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An Online Estimator for New Bronchopulmonary Dysplasia in Extremely Low Birth Weight Asian Infants

(*Running title: Bronchopulmonary dysplasia Estimator*)

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Abstract

Introduction: *Bronchopulmonary dysplasia is a major morbidity of extremely preterm infants. The advances in maternal, perinatal and neonatal intensive care have resulted in enhanced survival of extremely preterm infants in the last two to three decades. But there is a drift towards increasing rates of BPD with increasing survival of this cohort and thus prevention of BPD is an important challenge faced by the physicians. The study aims to evaluate the utility of a modified NICHD scoring system for the prediction of newBPD (nBPD)/Mortality in extremely low birth weight (ELBW) infants in Asia.*

Methods: *Cohort study of 318 live born ELBW infants over a period of 4 years. A web-based prediction model was developed using gestational age, birth weight, race, gender, and maximal respiratory support and O2 requirement on postnatal days 1,3,7,14, 21 and 28 of life. The severity of nBPD was used as a categorical variable (none, mild, moderate and severe) and analysed using the area under the curve (AUC).*

Results: *Mean gestational age and birth weight of the cohort were 26.3 ± 2 weeks and 765 ± 145gms, respectively. The prediction of nBPD/mortality improved with advancing postnatal age, increasing from AUC of 0.992 on Day1 to 1.0 on Day 28. Maximal respiratory support and FiO2 requirement served as the best predictors as postnatal age advanced.*

Conclusion: *This is the first online estimator for nBPD in Asia derived from relevant postnatal risk factors in ELBW infants born in the new millennium.*

Keywords: *Bronchopulmonary Dysplasia, Online Estimator.*

Introduction

Despite improving perinatal and neonatal care, bronchopulmonary dysplasia (BPD) remains a significant concern in the extremely low-birth-weight (ELBW) population [1,2]. This may partly be due to the improved survival rate of extremely premature infants and the advances in perinatal intensive care [3]. The BPD prevalence in infants below 29 weeks of gestation is around 40% [1] and at our center 67% of infants below 28 weeks had moderate to severe BPD [4].

In 1967, Northway and colleagues originally described the classic BPD in preterm infants as an injury pattern primarily affecting large airways caused by the deleterious effects of hyperoxia and barotrauma in an immature lung [5].

However, the new BPD is related to a developmental arrest in alveolar crest formation, leading to alveolosaccular and capillary hypoplasia and focal interstitial fibrosis [6]. The initial respiratory course is variable and therefore, the lung damage they are suffering from must be caused in part by other factors, which include injury and inflammation, followed by repair and healing [7]. The etiology of nBPD is multifactorial. Maternal chorioamnionitis, maternal hypertension, and intrauterine growth restriction (IUGR) are among common associated antenatal risk factors along with perinatal factors such as decreasing gestational age (GA) and birth-weight (BW), male gender, lower Apgar score, and need for intense resuscitation [8,9,10]. Postnatal factors such as prolonged aggressive ventilation, oxygen toxicity, infection, hemodynamically

significant patent ductus arteriosus (HsPDA), and poor nutrition also contribute to the development of nBPD [11]. Various treatment strategies to reduce the burden of BPD once established produce little impact thus emphasizing the need for early detection and prevention [12,13].

Physicians may benefit from a prediction model using readily available clinical parameters to help with clinical decision making and management. To date, only few scoring systems used birth weight, gestational age, sex, HsPDA, sepsis, and mechanical ventilation in their calculations [14,15,16].

None of these tools used postnatal age as a determining factor, and thus, the exposure of risk factors over time could not be quantified. The studies were done in a diversified group with no external validation done and thus in clinical care and research studies, the use of these models remained obsolete. Death was also not included as an outcome in most of these models [14,15].

In 2011, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) developed a web-based nBPD prediction model to predict the risk of BPD at different days of life and many centers have availed of the usefulness of this predictive tool [17]. The estimator uses readily available demographic and respiratory support data to provide objective estimates of risk for BPD of varying severity and for the computing death outcome. This model uses GA, BW, race and ethnicity, gender, respiratory support, and fraction of inspired oxygen (FiO_2), which helps in providing estimates of BPD severity and death for each postnatal day of life.

Developing validated and prognostic models can help physicians plan for preventive strategies and improved prognostic counseling. However, this model is designed for the North American population, which may be different from our cohort of patients which are of a different ethnic stratification. Singapore is a multi-racial population consisting predominantly of Chinese, Malay, or Indian ethnicities [18]. At present, no predictive models are in use in Singapore and given the multiethnic society, it would be useful to evaluate the usefulness of a model which includes ethnicity. Thus, this study primarily aims to develop a modified NICHD prediction model for nBPD/mortality among Asian ELBW infants.

Methodology of the study

We performed this study at KK Women's and Children's Hospital (KKH) which is the largest tertiary referral perinatal center in Singapore with an annual delivery rate of approximately 12,000. This study was approved by the institutional review board of the hospital and the waiver for informed consent was obtained.

The study period was from January 2012 to December 2015, and relevant data were obtained from a prospectively maintained neonatal database and individual case records. We included ELBW infants with a birth weight below 1000 g and who survived for more than 12 hours of life. Stillbirths and those babies given palliative care and infants with major congenital malformations were excluded from the study. The gestational age ranged from 23 weeks to 31 weeks.

Our earlier study on extremely low gestational age neonates below 28 weeks was to estimate the burden of nBPD and risk factors. We extended the study cohort to all the ELBW babies irrespective of the gestational age over the same period for this study [4]. The variables collected included maternal data such as maternal age, ethnicity, use of antenatal steroids (ANS), premature rupture of membranes, chorioamnionitis, (either clinical or histopathological) pregnancy-induced hypertension, and delivery mode. Neonatal data included BW, GA, type of delivery resuscitation needed, surfactant therapy, mode of assisted ventilatory support, and FiO_2 requirements. Neonatal outcomes included major neonatal morbidities and mortality. GA assessment was based on an early dating scan or the date of the last menstrual period. Intensive delivery room resuscitation included the need for endotracheal intubation, cardiac massage, or adrenaline. The definitions for complete ANS, respiratory distress syndrome (RDS), HsPDA, chorioamnionitis, sepsis, and necrotizing enterocolitis (NEC) were standardized as per Neonatal Research Network (NRN) as explained in our earlier publication [4,19].

Modes of assisted ventilator support included intermittent mandatory ventilation (IMV), high-frequency oscillatory ventilation (HFOV), nasal continuous positive airway pressure (NCPAP), or nasal intermittent mandatory ventilation (NIMV). Standard respiratory management included early NCPAP, early surfactant therapy, prophylactic caffeine, and extubation to NCPAP/NIMV and to nasal cannula. Infants who never received mechanical ventilation were also included in the study. If an infant had more than one respiratory support, the maximum form of ventilation for that day was used to score them. Infants who had either NCPAP or NIMV modes were grouped together.

BPD (Bronchopulmonary Dysplasia) Definition

BPD was defined as a categorical variable among survivors by the NICHD consensus definition of BPD. As per severity classification: no BPD, as not receiving supplemental oxygen (O_2) for 28 days or at 36 weeks; mild BPD, as receiving O_2 for ≥28 days but not at 36 weeks; moderate BPD, as receiving O_2 for ≥28 days plus <0.30 O_2 at 36 weeks PMA; and severe BPD, as receiving O_2 for ≥28 days plus ≥30% O_2 or positive pressure at 36 weeks PMA [6].

Statistical Methods

On each postnatal day, a set of variables were added based on the known risk factors for BPD. All variables, such as gestational age, birth weight, sex, race, lower segment caesarian section (LSCS), maternal chorioamnionitis, antenatal steroids, sepsis, air leaks, postnatal steroids, respiratory support, FiO_2, and HsPDA requiring treatment and NEC, were considered. Babies were included if they were alive on the day of prediction.

Although the major morbidities like sepsis, NEC and HsPDA were among the risk factors for BPD, they didn't change the outcome when the model was created similar to the model created by Laughon et al [17]. Finally, only six variables (gestational age, sex, birth weight, race, respiratory support, and FiO_2 requirement) were included in the final model as the other variables only marginally increased the predictive capacity of the model.

The predictive capability of the model was measured using a C statistic, which was similar to the area under the receiver operating characteristic curve (AUC). Multinomial regression using STATA 15.0 was performed to develop the prediction model using the variables of interest on the outcomes of BPD at each of the six time periods (1,3,7,14,21 &28). The C-statistic

of the individual predictor and the overall model were presented. Sensitivity, specificity positive predictive value, negative predictive value and likelihood ratio were calculated for each day's outcome. Statistical significance was set at 2-sided $p < 0.05$.

Results

Antenatal, perinatal, and neonatal demographics and outcomes. A total of 356 ELBW live born infants were admitted to the KKH NICU in the specified period. Among them 38 infants were excluded. 30 died within 12 hours of life and 8 were given palliative care. The study thus included 318 ELBW infants. The table 1 shows the risk factors for BPD which was classified as per their severity with death also included in the outcome measure.

Table1: Maternal and Neonatal Characteristics.

Outcomes	No BPD	Mild BPD	Moderate BPD	Severe BPD	Death	All	P values
No. of babies	n=59(18.5%)	n=55(17.3%)	n=93(29.2%)	n=60(18.8%)	n=51(16%)	n=318	
Birth weight (g) (mean±sd)	876.4±105	803±128	751.5±134	712.7±136	684±148	765.5±145	< 0.001
GA wk, (mean±sd)	29.3 ± 2	26.1 ± 1.5	25.6 ± 1.6	25.5 ± 1.8	25 ± 1.4	26.3 ± 2.2	< 0.001
Gender	Male	25 (42)	27 (49)	47 (51)	40 (67)	30 (59)	169 (53)
Ethnicity	Chinese	23 (39)	33 (60)	54 (58)	36 (60)	28 (55)	174 (55)
	Malay	14 (24)	10 (18)	27 (29)	15 (25)	13 (26)	79 (25)
	Indian	14 (24)	7 (13)	5 (5)	4 (7)	4 (8)	34 (11)
LSCS	53 (89)	39 (71)	59 (63)	32 (53)	29 (57)	212 (67)	< 0.001
Chorioamnionitis	14 (24)	23 (43)	45 (48)	32 (53)	26 (51)	140 (44)	0.008
HsPDA Medical treatment	2 (3)	21 (38)	33 (36)	20 (33)	16 (50)	92 (31)	< 0.001
HsPDA needing medical & ligation / ligation	0 (0.0)	8 (15)	21 (22)	21 (35)	1 (3)	51 (17)	< 0.001
Culture proven Sepsis (Early)	0 (0.0)	2(3)	0 (0.0)	1(2)	6(14)	9(3)	< 0.001
Culture proven Sepsis (Late)	1(2)	6(11)	17(18)	17(28)	10(23)	51(17)	< 0.001
Severe NEC Stage 3/4 &/or perforation	2 (3)	4 (7)	9(10)	13(22)	6 (17)	34 (11)	< 0.001
Air leaks	1(2)	5 (9)	15 (16)	12 (20)	7 (14)	40 (13)	0.025

GA: *gestational age;* ***HsPDA:*** *hemodynamically significant patent ductus arteriosus;* ***NEC:*** *necrotizing enterocolitis.*

The mean BW and GA for the cohort were 765 ± 145 g and 26.3 ± 2.2 weeks, respectively. The incidence of mild, moderate and severe BPD was 17% (55), 29% (93), 19% (60) respectively. About 67% (212) of neonates were born by LSCS. 89% (53) of the LSCS group had no BPD ($p<0.001$). Approximately 73% of mothers received antenatal steroids and chorioamnionitis was present in 44%. The mean BW was 712±136g and 684±148 g and the mean GA was 25.5±1.8 and 25±1.4 for severe BPD and death cohort respectively.

Babies with worsening BPD had comorbidities that included HsPDA, stage 3 NEC, and sepsis. About 35% of the babies in the cohort who were treated for HsPDA either medically or surgically had severe BPD. Thus, the burden of BPD was higher for those babies who needed medical or surgical treatment. About 37% of infants with sepsis died. BPD severity increased with late-onset sepsis and 28% of the babies with late onset sepsis had severe BPD. NEC (22%) was also associated with severe BPD.

Table 2 shows the relationship between modes of ventilation, FiO_2 requirements, and the severity of BPD. The use of CPAP as the maximum mode of ventilation was highest in the group with no BPD (61%) compared to those babies who developed severe BPD on day 1 of life (3.4%). In the group with severe BPD, the use of HFOV /IMV was high at 96.6 %.

Table 2: Respiratory support and mean Fio2 for each outcome by postnatal day

Day	Respiratory Support	No BPD n = 59(18.5%)	Mild BPD n = 55(17.3%)	Moderate BPD n = 93(29.2%)	Severe BPD n = 60(18.8%)	Death n = 51(16%)	P value
1	HFOV (%)	0 (0.0)	1 (1.8)	4 (4.3)	4 (6.8)	13 (25.5)	
	IMV (%)	22 (37.3)	48 (87.3)	86 (92.5)	53 (89.8)	37 (72.5)	
	CPAP (%)	36 (61)	6 (10.9)	3 (3.2)	2 (3.4)	1 (2)	< 0.001
	Nasal Cannula %	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	None %	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Mean FiO_2 %	26.7	35.1	40.5	37.0	57.5	
3	HFOV %	0 (0.0)	4 (7.3)	9 (9.7)	10 (16.9)	17 (33.3)	
	IMV %	7 (11.9)	22 (40.0)	45 (48.4)	28 (47.5)	11 (21.6)	
	CPAP %	38 (64.4)	29 (52.7)	39 (41.9)	21(35.6)	12 (23.5)	< 0.001
	Nasal Cannula %	1(1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	None %	13(22.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Mean FiO_2 %	21.1	25.4	30.0	29.4	54.2	
7	HFOV %	0 (0.0)	5 (9.1)	12 (12.9)	8 (13.6)	10 (19.6)	
	IMV %	0 (0.0)	9 (16.4)	34 (36.6)	25 (42.4)	7 (13.7)	
	CPAP %	29 (49.1)	40 (72.7)	47 (50.5)	25 (42.4)	8 (15.7)	
	Nasal Cannula %	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
	None %	28 (47.5)	1 (1.8)	0 (0.0)	1 (1.7)	0 (0.0)	
	Mean FiO_2 %	21.1	24.5	26.1	31.5	35.4	
14	HFOV %	0 (0.0)	1(1.8)	7 (7.5)	8 (13.6)	4 (8.0)	
	IMV %	1 (1.7)	11 (20.0)	34 (36.6)	31 (52.5)	11 (22.0)	
	CPAP %	17 (28.8)	42 (76.4)	52 (55.9)	18 (30.5)	4 (8.0)	
	Nasal Cannula %	1(1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	< 0.001
	None %	40(67.8)	1(1.8)	0 (0.0)	2(3.4)	0 (0.0)	
	Mean FiO_2 %	21.1	27.3	26.7	35.6	40.5	
21	HFOV %	0 (0.0)	0 (0.0)	3 (3.2)	6 (10.2)	2 (4.1)	
	IMV %	0 (0.0)	12 (21.8)	33 (35.5)	35 (59.3)	4 (8.2)	
	CPAP %	12 (20.3)	41 (74.5)	55 (59.1)	18 (30.5)	6 (12.2)	< 0.001
	Nasal Cannula %	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	None %	47 (79.7)	2 (3.6)	2 (2.2)	0 (0.0)	0 (0.0)	
	Mean FiO_2 %	21.0	24.1	29.2	34.8	41.1	
28	HFOV %	0 (0.0)	1 (1.8)	1(1.1)	5 (8.5)	1(2.0)	
	IMV %	0 (0.0)	4 (7.3)	29 (31.2)	37 (62.7)	3 (5.9)	
	CPAP %	3 (5.1)	49 (89.1)	63 (67.7)	16 (27.1)	2 (3.9)	< 0.001
	Nasal Cannula %	1 (1.7)	1(1.8)	0 (0.0)	1 (1.7)	0 (0)	
	None %	55 (93.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Mean FiO_2 %	21.0	24.1	28.6	31.2	42.0	

HFOV: *High Frequency Oscillatory Ventilation;* ***IMV:*** *Intermittent mandatory ventilation;* ***CPAP:*** *Continuous Positive Airway Pressure;* ***sd:*** *Standard Deviation.*

However, by day 3, 64.4% (38) of those who had mild BPD cohort needed only CPAP.

By day 28 of life, 71.2% of intubated babies had developed severe BPD. The FiO_2 was also higher in those babies who had severe BPD or died compared to those with mild and moderate BPD for each specified day of life.

BPD estimator

Table 3 shows the six variables which independently and collectively predicted outcome for BPD on each day of life as explained before. These factors in aggregation also improved the prediction outcome. Maximum respiratory support and FiO_2 requirement served as the best predictors on each specified day (AUC 0.85–1) (Table 3) while gestational age remained a significant factor in predicting outcome from day one of life onwards (0.937). The mode of respiratory support and FiO2 increased the probability of BPD from day 14 onwards and improved prediction from day 14 (0.985) and thus the collective prediction improved from 0.992 to 1 by day 21 of life.

Table 3: Model Prediction C statistic (Akin to Area under the receiver operating characteristic curve) and individual variables for Day 1-28 models for the development cohort

Day 1-calculator AUC=0.992		**Day 3-calculator AUC=0.996**		**Day 7-Calculator AUC =0.987**	
Variable	C Statistic	Variable	C Statistic	Variable	C Statistic
Gestational age	0.937	Gestational age	0.937	Gestational age	0.937
Birth weight	0.799	Birth Weight	0.799	Birth Weight	0.799
FiO_2	0.898	FiO_2	0..905	FiO_2	0.850
Respiratory Support	0.998	Respiratory Support	0.945	Respiratory Support	0.933
Race & ethnicity	0.713	Race & ethnicity	0.713	Race & ethnicity	0.713
Male Sex	0.799	Male Sex	0.799	Male Sex	0.799
Day 14-Calculator AUC=0.998		**Day 21-Calculator AUC=0.998**		**Day 28-Calculator AUC=1.0**	
Variable	C Statistic	Variable	C Statistic	Variable	C Statistic
Gestational age	0.937	Gestational age	0.937	Gestational age	0.937
Birth weight	0.799	Birth weight	0.799	Birth weight	0.799
FiO_2	0.937	FiO_2	0.982	FiO_2	0.984
Respiratory Support	0.985	Respiratory Support	0.985	Respiratory Support	1.000
Race & ethnicity	0.713	Race & ethnicity	0.713	Race & ethnicity	0.713
Male Sex	0.799	Male Sex	0.799	Male Sex	0.799
***AUC:** area under the curve*					

Table 4a shows that specificity and negative predictive values are high for each day from day1 till day 28 of prediction for all the different outcomes of BPD. The probability of predicting moderate to severe BPD ranged from 51-56% on day 14 of life.

Table 4a: showing sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratio

Day 1	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR+**
No	81.4	90.8	68.6	95.2	8.8
Mild	23.6	94.2	48.1	84.5	4.1
Moderate	65.6	59.0	42.1	79.1	1.6
Severe	33.9	90.0	45.5	84.6	3.4
Death	18.8	97.7	50.0	90.9	8.2

Day 3	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR+**
No	88.1	90.8	70.3	96.9	9.6
Mild	23.6	93.8	46.4	84.4	3.8
Moderate	64.5	62.0	43.5	79.4	1.7
Severe	32.2	91.2	47.5	84.5	3.7
Death	34.4	97.4	61.1	92.5	13.2
Day 7	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR+**
No	84.7	93.1	75.8	96.0	12.3
Mild	27.3	89.8	38.5	84.1	2.7
Moderate	59.1	64.1	43.7	77.0	1.6
Severe	44.1	90.1	53.1	86.4	4.5
Death	12.0	97.0	27.3	92.1	4.0

Day 14	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**LR+**
No	84.7	94.7	80.6	96.0	16.0
Mild	38.2	92.2	53.8	86.2	4.9
Moderate	71.0	67.2	51.2	82.7	2.2
Severe	49.2	89.8	55.8	87.1	4.8
Death	10.5	99.6	66.7	94.0	26.2

Day 21	Sensitivity	Specificity	PPV	NPV	LR+
No	84.7	96.3	86.2	95.9	22.9
Mild	36.4	90.1	47.6	85.2	3.7
Moderate	61.3	67.0	48.3	77.5	1.9
Severe	50.8	87.2	51.7	86.8	4.0
Death	8.3	99.6	50.0	96.0	20.7

Day 28	Sensitivity	Specificity	PPV	NPV	LR+
No	94.8	99.5	98.2	98.6	189.6
Mild	38.2	92.1	55.3	85.4	4.8
Moderate	67.7	69.1	53.4	80.4	2.2
Severe	55.9	88.7	57.9	87.9	4.9
Death	16.7	99.6	50.0	98.1	41.7
PPV positive predictive value; NPV negative predictive value; LR likelihood ratio					

Thus, a nBPD estimator tool that can predict individual estimates of nBPD risk or death at each postnatal day, i.e., D1, D3, D7, D14, D21, and D28, was developed, and a web-based version of the tool is made available. BPD prediction with the application of the estimator in two infants is shown in Table 4b.

Table 4b: Table of Estimated Probabilities of Bronchopulmonary Dysplasia or Death by Postnatal Day for Two Hypothetical Infants

24-week gestational age, 550-grams birth weight, Malay, male						
		Probability of Outcome				
Day	Respiratory support and FiO_2	Death	Severe BPD	Moderate BPD	Mild BPD	No BPD
1	IMV and FiO_2=35%	0.24	0.36	0.33	0.07	0.00
3	IMV and FiO_2=38%	0.18	0.36	0.40	0.05	0.00
7	IMV and FiO_2=24%	0.13	0.46	0.36	0.05	0.00
14	IMV and FiO_2=40%	0.17	0.55	0.27	0.01	0.00
21	HFOV and FiO_2 =35%	0.00	0.54	0.46	0.00	0.00
28	IMV and FiO_2 =40%	0.00	0.53	0.44	0,02	0.00

27-week gestational age, 710-grams birth weight, Chinese, male						
		Probability of Outcome				
Day	Respiratory support and FIO_2	Death	Severe BPD	Moderate BPD	Mild BPD	No BPD
1	IMV and FiO_2=35%	0.13	0.33	0.33	0.18	0.03
3	CPAP and FiO_2=21%	0.12	0.31	0.29	0.20	0.09
7	CPAP and FiO_2=35%	0.09	0.52	0.17	0.17	0.05
14	IMV and FiO_2=25%	0.14	0.46	0.30	0.09	0.01
21	CPAP and FiO_2=30%	0.11	0.31	0.46	0.12	0.00
28	CPAP and FiO_2=25%	0.05	0.18	0.46	0.30	0.00

Discussion

In modern neonatal practice, nBPD remains a great concern in the extremely preterm infants as no specific effective management strategy exists. A reliable nBPD predictive tool could identify infants at risk for developing BPD, especially those infants at risk of severe BPD. The predictive strategies are set with a goal of identifying those infants at high risk of developing BPD, thus aiming at reducing further damage to the immature lung and for prognostic purposes. Birth weight, GA, and gender were among the most important predictive variables in our cohort. The babies with moderate and severe BPD and those who died had the lowest GA compared to those who had no/mild BPD. Similarly, babies with the lowest BW had either severe BPD or death. Our previous study showed comparable results [4].

Several other studies have also shown similar comparable results with birth weight, gestation and gender being the major risk factors for nBPD [10,20]. Major morbidities like sepsis, NEC, and PDA, were good predictors for nBPD in our cohort like many other studies [21,22].

Mechanical ventilation has been shown to be a very significant factor associated with nBPD in many studies [17,21]. In our cohort group with moderate /severe BPD, the use of HFOV/IMV was high from day 1 onwards. By day 3 it can be assumed that if the child needed only CPAP, the risk of BPD is low. Similarly, use of CPAP as the maximum support had either no/mild BPD from day1 till 14 of life. However, as the days on mechanical ventilation progressed, BPD severity also increased.

Many types of prediction models have been constructed over the years particularly for predicting BPD/death to enable the doctors to modify risk factors and to aid anticipatory guidance to parents. However, most of the prediction studies were conducted before wide spread use of surfactant or HFOV was used as a mode of ventilation and before the concept of use of antenatal steroids and hence may not be applicable in modern neonatal practice where nBPD is the main type of chronic lung injury in ELBW infants [23,24].

The logistic regression equations used were very complicated and were not practical for bedside application [25]. Additionally, several studies did not emphasize the effect of modifying risk factors with advancing age nor death was included as a competing outcome [20]. The clinician would mainly be interested to have a reliable tool in their local population with better precision and real time insight.

systematic review and external validation study was conducted by Onland et al. [26], which included approximately 26 prediction models, among which only 14 used multivariate models for analysis. Only two models have classified BPD as per the grades of their severity [16,17].

Among them, only two models have shown good calibration and discrimination [17,27]. However, calculators by Ryan et al. [27] which was published nearly three decades ago estimates the 'old BPD' risk on the fourth day of life.

The web-based NRN BPD estimator has been validated and published to determine a risk estimate for BPD and the competing outcome of death by postnatal day. The NICHD estimator has also been used to establish eligibility, enrollment stratification, and sample size calculations in NRN trials.

So, our aim was to create a similar estimator, and the contributions of risk factors for predicting nBPD over several postnatal days have been investigated. Thus, this estimator shows high specificity from day 1 onwards till day 28 and thus gives an insight to the treating physician to consider preventive strategies and management options at early stages. Our model will be useful for the Asian population, and thus, it can be used in our multiethnic population study that includes Chinese, Malay, Indian, and other minorities. Table 4 shows two infants whose BPD was predicted using the model.

This is the only study performed in an Asian population taking into consideration of ethnicity and the risk factors pertaining in our population for the development of BPD. It is reassuring that the contributions of the covariates in our cohort are a way similar when compared with those of the NRN Estimator. The online BPD outcome estimator will be made readily available and could be easily accessible for neonatologists and pediatricians taking care of very premature infants in the region.

This model also helps us in planning preventive strategies such as postnatal steroid therapy and enable discussion with parents, thus preventing further worsening of lung injury and even death. A recent study used the NICHD BPD Outcome Estimator and showed that postnatal corticosteroid treatment could be decided and planned [28]. Therefore, our estimator could be of high value for clinical decisions supporting its clinical utility in deciding the timing of corticosteroid treatment.

This model can also serve as a basis for future research in the prevention of morbidities in this vulnerable population. However, this estimator may have some limitations on usage.

The NIH 2018 BPD work shop emphasized on considering newer modes of noninvasive ventilation and modifying the BPD classification [29]. The change in practice and use of high flow nasal cannula may create some setbacks to the use of this calculator. We started using high flow nasal cannula only recently.

However, the old definition is still being followed worldwide; thus, the estimator can be used in the present situation.

Another limitation of our study is that we didn't do separate validation for the study. We are planning to do external validation at other neonatal units in Singapore and some of the Asian countries to know the usefulness of our prediction model.

Conclusion

A reliable BPD estimator plays a great role in the early prediction of BPD, and this would help with the implementation of preventive strategies to reduce the severity of BPD. Moreover, it is an objective way of prognostic counseling which would l help parents in decision-making when faced with difficult situations. Further efforts will help in implementing this tool for future research projects and for QI initiatives. The BPD estimator will be available in the link below.

excel BPD estimator.xlsx

Conflict of Interest

The authors declare no conflict of interest.

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Contributor's Statement Page

Dr Geetha had full access to all of the data in this study, takes responsibility for the integrity of the data and the accuracy of the analyses. She conceptualized and designed the study, did the data collection and review of case notes, selected data for inclusion in analyses, and drafted initial manuscript.

Prof Rajadurai was the senior mentor and was involved in the study concept and design, data analysis and interpretation along with revision of the initial manuscript.

Dr Chua MC was involved in the review and revision and critical analysis of the manuscript.

Dr Pratibha Agarwal was involved in the study concept and in the review and revision of the manuscript.

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