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ARTICLE

Bronchopulmonary dysplasia: risk prediction models for very-low-birth-weight infants

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Abstract

Objective Our objective is to develop risk prediction models for moderate/severe bronchopulmonary dysplasia (BPD) and BPD and/or death in very-low-birth-weight infants (VLBWI) at birth, 3, 7, and 14 postnatal days.

Study design It is a multicenter study including 16,407 infants weighing 500–1500 g (2001–2015) from the Neocosur Network. BPD was defined as oxygen dependency at 36 weeks. Variables were selected using forward logistic regression models. Predictive values were evaluated using the ROC curve.

Results In total, 2580 (15.7%) presented BPD and 6121 (37.3%) BPD/death. The AUC values for the BPD models were 0.788, 0.818, 0.827, and 0.894 respectively. For BPD/death, the AUC values were 0.860, 0.869, 0.867, and 0.906. BW and gestational age had higher contribution at birth; at later ages, the length of oxygen therapy and ventilation had the highest contribution. All AUC values were statistically significant when compared with a neutral value of 0.5 (p-value < 0.001).

Conclusions We developed high predictive power models for moderate/severe BPD and BPD/death at four postnatal ages.

Introduction

Bronchopulmonary dysplasia (BPD) is the most frequent long-term respiratory morbidity in surviving very-low-birth-weight infants (VLBWI). BPD has been independently associated with worse respiratory and neurological long-term outcomes [1]. Northway first described and characterized BPD in 1967 [2]; multiple refinements of this definition have been suggested [3, 4]. In 2001, Jobe and Bancalari developed a new definition considering gestational age (GA) and oxygen requirements [5]. Their definition classifies infants based on GA and the need for oxygen and ventilatory support. Those born at <32 weeks who required oxygen >21% for at least 28 days where classified, according to their respiratory status at 36 weeks postmenstrual age (PMA): room air (mild), oxygen <30% (moderate) and oxygen >30%, and/or positive pressure ventilation or CPAP (severe). Further refinement based on the early experience of this classification established moderate and severe BPD as having a significantly worse long-term outcome compared with mild BPD [4].

Despite major advances in neonatal care, BPD incidence has not declined [6, 7]. International networks report incidences of moderate–severe BPD in VLBWI from 13.7 to 32% [8–10], while our incidence in the Neocosur network is 25% [11].

Originally, BPD was described as a clinical–radiological entity that presented as early severe respiratory failure that evolved into chronic lung disease in preterm infants exposed to mechanical ventilation, with high parameters and high oxygen needs [2]. The introduction of a surfactant and the use of antenatal steroids (ANS) and the less invasive respiratory techniques to approach respiratory distress syndrome (RDS) contributed to a decrease in the incidence of the classical BPD. Nevertheless, the survival of very preterm infants with lower birth weights and GA exposed to ANS, who are often treated with exogenous surfactant

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therapy [12], has been responsible for a new presentation of the disease, known as **"new BPD"** [7].

Chorioamnionitis, maternal hypertension, and intrauterine growth restriction (IUGR) have been the most common antenatal risk factors described in the literature [12, 13]. Perinatal risk factors include lower GA, low birth weight (LBW), male gender, Apgar score, and resuscitation maneuvers [14]. The known postnatal risk factors are RDS, sepsis, air leak, inadequate nutrition, patent ductus arteriosus (PDA), oxygen therapy, and magnitude and/or type of respiratory support [8, 15–17]. Histologically, new BPD is characterized by an altered structure of lung parenchyma, including a decreased number of alveoli and vasculature [18].

Currently, few therapies have demonstrated an effect in decreasing BPD, namely vitamin A and postnatal steroids [7], although systemic steroids present unacceptable long-term adverse effects. Early caffeine therapy has been associated with a decrease in BPD incidence, although the quality of evidence is low [19]. Under current investigation are intra-traqueal steroid and mesenchymal cell administration [20, 21]. The implementation of less invasive respiratory therapies has shown to decrease the risk of developing BPD, albeit the total effect is modest [22]. New therapies and strategies are urgently needed for early BPD prevention or attenuation of severity.

For this purpose, it is important to develop prediction models in order to select a high-risk population that may benefit from potential therapies at different postnatal ages. The aim of this study was to develop risk prediction models for future evaluation of moderate–severe BPD or death at four postnatal ages: at birth and at 3, 7, and 14 days.

Methods

This multicenter, observational, cohort study used information from the Neonatal Neocosur Network database, which includes 15 permanent centers from five South-American countries (Argentina, Chile, Paraguay, Peru, and Uruguay). The Neocosur network provides a continuous database gathering prospective information from all inborn VLBWI (BW from 500 to 1500 g) in the participating centers. Centers and patient identities are kept anonymous. Biodemographic characteristics and outcome data of all VLBWI born in these centers are collected, using predefined diagnostic criteria and an online data entry.

We included the data from all inborn infants with BW between 500 and 1500 g born between 2001 and 2015. Infants who died in the delivery room, infants with major malformations, and those with early transfer to another center were excluded.

Moderate BPD was defined as >28 days of oxygen plus oxygen dependency of <30% at 36 weeks PMA, while severe BPD with oxygen requirement of >30% at 36 weeks PMA or need of CPAP or mechanical ventilation (MV) [7]. The outcome BPD and/or death refers to the group of infants who developed moderate or severe BPD, plus all infants who died of any cause during their hospital stay. In the subgroup analysis done at different postnatal ages, infants were included, who were alive at each specific age. The Ethics Committee of the Faculty of Medicine, Universidad Catolica de Chile (database center) evaluated and approved the study.

Student's *t* test was used to compare populations with and without moderate–severe BPD. χ^2 tests were used to compare proportions. Continuous variables are shown as mean and standard deviation, whereas categorical variables are shown as number of cases and percentages, and Apgar score as median and interquartile range. All statistics analyses were done using R [23], a standard statistical software.

Multiple forward stepwise logistic regression modeling was used to select variables that significantly contributed to each of the eight models; that is, variables that were significantly associated with moderate–severe BPD or moderate–severe BPD and/or death. Variables included in the perinatal model (models 1 and 2) were PROM (defined as membrane rupture before labor), small for gestational age (SGA, BW below the 10th percentile by Fenton [24]), maternal hypertension, ANS (at least one course), GA, BW, gender, type of delivery, multiple birth, 1- and 5-min Apgar score, and endotracheal intubation at birth. For models 3 and 4—the 3-day analysis variables added were RDS, early-onset sepsis, surfactant use, MV, and air leaks. Furthermore, the 7 days' analysis (models 5 and 6) only added PDA to the other core variables. Finally, models 7 and 8 for 14 days are presented: MV for at least 7 days, and oxygen supplementation for at least 14 days and late-onset sepsis. The predictive power of each model was analyzed with the area under the curve of a receiver-operating characteristic curve (AUC).

All predictive models were validated by using a 20% test sample, previously set aside, and calculating the AUC statistic. In addition, we verified that the models predict outcomes in each center by calculating the AUC statistic, using only the data from the specific unit.

Results

Nineteen thousand eight hundred and ten preterm infants were born in the 15 centers from 2001 to 2015; 3403 met the exclusion criteria. Thus, 16,407 were included in the study, 80% as model sample, and 20% as test sample. The study population had a mean ± SD BW of 1099 ± 275 g, a

Table 1 Patient characteristics and outcomes of all infants included in the study, and those with and without moderate–severe BPD

Variable	All infants $n = 16.407$	BPD (–) $n = 13.827$	BPD (+) $n = 2.580$	p-value
Birth weight, g, mean ± SD	1099 ± 275	1122 ± 273	972 ± 242	<0.001
Gestation age, weeks, mean ± SD	29 ± 2.9	29.2 ± 2.9	27.7 ± 2.3	<0.001
Male, *n* (%)	8368 (51)	6499 (47)	1496 (58)	<0.001
1-min Apgar score, median (25th–75th)	7 (4–8)	7 (6–8)	6 (3–7)	<0.001
5-min Apgar score, median (25th–75th)	8 (7–9)	9 (8–9)	8 (7–9)	<0.001
Prenatal steroids, *n* (%)	12,633 (77)	4383 (81.7)	2110 (81.8)	0.910
Intubation at birth, *n* (%)	6727 (41)	3733 (27)	1522 (59)	<0.001
RDS, *n* (%)	12,469 (76)	9541 (69)	2425 (94)	<0.001
Surfactant use, *n* (%)	8368 (51)	5393 (39)	1909 (74)	<0.001
PDA, *n* (%)	6235 (38)	4425 (32)	1651 (64)	<0.001
ICH ≥ III, *n* (%)	1641 (10)	581 (4.2)	325 (12.6)	<0.001
NEC ≥ II, *n* (%)	1723 (10.5)	1189 (8.6)	387 (15)	<0.001
Late sepsis, *n* (%)	3117 (19)	2489 (18)	929 (36)	<0.001
Mechanical ventilation > 7 days, *n* (%)	3610 (22)	1798 (13)	1496 (58)	<0.001
$O_2 > 14$ days, *n* (%)	5414 (33)	3595 (26)	2477 (96)	<0.001
Mortality, *n* (%)	**3938 (24)**	442 (3.2)	163 (6.3)	<0.001

median GA of 29 weeks (CI 95%, 24–34 weeks), and 51% were male. Of the 16,407 VLBWI included, 2580 (15.7%) developed moderate–severe BPD, and 6121 (37.3%) presented with moderate–severe BPD or death. General characteristics and risk factors of the overall population, and the non-BPD and BPD population, are shown in Table 1. As expected, infants who developed BPD were smaller in weight and less mature by GA, had a higher incidence of intubation and surfactant administration at birth, and had lower Apgar scores. In addition, infants who developed BPD also had a significantly higher incidence of PDA, NEC, and late-onset sepsis, and a greater proportion required prolonged MV (>7 days).

The five variables that contributed the most to each selected outcome, based on the AUC statistics are shown in Table 2. The final predictive power of the full model for each postnatal age and their validation are shown in Fig. 1 and Table 2. The perinatal model had an AUC of 0.788 for BPD and 0.860 for BPD and/or death. Predictive power increased with postnatal age reaching a maximum at 14 days model with an AUC of 0.894 for BDP and 0.906 for BPD and/or death. All AUC in the eight models were statistically significant when compared with a neutral value of 0.5 (p-value < 0.001). The variability of the predictive power performance of each of these eight models applied to the 15 participating centers is shown as a box plot in Fig. 2.

Perinatal models

Birth weight contributed the most in explaining BPD, followed by GA and 1-min Apgar score. Another important contributing variable was male gender. The fifth variable for the BPD model was need for intubation at birth, while the fifth variable in BPD and/or death was ANS.

Day 3 models

The use of MV—as a dichotomous factor—has a strong effect on the outcomes of interest in the models; it is the second contributing factor after birth weight, which continues to be the variable that contributes the most in both models. The other variables with significant contribution to the BPD model at 3 days were RDS, gender, and maternal hypertension. Concerning the BPD and/or death model, the other three variables were gender, air leak, and 1-min Apgar score.

Day 7 models

At the age of 1 week, birth weight and the use of MV continue to be the most relevant contributors of the predictive models. Nevertheless, PDA appeared as the third contributing variable for the prediction of BPD or mortality. Gender continues to appear as a contributing factor, and

Table 2 Factors selected by stepwise logistic regression model that constitutes BPD and BPD/death prediction models at different postnatal ages with their cumulative contribution, and validation of final models

Perinatal				Day 3			
BPD		*BPD/death*		*BPD*		*BPD/death*	
Variable	AUC	Variable	AUC	Variable	AUC	Variable	AUC
Birth weight	0.740	Birth weight	0.813	Birth weight	0.740	Birth weight	0.800
Gestational age	0.762	1-min Apgar	0.838	Mechanical ventilation	0.793	Mechanical ventilation	0.849
1-min Apgar	0.775	Gestational age	0.847	RDS	0.800	Gender (male)	0.854
Gender (male)	0.782	Gender (male)	0.852	Gender (male)	0.806	Air leak	0.857
Birth intubation	0.784	Antenatal steroids	0.854	Maternal hypertension	0.809	1-min Apgar	0.861
Final model	**0.788**	**Final model**	**0.860**	**Final model**	**0.818**	**Final model**	**0.869**
Validation	***0.782***	***Validation***	***0.865***	***Validation***	***0.812***	***Validation***	***0.873***
Day 7				Day 14			
BPD		*BPD/death*		*BPD*		*BPD/death*	
Variable	AUC	Variable	AUC	Variable	AUC	Variable	AUC
Mechanical ventilation	0.705	Birth weight	0.795	Oxygen > 14 days	0.856	Oxygen > 14 days	0.845
Birth weight	0.800	Mechanical ventilation	0.847	MV > 7 days	0.879	MV > 7 days	0.885
PDA	0.810	PDA	0.853	SGA	0.883	Birth weight	0.899
Gender (male)	0.817	Gender (male)	0.858	RDS	0.886	Mechanical ventilation	0.903
RDS	0.822	Air leak	0.861	Gender (male)	0.890	Gender (male)	0.904
Final model	**0.827**	**Final model**	**0.867**	**Final model**	**0.894**	**Final model**	**0.906**
Validation	***0.805***	***Validation***	***0.856***	***Validation***	***0.892***	***Validation***	***0.910***

AUC area under curve, *PDA* patent ductus arteriosus, *RDS* respiratory distress syndrome, *MV* mechanical ventilation, *SGA* small for gestational age

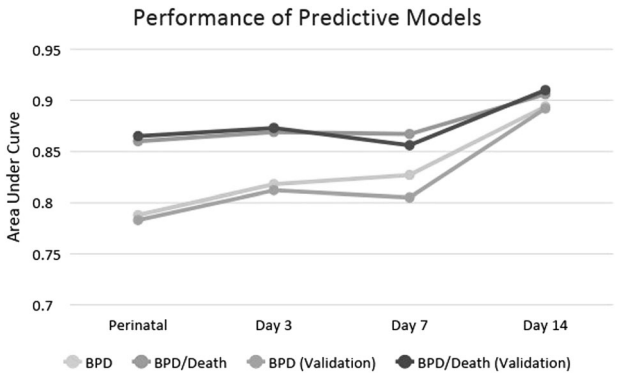

Fig. 1 Performance of predictive models at different postnatal ages

RDS is the fifth variable for the BPD model, while air leak is the fifth for BPD and/or death.

Day 14 models

Finally, at 14 days, the length of respiratory support therapies (oxygen and MV) is the main contributor to these models. The other three big contributors to the BPD model were IUGR, RDS, and gender. In the BPD and/or death model, the other contributors were birth weight, use of MV, and gender.

Several other variables, including type of delivery, 5-min Apgar score, PROM, surfactant use, early-onset sepsis, multiple birth, PDA treatment with NSAIDs, and late-onset sepsis, were statistically associated with BPD and BPD and/or death, but did not significantly contribute to improve the predictive power of the models.

Discussion

We developed several high predictive power models for BPD and BPD and/or death at four postnatal ages. Predictive power increases with postnatal age and is always greater for predicting BPD or death rather than BPD alone. In the later models (days 7 and 14), respiratory support therapies required by the patients appeared as important predictive factors, and thus, can be clinical clues

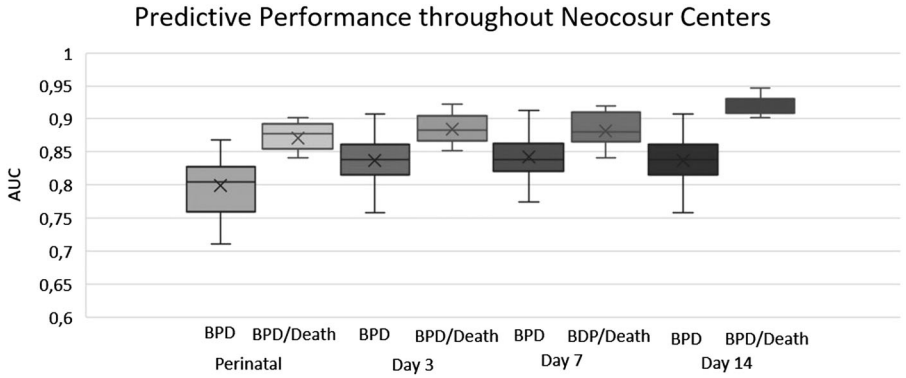

Fig. 2 Predictive performance of models throughout Neocosur centers

of high-risk patients. However, certain perinatal characteristics, such as birth weight and gender, persisted as risk factors throughout all models.

The rationale for selecting only infants with moderate–severe BPD is that these are the most vulnerable VLBWI, among which a poor respiratory and neurological outcome is expected [4, 25]. Birth weight was the most relevant predictive variable among all postnatal models. Gender was also an important contributor for all postnatal ages. This finding agrees with recent previous BPD predictive studies [6, 15, 26–28]. GA and 1-min Apgar score were important variables at the perinatal age model, and this has also been seen in other similar studies [26–28]. Intubation at birth appeared as an important contributor for BPD in the perinatal model. A previous study [29] suggested that intubation may play a role in the development of BPD. In addition, the current best evidence shows that stabilization with CPAP, avoiding intubation, decreases the risk of BPD and/or death in VLBWI [29–32]. Recent recommendations for initial delivery room management of VLBWI include avoidance of intubation, if possible [33, 34]. ANS appeared as a protective factor for the combined BPD and/or death outcome. The role of ANS has been extensively described in the literature, and although it decreases mortality, it has not been associated with a decrease in BPD [35], although it has been postulated that this could be a result of overadjustment for variables affected by ANS [36]. At later postnatal ages, other contributing variables were the presence of RDS, air leak, and PDA. These factors have been associated with increased risk of BPD in another recent study [28]. The need for MV is also an expected important contributor, as it has been considered a factor in the pathogenesis [7, 12, 15, 16] of BPD and has appeared as a predictive factor in other studies [8, 26–28]. The need for prolonged use of oxygen and MV are also expected contributors, at increasing postnatal age [7, 28, 37]. Moreover, oxygen is the treatment and used for the definition of BPD and MV may be part of the treatment. Interestingly, SGA appeared as a contributing factor for BPD prediction at age 14 days. There has been growing evidence that IUGR and possible other nutritional factors are involved in BPD development [7, 33].

In accordance with our proposal, measuring the predictive value at different postnatal ages has been commonly used in recent studies [26, 27], and higher predictive power at later postnatal ages was transversely described.

From the actual prediction models, Laughon et al.'s [26] web estimator is the most similar to our proposal. Our research was based on a multicenter study population using information from a database with predefined definitions collected prospectively in their participating centers. In contrast, Laughon's data included patients from only one country, while our study includes patients from five countries and from different regions. Both studies utilized the same statistical strategy to identify the predictive risk factors and developed models for different postnatal ages. However, the main differences between these studies were the use of five different outcomes: no BPD, mild BPD, moderate BPD, severe BPD, and death; while we only used two: moderate–severe BPD and moderate–severe BPD or death. The other important difference is that they identified the six strongest predictors (factors that enhanced predictive ability in the models) throughout the six models developed independently and then, they designed the final model using only those six factors in their different contributing role. In our case, each model was developed independently, so different factors appeared throughout the models at each postnatal age and for the two outcomes, making them more specific. A recent study was published using the NICHD BPD Outcome Estimator, supporting its clinical utility in deciding corticosteroid treatment [38]; therefore, considering our estimator is more specific, as it could be of high value for clinical decisions.

The present study has certain limitations; our database does not include all potential factors for BPD. Chorioamnionitis has been described as a risk factor for BPD in previous literature [14, 39]. Initially, it was not included in our models because its recording in the database started in 2012; therefore, there were 11 years with missing data. Yet, considering its importance, our group analyzed the

population from 2012 to 2015, to include chorioamnionitis in the analysis. The resulting models were similar to the original models, and chorioamnionitis had only a marginal contribution in the model for BDP prediction, in line with Ballard's 25-year cohort findings [39]. Another limitation of our study is that specific respiratory parameters are not registered in our database. Thus, fraction of inspired oxygen, peak inspiratory pressure, oxygenation index, and positive end-expiratory pressure that have been described as predictors of BPD in several studies [26, 27, 37], could not be analyzed.

The strengths of this study are many; the major strengths of the NEOCOSUR data is the inclusion of a large sets of data centers with high clinical standards and different population from five countries that meet international standards for neonatal care; the heterogeneity of the study populations makes these models widely applicable. In addition, in contrast to other predictive models, in our study each postnatal age was analyzed with all possible contributing variables recorded in our database, so all variables were considered in each analysis, and the resulting models display the actual contribution in each postnatal age. Finally, the eight models were applied in all 27 centers with no great variability among them, showing the stability of the model.

Future efforts should be made within the network following guidelines for quality improvement [32, 40, 41] regarding BPD, with the intention to decrease this most frequent sequel in surviving VLBWI.

Conclusions

We conclude that the developed prediction models for moderate–severe BPD are highly predictive and can be useful in the selection of VLBWI of greater risk, even with variables present early after birth. These models provide opportunities for selecting candidates for clinical trials of potential preventive therapies and identifying high-risk patients on whom one should allocate resources to prevent this long-term respiratory morbidity. Risk calculator can be accessed in www.neocosur.org.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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