Risk Factors for Severe Respiratory Morbidity at 6 months and 2 years of Life in Children Born Extremely Prematurely with Bronchopulmonary Dysplasia: Retrospective and Prospective Studies

Sophie Holcik

A thesis submitted to the University of Ottawa in partial fulfillment of the requirements for the Master of Science degree in Epidemiology

School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

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Abstract

Prematurity- associated lung disease remains a significant cause of respiratory morbidity beyond neonatal intensive care unit (NICU) discharge. This thesis evaluated predictors of post-prematurity respiratory disease (PRD) using both a retrospective cohort assessing PRD at 2 years of life, and a prospective multicentre cohort assessing PRD at 6 months corrected age. Clinical and physiological predictors were examined using univariable and multivariable Firth penalized logistic regression modeling. In the retrospective cohort, bronchopulmonary dysplasia (BPD), pulmonary hypertension, and elevated pCO_2 at discharge were associated with later PRD, with moderate discriminatory ability. In the prospective cohort, discharge on home supplemental oxygen and post-menstrual age at discharge were the strongest predictors of early PRD. These findings suggest that aspects of respiratory status and diagnoses at discharge may identify infants at risk for early morbidity and later PRD reflective of more established chronic lung pathology. Multivariable approaches may improve early risk stratification in this population.

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Abbreviations and Terminology

- AUC: area under the curve
- BPD: bronchopulmonary dysplasia
- BPD-PH: bronchopulmonary dysplasia associated pulmonary hypertension
- CA: corrected age
- CHEO: Children's Hospital of Eastern Ontario
- CI: confidence intervals
- CNN: Canadian Neonatal Network
- COPD: chronic obstructive pulmonary disease
- DAG: directed acyclic graph
- EMBLEM: early-life MRI biomarkers of longer-term respiratory morbidity in infants born extremely preterm
- EPT: extremely preterm
- ER: emergency room
- GA: gestational age
- IUGR: intrauterine fetal growth restriction
- MRI: magnetic resonance imaging
- NEC: necrotizing enterocolitis
- NICU: neonatal intensive care unit
- OR: odds ratios
- PDA: patent ductus arteriosus
- PH: pulmonary hypertension
- PMA: postmenstrual age

- PRD: post-prematurity respiratory disease
- PROP: Prematurity and Respiratory Outcomes Program
- ROC: receiver operating characteristic
- RR: rate ratios
- RVSP: right ventricular systolic pressure
- SD: standard deviation
- SGA: small for gestational age
- TOH: The Ottawa Hospital
- TR: tricuspid regurgitation
- VIF: variance inflation factors

Throughout this thesis, gestational age (GA) refers to age at birth, postmenstrual age (weeks) (PMA) refers to gestational age plus chronological age, and corrected age (CA) refers to chronological age adjusted for prematurity (1). Additionally, the term “predictors” is used to describe variables associated with outcomes of interest, without implying causality.

Chapter 1 – Overview and Rationale

Extremely preterm infants represent a growing and medically complex population. Advances in neonatal care have significantly improved survival over recent decades, however, many infants continue to experience substantial respiratory morbidity beyond neonatal intensive care unit (NICU) discharge (2–4). Recurrent wheezing, respiratory infections, emergency room visits, and hospital readmissions remain common in early childhood, contributing to ongoing healthcare utilization and family burden (2,5).

While bronchopulmonary dysplasia (BPD) has traditionally been used as a marker of long-term pulmonary risk, respiratory outcomes following prematurity exist along a broader spectrum (6,7). Some infants without formal BPD diagnoses experience long-term respiratory morbidity, whereas others with severe neonatal lung disease demonstrate improvement over time (6,7). This heterogeneity suggests that respiratory vulnerability evolves across infancy and early childhood and that BPD diagnosis alone does not identify all prematurity-associated lung disease (7).

The period surrounding NICU discharge represents a critical clinical transition, during which clinicians must counsel families regarding anticipated respiratory risk and determine appropriate follow-up intensity (2,5). However, uncertainty remains regarding which discharge-based clinical markers most accurately identify infants at highest risk for subsequent respiratory

morbidity. Additionally, it is unclear whether predictors of early post-discharge instability differ from those associated with more persistent respiratory disease later in childhood (7).

This thesis was designed to address these questions by examining early respiratory characteristics as predictors of post-prematurity respiratory disease (PRD) at two clinically meaningful time points: 6 months and 2 years of life. By integrating both retrospective and prospective cohort approaches, this works seeks to better characterize the evolving trajectory of prematurity- associated lung disease and to evaluate the combined predictive performance of clinically accessible variables available at discharge.

Improved identification of infants at highest risk for post-discharge respiratory morbidity has the potential to enhance follow-up planning, guide anticipatory counseling, and inform future risk stratification strategies in extremely preterm populations.

Chapter 2 - Background

The most common pulmonary complication in infants who are born extremely prematurely (< 29 weeks) is bronchopulmonary dysplasia (BPD) (8). Children who are diagnosed with BPD may present later in life with significantly impaired pulmonary function, including airflow limitation and reduced exercise tolerance (7,9). Clinically, this may manifest as respiratory symptoms of recurrent wheezing, cough, and exercise limitation as well as increased hospitalizations for respiratory infections during childhood (4,5). In addition, infants with BPD are at increased risk of developing pulmonary hypertension (PH), contributing to both early and long-term morbidity (10). Advances in neonatal intensive care have improved the survival of infants born at extremely low gestational age, leading to an increased incidence of BPD in recent years (11). In 2024, 11.1 % (1720) infants in Canada were born extremely prematurely, and among those born <29 weeks without congenital anomalies, 51.6% had chronic lung disease (which includes BPD) (12). Among these infants, survival increased with GA at birth, ranging from 40% at 22 weeks to 90% at 26 weeks, and 95% at 28 weeks (12).

2.1 Pathology and Pathogenesis of Prematurity-Associated Lung Disease

Normal mammalian lung development takes place in 5 stages (Figure 2.1, (13)): embryonic stage (3 – 6 weeks), pseudoglandular stage (6 – 17 weeks), canalicular stage (16-26 weeks), saccular stage (26 weeks – 36), and the alveolar stage (36 weeks – adolescence) (14). These five stages are crucial for the formation of the respiratory system and the maturation of the lungs. In humans, the alveolar phase occurs predominantly during early infancy. This final phase of lung development is characterized by a rapid increase in lung surface area due to the formation of

alveoli from the generation of secondary septa, which is crucial for effective and efficient gas exchange. Additionally, during this phase of development, there is rapid growth of pulmonary vasculature, which occurs in close coordination with alveolarization (15). This final step is necessary to accomplish effective gas exchange; however, in infants with BPD, late lung development is interrupted, because they are often born between the canalicular and saccular stages of lung development (16). This means that the peripheral sacculi have not undergone the process of septation in which they are further divided into airspaces. This interruption to alveolar growth results in the final lung surface area being drastically decreased compared to normal lungs, thereby reducing the available area for oxygen and carbon dioxide exchange to occur (3). Consequently, this impairment in gas exchange can lead to increased work of breathing and a greater risk of ongoing respiratory morbidity (17).

Over the last 50 years, the pathophysiology of BPD has changed in conjunction with improvements in respiratory management of extremely preterm and low birth weight infants, leading to a shift in both the clinical presentation and underlying structural lung abnormalities characteristic of BPD (16). The “old” definition of BPD is characterized by a heterogenous lung structure with airway epithelial lesions, airway smooth muscle hyperplasia, extensive alveolar septal fibrosis, and hypertensive remodeling of the pulmonary arteries (16). These are a product of elevated oxygen and ventilator-induced injury on an immature and surfactant-deficient lung (18) and are indicative of high levels of inflammation and severe lung disease (19).

In contrast, the “new” BPD phenotype reflects disrupted alveolar and vascular development rather than extensive fibrotic injury (20). Particularly, increased use of gentler

ventilation strategies, antenatal steroids, and surfactant have reduced the severity of ventilator – associated lung injury. This current form of BPD is characterized by more uniform lung tissue, larger but simplified alveolar structures, reduced and dysmorphic vascular bed, rare epithelial lesions, and mild airway smooth muscle thickening (16). Ventilator-induced lung injury is still a contributor to pathophysiology, resulting in interstitial thickening and alveolar infiltration of inflammatory cells; both of which are characteristic of tissue injury (19). Furthermore, pulmonary edema and increased protein permeability are caused by dysfunction of the endothelium and epithelium, as well as disruption of the alveolar-capillary barrier (19). The pathogenesis of BPD is complex and multifactorial, with antenatal, natal, and /or postnatal factors contributing to the lung injury, along with impaired lung development. These insults to the lung result in impaired alveolar and vascular growth, leading to the characteristic phenotype of abnormal lung development (16,19).

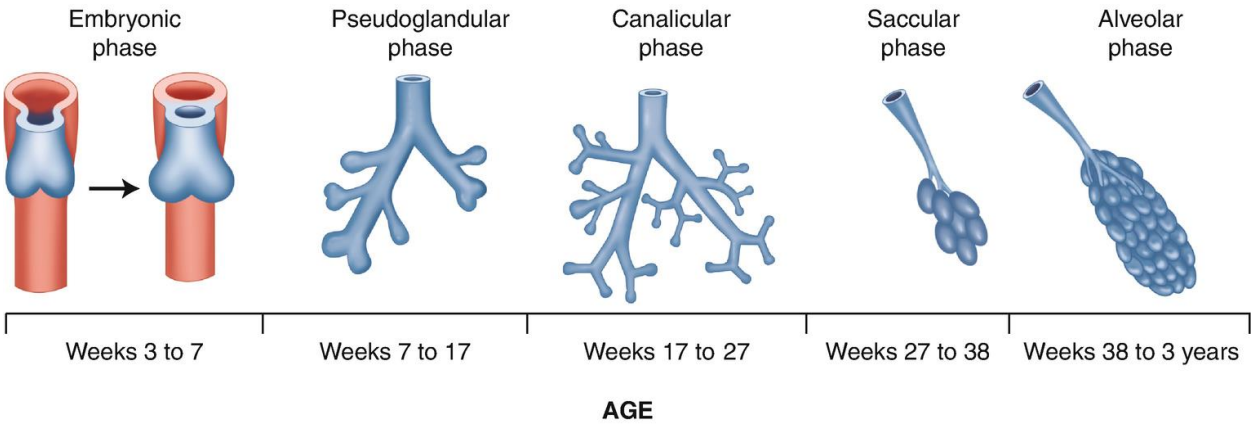

Figure 2.1: The five stages of normal human lung development from Bih et al. (13). The embryonic stage involves lung bud formation. The pseudoglandular stage establishes the conducting airway tree as the lung buds proliferate. The canalicular stage marks the development of respiratory bronchioles and early capillary networks. The saccular stage is characterized by

formation of terminal sacculi and increased surfactant production. The alveolar stage involves secondary septation and maturation of alveoli, resulting in a marked increase in gas-exchange surface area (3,14).

2.2 Current Classification of BPD

The improved survival rates of extremely preterm infants and change in the pathogenesis of BPD over the years have resulted in an evolution of its definition (21). BPD was first described in 1967 by Northway, who used clinical, radiographic, and histopathological findings to describe the four stages of BPD (21). In 2001, the National Heart, Lung and Blood institute included a BPD severity scale in the definition and characterized infants with more severe BPD as having higher mortality and greater rates of adverse outcomes after discharge (21). The newest classification system for BPD has been defined by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, published by Jensen et al. in 2019 (22). This classification system groups infants based on required respiratory support at 36 weeks postmenstrual age: no BPD = no support; Grade 1 = nasal cannula oxygen at ≤ 2 L/min; Grade 2 = nasal cannula> 2 L/min or non-invasive positive airway pressure; Grade 3= invasive mechanical ventilation (22). Based on this Jensen classification, infants with greater severity of BPD are at higher risk of health complications after neonatal intensive care unit (NICU) discharge as well as a greater risk of rehospitalization up to 1-year post-discharge (23). However, this association may be influenced by variability in clinical practices across centers, including differences in respiratory support use and discharge thresholds. Although several contemporary definitions of BPD exist, including the revised 2018 National Institute of Child Health and Human Development definition, recent studies have demonstrated similar predictive

performance for later respiratory morbidity across these definitions (24). The Jensen classification was selected for this thesis because it is based solely on the level of respiratory support required at 36 weeks' PMA, making it straightforward to apply in both clinical practice and research (24). The aim of this thesis was not to compare or validate existing BPD definitions, but rather to determine whether additional clinically accessible markers available around the time of NICU discharge could improve identification of infants at risk of PRD.

Table 2.1: Jensen classification of bronchopulmonary dysplasia based on level of respiratory support required at 36 weeks post-menstrual age (PMA) (22).

BPD Category	**Respiratory Support at 36 weeks PMA**
No BPD	No respiratory support
Grade 1 BPD	Nasal cannula oxygen at ≤2 L/min
Grade 2 BPD	Nasal cannula >2 L/ min or non-invasive positive airway pressure
Grade 3 BPD	Invasive mechanical ventilation

2.3 Risk Factors for BPD

The development of BPD is multifactorial, with a range of antenatal, natal, and postnatal factors contributing to lung injury and impaired pulmonary development. These risk factors are discussed below according to their timing relative to birth.

2.3.1 Antenatal Factors

Active and passive maternal smoking have been associated with adverse neonatal outcomes. Smoking during pregnancy has been linked to reduced birth weight, birth length, and reduced gestational age at time of delivery (25).

Intrauterine fetal growth restriction (IUGR) has been shown to have an important influence on airway and alveolar development, which highlights the crucial role of intrauterine growth in pulmonary development (26). Impaired fetal growth is associated with decreased pulmonary alveolarization and pulmonary vascularization, processes that are essential for effective gas exchange after birth. As a result, infants with IUGR may begin extrauterine life with structurally and functionally compromised lungs, increasing their susceptibility to lung injury and subsequent development of BPD (27). Additionally, IUGR has been identified as a major risk factor associated with bronchopulmonary dysplasia associated pulmonary hypertension (BPD-PH) (28). IUGR infants demonstrate pulmonary arterial remodeling and dysfunction in the early neonatal period. Furthermore, recent literature suggests that IUGR causes placental vascular dysfunction, resulting in BPD-PH, and evidence suggests that placental vascular abnormalities are associated with a risk for both BPD and PH (28).

2.3.2 Natal Factors

Gestational age*,* specifically extreme prematurity, has been found to be the strongest predictor of long-term respiratory morbidity outcomes (29).

Birth weight, specifically, very-low birth weight, has been associated with both childhood respiratory morbidity, including recurrent wheezing, asthma, and increased respiratory-related hospitalizations (30), as well as respiratory morbidity throughout adulthood (31). Infants who were born small for their gestational age (SGA), had increased respiratory morbidity in early childhood, characterized by higher rates of lower respiratory tract infections and wheezing (32). Irrespective of gestational age, low birth weight has been associated with reduced lung function, respiratory illness, and lower respiratory tract infections (26). Evidence suggests that this is in part due to nutrient restriction which induces lasting changes in the lung structure and function (26).

Sex has been found to influence respiratory course, as males seem to be more prone to respiratory morbidity after very premature birth (4). This disparity may be due to several factors, including surfactant production seen earlier on in lung development in females, and the role that sex hormones, particularly estrogen, have on fetal lung development (33).

2.3.3 Postnatal Factors / Clinical Care

Clinical care can impact respiratory outcomes in infants born extremely prematurely. Days on mechanical ventilation is a predictor for BPD (34), as ***prolonged exposure to mechanical ventilation*** can cause injury to the lung tissue, resulting in an inflammatory response, which can further exacerbate the damage to the lung tissue (19). In contrast, exposure to ***postnatal corticosteroids,*** such as dexamethasone and hydrocortisone, can be used in the prevention and/or management of BPD due to their anti-inflammatory effects, ultimately improving prognosis

(35,36). Although there are several neonatal risk factors for prematurity-associated lung disease, its prediction from clinical parameters in early life has been variable (37).

2.4 Long - Term Sequalae of BPD

The health complications associated with BPD begin in early infancy and may persist throughout childhood and into adulthood. Within the first year of life, up to 50% of infants diagnosed with BPD have high rates of readmission due to lower respiratory tract infections (38). Furthermore, BPD is associated with an increased risk of neurodevelopmental problems such as cognitive impairments, cerebral palsy, and sensory deficits (38).

Children with a BPD diagnosis were found to have considerable functional airway impairment within the first 5 years of life, demonstrated by abnormal forced expiratory volume in one second, vital capacity, and functional residual capacity measurements (39). Infants born extremely prematurely may later have an abnormal trajectory of their pulmonary function, as seen by a decreased rate of rise in lung function, decreased exercise tolerance, and a more rapid decline in lung function throughout adulthood (40). Additionally, BPD was strongly associated with continued use of a bronchodilator up to age 2 years, persistent wheezing between the ages of 2 and 5, as well as an asthma diagnosis in later childhood (39). Several studies have identified BPD as an independent risk factor for the development of asthma in childhood, and asthma was more prevalent in those with BPD compared to those without (39).

Compromised angiogenesis and abnormal pulmonary vasculature also result in increased risk of elevated pulmonary pressures or PH in those with BPD (41). Retrospective studies of

infants with BPD show that 25% - 37% of infants with BPD develop PH (41). Additionally, in children assumed to have recovered from BPD associated PH, there is risk of late pulmonary vascular disease in adulthood (41).

The effects of BPD on respiratory morbidity (respiratory symptoms, lung function impairment and cardiovascular risk) extend into adulthood. Those with a history of BPD were twice as likely to report wheezing and three times as likely to use asthma medications than those without a history of BPD (39). In women, those with a history of BPD had a significantly higher prevalence of doctor-diagnosed asthma, as well as had higher rates of shortness of breath during exercise than controls (39). Furthermore, emphysema was found to be common in young adult survivors, in addition to reduced exercise tolerance and severe dyspnea during exercise (39). Adults with a history of BPD are also at risk for developing early-onset adult respiratory disease, such as chronic obstructive pulmonary disease (COPD), and cardiometabolic disease (42,43). For this thesis we have chosen to focus on clinical risk factors among infants born extremely preterm both with and without BPD, that may predict PRD (primary outcome).

2.5 Primary Outcome: Post-Prematurity Respiratory Disease

PRD is a new outcome defined by the Prematurity and Respiratory Outcomes Program (PROP) that captures the respiratory morbidity in the first two years of life. It is defined by the presence of at least one of the following characteristics: ≥2 respiratory-related hospitalizations, home supplemental oxygen or any home respiratory support at 3 months corrected age (CA), systemic corticosteroids, or pulmonary vasodilators after discharge, and/or death secondary to a cardiopulmonary cause (44,45).

The PRD definition captures important elements of persistent early life respiratory morbidity, as it requires that infants demonstrate morbidity in one of the four post-NICU discharge domains (respiratory medications; hospitalizations for cardiopulmonary cause; coughing, wheezing, or other respiratory symptoms, or home technology dependence) (44,45). The four characteristics of PRD represent the persistence and severity of respiratory morbidity. A study by Greenough et al. in 2005 showed that more than 40% of infants born extremely prematurely had symptoms of respiratory morbidity at 6 or 12 months, and they defined respiratory morbidity as frequent cough, and/ or wheeze, and / or treatment required. The study showed that respiratory morbidity is common during infancy after very premature birth (4). PROP's definition of PRD captures these symptoms of morbidity and includes other markers of persistent respiratory morbidity in preterm infants (44).

Historically, the focus has been on infants with BPD developing PRD, yet not all infants with BPD have long-term respiratory morbidity, and not all infants with long-term respiratory morbidity had BPD (6). Thus, there are different phenotypes of prematurity associated lung disease (6) and the presence / absence of BPD cannot fully predict respiratory morbidity outcomes in the population of infants born EPT. Since BPD is not the only predictor of long-term respiratory morbidity, we need better predictors for the long-term prognosis of infants born EPT. The relationship between BPD and PRD, as well as the timing of outcomes is illustrated in Figure 2.2.

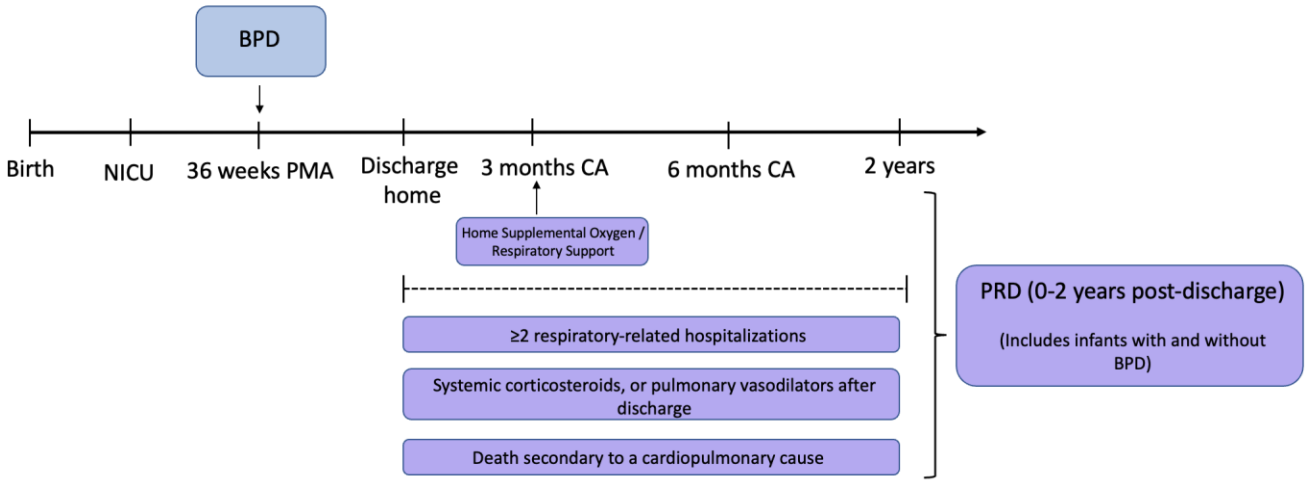

Figure 2.2: Conceptual relationship between BPD and PRD. BPD is defined at 36 weeks PMA and represents early lung disease following extremely preterm birth. In contrast, PRD captures respiratory morbidity occurring within the first two years of life after NICU discharge. The PRD definition includes multiple components assessed over time, including respiratory-related hospitalizations, use of systemic steroids or corticosteroids, and home respiratory support at 3 months CA. While some infants with BPD meet the criteria for PRD, not all do, and PRD may also occur in infants without a diagnosis of BPD, highlighting the heterogeneity of prematurity-associated respiratory outcomes.

2.6 Candidate Predictors for PRD

Since PRD can occur in infants without BPD, candidate predictors for PRD extend beyond just those for BPD. Several independent risk factors, described in detail below, have been identified in the prediction of longer-term cardiorespiratory outcomes of infants with prematurity-associated lung disease. This includes PH, hypercapnia, and discharge on home supplemental oxygen.

2.6.1 Pulmonary Hypertension

PH is an important pulmonary vascular complication of prematurity and may represent a clinically significant candidate predictor of PRD given its association with increased respiratory support requirements, hospitalizations, and mortality (28). Approximately 25% of infants with moderate to severe BPD develop PH (46). BPD-PH is characterized by inflammation, reduced alveolar cross-sectional area, abnormal vasoreactivity, and extracellular matrix remodeling within the pulmonary vasculature (28). Clinically, BPD-PH is associated with higher rates of tracheostomy, prolonged supplemental oxygen use, feeding difficulties, frequent hospital admissions, and cardiopulmonary morbidity (46). Insults to the developing lung vasculature, such as exposure to oxygen therapy or invasive mechanical ventilation, disrupt endothelial-epithelial signaling and impair angiogenesis. This leads to abnormal pulmonary vascular remodeling, increased pulmonary vascular resistance, and impaired alveolar development, which are pathological hallmarks of BPD (28). PH in early infancy can be categorized as early, early persistent, or late. Early PH occurs in the first 4 weeks of life and is typically identified in the setting of persistent hypoxemia with echocardiography evidence of elevated pulmonary arterial pressures and, in some cases, right to left shunting. PH diagnosed after 4 weeks of age or identified at or after 36 weeks postmenstrual age using echocardiography, is classified as late PH (47). Early-onset PH may persist beyond 36 weeks postmenstrual age, reflecting ongoing pulmonary vascular disease. Late PH has been associated with decreased survival in infants with BPD (10). ***Given that these complications overlap with the clinical criteria captured within the PRD definition, PH represents a biologically and clinically plausible predictor of persistent early-life respiratory morbidity.***

2.6.2 Hypercapnia

Another clinically relevant candidate predictor of PRD is pCO_2 level, which can be measured through capillary or arterial blood gas. Infants born extremely prematurely often require invasive mechanical ventilation, which, to the developing and immature lung, can cause injury. One of the strategies to minimize this lung injury, is permissive hypercapnia (48). Permissive hypercapnia tolerates relatively high levels of carbon dioxide while maintaining a normal blood pH, which allows for ventilation with lower tidal volumes, and therefore lessens the lung injury (48). Despite the benefits in mitigating lung injury, ***hypercapnia directly impairs oxygenation, as increasing levels of pCO_2 result in lower values of alveolar oxygen (48). Therefore, in infants with BPD, hypercapnia is reflective of more severe lung disease (49)***. Hypercapnia is associated with an increased risk of adverse events, including reintubation and readmission to hospital in infants with BPD (49). Hypercapnia during non-invasive respiratory support at 36 weeks postmenstrual age in severe BPD is also associated with rehospitalization risk (50). Given its association with impaired respiratory function and increased healthcare utilization, hypercapnia represents a plausible candidate predictor of persistent early-life respiratory morbidity captured by the PRD definition.

2.6.3 Home Supplemental Oxygen

Infants with moderate -severe BPD are often discharged on home supplemental oxygen if the infant is stable, with the goal of preventing the effects of chronic hypoxemia (51). Despite the potential benefits of being discharged on home supplemental oxygen, there is risk of a prolonged use resulting in pulmonary oxygen toxicity (2). ***Those discharged on home supplemental oxygen generally represent those with sicker lungs, making this an important candidate***

predictor for PRD. DeMauro et al., found that those discharged on home supplemental oxygen had an increased likelihood of being readmitted for a respiratory -related cause (2), while Lagatta et al., found that home supplemental oxygen use was not associated with 1-year admission and highlight that non-respiratory problems are important contributors to the risk of being readmitted (52).

2.6.4 Hypothesized Relationships of Candidate Predictors of PRD

Although several prenatal, perinatal, and postnatal risk factors that are associated with BPD have also been associated with PRD, the links on the causal pathways between these factors, BPD and PRD are poorly understood. Particularly, it is unclear which clinical characteristics independently and jointly predict PRD in early life, and whether those predictors differ from those traditionally associated with BPD severity. Figure 2.3 describes the hypothesized relationships between candidate predictors for PRD (4,29,34,53–55). Further investigation is therefore needed to better characterize the clinical factors that contribute to PRD and to identify infants at highest risk for persistent respiratory morbidity. In this context, the directed acyclic graph (DAG) was used to inform the selection of clinically relevant candidate predictors and to conceptualize relationships between variables. However, the objective of these analyses was not to estimate causal effects.

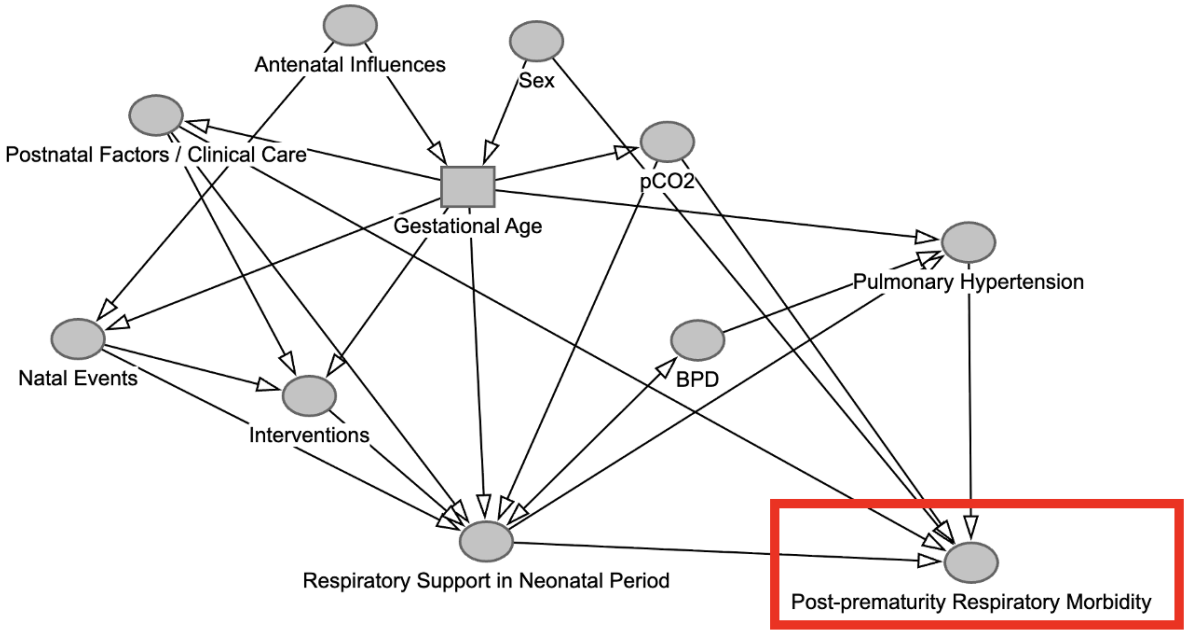

Figure 2.3: Directed acyclic graph (DAG) demonstrating the hypothesized relationships between various prenatal, postnatal, and perinatal risk factors, and the outcome of post-prematurity respiratory disease. Risk factors in the diagram such as prenatal influences, postnatal comorbidities, perinatal events, interventions (such as administration of systemic corticosteroids and/or pulmonary surfactant) and respiratory support in the neonatal period encompass multiple variables. *

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

2.7 Secondary Outcome: Emergency Room (ER) Visits

In addition to PRD as the primary outcome, health care utilization serves as an important indicator of respiratory morbidity in this population. ER visits are therefore examined as a secondary outcome in this study. Although there is no strong correlation between the number of

ER visits and the degree of severity of BPD (56), infants with BPD are at an increased risk of post-discharge respiratory illness, resource utilization, ER visits, and rehospitalization (57). Therefore, respiratory-related emergency room visits in the first year of life may serve as a clinically meaningful marker of ongoing pulmonary vulnerability. To capture this secondary outcome, information regarding ER visits was collected during chart review, including review of CHEO ER records and documentation of visits to other emergency departments recorded during standard neonatal follow-up visits.

2.8 Rationale for Current Study

Previous studies in infants with BPD have evaluated several risk factors for post-discharge respiratory morbidity with variable results, but have not used the Jensen definition of BPD, specifically in relation to PRD, nor have they considered multiple predictors in combination. Improved identification of risk factors at the time of initial discharge from the NICU, which can predict severe respiratory morbidity in early life, would allow clinicians and families to better prepare for and mitigate potential adverse events with earlier referral to pediatric respirology and closer follow-up.

2.9 Research Questions and Study Objectives

Identifying early neonatal predictors of PRD may allow clinicians to better understand risk prior to discharge, inform targeted follow-up strategies, and optimize early interventions aimed at reducing persistent respiratory morbidity. Improved understanding of clinical predictors may also guide resource allocation and parental counseling, ultimately contributing to improved long-

term respiratory outcomes in infants born extremely preterm. In this study, the term "predictors" is used to describe variables associated with outcomes of interest, without implying causality.

Retrospective Cohort Study

Research Question: Among infants with bronchopulmonary dysplasia (BPD), which neonatal clinical characteristics are associated with the development of PRD at 2 years of age?

Primary Objective: The primary objective of this study was to identify clinical factors prior to initial NICU discharge associated with severe PRD occurring from 3 months up to 2 years of life corrected age in children born extremely preterm.

Secondary Objective: The secondary objective was to compare the frequency of ER visits in the first two years of life, between infants born extremely preterm, with and without BPD.

Exploratory Objective: The exploratory objective was to compare the predictive performance of individual predictors of severe PRD, as well as a multivariable model, in a population of children born extremely preterm.

Prospective Cohort Study

Research Question

Among extremely preterm infants followed longitudinally after NICU discharge, which clinical risk factors in the neonatal period are associated with PRD at 6 months corrected age?

Primary objective: To evaluate the association between candidate neonatal and discharge-based risk factors, including PH, hypercapnia, home supplemental oxygen requirement at discharge, birth weight, small for gestational status, Jensen severity score of BPD, and duration of invasive mechanical ventilation, and PRD occurring between 3 months and 6 months corrected age using penalized univariable logistic regression modeling.

Secondary objectives: a) to assess the discriminatory performance of multivariable predictive models for identifying infants born extremely preterm, at risk of PRD; b) to examine the association between PRD status and early post-discharge healthcare utilization, including respiratory -related emergency room or clinic visits occurring between NICU discharge and 6 months corrected age.

Chapter 3.1 - Retrospective Cohort Study: Methods

3.1.1 Study Design and Setting

The population for this study included children from a previous cohort, born at <29 weeks GA between June 1, 2012, and April 18, 2016, who were admitted to either the Children's Hospital of Eastern Ontario (CHEO) NICU or The Ottawa Hospital (TOH) NICU, underwent ≥1 echocardiogram before first hospital discharge and survived to first hospital discharge (58,59). This retrospective study built upon an earlier project in which data during NICU admission was collected, adding follow-up data on these infants from NICU discharge until 2 years of life. Infants who died before initial NICU discharge and those transferred to a hospital outside of Ottawa, Ontario, before the first hospital discharge were excluded from this study.

3.1.2 Sample Size

For this retrospective study, the cohort was previously conceived and therefore the study sample of 125 was fixed. Based on an anticipated PRD event rate of approximately 35% (as reported in the PROP study (37)), it was estimated that 40-45 events would be observed. A commonly used rule of thumb in regression modeling is to include at least 10 events per predictor variable (60). However, the recommendations in the literature vary, with some suggesting higher thresholds such as 10-50 events per variable, depending on model complexity and context (61). Based on this approach, the available sample size would support the inclusion of up to four single-degree of freedom predictor variables in a multivariable model. Given the limitations of events per variable – based approaches, model performance and stability were also assessed using measures such as model convergence and confidence interval width to ensure that the model was not over – specified.

3.1.3 Candidate Predictors

Variables explored as candidate predictors of PRD at 2 years included diagnosis of BPD according to the Jensen definition (22), elevated pCO_2, and presence of PH.

BPD Diagnosis: We classified infants based on required respiratory support at 36 weeks PMA. Infants requiring no support at 36 weeks PMA were classified as having no BPD, whereas those requiring respiratory support were classified as having BPD. Among infants with BPD, severity was further categorized according to the Jensen classification as follows: Grade 1, nasal cannula oxygen at ≤ 2 L/min; Grade 2, nasal cannula> 2 L/min or non-invasive positive airway pressure; and Grade 3, invasive mechanical ventilation (22).

Pulmonary Hypertension (PH): We defined PH by the presence of any of the following criteria: (a) elevated right ventricular pressures as estimated by Doppler studies of tricuspid regurgitation jet-based measurement of right ventricular systolic pressure > half arterial systolic pressure or (b) flattening of the interventricular septum in end-systole and (c) any evidence of right-to-left shunting (62). All infants in the study underwent echocardiogram in the first week of life. Infants with elevated pulmonary pressures subsequently underwent serial echocardiograms every 2 weeks until resolution or hospital discharge. Early PH was defined as PH identified in the first week of life, while late PH was defined as PH present at or beyond 36 weeks PMA (10,63). Given the link between PH, BPD severity, and persistent cardiopulmonary instability, early and late PH were considered separately as candidate predictors of PRD in univariable modeling.

pCO_2 levels: These values were taken from the infants' last blood draw before discharge. Values were taken from a capillary blood sample. If those values were not available, venous, or arterial blood gas values were used. Given its association with greater respiratory support requirements and more severe BPD, elevated pCO_2 was evaluated as a candidate predictor of PRD.

A priori hypotheses and the number of predictors evaluated were restricted to these variables to ensure that there would be sufficient power with our sample size to evaluate the factors of greatest interest.

3.1.4 Study Outcomes

The primary outcome of interest of this study was the presence / absence of PRD within the first 2 years of life using the PROP definition of PRD, which states that PRD is present if the child has any of the following: ≥2 respiratory-related hospitalizations, home supplemental oxygen or any home respiratory support at 3 months CA, systemic corticosteroids, or pulmonary vasodilators after discharge, and/ or death secondary to a cardiopulmonary cause (44). Additional outcomes of interest included the number of ER visits for respiratory problems up to 2 years of age.

3.1.5 Study Procedures

Patient charts were reviewed to extract data on demographics, laboratory investigations, including blood gases and echocardiograms, and respiratory morbidity outcomes. Information on specific respiratory symptoms and diagnoses at presentation to the ER or hospital after NICU

discharge, within the first two years of life, was also collected from chart reviews. Data was stored in a secure REDCap database.

This study was approved by the Research Ethics Board (REB) at CHEO (REB Protocol No: CHEOREB#23/51X). Informed consent was waived, as the REB's criteria for a waiver were fully met.

3.1.6 Statistical Analysis

The association between the primary outcome (PRD) and the a priori risk factors, including the presence/ absence of BPD, pCO_2 level (mmHg), and presence of PH pre-discharge, was assessed using univariate and multivariable logistic regression with Firth correction. The association between the Jensen grade severity of BPD and PRD outcome was assessed using a univariate logistic regression. When the study was designed, we anticipated analyzing severity of BPD using "no BPD" (Jensen grade 0) as the reference category. We found, however, that none of the infants in our cohort without BPD met the criteria for PRD and therefore the planned analysis could not be carried out. We therefore used Jensen grade 0-1 as the reference category. The secondary analysis assessed the association of the same clinical factors with ER visits in the first 2 years of life, using a negative binomial regression model. Lastly, a receiver operating characteristic (ROC) curve analysis was conducted to explore the discriminative ability of multiple risk factors, including PH pre-discharge, a Jensen Score ≥ 2, and a pCO_2 level > 50 mmHg, to distinguish PRD cases.

Odds ratios (OR) (for logistic regressions) and rate ratios (RR) (for negative binomial) with associated 95% confidence intervals (CI) were reported. A two-sided $p < 0.05$ was considered statistically significant. All analyses were conducted using R statistical computing software (Version 4.3.1)(64).

Chapter 3.2 - Retrospective Cohort Study: Results

3.2.1 Baseline Characteristics

A total of 125 infants were included in the study (Figure 3.1). Table 3.1 describes the baseline characteristics of the study population. Fifty-three of the infants in the study (42%) had BPD, and 72 (58%) had no BPD. Those with BPD were further classified based on the Jensen definition: 30 babies (57%) had Grade 1 BPD, 18 (34%) had Grade 2 BPD, and 5 (9%) had Grade 3 BPD. Children with BPD had lower GA and birth weight, longer duration of respiratory support, and higher prevalence of retinopathy of prematurity (Table 3.1). Additionally, at initial discharge from the NICU, those with BPD tended to be older. There was no difference in the incidence of PH between those with BPD and those without BPD.

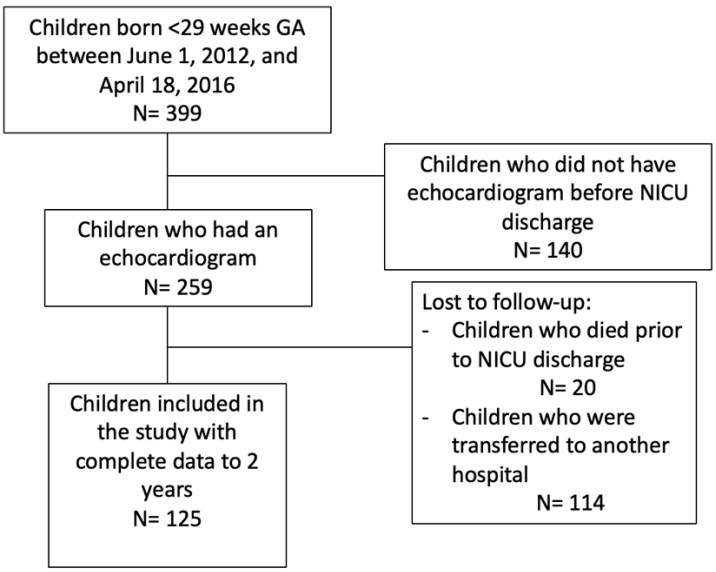

Figure 3.1: Study diagram outlining the size of the initial retrospective patient population, how many were excluded and the final sample size. *

*From: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

Table 3.1: Baseline characteristics of the retrospective population of the study. N= 125. *

Variable	N	Overall N = 125	No BPD N = 72	BPD N = 53
Gestational age (weeks)	125			
Median (Q1, Q3)		27.1 (25.9, 28.1)	27.7 (26.5, 28.3)	26.0 (25.0, 27.3)
Corrected gestational age (weeks) at discharge	124			
Median (Q1, Q3)		37.6 (34.6, 40.4)	35.4 (33.3, 37.7)	40.4 (39.1, 42.0)
Missing		1	1	0
Sex	125			
Male		61 (48.8%)	38 (52.8%)	23 (43.4%)
Female		64 (51.2%)	34 (47.2%)	30 (56.6%)
Birth weight (grams)	125			
Median (Q1, Q3)		970.0 (770.0, 1,175.0)	1,120.0 (895.0, 1,275.0)	830 (689, 1,000)
Pulmonary Hypertension at any time	125	75 (60.0%)	38 (52.8%)	37 (69.8%)
Pulmonary Hypertension pre-discharge	125	32 (25.6%)	17 (23.6%)	15 (28.3%)
Number of days on oxygen	73			
Median (Q1, Q3)		21.3 (10.1, 39.0)	11.0 (3.1, 22.6)	29.0 (12.3, 43.0)
Missing		52	47	5
Number of days on ventilation	123			
Median (Q1, Q3)		37.9 (11.1, 59.6)	17.6 (6.8, 38.0)	64.2 (42.9, 78.8)
Missing		2	2	0
Patent Ductus Arteriosus	125	98 (78.4%)	53 (73.6%)	45 (84.9%)
Necrotizing Enterocolitis	125	10 (8.0%)	3 (4.2%)	7 (13.2%)
Intraventricular Hemorrhage	125	52 (41.6%)	29 (40.3%)	23 (43.4%)
Retinopathy of Prematurity	125	35 (28.0%)	13 (18.1%)	22 (41.5%)
**Congenital Diseases ** **	125	22 (17.6%)	10 (13.9%)	12 (22.6%)
Sepsis	125	28 (22.4%)	10 (13.9%)	18 (34.0%)
Genetic Syndrome	125	8 (6.4%)	3 (4.2%)	5 (9.4%)

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

** Congenital diseases include duplex left kidney with hydronephrosis, patent urachal duct, hypospadias, nephrocalcinosis, tracheomalacia, Wolff-Parkinson-White syndrome, periventricular leukomalacia, hydronephrosis, fused eyelids, absent septum pellucidum, plagiocephaly, microcephaly, seizure disorder, hydrocephalus, bilateral hearing loss, liver calcifications, right inguinal hernia, syndactyly on bilateral toes, dysmorphic features, early rickets, hydronephrosis, severe metabolic syndrome, and laryngomalacia.

Twenty-four (19%) experienced a PRD event, whereas 101 (81%) did not. All the infants who experienced PRD had BPD (Table 3.2).

Table 3.2: Distribution of candidate predictors among infants with and without PRD. *

Variable	**PRD**, N = 24	**No PRD**, N = 101
BPD		
No BPD	0 (0.0%)	72 (71.3%)
BPD	24 (100.0%)	29 (28.7%)
PCO_2 level (mmHg)		
Median (IQR)	51.0 (46.0, 61.0)	47.0 (41.0, 52.3)
Missing	0	1
Pulmonary Hypertension at any time point	18 (75.0%)	57 (56.4%)
Pulmonary Hypertension pre-discharge	9 (37.5%)	23 (22.8%)

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

3.2.3 BPD Severity

BPD severity grade was stratified by PRD outcome in the 52 infants with BPD. All the infants with PRD had BPD. Of the 24 infants who experienced the PRD outcome, 14 (58.3%) had Grade 1 BPD, 7 (29.2%) had Grade 2 BPD, and 3 (12.5%) of them had Grade 3 BPD. Of the 29 infants with BPD who did not experience the PRD outcome, 16 (55.2%) had Grade 1 severity of BPD, 11 (37.9%) had Grade 2 severity of BPD, and 2 (6.9%) had Grade 3 severity of BPD. Table 3.3 shows the results of a univariate logistic regression of PRD with the Jensen definition for infants with BPD, with no differences detected between the severity grade of BPD and PRD outcome.

Table 3.3: Results of univariate logistic regression of PRD with Jensen score categories for infants with BPD only. *

Variable	N	OR[1]	95% CI[1]	p-value
Jensen Score				0.68
Grade 1	30	—	—	
Grade 2	18	0.73	0.21, 2.37	
Grade 3	5	1.71	0.25, 14.5	

[1]OR = Odds Ratio, CI = Confidence Interval

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

3.2.4 PH

PH at any time of the infant's NICU stay was present in 75/125 (60%) in this cohort and was more common in those with BPD (Table 3.1). Forty-eight infants out of the full cohort (38%) had early/ early persistent PH; 21 (44%) of those infants persisted to have late PH. Eleven babies without early/ early persistent PH were found to have PH at 36 weeks, making the total number of infants with late PH 32. In univariable and multivariable logistic regression modeling with Firth correction, PH was not, however, found to be significantly associated with PRD outcome (Table 3.4).

Table 3.4: Results of univariable and multivariable logistic regression of PRD outcome (univariate BPD and full multivariable model was fitted using logistic regression with Firth Correction). *

	Univariable		Multivariable		
Variable	**OR[1]**	**95% CI[1]**	**OR**	**95% CI[1]**	**p-value**
BPD					
No BPD	—	—	—	—	
BPD	120	15.8, 15,467	96.1	12.4, 12,383	<0.001
PCO_2 level (mmHg)	1.09	1.03, 1.16	1.05	0.98, 1.12	0.2
Pulmonary Hypertension pre-discharge					
No	—	—	—	—	
Yes	2.03	0.77, 5.21	2.28	0.69, 8.03	0.2

[1]OR = Odds Ratio, CI = Confidence Interval

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

3.2.5 pCO_2 Level

The pCO_2 levels before discharge from the NICU were widely distributed, ranging from 32.0 to 68.0 mmHg. At hospital discharge, 79/125 (64%) of infants had pCO_2 levels ≤50 mmHg, and 45/125 (36%) had pCO_2 levels > 50 mmHg. One infant was missing pCO_2 data. Figure 3.2 demonstrates the association between pCO_2 level before discharge and the PRD outcome. Although the mean pCO_2 level at discharge was higher amongst those who met the criteria for PRD compared to those who did not, this did not reach statistical significance (mean, SD 52.5 ± 9.1 mmHg vs. 46.7 ± 7.6 mmHg; *p=0.2)*. Of those who had pCO_2 levels > 50 mmHg, in 37 (84.1%) it was drawn from a capillary blood sample, three infants (6.8%) had venous blood samples, and four infants (9.1%) had arterial blood drawn. No significant associations were

found between pCO_2 level and PRD: with an odds ratio of 1.05 per mmHg increase in pCO_2 (95% CI of 0.98-1.12, and $p = 0.2$).

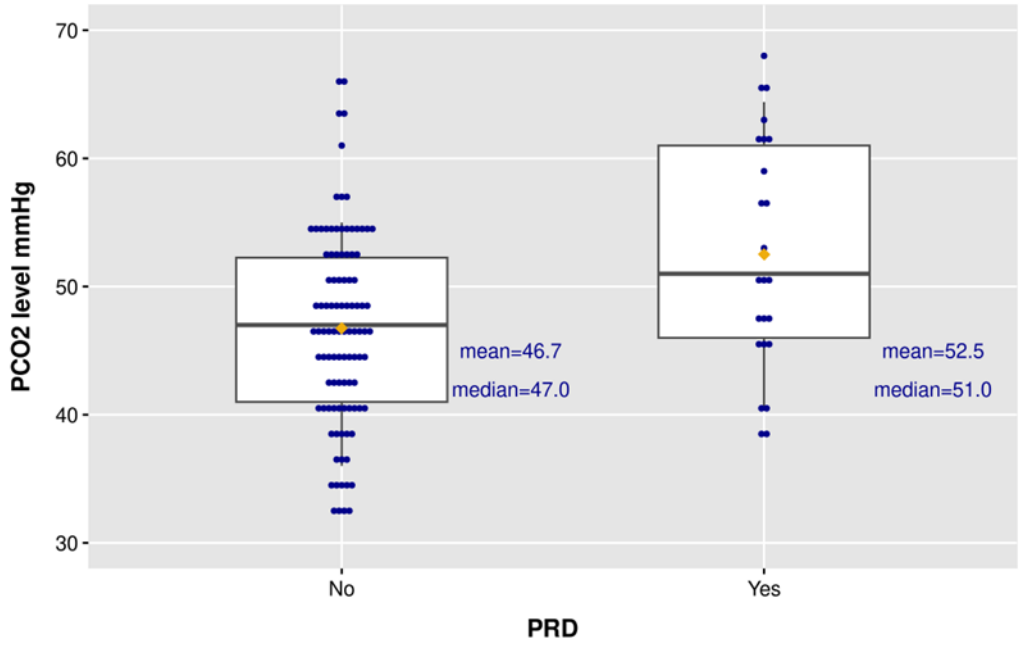

Figure 3.2: pCO_2 level before discharge and PRD outcome. Higher mean pCO_2 levels were observed among infants who met the criteria for PRD, however no significant association was found (odds ratio 1.05 per mmHg increase, 95% CI of 0.98-1.12, and $p = 0.2$). *

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

3.2.6 Multiple Predictors

Finally, the presence of multiple predictors was examined simultaneously in the context of PRD, including PH pre-discharge, a Jensen Score ≥2, and a pCO_2 level >50 mmHg. Table 3.5 and Figure 3.3 show the proportion of the study population with none, one, or two or more factors and the respective likelihood of PRD outcome. These findings demonstrate that a greater number of predictors is associated with a higher risk of having PRD. A ROC curve analysis of PRD and the number of predictors was performed, as seen in Figure 3.4. The area under the curve was 0.68 (95% CI: 0.55 - 0.81), and the point highlighted on the figure represents having 2 or more factors corresponding to a specificity of 87% and a sensitivity of 50%.

Table 3.5: Associations between the presence of none, one, two, or all the following (pCO_2 >50, pulmonary hypertension pre-discharge, Jensen Score ≥ 2) and PRD. *

Variable	N	PRD, N = 24	95% CI[1]	No PRD, N = 101	95% CI[1]
No factors	125	7 (29.2%)	15, 49	47 (46.5%)	37, 56
One factor	125	5 (20.8%)	9.2, 40	41 (40.6%)	32, 50
Two factors	125	9 (37.5%)	21, 57	12 (11.9%)	6.9, 20
Three factors	125	3 (12.5%)	4.3, 31	1 (0.99%)	0.17, 5.4
Two or more factors	125	12 (50.0%)	31, 69	13 (12.9%)	7.7, 21

[1]CI = Confidence Interval

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

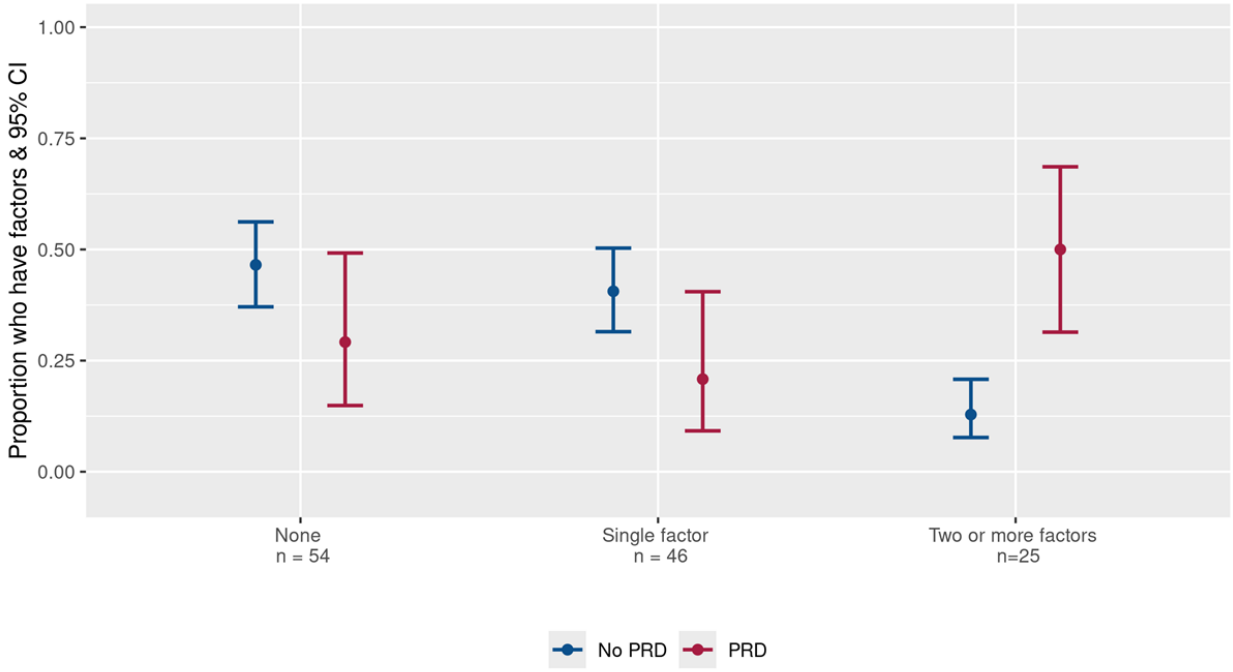

Figure 3.3: Proportions with 95% CI for having PRD or not for infants with none, one, two, or more of the following factors: pulmonary hypertension pre-discharge, Jensen score ≥ 2, and pCO_2 > 50 mmHg. *

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

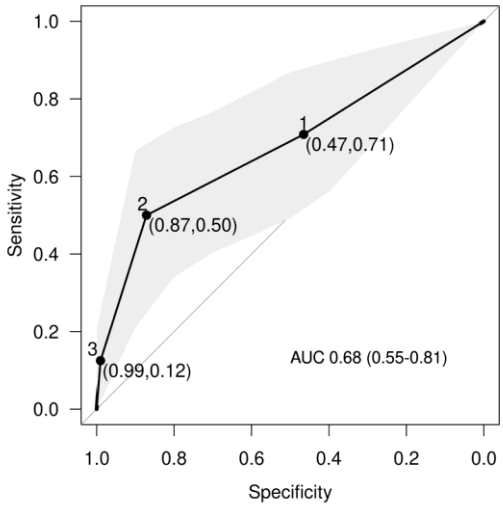

Figure 3.4: ROC curve of PRD and the number of factors (pCO_2 >50, Jensen Score ≥ 2, and PH pre-discharge). The point highlighted on the figure represents having 2 or more of the factors corresponds to a specificity of 87% and a sensitivity of 50%. *

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

3.2.7 Emergency Room Visits

The proportion of infants who had ER visits within the first 2 years of life was compared between those with BPD and those without BPD. Figure 3.5 demonstrates that infants with BPD tended to have more ER visits compared to those without BPD. A negative binomial regression of ER visits with BPD revealed that infants with BPD had 2.6 times more ER visits over the first 2 years of life than those without BPD (CI 1.47- 4.67; *p=0.001*).

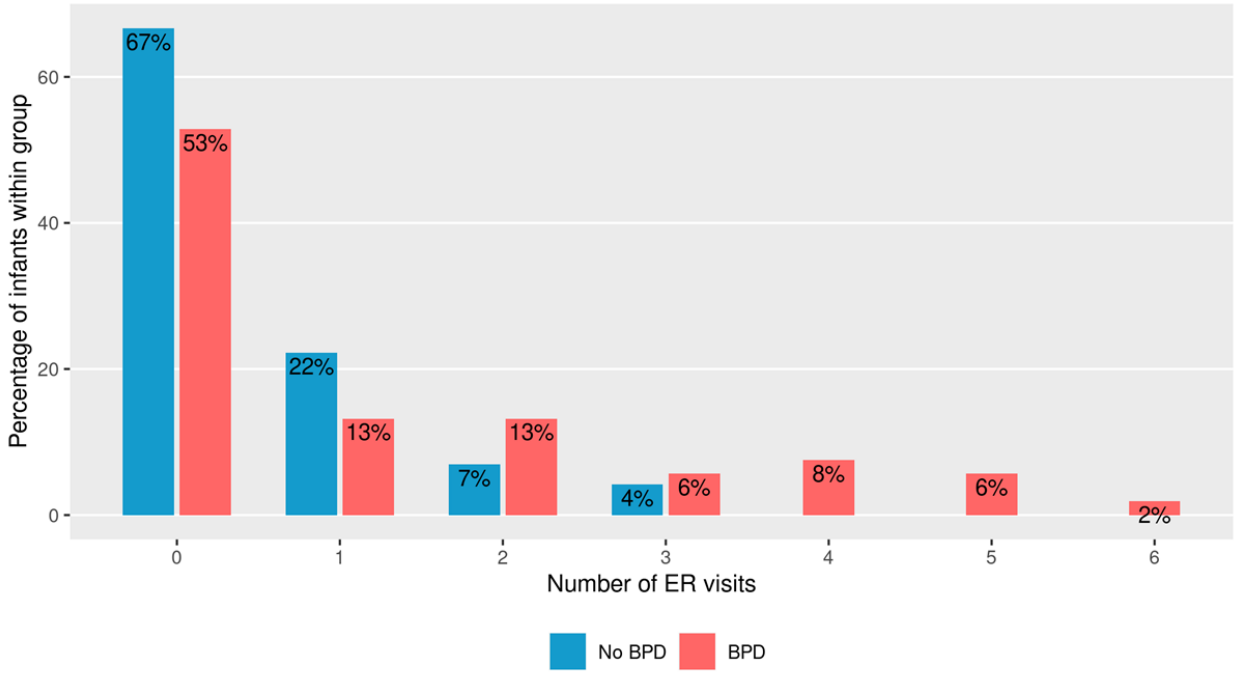

Figure 3.5: Count of total ER visits for infants with and without BPD over the first two years of life. N= 125. *

*Adapted from: Holcik, S., Hawayi, L., Dussah, N., Barrowman, N., Ben Fadel, N., Thébaud, B., & Katz, S. L. (2025). Risk Factors for Severe Respiratory Morbidity at 2 Years of Life in Children Born Extremely Preterm With Bronchopulmonary Dysplasia. *Pediatric pulmonology*, *60*(8), e71258. https://doi.org/10.1002/ppul.71258

Chapter 4.1- Prospective Study: Methods

This prospective study builds on the retrospective cohort described in Chapter 3, with key differences in outcome timing, study design, and analytic approach. A summary of similarities and differences between the two cohorts is seen in Table 4.1.

Table 4.1: Comparison of retrospective and prospective cohort study designs.

Feature	Retrospective Cohort	Prospective Cohort
Study Design	*Retrospective cohort*	*Prospective cohort (pilot study)*
Population	Extremely preterm infants (<29 weeks GA)	Extremely preterm infants (<29 weeks GA)
Setting	Multicenter *(CHEO and TOH)*	Multicenter *(CHEO, Mount Sinai, Sainte-Justine, and Montreal Children's Hospitals)*.
Outcome definition	PRD (PROP definition)	PRD (PROP definition)
Outcome Timing	*From 3 months CA up to 2 years of life*	*From 3 months CA to 6 months CA*
Primary objective	*Identify clinical factors prior to initial NICU discharge associated with severe PRD up to 2 years of life*	*Evaluate the association between candidate neonatal / discharge-based risk factors, and PRD at 6 months*
Predictors	*Univariate: BPD severity, PH, and pCO_2* *Multivariate: BPD severity, PH, and pCO_2*	*Univariate: Jensen Score, PH, hypercapnia, birth weight, SGA, duration of mechanical ventilation, sex, gestational age at birth, PMA at discharge, home supplemental oxygen at discharge* *Multivariate: Home supplemental oxygen and PMA at discharge*
Sample Size	*125*	*34 (in the analytic cohort)*
Modeling Approach	Firth penalized logistic regression	Firth penalized logistic regression
Purpose	*Identify longer-term respiratory morbidity patterns*	*Evaluate early post-discharge respiratory morbidity*

* Italicized font highlights the differences between the two studies

4.1.1 Study Design and Setting

This study was conducted as a pilot prospective study in a larger umbrella study designed to assess early-life magnetic resonance imaging (MRI) biomarkers of longer-term respiratory morbidity in infants born extremely preterm (EMBLEM Study, funded by CIHR, clinicaltrials.gov ID: NCT06065215). This study included children born extremely preterm (EPT), defined as <29 weeks GA, who were recruited at one of the four participating tertiary care pediatric centers: CHEO, Ottawa ON; Mount Sinai Hospital, Toronto ON; Centre Hospitalier Universitaire Sainte-Justine, Montreal QC; and Montreal Children's Hospital, Montreal QC. An EPT definition of <29 weeks' GA was used to ensure a consistent study population across both cohorts.

4.1.2 Study Population

The inclusion criteria for this study were: a) Infants born at <29 weeks' gestation; b) currently <36-44 weeks PMA; c) Participating in EMBLEM study (recruited from May 2024 to August 2025).

The exclusion criteria for this study were: b) known interstitial lung disease, congenital lung anomaly, ciliary dysfunction, immunodeficiency, cystic fibrosis, neuromuscular disease, or structural heart disease (other than atrial septal defect/hemodynamically insignificant ventricular septal defect/patent ductus arteriosus); c) genetic syndrome or congenital anomaly; d) contraindications for MRI or transport; e) invasive or non-invasive ventilation that cannot be safely removed for MRI; f) current respiratory infection; g) family cannot speak English/French; h) transferred to another hospital prior to baseline study visit; i) not receiving follow-up at one of the study centres.

4.1.3 Candidate Predictors

Candidate predictors were selected a priori based on biological plausibility (as seen in Figure 2.3), prior evidence linking neonatal clinical factors to persistent respiratory morbidity in extremely preterm infants and based on the results of the retrospective study. These included measures of BPD severity, pulmonary vascular disease, respiratory dysfunction, growth parameters, and perinatal characteristics.

BPD Severity: Similarly to the retrospective study, BPD severity was defined according to the Jensen classification based on respiratory support at 36 weeks PMA: Grade 1 = nasal cannula ≤2 L/min; Grade 2 = nasal cannula > 2 L/min or non-invasive positive airway pressure; Grade 3 = invasive mechanical ventilation (22). Given the established association between BPD severity and long-term respiratory morbidity, BPD severity was evaluated as a categorical predictor of PRD.

Pulmonary Hypertension (PH): PH (yes/no) was determined based on Doppler echocardiography prior to NICU discharge by estimated right ventricular systolic pressure greater than half-systemic pressure by tricuspid regurgitant jet velocity and/or septal flattening or bowing to the left during systole (59,65–67). Given its association with cardiopulmonary instability and increased respiratory morbidity, PH was evaluated as a candidate predictor of PRD.

Hypercapnia: hypercapnia (yes/no) was determined on last capillary blood gas (with one venous blood gas) prior to initial NICU discharge, >50 mmHg. Elevated pCO_2 reflects impaired

alveolar ventilation and more severe underlying lung disease (49) and was therefore considered a biologically plausible predictor of PRD. Given the limited sample size, pCO_2 was dichotomized at this threshold to reflect clinically relevant hypercapnia and to improve model stability. This cut-off was based on expert consensus from CHEO paediatric respirologists and is consistent with clinical practice.

Birth Weight: birth weight (grams) was recorded at birth and analyzed as a continuous variable. Lower birth weight has been associated with impaired lung development and increased respiratory morbidity (26), supporting its inclusion as a candidate predictor.

Small for gestational age: SGA (yes/no) was defined as a birth weight z-score of less than 1.28, which corresponds to the 10^{th} percentile assuming a normal standard deviation (68). Given the association between impaired intrauterine growth and altered pulmonary development (32), SGA status was evaluated as a candidate predictor.

Duration of Mechanical Ventilation: Duration of invasive mechanical ventilation was calculated as the cumulative number of days across all ventilation episodes. Infants who were never invasively ventilated were assigned a value of zero days. This variable was analyzed as a continuous predictor of PRD.

Sex: Biological sex (male vs female) was recorded at birth. Male sex has been associated with increased respiratory morbidity in extremely preterm infants (4) and was therefore evaluated as a potential predictor.

Gestational Age: gestational age (weeks) was initially considered but not included in the restricted a priori predictor set due to anticipated collinearity with related neonatal factors, such as birth weight. However, exploratory analyses were conducted to assess its independent contribution to PRD prediction. Given its demonstrated association with PRD and improvement in model performance, gestational age was retained in the final multivariable model.

Home Supplemental Oxygen at Discharge: home supplemental oxygen requirement at NICU discharge (yes/no) was defined as the need for supplemental oxygen at the time of discharge home. Infants discharged on home supplemental oxygen represent those with ongoing respiratory support needs and more severe residual lung disease (2) and were therefore evaluated as a clinically relevant candidate predictor of PRD.

The number of predictors evaluated was restricted to clinically relevant variables to maintain adequate statistical power and reduce the risk of model overfitting given the available sample size. Model stability was assessed through sequential model building and evaluation of collinearity between candidate predictors. Additionally, Firth penalized logistic regression was used to reduce small – sample bias and improve the stability of parameter estimates in the presence of sparse data and a limited number of outcome events. Firth penalization reduces bias and can provide finite, more reliable coefficient estimates when conventional logistic regression may produce unstable or non-convergent estimates because of rare outcomes or separation (69). However, Firth penalization does not address multicollinearity or eliminate the risk of overfitting, therefore, model complexity was further limited through careful predictor selection

and assessment of collinearity. Formal validation techniques such as cross-validation were not performed due to the limited sample size.

4.1.4 Study Outcomes

The prospective analysis builds on the same predictor definitions as the retrospective analysis, however outcomes are assessed at an earlier timepoint (6 months CA), allowing for evaluation of early-life respiratory morbidity.

The primary outcome was severe PRD in the first 6 months defined as any of: ≥ 2 respiratory-related hospitalizations, home supplemental oxygen or any home respiratory support at 3 months CA, systemic corticosteroid or pulmonary vasodilators after discharge home, or death secondary to a cardiopulmonary cause.

PRD status was determined among infants with complete follow-up data through 6 months CA. Infants without adequate follow-up were excluded from PRD analysis if follow-up data were incomplete due to relocation, loss to follow-up despite repeated contact attempts, or incomplete documentation of post-discharge respiratory outcomes.

The secondary outcome was the number of respiratory- related emergency room visits occurring between NICU discharge and 6 months CA.

4.1.5 Study Procedures

To recruit infants to the study, the site research coordinator screened the medical records of babies admitted to the NICU and identified those potentially eligible for participation. Given the potentially medically fragile state of the infants, the site research coordinator first confirmed with the infant's medical team and/or site investigators that it was appropriate to approach the family. Families of babies meeting entry criteria were contacted by a clinician within their circle of care to identify whether they would be interested in hearing more about upcoming research projects. Families who provided consent to contact were contacted by the site research coordinator, to provide information about the study, confirm eligibility, and obtain formal consent.

Data regarding patient demographics, laboratory investigations, including blood gases, echocardiograms, and respiratory morbidity outcomes during the NICU admission, were extracted through the patient charts.

A targeted neonatal echocardiogram was performed by a trained clinician at the bedside according to the American Society of Echocardiography guidelines (70). Measures representative of pulmonary hemodynamics and right and left ventricular function were collected. Each scan was similar to the standard clinical scan performed by the site's echocardiography service, using standard clinical equipment and image acquisition sequence. PH was assessed using echocardiographic parameters. Right ventricular systolic pressure (RSVP) was estimated from the tricuspid regurgitation (TR) jet velocity using Doppler measurements. PH was defined as an estimated RVSP greater than 50% of the systemic systolic blood pressure calculated as (TR-derived pressure + 5 mmHg) divided by systolic pressure (65). If PDA was

present, PH was determined based on interventricular septal flattening. This was quantified by the eccentricity score index which was calculated as the ratio of the parallel (D2) to perpendicular (D1) diameters of the left ventricle in end-systole. If the patient had an Eccentricity index ≥1.3, they were said to have PH (65,71).

Follow-up phone calls with the infants' guardians were made every 3 months, to capture additional data including use of home supplemental oxygen, respiratory-related admissions, prescription medications, and home environment. All collected data was entered into a secure REDCap database.

Each participant was assigned a unique study ID and identifying information was stored separately to maintain confidentiality. I performed the follow-up calls and data entry into the REDCap database for the CHEO site.

4.1.6 Statistical Analysis

Descriptive statistics were used to summarize the demographic and baseline characteristics of all patients enrolled in this study. Continuous variables were summarized using means and standard deviations. Categorical variables were summarized using frequencies and percentages.

To assess the association between candidate predictors and PRD at 6 months CA, univariable Firth penalized logistic regression models (69) were performed to evaluate individual associations between candidate predictors and PRD. Given the small sample size, limited number of outcome events, and potential for sparse data, Firth penalized likelihood estimation was

employed to reduce small-sample bias inherent in conventional maximum likelihood estimation. Firth penalization is useful in the presence of spare data or rare outcomes, where standard logistic regression may produce unstable estimates or fail to converge (69). However, because Firth penalization does not address multicollinearity or eliminate the risk of overfitting, these issues were addressed separately through careful predictor selection and assessment of collinearity.

Variables considered clinically relevant based on prior literature and findings from the retrospective study were identified a priori. All candidate predictors were first evaluated using univariable Firth penalized logistic regression models. A forward selection approach was used to guide multivariable model construction, beginning with the strongest univariable predictors, and sequentially considering additional clinically relevant variables. Given the limited number of outcome events, multivariable models were restricted to a small number of predictors selected based on clinical relevance, evidence of association in univariable analyses, and consideration of collinearity to minimize the risk of overfitting. During multivariable model construction, particular attention was given to the overlapping nature of neonatal respiratory severity markers. Specifically, BPD severity (Jensen classification), duration of mechanical ventilation, and hypercapnia were considered closely related indicators of underlying lung disease severity. Collinearity between candidate predictors was assessed using variance inflation factors (VIF), which demonstrated substantial collinearity between markers of respiratory disease severity, including home supplemental oxygen use and BPD severity, whereas gestational age demonstrated low collinearity within the model. To avoid overadjustment and model instability, these variables were not included simultaneously in the same multivariable model. Model

selection prioritized parsimony, clinical interpretability, and stability of effect estimates. Where collinearity was identified based on VIF, alternative model specifications were explored, and the variable demonstrating stronger associations with PRD, as reflected by effect size estimates and model fit statistics, was retained. Final candidate predictors retained in the multivariable model were home supplemental oxygen requirement at discharge and PMA at discharge. PMA at discharge was calculated for all infants using gestational age at birth and duration of hospitalization derived from date of birth and date of discharge. Although PMA at discharge was not independently associated with PRD after adjustment, it was retained in the final model to evaluate its contribution to overall model performance.

Model discrimination was assessed using ROC curve analyses, and the area under the curve (AUC) was reported to evaluate the model's ability to distinguish between infants with and without PRD. OR and 95% confidence intervals (CI) were reported, and a two- sided p-value <0.05 was considered statistically significant.

The association between PRD status and the occurrence of at least one respiratory-related emergency within the first 6 months of life was evaluated using Firth penalized logistic regression.

Continuous predictors were modeled per clinically meaningful unit increase (per week of gestation, per 100 g of birth weight, and per day of mechanical ventilation). Jensen severity was modeled as an ordinal variable, with odds ratios reflecting the linear trend across increasing severity categories.

All analyses were conducted using R statistical computing software (Version 4.3.1)(64)

Chapter 4.2- Prospective Study: Results

4.2.1 Baseline Characteristics

Between May 2024 and August 2025, a total of 76 infants were enrolled into the study and had baseline data available. Follow -up data at 6 months CA was available for 34 infants, who comprised the analytic cohort for models evaluating predictors of PRD. Among infants in the analytic cohort, 12 (35%) met criteria for PRD at 6 months CA.

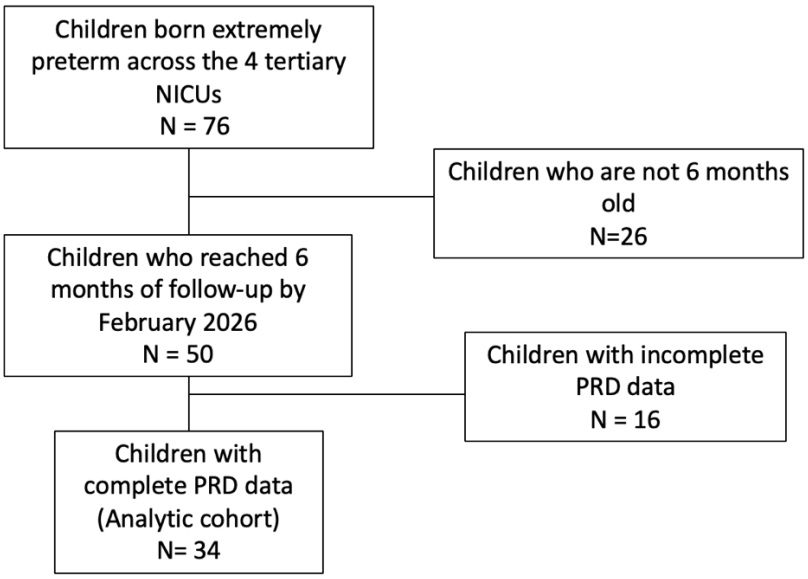

Figure 4.1: Study flow diagram outlining the size of initial prospective patient population, how many were excluded and the final analytic sample size

Table 4.2 describes the baseline characteristics of the study population. Infants with PRD were born at a significantly lower gestational age and had lower birth weight compared to those without PRD. BPD was present in 20 of the 34 infants (58.8%) in the analytic cohort (those with available 6-month follow-up data). BPD was more common among infants who met the criteria for PRD compared to those who did not (83.3 % vs 45.5%). However, PRD was also observed in

a small number of infants without BPD (16.7%), indicating that respiratory morbidity at 6 months was not limited to infants meeting the criteria for BPD at 36 weeks post-menstrual age. Those with PRD tended to have lower GA, birth weight and tended to be sicker overall as seen by higher incidences of patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and sepsis.

Table 4.2: Baseline demographic and neonatal clinical characteristics of the prospective cohort, stratified by PRD status at 6 months CA.

Variable	Overall N = 34	No PRD N = 22	PRD N = 12	Missing (%)
Gestational age (weeks)				
Mean (SD)	26.1 (1.8)	26.91 (1.2)	24.67 (1.8)	0.0
Post-menstrual age at discharge (weeks)				
Mean (SD)	41.1 (3.3)	40.2 (3.4)	42.6 (2.5)	2.9
Sex (%)				
Male	16 (47.1)	9 (40.9)	7 (58.3)	0.0
Birth weight (grams)				
Mean (SD)	954 (263.3)	1038 (220.1)	786 (271.4)	2.9
Small for Gestational Age (%)				
Yes	5 (15.6)	3 (13.6)	2 (20.0)	
PDA (%)				17.6
Yes	21 (75.0)	10 (62.5)	11 (91.7)	
Retinopathy of Prematurity (%)				
Yes	23 (67.6)	12 (54.5)	11 (91.7)	
Intraventricular Hemorrhage (%)				0.0
Yes	13 (38.2)	7 (31.8)	6 (50.0)	
Necrotizing Enterocolitis (%)				2.9
Yes, Stage I (suspected)	2 (6.1)	1 (4.8)	1 (8.3)	
Yes, Stage II (Definite)	3 (9.1)	0 (0.0)	3 (25.0)	
Pulmonary Hypertension at 36 weeks (%)				50
Yes	1 (5.9)	1 (7.7)	0 (0.0)	
BPD (%)				0.0
Yes	20 (58.8)	10 (45.5)	10 (83.3)	
Jensen Severity* (Among those with BPD) (%)				2.9
Grade 1	5 (15.2)	4 (19.0)	1 (8.3)	
Grade 2	15.2 (45.5)	6 (28.6)	9 (75.0)	
Sepsis				
Yes	9 (26.5)	2 (9.1)	7 (58.3)	
Hypercapnia (Based on last blood gas closest to discharge) (%)				5.9
Yes	10 (31.2)	4 (20.0)	6 (50.0)	
Home Supplemental Oxygen at Discharge (%)				20.6
Yes	5 (18.5)	1 (5.0)	4 (57.1)	

*No infants had Jensen Grade 3 severity of BPD

4.2.2 BPD Severity

BPD severity grade was stratified by PRD outcome in the 20 infants who had BPD. Among infants with PRD (n = 12), 2 (16.7 %) had no BPD. 1 infant (8.3 %) had Grade 1 Severity, and 9 infants (75.0%) had Grade 2 severity. No infants in the analytic cohort met the criteria for Grade 3 severity. Table 4.3 shows the results of a univariate logistic regression of PRD with the Jensen definition for infants with BPD. An increase in Jensen severity grade was associated with an increased odds of PRD. More specifically, infants with a Grade 2 Jensen severity score at 36 weeks PMA had 6.8 times the odds (95% CI: 1.4 - 44.5, $p = 0.018$) of developing PRD at 6 months compared to infants with no BPD.

4.2.3 Pulmonary Hypertension

In the analytic cohort, 5.9% (1) had PH at 36 weeks PMA, while 94.1% (16) did not. In univariable analysis, PH was not significantly associated with PRD (OR 0.9, 95% CI 0.01-21.1, $p = 1.0$). PH data was available for only 50% of the analytic cohort. As a result, the estimate is based on a substantially reduced sample size, and the confidence interval is wide.

4.2.4 pCO_2 Level

Of the infants in the analytic cohort, 10 (31.2 %) had hypercapnia prior to discharge, while 22 (81.5%) did not. Amongst those with PRD, 50% of infants (6) had hypercapnia prior to discharge. Two babies did not have complete baseline data regarding pCO_2 level, resulting in 5.9% of missingness for this variable. The univariable logistic regression with Firth correction demonstrated that those with hypercapnia (pCO_2 > 50 mmHg) prior to NICU discharge

suggested higher odds of PRD, although this was not statistically significant (Table 4.3). Blood gas measurements closest to discharge were predominantly obtained from capillary samples (92%), with one venous sample and no arterial samples. Among capillary samples, 21 infants had no hypercapnia, and 10 had hypercapnia. The venous sample did not have hypercapnia.

4.2.5 Birth Weight

The mean birth weight of the analytical cohort was 954 grams (SD 263.3). Infants who met the criteria for PRD had a lower mean birth weight (786 grams, SD 271.4) compared to those without PRD (1038 grams, SD 220.1). Higher birth weight was associated with reduced odds of PRD in univariable Firth penalized regression analysis. For every 100-gram increase in birth weight, the odds of PRD decreased by 32% (OR 0.7, 95% CI 0.5-0.9, $p = 0.009$).

4.2.6 Small for Gestational Age

In the analytic cohort, 84.4 % (27) were not small for gestational age, and 15.6% (5) were. Among infants who met the criteria for PRD, 80% (8) were not SGA while 20% (2) were. Among infants who did not meet the criteria for PRD, 86.4% (19) were not SGA, while 13.5% (3) were. Infants classified as SGA were not significantly more likely to meet the criteria for PRD compared to those who were not SGA. In univariable Firth penalized logistic regression analysis, SGA status was not associated with PRD at 6 months CA (OR 1.6, 95% CI 0.2- 10.6, $p = 0.60$).

4.2.7 Duration of Mechanical Ventilation

Duration of invasive mechanical ventilation was not significantly associated with PRD in univariable Firth penalized logistic regression analysis. Each additional day of mechanical ventilation was not associated with increased odds of PRD (OR 1.00, 95% CI 0.9-1.1, $p = 0.7$).

4.2.8 Sex

In the analytic cohort, 52.9% (18) were female, and 47.1% (16) were male. Among infants who met the criteria for PRD, 7 (58.3%) were male, and 5 (41.7%) were female. Sex was not significantly associated with PRD. Female infants had lower odds of PRD compared to males (OR 0.5, 95% CI 0.1 – 2.0, $p = 0.3$), although this did not reach statistical significance

4.2.9 Gestational Age at Birth and PMA at Discharge

There was a difference between gestational age at birth and postmenstrual age at time of discharge in those with PRD compared to those without. The mean gestational age at birth in the analytic cohort was 26.1 weeks (SD of 1.8). Infants who met the criteria for PRD were born earlier on average (24.7 weeks, SD of 1.8) compared to those without PRD (26.9 weeks, SD 1.2). Lower gestational age at birth was significantly associated with increased odds of PRD (OR 0.5 per week GA increase, $p < 0.001$), indicating that each additional week of gestation reduced the odds of PRD.

PMA at discharge was calculated using gestational age at birth and the duration of hospitalization derived from date of birth and date of discharge. The mean PMA at discharge was 42.8 weeks (SD of 3.3) in the analytic cohort. Infants without PRD had a mean gestational age of 40.2 (SD of 3.4) at discharge, and those with PRD had a mean gestational age of 42.6 weeks (SD

of 2.5) at discharge. The latest discharge occurred at 48.1 weeks PMA. In univariable Firth penalized logistic regression analysis, each additional week of PMA at discharge was associated with a 26% increase in the odds of PRD at 6 months (OR 1.3, 95% CI 1.0 -1.7, $p = 0.05$) as seen in Table 4.3.

4.2.10 Home Supplemental Oxygen at Discharge

Of the 34 infants in the analytical cohort, 5 (18.5%) were discharged on home supplemental oxygen. No infants were discharged on invasive or non-invasive mechanical ventilation. Of those who had PRD (n = 12), 4 (57.1%) infants were discharged on home supplemental oxygen. Of those with no PRD (n = 22), 1 infant (5.0%) was discharged on home supplemental oxygen. Univariable logistic regression showed that infants discharged on home supplemental oxygen had around 16.7 -fold higher odds of having PRD at 6 months compared to those who were not discharged on home supplemental oxygen (OR = 16.7, $p = 0.005$). However, due to the wide confidence interval (2.3, 212.7), this should be interpreted with caution.

Table 4.3: Univariable Firth penalized logistic regression models evaluating candidate neonatal and discharge predictors of PRD at 6 months CA. Odds ratios (OR) represent unadjusted associations. Continuous predictors were modeled per clinically meaningful unit increase (per week of gestational age, per 100 grams of birth weight, and per day of mechanical ventilation).

Variable	OR[1]	95% CI[1]	p-value
Jensen Score			
No BPD	Reference		
Grade 1	1.5	0.1, 15.3	0.7
Grade 2	6.8	1.4, 44.5	0.018
PH			
No	Reference		
Yes	0.9	0.01, 21.1	1.0
Hypercapnia (pCO_2 > 50 mmHg) at discharge			
No	Reference		
Yes	1.3	0.2, 2.9	
Birth Weight (per 100g)	0.7	0.5, 0.9	0.009
SGA			
No	Reference		
Yes	0.9	0.01, 21.06	1.0
Duration of Mechanical Ventilation (per day)	1.0	0.9, 1.1	0.7
Sex			
Male	Reference		
Female	0.5	0.1, 0.9	0.009
Gestational Age at Birth (weeks)	0.5	0.3, 0.7	< 0.001
PMA at Discharge (weeks)	1.3	1.0, 1.7	0.05
Home Supplemental Oxygen at Discharge			
No	Reference		
Yes	16.7	2.3, 212.7	0.005

[1]OR = Odds Ratio, CI = Confidence Interval

4.2.7 Multiple Predictors

Table 4.4 shows an exploratory forward-selection multivariable Firth logistic regression model that was conducted using predictors from time of discharge. All pre-specified candidate predictors were initially evaluated in univariable Firth logistic regression models. Given the small sample size and limited number of outcome events, multivariable modeling was restricted to discharge-level predictors demonstrating statistical association and/or strong clinical relevance in univariable analyses to reduce the risk of model overfitting. PH and hypercapnia were not statistically significantly associated with PRD in univariable analyses and were therefore not advanced into forward selection modeling.

In the multivariable model, home supplemental oxygen requirement at time of discharge remained independently associated with PRD at 6 months CA (adjusted OR 15, 95% CI 1.9 - 216.2, $p = 0.0098$). In contrast, PMA at discharge was not independently associated with PRD after adjustment (adjusted OR 1.0, 95% CI 0.7 - 1.4, $p = 0.995$).

The final multivariable model included home supplemental oxygen at discharge and PMA at discharge and was statistically significant with a likelihood ratio χ^2 of 7.4, and a *p-value* of *0.025*. Model discrimination was assessed using ROC curve analysis, yielding an AUC of 0.76 (95% CI 0.5-1.0) as seen in Figure 4.2.

Table 4.4: Final forward-selection multivariable Firth penalized logistic regression model evaluating the association between discharge characteristics and PRD at 6 months in the prospective cohort.

Variable	Adjusted OR[1]	95% CI[1]	p-value
Home Supplemental Oxygen at Discharge			
Yes	15	1.9, 216.2	0.0098
PMA at Discharge (per week)	1.0	0.71, 1.4	0.995

[1]OR = Odds Ratio, CI = Confidence Interval

Likelihood Ratio χ^2 (2) = 7.4, p = 0.025

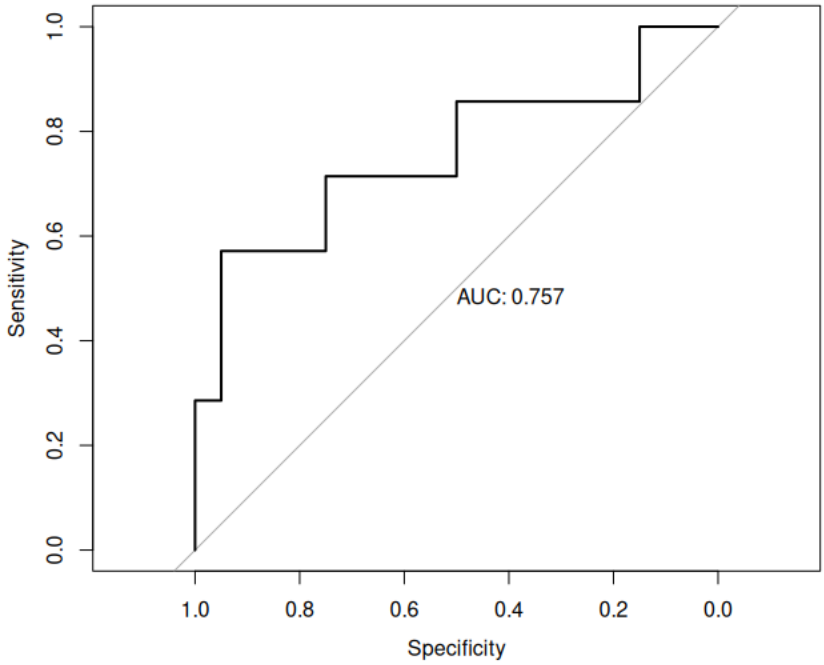

Figure 4.2: Receiver operating characteristic (ROC) curve for the final multivariable Firth logistic regression model predicting post-discharge respiratory disease (PRD) at 6 months CA. The model included home supplemental oxygen at discharge and corrected gestational age at

discharge. The area under the curve (AUC) is 0.7 (95% CI 0.51- 1.00), indicating moderate discriminatory ability.

4.2.8 Emergency Room Visits

In an exploratory analysis, we examined healthcare utilization for a respiratory related cause in the first 6 months of life. This exploratory analysis found that infants with PRD had approximately 5.6 times higher odds of having at least one respiratory related ER or clinic visit in the first 6 months of life compared to infants without PRD (OR 5.6, 95% CI 1.2- 30.0 $p = 0.027$). Figure 4.3 illustrates the distribution of respiratory emergency room and clinic visits in the first 6 months of life stratified by PRD status. Infants with PRD had a higher frequency of respiratory healthcare visits compared to those without PRD. While the majority of infants in both groups had no visits, a greater proportion of infants with PRD experienced one or more visits.

Table 4.5: Penalized logistic regression for emergency room visits in the first 6 months of life for infants with and without PRD.

Variable	OR[1]	95% CI[1]	p-value
PRD			
No	—	—	—
Yes	5.6	1.2, 30.0	0.027

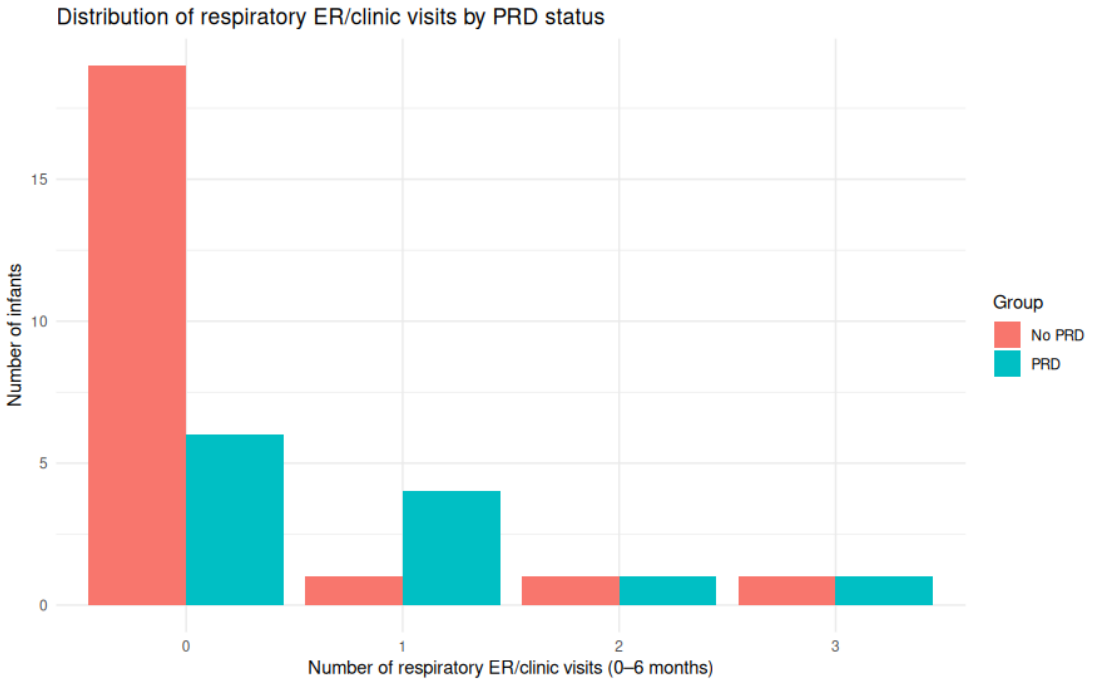

Figure 4.3: Distribution of respiratory emergency room and clinic visits in the first 6 months of life stratified by PRD status. Infants with PRD demonstrated a higher frequency of respiratory healthcare utilization compared to those without PRD.

Chapter 5 – Discussion

In this thesis, we examined early respiratory characteristics as potential predictors of PRD at 6 months and 2 years of life using both retrospective and prospective cohort designs. Across both analyses, clinical indicators reflecting respiratory vulnerability around the time of NICU discharge were associated with PRD, although the strength and independence of these associations varied depending on modeling strategy and cohort characteristics.

5.1 Baseline Characteristics and Generalizability

The baseline characteristics of both cohorts were broadly consistent with those reported in recent Canadian extremely preterm cohorts. In the retrospective cohort, 42% of infants met criteria for BPD based on the Jensen definition at 36 weeks' PMA. This prevalence is comparable to the Canadian Neonatal Network (CNN) data reporting chronic lung disease in approximately 44% of neonates born <29 weeks' gestation (12). Rates of major neonatal morbidities were similarly aligned with the national benchmarks, including necrotizing enterocolitis (8% in our cohort vs 7.9% in the CNN data) and sepsis (22.4 % in our cohort vs 23% reported for late-onset sepsis among neonates <29 weeks) (12). Together, these findings suggest that the retrospective cohort reflects the clinical complexity typical of extremely preterm infants managed in Canadian tertiary NICUs.

The baseline morbidity of the prospective cohort was also generally consistent with what is expected in extremely preterm infants cared for in tertiary NICUs. The sepsis rate (26.5%) appears high, but it is broadly in line with the CNN estimates for extremely preterm infants, where late-onset sepsis has been reported in around 23% of infants. The prevalence of BPD in

this cohort (58.8%) was somewhat higher than national chronic lung disease estimates, which may reflect the small analytic sample and a higher proportion of infants with complex neonatal courses.

Overall, the demographic and clinical characteristics of these cohorts are reflective of high-risk extremely preterm infants in tertiary care settings, supporting the clinical relevance and potential generalizability of these findings to similar populations. However, as both cohorts were derived from Canadian tertiary neonatal centers, these findings are likely most applicable to high-income healthcare settings with comparable neonatal care practices and resources.

5.2 Factors Associated with PRD

BPD

Across both the prospective cohort, which assessed PRD at 6 months of life, and the prospective cohort, which assessed PRD at 2 years of life, BPD emerged as an important risk factor for later respiratory morbidity. This is consistent with prior studies demonstrating that infants with BPD are at increased risk of recurrent wheezing, respiratory hospitalizations, and persistent lung function abnormalities in early childhood (5,22,57).

In the prospective cohort, a small proportion of infants (n=2) met the criteria for PRD by 6 months despite not meeting the criteria for BPD at 36 week's PMA. This finding aligns with emerging literature suggesting that BPD does not fully encompass the spectrum of prematurity-associated lung disease, and that respiratory vulnerability may extend to infants not meeting formal diagnostic criteria (6). This is further supported with emerging literature by Du Berry et

al. who highlight that abnormal lung function trajectories can occur in individuals born preterm regardless of strict BPD labeling, and that lung function deficits are seen across gestational ages (7).

In contrast, all infants in the retrospective analysis who met the definition of PRD within the first 2 years of life had a history of BPD, suggesting that more persistent respiratory morbidity in early childhood may occur predominantly among those with more established lung disease. This is in line with literature describing a chronic prematurity-associated lung disease phenotype characterized by persistent symptoms and healthcare utilization (6).

The relationship between BPD severity and subsequent PRD differed between the two cohorts. However, BPD severity was not independently associated with PRD in either cohort. In the retrospective cohort, BPD severity did not discriminate long-term PRD risk. Similarly, in the prospective cohort, higher Jensen severity grade was associated with increased odds of PRD in univariable analyses, but this association was not retained after adjustment for gestational age at discharge. Prior literature evaluating the Jensen classification has demonstrated improved predictive validity for early childhood respiratory morbidity (22). The attenuation of this association following adjustment, together with the lack of an independent association in the retrospective cohort, suggests that the observed univariable relationship may have been partly explained by developmental immaturity of the lung rather than BPD severity alone (72).

Although the Jensen classification was selected because of its ability to predict later respiratory morbidity, our findings suggest that BPD severity alone may not fully capture the spectrum of PRD. This may be in part due to misclassification of other respiratory conditions,

such as upper airway anomalies (73). This may partly explain the limited discriminatory ability of BPD diagnosis for predicting PRD at both 6 months and 2 years in our studies.

Together, these findings suggest that although BPD remains an important indicator of respiratory vulnerability across early childhood, its association may vary depending on the timing of outcome assessment. Early respiratory morbidity at 6 months may reflect a broader spectrum of post-discharge instability, whereas PRD persisting to 2 years may represent a more chronic phenotype linked to established BPD.

Pulmonary Hypertension

Both the retrospective and prospective cohorts demonstrated similar trends, with no statistically significant associations between PH and PRD. This may reflect the relatively high prevalence of PH in early life among extremely preterm infants, particularly among those with severe BPD, which could limit its discriminatory value within an already high-risk population (74).

From a pathophysiological standpoint, PH in preterm infants arises primarily from disrupted pulmonary vascular development and abnormal vascular remodeling, leading to increased pulmonary vascular resistance in the context of impaired alveolarization (3,74). Although PH has been consistently associated with increased mortality and prolonged respiratory support during the NICU course, its relationship with longer-term morbidity among survivors is less clearly defined (10,74). It is therefore possible that early PH functions more as a marker of acute disease severity rather than as direct determinant of persistent respiratory symptoms following discharge.

In contrast, at 6 months and 2 years, ongoing airway obstruction, parenchymal injury, and susceptibility to viral respiratory infections are greater factors for PRD development than PH alone (6). In this context, PH may not independently identify infants at highest risk of post-discharge respiratory morbidity beyond what is already reflected in broader measures of lung disease severity.

However, given the small sample size of the prospective cohort, smaller effect sizes may not have been detectable, and conclusions should be interpreted cautiously.

Hypercapnia

Elevated pCO_2 levels prior to discharge have been associated with adverse respiratory outcomes, including reintubation and hospital readmission (49). In the prospective cohort, hypercapnia ($pCO_2 > 50$ mmHg) appeared more frequent among infants who met the criteria for PRD, however this association did not reach statistical significance in univariable modeling. Similarly, in the retrospective cohort, mean pCO_2 levels at discharge appeared higher among infants who later met the criteria for PRD compared to those who did not (52.5 ± 9.1 mmHg vs 46.7 ± 7.6 mmHg), although this difference was not statistically significant.

Previous studies have demonstrated that infants with BPD and elevated pCO_2 are at increased risk of respiratory instability, rehospitalization, and prolonged oxygen dependence, suggesting that hypercapnia may reflect ongoing pulmonary vulnerability (57). From a physiological standpoint, elevated pCO_2 at discharge reflects impaired alveolar ventilation (75),

and may signal reduced effective alveolar surface area and ongoing parenchymal lung disease associated with disrupted lung development (3,6). Our findings were directionally consistent with prior studies, however the magnitude of association was smaller and did not reach statistical significance, likely reflecting limited sample size and event counts.

In both cohorts, the majority of blood gas measurements were obtained from capillary sampling, minimizing heterogeneity in the sampling source. The lack of statistical significance may therefore reflect limited power, the timing of blood gas measurement relative to clinical stability, or the multifactorial nature of PRD.

To our knowledge, this is the first study to examine pCO_2 levels prior to NICU discharge specifically in relation to post-prematurity respiratory disease at both 6 months and 2 years of age.

Birth Weight

Lower birth weight was associated with increased odds of PRD in univariable analysis in the prospective cohort. However, birth weight was not included in multivariable modeling, as model construction prioritized clinically relevant discharge-era variables at the time of NICU discharge. This approach is consistent with the study objective of identifying predictors of post-discharge respiratory morbidity. This finding is consistent with prior literature demonstrating that lower birth weight reflects greater biological immaturity and vulnerability to disrupted lung development, particularly in the context of extreme prematurity (3,6). Reduced birth weight may indicate impaired in utero growth, diminished pulmonary reserve, and heightened susceptibility

to inflammatory and ventilator-related lung injury (3). However, birth weight is closely correlated with gestational age, and its independent contribution beyond developmental immaturity may be difficult to differentiate in small samples. Nonetheless, the observed association reinforces the role of early biological vulnerability in shaping post-discharge respiratory outcomes.

Small for Gestational Age

SGA status was not significantly associated with PRD in univariate modeling in the prospective cohort. Although SGA has been linked to altered lung growth trajectories and increased respiratory morbidity in very preterm infants, its independent association beyond gestational age and illness severity remains uncertain (32). It is possible that the impact of SGA on respiratory outcomes is mediated through gestational age or overall illness severity rather than acting as an independent predictor. The lack of association in this cohort may also reflect limited power or the relatively small number of infants meeting SGA criteria.

Duration of Mechanical Ventilation

Duration on mechanical ventilation was not significantly associated with PRD in the prospective cohort. Prolonged invasive ventilation has been associated with increased risk of BPD and structural lung injury due to barotrauma and volutrauma, suggesting a biologically plausible link with later respiratory morbidity (3). However, in this cohort, duration of ventilation may have overlapped with other markers of respiratory severity, including BPD classification and home supplemental oxygen requirement at discharge. As a result, its independent contribution to post-

discharge respiratory disease may have been attenuated. Additionally, limited sample size may have reduced the ability to detect smaller effect sizes.

Birth weight, SGA status, and duration of mechanical ventilation were evaluated primarily in the prospective cohort, as the retrospective analysis focused on BPD classification and discharge-level respiratory markers.

Gestational age / Post- Menstrual Age

Lower gestational age at birth is one of the most consistently reported predictors of respiratory morbidity in preterm infants, including recurrent wheezing, rehospitalization, and persistent lung function impairment in early childhood (29,76). Gestational age reflects baseline pulmonary immaturity, with earlier birth occurring during critical stages of lung development. It is accompanied by increased susceptibility to injury-inducing exposures such as mechanical ventilation, oxygen therapy, and inflammatory insults that can disrupt alveolar development therefore reducing effective gas-exchange surface area (3,6,7). In the prospective cohort, lower GA at birth was significantly associated with increased odds of PRD at 6 months, consistent with prior literature demonstrating that developmental immaturity is a fundamental determinant of later respiratory outcomes (7).

PMA at discharge has been less extensively studied but may serve as a surrogate marker of prolonged hospitalization and delayed respiratory stabilization. Infants discharged at a later PMA may have greater illness severity, prolonged respiratory support, or slower clinical recovery. In our prospective cohort, each additional week of PMA at discharge was associated

with a 26% increase in the odds of PRD in univariable analyses, however, this association was attenuated in multivariable modeling after accounting for home supplemental oxygen requirement, suggesting overlapping information between these markers of respiratory vulnerability.

Gestational age was not extensively modeled in the retrospective cohort due to collinearity with downstream indicators of neonatal illness severity. In contrast, in the prospective cohort, gestational age demonstrated a strong and stable association with PRD during exploratory modeling and was retained while carefully separating it from closely related clinical severity variables to minimize redundancy and overadjustment.

Together, these findings reinforce the central role of developmental immaturity in shaping respiratory outcomes, consistent with literature demonstrating that gestational age influences subsequent lung growth trajectories and long-term respiratory vulnerability (6,7).

Home Supplemental Oxygen

Discharge from the NICU on home supplemental oxygen is a clinically accessible marker of ongoing pulmonary vulnerability and reflects persistent oxygen requirement beyond the acute neonatal period (77). Prior studies have demonstrated that infants discharged on supplemental oxygen are at increased risk of rehospitalization, recurrent respiratory symptoms, and prolonged respiratory support in early childhood, suggesting that home supplemental oxygen requirement serves as a marker of more severe underlying lung disease (2).

In the prospective cohort, discharge on home supplemental oxygen was significantly associated with PRD at 6 months in both univariable and multivariable analyses. Notably, home supplemental oxygen requirement emerged as the strongest pre-discharge clinical predictor in the prospective model and demonstrated good discriminatory performance for identifying infants at risk of early PRD. In contrast, in the retrospective cohort, no significant association was observed between discharge on home supplemental oxygen and PRD at 2 years of life.

The discrepancy between cohorts is likely due to the smaller sample size in the prospective study, which limits statistical power, although differences in outcome timing may also contribute. Collectively, these findings suggest that the need for home supplemental oxygen at discharge may represent an early and clinically accessible risk stratification marker for short-term respiratory morbidity.

Multivariable Modeling

In both cohorts, multivariable modeling was used to evaluate the combined discriminative ability of clinically relevant factors for PRD. The prospective multivariable model for PRD at 6 months demonstrated a stronger performance (AUC of approximately 76%) and incorporated discharge on home supplemental oxygen and PMA at discharge. These predictors may represent early respiratory vulnerability and slower lung maturation, rather than fixed structural lung disease. Early post-discharge respiratory morbidity may therefore be more closely related to transitional vulnerability and residual oxygen requirement, whereas PRD persisting to 2 years may reflect a more stable chronic phenotype of prematurity-associated lung disease.

In contrast, in the retrospective study, the simultaneous consideration of multiple variables improved model performance compared to individual predictors alone. The combination of pre-discharge PH, Jensen Score ≥2, and pCO_2 > 50 mmHg demonstrated the strongest discriminative ability for PRD at 2 years, with area under the ROC indicating approximately 70% discriminatory ability. These predictors primarily reflect established structural and vascular lung disease, consistent with literature describing a chronic prematurity-associated lung disease phenotype characterized by persistent airflow limitation and ongoing healthcare utilization beyond infancy (3,6,72).

This distinction aligns with emerging literature suggesting that respiratory trajectories in extremely preterm infants evolve over time (7), with early-life respiratory events reflecting instability and incomplete maturation, and later morbidity reflecting fixed structural and vascular changes in the developing lung (6,7). The divergence in predictors between cohorts therefore likely reflects differences in outcome timing the dynamic evolution of lung disease across infancy and early childhood.

Although both models demonstrated moderate discrimination, these estimates reflect apparent performance derived from small sample sizes. As a result, the findings should be considered exploratory and require validation in larger, independent cohorts. The findings do, however, highlight the value of multivariable approaches and suggest that discharge-based markers may provide particularly robust short - term risk stratification.

ER visits/Respiratory-related healthcare utilization

Emergency room and acute care visits were examined as exploratory outcomes in both cohorts, although within slightly different clinical contexts. In the retrospective study, these visits were captured during chart review, including review of CHEO ER records and documentation of visits to other emergency departments recorded during standard neonatal follow-up visits. However, it is possible that not all emergency department visits were captured, which may have resulted in an underestimation of the association. We found that children with BPD had more ER visits compared to those without BPD, consistent with prior literature demonstrating increased healthcare utilization among preterm infants with chronic lung disease (56,57). This aligns with studies showing that BPD is associated with recurrent respiratory exacerbations, viral-triggered illness, and greater healthcare resource use in early childhood (2,4).

In the prospective cohort, infants who met the criteria for PRD experienced higher healthcare utilization within the first 6 months of life. Although confidence intervals were wide due to small sample size, the direction and magnitude of effect suggests a clinically meaningful increase in early respiratory instability among infants meeting PRD criteria.

Together, these findings illustrate the substantial healthcare burden associated with PRD. They further suggest that early post-discharge respiratory vulnerability translates into measurable respiratory-related healthcare utilization, highlighting the importance of identifying high-risk infants prior to NICU discharge.

5.3 Strengths

This study has several strengths. First, the use of both retrospective and prospective cohort designs allowed for the evaluation of respiratory outcomes across different timepoints, providing a more comprehensive understanding of early-life respiratory morbidity. Secondly, the focus on clinically accessible discharge – era variables enhance the potential applicability of these findings for early risk stratification. Finally, the use of standardized definitions of PRD and detailed clinical data strengthens the internal validity of the study.

5.4 Limitations

Retrospective Study

Several limitations should be considered when interpreting these findings. First, the clinical definition of BPD has evolved over time, with substantial variability across consensus definitions and classifications systems (3,20). Since BPD definitions differ in their reliance on oxygen exposure, respiratory support thresholds, and timing of assessment, comparisons across studies may be imperfect. This is important because variation in diagnostic criteria may influence both the estimated prevalence of BPD and its observed relationship with later respiratory outcomes.

Furthermore, BPD severity in this study was determined at a single timepoint (36 weeks' PMA) based on respiratory support requirements. This approach may not fully capture the longitudinal trajectory of respiratory disease (7). Fluctuating oxygen needs may result in the over or under rating of BPD severity at a single point in time (74). In addition, reliance on oxygen and respiratory support criteria may inadvertently capture heterogenous conditions that mimic chronic lung disease, such as upper airway obstruction, diaphragmatic dysfunction, residual pulmonary edema, or evolving PH (73,74) . Such heterogeneity may contribute to

misclassification and reduce the discriminatory ability of BPD severity grading for predicting later PRD.

The relatively small number of infants with severe BPD (Jensen Grade 3, n = 5) limited power to detect meaningful differences across severity strata. As a result, associations between higher BPD grades and PRD at 2 years may not have been identified.

Another limitation was the retrospective nature of the study. Missing data were present for some variables, particularly among infants who were transferred to community hospitals and subsequently lost to follow-up at our tertiary care centers. Neonatal data was not available on infants who were not included in this cohort, limiting the ability to compare included and non-included infants. This is important because selection bias may have occurred if infants with more complex respiratory courses were preferentially followed at our center, while healthier infants received follow-up care closer to home and may not have had follow-ups at our center after their first hospital discharge. This may have resulted in a cohort with a higher proportion of medically complex infants, which could overestimate the association between neonatal respiratory severity markers and later PRD. However, when compared with national CNN data (12), the prevalence of BPD and other major neonatal morbidities in this cohort was broadly consistent with reported rates for extremely preterm infants. This suggests that, despite potential follow-up bias, the cohort remains representative of a high-risk tertiary NICU population.

Variability in the timing of pre-discharge pCO_2 measurement is another limitation. The final blood gas prior to discharge was used, but timing was not standardized. In many cases,

blood gases were not repeated once capillary values normalized (<50 mmHg). This could result in measurement variability unrelated to true physiological stability, potentially attenuating associations between hypercapnia and PRD.

Similarly, echocardiographic assessment of PH was not performed according to a uniform protocol. Although all infants underwent early echocardiographic evaluation and those with elevated pulmonary pressures were followed longitudinally, differences in timing and indication for repeat studies may have influenced PH classification.

Together, these limitations highlight the challenges inherent in retrospective cohort studies while supporting cautious interpretation of the observed associations.

Prospective Study

Several limitations should be considered when interpreting the findings of the prospective cohort. Although data collection was standardized across the 4 sites, the sample size was small, which may have limited power to detect smaller effect sizes and may have influenced model stability. Some candidate predictors were limited by sparsity, resulting in wide confidence intervals, and restricting their inclusion in multivariable models.

PH and PDA variables were limited by a high degree of missingness in the prospective cohort. This was largely related to delays in receipt of complete data from participating sites at the time of analysis. As a result, these variables could not be robustly incorporated into

multivariable modeling, which may have limited the ability to fully evaluate their associations with PRD.

Collinearity among markers of neonatal respiratory severity was another important consideration. Gestational age, respiratory support requirements, and other indicators of pulmonary morbidity are closely interrelated, making it challenging to distinguish their independent contributions to PRD risk. To address this, model construction prioritized clinically relevant discharge – era variables and avoided the simultaneous inclusion of closely related measures of disease severity to reduce redundancy and model instability. As a result, individual effect estimates should be interpreted with caution, as they may reflect overlapping aspects of underlying respiratory disease.

Additionally, PRD at 6 months reflects early post-discharge respiratory morbidity and may not fully predict longer-term respiratory outcomes. Prior literature has demonstrated that respiratory trajectories in preterm infants are heterogenous, with some children experiencing early wheezing and recurrent respiratory symptoms that improved our time, while others develop persistent airflow limitation and obstructive respiratory patterns later in childhood (7). Studies examining lung function trajectories in individuals born preterm have shown that impairments may evolve over time, rather than remain static (6,7). Therefore, infants classified as having PRD at 6 months may experience clinical improvement, whereas others without early morbidity may develop later respiratory complications. The prognostic implications of early PRD beyond infancy remain uncertain. However, ongoing follow-up of this cohort may help clarify whether early respiratory morbidity persists or evolves over time.

Finally, because infants were recruited from tertiary-care institutions, the cohort may not be fully representative of broader neonatal populations, which may limit generalizability, although most babies born extremely preterm receive ongoing tertiary care before and after hospital discharge.

5.5 Future Directions

Future research should aim to validate our research findings in larger, multicenter cohorts to assess reproducibility and generalizability. A larger sample size would allow for more stable multivariable modeling, facilitate exploration of the relationships among neonatal respiratory severity predictors, and permit simultaneous inclusion of multiple clinically relevant predictors in multivariable models. External validation of discharge-based predictive models would be particularly valuable to determine their clinical utility across diverse neonatal populations.

Additionally, longitudinal follow-up beyond 6 months may clarify whether early predictors of PRD retain prognostic value for longer term respiratory outcomes, and healthcare utilization later in childhood. This may further contextualize the differences observed between the retrospective and prospective cohorts and contribute to a more comprehensive understanding of the respiratory trajectories following extreme prematurity.

Future multicenter studies using consistent PRD definitions and standardized follow-up protocols may further strengthen comparability and improve external validation efforts.

Incorporating longitudinal measurements overtime, applying alternative analytic approaches, and addressing missing data through appropriate imputation methods may further enhance the robustness of future analyses. Together, these future directions may support the development of more precise and clinically applicable risk stratification strategies for infants born extremely preterm.

5.6 Conclusions

In conclusion, this thesis demonstrates that early markers of respiratory vulnerability are associated with post-prematurity respiratory disease, although the strength and independence of these associations vary depending on the timing of outcome assessment. In the retrospective cohort, markers reflecting established lung disease, particularly BPD severity, PH, and elevated pCO_2, were associated with PRD at 2 years of life, supporting the link between more severe neonatal respiratory morbidity and persistent early childhood respiratory outcomes.

In the prospective cohort assessing PRD at 6 months of life, discharge-based clinical variables, particularly home supplemental oxygen requirement and post-menstrual age at discharge, emerged as meaningful predictors of early post-discharge respiratory morbidity. These findings suggest that readily accessible discharge markers may help identify infants at risk for short-term respiratory instability, while predictors of longer-term morbidity assessed in the retrospective cohort may reflect more established lung disease patterns. Multivariable modeling improved discriminatory performance in both cohorts and highlighted the importance of combining clinically available markers rather than relying on single predictors in isolation.

These findings add to the existing literature by demonstrating that clinically available discharge characteristics may provide meaningful early risk stratification for post-prematurity respiratory disease in extremely preterm infants. While previous studies have primarily focused on predicting longer-term respiratory outcomes from BPD, this thesis shows that discharge on home supplemental oxygen is a clinically relevant indicator of short-term respiratory morbidity at 6 months of life and supports the use of readily available discharge markers to identify infants at increased risk for early post-discharge respiratory instability. By examining predictors across both short- and longer-term follow-up, this work further highlights that the factors associated with respiratory morbidity may differ depending on the timing of outcome assessment.

Together, these findings support the potential value of structured discharge risk assessment in extremely preterm infants. Early identification may facilitate targeted follow-up and resource allocation aimed at mitigating post-discharge respiratory burden. Incorporating objective discharge markers into follow-up planning may help guide the intensity of monitoring, inform family counseling, and identify infants who may benefit from closer respiratory surveillance. In practice, this may include considerations such as timing of daycare exposure, intensity of outpatient follow-up, and optimization of preventative strategies.

As novel therapies for prematurity-associated lung disease continue to be developed, improved early risk stratification may also help identify infants most likely to benefit from future targeted interventions. Further research in larger cohorts with longer follow-up will be important to validate these findings and clarify their long– term clinical implications.

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Appendix

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