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RESEARCH

Pulmonary function and bronchopulmonary dysplasia classification: insights from the Spanish Registry

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Abstract

In 2016, the Spanish Research Group on Bronchopulmonary Dysplasia (BPD) (GEIDIS) established a national registry with participation of 66 hospitals to collect information on clinical characteristics and long-term outcomes of BPD infants into adulthood. The aim of this observational study is to examine forced spirometry data in early childhood and to assess their correlation with the respiratory support required at 36 weeks postmenstrual age (PMA). The study analyzed data from preterm infants with BPD born between January 2016 and December 2017 who underwent forced spirometry at 5–7 years of age. Statistical analyses were conducted to investigate the relationships between spirometry results, perinatal factors, and the required respiratory support at 36 weeks PMA. The study involved 143 patients with a median gestational age (GA) of 27.3 weeks (range 25.7–28.7) and a median weight of 880 g (range 740–1135). Abnormal spirometry results were observed in 39.2% (56) of the patients. Among patients diagnosed with BPD type 3, those requiring over 30% oxygen at 36 weeks PMA exhibited an increased risk of abnormal spirometry results (OR 4.48; 95% CI 1.11–18.13) compared to those requiring positive pressure with less than 30% oxygen. In addition, this subgroup had a higher risk of developing a restrictive-mixed pattern compared to those with BPD type 1 (OR 10.65; 95% CI 2.06–54.98) and BPD type 2 (OR 6.76; 95% CI 1.09–42.06). No significant differences were found in the incidence of an obstructive pattern between BPD types.

Conclusion: The requirement of more than 30% oxygen at 36 weeks PMA serves as a risk indicator for pulmonary function impairment in school-aged children with BPD. These findings suggest persistent airway and parenchymal injury in this specific patient population, and highlight the importance of careful monitoring to evaluate their long-term effects on lung function.

What is Known:

- *Premature patients with bronchopulmonary dysplasia (BPD) may present abnormalities in pulmonary function tests during school age. However, the predictive accuracy of consensus BPD severity classification remains uncertain.*

What is New:

- *The requirement of more than 30% oxygen at 36 weeks postmenstrual age (PMA) indicates a potential risk of pulmonary function impairment in school-aged children with BPD. Additionally, a significant correlation has been observed between a restrictive-mixed pattern with exposure to mechanical ventilation and the development of severe forms of BPD.*

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Abbreviations

BPD	Bronchopulmonary dysplasia
GEIDIS	Spanish Research Group on Bronchopulmonary Dysplasia
PMA	Postmenstrual age
GA	Gestational age
FVC	Forced vital capacity
FEV1	Forced expiratory volume in the first second
LLN	Lower limit of normal
IQR	Interquartile range
NIH	National Institute of Health

Introduction

Bronchopulmonary dysplasia (BPD) is one of the most common morbidities associated with prematurity, contributing to a significant impact on respiratory health throughout childhood and into adulthood [1].

The diagnosis of BPD is usually established at 36 weeks postmenstrual age (PMA) based on the respiratory support required up to that point. Traditionally, patients are classified as having BPD if they have required oxygen supplementation above 21% for more than 28 days and are classified according to the respiratory support required at 36 weeks PMA as type 1 (mild: no support), type 2 (moderate < 30% oxygen), or type 3 (severe ≥ 30% oxygen or positive pressure) [2].

Improvements in the care and management of preterm infants have had a profound impact on the pathophysiology of this condition [3]. The introduction of less invasive respiratory strategies has attenuated the lung injury associated with mechanical ventilation and oxidative stress. Simultaneously, technological innovations and comprehensive antenatal and postnatal care have significantly enhanced the survival rates of infants born at gestational ages (GA) as low as 23–24 weeks, representing a substantially earlier stage of pulmonary development compared to historical cohorts [4].

These substantial advances have generated considerable debate regarding the efficacy of traditional BPD classification in predicting respiratory morbidity and long-term lung function abnormalities in contemporary BPD patients. Alternative classification criteria based on modern respiratory interventions have been proposed [5, 6], but consensus on the optimal criteria remains to be reached [7].

The Spanish Bronchopulmonary Dysplasia Research Group (GEIDIS), established in 2016 as a network comprising 66 hospitals, gathers data on the perinatal characteristics and long-term outcomes of patients diagnosed with BPD. Its purpose is to enhance the understanding of respiratory progression and impact during childhood and adulthood in patients who develop BPD today.

The aim of this study is to evaluate pulmonary function at 5–7 years of age in premature infants diagnosed with BPD and to examine their correlation with perinatal risk factors and the respiratory support and oxygen requirements at 36 weeks PMA.

Materials and methods

The study retrospectively analyzed data from infants who were prospectively enrolled in the GEIDIS registry and were born between January 2016 and December 2017.

Inclusion criteria

Patients born at less than 32 weeks GA, diagnosed with BPD (more than 28 days on respiratory support or an $FiO_2 > 21\%$ considered at 36 weeks PMA) [2], who had been entered into the GEIDIS registry database, and has an acceptable forced spirometry recorded between 5 and 7 years of age.

Definitions of the variables

Used in the study (specified in the database) (Appendix 1).

Lung function parameters

The measurements were performed according to American Thoracic Society/European Respiratory Society guidelines [8]. The following parameters were recorded in the database: forced vital capacity (FVC); forced expiratory volume in the first second (FEV1) and FEV1/FVC. Z-scores for spirometry parameters were calculated using the Global Lung Function Initiative 2012 (GLI-2012) equations, allowing the determination of the percentage of children below the lower limit of normal (LLN) for each parameter (5th percentile or z-score of − 1.64) [9]. These equations were recently validated in healthy Spanish Caucasian preschool children aged 3–6 years [10]. Abnormal *spirometry results* were defined as FEV1/FVC z-score < − 1.64 or FVC z-score < − 1.64, while a *normal pattern* was defined as FEV1/FVC ≥ − 1.64 z-score, FEV1 ≥ − 1.64 z-score, and FVC ≥ − 1.64 z-score. *An obstructive pattern* was defined by an FEV1/FVC < − 1.64 z-score, a *restrictive pattern* by an FVC < − 1.64 z-score, and a *mixed pattern* by a combination of the two patterns.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics software package, version 21 (IBM Corp., Armonk, NY, USA, 2012). Descriptive analysis summarized quantitative variables using measures of central tendency and dispersion,

while qualitative variables were presented as percentage distributions. Comparative analysis of categorical variables employed the chi-squared test (χ^2) or Fisher's exact test, with Bonferroni correction for multiple comparisons. The Kruskal-Wallis test, adjusted with Bonferroni correction, was used to analyze non-normally distributed quantitative variables. The significance level was set at p-value < 0.05. Binary logistic regression was used for multivariate analysis of binary response variables, while linear regression was employed for quantitative variables. Variables were selected based on theoretical relevance and significance observed in bivariate analysis. Gestational age (GA) was included in all models due to its clinical importance.

Informed consent was obtained from the legal guardians of all participants.

Results

A total of 989 patients diagnosed with BPD and born at less than 32 weeks GA between 2016 and 2017 were included in the registry. Of these, pulmonary function test data were available for 143 patients between 5 and 7 years of age constituting the study population. A comparative analysis revealed no statistically significant differences in GA and birth weight between the study population (median GA 27.3 weeks, interquartile range (IQR) 3 and median birth weight 880 g, IQR 395) and those patients lacking pulmonary function data within the registry (median GA 27 weeks, IQR 2.5 and median birth weight 895 g, IQR 310) ($p = 0.722$). Furthermore, the distribution of infants according to the NIH 2001 BPD Classification did not differ between included and non-included patients. The proportion of patients with type 1 was 51% versus 55.1%, type 2 was 20.3% versus 23.6%, and type 3 BPD was 28.7% versus 21.3% between the included and non-included patients, respectively ($p = 0.138$).

Perinatal characteristics and spirometry values according to the NIH 2001 Classification of BPD (Table 1)

No significant differences in perinatal characteristics were observed between patients with BPD types 2 and 3. However, patients with BPD type 1 had a lower incidence of oligohydramnios, a lower requirement for more than 30% oxygen at birth, and a shorter duration of exposure to mechanical ventilation compared with patients with BPD types 2 and 3.

The analysis of spirometry values did not reveal any significant differences between patients with type 2 and type 3 BPD (Table 2).

Patients diagnosed with type 1 BPD exhibited higher predicted FVC and FEV1 values, as well as higher FEV1 z-scores. Additionally, a greater proportion of patients had spirometry values in the normal range.

28.2% of patients (39) exhibit an obstructive pattern, 10.1% (14) a restrictive pattern, and 2.1% (3) a mixed

Table 1 Perinatal characteristics of patients according to NIH 2001 Consensus Classification

	BPD type 1 (51%; *n* 73)	**BPD type 2 (20.3%; *n* 29)**	**BPD type 3 (28.7%; *n* 41)**	***p***	**Total (143)**
Gestational age (weeks) Median (IQR)	27.4 (26–28.3)	27.5 (26–28.3)	26.6 (25.2–28.8)	0.536	27.3 (25.7–28.7)
< 26 weeks GA (*n*, %)	32(43.8%)	9 (32.8%)	21 (51.2%)	0.292	62 (43.7%)
Birth weight (g)	910 (765–1150)	950 (700–1187.5)	796 (687.5–977.5)	0,053	880 (740–1135)
Female sex (*n*, %)	34 (46.6%)	14 (48.3%)	13 (31.7%)	0.262	61 (42.7%)
Oligohydramnios (*n*, %)	8 (11.1%)	8 (29.6%)	11 (28.2%)	0.032[a]	27 (19.6%)
Histological chorioamnionitis (*n*, %)	10 (13.7%)	4 (13.8%)	5 (12.8%)	1	19 (13.3%)
Intrauterine growth restriction (*n*, %)	14 (19.2%)	5 (20%)	10 (25%)	0.761	29 (21%)
Prenatal corticosteroids (*n*, %)	68 (93.2%)	27(93.1%)	38 (92.7%)	0.995	133 (93%)
- Complete course	52 (77.6%)	21(75%)	36 (87.8%)	0.301	103 (80.1%)
Intubation in delivery room (*n*, %)	25 (34.2%)	12 (41.4%)	14 (34.1%)	0.772	51 (35.7%)
$FiO_2 \geq 30\%$ in delivery room (*n*, %)	43 (58.9%)	25 (89.3%)	33 (82.5%)	0.002[a]	101 (71.6%)
Surfactant therapy (%, *n*)	64.8% (46/71)	75% (21/28)	82.9% (34/41)	0.111	72.1% (101/140)
Days of mechanical ventilation; median (IQR)	1 (0–11)	7.5 (0.25–28.25)	11 (3.5–31.5)	< 0.001[a]	6 (0–19)
Pulmonary hypertension (%, *n*)	5.6% (4/71)	17.9% (5/28)	15.4% (6/39)	0.115	10.9% (15/138)

[a]Difference between BPD type 1 and BPD type 2 and between BPD type 1 and BPD type 3

[b]BPD types 1 and 3

Table 2 Lung function parameters according to NIH 2001 Consensus Classification

	BPD type 1 (*n* 73)	BPD type 2 (*n* 29)	BPD type 3 (*n* 41)	*p*	Total (143)
Corrected age (years)	5.3 (5.0–6.4)	5.8 (5.3–6.2)	5.9 (5.2–6.5)	0.570	5.96 (5.28–6.39)
FEV1%	95 (83–103)	85 (76.6–97.4)	83 (69.9–95)	0.001[a]	89 (79–100)
FEV1 z-score	−0.48 (−1.25 to 0.29)	−1.02 (−1.72 to −0.27)	−1.14 (−1.99 to −0.52)	0.005[a]	−0.86 (−1.47 to 0.01)
FVC %	99 (89–109)	91.2 (84.5–103)	88 (76–100.6)	0.009[b]	94 (82–105)
FVC z-score	0.01 (−0.92 to 0.64)	−0.33 (−1.02 to 0.31)	−0.7 (−1.59 to 0.26)	0.061	−0.29 (−0.05 to −0.09)
FEV1/FVC	90.9 (83.35 − 94.5)	86.7 (79 − 93)	85 (78 − 98)	0.190	88.7 (80.6 − 94.7)
FEV1/FVC z-score	−0.61 (−1.63 to 0.46)	−0.45 (−2.04 to 0.82)	−1.08 (−1.97 to 0.74)	0.761	−0.64 (−1.84 to 0.63)
Pathological spirometry (FVC or FEV1/FVC z-score < −1.64)	23 (31.5%)	12 (41.4%)	21 (51.2%)	0.038[b]	56 (39.2%)
- < 26 weeks	12 (37.5%)	5 (55.6%)	10 (47.5%)	NS	43.5%
- ≥ 26 weeks	11 (26.8%)	7 (35%)	11 (52.4%)		35.8%
Normal spirometry (FEV1, FEV1/FVC, and FVC z-score ≥ −1.64)	49 (67.1%)	16 (55.2%)	17 (41.5%)	0.028[b]	82 (57.3%)
- < 26 weeks	20 (62.5%)	4 (44.4%)	9 (42.6%)	NS[c]	53.2%
- ≥ 26 weeks	29 (70.7%)	12 (60%)	8 (40%)		60.5%
Obstructive pattern (FEV1/FVC z-score < −1.64 and FVC z-score ≥ −1.64)	18 (25%)	9 (32.1%)	12 (31.6%)	0.676	39/138 (28.3%)
- < 26 weeks	9 (28.1%)	4 (44.4%)	5 (26.3%)	NS[c]	30%
- ≥ 26 weeks	9 (22.5%)	5 (26.3%)	7 (36.8%)		26.9%
Restrictive/mixed pattern (FVC z-score < −1.64)	5 (6.9%)	3 (10.7%)	9 (23.7%)	0.043[b]	17/138 (12.3%)
- < 26 weeks	3 (9.4%)	1 (11.1%)	5(26.3%)	NS[c]	15%
- ≥ 26 weeks	2 (5%)	2 (10.5%)	4 (21.1%)		10.3%

[a]Differences between BPD type 1 and BPD type 2 and between BPD type 1 and BPD type 3

[b]Difference between BPD type 1 and BPD type 3

[c]No significant differences between < 26 weeks GA and ≥ 26 weeks GA

pattern. Patients with restrictive and mixed patterns have been grouped for comparison. There are no significant differences in the percentage of patients with an obstructive pattern among BPD types. However, a higher proportion of patients with a restrictive-mixed pattern is observed in BPD type 3 compared to those with BPD type 1 (OR 3.82; 95% CI 1.19–12.34).

Of the 39 patients with an obstructive pattern, 26 (66.6%) had an FEV1 z-score > −1.64, indicative of mild obstruction, with a higher rate between BPD type 1 patients, 16 (88.8%), compared to BPD type 2, 4 (44.4%), and BPD type 3, 6 (50%) ($p = 0.02$). The remaining 13 patients exhibited an FEV1 z-score between −2.55 and −1.64, indicating moderate obstruction.

Spirometry values grading type 3 BPD according to respiratory and oxygen support at 36 weeks PMA

Individuals requiring positive pressure support with equal or more than 30% oxygen at 36 weeks PMA exhibit a significantly higher incidence of abnormal spirometry results (88.9%) compared to their counterparts relying on positive pressure support with less than 30% oxygen (38.5%) ($p = 0.028$) (Fig. 1).

The need for ≥ 30% oxygen at 36 weeks PMA (with nasal canula or positive pressure) is associated with an increased risk of presenting abnormal spirometry results compared to requiring positive pressure with < 30% oxygen (OR 4.48; 95% CI 1.11–18.13).

None of the patients who required positive pressure support with ≥ 30% oxygen at 36 weeks PMA met criteria for normal spirometry, compared to 57.7% of those requiring positive pressure with < 30% oxygen ($p = 0.04$).

The need for positive pressure with ≥ 30% oxygen at 36 weeks is associated with an increased incidence of restrictive-mixed patterns compared to BPD type 1 (OR 10.65; 95% CI 2.06–54.98) and BPD type 2 (OR 6.76; 95% CI 1.09–42.06). No significant differences in the incidence of obstructive patterns are observed (Fig. 2).

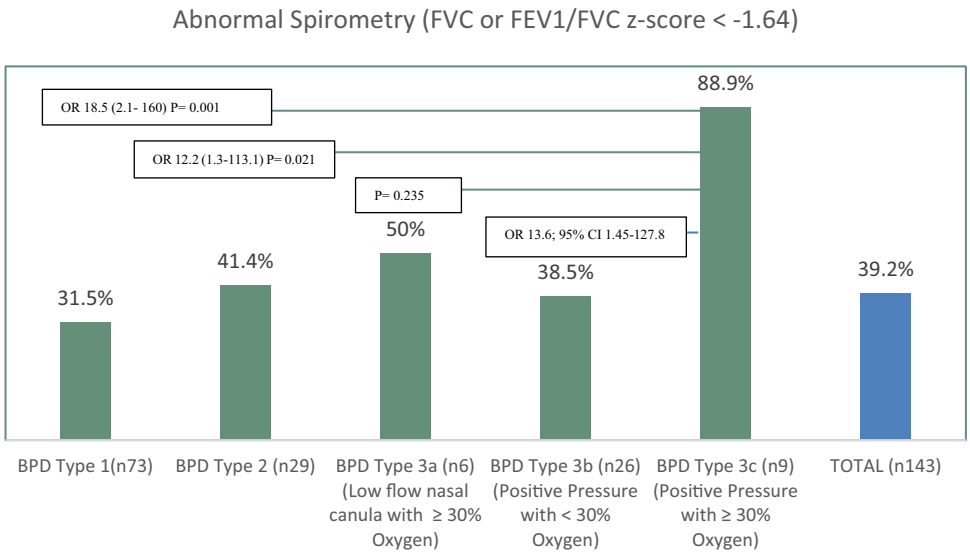

Fig. 1 This graph illustrates the percentage of pathological spirometry across different types of bronchopulmonary dysplasia (DBP), subdividing BPD type 3 according to respiratory support and oxygen required at 36 weeks PMA

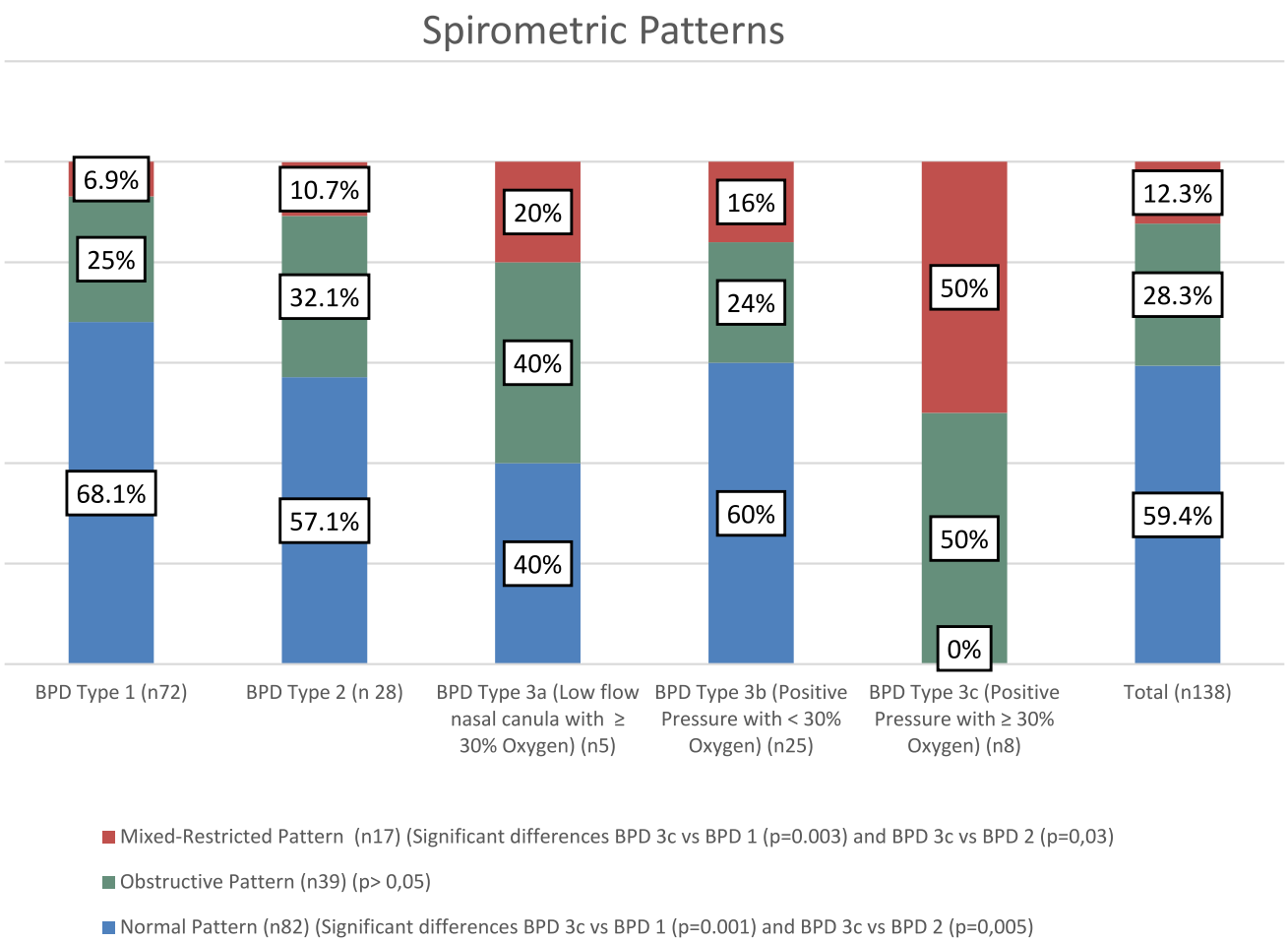

Fig. 2 This graph illustrates the spirometry patterns based on the different types of bronchopulmonary dysplasia (DBP), subdividing BPD type 3 according to respiratory support and oxygen required at 36 weeks PMA. (At 36 weeks PMA, two patients were on mechanical ventilation. One patient, who required less than 30% oxygen, presented with a normal spirometry pattern. The other patient, who required equal to or more than 30% oxygen, developed a restrictive pattern)

Perinatal risk factors and respiratory morbidity associated with spirometry patterns (Table 3)

Five patients have an FEV1 z-score below − 1.64, without meeting criteria for abnormal spirometry results (FEV1/FVC z-score < − 1.64 or FVC z-score < − 1.64); four of them have an FVC z-score below the 10th percentile (< − 1.25), and the other one has an FEV1/FVC z-score of − 1.64 (fifth percentile). Since they do not have a normal spirometry but do not strictly meet the criteria for restrictive, obstructive, or mixed patterns, they have been excluded from the comparative spirometry pattern table (Table 3).

The diagnosis of oligohydramnios is associated with a lower proportion of patients meeting criteria for normal spirometry (37% vs 61.3%, $p = 0.03$) being associated with a lower z-score value of FEV1/FVC, − 0.17 (95% CI − 1.26 to − 0.015).

Histological chorioamnionitis is associated with a higher incidence of obstructive pattern (OR 3.19; 95% CI 1.13–8.95). There was no significant association between chorioamnionitis and the incidence of restrictive-mixed pattern.

The requirement for more than or equal to 30% oxygen at birth, within the first 10 min, is associated with a higher proportion of abnormal spirometry results (45.9% vs 15%). This oxygen requirement at birth is associated with a higher incidence of an obstructive pattern (33.7% vs 12.5%: $p = 0.012$) (OR 3.55; 95% CI 1.27–9.88) and a restrictive-mixed pattern (15.8% vs 2.5%; $p = 0.041$). However, the association with the restrictive-mixed pattern loses statistical significance after adjusting for GA.

Table 3 Risk factors according to lung function patterns

	Normal pattern (*n* 82)	Obstructive pattern (*n* 39)	Restrictive-mixed pattern (*n* 17)	*P*
Gestational age (weeks), median (IQR)	27.57 (25.82–28.71)	27.28 (25.71–28.86)	26.00 (25.21–28.71)	0.711
Birth weight (grams), median (IQR)	905 (737.5–1136.25)	885.00 (750–1185)	790 (692.5–1045)	0.539
Female gender (*n*, %)	46.3% (38)	43.6% (17)	29.4% (5)	0.498
Oligohydramnios (*n*, %)	12.8% (10)	28.9% (11)	23.5% (4)	0.079
Intrauterine growth restriction (*n*, %)	17.7% (14)	21.1% (8)	25.0% (4)	0.165
Histological chorioamnionitis	11.0% (9)	23.1% (9)	5.9% (1)	0.216
Prenatal corticosteroids;	93.9% (77)	92.3% (36)	88.2% (15)	0.705
- Complete course (*n*, %)	76.3% (58)	84.2% (32)	82.4% (14)	0.664
Intubation at birth (*n*, %)	34.1% (28)	41.0% (16)	29.4% (5)	0.485
$FiO_2 \geq 30\%$ at birth (*n*, %)	60.5% (49/81)	87.2% (34)	94.1% (16)	0.003[a] 0.009[b]
Exposure to more than 1 day of mechanical ventilation (*n*, %)	51.2% (41/80)	65.8% (25/38)	94.1% (16/17)	0.001[b] 0.043[c]
Days of mechanical ventilation, median (IQR)	2 (0–13.75)	4.5 (0–16.25)	19 (6.5–31.5)	0.001[b] 0.01[c]
Days of positive pressure support, median (IQR)	25 (13–36.5)	34 (16–47)	45 (21.7–68.2)	0.048[a] 0.022[b]
Days of oxygen therapy, median (IQR)	42 (27.5–53.5)	59 (38–76)	40 (25.5–89)	0.009a
Pulmonary hypertension (*n,* %)	6.3% (5/80)	13.5% (5/37)	29.4% (5/17)	0.014[b]
Oxygen at discharge (*n,* %)	17.1% (14)	23.1% (9)	41.2% (7)	0.046[b]
Postnatal corticosteroids (*n,* %)	23.2% (19)	35.9% (14)	41.2% (7)	0.157
Breastfeeding at discharge (*n,* %)	62.2% (51)	64.1% (25)	58.8% (10)	0.978
Respiratory hospitalizations (*n,* %)	42.2% (27/64)	62.1% (18/29)	42.9% (6/14)	0.207
Regular asthma medications (*n,* %)	35.4% (29)	59.0% (23)	52.9% (9)	0.018[a]

The characteristics of the excluded patients due to an altered spirometry pattern (FEV1 z-score < − 1.64) without meeting criteria for obstructive or restrictive pattern are as follows: median gestational age of 27.14 weeks (range 25.3–27.5) and a weight of 780 g (range 753.5–989.5). Two of them (40%) were diagnosed with oligohydramnios, while the other three had intrauterine growth restriction (60%). Two patients required intubation at birth, and four patients (80%) required more than 1 day of mechanical ventilation during hospitalization, with a median duration of 39 days (range 4.5–49). Four patients received postnatal corticosteroids, and three patients (60%) were discharged on oxygen

[a]Obstructive pattern vs normal pattern

[b]Restrictive-mixed pattern vs normal pattern

[c]Obstructive pattern vs restrictive-mixed pattern

Exposure to mechanical ventilation for more than 24 h is also associated with an increased incidence of abnormal spirometry results (47.7% vs 25.9%), regardless of severity of BPD (OR 2.46; 95% CI 1.09–5.56). Patients exposed to mechanical ventilation exhibit a higher incidence of a restrictive pattern (18.6% vs 1.9%, $p = 0.002$) with no differences in the incidence of an obstructive pattern (29.1% vs 24.1%, $p = 0.563$).

Each day of mechanical ventilation increases the risk of developing a restrictive-mixed pattern by 4.3% (OR 1.04; 95% CI 1.01–1.08) and decreases the z-score of FVC by − 0.018 (95% CI − 0.025 to − 0.011).

Discussion

In our study of premature patients with BPD, we found a high incidence of abnormal spirometry results (39.2%) between 5 and 7 years of age, exceeding the rates reported in patients less than 32 weeks of age without BPD (14.1%) and in term controls (5–10%) [11–14].

Although we observed a correlation between the severity of BPD, as defined by the NIH 2001 classification [2], and a decline in lung function values, our study did not find any significant differences between BPD type 2 and BPD type 3. However, upon examination of the requirement for oxygen exceeding 30% at 36 weeks PMA, an increase in the incidence of abnormal spirometry became evident. It is noteworthy that none of the patients requiring positive pressure support with ≥ 30% oxygen at 36 weeks PMA met the criteria for normal lung function, in contrast to the 57.7% of patients requiring positive pressure support with < 30% oxygen. In a previous study investigating perinatal risk factors among preterm infants included in the registry and their association with BPD severity, it was found that among patients with BPD type 3, the need for more than 30% oxygen at 36 weeks PMA was associated with increased morbidity both during hospitalization and at discharge, in contrast to those requiring positive pressure support with less than 30% oxygen [15].

One of the most debated aspects of BPD lies in its diagnostic criteria and classification, which depend on the respiratory support received at a specific time. This results in significant variation in long-term predictive capabilities for morbidity across different centers, which can be attributed to differences in respiratory support protocols and oxygen utilization [5, 16].

Although there have been several proposed classifications in recent years [5, 6], a unanimous consensus on the most suitable classification has yet to be reached [7].

In addition, the shift in the pathophysiology of this disease as a consequence of extremely premature birth adds complexity to determining the level of impairment that constitutes the diagnosis of BPD. Patients born during the canalicular or saccular phase of pulmonary development will inevitably experience some degree of alteration in lung development. This is particularly evident in studies of premature infants born before 27–28 weeks of gestation, where those who do not meet the diagnostic criteria for BPD still exhibit lung function abnormalities by school age, albeit to a lesser extent than their BPD-diagnosed counterparts [17, 18]. Therefore, it is crucial to consider BPD not as a simple binary condition but as a spectrum of severity.

In our cohort, even though the differences in lung function abnormalities between those under and over 26 weeks in each BPD group do not reach statistical significance, patients born under 26 weeks had a similar proportion of abnormal spirometry results as those born over 26 weeks but with a higher grade in the BPD classification. For instance, patients classified as having type 1 BPD exhibited a similar proportion of abnormal lung function (37.5%) as those with BPD type 2 born at or after 26 weeks (35%), highlighting the importance of follow-up and evaluation for patients with BPD type 1, particularly those with lower gestational age, to elucidate the impact of these milder forms of BPD on long-term outcomes.

In premature patients with BPD, the most common abnormal pattern observed is the obstructive pattern, as reported in previous studies [19–21]. Consistent with these findings, our study shows that 28.2% of cases have an obstructive pattern. In addition, 10.1% have a restrictive pattern and 2.1% have a mixed pattern. Notably, there is a progressive increase in the occurrence of the restrictive-mixed pattern with the severity of BPD, reaching its peak at 50% in the most severe cases when oxygen requirements are considered. This correlation between the restrictive pattern and severe forms of BPD has also been documented in recent studies [11, 22, 23].

In line with the findings reported by Lai et al. [23], a decline in FVC z-score correlates with exposure to and duration of mechanical ventilation. Furthermore, within our cohort, the presence of a restrictive-mixed pattern is additionally associated with the administration of more than 30% oxygen at birth, diagnosis of pulmonary hypertension, length of mechanical ventilation exposure, and the necessity for oxygen therapy upon discharge. These correlations suggest an increased level of structural lung damage contributing to the development of a restrictive pattern.

In our cohort, the use of oxygen exceeding 30% at birth correlates with a higher prevalence of compromised lung function in school age. However, due to the observational nature of our study, determining the precise influence of this variable presents important limitations. It likely serves as an indicator of prenatal lung injury, exacerbated by known oxygen-related damage and the established correlation between even brief oxygen exposures at birth and the development of

BPD [24]. Additionally, it is important to note that the use of oxygen may be influenced by factors other than pulmonary pathology and even depend on the protocols of each center.

Regarding the obstructive pattern, it is observed in up to 25% of patients diagnosed with type 1 BPD. Although variations in FEV1 z-score with the severity of BPD are apparent, differences in the occurrence of the obstructive pattern do not reach statistical significance. Interestingly, it is not correlated with exposure to mechanical ventilation, but rather associated with the use of oxygen exceeding 30% at birth, histological chorioamnionitis, and oligohydramnios. This suggests the presence of distinct etiopathogenic mechanisms underlying the development of obstructive versus restrictive-mixed patterns.

Airflow obstruction is a common impairment associated with prematurity, particularly prevalent in patients diagnosed with BPD, and tends to persist into adulthood, as indicated by a recent meta-analysis [25]. This obstruction often arises from a mismatch between distal airway growth and lung volume, known as dysanapsis, resulting from disruptions in normal pulmonary development [26, 27]. In our study cohort, we found that over half of the cases with an obstructive pattern were mild forms. Notably, this proportion was significantly higher (88.8%) in patients diagnosed with BPD type 1 compared to those with BPD types 2 (44.4%) and 3 (50%). None of the patients had a pattern of severe obstruction. In several studies, a gradual improvement in lung function has been observed over time among premature infants with mild forms of BPD, suggesting a potential restoration of disrupted lung development during childhood. Conversely, preterm infants with more severe BPD often exhibit persistent abnormalities in lung function, with values not only lower than those of controls but also falling below the lower limit of normality (LLN) [14, 21, 23, 28]. Therefore, conducting long-term follow-up studies of patients with severe BPD is imperative, given its potential association with the development of a restrictive lung pattern and the significant morbidity and mortality linked to this pattern in adulthood [29, 30].

Limitations

This study is an observational analysis utilizing data sourced from a national database, which offers extensive coverage but also introduces certain constraints. The database exclusively includes patients diagnosed with BPD, thereby precluding the evaluation of the impact of prematurity itself on lung function values. One notable limitation is the low proportion of BPD patients with recorded lung function values within the database between 5 and 7 years of age, potentially leading to selection bias. GEIDIS operates as a non-funded research consortium. Participation by collaborators from individual centers is voluntary and does not involve financial remuneration. Additionally, due to the diverse computer systems utilized across these centers, collaborators are required to input patient data twice: once into each center's electronic medical record system and once into the GEIDIS registry. The fact that data collection in GEIDIS requires additional time may have contributed to the relatively low inclusion of patient data in the registry. Notably, the protocol for monitoring pediatric patients with bronchopulmonary dysplasia (BPD), as stipulated by the Spanish Society of Pediatric Pulmonology, advocates for annually spirometry test [31]. Additionally, the limited number of patients further constrains the ability to detect statistically significant differences among the gestational age groups. Although spirometry values were carefully provided by pediatric pulmonology specialists at each participating center, the lack of available data on childhood secondhand smoke exposure, lung volumes, and bronchodilator response precluded their inclusion in the analysis. These limitations underscore the need for caution in interpreting the results and highlight areas for future research to address gaps in data availability and improve the comprehensiveness of analyses in this area.

In conclusion, this study emphasizes the high prevalence of pulmonary function abnormalities in patients with BPD and highlights oxygen supplementation greater than 30% at 36 weeks postmenstrual age (PMA) as a valuable marker of disease severity. Of particular note is the identification of a significant association between a restrictive-mixed pattern and severe forms of BPD. These findings underscore the urgent need for close patient follow-up, given the significant morbidity and mortality associated with a restrictive pattern in adulthood. Further research is essential to refine management strategies to improve outcomes for this vulnerable population.

Appendix 1. Definitions of variables

Gestational age (GA): calculated from the first day of the last period or based on the first-trimester ultrasound; sex; birth weight (grams); antenatal corticosteroids: a single course of two doses of 12 mg of betamethasone i.m. 24 h apart or four doses of 6 mg of dexamethasone every 12 h; intrauterine growth restriction (IUGR): fetuses with an estimated fetal weight below P3 or between P3 and P10 and with abnormal cerebral-umbilical or uterine artery flow; oligohydramnios: fluid volume below 2 SD or an amniotic fluid index < 5; histological chorioamnionitis: based on the results of the placental pathological analysis; type of respiratory support received at birth, in the first hour after delivery, during hospitalization, and the respiratory support required at 36 weeks' PMA; need for treatment with corticosteroids during hospitalization. Length of exposure to mechanical ventilation (MV) in days. Respiratory support at the time of

discharge. Bronchopulmonary dysplasia was graded according to the National Institutes of Health (NIH) 2001 definition [2], considering patients who required high-flow oxygen (more than 2 L/min) at 36 weeks postmenstrual age (PMA) as receiving positive pressure and therefore as having type 3 BPD. For subsequent analysis, the group of patients with type 3 BPD was subdivided according to the need for pressure support and oxygen requirements at 36 weeks PMA. Patients receiving nasal cannula with $FiO_2 \geq 30\%$ are classified as BPD 3a; those receiving positive pressure with $FiO_2 < 30\%$ are classified as BPD 3b; and those receiving positive pressure with $FiO_2 \geq 30\%$ are classified as BPD 3c.

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Authors' contributions CRN 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. GRN collected the data. 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.

Declarations

Ethical approval This study was conducted in accordance with the Declaration of Helsinki. The study was approved by local research ethics committees and by the Spanish Agency for Medicines and Medical Devices (AEMPS). All data were anonymized.

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.

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