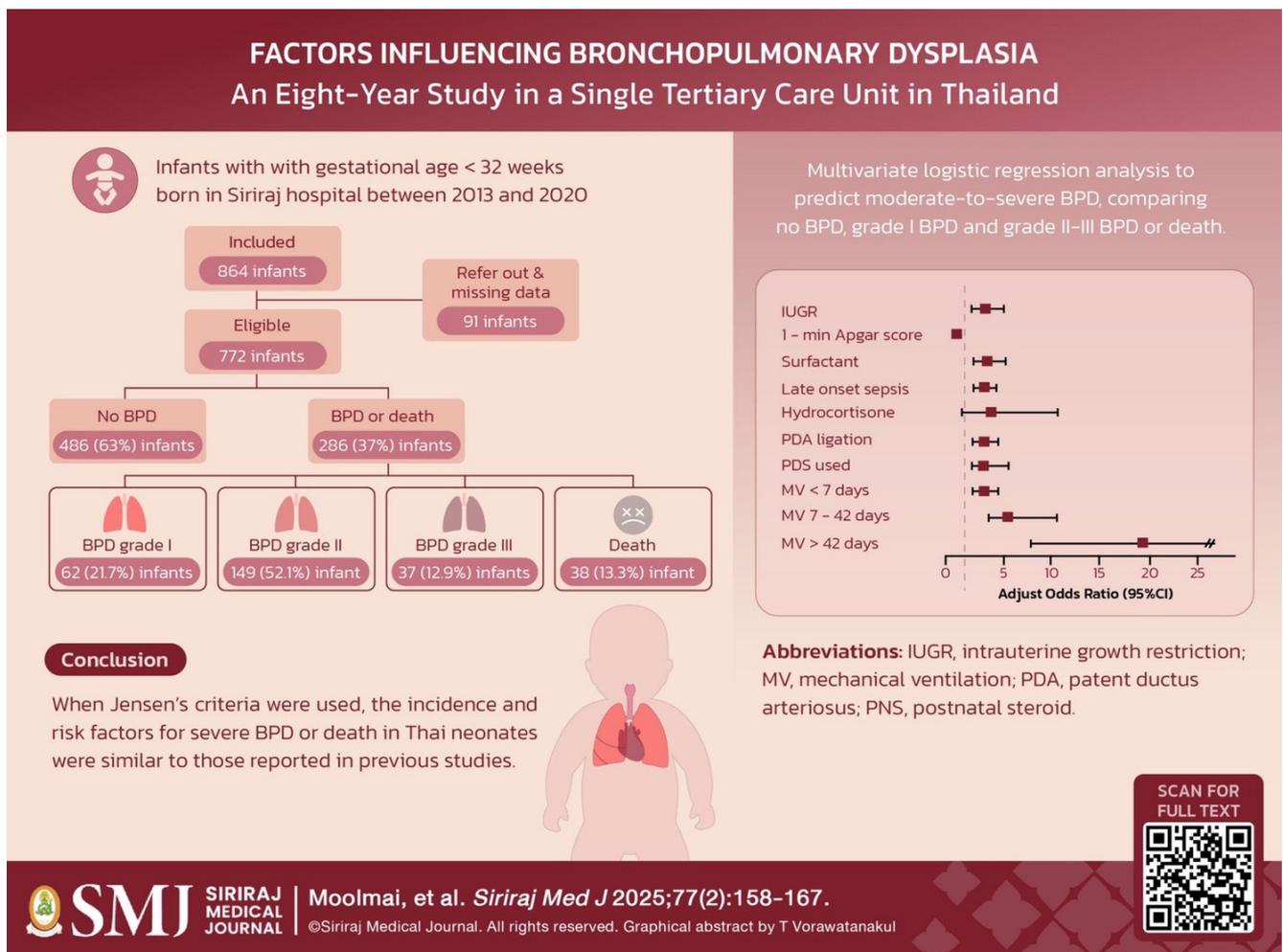


Factors Influencing Bronchopulmonary Dysplasia: An Eight-Year Study in a Single Tertiary Care Unit in Thailand

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Received 23 September 2024 Revised 5 November 2024 Accepted 5 November 2024

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<https://doi.org/10.33192/smj.v77i2.271246>



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ABSTRACT

Objective: To assess the incidence trends of severe BPD or death, identify associated risk factors, and develop a predictive model using Jensen's BPD grading system.

Materials and Methods: This retrospective study included infants with a gestational age (GA) < 32 weeks born between 2013 and 2020. Infants were classified into no BPD and BPD (all grades) or death categories. Risk factors and a predictive model for outcomes were identified using multivariable logistic regression and evaluated with a receiver operating characteristic (ROC) curve.

Results: Among the 772 infants, 286 (37%) were classified into the BPD group. The incidence of BPD continuously increased from 16.3% in 2013 to 49.4% in 2020. Multivariate analyses revealed factors associated with severe BPD, including IUGR, the 1-minute Apgar score, surfactant administration, late-onset sepsis, hydrocortisone, PDA ligation, postnatal steroid and mechanical ventilation (MV) days. The highest adjusted odds ratio (aOR) was for MV > 42 days at 19.29 (95% CI; 7.22–51.55; $p < 0.001$). The area under the curve (AUC) was 0.898, with 80.68% sensitivity and 84.83% specificity.

Conclusion: When Jensen's criteria were used, the incidence and risk factors for severe BPD or death in Thai neonates were similar to those reported in previous studies. The regression model exhibited good predictive value, potentially assisting clinicians in targeted interventions.

Keywords: Bronchopulmonary dysplasia (BPD); respiratory outcomes; mortality; Thailand (Siriraj Med J 2025; 77: 158-167)

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most important respiratory complication in preterm infants. Over time, advancements in technologies as well as neonatal care treatment strategies, including surfactant replacement therapy, new models of mechanical ventilation such as targeted tidal volume, high-frequency oscillatory ventilation (HFOV), noninvasive ventilation (NIV) and postnatal steroids, have increased the survival rate of preterm infants, especially extremely preterm infants born at 22–24 weeks.¹ However, the incidence rate of BPD remains unchanged. For infants born at a gestational age (GA) of less than 29 weeks, it is estimated to be between 48% and 68%, with the incidence inversely proportional to GA.² In the post-surfactant era, with the widespread adoption of NIV for implementing protective lung strategies in very preterm infants, the new definition of BPD aligns with the criteria set forth by the National Institutes of Health (NIH) in 2018³ and Jensen in 2019.⁴ However, the NIH 2018 definition has various limitations, with a primary concern being its ability to predict long-term outcomes.⁵ In 2019, Jensen addressed and resolved this particular issue.^{6,7}

Although numerous studies have explored risk factors associated with BPD outcomes in the past, few studies have focused on the Asian population, particularly in Thailand. This gap can be attributed to limited resources, variations in equipment, differing treatment guidelines

across countries, and the use of different BPD definitions to assess outcomes. Geetha et al. reported that the prevalence and risk factors for BPD among extremely low gestation age neonates (ELGANs) with a composite outcome of moderate to severe BPD/death was 67%; however, they used the NIH 2001 definition, which may not accurately reflect current clinical practices.⁸ Siriraj Hospital is a university hospital with a level IV NICU in Thailand and has an annual delivery rate of approximately 150 infants born premature with a GA less than 32 weeks.

Our study investigated the incidence of moderate to severe BPD and/or mortality and explored the associated risk factors among preterm infants, thereby providing comprehensive insights that reflect the broader landscape of the neonatal population in Thailand.

MATERIALS AND METHODS

We conducted a retrospective cohort data collection from the Siriraj Informatics and Data Innovation Center (SiData+) to include neonates who were born at a GA < 32 weeks between January 2013 and December 2020. Infants with major congenital anomalies (trisomy 13, 18, or 21 or hydrops fetalis), congenital heart disease or congenital lung and airway malformation were excluded. The definition of BPD was defined by Jensen in 2019⁴, categorized BPD severity based on the mode of respiratory support administered at 36 weeks postmenstrual age (PMA). Infants on nasal cannula 2 L/min were classified as grade

I BPD, while those on nasal cannula greater than 2 L/min or non-invasive respiratory support were classified as grade II BPD. Infants on mechanical ventilation at 36 weeks PMA were identified as grade III BPD.

Outcome measurements

The maternal demographic data included maternal age, antenatal steroids, maternal complications that lead to preterm labor and the risk for BPD in infants, such as diabetes mellitus (DM), hypertensive disorders, and chorioamnionitis, which was defined as a clinical diagnosis of intra-amniotic infection⁹, intrauterine growth restriction (IUGR), and multiple pregnancies. The demographic data of the neonates included GA, birth weight (BW), sex, and Apgar scores at 1 and 5 minutes.

Neonatal outcomes

The neonatal outcomes included intubation in the delivery room (DR), respiratory comorbidities such as respiratory distress syndrome (RDS), surfactant administration, pulmonary hemorrhage, persistent pulmonary hypertension of the newborn (PPHN), and inotropic drug use during the first week of life. Late-onset sepsis (LOS) was defined as positive hemoculture occurring after 72 hours of life or negative blood culture, but clinicians decided to administer antibiotics for more than 5 days on the basis of clinical sepsis. Necrotizing enterocolitis (NEC) stage ≥ 2 was diagnosed using modified Bell's criteria.¹⁰ The hemodynamic significance of the patent ductus arteriosus (HsPDA) was defined as a ductal diameter exceeding 1.5 mm with a left-to-right shunt and a left atrium to aorta diameter ratio (LA:Ao) greater than 1.5.

Respiratory outcome measurements

The modes of assisted ventilatory support were collected and specified as invasive mechanical ventilation (IMV), HFOV, and NIV. The postmenstrual age (PMA) at the time of the last extubation and the total number of days of mechanical ventilation (MV) were recorded. Postnatal steroids (PNS) were used for prolonged mechanical ventilation after 2 weeks of life. The respiratory severity index (RSI; mean airway pressure (MAP) multiplied by FiO_2 ($\text{MAP} \times \text{FiO}_2$)) was calculated on Days 7, 14, 21 and 28 of life. The BPD definition reported by Jensen in 2019⁴ was chosen to assess the severity of BPD in this cohort. During the time of the study, pulmonary hypertension (PHT) resulting from BPD was not routinely addressed. Nevertheless, infants underwent echocardiography when facing clinical instability and when an acute pulmonary hypertensive crisis was suspected.

Statistical analysis

SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) was used for all the statistical analyses. Continuous variables are expressed as the means \pm SD or medians (interquartile ranges), and categorical variables are expressed as counts and percentages. The chi-square test and Fisher's exact test were used for categorical variables, and Student's *t* test was used for continuous variables for the appropriate comparisons of interest. A *p*-value < 0.05 was considered statistically significant. Significant variables with *p*-values < 0.2 were included in the model for univariate analyses, and the associations between potential risk factors for BPD were calculated. A multivariate logistic regression model was developed to identify independent significant risk factors for BPD of any grade or death and BPD Grades II and III or death, and odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

RESULTS

Maternal and neonatal characteristics

A total of 941 infants were born at GA < 32 weeks. In addition to 77 infants with congenital anomalies, 92 infants were excluded from our cohort: 89 were transferred to other hospitals before BPD diagnosis, and three infants had incomplete data. The final analysis included a total of 772 infants (Fig 1). Among these, 248 (32.1%) infants developed BPD, and 38 (13.3%) infants died before 36 weeks PMA. The overall incidence rates of BPD Grades I, II, and III were 21.7% (62/286), 52.1% (149/286) and 12.9% (37/286), respectively. The cohort experienced a mortality rate of 6.5% (50/772), and the majority of infants died from respiratory complications.

We categorized the infants into two groups: those without BPD and those with BPD of any grade or who died. No statistically significant difference in maternal characteristics was noted between the two groups, except for a greater prevalence of IUGR in the BPD group (39 (8%) vs. 36 (12.6%), $p = 0.04$) (Table 1). Compared with those without BPD, infants in the BPD groups had lower GA, lower birth weights, more male infants and lower Apgar scores at 1 minute and 5 minutes (Table 1).

Neonatal comorbidities

Infants diagnosed with BPD were more likely to be critically ill than those without BPD. This was evident in significantly increased neonatal complications, such as higher rates of intubation at the delivery room, surfactant administration, pulmonary hemorrhage, PPHN, and hemodynamic instability requiring inotropic drugs, as well as hydrocortisone treatment. Additionally, there was a higher incidence of late-onset neonatal sepsis and NEC

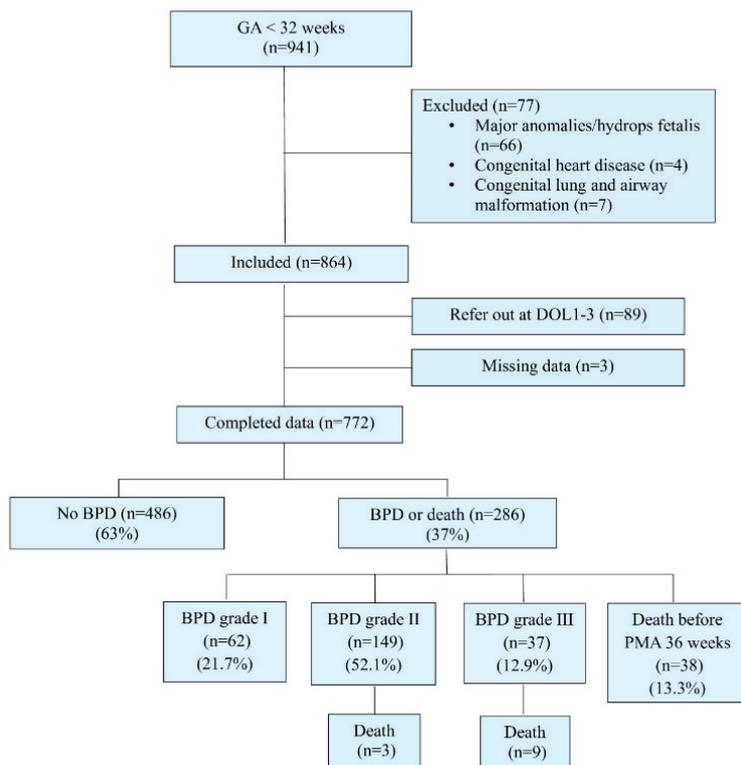


Fig 1. Summary flow chart

Abbreviations: BPD, bronchopulmonary dysplasia; DOL, day of life; GA, gestational age; PMA, postmenstrual age.

TABLE 1. Demographic data for patients with no BPD and those with BPD of all grades or death.

	No BPD (n=486)	BPD or death (n=286)	p-value
Maternal			
Maternal age (year)	29.41 (± 6.9)	29.89 (± 7.2)	0.36
Antenatal steroid	451 (92.8)	260 (90.9)	0.35
Completed dose	287 (59.1)	152 (53.1)	0.11
Diabetes mellitus	55 (11.3)	31 (10.8)	0.84
Hypertensive disorder	110 (22.6)	62 (21.7)	0.76
Chorioamnionitis	33 (6.8)	27 (9.4)	0.18
IUGR	39 (8.0)	36 (12.6)	0.04
Cesarean section	288 (59.3)	182 (63.6)	0.23
Multiple pregnancy	121 (24.9)	68 (23.8)	0.73
Neonatal			
GA (weeks)	30.1 (± 1.5)	27.9 (± 2.0)	< 0.001
24 ^{0/7} -26 ^{6/7} weeks	23 (4.7)	103 (36.0)	< 0.001
27 ^{0/7} -31 ^{6/7} weeks	463 (95.3)	183 (64.0)	< 0.001
Birth weight (grams)	1371.5 (± 348.8)	985.3 (± 314.6)	< 0.001
Male	256 (52.7)	173 (60.5)	0.04
1-minute Apgar score	7 [5-8]	4 [1-6]	< 0.001
5-minute Apgar score	9 [8-9]	7 [5-8]	< 0.001

Expressed as the count (%), mean± SD, median [IQR].

Abbreviations: GA, gestational age; IUGR, intrauterine growth restriction.

stage ≥ 2 (Table 2). Among infants without BPD, 22.8% received PDA treatment, whereas 59.8% in the other groups did ($p < 0.001$). For infants receiving medications to close the PDA, 90.1% of infants without BPD were successfully closed before discharge. However, it was closed in only 59.6% of infants with BPD ($p < 0.001$). There was no difference in the age at PDA ligation between the groups (31.5 (± 1.2) vs. 30.5 (± 3.4) weeks; $p = 0.36$) (Table 2). Nevertheless, when infants with each BPD grade were compared, infants with BPD Grades II and III experienced more complications, with the exception of pulmonary complications, hydrocortisone use and stage ≥ 2 NEC (Supplemental Tables 1-2).

Respiratory variables

The total incidence of BPD or death was 37%. Among infants born at < 29 weeks, the incidence of BPD was 61.3% (152/248), and the incidence of Grade II–III BPD was 49% (122/248). Compared with those without BPD, infants with BPD had an extended duration of mechanical ventilation (0 [0–3] vs. 15 [3–44]; $p < 0.001$), and their length of hospital stay was longer. The PMA at discharge was 42.9 (± 12.3) vs. 37.4 (± 2.9) weeks; $p < 0.001$ (Table 2). We investigated the type of respiratory support and RSI on Days 7, 14, 21, and 28. The percentages of infants with BPD who required MV on Days 7, 14, 21, and 28 were 56% (139), 50% (124), 44.4% (110), and 40.3%

TABLE 2. Neonatal comorbidities between the no BPD group and the all-grade BPD or death group.

	No BPD (n=486)	BPD or death (n=286)	p-value
Intubation at DR	110 (22.6)	194 (67.8)	< 0.001
Intubation at NICU during admission	192 (39.5%)	258 (90.2%)	< 0.001
Surfactant administration	39 (8.0)	116 (40.6)	< 0.001
Repeated dose of surfactant	0	13 (4.5)	< 0.001
Pulmonary hemorrhage	10 (2.1)	32 (11.2)	< 0.001
PPHN	6 (1.2)	36 (12.6)	< 0.001
iNO initiation	0	9 (3.1)	< 0.001
Use of inotropic drugs	73 (15.0)	152 (53.1)	< 0.001
Use of hydrocortisone	5 (1.0)	36 (12.8)	< 0.001
Late onset sepsis	91 (18.7)	141 (51.5)	< 0.001
NEC stage ≥ 2	69 (14.2)	58 (20.9)	0.02
Surgical treatment	6 (8.7)	18 (31)	0.001
Treatment of PDA	111 (22.8)	171 (59.8)	< 0.001
Medical closure	100 (90.1)	102 (59.6)	< 0.001
PDA ligation	11 (9.9)	69 (42.9)	< 0.001
Age at PDA ligation (days)	23 [16-25]	19 [15-27]	0.85
PMA at PDA ligation (weeks)	31.5 (± 1.2)	30.5 (± 3.4)	0.36
Postnatal steroid	19 (3.9)	73 (26.2)	< 0.001
PHT at 34-36 weeks PMA	7 (7.1)	19 (6.6)	< 0.001
Total MV days	0 [0-3]	15 [3-44]	< 0.001
PMA at discharge (weeks)	37.4 (± 2.9)	42.9 (± 12.3)	< 0.001

Expressed as the count (%), mean \pm SD, median [IQR].

Abbreviations: DR, delivery room; iNO, inhaled nitric oxide; MV, mechanical ventilation; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PHT, pulmonary hypertension; PMA, postmenstrual age; PPHN, persistent pulmonary hypertension of the newborn.

(100), respectively. In contrast, a smaller proportion of infants without BPD were on MV on these days (10.3% (50/486), 5.3% (26/486), 4.5% (22/486), and 3.7% (18/486), respectively). Infants diagnosed with Grade III BPD presented a significantly elevated RSI, which increased over time at Days 7, 14, and 21 (2.89 [1.84–6.13], 4.20 [2.24–7.50], and 5.25 [2.40–9.10], respectively). However, there was a slight decrease in the RSI from Day 28 to 4.21 [2.85–7.41] (Fig 2). A total of 18 (2.3%) of the 772 infants with BPD required home oxygen, and two of them underwent tracheostomy before discharge with home ventilation.

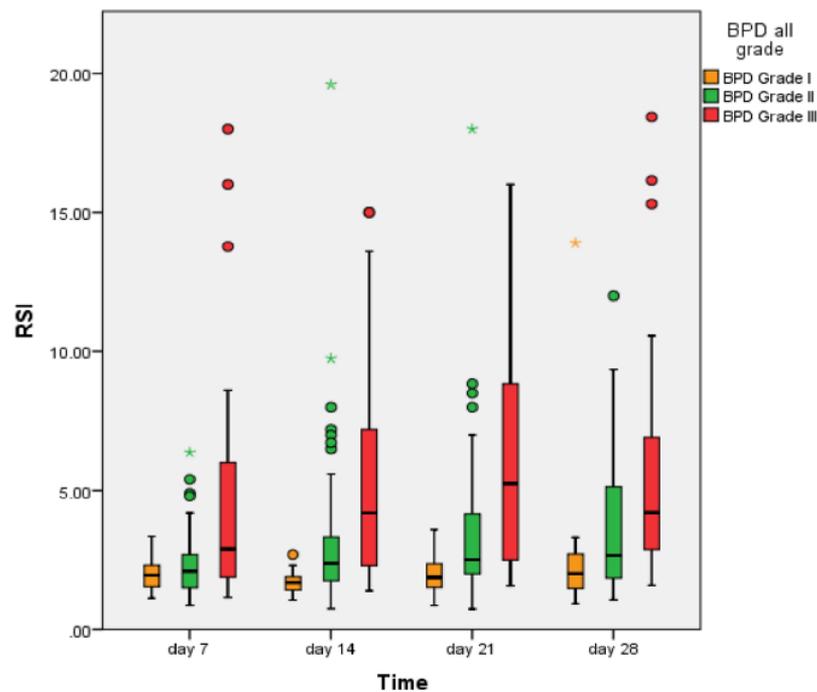
Model for the prediction BPD Grades II-III or death

Univariate analyses were conducted to predict BPD outcomes by comparing the no BPD group with the all-grade BPD or death group (Supplemental Table 3).

Multivariate logistic regression analysis identified a subset of independent risk factors for BPD of any grade or death (Table 3) and BPD Grades II-III or death (Table 4). The receiver operating characteristic (ROC) curve was constructed utilizing the final model, and the cutoff value was 0.3 according to the Youden index, resulting in a sensitivity of 80.68%, specificity of 84.83%, positive predictive value (PPV) of 66.80%, and negative predictive value (NPV) of 92.06% (Supplemental Fig 1). The final equation is shown in the Appendix.

DISCUSSION

We demonstrated the incidence of BPD in preterm infants born at < 32 weeks of gestation using the new severity-based diagnostic criteria proposed in 2019 by the NICHD Neonatal Research Network.⁴ The overall incidence of BPD or death was 37%, with 24% of those

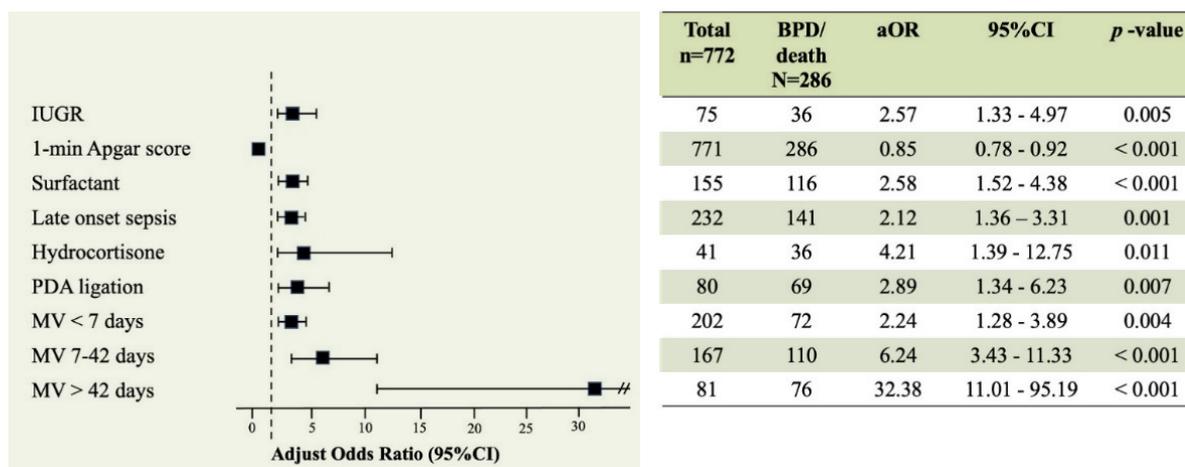


Expressed as median [IQR].

Postnatal day	N	BPD Grade I	BPD Grade II	BPD Grade III	p-value
7	139	1.99 [1.50-2.36]	2.10 [1.49-2.70]	2.89 [1.84-6.13]	0.003
14	123	1.69 [1.37-1.99]	2.38 [1.76-3.42]	4.20 [2.24-7.50]	0.004
21	110	1.88 [1.51-2.38]	2.52 [2.00-4.20]	5.25 [2.40-9.10]	0.001
28	117	2.01 [1.44-2.80]	2.67 [1.85-5.14]	4.21 [2.85-7.41]	0.027

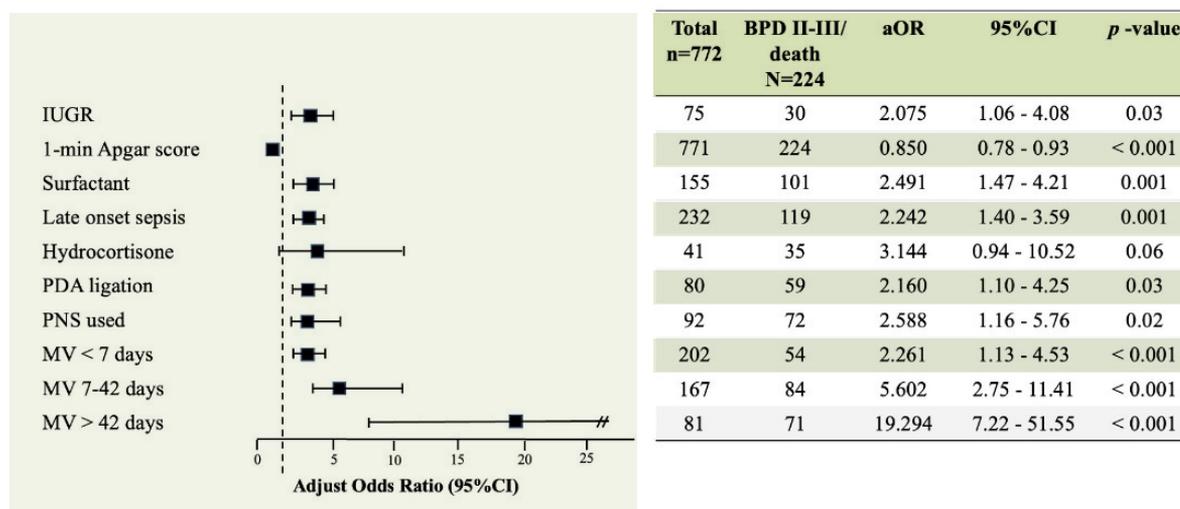
Fig 2. Respiratory severity index (RSI) at 7, 14, 21 and 28 DOL in inats with BPD.

TABLE 3. Multivariate logistic regression analysis of risk factors for BPD compared between the no BPD group and the all-grade BPD or death group.



Abbreviations: IUGR, intrauterine growth restriction; MV, mechanical ventilation; PDA, patent ductus arteriosus.

TABLE 4. Multivariate logistic regression analysis to predict moderate-to-severe BPD, comparing no BPD, grade I BPD and grade II-III BPD or death.



Abbreviations: IUGR, intrauterine growth restriction; MV, mechanical ventilation; PDA, patent ductus arteriosus; PNS, postnatal steroid.

who survived until 36 weeks PMA being diagnosed with Grade II-III BPD or death. Notably, for ELGANs, the incidence increased to 61.3%, and 49% of the surviving infants exhibited Grade II-III BPD. Compared with international data, specifically the 2022 figures from the Canadian Neonatal Network (CNN)¹¹, where the incidence of BPD in infants younger than 33 weeks was reported as 32.6%, and considering Yang et al.’s findings¹² of a 61% BPD rate in infants born before 32 weeks in their study (utilizing the NIH 2001 definition),

our results fall within an acceptable range. Nevertheless, within the ELGANs group, our observed rate of BPD surpassed that reported by Jensen et al.¹³ In their cohort, the incidence of BPD, which was determined using a definition similar to ours, was 45.5%. In global cohorts, the overall BPD incidence varies widely, with values of 25–56% in Asia, 17–73% in Europe and 18–75% in North America.¹⁴ In addition, a notable rate of 67% was reported in a Singaporean cohort.⁸ However, they used different BPD definitions for grading severity,

which might not accurately reflect recent practices and outcomes. Previously, at our center, we did not have a unit protocol for respiratory management in preterm infants < 32 weeks; however, all neonatologists followed standard guidelines for RDS treatment, such as early CPAP and rescue surfactant therapy, using conventional methods with slow weaning. The less invasive surfactant administration (LISA) method, oxygen reduction test (ORT) to determine BPD at 36 weeks PMA, and respiratory management protocol for preterm infants < 32 weeks were introduced in 2018. A comparable trend was observed in the ELGANs population. However, infants exhibited greater critical illness during this period than during the earlier period, with an increase in IUGR cases, lower birth weight, lower 1-minute Apgar scores, an elevated need for surfactant treatment, an increased incidence of LOS and a greater requirement for postnatal steroids.

BPD is a chronic lung disease that results from multiple factors, including genetic, prenatal, or postnatal influences. Antenatal corticosteroids are considered the standard of care for accelerating fetal lung maturity to prevent RDS but not BPD. Owing to the widespread use of antenatal steroids following the WHO guidelines¹⁵ to improve preterm birth outcomes, there were no differences in antenatal steroid usage between the non-BPD and BPD groups in our study, which is consistent with recent previous studies.^{13,16} The use of antenatal steroids in our unit was consistent with the broader cohort. Our findings identify the factors associated with a composite of Grades II-III or death, including eight factors (Table 4), which aligns with known factors reported in other studies.^{12,16-18}

Timing of surfactant replacement therapy (SRT) is one of the crucial factors that determine the outcome of BPD. A previous systematic review demonstrated that intubated infants who received early selective surfactant administration had a decreased risk of BPD or death at 28 days compared to those who received late SRT (after more than 2 hours).¹⁹ However, data from a recent cohort indicated that early SRT was associated with a longer duration of mechanical ventilation, with no significant difference in the rate of BPD.²⁰ In our cohort, we do not have recorded data on the timing of surfactant administration due to the retrospective nature of the study. European Consensus guidelines on the management of respiratory distress syndrome recommended that intubated infants less than 30 weeks' gestation should receive SRT and rescue surfactant should be administered early in the course of the disease using a thin catheter when infants required CPAP pressure greater than 6 cmH₂O or FiO₂ > 0.3.²¹

We opted to exclude PDA treatment from the

model, as numerous randomized controlled trials (RCTs) comparing early treatment with conservative approaches have failed to demonstrate a significant impact on the increased rate of BPD or death outcomes.^{22,23} Given the absence of a standardized definition for HsPDA, infants in our units underwent echocardiography based on the presence of a murmur. The decision to pursue medical closure was exclusively determined using criteria involving the ductal diameter and the LA:Ao ratio. We considered that this could be a confounding factor leading to excessive PDA treatment, making the establishment of a direct association with the outcome of BPD challenging. Therefore, we chose to include only PDA ligation in the model, which is supported by prior research indicating an association between PDA ligation and moderate to severe BPD.^{24,25}

One commonly recognized factor contributing to BPD is chorioamnionitis. However, in our cohort, no significant difference was observed between the two groups. We hypothesize that the clinical diagnosis of chorioamnionitis may lead to over recognition. Only half of the clinically diagnosed cases of chorioamnionitis had confirmed placental pathology indicating acute inflammation, as per unpublished local data. The longer the duration of MV is, the greater the increase in the incidence and severity of BPD as well as the likelihood of requiring home oxygen at discharge and experiencing neurodevelopmental impairment.²⁶ We observed a similar trend in our cohort, where infants with MV days had a significantly increased OR.

The strengths of this study include the use of our own cohort to represent our practices and to develop a care bundle for improving BPD outcomes. We also plan to create an BPD calculator for the Thai population. Another strength is the adoption of the Jensen 2019 BPD definition, which aligns more closely with contemporary practices and allows for better prediction of short-term and long-term outcomes. This study has several limitations. First, it involves a small cohort and is representative of a single center. Second, the data retrieval spans from 2013, and treatment strategies may have evolved. Thus, recent populations were potentially not captured. Third, our study does not incorporate long-term outcomes, such as neurodevelopmental impairment.

CONCLUSION

The overall incidence of BPD in our study correlated with the global incidence. Factors such as IUGR, the 1-minute Apgar score, surfactant administration, late-onset sepsis, hydrocortisone use for hemodynamic instability, PDA ligation, and total MV days independently contribute

to the risk of all grades of BPD. Our findings suggest that prospective research could utilize our developed model for external validation to predict the probability of Grade II–III BPD in Asian preterm infants.

ACKNOWLEDGEMENT

None

DECLARATION

Grants and Funding Information

None

Conflicts of Interest

None

Author Contributions

Conceptualization and methodology, P.M., P.W., P.R.; Investigation, P.M., P.R., P.W.; Formal analysis, P.M., B.Y., P.W.; Visualization and writing - original draft, P.M. and P.W.; Writing - review and editing, B.Y. and P.W.; Supervision, P.W. All authors have read and agreed to the final version of the manuscript.

Data Availability

Derived data generated will be shared upon reasonable request to the corresponding author.

Ethics Statement

The study was approved by the Siriraj Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University (CoA no. Si 298/2022).

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