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ORIGINAL ARTICLE

Risk factors and bronchopulmonary dysplasia severity: data from the Spanish Bronchopulmonary Dysplasia Research Network

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Abstract

GEIDIS is a national-based research-net registry of patients with bronchopulmonary dysplasia (BPD) from public and private Spanish hospitals. It was created to provide data on the clinical characterization and follow-up of infants with BPD until adulthood. The purpose of this observational study was to analyze the characteristics and the impact of perinatal risk factors on BPD severity. The study included 1755 preterm patients diagnosed with BPD. Of the total sample, 90.6% ($n = 1591$) were less than 30 weeks of gestation. The median gestational age was 27.1 weeks (25.8–28.5) and median birth weight 885 g (740–1,070 g). A total of 52.5% ($n = 922$) were classified as mild (type 1), 25.3% ($n = 444$) were moderate (type 2), and 22.2% ($n = 389$) were severe BPD (type 3). In patients born at under 30 weeks' gestation, most pre-and postnatal risk factors for type 2/3 BPD were associated with the length of exposure to mechanical ventilation (MV). Independent prenatal risk factors were male gender, oligohydramnios, and intrauterine growth restriction. Postnatal risk factors included the need for FiO_2 of > 0.30 in the delivery room, nosocomial pneumonia, and the length of exposure to MV.

Conclusion: In this national-based research-net registry of BPD patients, the length of MV is the most important risk factor associated with type 2/3 BPD. Among type 3 BPD patients, those who required an $FiO_2 > .30$ at 36 weeks' postmenstrual age had a higher morbidity, during hospitalization and at discharge, compared to those with nasal positive pressure but $FiO_2 < .30$.

What is Known:

- *BPD is a highly complex multifactorial disease associated with preterm birth.*

What is New:

- *The length of exposure to mechanical ventilation is the most important postnatal risk factor associated to bronchopulmonary severity which modulate the effect of most pre and postnatal risk factors.*
- *Among patients with BPD, the requirement for FiO2 >.30% at 36 weeks of postmenstrual age is associated with greater morbidity during hospitalization and at discharge.*

Keywords Bronchopulmonary dysplasia · GEIDIS network · Preterm infants · Mechanical ventilation · Intrauterine growth restriction · Oligohydramnios

Abbreviations

BPD	Bronchopulmonary dysplasia
EN	Enteral nutrition
GA	Gestational age
GEIDIS	Spanish Bronchopulmonary Dysplasia Research Group
iNO	Inhaled nitric oxide therapy
IUGR	Intrauterine growth restriction
MV	Mechanical ventilation
NEC	Necrotizing enterocolitis
PDA	Paten ductus arteriosus
PMA	Postmenstrual age

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Introduction

Bronchopulmonary dysplasia (BPD) is the most frequent sequelae of prematurity and results in significant long-term health consequences and high healthcare costs [1–3]. It is characterized by impaired development of the alveoli, airways, and pulmonary vasculature, which is often associated with structural changes of the airways and vasculature. The main risk factor is immaturity, and the incidence increases as gestational age decreases. As a multifactorial disease, many external factors are involved in its severity such as invasive mechanical ventilation-induced lung injury, oxidative stress, infections, inflammation, pulmonary overflow, nutritional disorders, and others that can affect the lungs' normal growth at early stages of their development.

A better understanding of factors linked to lung damage have led to changes in the management of very immature newborns, as controlling oxygen therapy, noninvasive respiratory support, early and less invasive surfactant therapy, prophylactic caffeine, infection prevention, and nutrition improvement among others, minimizing lung damage and promoting a better lung growth and development [1].

The incidence of BPD has not declined over the last decade [2], possibly because of an increase in the survival rate of the most premature infants who have a greater risk of developing BPD. Simultaneously, there has been a decrease in the severity of BPD [3].

Currently reported BPD rates in Spain in preterm babies born with a weight under 1500 g range between 34.9% in 2013 and 32.2% in 2016 [4, 5].

The Spanish Bronchopulmonary Dysplasia Research Group (GEIDIS) is a national research network with a prospective online case registry of patients diagnosed with BPD from 66 Spanish hospitals created to better understand risk factors and long-term consequences until adulthood.

The purpose of this initial study was to define and analyze the characteristics of the BPD patients in the GEIDIS registry and describe the impact of pre- and postnatal factors on the severity of the disease.

Methods

The study involves the analysis of the data collected prospectively in the GEIDIS registry between January 2016 and August 2020.

Inclusion criteria

Preterm patients (under 37 weeks of gestational age) diagnosed with BPD (more than 28 days on respiratory support or an $FiO_2 > 0.21$ evaluated at 36 weeks postmenstrual age [PMA]) who had been entered in the GEIDIS registry database [6].

The following are the definitions of the variables used in the study (specified in the database and described in Supplementary Information 1:

- Perinatal variables: Gestational age (GA); sex; birth weight (grams); maternal age (years); antenatal corticosteroids; intrauterine growth restriction (IUGR); oligohydramnios; clinical and histological chorioamnionitis; type of respiratory support received at birth, during hospitalization, and at 36 weeks' PMA; need for treatment with surfactant, inhaled nitric oxide therapy (iNO), postnatal corticosteroids therapy, diuretics, caffeine, and bronchodilators during hospitalization; length of exposure to invasive mechanical ventilation (MV) in days; respiratory support and treatments at discharge; patent ductus arteriosus (PDA); nosocomial sepsis; nosocomial pneumonia; air leak syndrome (pneumothorax or interstitial emphysema); pulmonary hypertension; necrotizing enterocolitis requiring surgery (NEC); intraventricular hemorrhage; hemorrhagic stroke; periventricular leukomalacia; hydrocephalus requiring a shunt; and retinopathy of prematurity.
- BPD was graded according to the agreed definition [4] into type 1 BPD (mild), type 2 BPD (moderate), and type 3 BPD (severe). Patients with type 3 BPD who need a $FiO_2 > 0.30$ were compared to patients who received positive-pressure respiratory support but at an $FiO_2 < 0.30$ at 36 weeks' PMA. Those on high-flow nasal cannula (more than 2 L/min) at 36 weeks' PMA were classified as type 3 BPD.

Statistical analysis

The statistical data analysis was carried out with the aid of the IBM SPSS software package for Mac, version 21 (Chicago, Illinois).

The descriptive data analysis used measures of central tendency and measures of dispersion to summarize the quantitative variables and percentage distribution in the case of qualitative variables.

We used the chi-squared test (χ^2) for the comparative analysis of categorical variables with the Bonferroni correction for multiple comparisons, and the Kruskal–Wallis test with Bonferroni adjustment for the quantitative variables, as they did not meet the normality criteria. Statistical significance was set to a $p < 0.05$.

Binary logistic regression was used for the multivariate analysis of binary response variables and linear regression for quantitative variables. The variables analyzed were selected according to their theoretical relevance and the level

of significance observed in the bivariate analysis. The number of variables included in each analysis was determined based on the number of events/nonevents for the response variable. Given its clinical relevance, GA was included in all models. The approximate models included the interactions of the main study variable with the rest of the variables included, proceeding to stratification in the case of significant interactions.

The study was assessed and approved by the Local Research Ethics Committees and authorized by the Spanish Agency for Medicines and Medical Devices (AEMPS). Informed consent was obtained from the legal guardians of participants included in the study.

Results

The total sample included 1755 patients with a diagnosis of BPD, 922 (52.5%) with type 1 BPD, 444 (25.3%) with type 2 BPD, and 389 (22.2%) with type 3 BPD. The respiratory support needed by patients with type 3 BPD is detailed in Supplementary Table S1.

A total of 90.6% (1591/1755) were less than 30 weeks of gestation. The median GA was 27.1 weeks (25.8–28.5), and the median birth weight was 885 g (740–1070 g).

The proportion of type 2/3 BPD decreased as GA increased until 30 weeks of gestation; over this gestational age, the frequency of type 2/3 BPD increased (Fig. 1).

Patients with type 2/3 BPD had a higher rate of respiratory morbidity from birth and required respiratory support and oxygen for a longer time. They were also associated with a greater morbidity during hospitalization (Table 1), and at discharge (Table 2), especially for those with type 3 BPD.

When considering only infants born < 30 weeks of gestation, all of the risk factors analyzed were also associated with a greater length of exposure to MV (Supplementary Table S2); only histological chorioamnionitis seemed to be linked to less exposure to MV when adjusted for GA. However, the percentages of patients who needed MV was very similar for those with and without histological chorioamnionitis (74.3% and 78.3%, respectively, p 0.179), as was the length of exposure to MV, median of 10.5 days (3.2–22) for patients with histological chorioamnionitis and 11 (4–26) for patients without histological chorioamnionitis ($p = 0.400$). A total of 99.4% ($n = 1581$) of < 30 weeks GA infants were treated with caffeine, 87.5% ($n = 1383$) in the first 24 h after birth.

When the estimation of the effect of the independent variables was adjusted for the length of exposure to MV, sex (male), IUGR, oligohydramnios, need for $FiO_2 > 0.30$ at birth, nosocomial pneumonia, and surgical closure of PDA were associated with a higher incidence of type 2/3 BPD. All the other variables, including GA, were not associated with a significant effect on type 2/3 BPD (Table 3). A total of 94.9% ($n = 188$) of the patients with surgical PDA closure had a previously failed pharmacological treatment.

In infants born ≥ 30 weeks, none of the variables were longer significant when adjusted for the length of exposure to MV (Supplementary Table S3).

In the group of patients < 30 weeks' gestation with type 3 BPD, those who required an $FiO_2 > 0.30$ at 36 weeks' PMA had a higher morbidity, both during hospitalization and at discharge, compared to the group of patients with nasal positive pressure but at a $FiO_2 < 0.30$ (Supplementary Table S4). There was an increased incidence of oligohydramnios in patients who required > 30% oxygen at 36 weeks' PMA

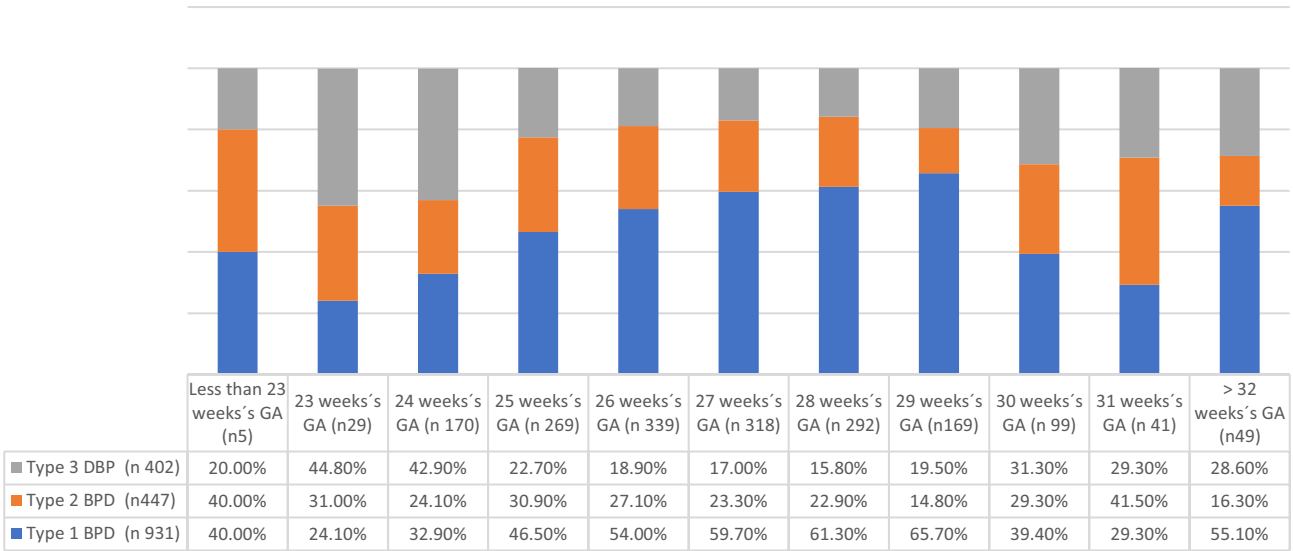

Fig. 1 Distribution of types of bronchopulmonary dysplasia according to gestational age at birth in weeks (week's GA)

Table 1 Incidence of pre- and postnatal factors by severity of BPD. Data expressed in percentage (*n*) or median (interquartile range)

	Type 1 BPD (*n* = 922)	Type 2 BPD (*n* = 444)	Type 3 BPD (*n* = 389)	*p*
Gestational age (weeks)	27.3 (26.1–28.6)	26.8 (25.6–28.3)*	26.6 (25–28.4)*	< .01
Weight (g)	932 (790.1–1104)	847.5 (725.75–1000)*	800 (650–1000)*†	< 0.01*†0.025
Prenatal corticosteroids (complete course)	77.6% (598/771)	82.2% (304/370)	79.6% (262/328)	0.197
Sex (male)	52.4% (478/912)	56.7% (251/443)	61.8% (239/387)*	0.007
Clinical chorioamnionitis	15.1% (139/922)	13.7% (61/444)	14.1% (55/389)	0.782
Histological chorioamnionitis	14.4% (133/922)	14.6% (65/444)	11.8% (46/389)	0.404
Intrauterine growth restriction	16.5% (145/881)	20.8% (88/423)	25.9% (94/363)*	0.001
Oligohydramnios	10.4% (94/903)	15.1% (66/370)*	16.3% (62/380)*	0.004
Maternal age	34 (29–37)	33 (29–37)	34 (30–37)	0.931
Mother smoked during pregnancy	17.2% (34/198)	14.3% (13/91)	13.9% (11/79)	0.724
Asthmatic mother	10.3% (20/195)	13.6% (12/88)	12% (9/75)	0.701
Asthmatic father	7.9% (15/190)	9.4% (8/85)	5.9% (4/68)	0.723
Intubation at birth	40.8% (376/922)	50.2% (223/444)*	56% (218/389)*	<0.001
FiO2 > 0.30 at birth	68.3% (624/914)	77.5% (338/436)*	80.4% (308/383)*	<0.001
FiO2 > 0.60 at birth	14.6% (133/914)	24.3% (106/436)*	30.0% (115/383)*	<0.001
Intubation in first hour of life	45.9% (421/922)	58.1% (258/444)*	61.2% (238/389)*	<0.001
Surfactant	72% (655/910)	80.3% (350/436)*	79.3% (303/382)	0.001
Two or more surfactant doses	27.1% (169/624)	38.7% (128/331)*	47.1% (138/293)*†	<0.001
Caffeine therapy	9.2% (912/919)	98.9% (434/439)	98.4% (378/384)	0.414
MV during hospitalization	66.8% (613/918)	82.7% (364/440)*	88.6% (343/387)*†	<0.001
Noninvasive respiratory support	99.3% (915/921)	99.3% (438/441)	97.9% (375/383)	0.042
Nitric oxide therapy	6.1% (56/916)	14.1% (61/434)*	26.4% (101/383)*†	<0.001
Ectopic air	4.7% (43/922)	8.1% (36/444)	12.6% (49/389)*†	<0.001
MV, days	6 (2–14)	12 (5–25)*	26 (10–42)*†	<0.001
Positive pressure, days	25 (14–36)	33 (18–48)*	45 (30–66)*†	<0.001
High-flow oxygen, days	11 (0–21)	13 (3–24)	25 (12.2–39)*†	0.001
Oxygen, days	42 (30–54)	67 (50–82)*	73 (49.5–103.5)*	<0.001
Postnatal corticosteroids for BPD	17.8% (164/922)	30.4% (136/444)*	53.2% (205/389)*†	<0.001
Nosocomial sepsis	51.7% (470/909)	60.8% (265/436)*	74.6% (288/386)*†	<0.001
Nosocomial pneumonia	5.8% (52/912)	18.6% (81/435)*	35.1% (132/376)*†	<0.001
Patent ductus arteriosus (PDA)	46.9% (424/904)	56.0% (243/434)*	65.8% (246/374)*†	<0.001
PDA surgical closure	4.9% (45/922)	14.9% (66/444)*	22.9% (89/389)*†	<0.001
Necrotizing enterocolitis (surgical)	4.3% (39/904)	4.8% (21/435)*	8.6% (32/371)*	0.007
Maximum volume of fluid in first 72 h	110 (100–120)	110 (110–120)	110 (100–125)	0.867
Time until exclusively EN	13 (10–20)	17 (11.5–26)*	20 (12–30)*†	*<0.001; †0.035
Time until exclusively EN by mouth	60 (49–73)	70.5 (60–85)*	88 (69–105)*†	<0.001

g grams, *FiO2* fraction of inspired oxygen; *MV* mechanical ventilation, *HFO* high-flow oxygen, *BPD* bronchopulmonary dysplasia, *PDA* patent ductus arteriosus, *PH* pulmonary hypertension, *EN* enteral nutrition, *h* hours

*Significant difference with type 1 BPD

†Significant difference with type 2 BPD

compared to those who needed positive-pressure ventilation, which was significant when adjusted for the rest of the prenatal risk factors (OR 2.201; 95% CI 1.227–3.947).

Surgical NEC was associated with a reduced incidence of type 2/3 BPD when adjusted for the length of MV (Table 3). Each day on MV in patients with NEC was associated with an increased incidence of type 3 BPD of at least 2.8% (OR 1.060; 95% CI 1.028–1.093) compared to 5.8% in the other patients (OR 1.070; 95% CI 1.058–1.081).

For patients who did not require MV (*n* = 353; 22.2% of the sample), prenatal factors (male, IUGR, oligohydramnios) were associated with a greater incidence of type 2/3 BPD, but none of the postnatal factors presented a significant association (Supplementary Table S5). In this group,

Table 2 Incidence of hospital morbidity by type of BPD. Data expressed in percentage (*n*)

	Type 1 BPD (*n* = 922)	Type 2 BPD (*n* = 444)	Type 3 BPD (*n* = 389)	*p*
Leukomalacia (> grade 1)	3.8% (34/885)	4.5% (19/425)	9.9% (37/381)*†	< 0.001
IVH (grade 3 or higher)	6.2% (55/889)	7.8% (33/424)	10.4% (38/366)*	0.036
Periventricular infarction	16.3% (130/794)	16.6% (60/360)	7.9% (60/334)	0.375
Ventriculoperitoneal shunt	2.1% (13/25)	2.6% (7/272)	3.3% (10/306)	0.548
Retinopathy	33.0% (289/877)	47.1% (181/384)*	51.6% (177/343)*	< 0.001
Retinopathy greater than grade 2	19.7% (58/294)	27.8% (52/187)	42.9% (78/182)*†	< 0.001
Respiratory support at discharge	3.9% (35/903)	29.1% (126/433)*	47.2% (171/ 362)*†	< 0.001
Feeding by NGT/gastrostomy	2.5% (23/922)	2.7% (12/444)	12.6% (49/389)*†	< 0.001
Pulmonary Hypertension (diagnosis > 28dol)	0.1% (1/922)	3.4% (15/444)*	9% (35/389)*†	< 0.001
Sildenafil treatment	0.1% (1/922)	1.8% (8/444)*	8.7% (34/389)*†	< 0.001
Bronchodilators	1.3% (12/922)	3.6% (16/444)*	12.1% (47/389)*†	< 0.001
Inhaled corticosteroids	6.7% (62/922)	16.2% (72/444)*	19.5% (76/389)*	< 0.001
Diuretics	5% (46/922)	8.1% (36/444)*	19.5% (76/389)*†	< 0.001
Antireflux treatment	3.7% (34/922)	8.6% (38/444)*	18.0% (70/389)*†	< 0.001
Mortality	0.7% (6/895)	0.7% (3/425)	4.4% (16/366)*†	< 0.001

IVH intraventricular hemorrhage, *NGT* nasogastric tube

*Significant difference with type 1 BPD

†Significant difference with type 2 BPD

76.2% (*n* = 269) developed type 1 BPD, 15.6% (*n* = 55) type 2 BPD, and 8.2% (*n* = 29, of whom only five patients required > 30% oxygen at 36 weeks' PMA) were type 3 BPD. This is in contrast to patients who did require MV, where type 1 BPD was 47.2% (*n* = 680), type 2 BPD 27.2% (*n* = 334), and type 3 BPD 25.6% (*n* = 314) (*p* < 0.001).

When stratified according to GA, patients born > 30 weeks' gestation had a higher proportion of males, IUGR, more cases of pneumothorax, pulmonary hypertension, iNO therapy, longer exposure to MV, and a similar percentage of type 2/3 BPD to infants born at less than 26 weeks (Table 4).

Discussion

This study confirms the important role of immaturity as a predisposing factor in the development of BPD. In addition, exposure to MV seems to act as an intermediary agent between risk factors and the severity of BPD. It is hard to establish the individual influence of each of the known risk factors on the severity of BPD, as they are all associated with exposure to MV. Evidence derived from both animal studies and randomized clinical trials has shown that MV is the most important factor associated to the development of BPD [7–10]. In this observational study, MV also acts as a variable in the causal pathway between most of the prenatal and postnatal risk factors and the development of type 2/3 BPD.

Most of the risk factors studied were associated with a longer exposure to MV; only higher GA and chorioamnionitis were protective factors.

GA is the strongest predictor of the development of BPD [2, 11–13], which is also related to MV [14, 15]. Immaturity, both pulmonary and neurological, results in a more severe respiratory failure, more need for surfactant therapy, central apnea, and morbidity during hospitalization [12], which means more exposure to MV. In our study, the effect of GA on the severity of BPD was no longer significant when adjusted for the length of exposure to MV.

It should be noted that the effect of GA in our sample may be partly conditioned by the diagnostic criteria for BPD, which currently generate controversy [16–19].

The current classification of BPD lies mostly on the respiratory support required. It is defined BPD if needing more than 28 days oxygen therapy at a PMA of 36 weeks and grading the severity of BPD based on the respiratory support required [4]. One of the most controversial points is the diagnosis of type 1 BPD, patients who do not require respiratory support at 36 weeks' PMA but need oxygen for 28 days, as some authors believe that this can be attributed to immaturity [20] and does not imply the development of chronic lung disease [21]. In fact, some proposals for the disease's diagnosis and classification exclude the concept of type 1 BPD [22, 23]. In our population, we observed a higher proportion of type 1 BPD in neonates < 30 weeks; in fact, most patients with BPD (90.6%) were in this GA group.

Table 3 Analysis of the association of pre- and postnatal factors with the development of type 2/3 BPD vs type 1 in infants born with less than 30 weeks of GA. Raw and adjusted OR with 95% CIs

< 30 weeks GA ($n = 1591$)		TYPE 2/3 BPD vs 1 (raw)			TYPE 2/3 BPD vs 1 (adjusted for prenatal factors: GA, sex, IUGR, oligohydramnios)			TYPE 2/3 BPD vs 1 (adjusted for prenatal factors and length of exposure to MV)		
		OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
GA (weeks)		0.767	0.719 -0.819	< 0.001	0.734	0.683–0.789	< 0.001	0.923	0.847–1.005	0.065
Weight (g)		0.998	0.997–0.998	< 0.001	0.998	0.997–0.999	< 0.001	0.999	0.998–1.000	0.237
Sex, male		1.278	1.047–1.559	0.016	1.567	1.264–1.943	< 0.001	**1.425**	**1.134–1.791**	**0.003**
Oligohydramnios		1.598	1.182–2.162	0.002	1.530	1.11–2.108	0.009	**1.547**	**1.120–2.212**	**0.009**
IUGR		1.531	1.169–2.005	0.002	2.134	1.583–2.875	< 0.001	**1.714**	**1.250–2.348**	**0.001**
Histological chorioamnionitis		0.947	0.719–1.246	0.696	0.866	0.643–1.166	0.343	1.097	0.799–1.504	0.567
Intubation at birth		1.743	1.428–2.126	< 0.001	1.442	1.157–1.798	0.001	1.075	0.848–1.364	0.551
$FiO_2 > 0.30$ at birth		1.904	1.503–2.412	< 0.001	1.620	1.258–2.087	< 0.001	**1.434**	**1.098–1.874**	**0.008**
$FiO_2 > 60$ at birth		2.186	1.708–2.798	< 0.001	1.810	1.387–2.361	< 0.001	**1.607**	**1.211–2.132**	**< 0.001**
Intubation in first hour of life		1.900	1.554–2.323	< 0.001	1.584	1.269–1.976	< 0.001	1.140	0.898–1.448	0.592
Surfactant		1.719	1.349–2.190	0.001	1.682	1.296–2.184	< 0.001	1.268	0.960–1.675	0.095
Two or more surfactant doses		2.011	1.572–2.574	< 0.001	1.741	1.337–2.266	< 0.001**	1.291	0.974–1.713	0.076
MV during hospitalization		3.578	2.733–4.684	< 0.001	2.801	2.088–3.759	< 0.001	**1.515**	**1.104–2.079**	**0.010**
Duration of invasive MV, days		1.062	1.053- 1.071	< 0.001	1.060	1.048–1.072	< 0.001			
Nitric oxide therapy		3.947	2.820–5.525	< 0.001	3.373	2.362–4.817	< 0.001	**1.760**	**1.189–2.604**	**0.005**
Indication for Nitric oxide therapy	*Pulmonary Hypertension*	3.145	1.959–5.049	< 0.001	2.498	1.515–4.122	< 0.001	1.442	0.835–2.489	0.189
	Refractory hypoxemia	3.822	2.595–5.629	< 0.001	3.496	2.319–5.272	< 0.001	**1.885**	**1.206–2.947**	**0.005**
Ectopic air		2.153	1.435–3.230	< 0.001	1.937	1.253–2.996	< 0.001	1.171	0.731–1.875	0.512
NEC (surgical)		1.547	1.001–2.393	0.050	1.309	0.818–2.094	0.001	**0.491**	**0.283–0.854**	**0.012**
PDA		1.966	1.602 -2.413	< 0.001	1.659	1.318–2.089	< 0.001	1.232	0.963–1.576	0.098
PDA surgical closure		4.696	3.313–6.657	< 0.001	3.605	2.484–5.232	< 0.001	**1.752**	**1.160–2.645**	**0.008**
Nosocomial sepsis		1.979	1.604 -2.442	< 0.001	1.491	1.183–1.878	0.014	1.166	0.912–1.491	0.220
Nosocomial pneumonia		6.074	4.382–8.418	< 0.001	5.856	4.094–8.376	< 0.001	**3.231**	**2.192–4.764**	**< 0.001**
Periventricular leukomalacia (> grade 1)		1.475	1.254–1.736	< 0.001	1.804	1.129–2.883	0.014	1.369	0.828–2.263	0.221

BPD bronchopulmonary dysplasia, *GA* gestational age, *IUGR* intrauterine growth restriction, *g* grams, FiO_2 fraction of inspired oxygen, *MV* mechanical ventilation, *PDA* patent ductus arteriosus

*Adjusted for GA only

**Interaction between exposure to mechanical ventilation and gestational age

†All patients were exposed to MV

Table 4 Incidence of risk factors by gestational age groups. Data expressed in percentage (*n*) or median (interquartile range)

	< 26 wk GA (473)	26–28 wk. GA (657)	28–30 week GA (461)	≥ 30 week GA (164)	*p*
GA (weeks)	25 (24.5–25.4)	26.8 (26.4–27.4)*	28.7 (28.3–29.1)*,†	30.7 (30.2–31.4)*,†,γ	< 0.001
Weight (g)	711 (623–800)	900 (780–1000)*	1055 (890–1200)*,†	1200 (952–1433)*,†,γ	< 0.001
Sex, male	49.80% (234/470)	56.00% (366/654)*	56.80% (259/456)*	67.3% (109/162)*,†,γ	0.001
Corticosteroids (Complete course)	72.60% (289/398)	78.40% (421/537)*	82.50% (127/395)*	91.4% (127/139)*,†,γ	0.022
Intrauterine growth restriction	5.20% (23/443)	16.10%(101/626)*	30.10% (133/442)*,†	44.90% (70/156)*,†,γ	< 0.001
Oligohydramnios	11.00% (51/463)	13.60% (88/646)	12.70% (57/448)	16.00% (26/162)	0.361
Histological chorioamnionitis	21.60% (102/473)	16.60% /109/657)*	6.50% (30/461)*,†	1.80% (3/164)*,†,γ	< 0.001
Intubation at birth	68.30% (323/473)	47.00% (309/657)*	31.50% (145/461)*,†	24.00% (40/164)*,†	< 0.001
$FiO_2 > 0.60$ at birth	31.00% (144/465)	21.10% (137/650)*	12.10% (55/456)*,†	11.10% (18/162)*,†,γ	< 0.001
Surfactant	80.40% (373/464)	76.60% (498/650)	73.60% (335/455)*	64.20% (102/159)*,† γ	< 0.001
Caffeine therapy	99.6% (464/466)	99.2% (647/552)	99.3% (457/460)	95.1% (156/164)*,†,γ	< 0.001
Refractory hypoxemia	13.50% (64/473)	7.90% (52/657)*	6.50% (30/461)*	4.90% (8/164)*	0.001
MV during hospitalization	93.40% (437/468)	78.30% (512/654)*	60.80% (279/459)*,†	56.10% (92/164)*,†	< 0.001
Duration of MV, days	22 (10–35)	8 (3–20)*	5 (1–11)*,†	7 (3–14.00)*	< 0.001
Nitric oxide therapy	18.70% (87/465)	9.70% (63/651)*	10.30% (47/456)*	9.60% (21/161)	< 0.001
Postnatal corticosteroids	50.30% (238/473)	26.30% (173/657)*	15.80% (73/461)*,†	12.80% (21/164)*,†	< 0.001
Patent ductus arteriosus	74.70% (343/459)	56.30% (363/645)*	37.00% (166/449)*,†	28.60% (47/164)*,†,γ	< 0.001
Nosocomial sepsis	76.80%(351/457)	59.90% (385/643)*	47.50% (211/444)*,†	39.10% (63/161)*,†	< 0.001
Necrotizing enterocolitis (surgical)	8.30% (38/458)	6.00% (39/647)	2.20% (10/445)*,†	5.40% (5/160)*	< 0.001
Ectopic air	9.80% (46/468)	5.80%(38/652)*	5.40% (25/459)*	12.20% (20/164)†,γ	0.003
Type 2/3 bronchopulmonary dysplasia	59.80% (283/473)	43.20% (284/657)*	37.10% (171/461)*,†	57.90% (44/164)†,γ	< 0.001
Type 3 bronchopulmonary dysplasia	31.30% (148/473)	18.00% (118/657)*	17.10% (79/461)*	26.80% (44/164)†,γ	< 0.001

wk. weeks, *FiO2* fraction of inspired oxygen, *MV* mechanical ventilation, *PH* pulmonary hypertension

*Significant difference with the less than 26 weeks' gestation group

†Significant difference with the 26–28 weeks' gestation group

γSignificant difference with the 28–30 weeks' gestation group

Also, the need for more than 28 days of oxygen or respiratory support selects a small and probably unrepresentative sample of the whole population of preterm infants born after 30 weeks, as they have higher morbidity (pneumothorax and pulmonary hypertension) and higher type 2/3 BPD proportion than more immature premature infants (26–30 weeks of gestation). This may interfere in the analysis of the impact of GA on BPD severity in our sample.

Jensen et al. analyzed the predictive power of 18 BPD classifications with respect to long-term respiratory morbidity and reported that the better predictive value for a classification was based solely on respiratory support, without including oxygen requirements at 36 weeks' PMA [23]. In our sample, a requirement of > 0.30 FiO2 at 36 weeks' PMA was associated with increased morbidity during hospitalization compared to the need for positive pressure support. The need for more supplemental oxygen is considered a better marker of both alveolar and vascular parenchymal lung disease than the need for positive-pressure therapy, which may be due to other causes, such as large airway diseases or central apnea [24]. However, it is also true that many patients often require an oxygen concentration above 30% with a low-flow nasal cannula due to atelectasis or airway collapse which can be reversed with positive-pressure treatment, and consequently, the oxygen supply can be reduced. We are dealing, therefore, with an extremely complex disease with different phenotypes that appear to overlap in most cases [25].

Our series differs from others as it includes a low proportion of intubated patients at 36 weeks' PMA, only 4.4% compared to 13% in the US series analyzed by Jensen et al. [23], a greater use of noninvasive positive pressure (40.7% vs 32.4%), and a very similar percentage of patients with low-flow nasal cannula (55.5% vs 54.5%). It also features relatively low percentages of patients with oxygen requirements above 30%; 16% of the patients who needed respiratory support at 36 weeks and 33.6% when considering patients with type 3 BPD, compared to 46.7% and 87%, respectively, in the Prematurity and Respiratory Outcomes Program cohort [26].

Given the above, we analyzed all the patients with type 3 BPD together (i.e., those requiring oxygen at > 30% combined with patients in need of positive-pressure respiratory support), although we do believe that an analysis of

the differences between each type of respiratory support received at 36 weeks' PMA is very important when assessing long-term follow-up.

We found that chorioamnionitis was associated with a reduced need of MV after adjusting for GA. However, the percent of patients requiring MV and its duration were very similar for newborns with and without chorioamnionitis. The fact that chorioamnionitis was diagnosed more frequently among the most immature patients, and consequently those with a greater exposure to MV, means that the adjustment for GA might be distorting the true impact of chorioamnionitis, which remains a causal factor for preterm birth. Other authors have also reported that the effect of chorioamnionitis is dependent on GA [27, 28]. Pietrasanta et al. went so far as to question the suitability of adjusting the effect of chorioamnionitis for GA [28]. In this study, if chorioamnionitis is not adjusted for GA, it does not correlate with the need for intubation at birth or the incidence of more severe forms of BPD.

Due the high rate of preterm infants treated with caffeine, its effect on MV exposure and BPD severity cannot be analyzed.

Male gender, oligohydramnios, IUGR, and requirement for FiO2 > 0.30 at birth were independently associated with the development of type 2/3 BPD versus type 1.

Nosocomial pneumonia diagnosis was also 3 times more frequent on type 2/3 BPD patients versus type 1 but, as not time point at diagnosis has been recorded in the database, it cannot be considered as a risk factor, although both diagnostics are strongly related.

Hemodynamically significant PDA was no longer significantly associated to BPD severity when adjusted for the duration of MV exposure which is consistent with data published in the literature [29], but in case of surgical PDA closure, it is associated to at least 16% increase in BPD 2/3. One possible explanation could be a longer exposure to a hemodynamically significant PDA, as most of these patients have a previously failed pharmacological treatment. This observation has been evaluated recently in a large observational study, in which exposure to a moderate to large PDA of 7 to 13 days led to an increase of the combined outcome of BPD or death (OR 2.12, 95% CI 1.04–4.32) [30], but no specific data about the duration of exposure to PDA has been evaluated in our study.

The association between male sex and an increased severity of BPD has already been reported by others [31, 32]. In neonates born at under 32 weeks' gestation, the lungs of males are less mature than of females at the same GA, which suggests a sex-dependent differences in the canalicular and saccular phases of lung development [33, 34]. In function of sex, different genetic patterns have also been described in mesenchymal cells taken from tracheal aspirates [35]. In our study, being male correlated with a greater exposure to MV, but its effect on the development of type 2/3 BPD was still significant after adjusting for this variable. Furthermore, in patients who were not exposed to MV, being male was also associated with a greater incidence of severe forms of BPD; that is, there were sex-dependent differences in lung development that were independent of a higher rate of initial respiratory morbidity.

The effects of oligohydramnios and intrauterine growth restriction are also independent of exposure to MV. Oligohydramnios restricts intrauterine fetal lung growth, which causes pulmonary hypoplasia [36–38]. In our study sample, oligohydramnios is associated to a higher proportion of patients requiring > 30% oxygen at 36 weeks' PMA. This effect is consistent with the findings of other series in which oligohydramnios was associated with parenchymal pulmonary compromise, pulmonary vascular alterations [39–41], and pulmonary hypertension [42]. The correlation between impaired pulmonary vascular development and the emergence of BPD is widely discussed in the literature [43], with some authors suggesting it is one of the etiopathogenic mechanisms behind BPD (vascular theory of BPD) in which the impaired development of pulmonary vessels would dictate any alteration in distal airspace growth [44, 45].

The effect of intrauterine growth restriction (IUGR) on the development of BPD seems to be related also to an inhibition of lung growth involving altered angiogenesis. Alterations in placental vascularization and perfusion observed in premature patients with IUGR appear to affect both lung development and vascular growth, resulting in a greater susceptibility to develop BPD and pulmonary hypertension [46, 47].

In our sample, we also observed a relationship between an increased need for respiratory support at birth and the development of type 2/3 BPD. This pattern of severe respiratory failure from birth is the most frequently related to BPD development in other series [48]. The correlation between a greater need for respiratory support at birth and the appearance of type 2/3 BPD in our series occurred independently of the length of the subsequent exposure to MV, which indicates pulmonary involvement from birth that predisposes the development of more severe forms of BPD.

Another interesting feature is the association between a diagnosis of NEC and a lower incidence of both type 2/3 BPD after adjusting for the length of exposure to MV. It is worth noting that since these patients underwent surgery, they were all exposed to MV. On the other hand, this exposure was due to their abdominal process that in many cases causes the need for sedation, rather than a respiratory disease, so usually this group of patients requires a lower level of ventilatory assistance than those patients who had respiratory failure. In fact, MV had a lesser effect on the development of type 3 BPD in patients with surgical enterocolitis than in the rest of the sample. This highlights

the complexity of the mechanisms involved in lung damage and the difficulty of assessing their effect outside the controlled environment of animal studies. Nowadays, minimizing exposure to MV is an objective in all neonatal units, so its use is restricted to patients with severe respiratory failure when noninvasive respiratory support fails. The deleterious effect of MV is possibly greater in these patients who have lung disease and, therefore, an increased need for respiratory support and oxygen; but what is more, the necessity for MV leads us to select a group of patients with a higher risk of developing severe forms of BPD.

In patients who did not require MV during hospitalization, only being male and oligohydramnios were associated with a higher likelihood of developing type 2/3 BPD; however, none of the postnatal factors correlated with the emergence of type 2/3 BPD, which again emphasizes the role of MV as a mediator between these factors and the onset of the gravest forms of BPD.

This study has some limitations as we only included patients with a diagnosis of BPD, and given the observational character of the study, our assessment of the effect of the risk factors may be subject to significant biases, as the analysis only indicates the relationship between the risk factors and severity of BPD, as opposed to their effect on its incidence. Also, mortality in the first 28 days of life has not been considered and also no data about preeclampsia or placental vascular pathology are recorded in the database. On the other hand, the large sample size provides a very representative description of the Spanish population with BPD, even though not all of the neonatal units attending preterm infants have participated.

In conclusion, in our national-based research-net registry of patients with bronchopulmonary dysplasia, prenatal risk factors for the development of type 2/3 BPD versus type 1 BPD were male sex, IUGR, and oligohydramnios. Exposure to MV is the main postnatal risk factor associated with the development of type 2–3 BPD, which also acts as an intermediary factor between all the other postnatal risk factors and the development of more severe types of BPD. Among type 3 BPD patients, those who required an $FiO_2 > 0.30$ at 36 weeks' PMA had a higher morbidity, during hospitalization and at discharge, compared to those with nasal positive pressure but with $FiO_2 < 0.30$.

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Authors' contribution CN designed the study, performed the acquisition and analysis of the data, and draft the test. EMR, ACG, SPT, SRE, AST, MSS, and ESL designed the study, collected data during the study period, and revised the draft. MSL designed the study, made contributions on the conception of the work, and revised the draft critically.

Data availability Data are available on the online GEIDIS registry platform.

Code availability N/A.

Declarations

Ethical approval This article does not contain any interventional studies with human participants or animals performed by any of the authors. This study was approved and monitored by the Clinical Research Ethics Committee at Virgen de la Arrixaca Hospital. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Consent to participate Informed consent was obtained from the legal guardians of participants included in the study.

Consent for publication All the authors revised and approved the final version of the text and consents its publication.

Conflict of interest The authors declare no competing interests.

References

1. Owen LS et al (2017) The evolution of modern respiratory care for preterm infants. Lancet 389(10079):1649–1659
2. Stoll BJ et al (2015) Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. JAMA 314(10):1039–1051
3. Abman SH, Bancalari E, Jobe A (2017) The evolution of bronchopulmonary dysplasia after 50 years. Am J Respir Crit Care Med 195(4):421–424
4. Álvarez-Fuente M et al (2017) The economic impact of prematurity and bronchopulmonary dysplasia. Eur J Pediatr 176(12):1587–1593
5. SEN1500 (2016) Análisis de los datos de morbimortalidad año
6. Jobe AH, Bancalari E (2001) Bronchopulmonary dysplasia. Am J Respir Crit Care Med 163(7):1723–1729
7. Hernandez LA et al (1985) Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol 66(5):2364–2368
8. Jobe AH (2015) Animal models, learning lessons to prevent and treat neonatal chronic lung disease. Front Med (Lausanne) 2:49
9. Philip AG (1975) Oxygen plus pressure plus time: the etiology of bronchopulmonary dysplasia. Pediatrics 55(1):44–50
10. Dreyfuss D et al (1988) High inflation pressure pulmonary edema: respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137(5):1159–1164
11. Isayama T et al (2012) Comparison of mortality and morbidity of very low birth weight infants between Canada and Japan. Pediatrics 130(4):e957–e965
12. Stoll BJ et al (2010) Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics 126(3):443–456
13. Klinger G et al (2013) Perinatal risk factors for bronchopulmonary dysplasia in a national cohort of very-low-birthweight infants. Am J Obstet Gynecol 208(2):115.e1–9
14. Dargaville PA et al (2016) Incidence and outcome of CPAP failure in preterm infants. Pediatrics 138(1):15
15. Fuchs H et al (2011) Predictors of early nasal CPAP failure and effects of various intubation criteria on the rate of mechanical ventilation in preterm infants of <29 weeks gestational age. Arch Dis Child Fetal Neonatal Ed 96(5):F343–F347
16. Bancalari E, Jain D (2018) Bronchopulmonary dysplasia: can we agree on a definition? Am J Perinatol 35(6):537–540
17. Hines D et al (2017) Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus. Acta Paediatr 106(3):366–374
18. Ibrahim J, Bhandari V (2018) The definition of bronchopulmonary dysplasia: an evolving dilemma. Pediatr Res 84(5):586–588
19. Jobe AH, Steinhorn R (2017) Can we define bronchopulmonary dysplasia? J Pediatr 188:19–23
20. Kinsella JP, Greenough A, Abman SH (2006) Bronchopulmonary dysplasia. Lancet 367(9520):1421–1431
21. Ronkainen E et al (2015) New BPD predicts lung function at school age: follow-up study and meta-analysis. Pediatr Pulmonol 50(11):1090–1198
22. Higgins RD et al (2018) Bronchopulmonary dysplasia: executive summary of a workshop. J Pediatr 197:300–308
23. Jensen EA et al (2019) The diagnosis of bronchopulmonary dysplasia in very preterm infants: an evidence-based approach. Am J Respir Crit Care Med 200(6):751–759
24. Bancalari E, Claure N, Jain D (2019) Diagnostic classification of bronchopulmonary dysplasia: a compromise between defining lung disease versus long-term outcome prediction. Am J Respir Crit Care Med 200(10):1322–1323
25. Wu KY et al (2020) Characterization of disease phenotype in very preterm infants with severe bronchopulmonary dysplasia. Am J Respir Crit Care Med 201(11):1398–1406
26. Poindexter BB et al (2015) Comparisons and limitations of current definitions of bronchopulmonary dysplasia for the prematurity and respiratory outcomes program. Ann Am Thorac Soc 12(12):1822–1830
27. Villamor-Martinez E et al (2019) Association of chorioamnionitis with bronchopulmonary dysplasia among preterm infants: a systematic review, meta-analysis, and metaregression. JAMA Netw Open 2(11):e1914611
28. Pietrasanta C et al (2019) Impact of different stages of intrauterine inflammation on outcome of preterm neonates: gestational age-dependent and -independent effect. PLoS One 14(2):e0211484
29. Clyman RI et al (2021) Prolonged tracheal intubation and the association between patent ductus arteriosus and bronchopulmonary

dysplasia: a secondary analysis of the PDA-TOLERATE trial. J Pediatr 229:283-288.e2
30. Clyman RI et al (2020) Relationship between duration of infant exposure to a moderate-to-large patent ductus arteriosus shunt and the risk of developing bronchopulmonary dysplasia or death before 36 weeks. Am J Perinatol 37(2):216–223
31. Zysman-Colman Z et al (2013) Bronchopulmonary dysplasia: trends over three decades. Paediatr Child Health 18(2):86–90
32. Laughon MM et al (2011) Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med 183(12):1715–1722
33. Naeye RL, Freeman RK, Blanc WA (1974) Nutrition, sex, and fetal lung maturation. Pediatr Res 8(3):200–204
34. Lorente-Pozo S et al (2018) Influence of sex on gestational complications, fetal-to-neonatal transition, and postnatal adaptation. Front Pediatr 6:63
35. Fulton CT et al (2018) Gene expression signatures point to a male sex-specific lung mesenchymal cell PDGF receptor signaling defect in infants developing bronchopulmonary dysplasia. Sci Rep 8(1):17070
36. Kitterman JA et al (2002) Effects of oligohydramnios on lung growth and maturation in the fetal rat. Am J Physiol Lung Cell Mol Physiol 282(3):L431–L439
37. Lindner W et al (2002) Acute respiratory failure and short-term outcome after premature rupture of the membranes and oligohydramnios before 20 weeks of gestation. J Pediatr 140(2):177–182
38. Weiner E et al (2019) Amniotic fluid volume at presentation with early preterm prelabor rupture of membranes and association with severe neonatal respiratory morbidity. Ultrasound Obstet Gynecol 54(6):767–773
39. Aikio O et al (2012) Transient defect in nitric oxide generation after rupture of fetal membranes and responsiveness to inhaled nitric oxide in very preterm infants with hypoxic respiratory failure. J Pediatr 161(3):397-403.e1
40. Mirza H et al (2018) Natural history of postnatal cardiopulmonary adaptation in infants born extremely preterm and risk for death or bronchopulmonary dysplasia. J Pediatr 198:187-193.e1
41. Chandrasekharan P et al (2017) Early use of inhaled nitric oxide in preterm infants: is there a rationale for selective approach? Am J Perinatol 34(5):428–440
42. Kim DH et al (2012) Risk factors for pulmonary artery hypertension in preterm infants with moderate or severe bronchopulmonary dysplasia. Neonatology 101(1):40–46
43. Mourani PM, Abman SH (2013) Pulmonary vascular disease in bronchopulmonary dysplasia: pulmonary hypertension and beyond. Curr Opin Pediatr 25(3):329–337
44. Abman SH (2001) Bronchopulmonary dysplasia: "a vascular hypothesis." Am J Respir Crit Care Med 164(10 Pt 1):1755–1756
45. Bhatt AJ et al (2001) Disrupted pulmonary vasculature and decreased vascular endothelial growth factor, Flt-1, and TIE-2 in human infants dying with bronchopulmonary dysplasia. Am J Respir Crit Care Med 164(10 Pt 1):1971–1980
46. Check J et al (2013) Fetal growth restriction and pulmonary hypertension in premature infants with bronchopulmonary dysplasia. J Perinatol 33(7):553–557
47. Taglauer E, Abman SH, Keller RL (2018) Recent advances in antenatal factors predisposing to bronchopulmonary dysplasia. Semin Perinatol 42(7):413–424
48. Laughon M et al (2009) Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. Pediatrics 123(4):1124–1131

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