Personalized lung care: "Bronchopulmonary Dysplasia Risk Prediction Tool Tailored for Neonates Born in the Resource-limited Settings."

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Abstract

Purpose: Predicting Bronchopulmonary dysplasia (BPD) to assess the risk-benefit of the therapy is necessary due to the side effects of medications. We developed and validated an instrument for predicting BDP and compared it with an instrument currently used in neonates born in a Brazilian hospital. **Methods:** Retrospective cohort of patients born between 2016 and 2020, with gestational ages (GA) between 23 and 30 weeks. Predictive equations were elaborated using methods of selection of component variables: stepwise, conditional inference tree, Fisher's exact test and all the collected variables; 70% of the sample was randomly selected for the construction of risk prediction equations, and the remaining 30% were used for their validation, application and comparison with the National Institute of Child Health and Human Development (NICHD) instrument published in 2011, currently used in that institution. Sensitivity, specificity, and predictive values of the equations were calculated. **Results:** The equation that used variables whose p-value was lower than 5% in Fisher's exact test (clinical chorioamnionitis, GA, birth weight, sex, need for surfactant, patent ductus arteriosus, late-onset sepsis, inspired fraction of oxygen, and respiratory support) presented the best results: specificity of 98% and positive predictive value of 93%. Our instrument allowed applying the prediction to small-for-gestational-age (SGA). The currently used calculator applied to our population had a specificity of 93% and a positive predictive value of 75% and could not be applied to SGA patients. **Conclusion:** Our tool has a higher specificity and positive predictive value than the foreign instrument and is suited for SGA.

Title page

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Ethics approval

Ethical Approval: the study received ethical approval from the Institution's Human Research Ethics Committee of the Ribeirão Preto Medical School (CEP FMRP), Opinion number: 1.903.783/CAAE 63764517.4.0000.5505).

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Not applicable.

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The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All the authors contributed to the study conception and design. Data collection was performed by Flavia Maria de Medeiros Cavalcante Meneghetti, Cristina Calixto, Cristina Helena Faleiros Ferreira and Elaine Fukumoto Vieira. Material preparation and analysis were performed by Flavia Maria de Medeiros Cavalcante Meneghetti, Walusa Gonçalves Assad Ferri and Davi Casale Aragon. The first draft of the manuscript was written by Flavia Maria de Medeiros Cavalcante Meneghetti and all authors commented on previous version of the manuscript. All authors read and approved the final manuscript.

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Running Head: "Personalized Bronchopulmonary Dysplasia Prediction Tool"

Abstract

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What is Known:

Postnatal corticosteroid is a proposed strategy for preventing Bronchopulmonary Dysplasia (BPD) in preterm neonates. However, it is known that corticosteroids have potential side effects, demanding a careful assessment of their risk-benefit profile before administration.

The predictive tools for BPD developed until the moment have limitations when applied to populations with unique characteristics like preterm born in developing countries, which could affect their accuracy.

What is New:

A predictive tool specifically designed for a developing country's population demonstrates superior specificity and positive predictive value performance compared to the currently used foreign instrument. The new tool is more accurate in predicting BPD, which could lead to more targeted and effective interventions.

The predictive tool can predict BPD in small-for-gestational-age (SGA) patients, which the NICHD model could not do effectively. The data highlights the suitability of the new instrument to the specific needs of the local population.

1 Introduction

Bronchopulmonary dysplasia (BPD) is one of the main morbidities in premature infants [1,2]. Its multifactorial etiology includes genetic predisposition associated with environmental and behavioral factors [3].

Early interventions may decrease the risk of BPD [4], with corticosteroids being the most studied medication for preventing the disease [5,6]. However, the risks and benefits of their use must be better investigated due to side effects[7].

Doyle *et al.* observed in 2005 and 2014 that administering corticoids in patients with an estimated risk $>$ 60% of developing moderate and severe BPD showed higher benefits in preventing cerebral palsy development [8,9].

In 2011, the National Institute of Child Health and Human Development (NICHD) published a BPD risk prediction tool (https://neonatal.rti.org/) capable of estimating individual risks of BPD or death[10]. Since then, this instrument has proved particularly useful in selecting patients for corticoid use. However, this equation was developed in a North American population.

The prediction of BPD should be based on the characteristics of the served population, with the translational aspect of predictive equations developed in different realities needing to be more questionable[11].

This study aimed to build a predictive equation for BPD in premature patients born at our institution, comparing the risks determined by it with the predictive values of the foreign instrument currently used in our service. The elaboration of a specific instrument will allow the proper identification of local candidates to prevent moderate and severe forms of the disease using postnatal corticoids, improving the treatment effectiveness.

2 Methods

A retrospective cohort study was conducted with patients registered in the Neonatal Database of a Brazilian tertiary hospital, born in the years 2016 to 2020 (5 years), with gestational ages between 23 and 30 weeks and birth weight between 401 and 1250 g.

Newborns with complex congenital heart disease diagnoses, major lung malformations, and deaths before 28 days of life were excluded from the study.

The analyzed antenatal variables consisted of maternal systemic arterial hypertension (chronic or pregnancy-induced arterial hypertension, with or without edema and proteinuria), maternal smoking, chorioamnionitis (considered through clinical or laboratory criteria: maternal leukocytosis, with no other identifiable infectious focus that would justify it), and use of antenatal corticosteroids (betamethasone, complete and incomplete cycles). The analyzed postnatal variables were gestational age (GA), birth weight in grams (BW), gender (male or female), adequacy for gestational age using Intergrowth-21st curves[12], with birth weight below the 10th percentile for gestational age classified as small for gestational age (SGA), and birth weight above the 90th percentile classified as large for gestational age (LGA), need for surfactant, patent ductus arteriosus (clinical or echocardiographic diagnosis), early sepsis (clinical-laboratory criteria with the use of antibiotics for at least five days, starting up to the 3rd day of life), late sepsis up to the 14th day of life (clinical-laboratory criteria with the use of antibiotics for at least five days, starting after the 3rd day of life), necrotizing enterocolitis, defined using the Bell Criteria [13], and respiratory support and fraction of inspired oxygen (FiO2) on the 14th day of life.

Respiratory support was characterized as nasal oxygen catheter (simple or high-flow nasal catheter), nasal continuous positive airway pressure (CPAP) or non-invasive intermittent positive pressure ventilation (NIPPV), conventional invasive mechanical ventilation (MV), and high-frequency ventilation (HFV).

The evaluated FiO2 and respiratory support were the most frequently recorded on the day (higher needs that occurred transiently were discarded). The type of ventilation device and its manufacturer were not considered.

The analyzed outcomes were defined by the presence of bronchopulmonary dysplasia and their classifications, made according to the definitions of the National Heart, Lung and Blood Institute (NHLBI) in 2000: no bronchopulmonary dysplasia, mild bronchopulmonary dysplasia (patients requiring supplemental oxygen with 28 days of life or more but not at 36 weeks corrected gestational age), moderate bronchopulmonary dysplasia (Patients requiring supplemental oxygen at 28 days of age and maintaining a FiO2 requirement of less than 30% at 36 weeks of corrected gestational age), and severe bronchopulmonary dysplasia (patients in need of supplemental oxygen at 28 days of life and maintaining the need for FiO2 higher than or equal to 30% or positive pressure at 36 weeks of corrected gestational age)[14,15].

The associations between the factors of interest and BPD and their classifications were made by adjusting single and multiple log-multinomial regression models, obtaining crude and adjusted relative risks (RRaj), and using gestational age and antenatal corticosteroids as covariates. The software SAS 9.4 was used.

For the elaboration of the predictive instruments, the database was randomly divided into a training sample (70%), used for the elaboration of the moderate and severe BPD prediction equations, and the rest of the sample (30%) was used for validation.

For the instrument's construction, respiratory supports were classified into three categories: none, use of nasal oxygen catheter/CPAP/NIPPV, and conventional mechanical/high-frequency ventilation.

Four strategies were proposed for building the equations, as described in table 1. Thus, the probabilities of BPD were obtained, considering moderate and severe degrees versus mild and null, thus being a binary variable. A logistic regression model allowed each of the four variable selection strategies to result in BPD prediction probabilities (p).

The equations were obtained from the training sample and validated in the validation sample; that is, the probabilities were obtained from the data of the last-mentioned sample, from which the probability of BPD was also calculated using the NICHD instrument currently used in that institution. During validation, patients on an O2 catheter had FiO2 values classified as 29%; the entire sample was considered "Hispanic" regarding ethnicity when using the NICHD instrument.

The results were compared with the actual status of the sample for BPD (confusion matrix), and then sensitivity, specificity, and predictive values were calculated. Kappa indices were calculated to compare the results obtained by the equations with those obtained by the NIHCD method, obtaining agreement between the methods, given that none of the methods can be considered a gold standard.

The project received ethical approval from the Institution's Human Research Ethics Committee of the Ribeirão Preto Medical School (CEP FMRP), Opinion number: 1.903.783/CAAE 63764517.4.0000.5505).

3 Results

Six hundred seventy-two eligible newborns were identified in the Neonatal Database from 2016 to 2020. After analyzing the database, 371 newborns met the inclusion criteria.

Subsequently, 129 patients were excluded because they were discharged before 14 days of life, and one neonate was excluded due to pulmonary agenesis.

During the analysis of medical records, 13 patients were excluded from the outcome analysis and equation formulation due to their passing before 28 days of life. Additionally, there were no discharges recorded before the 28-day mark.

The mean birth weight of the sample was 922.6 grams (standard deviation (SD): 185 g), with patients with moderate BPD having 872 grams (SD: 175.83 g) and those with severe BPD having 802.6 grams (SD: 180.8 g), while the mean gestational age was 27.6 weeks (SD: 1.76), and those with moderate BPD having 27.2 weeks (SD: 1.47) and severe BPD 26.5 weeks (SD: 1.71).

Females were present in 54.8% of the total sample. Rates of antenatal corticosteroid use were observed in 87.9% and surfactant use in 66.8%.

At 28 days of life, among the 228 who survived, 31.1% did not require respiratory support, considered without bronchopulmonary dysplasia, 26.7% were considered with mild bronchopulmonary dysplasia, 18.8% with moderate bronchopulmonary dysplasia, and 23.2% with severe bronchopulmonary dysplasia.

Table 2 shows patients' antenatal and postnatal characteristics according to BPD and their classifications and relative risks.

After analyzing the variables, we elaborated prediction equations for BPD using 70% of the sample, with 160 patients (training sample), in which four strategies were evaluated (Table 1). The equations were validated using the remaining 30% of the sample (68 patients), and the instrument currently used in that institution was also applied to these patients.

The risks in three patients could not be obtained in the analysis with the instrument currently used, as this calculator does not offer resources to calculate BPD in SGA patients. In this case, two patients had a birth weight of less than 501 g, and one was SGA (birth weight of 630 g and a GA of 29 weeks and four days).

Equation 4 failed to predict any positive results in the sample. However, the other equations showed specificities and positive predictive values superior to those of the instrument currently used in that institution, standing out Equation 2, with a specificity of 98% and a positive predictive value of 93% (Table 3).

The calculated Kappa indices showed low agreement between the developed equations and the current foreign instrument (Table 4).

4 Discussion

Our study confirms that a BPD prediction instrument has superior performance when developed in the place where it will be applied, demonstrating that individualized treatment has been increasingly gaining strength in neonatology.

We found a total incidence of BPD of 42% when considering the need for respiratory support at 36 weeks of GA, corresponding to what has been observed in recent years in the literature [16-21] and demonstrating the immense need for therapies that can reduce the world's DBP rate.

The presence of ductus arteriosus and the need for surfactant were associated with moderate BPD, whereas early sepsis was associated with severe BPD. Several publications have associated these predictors with BPD [1-3,22-25]. High oxygen requirement at 14 days of life and non-invasive or invasive ventilatory support were events strongly associated with the moderate and severe forms of the disease, confirming well-established data in the literature on the role of respiratory support in the development of BPD[3,10,23,26-32].

The current foreign instrument showed low sensitivity, good specificity, and a good positive predictive value. However, it presented specificity values and a positive predictive value lower than those of our equations (Table 3), with a low agreement of this instrument with the instruments elaborated in this study, with Kappa indices below 0.50 (Table 4).

We also observed the impossibility of analyzing newborns with birth weights less than 501 g and SGA newborns in the external instrument currently used at the service. It shows that it is indicated for evaluating only patients born at more than 23 weeks and appropriate for gestational age, making our equations superior. The sample had 21.1% SGA, reflecting the number of developing countries where many SGA newborns occur [21].

Another crucial point was that the classification of our sample as "Hispanic" may limit the veracity of the results according to the instrument currently in use because the Brazilian has great miscegenation and genetic diversity [33].

The NICHD model published in 2011 was based on a population whose characteristics and neonatal care differ from ours, and the author himself recommends its careful use in other regions[10].

NICHD published 2022 an update of the risk prediction instrument for BPD[34]. The model predicts the risk for the disease based on a new BPD classification proposal [35], no longer using ethnicity as a predictive factor, which may be helpful in other populations. However, this new instrument can also not predict risk in SGA patients. It is restricted to the population with GA up to 28 weeks[34], limiting its use in places where BPD is still considerable in newborns with GA up to 30 weeks [21].

Some other risk prediction models for BPD have been published in recent years. Bhering published a model in Brazil that calculates the risks for BPD on the seventh day of life but without considering the classifications of severity [23], a fact that may limit its usefulness for the decision on the use of postnatal corticosteroids. In Turkey, Gursoy developed an instrument that assesses the risk for BPD through a scoring system, using variables in the first 72 hours of life, also without defining the severity of the disease but suggesting the use of postnatal corticosteroids when the score is higher than 6[36].

Sharma in the United States [29] and El Faleh in Switzerland [31] built practical and easy "web-based" instruments with prediction capable of identifying later lung deterioration phenotypes and predicting severity. However, these models may not reflect the reality of most neonatal units, ethnically representing only the local population.

Zhang published a nomogram in China that is easy to use in clinical practice. However, the risk calculation is only performed on the seventh day of life and using the serum level of NT-pro-BNP (N-terminal-pro

brain natriuretic peptide) [30], a marker not readily available in many services, especially those with limited resources. Also, identification before 14 days of life may fail to identify later phenotypes of BPD development [37,38].

We sought to develop a prediction model using newborns in our population as a basis, enabling the appropriate indication of the use of postnatal corticosteroids, as they may be associated with side effects. Therefore, the indication must be precise, requiring good specificity and good positive predictive value, which are fundamental to guiding the choice of patients.

We observed that all the elaborated equations presented a superior performance than that estimated by the calculator currently in use at the service. However, Equation 2, which considered only the variables that presented $p<0.05$, had the best specificity and positive predictive value.

Our study was conducted retrospectively, but we emphasize that the data were collected prospectively and according to well-established criteria (Brazilian Neonatal Network/Vermont-Oxford Network)[39]. A sample from a single Center of Neonatology was also used in the research. However, this fact can be seen as a workforce, as we have a homogeneous population and uniform conduct.

Predicting the risk for a disease such as BPD is still a challenge. The literature suggests that predictive instruments external to the place should be validated, as it is the most appropriate way to use these calculators in clinical practice safely. It reinforces that, when possible, elaborating an equation specific to each service is still ideal [11,40].

Therefore, developing our prediction instrument, with specificity and positive predictive value higher than the currently used, will allow us to define more precise candidates for postnatal corticosteroids to prevent BPD. Prospective studies to evaluate its clinical impact have been designed.

5 Conclusion

We present a predictor instrument with high specificity and positive predictive value, built in a developing country population and suitable for small-for-gestational-age patients, performing better than the foreign tool currently used. Higher precision and safety in using postnatal corticosteroids are possible by developing local predictive instruments.

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Table 1 –Mathematic model for prediction of bronchopulmonary dysplasia tailored with local population and National Institute of Child Health and Human Development tool (NICHD)

Equations	Selected variables
Equation 1	All the collected variables
Equation 2	Chorioamnionitis, gestational age, birth weight, gender, need for surfactant, patent ductus art
Equation 3	Gestational age, gender, fio2 and respiratory support on the 14th day of life **(using the step**
Equation 4	Gender, patent ductus arteriosus and respiratory support on the 14th day of life **(using a co**
NICHD calculator for BPD	Birth weight, gestational age, gender, respiratory support on the 14th day of life

GENDER – male; Adequacy – small for gestational age ; Hypertension – maternal systemic arterial hypertension; Smoking – maternal smoking; Chorio – chorioamnionitis; Antenatal_cortic – antenatal corticosteroids; SURF – need for surfactant; RespSupp14th_0 – none respiratory support on the 14th day of life (0); RespSupp14th_1e2 – nasal oxygen catheter/CPAP/NIPPV (1) or MV/HFV (2) on the 14th day of life; PDA – patent ductus arteriosus; NEC_uptothe14th – necrotizing enterocolitis up to the 14th day of life; EARLYSEPSIS – early sepsis; LATESEPSIS – late sepsis up to the 14th day of life; GAdays – gestational age in days; WEIGHT_g – birth weight in grams; FiO214th – fraction of inspired oxygen on the 14th day of life.

Table 2 – Association between antenatal and postnatal variables and bronchopulmonary dysplasia according to its severity

Preditores	Mild BPD (n=61)	Mild BPD (n=61)	Moderate BPD (n=43)	Mo
	Percentage	**RRaj (CI 95%)**	**Percentage**	**RR**
Maternal systemic arterial hypertension [a]	34.4%	1.0 (0.62; 1.92)	33.3%	1.0
Maternal smoking [b]	15.25%	1.0 (0.50;2.14)	13.9%	0.9
Chorioamnionitis	17.7%	0.9 (0.45; 1.75)	23.2%	1.2
Antenatal corticosteroids	83.6	0.7 (0.37; 1.54)	90.6%	1.8
Male	45.9%	1.0 (0.61; 1.72)	46.5%	1.0
SGA	16.3%	0.7 (0.37; 1.53)	23.2%	1.3
Need for surfactant	78.3%	1.8 (0.94; 3.36)	88.3%	**4.1**
Patent ductus arteriosus	37.7%	0.6 (0.38; 1.18)	65.1%	**2.0**
Early sepsis	37.7%	1.1 (0.64; 1.83)	53.4%	0.7
Late sepsis up to the 14th day of life	34.4%	0.9 (0.53; 1.53)	41.8%	1.2
Necrotizing enterocolitis up to the 14th day of life	8.1%	0.7 (0.28; 1.80)	4.6%	0.4
FiO2>30% on the 14th day of life [c]	16.6%	**0.4 (0.21; 0.89)**	30.5%	2.0
Nasal oxygen catheter	50%	**3.2 (1.40; 7.53)**	10,7%	3.3
CPAP/ NIPPV	41.2%	**2.5 (1,13; 5,71)**	27.4%	**8.2**
MV	21.2%	1.2 (0.48; 3.07)	29.7%	**8.8**
HFV	13.0	0.7 (0.18; 2.82)	21.7	**6.4**

SGA– small for gestational age; FiO2– fraction of inspired oxygen; CPAP- nasal continuous positive airway pressure; NIPPV- non-invasive intermittent positive pressure ventilation; MV – conventional invasive mechanical ventilation; HFV - high-frequency ventilation; RRaj - adjusted relative risks (using gestational age and antenatal corticosteroids as covariates) and its 95% confidence interval.

[a] Excluded 1 patient where it was not possible to obtain data on maternal hypertension.

[b]Excluded 4 patients where it was not possible to obtain data on maternal smoking.

[c]Excluded 25 patients where it was not possible to calculate the value due to the use of a simple nasal oxygen

catheter.

Table 3 – Performance measures for the four internal bronchopulmonary dysplasia prediction tools compared with the National Institute of Child Health and Human Development tool (NICHD)

Prediction equations for BPD	Sensitivity (CI 95%)	Specificity (CI 95%)	Positive predictive value (CI 95%)	Negative predictive value (CI 95%)
1	0.28(0.14;0.49)	**0.98(0.85;1.00)**	**0.89(0.69;1.00)**	0.66(0.61;0.71)
2	0.50(0.31;0.69)	**0.98(0.85;1.00)**	**0.93(0.81;1.00)**	0.74(0.66;0.81)
3	0.36(0.19;0.56)	**0.95(0.82;0.99)**	**0.83(0.63;1.00)**	0.68(0.62;0.74)
4	[a]	**1.00(0.93;1.00)**	[a]	[a]
NICHD	0.32(0.17;0.52)	**0.93(0.79;0.98)**	**0.75(0.52;0.98)**	0.66(0.60;0.72)

(CI 95%)- 95% confidence interval; [a] Equation 4 failed to predict any positive results in the sample**.**

Table 4 – Agreement level between internal bronchopulmonary dysplasia prediction tools and the National Institute of Child Health and Human Development tool (NICHD)

Prediction equations for BPD	Calculated Kappa indices (CI 95%)
Equation 1	0,38(0,08;0,68)
Equation 2	0,49(0,23;0,75)
Equation 3	0,39(0,11;0,67)
Equation 4	[a]

(CI 95%)- 95% confidence interval; [a]Equation 4 failed to predict any positive results in the sample.

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`Tables.docx` available at https://authorea.com/users/700887/articles/687627-personalized-lung-care-bronchopulmonary-dysplasia-risk-prediction-tool-tailored-for-neonates-born-in-the-resource-limited-settings