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ORIGINAL ARTICLE

Risk factors associated to bronchopulmonary dysplasia in premature newborns in a hospital of the metropolitan region of Curitiba

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Abstract

Objective: To analyse clinical and epidemiological factors of premature newborns and check associations to bronchopulmonary dysplasia (BPD). **Methods:** A transversal, analytical, retrospective study of clinical and epidemiological variables of patients with gestational age = 32 weeks and weight = 1500 grams. The Chi-Squared test or Fishers exact test were used to select variables. The area under the ROC Curve was calculated towards final models. **Results:** 54 patients were selected, from which 53.7% developed BPD. When comparing patients with and without BPD: gestational age (OR: 0.35 and CI95%: 0.17-0.60) (*p*=0.001), maternal age (OR: 0.85 and CI95%: 073-0.96) (*p*=0.019), male sex (OR: 4.66 and CI95%: 1.12-2.38) (*p*=0.044), need of orotracheal intubation (OTI) in the delivery room (OR: 12.32 and CI95%: 2.91-86.01) (<0.001), invasive mechanical ventilation (IMV) at the fourteenth day of life (OR: 9.5 and CI95%: 1.18-202.22) (*p*=0.05) and receiving DART protocol (OR: 20 and CI95%: 3.54-173.36) (*p*<0.001) were considered risk factors for BPD. Comparing patients with moderate to severe BPD and patients without moderate to severe BPD, only gestational age (OR: 0.43 and CI95%: 0.23-6.87) (p=0.001), motherly age (OR: 0.86 and CI95%: 0.76-9.69) (*p*=0.01) and need of OTI in the delivery room (OR: 11 and CI95%: 2.60-76.58) (*p*=0.003) were significant. **Conclusion:** 53.7% of patients developed BPD, being gestational age, motherly age, male sex, need of OTI in the delivery room, IMV at the fourteenth day of life and receiving DART protocol considered risk factors, although IMV at the fourteenth day of life, receiving DART protocol and male sex ceased to be risk factors when only patients with moderate to severe BPD were selected.

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) was initially described by Northway et al.[1] in 1968, considering the need for supplemental oxygen use at 28 days of life. In 2001, the National Institute of Child Health and Human Development (NICHD) introduced a new definition, which considered, in addition to the use of supplemental oxygen for at least 28 days, the need to verify oxygen dependence at 36 weeks of corrected gestational age (CGA) for preterm infants born before 32 weeks of gestation until 56 days of life or at the time of hospital discharge for preterm infants born after 32 weeks of gestation[2].

BPD is a chronic lung disease that has its own clinical, imaging, and histological characteristics[3]. It is the most common complication in premature infants, especially those with very low birth weight (<1500 grams)[4], affecting approximately 30% of preterm infants born before 32 weeks[5] and 20-30% of very low birth weight newborns[6].

Different interacting factors can disrupt lung growth, such as prematurity, mechanical ventilation, oxygen toxicity, inflammation, infection, and genetics. However, various lung remodeling responses can determine individual variations in morbidity[7]. These patients experience increased mortality, and survivors endure heightened morbidity, deteriorating quality of life, and escalating treatment costs[5].

This study examines the clinical and epidemiological risk factors for BPD in preterm infants with gestational ages of 32 weeks or less and body weights of 1500 grams or less, who were born in a hospital in the metropolitan region of Curitiba between 2018 and 2021.

METHODS

This cross-sectional, analytical, retrospective study included the medical records of individuals born in a hospital in the metropolitan region of Curitiba from 2018 to 2021. A total of 6,872 medical records were evaluated. Individuals with a gestational age of 32 weeks or less and who weighed 1,500 grams or less were included, while neonatal deaths were excluded. The medical records of 54 patients met the inclusion criteria. The data collected for descriptive analysis of the population included gestational age and maternal age; weight; small for gestational age (SGA) according to the Fenton chart (<p10)[8]; use of antenatal corticosteroids; maternal chorioamnionitis or systemic hypertension (SH); twinning; 5-minute Apgar score <7; vaginal delivery; male sex; orotracheal intubation (OTI); and the use of cardiac massage or adrenaline for resuscitation in the delivery room according to the standards of the Brazilian Society of Pediatrics[9].

Medical records were also analyzed for the presence and severity of BPD, as follows: BPD (need for supplemental oxygen at 28 days of life); mild BPD (not FiO_2-dependent – oxygen supplementation at 36 weeks of life or discharge, depending on which occurred first); moderate BPD (FiO_2 < 30% at 36 weeks of life or discharge); or severe BPD (FiO2 > 30% or positive pressure at 36 weeks of life or discharge)[2]. Additionally, the following data was captured: days of hospitalization; discharge with the use of oxygen supplementation; patent ductus arteriosus (PDA) diagnosed on an echocardiogram; surgical or drug treatment for PDA; enterocolitis (according to the Modified Bell's Staging Criteria [10]); retinopathy of prematurity; sepsis (in case of a positive blood culture); intraventricular hemorrhage (diagnosed based on transfontanellar ultrasound examination); osteopenia; and the start of enteral diet on the first day of life.

Furthermore, measures regarding the need for respiratory support were also investigated: use of CPAP in the delivery room; FiO_2 on the 1st, 3rd, 7th, and 14th day of life; need for invasive mechanical ventilation (IMV) on those same days; and use of surfactants, caffeine, and dexamethasone as prescribed in the DART protocol (Dexamethasone: A Randomized Trial[11]) during hospitalization.

The data obtained were processed in an Excel spreadsheet. For descriptive analysis, means and standard deviations were calculated for quantitative variables, while absolute frequencies and proportions were computed for qualitative variables. A significance level of 5% was considered. The Chi-Square or Fisher's Exact Test was employed to determine which variables should remain in the model. The model was first run with all studied variables and then with those that presented statistical significance. The area under the ROC curve (AUC) was calculated in the final models. R software version 4.1.2 was used for statistical analysis.

This study received approval from the ethics committee for research involving human subjects at the institution where it was conducted (certificate 5.111.870).

RESULTS

From 2018 to 2021, 54 patients with a gestational age of 32 weeks or less and a weight of 1500 g or less survived the neonatal period. Of these, 38 (70.37%) were born after 28 weeks of gestation, with a mean gestational age of 29.12 weeks (± 1.82) and a weight of 1185 grams (± 222.62). The mean maternal age was 28.24 years (± 7.18). Most deliveries were by cesarean section, with only 31.48% being vaginal. Most newborns (61.11%) were males, and 31.48% were intubated in the delivery room, as shown in Table 1.

Table 2 shows that the average length of hospital stay was 51.12 ± 25.37 days. The length of stay for patients with gestational ages of less than 28 weeks was 70.56 ± 30.08 days, which is notably higher than for infants born after 28 weeks of gestation or longer (42.94 ± 17.98 days), as expected. More than half of the newborns included in the study (53.7%) developed BPD, and 35.18% had moderate to severe BPD. A considerable portion (93.75%) of the newborns with a gestational age of less than 28 weeks developed BPD, while among patients with higher gestational ages, this number was

36.85%. A significant number of patients (18.51%) left the hospital still requiring oxygen. Of the patients with a patent ductus arteriosus (PDA) identified in the echocardiogram report (44.44%), a minority required drug or surgical treatment. Many patients experienced complications such as sepsis (33.33%), intraventricular hemorrhage (31.48%), enterocolitis (12.96%), retinopathy (9.25%), and osteopenia (9.25%).

When comparing patients with and without BPD concerning perinatal data, Table 3 shows that the variables gestational age (OR: 0.35 and 95% CI: 0.17-0.60) (p=0.001), maternal age (OR: 0.85 and 95% CI: 0.73-0.96) (p=0.019), and male sex (OR: 4.66 and 95% CI: 1.12-2.38) (p=0.044) were statistically significant, indicating that they can be considered risk factors for BPD. Notably, being male increases the chance of having BPD by 4.66 times. Regarding care measures needed in the delivery room, undergoing OTI (OR: 12.32 and 95% CI: 2.91-86.01) (<0.001) raised the risk of BPD by 12 times. In neonatal care, requiring invasive mechanical ventilation on the 14th day of life (OR: 9.5 and 95% CI: 1.18-202.22) (p=0.05) and receiving the DART protocol (OR: 20 and 95% CI: 3.54-173.36) (p<0.001) were statistically associated with BPD, increasing risk by 9.5 and 20 times, respectively.

Table 4 presents groups of patients with or without moderate or severe BPD. The group without moderate or severe BPD includes individuals who did not have BPD or who had it in mild form. Gestational (OR: 0.43 and 95% CI: 0.23-6.87) (p=0.001) and maternal age (OR: 0.86 and 95% CI: 0.76-9.69) (p=0.01) are perinatal risk factors for BPD. Among the variables related to care provided in the delivery room, OTI (OR: 11 and 95% CI: 2.60-76.58) (p=0.003) remained significantly associated with BPD, indicating an 11-fold risk increase. The variables IMV on the 14th day, DART protocol, and male sex were no longer statistically significant after the groups were divided based on the severity of BPD.

DISCUSSION

Improvements in the quality of care have enhanced the survival of premature infants born at increasingly lower gestational ages. Therefore, it is necessary to discuss factors that can predict diseases influencing the morbidity and mortality of this group while also assessing the potential cost impacts on the healthcare system.

According to the iNeo database[12], the present study's incidence of moderate to severe BPD (35.18%) was similar to that demonstrated in countries such as New Zealand and Australia (34.3%) and the United Kingdom (38.4%). This figure was higher than that observed in the units that make up the Brazilian Neonatal Research Network, where the reported incidence was 19% for preterm newborns with a birth weight of less than 1500 grams[13].

The incidence of BPD varies greatly in published literature, possibly due to factors such as the centers providing care to newborns and the different definitions of BPD used in each study. Despite these variations, gestational age remains a relevant factor[13] since premature birth disrupts lung development.

Unlike the present study, other authors did not describe maternal age or male sex as factors that increase the chances of developing BPD[4-14-15]. Birth weight, a significant variable in most studies[14-15], was not significantly associated with BPD in our research. This result likely reflects the tendency of

Table 1. Descriptive analysis of perinatal and delivery room resuscitation variables.

	Total (n=54)	≤ 28 weeks (n=16)	> 28 weeks (n=38)
VARIABLE $\bar{X}$ ± DS			
Gestational age (weeks)	29.12 ±1.82	26.81 ±1.16	30.10 ±0.95
Weight	1185±222.62	1039.06±215.37	1246.71±197.64
Maternal age	28.24±7.18	28.37±8.15	28.18±6.90
VARIABLE N (%)			
SGA[1]	5 (9.25)	0	5 (13.15)
Antenatal steroids	40 (74.07)	11 (68.75)	29 (76.31)
Chorioamnionitis	2 (3.70)	2 (12.5)	0
Twins	5 (9.25)	0	5 (13.15)
5-min Apgar <7[2]	12 (22.22)	9 (56.25)	3 (7.89)
Vaginal delivery	17 (31.48)	9 (56.25)	8 (21.05)
Male sex	33 (61.11)	11 (68.75)	22 (57.89)
SH[3]	21 (38.89)	4 (25)	1 /(44.73)
OTI[4]	17 (31.48)	12 (75)	5 (13.15)
Cardiac massage	2 (3.70)	2 (12.5)	0
Adrenaline	1 (1.81)	1 (6.25)	0

Key: 1. SGA – small for gestational age; 2. 5-min. Apgar <7 – 5-minute Apgar score os less than 7; 3. SH – systemic hypertension; 4. OTI – orotracheal intubation.

Table 2. Descriptive analysis of patient progression.

	Total (n=54)	≤ 28 weeks (n=16)	> 28 weeks (n=38)
VARIABLE $\bar{X}$ ± DS			
Days in hospital	51,12±25,37	70,56±30,08	42,94±17,98
VARIALBLE N (%)			
BPD[1]	29 (53,70)	15 (93,75)	14 (36,84)
MOD-SVR BPD[2]	19 (35,18)	9 (56,25)	10 (26,31)
Oxigênio na alta	10 (18,51)	7 (43,75)	3 (7,89)
PCA[3]	24 (44,44)	10 (62,5)	14 (36,84)
PCA[3] tratamento cirúrgico	4 (7,40)	3 (18,75)	2 (5,26)
PCA[3] tratamento medicamentoso	5 (9,25)	3 (18,75)	4 (10,52)
Enterocolite	7 (12,96)	3 (18,75)	2 (5,26)
Retinopatia	5 (9,25)	3 (18,75)	2 (5,26)
Sepse	18 (33,33)	9 (56,25)	9 (23,68)
Hemorragia	17 (31,48)	10 (62,5)	7 (18,42)
intraventricular			
Osteopenia	5 (9,25)	3 (18,75)	2 (5,26)
Dieta no 1º dia	37 (68,51)	18 (33,33)	19(35,18)

1. PIG - Pequeno para Idade Gestacional; 2. Apgar <7 no 5 min – Apgar menor que 7 no quinto minuto de vida; 3. HAS – Hipertensão Arterial Sistêmica; 4. IOT – Intubação Orotraqueal.

disease characteristics associated with lower birth weight at a time when prenatal treatment with corticosteroids is well established[4].

In another study, the need for IOT during resuscitation in the delivery room was considered a relevant factor that increased the risk of BPD by 5.22 times (95% CI: 2.25-12.1) (p<0.001). Our study found an even stronger association, leading to a 12.32-fold increase in the risk of BPD (OR: 12.32 and 95% CI: 2.91-86.01) (p<0.001).

Another study correlated a longer duration of IMV with the occurrence of BPD,[16], and a decreased incidence of BPD with a shorter time of IMV. Another article reported that premature infants on IMV for seven days or longer had more severe involvement, although multiple logistic regression analysis revealed the finding to be nonsignificant [4]. Unlike previous studies, this study suggests that being on IMV on the 14th day of life is an isolated risk factor for developing BPD, increasing the risk by 12.32 times. Like oxygen therapy, mechanical ventilation plays a significant role in the pathogenesis of BPD.

IMV-induced lung injury is complex, as it depends on the interaction between the ventilation method and the individual's intrinsic factors. Barotrauma, volutrauma, atelectrauma, and biotrauma can be determining factors. These can result in an inflammatory cascade that disrupts the signaling pathways involved in lung development and repair, contributing to the development of BPD[17].

Corticosteroids are potent negative regulators of inflammation and are widely used postnatally to prevent and treat BPD. Concerns about the adverse effects of this medication, especially neurological impairment, led to recommendations against its use in the early 2000s[18]. However, evidence has suggested that the benefits may outweigh the risks when the risk of BPD is high (>50%)[19]. Currently, there is much debate regarding the prescription of corticosteroids.

A study conducted in the Spanish public health system divided patients into groups with moderate to severe BPD and without moderate to severe BPD[5]. Even though it included a larger number of patients (202) than our study and the mean gestational age was very similar (29.5 ± 2.1 years), the authors reported a lower incidence of BPD (28.7%) and moderate to severe BPD (10.4%). They also described an association between BPD and the need for IMV on the 5th day of life, sepsis, and FiO2 on the 14th day of life. In the case of moderate to severe BPD, the association was with sepsis and receiving IMV on the 3rd and 5th days of life. The impact of sepsis, which has been identified as a risk factor in many studies[5-14-15-20], was not the same as in our study. American data show that 36% of newborns with gestational ages of 28 weeks or more have at least one episode of sepsis, with up to 50% mortality. Compared to full-term newborns, sepsis in preterm babies is much more frequent, being a cause of mortality and disordered neurological development[21], in addition to inducing inflammation and fibrosis in the lungs of premature babies[22].

Table 3. Fatores de risco para displasia broncopulmonar.

		BDP[1] (n=29)	Sem BPD[1] (n=25)	OR[2]	IC[3] 95%	*p*-valor	OR2	IC[3] 95%	*p*-valor
Perinatal variables	VARIALBLE $\bar{X}$ ± DS								
	Gestational age	28.31±1.96	30.08±1.03	0.37	(0.15;0.70)	0.012	0.35	(0.17; 0.60)	0.001
	Weight	1136.20±234.40	1242±197.69	0.97	(0.89;1.05)	0.501	-	-	-
	Maternal age	26.65±7.15	30.08±6.98	0.86	(0.73;0.99)	0.049	0.85	(073;0.96)	0.019
	VARIABLE N (%)								
	SGA[4]	2 (6)	3 (12)	1.74	(0.04; 5.94)	0.752	-	-	-
	Antenatal steroids	21 (72)	19 (76)	0.79	(0.12;4.39)	0.765	-	-	-
	Chorioamnionitis	2 (6)	0	<0.001	-	0.996	-	-	-
	Twin	1 (3)	4 (16)	0.3	(0.01;4.06)	0.402	-	-	-
	Vaginal delivery	12 (41)	5 (20)	0.96	(0.12;8.01)	0.972	-	-	-
	Male sex	21 (72)	12 (48)	6.85	0.48;0.59)	0.039	4.66	(1.12; 2.38)	0.044
	SH[5]	10 (34)	11(44)	0.98	(0.17;6.18)	0.998	-	-	-
Resuscitation in the delivery room	VARIABLE N (%)								
	OTI[6]	15 (51.72)	2 (8)	7.69	(1.25;78.09)	0.043	12.32	(2.91;86.01)	<0.001
	Cardiac massage	2 (6)	0	-	-	-	-	-	-
	Adrenaline	1 (3)	0	-	-	-	-	-	-
	5-min. Apgar <7[7]	10 (34)	2 (8)	1.72	(0.18;15.75)	0.608	-	-	-
	CPAP[8]	10 (34)	16 (64)	0.65	(0.17;2.58)	0.5312	-	-	-
Neonatal development	VARIABLE $\bar{X}$ ± DS								
	FiO_2[9] day 1	62.79±31.14	41.84±21.66	0.58	(0.01;1.21)	0.25	-	-	-
	FiO_2[9] day 3	46.96±23.03	29.4±8.58	0.18	(0.08;5.85)	0.19	-	-	-
	FiO_2[9] day 7	34.17±16.53	34.68±22.25	0.29	(0.08;2.22)	0.17	-	-	-
	FiO_2[9] day 14	42.75±25.27	29.8±20.17	0.18	(0.09;1.68)	0.24	-	-	-
	VARIABLE N (%)								
	Surfactant	19 (65)	6 (24)	0.04	(0.09;2.22)	0.78	-	-	-
	Caffeine	26 (90)	22 (88)	<0.001	(<0.001;0.09)	0.08	-	-	-
	DART[10]	27 (93)	1 (20)	<0.001	(3.21;4.38)	0.08	20	(3.54; 173.36)	<0.001
	IMV[11] day 1	17 (58)	5 (20)	<0.001	(0.03;2.31)	0.53	-	-	-
	IMV[11] day 3	20 (68)	6 (24)	0.001	(<0.001;4.76)	0.34	-	-	-
	IMV[11] day 7	19 (65)	3 (12)	<0.001	(0.99;2.64)	0.06	-	-	-
	IMV[11] day 14	19 (65)	1 (4)	0.1	(0.001;4.25)	0.04	9.5	(1.18; 202.22)	0.05
	Sepsis	14 (48)	4(16)	0.001	(<0.001;0.82)	0.15	-	-	-
	PDA[12]	20 (68)	4(16)	0.04	(0.06;2.93)	0.18	-	-	-
	PDA[12] repaired surgically	4 (13)	0	0.01	(<0.001;5.33)	0.99	-	-	-
	PDA[12] treated with drug therapy	5(17)	0	<0.001	(<0.001; 1.05)	0.99	-	-	-
	Diet o 1st day	13 (55)	12 (45)	-1.46	(-7.43;3.42)	0.55	-	-	-

Key: 1. BPD – bronchopulmonary dysplasia; 2. OR – Odds Ratio; 3. 95% CI –95% confidence interval; 4. SGA – small for gestational age; 5. SH – systemic hypertension; 6. OTI – orotracheal intubation; 7. 5-min. Apgar <7 – 5-minute Apgar score lower than 7; 8. CPAP - continuous positive airway pressure; 9. FiO_2 – fraction of inspired oxygen; 10. DART - Dexamethasone: A Randomized Trial; 11. IMV – invasive mechanical ventilation, 12. PDA – patent ductus arteriosus.

Table 4. Risk factors for moderate to severe bronchopulmonary dysplasia.

		MOD-SVR BPD[1] (n=30)	No MOD-SVR BPD[1] (n=24)	OR[2]	95% IC[3]	*p*-valor	OR[2]	95% IC[3]	*p*- valor
	VARIÁVEL $\overline{X}$ ± DS								
	Idade gestacional	28.40±1.99	30.04±1.04	0.42	(0.18; 2.23)	0.01	0.43	(0.23;6.87)	0.001
	Peso	1147±238.25	1232.50±196.03	0.99	(0.19;1.81)	0.87	-	-	-
	Idade materna	26.5±7.07	30.41±6.92	0.87	(0.75;.099)	0.06	0.86	(0.76;9.69)	0.01
	VARIÁVEL N (%)								
Perinatal variables	PIG[4]	2 (6)	3 (12)	0.9	(0.16;5.13)	0.9	-	-	-
	Corticoesteroide antenatal	22 (73)	18 (75)	0.96	(0.16;5.46)	0.99	-	-	-
	Corioamnionite	2 (6)	0	-	-	0.33	-	-	-
	Gemelar	1 (3)	4 (17)	0.26	(0.009;3.23)	0.96	-	-	-
	Parto vaginal	13 (43)	4 (17)	1.76	(0.25;1.45)	0.56	-	-	-
	Sexo masculino	21 (70)	12 (50)	3.3	(0.65;2.01)	0.16	-	-	-
	HAS[5]	10 (33)	11 (46)	1.66	(0.005;4.57)	0.76	-	-	-
	VARIÁVEL N (%)								
	IOT[6]	15 (50)	2 (8)	4.95	(0.25;2.22)	0.09	11	(2.60;76.58)	0.003
Resuscitation in the delivery room	Massagem cardíaca	2 (6)	0	-	-	-	-	-	-
	Adrenalina	1 (3)	0	-	-	-	-	-	-
	Apgar <7 no 5º min[7]	11 (36)	1 (4)	5.27	(0.84;42.66)	0.16	-	-	-
	CPAP[8]	11 (36)	15 (62.5)	0.71	(0.19;2.76)	0.62	-	-	-
	VARIÁVEL $\overline{X}$ ± DS								
	FiO_2[9] day 1	61.7±31.18	42.33±21.98	0.7	(0.20;1.17)	0.27	-	-	-
	FiO_2[9] day 3	46.23±22.98	29.58±8.17	1.14	(0.02.1.16)	0.32	-	-	-
	FiO_2[9] day 7	37.73±16.42	35.25±22.54	1.36	(0.79;3.32)	0.45	-	-	-
	FiO_2[9] day 14	42.03±25.15	30.16±20.52	1.12	(0.64;4.47)	0.39	-	-	-
	VARIABLE N (%)								
	Surfactant	20 (67)	5 (20)	0.09	(0.005;1.25)	0.98	-	-	-
	Caffeine	27 (90)	21 (87)	<0.001	(<0.001;0.10)	0.13	-	-	-
Neonatal development	DART[10]	27 (90)	5 (20)	4.81	(0.09;1.20)	0.14	12.66	(2.53;82.65)	0.003
	IMV[11] day 1	17 (57)	5 (20)	1.04	(0.013;5.98)	0.98	-	-	-
	IMV[11] day 3	20 (67)	6 (25)	0.007	(0.001;1.21)	0.09	-	-	-
	IMV[11] day 7	19 (64)	3 (12)	5.49	(1.02;8.74)	0.04	-	-	-
	IMV[11] day 14	19 (64)	1 (4)	1.13	(<0.001;0.03)	0.2	9.49	(1.18;202)	0.04
	Sepsis	15 (50)	3 (12)	7.77	(1.67;8.31)	0.13	-	-	-
	PDA[12]	20 (67)	4 (16)	1.12	(0.02;3.78)	0.25	-	-	-
	PDA[12] treated surgically	4(13)	0	-	-	-	-	-	-
	PDA[12] treated with drug therapy	5 (16)	0	-	-	-	-	-	-
	Diet on 1st day	12 (50)	12(0)	0.07	(0.02;5.53)	0.29	-	-	-

This study has several limitations, primarily related to its retrospective nature and the enrollment of a relatively small population (54 patients). The definition of BPD (oxygen dependence at 28 days of life) may also serve as a limiting factor, given that the 2021 NICHD Consensus refers to oxygen dependence for 28 days[2].

The clinical data collected in this study revealed that more than half of the patients (53.7%) had BPD, with 35.18% developing moderate to severe BPD. Gestational age, maternal age, male sex, OTI in the delivery room, IMV on the 14th day of life, and the need for the DART protocol were identified as risk factors for BPD. IMV on the 14th day, the DART protocol, and male sex were no longer considered risk factors when we selected patients with moderate to severe BPD. This study can serve as a foundation for developing other early predictive models and comparing new tools' predictive capacity with clinical variables.

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