 3 Neonatal Intensive Care Unit (NICU) in the south of Riyadh. The study period was from January 2018 to December 2022. The study included LBW infants born weighing < 2,500 g with GA ≤ 32 weeks. Infants with intrauterine growth retardation (IUGR), GA > 32 weeks, major congenital malformations, or preterm delivery < 23 weeks, and those receiving palliative care were excluded from the study.

Demographic data and neonatal outcomes

Relevant retrospective data were obtained from the electronic files of mothers and neonates. Maternal data such as maternal age, nationality, usage of antenatal steroids, premature membrane rupture, chorioamnionitis, pregnancy-induced hypertension, and mode of delivery were collected. Neonatal data included birth weight, GA, neonatal resuscitation in the delivery room, surfactant therapy, the mode/duration of ventilatory support, and oxygen requirements. The primary neonatal outcome was BPD(+) or BPD(-) at 36 weeks' corrected GA. The secondary outcome including other major neonatal morbidities as retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) were recorded. The date of the last menstrual period or an early ultrasound scan was used to determine the GA assessment. The hospital follows a structured resuscitation policy where the limit of viability is set at 23 weeks' gestation.

The definitions for complete antenatal steroid course, chorioamnionitis, RDS, hemodynamically significant patent ductus arteriosus (HsPDA), NEC, and early/late-onset sepsis were standardized as per the Neonatal Research Network (NRN) [21]. Ventilatory support mode needed on days 1 and 7 were recorded along with oxygen (O_2) requirements needed to maintain SpO_2 levels between 88% and 95% [22]. We used standard respiratory management including early nCPAP, non-invasive surfactant therapy, prophylactic caffeine for neonates ≤ 29 weeks with early extubation to non-invasive respiratory support. DART protocol always started if neonates still on MV more than 14 days.

In this study BPD classification was further stratified into two groups: BPD(-) were defined as infants with no/mild BPD and BPD(+) infants as those with moderate/severe BPD.

The study protocol was approved by the Committee of the Institutional Review Board (IRB), King Saud Medical City, KSA (number: H1RE-04-Jun23-0).

Statistical analysis

Data were analyzed using STATA® version 17.0 (Stata Statistical Software: Release 17.0; College Station, TX: StataCorp LP). Quantitative data were represented as mean, standard deviation (SD), median, and range. Data were analyzed using Student's t-test to compare means of two groups. When the data were not normally distributed, a Mann-Whitney test was used. Qualitative data was presented as number and percentage and compared using either a Chi-square test or Fisher's exact test. A binary logistic regression model was used to calculate the odds ratio (OR), 95% confidence interval (CI), and p-value of the risk factors of BPD. Graphs were produced by using Excel®. A result was considered significant at $p \leq 0.05$.

Results

In this retrospective study, a total of 461 LBW infants and GA ≤ 32 weeks met the inclusion criteria. Of them, 66/461 (14.32%) died before reaching 36 weeks' corrected GA. The remaining 395 LBW infants were assessed for BPD at 36 weeks' corrected GA. As shown in **Fig. 1**, the frequency of BPD in LBW infants was 39/395 (9.87%), and the frequency of BPD in ELBW infants was 24/75 (32%). The BPD rate in extremely preterms was 27/88 (30.68%). BPD was present in 12/320 (3.75%) preterms with GA from 28 to 32 weeks' GA. However, the rate of BPD plus death at 36 weeks' corrected GA was (39 + 66)/461 (22.78%). Furthermore, as shown

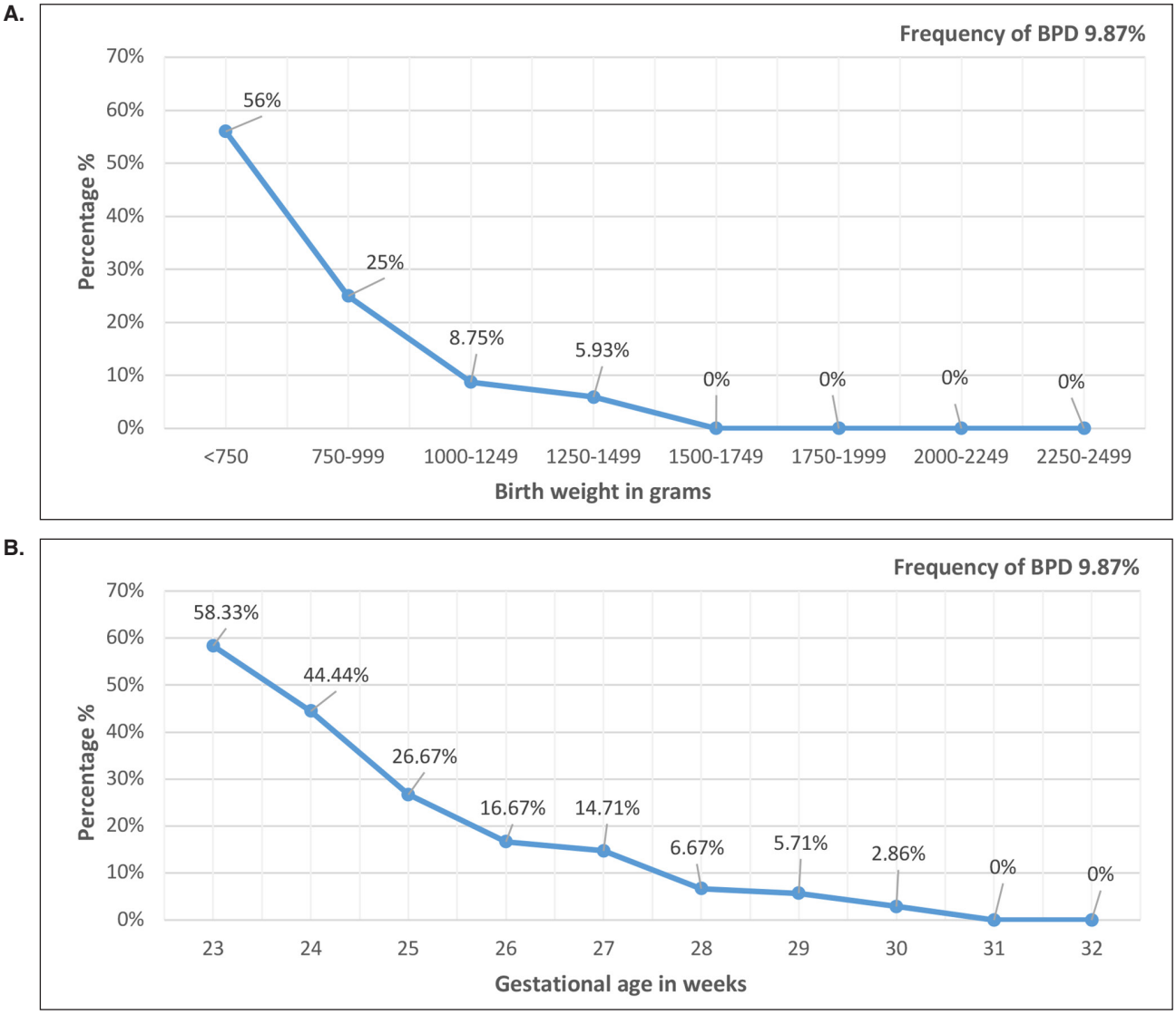

Figure 1. Frequency of bronchopulmonary dysplasia (BPD) in relation to birth weight (**A**) and gestational age (**B**).

in **Fig. 2**, the mortality rate was 90/461 (19.52%) among the LBW infants included in the study, 56/145 (38.62%) in ELBW infants, and 67/172 (38.95%) in extremly preterms.

As shown in **Tab. 1**. There were no significant differences between the BPD(+) and BPD(-) groups regarding maternal characteristics such as maternal age, nationality, mode of delivery, and premature membrane rupture. As regards antenatal steroid administration, there was no significant difference between the number of patients that received the course in both groups: BPD(+) 36/39 (92.31%) compared to 316/356 (88.76%) ($p = 0.51$). However, the BPD(+) group had a significant higher rate of maternal chorioamnionitis infection than the BPD(-) group (8/39 [20.51%] vs 25/356 [7.02%]; $p = 0.004$).

As shown in **Tab. 2**, the mean (± SD) GA was found to be significantly different between the BPD(+) (26 ± 2.68 weeks) and BPD(-) groups (29 ± 2.56 weeks) ($p < 0.0001$). Furthermore, the mean (± SD) birth weight was found to be significantly different between the BPD(+) (830 ± 340 grams) and BPD(-) groups (1,395 ± 470 grams) ($p < 0.0001$). Apgar score at 5 minutes was significantly lower and the rate of late-onset sepsis was significantly higher in the BPD(+) group than the BPD(-) group. Premature comorbidities, such as PVL and ROP ≥ stage 2, were elevated significantly in the BPD(+) group compared to the BPD(-) group ($p = 0.05$ and 0.01, respectively). However, as shown in **Tab. 2**, there was no statistically significant difference between the BPD(+) and BPD(-) groups as regards neonatal gender, the presence of early-onset sepsis, IVH, HsPDA, NEC, pneumothorax, or the development of neonatal pulmonary hemorrhage.

As shown in **Tab. 3**, regarding LBW infants management during hospital stay and the healthcare

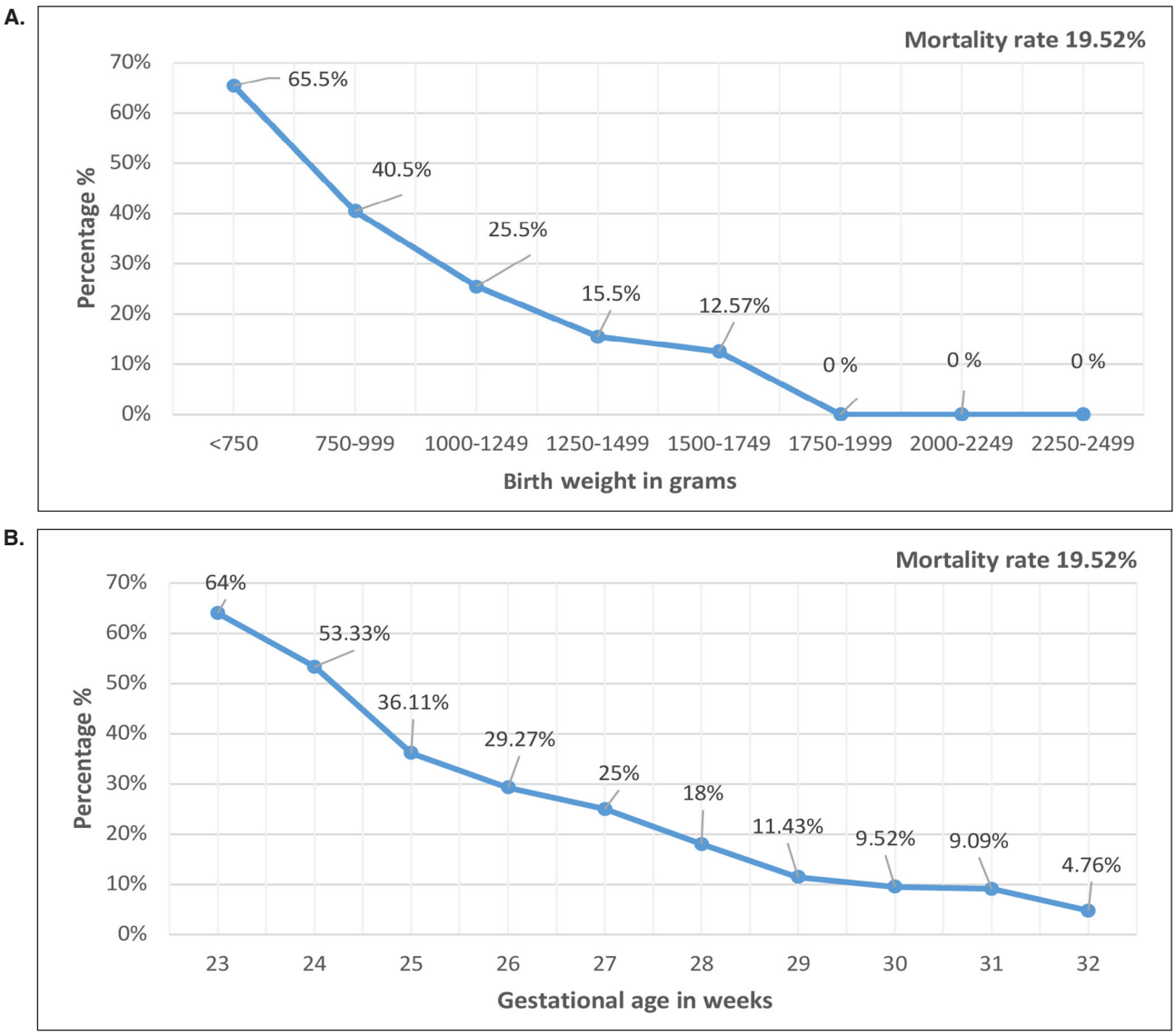

Figure 2. Mortality rate in low-birth-weight (LBW) infants in relation to birth weight (**A**) and gestational age (**B**).

Table 1. Maternal characteristics of low-birth-weight (LBW) infants with/without bronchopulmonary dysplasia (BPD).

Variable		BPD(+) (n = 39)	BPD(-) (n = 356)	p-value
Maternal age	**Mean ± SD**	32 ± 4	30 ± 7	0.28
	Median (range)	33 (26-38)	31 (14-42)	
Nationality	**Non-Saudi**	10 (25.64%)	117 (32.87%)	0.80
	Saudi	29 (74.36%)	239 (67.13%)	
Mode of delivery	**Normal**	17 (43.59%)	134 (37.64%)	0.41
	CS	22 (56.41%)	222 (62.36%)	
PROM > 18 hours		4 (10.26%)	46 (12.92%)	0.47
Mg sulphate therapy		9 (23.08%)	75 (21.07%)	0.70
Antenatal steroids		36 (92.31%)	316 (88.76%)	0.51
Chorioamnionitis		8 (20.51%)	25 (7.02%)	**0.004**
Maternal hypertension	**Normotensive**	27 (69.23%)	258 (72.47%)	0.42
	Pregnancy induced	8 (20.51%)	45 (12.64%)	
	Chronic hypertension	4 (10.26%)	53 (14.89%)	

Data are presented as n (%) if not otherwise stated.
BPD: bronchopulmonary dysplasia; CS: cesarean section; PROM: premature rupture of the membranes.

Table 2. Neonatal characteristics and outcome of low-birth-weight (LBW) infants with/without bronchopulmonary dysplasia (BPD).

Variable		BPD(+) (n = 39)	BPD(-) (n = 356)	p-value
GA (weeks)	Mean ± SD	26 ± 2.68	29 ± 2.56	< 0.0001
	Median (range)	26 (23-31)	29 (23-32)	
Birth weight (grams)	Mean ± SD	830 ± 340	1,395 ± 470	< 0.0001
	Median (range)	690 (530-1,470)	1,315 (690-2,490)	
Gender	Male	21 (53.85%)	219 (61.52%)	0.35
	Female	18 (46.15%)	137 (38.48%)	
Apgar score at 5 minutes, median (range)		7 (5-9)	8 (4-10)	**0.0003**
Early-onset sepsis		1 (2.56%)	10 (2.81%)	0.43
Late-onset sepsis		11 (28.21%)	54 (15.17%)	**0.04**
IVH grade III-IV		3 (7.69%)	30 (8.42%)	0.70
HsPDA		5 (12.82%)	28 (7.87%)	0.29
Pneumothorax		3 (7.69%)	14 (3.93%)	0.27
PVL grade III-IV		3 (7.69%)	17 (4.78%)	**0.05**
NEC stage II-III		2 (5.13)	18 (5.06%)	0.98
Pulmonary hemorrhage		1 (2.56%)	5 (1.40%)	0.57
ROP ≥ stage 2		4 (10.26%)	9 (2.53%)	**0.01**

Data are presented as n (%) if not otherwise stated.
BPD: bronchopulmonary dysplasia; GA: gestational age; HsPDA: hemodynamically significant patent ductus arteriosus; IVH: intraventricular hemorrhage; NEC: necrotising enterocolitis; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity.

Table 3. Management of low-birth-weight (LBW) infants with/without bronchopulmonary dysplasia (BPD) during hospital stay.

Variable	BPD(+) (n = 39)	BPD(-) (n = 356)	p-value
Intubation in delivery room	23 (58.97%)	96 (26.97%)	< 0.0001
Doses of surfactant therapy ≥ 1	35 (89.74%)	168 (47.19%)	< 0.0001
Invasive ventilation on day 1	27 (69.23%)	128 (35.96%)	< 0.0001
Invasive ventilation on day 7	23 (58.97%)	40 (11.24%)	< 0.0001
Conventional MV (days), mean ± SD	27.33 ± 18.63	2.05 ± 3.98	< 0.0001
HFV (days), mean ± SD	0.31 ± 0.66	0.17 ± 1.18	0.0001
CPAP (days), mean ± SD	10.25 ± 16.23	3.52 ± 5.19	< 0.0001
N(s) SIMV (days), mean ± SD	27.85 ± 20.02	3.44 ± 7.12	< 0.0001
LFNC (days), mean ± SD	26.05 ± 39.03	6.67 ± 8.04	< 0.0001
Duration of oxygen > 21% (days), mean ± SD	53.74 ± 42.39	15.05 ± 8.19	< 0.0001
Maximum FiO_2 supply at day 7, mean ± SD	0.35 ± 0.70	0.21 ± 0.40	0.05
Postnatal steroids therapy	2 (5.13%)	8 (2.25%)	0.20
Caffeine citrate	32 (82.05%)	90 (25.28%)	< 0.0001
Total hospitalization (days), mean ± SD	115.41 ± 92.14	43.72 ± 27.98	< 0.0001

Data are presented as n (%) if not otherwise stated.
BPD: bronchopulmonary dysplasia; CPAP: continuous positive airway pressure; HFV: high-frequency ventilation; LFNC: low-flow nasal canula; MV: mechanical ventilation; SIMV: synchronized intermittent mandatory ventilation.

burden, BPD cases had a statistically significant ($p < 0.0001$) risk for intubation in the delivery room, more doses of pulmonary surfactant, and invasive ventilation on day 1 and day 7. Furthermore, BPD cases spent more days on oxygen therapy, higher oxygen supply at day 7, and more days on invasive and non-invasive ventilatory support. In this study BPD(+) cases were more commonly treated with caffeine citrate than BPD(-) ($p < 0.0001$). Moreover, regarding the mean (± SD) total hospitalization days, the BPD(+) group had a significantly longer duration of stay (115.41 ± 92.14 days) than the BPD(-) group (43.72 ± 27.98 days) ($p < 0.0001$).

The effects of categorical independent variables of chorioamnionitis, late-onset sepsis, PVL, ROP, intubation in the delivery room, invasive MV, maximum oxygen supply, doses of surfactant therapy, and caffeine citrate therapy on BPD incidence were assessed with binary logistic regression analysis (**Tab. 4**).

Table 4. Perinatal and neonatal possible risk factors for bronchopulmonary dysplasia (BPD) development.

Risk factor	Odds ratio	95% CI	p-value
Chorioamnionitis	3.42	1.42-8.21	**0.004**
Late-onset sepsis	2.1971	1.03-4.68	**0.04**
PVL grade III-IV	1.6618	0.46-5.94	**0.05**
ROP ≥ stage 2	4.41	1.29-15.05	**0.01**
Intubation in delivery room	3.8932	1.97-7.68	**< 0.0001**
Doses of surfactant therapy ≥ 1 dose	9.7917	3.40-28.13	**< 0.0001**
Invasive ventilation on day 1	4.0078	1.96-8.18	**< 0.0001**
Invasive ventilation on day 7	11.3563	5.54-23.28	**< 0.0001**
Maximum FiO_2 supply at day 7, mean ± SD	1.13	1.05-1.23	**0.05**
Caffeine citrate therapy	13.5111	5.7631-31.6759	**< 0.0001**

Data are presented as n (%) if not otherwise stated.
CI: confidence interval; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity.

Discussion

In this retrospective cohort study, we found that the frequency of BPD was low in LBW infants, about 10%; however, it was increased in ELBW infants/extremely preterms to around 30%. The mortality rate in LBW infants was around 20% and increased in ELBW infants/extremely preterms up to 40%. The frequency of BPD increased with lower GA and birth weight and associated with other neonatal morbidities such as ROP and PVL. BPD cases had a higher risk for intubation in the delivery room, received more frequently more than one dose of surfactant, stayed more days on either invasive or non-invasive ventilatory support, had longer duration on oxygen therapy, had a higher maximum FiO_2 supply at day 7 and had longer hospital stays.

The frequency of BPD differs widely between centers according to the definitions and GA cut-points used. In this study, we included only moderate/severe BPD as BPD(+) and no/mild as BPD(-). Also, we used the NIH definition depending on the oxygen requirement at 36 weeks GA. Other reports used Jensen's definition, which classified BPD severity in infants at 36 weeks GA according to respiratory support, regardless of the oxygen need, into grades: grade 1 if a nasal cannula 2 L/min or less is required, grade 2 if a nasal cannula more than 2 L/min or other forms of non-invasive ventilation support are required, and grade 3 if invasive MV is required [19].

Although there have been many clinical trials and bundles aimed at decreasing the frequency of BPD, it appears that the frequency is either staying the same or even rising. The rising numbers of infants with BPD might be due to the improvement in the survival of extremely preterm, the neonates most likely at risk of BPD. According to the Vermont Oxford Network in 2010, the rates of BPD vary from 12% to 32% in between neonates born ≤ 32 weeks GA. In another cohort including 15,779 preterm infants between 22 and 29 weeks GA, combined BPD or death rates across 116 NICUs varied from 17.7% to 73.4% [23]. In another research cohort, the death rate decreased while the rate of BPD remained stable year over year. BPD occurred in 23.5% of the total cohort, 44.9% of infants born before 28 weeks of gestation and 45.2% of infants with ELBW [24]. In our study, the overall mortality rate in LBW infants was 19.52%. Mortality decreased from 64% at 23 weeks to 25% at 27 weeks. Our result was almost similar to the 24% mortality rate in the NRN for infants born between 22 and 28 weeks [7].

In this study, we found that with the decrease in GA/birth weight, the frequency of BPD/mortality increased: for 23 weeks GA, the BPD rate was 58.33% and the death rate 64%; by contrast, for 28 weeks GA, BPD was 6.67% and mortality 18%. These result are in accordance with other reports [7, 25]. In a large study by the Institute of Child Health and Human Development (NICHD), they found that BPD affected nearly all surviving infants born before 23 weeks GA, while by 30 weeks GA, the risk dropped to 1% [7, 26]. Additionally, according to Younge et al. [27], only 20% of infants born at 28 weeks GA developed BPD, compared to 80% of extremely preterm between the ages of 22 and 24 weeks GA. We did not find that male gender was associated with a high risk of BPD, in agreement with Collaco et al. [28]. However, in contrast to other results, some reports found BPD more frequently in male than in female infants [25, 29].

In our study, resource utilization and the healthcare burden was significantly higher in infants

with BPD. From the calculations of the regression model, BPD cases had a higher risk for intubation in the delivery room, received more frequently more than one dose of pulmonary surfactant, spent more days on oxygen therapy, were more likely to receive MV on day 1, and were more likely to stay ventilated on day 7, with higher oxygen requirement, and a longer hospital stay. These result agree well with Li et al. [29]. They found in multivariate analysis that the risk factors for BPD were male, intubated in delivery room, exposed to ≥ 2 doses of pulmonary surfactants, and MV ≥ 7 days. The association between MV and BPD has been linked to ventilator-associated lung injury [12, 20, 30].

By increasing pulmonary blood flow, HsPDA can contribute to the initial development of BPD by producing damage to the lungs and inflammation. Additionally, both PDA and BPD can contribute to the development of neonatal pulmonary hypertension by increasing pulmonary blood flow and pulmonary vascular resistance, which can lead to *cor pulmonale* [31]. In this study, HsPDA did not increase the risk for BPD. In agreement with our results, Willis and Weems [32] found that treatment of a PDA was not shown to prevent BPD, and some therapies may increase the risk of BPD. However, in contrast to our study, Gentle et al. [33], in a recent study, found that in extremely preterm infants on respiratory support, the presence of HsPDA and its duration were significantly associated with the development of BPD and pulmonary hypertension.

ROP and BPD are diseases that occur only in preterm infants. The relationship between ROP and BPD appears to be complex and modified by various factors [34]. In this study, preterm infants with BPD were associated with an increased risk for ROP ≥ stage 2 and needed a longer duration of oxygen therapy. In agreement with us, Singh et al. [35] stated that newborns with BPD showed advanced stages of ROP more often than those without BPD. They hypothesize that both diseases have links with a common pathogenesis. However, we found that BPD cases needed more days in oxygen therapy, with higher maximum oxygen at day 7, which may play a significant role in the development of these diseases. When the target oxygen saturation ranges 85% to 89% and 91% to 95% were compared, lower target oxygen saturation was associated with a reduced rate of ROP ($p = 0.045$) but an increased risk of death [36].

Due to oxidative damage to immature tissues, moderate/severe forms of BPD, ROP, and PVL are considered major morbidities with long-term neurodevelopmental deficits in preterm infants. In our results, BPD cases were associated with PVL. In agreement with our result, Grelli et al. [37] found that BPD cases with total supplemental oxygen over the 2 weeks of life were independently significantly associated with PVL. Furthermore, in this study we did not find that the BPD(+) group was associated with an increased risk for NEC. However, others showed that BPD occurred in the majority of preterm infants with surgical NEC [38].

The mode of delivery can impact on lung fluid clearance and gut colonization [39]. In our study, there were no significant differences between the BPD(+) and BPD(-) groups regarding maternal characteristics such as maternal age, nationality, mode of delivery, premature membrane rupture, and antenatal steroid administration. In accordance with our results, Ehrhardt et al. [40] in a recent cohort study found that, compared to vaginal delivery, delivery by planned C-section was not associated with a decreased incidence of BPD or the composite outcome of death or BPD.

Antenatal steroids are used for accelerating fetal lung maturation in pregnant women at risk of preterm delivery [41]. In our study, antenatal steroids were administered in about 90% of both studied groups, and we did not find a positive effect of antenatal steroids on the frequency of BPD. Roberts et al. [41], in a *Cochrane* review and meta-analysis, found that antenatal steroid use reduces the risk of perinatal death, neonatal death, RDS, NEC, PDA, and ROP and probably reduces the risk of IVH but not BPD. In accordance with ours, studies by Travers et al. [42] and Manktelow et al. [43] found that antenatal steroids were not associated with a lower rate of BPD. Evidence suggests antenatal steroids have had little to no effect on the incidence rate of BPD [44]. One explanation for why antenatal steroid use improves neonatal morbidity and mortality with no effect on the frequency of BPD is that antenatal steroids may improve the rate of BPD in some population groups, but on the other hand, another group of patients shifted from non-survival to survival with the effect of short-term improved of lung function with antenatal steroid use, especially in extremely preterms, which may have resulted in more infants being diagnosed as having BPD at 36 weeks' GA [41]. Furthermore, in our study only 2 (5.13%) cases in the BPD(+) group received postnatal steroids therapy versus 8 (2.25%) cases in the BPD(-) group ($p = 0.20$). In contrast to our results, Doyle et al. [45], in a recent meta-analysis, found that late systemic postnatal corticosteroid treatment (at the age of ≥ 7 days) reduces the risks of BPD in extremely preterms.

Antenatal inflammation, such as chorioamnionitis, is associated with an increased rate of lung maturation and a significant decrease in the incidence of RDS [46]. However, the vascular permeability of the lungs is impaired by sepsis and chorioamnionitis, which can be associated with a disturbance in the normal lung maturation and growth process and may affect the development of BPD. A recent meta-analysis suggested that a significant association between chorioamnionitis and an increased risk for BPD exists [47]. This agrees with our results, we found that with calculations of the regression model, maternal chorioamnionitis and late-onset sepsis, but not early-onset sepsis, increased the risk of BPD. Cokyaman and Kavuncuoglu [25] agree with our results. They found that no risk correlation identified between early-onset sepsis and BPD; however, a significant correlation was shown for late-onset sepsis and chorioamnionitis with an increased incidence of BPD. Kardum et al. [48] found that late-onset sepsis was shown to be an ultimate risk factor for the development of BPD ($p = 0.03$), as injury to the underdeveloped lung is a major risk factor for the development of BPD. However, in contrast to our result, Lahra et al. [49] found that chorioamnionitis with umbilical vasculitis and older GA were associated with a reduced incidence of BPD and stated that postnatal rather than antenatal inflammation was associated with an increased risk of BPD.

Limitations of the study

The limitations of this study were the small sample size and the fact that the patients were from a single geographical area and did not represent the whole country. The non-availability of electronic file systems in some hospitals was the main reason. Furthermore, another limitation of the present study is its retrospective design; therefore, further randomized clinical trials are still needed to support these findings.

Conclusions

In conclusion, ELBW infants had a 2-fold higher rate of mortality and a 3-fold higher rate of BPD, compared to LBW infants. In this study, BPD(+) was associated with other neonatal morbidities, such as ROP and PVL. In this study, binary logistic regression analysis showed that BPD(+) cases were more frequently intubated in the delivery room, received more frequently more than one dose of pulmonary surfactant, remained for more days on both invasive and non-invasive ventilatory support, received more days of oxygen therapy, and had longer hospital stays.

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Data availability statement

The Authors confirm that all data supporting the findings of this study are available within the article, and upon reasonable request.

Ethics approval statement

The study protocol was scrutinized and approved by the Committee of the Institutional Review Board (IRB), King Saud Medical City, KSA, (Number: H1RE-04-Jun23-0).

Declaration of interest

The Authors have no conflicts of interest with the content of this paper. No funding to declare.

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