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Bronchopulmonary dysplasia prediction model for 7-day-old infants

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Abstract

Objective: To develop a predictive model capable of identifying which premature infants have the greatest probability of presenting bronchopulmonary dysplasia (BPD), based on assessment at the end of their first week of life.

Methods: Data were collected retrospectively from January 1998 to July 2001, and prospectively from August 2001 to July 2003. All children born at the institution with gestational age < 34 weeks and birth weight < 1,500 g were included. The principal risk factors for BPD were subjected to univariate analysis followed by logistic regression. Significant variables were used to construct a formula to calculate the probability of BPD. The model was calibrated and its discriminative power assessed using receiver operating characteristic (ROC) curves. Between August 2003 and July 2005 the model was then applied to a different population for validation.

Results: The sample comprised 247 children, of whom 68 developed BPD, classified as follows: mild = 35 (51.4%), moderate = 20 (29.4%) and severe = 8 (11.7 %). Four variables maintained significance with relation to BPD: gestational age ≤ 30 weeks, persistent ductus arteriosus, mechanical ventilation > 2 days and loss of > 15% of birth weight on the seventh day of life. Where patients exhibited all of these variables, the model had a 93.7% probability of being correct. The model was further validated when using another sample of 61 newborns; similar figures were obtained.

Conclusions: At the end of the first week of life, the predictive model developed from our population was capable of identifying newborn infants at increased risk of developing BPD with a high degree of sensitivity.

J Pediatr (Rio J). 2007;83(2):163-170: Bronchopulmonary dysplasia, predictive model, chronic neonatal lung disease, mechanical ventilation, prematurity.

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Introduction

Bronchopulmonary dysplasia (BPD) is still the most common cause of morbidity among extremely low birth weight (ELBW) newborns, although the incidence, risk factors and severity of the disease have changed substantially since the introduction of new treatments and mechanical ventilation techniques.[1-3] Pathogenesis is the result of multiple factors including immaturity, infection, barotrauma or volutrauma and oxygen toxicity. Excessive ingestion of liquids and sodium have also been suggested as additional risk factors.[1]

Strategies and interventions that might reduce the incidence of BPD have been widely investigated. Recently, Schmidt et al.[3] reported on a multicenter study whose results demonstrated that administration of caffeine during the first days of life was capable of reducing BPD incidence in a population of very low birth weight (VLBW) newborns.[4] Nevertheless, in order that such measures achieve greater efficacy, it is necessary to identify early and precisely the newborn population that is at greatest risk of developing the condition.[5] Working from this principle, several predictive models have been developed over the last 25 years achieving sensitivity rates that varied from 64 to 92.7%.[6-9] However, one factor that has limited widespread adoption of any of these models is the fact that they were developed in specific centers and populations and were not tested prospectively on other populations.

The principal objective of this study was to develop and apply a model to predict BPD at a neonatal intensive care unit in Brazil, using a local population of VLBW infants assessed at the end of their first week of life.

Methods

The study was carried out at the Instituto Fernandes Figueira (IFF), part of the Fundação Oswaldo Cruz (FIOCRUZ), after approval by the Institute's Research Ethics Committee.

Study period

The study employs data from two distinct periods. From January 1998 to July 2003, a predictive model was developed through analysis of the principle risk factors associated with BPD. Data were collected retrospectively, during the period January 1998 to July 2001, by means of direct consultation of patient records and the computerized database at the Department of Neonatology. The data were collected prospectively from August 2001 to July 2003, by means of a spreadsheet. During the second period, August 2003 to July 2005, the predictive model that had been developed was validated. All of the data, whether retrospective or prospective, were collected by just two of the researchers involved in the study (C.A.B. and C.C.M.).

Study population

All children born at the IFF with gestational ages (GA) < 34 weeks and birth weight (BW) < 1,500 g were included if they were free from complex genetic malformations and congenital infections, their mother's were not HIV-positive, and they survived past their 28th day of life.

Definition of bronchopulmonary dysplasia

This study employed the BPD definition based on disease severity proposed by Jobe & Bancalari[10] and later validated by Ehrenkranz et al.[11] Infants were thus defined as suffering from BPD if they were on oxygen support ≥ 28 days. These newborns were then reassessed when they reached 36 weeks' corrected GA (if GA < 32 weeks) or on the 56th day of life (if GA ≥ 32 weeks) or at hospital discharge. Those who were on room air at the time of reevaluation were classified as having had mild BPD. Those receiving less than 30% fraction of inspired oxygen (FiO_2) were classified as having moderate BPD and those on FiO_2 > 30% and/or continuous positive airway pressure (CPAP) and/or mechanical ventilation were classified as having severe BPD.

Variables and definitions employed

During the initial phase of developing the model, countless variables considered to be possible risk factors for the development of BPD were included. Percentage birth weight lost was assessed on the seventh day and expressed as a percentage (> 10%, > 15% or > 20%). Time on mechanical ventilation during the first week of life was categorized into number of days (> 2 days, > 3 days, > 4 days or > 5 days). Any day on which a child was ventilated for more than 12 hours was counted as a day on ventilation. Scores on the clinical risk index for babies (CRIB) were split into degrees (degree 1 = 0-5; degree 2 = 6-10; degree 3 = 11-15; degree 4 >15). Persistent ductus arteriosus (PDA) was defined by the presence of clinical signs (systolic murmur, wide pulse and hyperdynamic precordium) and the need for clinical and/or surgical treatment was confirmed using echocardiography. Sepsis was defined as the presence of at least one positive blood culture (confirmed sepsis) or clinical signs indicative of sepsis (suspected sepsis), and classified as either early (up to 72 h) or late (> 72 h).

Development of the predictive model, sample size calculation and statistical analysis

Initially, each possible risk factor was assessed in isolation (n = 66) in order to identify variables that had a significant relationship with BPD. The 36 most significant variables (where $p < 0.25$) were then selected for the logistic regression model, which was produced using the stepwise forward method with the cutoff for significance set at

$p < 0.05$. Only variables that were capable of providing results before the end of the early neonatal period were tested (n = 25).

Once logistic regression had been performed, four variables maintained a significant relationship with the outcome and were used to construct the formula to calculate the probability of BPD [Probability (%) = (e^{logit}) / (1+(e^{logit}), where **logit** is the β value for each variable multiplied by the corresponding variable minus the constant (logit = β x variable (0/1) + β x variable (0/1) – constant) and **e** is the base for natural logarithms with a value of 2.71828].

The model was calibrated using the Hosmer & Lemeshow[12] test by means of the goodness of fit statistic, with the aim of describing the precision of predicted and observed results as a whole. For this test, patients are grouped by degree of risk and categorized by diagnosis. The program uses the C statistic which selects groups of different degrees of risk that contain approximately the same number of cases. From this, the observed number is compared with the predicted number for each group and differences are summed to calculate the chi-square test p value. In this case, in contrast with usual interpretations, the larger the value of p, the better calibrated the model. Next the model's discriminatory power was evaluated by calculating the area under the receiver operating characteristic (ROC) curve, which identifies the degree of sensitivity and specificity with which the model discriminates between patients who will or will not develop the outcome of interest.

A logistic regression model is considered reliable if the number of patients is 10 to 20 times the number of variables associated with the outcome of interest.[13] In our model, containing four significant variables, the size of the BPD patient sample was calculated at between 40 and 80 individuals. Univariate frequency analyses and logistic regression were performed using the statistical package SPSS 11.0 (SPSS Inc., Chicago, IL, USA). The univariate analysis employed the chi-square or Fisher tests for categorical variables and the Mann-Whitney or Student's t tests to compare mean values. Values of $p < 0.05$ were considered significant.

Results

During the study period, 386 children meeting the inclusion criteria were born. One hundred and twenty-four (124) children were excluded due to death before the 28th day of life (32.1% of the total), 12 due to congenital malformations, two because of congenital infections and one whose mother was HIV-positive. Excluding infants born with malformations, the mortality rate was 29% (n = 112). The final sample, therefore, included 247 children with a mean BW of 1,083±237 g and mean GA of 29.1±2.4 weeks.

Sixty-eight newborns (27.5%) developed BPD, with the following classifications: mild, n = 35 (51.4%); moderate, n = 20 (29.4%); and severe, n = 8 (11.7 %). Five (7.3 %) children could not be classified since, although they were diagnosed with BPD, they died before the classification point. Twenty-eight (11.3 %) were still dependent on oxygen at 36 weeks' corrected GA. Table 1 lists the principal characteristics of the sample during the perinatal and neonatal periods, broken down by whether or not patients developed BPD, together with the significance of the differences between the two sets.

Four of the variables analyzed in the logistic regression maintained their significance with relation to BPD: GA ≤30 weeks, PDA and mechanical ventilation for > 2 days during the first week of life and loss of > 15% of BW by the seventh day of life (Table 2). The model was calibrated using the following values: *C^* test = 8.0067; degrees of freedom = 5 and p = 0.1559. As evaluated by the ROC curve, the model's discriminatory power was excellent (Figure 1A) with an area under the curve of 0.906±0.021 (95%CI 0.864-0.947). Where all four variables were present, the model allowed for a maximum correct identification probability of 93.7% (Table 3).

In order to validate the model, we applied it to 61 newborns who had not participated in the initial sample and who exhibited similar characteristics (with and without BPD): GA (31.6±1.4 and 29.3±2.8 weeks), birth weight (1,229±218 and 926±270 g), male sex (n = 40, 55%), CRIB (2.7±3.3 and 9.8±3.8), PDA (17 and 55%), time on IMV (0.7±9 and 10.1±1.8), % of birth weight lost (11.5±5 and 19.8±5.3%). For this group, calibration values were: *C^* test = 7.6957; degrees of freedom = 5 and p = 0.1738. The area under the ROC curve was 0.935±0.0032 (95%CI 0.873-0.997), confirming the sensitivity of the predictive model developed (Figure 1B).

Discussion

In our population, assessed at 7 days, the probability model developed here demonstrated an elevated level of sensitivity for the identification of those newborns with the greatest chance of developing BPD. This early identification is essential to the development of strategies that may act in a preventative manner, reducing the incidence of this disease. Nevertheless, our model exhibits certain differences that should be discussed, particularly in relation to the most significant variables. For the sake of clarity, significant variables and the existing probabilistic models and their relevance are discussed separately.

Significant variables in the model

GA ≤ 30 weeks

In the model, prematurity was one of the four principal risk factors associated with the development of BPD. In other

predictive models, which employed similar variables in their multivariate analyses, GA was the most significant independent predictive factor.[14] Recently, Henderson-Smart et al.[15] applied a logistic regression model to 11,453 children and found a significantly higher chance of BPD from 30 weeks' GA.

Indeed, the most marked characteristic of BPD since the introduction of surfactant and of new mechanical ventilation techniques is the alteration to normal alveolar development, by which the pulmonary maturation process is interrupted.[16] Therefore, the more premature an infant is, the greater the chances it has of developing BPD. It is estimated that, from 31 weeks' GA, for each week less, the chances of BPD increase by approximately 2 times.[15]

Mechanical ventilation for more than 48 h

Ventilatory support is a well-known potential mechanism of pulmonary injury in preterm infants. Nevertheless, the incidence of BPD increases when invasive forms of ventilatory

Table 1 - Characteristics of the study population

	BPD (n = 179)	No BPD (n = 68)	p (univariate analysis)	Odds ratio (95%CI)
Perinatal				
Prenatal	164 (91.6)	64 (94.1)	0.51	0.4 (0.4-4.5)
Prenatal consultations	4.1±2.3	3.6±1.7	0.17	
HDP	71 (39.6)	13 (19.1)	0.002	0.3 (0.1-0.7)
Corticoid	145 (81)	48 (70.5)	0.07	0.5 (0.2-1.0)
Chorioamnionitis	44 (24.5)	18 (26.4)	0.79	1.0 (0.5-2.0)
Premature labor	57 (31.8)	32 (47)	0.03	1.8 (1.0-3.2)
PROM	51 (28.4)	18 (26.4)	0.71	0.8 (0.4-1.6)
Vaginal delivery	57 (31.8)	33 (48.5)	0.02	0.5 (0.2-0.9)
Neonatal				
GA (weeks)	29.6±2.1	27.2±2.0	< 0.001	
BW (g)	1,150±214	907±202	< 0.001	
Male sex	84 (46.9)	35 (51.4)	0.52	0.8 (0.4-1.4)
PPV	78 (43.5)	49 (72)	<0.001	3.5 (1.9-6.5)
OEI	36 (20.1)	37 (54.4)	<0.001	4.7 (2.5-8.6)
CRIB	2.4±2.8	6.5±4.1	< 0.001	
HMD	55 (29.6)	53 (77.9)	< 0.001	7.9 (4.1-15.3)
Surfactant doses	0.4±0.7	1.5±1.0	< 0.001	
Diuretics	12 (6.7)	15 (22)	< 0.05	
Confirmed sepsis	21 (11.7)	14 (20.5)	0.08	2.2 (1-4.8)
PDA (up to 7 days of life)	13 (7.2)	35 (51.4)	<0.001	13.5 (6.4-28.3)
Time on IMV (days)	1.6±3.5	17.8±18	<0.001	
Total time on O_2 (days)	6.5±8.4	55.3±25.6	<0.001	
Loss of BW (%)	12.5±4.8	20.0±6.0	< 0.001	
Length of hospital stay (days)	46±19	81±27	< 0.001	

Values expressed in: n (%) or mean ± standard deviation.
95%CI = 95% confidence interval; BPD = bronchopulmonary dysplasia; BW = birth weight; CRIB = clinical risk index for babies; GA = gestational age; HDP = hypertensive disorders of pregnancy; HMD = hyaline membrane disease; IMV = intermittent mechanical ventilation; OEI = oral endotracheal intubation in the delivery room; PDA = persistent ductus arteriosus; PPV = positive pressure ventilation; PROM = premature rupture of membranes.

support are employed, such as intermittent mechanical ventilation. Ammari et al.[17] report a very much reduced incidence of BPD among infants who were started and maintained on nasal CPAP from the moment of birth, even when extremely premature. This more conservative conduct is currently being evaluated in a multicenter study, the first phase of which has confirmed the viability of this intervention.[18]

In our study, all of the variables related to invasive ventilatory support exhibited significant differences between subsets, with mechanical ventilation and time on ventilation being the most important ($p < 0.001$). Those infants who required mechanical ventilation for more than 2 days during the first week of life had a greater risk of developing BPD. Indeed, this was the most expressive variable in the entire model. Its simple removal (with the other three variables present) reduced the percentage chance of developing BPD from 93.7 to 61.6% (Table 3).

Persistent ductus arteriosus

The association between PDA and BPD is well delineated in the literature.[19,20] In our study, infants with PDA at the end of the first week of life exhibited an increased risk of developing BPD (OR = 13.5; 95%CI 6.4-28.3). Despite this robust association, prophylactic use of indomethacin or ibuprofen reduced the incidence of PDA without modifying the incidence of BPD.[19] Nevertheless, it is important to point out that in none of these studies the principal object was to assess the effects of this treatment on the incidence of BPD. Although some hypotheses have been developed in an attempt to explain these conflicting results,[20,21] it is believed that treatment that may be effective at reducing the incidence of BPD should be directed to the abnormal development of immature lungs, and not at other factors associated with prematurity, such as PDA.[22]

Loss of > 15% of birth weight on seventh day of life

In the post-surfactant era, three studies have assessed a possible correlation between fluids and weight loss and the development of BPD.[1,20,23] In these studies, percentage weight loss was similar on the fifth day of life,[23] significantly lower between the sixth and ninth days of life[1] or significantly lower on the seventh day of life.[20] The most important differences between these studies and ours was that, in the first two, infants who developed BPD were given significantly more liquids throughout the evaluation period.[1,23] In the third study, prophylactic indomethacin was used and the volume of liquids administered was not provided.[20] In our population, the volume of liquids administered was similar in both groups and indomethacin was not used prophylactically. Furthermore, those infants who did develop BPD lost a much greater percentage of birth weight by the end of the first week than in the studies cited (~ 20%).

Calorie intake of the infants who developed BPD was significantly lower on the sixth ($p = 0.01$) and seventh days ($p = 0.03$) of life. These children's scant reserves associated with inadequate nutritional support, may have contributed to a state of catabolism and protein deficiency, which has been described as capable of altering both pulmonary growth and healing and control of the inflammatory response, promoting pulmonary injuries.[24-26] Furthermore, although just 11% of the total number of patients were treated with diuretics,

Table 2 - Variables significantly related to bronchopulmonary dysplasia employed in the predictive model

	β	**SE**	**p**	**OR**	**95%CI**
	β	SE	p	OR	95%CI
Persistent ductus arteriosus	1.37	0.47	0.004	3.94	1.56-9.98
Intermittent mechanical ventilation > 2 days	1.91	0.43	< 0.0001	6.76	2.92-15.64
Loss >15 % of birth weight	1.07	0.43	0.013	2.91	1.25-6.80
Gestational age ≤30	1.56	0.45	0.0005	4.76	1.97-11.51

95%CI = 95% confidence interval; β= beta; OR = odds ratio; SE = standard error.
According to the table above, the most significant variable was intermittent mechanical ventilation > 2 days during the first week of life.

these were started after the fourth day of life and in a significant manner among the subset of children who would develop BPD.

In conclusion, in a population of infants with GA ≤ 30 weeks receiving similar amounts of fluids throughout the first week of life, the increased use of diuretics from the fourth day on, as well as the reduced calorie intake on the sixth and seventh days, was responsible for the greater percentage loss of birth weight by the end of that first week. This basically reflects the greatest severity of the subset (see CRIB) and the reason for the significant association with the development of BPD.

Predictive models and their relevance

Other probabilistic models have been proposed for BPD. Cohen et al.[27] used BW (< 1,250 g) and mechanical ventilation at 48 h and obtained an estimated risk of 61%. In the same study, infants that were on FiO_2 > 60% for > 2 h within the first 48 h of life had a risk of 81%. Other authors have used birth weight and ventilatory data to predict the risk of BPD at 12 h to 10 days of life. A sensitivity of 75% was obtained using FiO_2 on the 10th day and MAP on the fifth day, in association with birth weight and GA.[28] Palta et al.[29] obtained a maximum probability of 85% with a logistic model that used the variables: severity score, X ray assessment and BW. In our model, the estimation possibilities varied from 3.9% (all four variables absent) to 93.7% (all variables present), indicating a maximum predictive capacity superior to those of all of the studies published to date.

Our study involves some important limitations, such as the retrospective data collection during the first period. Nevertheless, it is important to point out that the patients

Table 3 - Possible combinations of the four significant variables with their corresponding probabilities for the development of bronchopulmonary dysplasia

	PDA	Lost > 15% do BW	IMV > 2 days	GA ≤30	BPD (%)
1	Yes	Yes	Yes	Yes	93.7
2	Yes	No	Yes	Yes	80.5
3	No	Yes	Yes	Yes	76.5
4	Yes	Yes	Yes	No	72.8
5	Yes	Yes	No	Yes	61.6
6	No	No	Yes	Yes	54.4
7	Yes	No	Yes	No	49.5
8	No	Yes	Yes	No	43.7
9	Yes	No	No	Yes	37.0
10	No	Yes	No	Yes	31.7
11	Yes	Yes	No	No	27.6
12	No	No	Yes	No	22.1
13	No	No	No	Yes	14.5
14	Yes	No	No	No	12.2
15	No	Yes	No	No	9.9
16	No	No	No	No	3.9

BPD = bronchopulmonary dysplasia; BW = birth weight; GA = gestational age; IMV = intermittent mechanical ventilation; PDA = persistent ductus arteriosus.
See text (methods) for the definitions of significant variables. Note that the simple exclusion of the variable IMV > 2 days reduces the chances of BPD by approximately 32% (from 93.7 to 61.6%).
Probability formula: $(\%) = (e^{logit}) / (1+(e^{logit}))$.

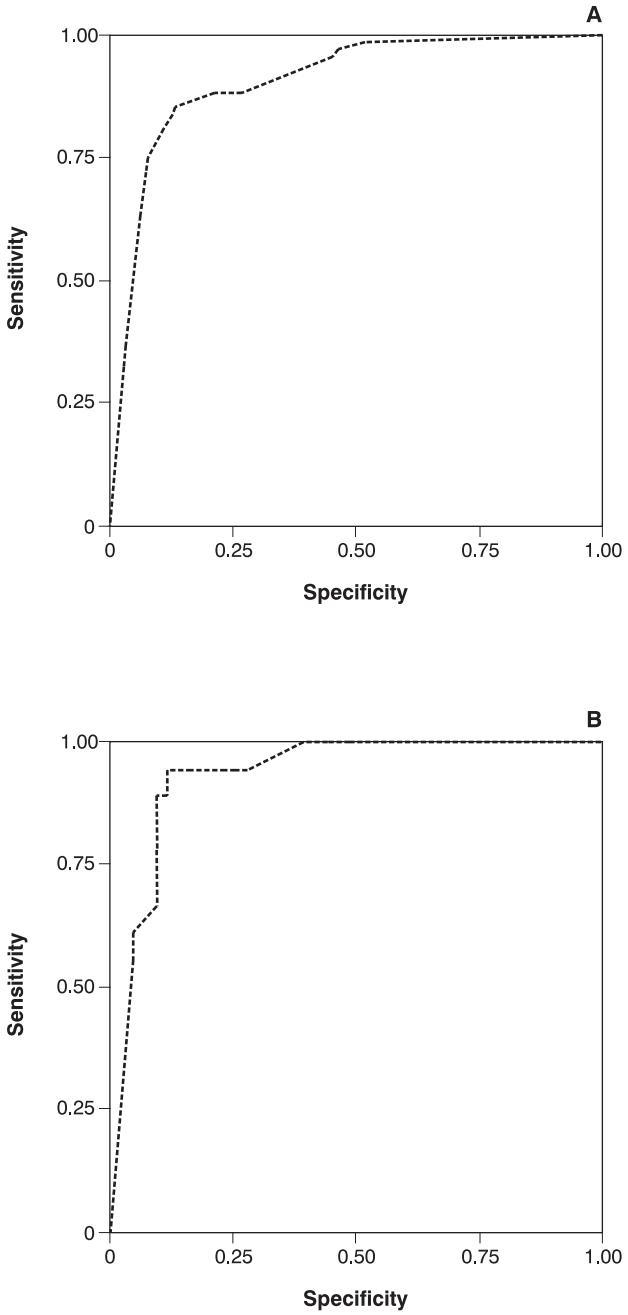

Figure 1 - Receiver operating characteristic curves for discrimination (A) and validation (B) of the model (the greater the area under the curve, the more powerful the model). A) Area under the curve = 0.906±0.021 (95%CI 0.864-0.947). B) Area under the curve = 0.935±0.0032 (95%CI 0.873-0.997)

whose data were collected retrospectively were the same patients used in another prospective study performed at our institution.[3] As a result, the proportion of data that could not be collected was extremely small, having no effect on analysis of the results. Another limitation is the incapacity of the model to detect the degree of BPD that an infant will develop (mild, moderate or severe). While this was not the objective of the study, it is known that infants with mild BPD are breathing room air by 36 weeks' corrected GA, which is evidence of lesser severity, and therefore are of a different clinical relevance when compared with infants with moderate or severe BPD. The capacity to predict severity could be of aid when making critical decisions, such as the use of corticosteroids during the postnatal period. Doyle et al.[5] performed a regressive meta-analysis demonstrating that postnatal corticosteroids could be more beneficial than detrimental when given to infants at greatest risk of developing moderate or severe BPD.

Recently, Ballard et al.[30] demonstrated that administering nitric oxide to preterms on mechanical ventilation between 7 and 21 days of life reduced the incidence of BPD, an effect only observed when treatment was started between 7 and 14 days of life. One limitation of that study was the fact that the authors had included all preterms on mechanical ventilation without selecting a population at greater risk of developing moderate or severe BPD, which according to the authors themselves could have significantly modified the final results.

Conclusions

BPD is still a common cause of morbidity among ELBW infants, and the risk factors related with this disease are countless. At the end of their first week of life, the predictive model developed in this study was capable of identifying those infants with the greatest probability of developing BPD with a high degree of sensitivity. When the model was prospectively applied to a different population, this sensitivity was confirmed, validating the model. This type of identification makes it possible to intervene in specific populations in a timely manner. Based on our model, reducing the time spent on mechanical ventilation and optimizing fluid and nutrition management could contribute to reducing BPD incidence in our population. Furthermore, the model could also be used to select target populations for further studies of BPD that will be carried out at our institution.

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