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Peri and Neonatal Risk Factors and Structural Lung Abnormalities Predict Hypoxic Challenge Test Failure in Infants With Severe Bronchopulmonary Dysplasia

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ABSTRACT

Introduction: Infants with severe bronchopulmonary dysplasia (BPD) are at increased risk of hypoxemia and often fail hypoxic challenge testing (HCT). The predictive value of clinical characteristics and structural lung abnormalities on HCT outcomes is unclear.

Methods: This prospective cohort study included preterm-born infants (≤ 32 weeks of gestation) with severe BPD enrolled in a standardized follow-up program. Perinatal and neonatal data were extracted from medical records. At 6 months corrected gestational age, structural lung abnormalities were quantified on chest CT using PRAGMA-BPD scoring. HCT was performed using a sealed body plethysmograph and failure was defined as inability to maintain oxygen saturation ≥ 85% for 20 min. Univariate and multivariable logistic regression analyses identified predictors of HCT failure.

Results: Among 156 infants, 28.8% failed HCT. Of the perinatal and neonatal factors, patent ductus arteriosus (odds ratio 2.73, 95% confidence interval 1.29–6.14), pulmonary hypertension (2.57, 0.99–6.62), and longer duration of supplemental oxygen therapy (odds ratio per interquartile range increase [OR_{IQR}] 2.40, 1.55–3.71) were associated with failure. For structural lung abnormalities, higher composite PRAGMA-BPD scores (OR_{IQR} 2.18, 1.36–3.48), higher hyper-attenuation (OR_{IQR} 1.75, 1.17–2.63), and hypo-attenuation (OR_{IQR} 1.45, 1.08–1.98) scores predicted failure. In multivariable analysis, only longer duration of supplemental oxygen therapy (OR_{IQR} 2.04, 1.22–3.42) and higher composite PRAGMA-BPD scores (OR_{IQR} 1.95, 1.15–3.31) remained independent predictors.

Conclusion: Duration of supplemental oxygen therapy and structural lung abnormalities independently predict HCT failure, highlighting the clinical relevance of both structural and functional impairments in severe BPD.

1 | Introduction

Survivors of preterm birth are at increased risk of long-term respiratory complications, including persistent symptoms, recurrent hospitalizations, and persistent impairments in lung function [1, 2]. These sequelae, collectively referred to as prematurity-associated lung disease (PALD), encompass a broad spectrum of structural and functional lung abnormalities resulting from disrupted lung development [3]. At the most severe end of the spectrum of PALD lies bronchopulmonary dysplasia (BPD), which carries a substantial burden of respiratory and systemic complications and demonstrates marked clinical heterogeneity across patients [1, 4, 5].

Infants and children with BPD are particularly vulnerable to hypoxemia during respiratory infections or commercial air travel, as even mild hypoxic conditions that are well tolerated by healthy individuals can pose substantial risks to those with impaired lung function [6]. Hypoxic challenge testing (HCT) may be used to assess an individual's ability to tolerate hypoxic conditions and might serve as a surrogate measure of pulmonary reserve. The British Thoracic Society provides recommendations on the use of HCT to evaluate the safety of air travel in individuals with lung disease, including infants with BPD [7].

In contrast to term and preterm infants without BPD, infants and children with BPD often fail HCT [8–13]. A recent study revealed that factors such as BPD severity, postnatal corticosteroid administration, respiratory support at neonatal intensive care unit (NICU) discharge, and a history of pulmonary hypertension (PH) were associated with HCT failure, underscoring the clinical heterogeneity within the BPD population [12].

A substantial proportion of preterm-born individuals exhibits structural abnormalities on chest computed tomography (CT) scans, with more extensive abnormalities observed in children with BPD [14, 15]. Several studies have linked these abnormalities to impaired lung function in both infants and children with BPD, suggesting that structural lung abnormalities may contribute to reduced tolerance of hypoxic conditions [14, 16, 17]. However, the relationship between structural lung abnormalities and HCT outcomes has not been investigated.

Identifying clinical and structural factors associated with HCT failure is clinically relevant for several reasons. First, HCT is not universally available and is not routinely performed in all follow-up programs. Second, risk stratification may support clinical decision-making, caregiver counseling, and prioritization of testing in infants at higher risk of hypoxemia during hypoxic stress, such as respiratory infections or air travel. Understanding this relationship could help identify those infants and children at highest risk of persistent and intermittent hypoxemia and adverse long-term respiratory outcomes. Therefore, this study aimed to identify peri- and neonatal factors and structural lung abnormalities (assessed using the Perth-Rotterdam-Annotated-Grid-Morphometric-Analysis [PRAGMA]-BPD scores) that are predictive of HCT outcomes.

2 | Methods

2.1 | Study Population

This study was embedded within a dynamic hospital-based prospective cohort study in Erasmus MC, Sophia Children's Hospital, Rotterdam, The Netherlands. Preterm-born children ($\leq$ 32 weeks of gestational age) with severe BPD were included in our standardized multidisciplinary care program from April 2013 onwards.

BPD was defined according to the 2018 National Institute of Child Health and Human Development (NICHD) definition as the need for supplemental oxygen for $\geq$ 28 days between birth and 36 weeks of postmenstrual age (PMA) [18]. Severe BPD was defined as the need for $\geq$ 30% oxygen and/or positive pressure ventilation and/or nasal continuous positive airway pressure and/or high flow nasal cannula at 36 weeks PMA.

Patients were eligible for inclusion if they had undergone both a chest CT scan and HCT at 6 months corrected gestational age (CGA) as part of routine clinical follow-up. In infants who remained on supplemental (home) oxygen therapy at 6 months CGA, HCT was not performed due to clinical considerations. These infants were pragmatically classified as HCT failure, reflecting their inability to maintain adequate oxygen saturation under ambient conditions.

All parents or legal guardians provided written informed consent for the use of these data for research purposes. Ethical approval for this study was obtained from the medical ethics committee of Erasmus MC (MEC2015-694).

2.2 | Candidate Predictors

Candidate predictors were identified from findings of previous prediction studies or cohort studies examining associations of perinatal and neonatal characteristics or lung structure abnormalities with the risk of respiratory morbidity, which are speculated to be related to HCT outcomes [10–12]. Perinatal and neonatal characteristics and treatments, interventions, and clinical events during NICU admission were extracted from medical records.

Patent ductus arteriosus (PDA) was defined as a hemodynamically significant PDA diagnosed during NICU admission based on echocardiography. Routine echocardiography was not performed at 6 months CGA; therefore, PDA status reflects neonatal diagnosis and not persistence at the time of HCT. PH was diagnosed during NICU admission based on echocardiographic findings documented in the medical record. No standardized echocardiographic assessment for PDA and PH was performed at 6 months of CGA. Duration of invasive and noninvasive respiratory support after NICU discharge was not included as a continuous predictor, as these data were incompletely and inconsistently recorded following transfer to regional hospitals. Therefore, respiratory support was analyzed as a binary variable (any invasive respiratory support during NICU admission: yes/no).

Lung structure abnormalities were assessed using free-breathing chest CT scans in supine position without sedation using a standardized protocol on a SOMATOM Drive scanner (Siemens, Erlangen, Germany). Acquisition parameters included:

CAREDose4D and CARE kV enabled, quality reference mAs 60, reference kV 120, collimation 128 $\times$ 0.6 mm, pitch 3, craniocaudal scan direction, scan FOV 332 mm, rotation time 0.28 s, and total scan time 0.51 s. Images were reconstructed in the

axial plane with a slice thickness of 1 mm. Reconstruction kernels Bl57 was used for lung views and quantitative scoring.

All scans were scored using the validated PRAGMA-BPD scoring method [15]. This involves visual assessment of the lung and categorizing abnormalities into: hypo-attenuation (mosaic perfusion, emphysema, and bullae), hyper-attenuation (linear or subpleural triangular opacities, septal thickening, consolidations, and atelectasis), and bronchial wall thickening. Scoring followed a hierarchical approach prioritizing categories in the following order: hypoattenuation, hyperattenuation, bronchial wall thickening, and normal lung tissue. Each category was expressed as a percentage of total lung volume and as an absolute number of milliliters. A composite score representing total affected lung tissue was calculated by summing the percentages of all abnormalities, providing an overall measure of structural lung disease burden.

2.3 | HCT

HCT was performed using a sealed body plethysmograph (MasterScreen Body, Erich Jaeger GmbH & Co. KG, Germany). Baseline oxygen saturation (SpO_2) and heart rate (HR) were recorded prior to testing using a Masimo SET Rad-87 pulse oximeter (Masimo Corporation, Irvine, California). During the test, the infant was seated on a parent's or caregiver's lap, with continuous SpO_2 and HR monitoring. The fraction of inspired oxygen (FiO_2) was gradually reduced over 5 min to a stable level of approximately 15% (range 14%–17%) by introducing nitrogen into the plethysmograph. The test lasted 20 min, in accordance with British Thoracic Society guidelines, with an SpO_2 threshold set at 85% [7]. The test was considered successful if SpO_2 remained $\geq 85\%$ throughout. If SpO_2 fell below 85%, the test was immediately stopped by opening the plethysmograph to restore ambient FiO_2. Infants were monitored until SpO_2 returned to baseline, with supplemental oxygen provided via nasal prongs if needed.

2.4 | Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Univariate logistic regression analyses were performed to assess the association of each candidate predictor with HCT failure. As this study was embedded within an ongoing prospective clinical hospital cohort, no a priori sample size calculation was performed. To improve clinical interpretability, regression coefficients (95% confidence intervals [CIs]) of continuous variables were expressed per interquartile range (IQR) increase, calculated as the regression coefficient multiplied by the difference between the 75th and 25th percentiles of the predictor. The resulting IQR odds ratio (OR) can therefore be interpreted as the odds of HCT failure for an infant at the 75th percentile of a predictor compared to one at the 25th percentile. For categorical variables, ORs represent the odds of HCT failure between two defined categories.

To identify independent predictors, multivariable logistic regression was applied and included all significant candidate predictors from univariate analyses ($p < 0.05$). We followed the rule-of-thumb of including a maximum of one predictor variable per 10 events (i.e., failed HCT) in the data set, in order to prevent overfitting the model resulting in a maximum of five predictors. Overall model discrimination was evaluated using the area under the receiver operating characteristic curve (AUC-ROC).

A p value of < 0.05 was considered significant. Analyses were performed using IBM SPSS Statistics version 28.0.1.0 (IBM Corporation, Armonk, NY).

3 | Results

A total of 156 infants with severe BPD were included. The cohort predominantly consisted of extremely preterm and extremely low birth weight infants, with a median gestational age of 26 + 3 weeks (IQR 25.3–27.1) and a median birth weight of 785 grams (IQR 660–940) (Table 1). Of these infants, 76% were born at ≤ 28 weeks gestation and 75% weighed < 1000 g. At 6 months CGA, 111 infants (71.2%) passed HCT while 45 infants (28.8%) failed.

3.1 | Candidate Predictors of HCT Outcome

Univariate regression analyses showed that among perinatal and neonatal candidate predictors, the presence of a PDA and PH were associated with higher odds of HCT failure (OR 2.73, 95% CI 1.29–6.14) and (OR 2.57, 95% CI 0.99–6.62), respectively (Table 1). Longer duration of supplemental oxygen therapy was associated with increased odds of HCT failure (OR_{IQR} 2.40, 95% CI 1.55–3.71). Other candidate predictors showed no significant associations (Table 1).

For structural lung abnormalities, higher hyper-attenuation scores (OR_{IQR} 1.75, 95% CI 1.17–2.63), higher hypo-attenuation scores (OR_{IQR} 1.45, 95% CI 1.08–1.98), and composite PRAGMA-BPD scores (OR_{IQR} 2.18, 95% CI 1.36–3.48), reflecting the total proportion of structurally abnormal lung tissue, were all associated with increased odds of HCT failure. In contrast, bronchial wall thickening showed no significant associations (OR_{IQR} 0.94, 95% CI 0.57–1.55).

Figure 1 shows the distribution of PRAGMA-BPD scores stratified by HCT outcome, visualizing the extent and variability of structural abnormalities in infants who passed versus those who failed.

3.2 | Independent Predictors of HCT Failure

Based on the outcomes of univariate analyses, significant predictors were included to evaluate the combined predictive value of perinatal and neonatal factors and structural lung abnormalities for HCT outcomes. After backward stepwise selection, PH ($p = 0.54$) and PDA ($p = 0.066$) were excluded from the final model.

Both the duration of supplemental oxygen therapy and the PRAGMA-BPD composite score emerged as independent predictors of HCT failure (Table 2). Infants with a longer duration of supplemental oxygen therapy (75th percentile: 168 days) had twice the odds of failure compared to those with shorter durations (25th percentile: 79 days) (OR_{IQR} 2.04, 95% CI 1.22–3.42). Similarly, infants with a composite PRAGMA-BPD score at the 75th percentile had nearly double the odds of HCT failure

TABLE 1 | Characteristics of the study population and univariate relationship with HCT failure at 6 months CGA.

OBJ	All infants ($n = 156$)	Infants who failed HCT ($n = 45$)	OR (95% CI) for HCT-failure	p value
Perinatal characteristics	—	—	—	—
Male sex, *n* (%)	87 (55.8%)	20 (44.4%)	0.53 (0.26–1.06)	NS
Gestational age, median (IQR)	26 + 3 weeks (25 + 1 to 27 + 6)	26 + 3 weeks (25 + 0 to 27 + 1)	0.85 (0.51−1.45) per IQR	NS
Birth weight (g), median (IQR)	800 g (680–892.5)	800 g (692.5−1000)	1.00 (0.63−1.59)	NS
Birth weight *Z*-score, median (IQR)	−0.04 (−1.00 to 0.50)	0.2 (−0.80 to 0.62)	1.19 (0.70−2.0)	NS
Maternal hypertension, *n* (%)	42/145 (29%)	13/41 (31.7%)	1.20 (0.54–2.60)	NS
Premature rupture of membranes (PPROM), *n* (%)	31/145 (21.4%)	7/42 (16.7%)	0.66 (0.24–1.61)	NS
Prenatal systemic steroids, *n* (%)	148 (94.9%)	43 (95.6)	—	—
* None (reference), *n* (%)	20 (13.5%)	5 (11.6%)	1.0 (Ref)	—
* Incomplete, *n* (%)	30 (20.3%)	9 (20.9%)	1.29 (0.37–4.90)	NS
* Complete, *n* (%)	98 (66.2%)	29 (67.4%)	1.26 (0.44–4.17)	NS
Neonatal characteristics	—	—	—	—
Surfactant administration, *n* (%)	140/154 (90.3%)	41 (91.1%)	1.15 (0.37–4.35)	NS
Postnatal systemic steroids, *n* (%)	71/154 (45.5%)	21 (46.7%)	1.03 (0.51–2.08)	NS
Invasive respiratory support, *n* (%)	133/154 (85.3%)	40/44 (88.9%)	1.83 (0.63–6.67)	NS
High-frequency ventilation, *n* (%)	94/152 (61.8%)	30/42 71.4%)	1.80 (0.85–3.98)	NS
Supplemental oxygen at discharge, *n* (%)	71/150 (45.5%)	26/44 (57.8%)	1.96 (0.96–4.05)	NS
Patent ductus arteriosus (PDA), *n* (%)	93 (59.6%)	34 (75.6%)	2.73 (1.29–6.14)	0.011
Pulmonary hypertension (PH), *n* (%)	21/155 (13.5%)	10 (22.2%)	2.57 (0.99–6.62)	0.049
Clinical early-onset sepsis, *n* (%)	58/155 (37.2%)	16 (35.6%)	0.89 (0.43–1.83)	NS
Proven early-onset sepsis, *n* (%)	8/155 (5.2%)	2 (4.4%)	0.81 (0.12–3.66)	NS
Proven late-onset sepsis, *n* (%)	80/155 (51.6%)	28 (62.2%)	1.84 (0.91–3.79)	NS
Duration of supplemental oxygen therapy (days), median (IQR)	109 (79−168)	157 (92–266)	2.4 (1.55−3.71)	< 0.001
Structural lung abnormalities using PRAGMA-BPD	151 (96.7%)	43 (95.6%)	—	—
Hyper-attenuation (%), median (IQR)	5.31 (2.41−8.60)	6.84 (2.24−12.22)	1.75 (1.17−2.63)	0.007
Hypo-attenuation (%), median (IQR)	2.13 (0.61−6.13)	2.43 (0.86−8.73)	1.45 (1.08−1.98) per IQR	0.013
Bronchial wall thickening (%), median (IQR)	0.49 (0.16−1.00)	0.49 (0.16−1.09)	0.94 (0.57−1.55)	NS
Composite PRAGMA-BPD score (%), median (IQR)	9.07 (4.90−16.65)	12.33 (6.55−22.7)	2.18 (1.36−3.48)	< 0.001

Note: All continuous variables are presented as median with interquartile range (IQR) to enhance clinical interpretability of odds ratios (OR) per IQR increase. Categorical variables are reported as counts with corresponding percentages. Denominators reflect the number of infants with available data for each variable.
Abbreviations: CGA, corrected gestational age; NS, not significant; PDA, persistent ductus arteriosus; PH, pulmonary hypertension; PPROM, preterm premature rupture of membranes; PRAGMA-BPD, Perth-Rotterdam-Annotated-Grid-Morphometric-Analysis for Bronchopulmonary Dysplasia.

compared to those at the 25th percentile (16.65% vs. 4.9%) (OR_{IQR} 1.95, 95% CI 1.15–3.31). The model demonstrated good discriminative ability, with an AUC of 0.769 (95% CI 0.682–0.855).

4 | Discussion

This prospective cohort study, embedded within a structured follow-up program for infants with severe BPD, evaluated factors predicting HCT outcomes at 6 months of CGA. Twenty-nine percent of infants with severe BPD failed HCT. Infants who required longer durations of supplemental oxygen therapy and who had more extensive structural lung abnormalities on chest CT were more likely to fail HCT.

Previous studies have reported highly variable HCT failure rates in infants and children with BPD, ranging from 17% to 71.9% [9–13]. This variability likely reflects differences in study design, patient characteristics, and timing of testing. Notably, many studies were conducted in referral populations undergoing HCT for fitness-to-fly assessments, which may have included more medically complex cases with a higher likelihood of reduced tolerance to hypoxic conditions [11–13].

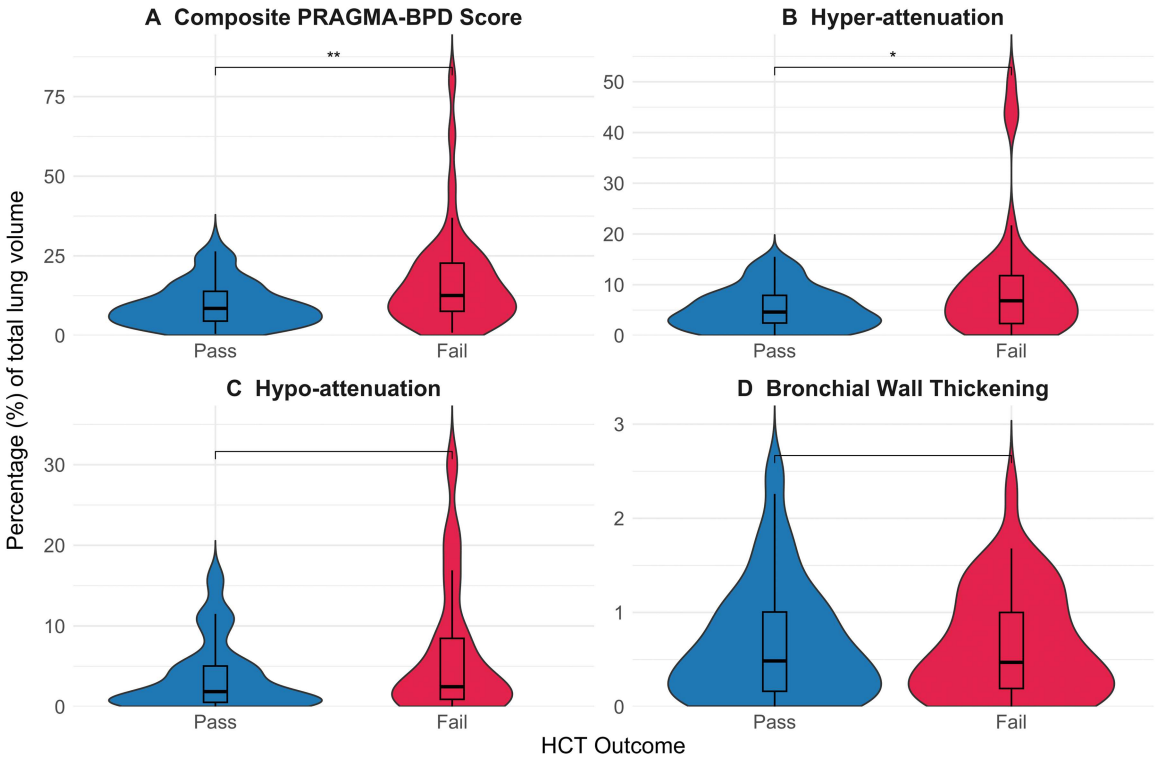

FIGURE 1 | Distribution of PRAGMA-BPD CT scores stratified by HCT outcome in preterm infants. Violin plots showing the distribution of PRAGMA-BPD CT scores for preterm infants stratified by hypoxic challenge testing (HCT) outcome (pass vs. fail). The four panels represent: (A) Composite PRAGMA-BPD score, (B) hyper-attenuation, (C) hypo-attenuation, and (D) bronchial wall thickening. Wilcoxon rank-sum tests were used to compare HCT groups; Significance is indicated as $^{**}p < 0.01$ and $^{*}p < 0.05$. Percentage values reflect the proportion of total lung volume affected. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 | Final multivariable logistic regression model predicting HCT failure.

Variable	AUC-ROC	95% CI	OR (per IQR increase)	95% CI (per IQR)	*p* value
PRAGMA-BPD composite score	—	—	1.95	1.15–3.31	0.015
Days of supplemental oxygen	—	—	2.04	1.22–3.42	0.004
Model performance	—	—	—	—	—
Area under the curve (AUC)	0.769	0.682–0.855	—	—	—

Note: Odds ratios (OR) and 95% confidence intervals (CI) are presented per unit, and the interquartile range (IQR) increases for each predictor. The *p* values indicate the statistical significance of the associations. The area under the receiver operating characteristic curve (AUC-ROC) reflects the model's discriminative performance.
Abbreviations: HCT, hypoxic challenge testing; PRAGMA-BPD, Perth-Rotterdam-Annotated-Grid-Morphometric-Analysis for Bronchopulmonary Dysplasia.

Conversely, our study evaluated a more homogeneous cohort of infants with severe BPD within a structured follow-up program with standardized time of testing.

A recent registry-based study reported a 67% HCT pass rate at 6 months of CGA, closely aligning with our findings [17]. This study included 63 infants across the BPD severity spectrum, with severe BPD being associated with reduced odds of HCT success. Univariate analyses identified longer time to pass among infants with tracheostomies, postnatal corticosteroid exposure, and respiratory support at NICU discharge as risk factors. In multivariable models, prolonged invasive ventilation (> 14 days), postnatal corticosteroid use, respiratory support at 36 weeks PMA (after correction for gestational age, birth weight, and sex), and PH (after correction of gestational age, birth weight, sex, and severe BPD) were associated with HCT failure.

In our study, PH during the neonatal period was predictive of HCT failure in univariate analysis, which is in line with results from Levin et al. [12]. The predictive value of PH may be causal as the association is physiologically plausible. BPD-associated PH arises from impaired alveolarization and vascular remodeling, leading to increased vascular resistance [19]. Hypoxia-induced pulmonary vasoconstriction further increases vascular resistance, impairing oxygenation and increasing the likelihood of HCT failure [20]. However, a limitation of both our study and that of Levin et al. is that PH was assessed retrospectively based on neonatal echocardiography. In our cohort, PH status was determined from echocardiograms performed during NICU stay, whereas Levin et al. used echocardiograms conducted after 36 weeks of PMA or assumed absence of PH if no echocardiogram was available. Additionally, PDA was associated with HCT failure in univariate analysis. A PDA may contribute to pulmonary overcirculation, vascular remodeling, and PH [21]. However, recent studies have reported inconsistent associations between PDA and PH in BPD populations [22–25]. Given the nature of PH assessment and

limited data on PDA management, the independent effect of PDA on HCT outcomes remains uncertain.

In contrast to Levin et al., postnatal corticosteroid exposure was not significantly associated with HCT outcomes in our study. Despite their cohort including infants across the full spectrum of BPD severity, corticosteroid use was higher than in our cohort. This may reflect differences in treatment practices or disease severity between centers. We could not assess the duration of invasive ventilation due to substantial missing data. Restricting analyses to a subset with complete data would have substantially reduced the sample size and could have introduced selection bias.

We found that a longer duration of supplemental oxygen therapy independently predicted HCT failure. This aligns with findings from Martin et al., who reported that prolonged oxygen therapy predicted HCT failure using an SpO_2 threshold of 85% [10]. Additionally, Udomittipong et al. demonstrated that the time since discontinuation of supplemental oxygen predicted HCT failure in infants with BPD in multivariable analysis [11]. It is unsurprising that a prolonged need for supplemental oxygen predicts HCT failure, as it reflects limited pulmonary reserve. However, Howells et al. did not observe a significant association between duration of supplemental oxygen therapy, possibly due to insufficient power, given their sample size was about half of ours, despite reporting a near-significant p value (0.056) [13]. Importantly, the duration of supplemental oxygen was an independent predictor and not driven by gestational age. This reflects the marked heterogeneity in infants with (severe) BPD. Overall, the evidence suggests that both the duration of oxygen dependency and the time since its discontinuation are valuable clinical indicators of reduced pulmonary reserve in infants with BPD. Infants with longer oxygen requirements or shorter intervals since discontinuation may therefore be at the highest risk of hypoxemia during viral respiratory infections or hypoxic conditions such as air travel.

We found that both hyper-attenuation (linear or subpleural triangular opacities, septal thickening, consolidations, and atelectasis) and hypo-attenuation (mosaic perfusion, emphysema, and bullae) scores and greater composite PRAGMA-BPD scores were associated with HCT failure. A previous study using PRAGMA-BPD found that increased hypo-attenuation correlated with lower mean SpO_2 and that each additional affected lung segment was linked to a higher oxygen desaturation index during polysomnography at 6 months CGA [26]. However, these associations did not remain significant after adjusting for birth characteristics.

Studies examining the relationship between structural lung abnormalities and functional testing in infancy are limited. Mahut et al. reported an inverse correlation between linear and subpleural opacities (hyper-attenuation) and functional residual capacity (FRC) in infants with BPD [16].

In older children, lower forced expiratory volume in one second (FEV_1), forced expiratory flow at 50% of vital capacity (FEF_{50}), and forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) have been associated with linear or triangular opacities and higher total CT scores, with hypo-attenuation also linked to significantly lower FEV_1 [27]. Higher CT scores, including more linear/triangular opacities, bronchial wall thickening, and hypo-attenuation, correlated with lower FEV_1, FEV_1/FVC, and FEF_{25-75} in preterm-born children aged 9–11 years [14]. In addition, an inverse association between CT-scores and FEV_1, FEV_1/FVC, FVC, FEF_{25-75}, and total lung capacity has been reported in school-aged children born preterm [17]. This latter study found no significant associations between CT abnormalities and diffusion capacity (DLCO). However, borderline reductions in DLCO Z-scores over time have been observed in children with hypo-attenuation on CT, suggesting subtle impairments in gas exchange efficiency [28].

Collectively, these studies highlight that structural lung abnormalities are consistently associated with impaired lung function in preterm-born individuals. Our findings extend this knowledge by demonstrating that greater structural abnormalities, independent of perinatal risk factors predict HCT failure in infants with severe BPD. This suggests that PRAGMA-BPD, as a quantitative measure of structural lung abnormality severity, has prognostic value for functional tolerance to hypoxic conditions, supporting risk stratification rather than individual-level prediction. Moreover, previous research has linked structural abnormalities to progressive lung function decline, indicating that these findings may reflect ongoing disease processes contributing to long-term respiratory morbidity. [28].

While HCT may serve as an early-life surrogate marker of pulmonary reserve, it is not universally available and therefore not routinely performed in follow-up care for infants with BPD. Similarly, chest CT is not commonly used in this population outside specific clinical indications such as infants with a severe course of BPD or with frequent re-admissions. In this context, our findings suggest that readily available clinical information, such as duration of supplemental oxygen therapy, together with quantitative assessment of structural lung abnormalities, provides complementary insight into hypoxemia risk in infants with severe BPD. Importantly, these factors should not be viewed as substitutes for HCT, but rather as complementary tools that enhance understanding of disease severity, inform risk stratification, guide clinical vigilance, and support decision-making regarding testing, monitoring, and counseling of families. By clarifying the structural–functional relationships underlying hypoxemia risk, this study also provides a framework for future efforts to develop more accessible, noninvasive strategies for identifying infants at highest risk.

5 | Strengths and Limitations

This study has several strengths. We included a large, well-characterized cohort of infants with severe BPD, enabling robust analyses of both structural and functional markers of lung disease. The paired assessments of HCT outcomes and quantitative chest CT findings using the PRAGMA-BPD scoring system provided objective insights into the relationship between structural lung abnormalities and functional performance. Compared to earlier studies, our implementation within a standardized follow-up program ensured a more homogeneous population and consistent timing of assessments, reducing potential confounding.

However, several limitations should be acknowledged. Although this study represents one of the larger cohorts of infants with severe BPD undergoing paired HCT and quantitative chest CT assessment, the number of HCT failure events was modest. This constrained the number of predictors that

could be included in multivariable analyses and limited the extent of adjustment for all potential confounders. To mitigate overfitting, multivariable models were restricted to predictors significant in univariate analyses.

Some clinical data were incomplete, particularly regarding the duration of invasive and noninvasive ventilation, limiting our ability to fully assess their contributions to HCT outcomes. Additionally, while PH and PDA were associated with HCT failure in univariate analyses, the retrospective nature of PH assessments and limited data on PDA management complicate interpretations of their independent effects.

Our binary classification of HCT outcomes (pass/fail) did not capture more nuanced physiological information, such as time to failure or desaturation dynamics (e.g., AUC SpO_2), which may provide additional insights into pulmonary reserve. These limitations highlight the need for comprehensive, longitudinal studies to better understand the complex interplay among neonatal risk factors, lung structure, functional outcomes, and long-term respiratory morbidity in infants with BPD. This might enable us to identify children most at risk for long-term complications who may benefit from more intense monitoring and treatment.

6 | Conclusion

In conclusion, our study demonstrates that prolonged duration of supplemental oxygen therapy and greater structural lung abnormalities on chest CT using PRAGMA-BPD independently predict HCT failure in infants with severe BPD. These findings underscore the predictive value of integrating clinical data with quantitative structural imaging to identify infants at risk of hypoxemia. Incorporating both clinical characteristics and structural imaging into routine follow-up may provide a more comprehensive assessment of respiratory health, support risk stratification and tailored care strategies to improve long-term respiratory outcomes in this vulnerable population.

Author Contributions

Kishan D. Tsang contributed to the study design, conducted data analyses, and drafted the manuscript. Daan Caudri contributed to the study design, data analysis planning, data collection and interpretation, writing, and critically reviewed the manuscript. Citta Zaat contributed to data collection, analyses, and critically reviewed the manuscript. Gerdien A. Tramper-Stranders contributed to the study design and critically reviewed the manuscript. Isme M. de Kleer contributed to the study design and critically reviewed the manuscript. Pierluigi Ciet contributed to the study design, data collection, analyses, and interpretation, and participated in writing and critically reviewed the manuscript. Irwin K. M. Reiss contributed to the study design, data collection, writing, and critically reviewed the manuscript. Liesbeth Duijts contributed to the study design, data analysis plan, data collection, writing, and data interpretation, and critically reviewed the manuscript. Mariëlle W. Pijnenburg designed the study, contributed to data analysis plan, data collection, and data interpretation, writing and critically reviewed the manuscript. All authors have read and approved the final manuscript and have given consent for submission.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The metadata supporting the findings of this study are publicly available via the following repository: https://doi.org/10.34894/HLIGDM. Due to privacy and ethical restrictions, the individual-level participant data are not publicly available but can be obtained from the corresponding author upon reasonable request and in accordance with institutional and ethical regulations.

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