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Risk Factors Contributing to the Development of Bronchopulmonary Dysplasia among Preterm Infants

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RISK FACTORS CONTRIBUTING TO THE DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA AMONG PRETERM INFANTS

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ABSTRACT

RISK FACTORS CONTRIBUTING TO THE DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA AMONG PRETERM INFANTS

December 2020

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Bronchopulmonary dysplasia (BPD) is a pulmonary disease that effects infants born < 32 weeks gestational age. Despite improved survival among preterm infants, the incidence and severity of BPD has not improved, rather the features and severity of BPD have evolved (Abman et al., 2017). BPD is a disease that has significant impact on the outcomes of preterm infants, including poor pulmonary and neurodevelopmental outcomes (Abman et al., 2017). Since its identification in 1967, and many iterations to its defining criteria, healthcare practitioners are unable to accurately predict infants' risk of developing BPD. Further, there is significant family, social, and economic impacts from BPD. This dissertation research examined risk factors for BPD, as identified in a mid-range theory developed from a systematic review of the literature. This mid-range theory is framed using the Neuman Systems Model (NSM) (2011). The research utilized a secondary analysis of data from a database including a cohort of infants born at < 32

weeks' gestation (n=455) treated at Boston Children's Hospital. Findings from this research demonstrated that multiple intrapersonal risk factors are associated with development of BPD and the grades of BPD severity including gestational age, birth weight, surfactant administration, necrotizing enterocolitis, infections, mechanical ventilation duration, and patent ductus arteriosus. This research adds to the current body of research by demonstrating specific risks associated with BPD. Findings of this research could be used to identify maternal infant dyads that would benefit from early therapy(s) to reduce BPD risk.

DEDICATION

This dissertation represents years of doctoral work, and years of dedication to the neonatal intensive care unit working with preterm infants and their families. Days, nights, weekends, holidays, and time ruminating at home; improving the care and outcomes for these infants and their families is constantly a consideration when the neonatal intensive care unit is a passion. In reviewing the charts of the subjects, I envisioned them, their beds, their families, and time spent at their bedside. This work is the beginning of my research aimed at improving their outcomes.

Further, this work would not have been possible without the support of my amazing family. My husband, Jack, has always backed my academic pursuits. I am forever grateful for his partnership. I began this program with an infant and I complete my work with a preschooler and a toddler. Thomas and Patrick – your chaos provides a balance to the organization in academia. For Carter, a constant companion during my quiet work, you are an angel. Mom, Dad, Ann, Buddy, Meri, Bonnie – your help with the boys and your encouragement was invaluable.

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CHAPTER I

INTRODUCTION

Background and Significance

Bronchopulmonary dysplasia (BPD; see Table 1) is a chronic lung disease unique to premature infants. The disease was first identified in 1967 among a group of primarily preterm infants with the following characteristics: 1) diagnosed with respiratory distress syndrome (RDS, see Table 2); 2) exposed to oxygen and/or trauma related to mechanical ventilation; and 3) demonstrated evidence of persistent pulmonary disease at 28 days of life (Northway, Rosan, & Portar, 1967). The initial diagnostic criteria for BPD included persistent oxygen requirement and abnormal respiratory symptoms until ≥ 28 -30 days of age, chest radiographic (CXR) findings including heterogeneous aeration, and (when available) evidence of pathology throughout the airway and lungs on postmortem examination (Northway et al., 1967). Among the 32 infants in the first observational cohort the mean gestational age was ≥ 32 weeks' gestation. For those diagnosed with BPD in this cohort, the mortality rate was significant as 19 of the 32 infants did not survive (Northway et al., 1967).

There were significant improvements in the care of preterm infants since 1967. The improvements that had major impacts on the pulmonary health for preterm infants included antenatal steroids, postnatal surfactant administration, and gentle ventilation techniques. These will be discussed further in this paragraph. In the 1970's, administration of antenatal steroids to mothers experiencing preterm labor was examined as it was hypothesized to reduce the incidence of RDS by releasing endogenous surfactant facilitating lung maturity, (Liggins & Howie, 1972). During the trial in 1972 (Liggins & Howie, 1972), infants whose mothers received antenatal steroids had significantly less RDS than those in the control group. Since the 1970's, antenatal steroid administration for mothers in preterm labor is standard of care. Surfactant, a lipoprotein, increases in production in the final trimester of pregnancy and works to reduce pulmonary surface tension allowing for improved gas exchange. Typically, present in adequate amounts in full term infants, surfactant is deficient in preterm infants. This deficiency increases the risk for RDS (Halliday, 2008). Exogenous surfactant (see Table 2) trials during the mid-to-late 1980's demonstrated evidence that administration of surfactant during the first hours to days of life decreased the incidence of RDS and improved the survivability of preterm infants. The United States Food & Drug Administration (FDA) approved the use of exogenous surfactant for the treatment of RDS in 1990 (NORD, 2004). Following approval of surfactant, gentle ventilation techniques became routine, leading to less pressure-induced lung damage (Ehrenkranz et al., 2005; Jobe & Bancalari, 2001). Yet, despite these interventions and improvements in the care of premature infants the incidence of BPD did not decrease. While more infants survived

at younger gestational ages, improved survival led to a new, more complex form of BPD termed "new BPD" (Abman et al., 2017).

The initial hallmark of BPD was heterogeneous lung expansion, demonstrated on CXR and consistent with surfactant deficiency (Northway et al., 1967). Findings associated with the "new BPD" are more complicated and hallmarked by arrested lung development (Jobe & Bancalari, 2001). To account for the changing population of preterm infants and the evolving pathology of BPD, the diagnostic criteria created in 1967 and edited minimally through the subsequent years needed to be adapted. The accepted criteria for grading BPD, still used today, was decided upon at a workshop attended by the members of the National Institute of Child Health and Human Development (NICHD), the National Heart, Lung, and Blood Institute (NHLBI), and the Office of Rare Diseases (ORD) in 2000. These governing institutes/offices determined time points and respiratory support requirements demarcating diagnostic criteria for the grading of BPD (see Table 1). The diagnosis of BPD is made at 36 weeks' postmenstrual age ([PMA] see Table 2) and is based on the need for oxygen delivered by a nasal cannula, non-invasive ventilation, or invasive ventilation at 28 days, as originally proposed by Shennan, Dunn, Ohlsson, Lennox, & Hoskins (1988). The new criteria proposed in 2000 added grading (i.e., mild, moderate, and severe BPD [see Table 1]) (Jobe & Bancalari, 2001) to account for the differing severity in BPD presentation and symptoms. The risks, costs, and outcomes for infants becomes more complicated as BPD severity increases.

These new diagnostic criteria were validated in a research study examining the outcomes of 4866 infants born at < 32 weeks' gestation. When this cohort of preterm

infants was assessed between 18-22 months in follow-up clinics, the new BPD criteria was shown to be effective at identifying infants with abnormal pulmonary symptoms at 28 days and 36 weeks' PMA. Further, this criterion was effective at identifying those infants with a higher risk for pulmonary and neurodevelopmental sequelae up to their 18-22-month assessment in follow up clinic (Ehrenkranz et al., 2005).

There are recognized risk factors that are related to the development of BPD, especially severe forms of BPD. The most significant risk factor is preterm birth in that there is an inverse relationship between gestational age at birth and the incidence of BPD. Strong associations for the development of BPD include male sex and duration of mechanical ventilation (Abman et al., 2017). Additionally, certain postnatal conditions are associated with an increased risk of developing BPD (i.e., patent ductus arteriosus, sepsis, and necrotizing enterocolitis requiring surgery) [see Table 2] (Abman et al., 2017). Other proposed risks, some controversial, include race/ethnicity and chorioamnionitis, an intrauterine inflammatory and infectious process. Laughon et al. (2011) developed a tool to evaluate the risk of BPD development among preterm infants. This tool employs some of the risks found in the literature. However, with continual evolution of the preterm infant population, reevaluation of risk must be conducted.

Infants born at < 32 weeks' gestation represent only 1.6% of the total births in the United States (Martin, Hamilton, Osterman, Driscoll, & Matthews, 2017). BPD is a rare disease compared to other childhood illnesses but is one of the most common morbidities among infants born at < 32 weeks' gestation (Abman et al., 2017). The clinical course of infants with BPD is complicated by multiple comorbidities. These morbidities include neurodevelopmental impairment, extrauterine growth restriction (EUGR), pulmonary

hypertension, gastroesophageal reflux, feeding issues, retinopathy of prematurity, and systemic hypertension (Abman et al., 2017; Glass et al., 2015; Gou, Yang, & Xiao, 2018) (see Table 2). These complications become worse as BPD severity increases. As a result of the morbidities this multisystem disease is considered a significant challenge for healthcare providers as well as the families.

Despite identification of BPD more than 50 years ago as well as multiple iterations of the diagnostic criteria, there has been no improvement in the incidence, morbidity, or mortality rates since the adoption of the criteria in 2001 (Abman et al., 2017). There are several grades of BPD, each with associated prevalence in the population of infants born at < 32 weeks' gestation: no BPD (23.1%), mild BPD (30.3%), moderate BPD (30.2%), and severe BPD (16.4%) (Ehrenkranz et al., 2005). Despite reduction efforts, the incidence and severity of BPD has not changed since 2005 (Abman et al., 2017). One conservative estimate is that 2,000 infants and children require home ventilation in the United States due to BPD (Abman et al., 2017). Mortality related to BPD is similarly not well understood, as cause of death for those infants could also be attributed to prematurity, respiratory failure, and comorbidities such as pulmonary hypertension.

The economic impact of BPD is unknown but is considered one of the most expensive morbidities of prematurity (Johnson, Patel, Jegier, Engstrom, & Meier, 2013; Lapcharoensap, Lee, Nyberg, & Dukhovny, 2018). Another significant barrier to cost estimates is that most reports only evaluate the cost of neonatal intensive care hospitalization. BPD, especially more severe forms of BPD, has many additional costs beyond the NICU such as the cost of specialty services, tracheostomy placement, in-

patient rehabilitation, home care, durable medical equipment, home medication, outpatient providers, and rehospitalization (Abman et al., 2017). These costs incurred post NICU hospitalization are not included in economic estimates. Further, chronic morbidities such as neurodevelopmental impairment increases lifetime healthcare costs but is not included (Abman et al., 2017; Lapcharoensap et al., 2018).

One estimate for the cost of BPD is an additional average cost of $31,565 above the costs incurred during neonatal intensive hospitalization. This cost increased as birth weight decreased (cost ranging $19,970 for larger preterm infants to $43,312 for smaller infants; Johnson et al., 2013). A more encompassing estimation of costs included care during NICU hospitalization and associated morbidities, cumulating to a median cost of $102,000 for infants with BPD (Lapcharoensap et al., 2018). In contrast, the cost of hospitalization for uncomplicated full-term newborns is $500, and $36,800 for an uncomplicated infant born at < 28 weeks' gestation (Lapcharoensap et al., 2018). These cost estimates do not account for lost productivity or wages of either caregivers or those with BPD. Reports on the societal impact for BPD are sparce, but significant. From a psychologic perspective, mothers of infants with BPD are more likely to have significant postpartum depression than those without BPD (Brady, Zhang, Kirpalani, & DeMauro, 2019; Moura et al., 2017). BPD is a diagnosis that poses great challenges to the patients and their families from a psychological and economic perspective.

The care for preterm infants has changed significantly and so have the limits of viability, thus younger preterm infants are surviving. BPD is no longer a sequalae of surfactant deficiency. The "new BPD" is characterized by an arrest in lung development, simplified alveoli, and reduced pulmonary microvasculature (Abman et al., 2017).

Societal and economic impact is significant with BPD, especially as the severity of BPD increases (Abman et al., 2017; Johnson, Patel, Jegier, Engstrom, & Meier, 2013; Lapcharoensap, Lee, Nyberg, & Dukhovny, 2018). While BPD is a rare outcome considering all other childhood illnesses, it has significant health, economic, and societal costs. The purpose of this study is to examine the risk factors for BPD as identified in the developed mid-range theory. The variables in this mid-range theory can be used to identify infants at risk for BPD. Further, understanding the stressors and identifying infants at risk may lead to risk reduction and treatment strategies that can be targeted to prevent BPD.

CHAPTER II

LITERATURE REVIEW

Impact of BPD on Families and Society

Less than two percent of infants in the United States are born at < 32 weeks' gestation (Martin et al., 2017). While BPD is a rare disease among all children, it is a common diagnosis for infants born at < 32 weeks (Abman et al., 2017). Of infants born at < 32 weeks' gestation 76.9% are diagnosed with BPD (Ehrenkranz et al., 2005).

A diagnosis of BPD increases the cost of neonatal intensive care hospitalization by an average of $31,565, for each infant. When NICU hospitalization and associated morbidities were combined, the median hospital costs for infants with BPD were $102,000 (Lapcharoensap et al., 2018). Lost productivity and wages for caregivers are not included in these estimates. There are also scant although important reports on the societal impact of BPD. From a psychologic perspective, mothers of infants with BPD are more likely to have higher rates of postpartum depression and poorer perceived quality of life than mothers whose infants do not have BPD (Brady, Zhang, Kirpalani, & DeMauro, 2019; Moura et al., 2017).

Historical/Sociological/Political/Economic aspects

Kingdon (2011) described the convergence of three streams (problem, politics, and policy) as the means to address a political agenda. Prior to the 1960's the morbidity and mortality of preterm infants was staggering. Health care professionals and researchers were working to improve the survivability of preterm infants. Advancing the care of preterm infants became a national priority with the death of President John F. Kennedy's son who died as a result of his premature birth in 1963 (Altman, 2013). Patrick Kennedy was born prematurely at almost 35 weeks' gestation and suffered from RDS. RDS is caused by a lack of surfactant in the lungs, which leads to reduced pulmonary surface tension and causes significant difficulty with ventilation and oxygenation (Altman, 2013; Halliday, 2008). In 1963 only supportive care could be offered for RDS. Unfortunately, he died at two days-of-life.

After Patrick's death the political climate was right to advance the political and research agenda to improve the care for preterm infants, by increasing National Institutes of Health funding (Halliday, 2008). One of the most important advances was the administration of exogenous surfactant to treat RDS (Halliday, 2008). Clinical trials were conducted in the 1980s and surfactant was approved by the FDA in 1990 for the treatment of RDS (NORD, 2004). Administering surfactant to preterm infants is now standard of care. Were Patrick Kennedy to have been born today, administration of exogenous surfactant would have near guaranteed his survival. The political climate of the early 1960's was an ideal environment for this convergence to change the policies and practices involved in the care of preterm infants. Legislators and healthcare personnel

were motivated by prematurity and cognitive impairment (problems), which led to political action and ultimately a change in health care policy.

Conceptual Framework

The conceptual model guiding this dissertation is the Neuman Systems Model (NSM) (2011), a holistic systems approach. The aim of NSM is to reduce stress factors and adverse conditions which either affect or could affect optimal functioning in a client population (Fawcett & Neuman, 2011). The stressors that affect a given client population can be viewed as extrapersonal (occurring outside the individual), interpersonal (occurring between one or more individuals), and intrapersonal (occurring within the individual) (Fawcett & Neuman, 2011). The goal of the individual is to achieve homeostasis to adequately cope with the stressors and/or regain their optimal state of health following a reaction to a stressor. In regard to the development of BPD, many stressors have been identified in the literature.

A systematic review of the literature was conducted to identify the most influential risk factors that leads to the development of BPD. Employing the NSM, these factors were categorized by extrapersonal, interpersonal, and intrapersonal stressors. Extrapersonal stressors are represented by maternal race/ethnicity and genetics, including the sex of the neonate. In the literature the role of maternal race/ethnicity in BPD development was conflicting and found to be both a risk for BPD and a protective factor against BPD development (Janevic et al., 2018; Lapcharoensap et al., 2015). The interpersonal stressors represented prenatal risks of inflammation, infection, and maternal vascular underperfusion (e.g., chorioamnionitis). Finally, intrapersonal stressors are

represented by risk within the premature infant that requires intervention(s) and care in the NICU (e.g., surfactant administration).

Chronic exposure to racism experienced by Black Americans is also known as an allostatic load (Alhusen, Bower, Epstein, & Sharps, 2016; Bediako, BeLue, & Hillemeier, 2015; Scott, Britton, & McLemore, 2019). This allostatic load can manifest as physiologic alterations. Racism and allostatic load affect each of the stressors in the NSM. This research will test a mid-range theory developed from the systematic review focusing on the extrapersonal, interpersonal, and intrapersonal stressors contributing to the development of BPD among infants born at < 32 weeks' gestational age. The review of studies that focused on risk factors in the development of BPD showed an interrelationship between the three stressors of the NSM (see Figure 1).

The confluence of extrapersonal and interpersonal risks can culminate into premature delivery, leading to a decrease in the number of alveoli, and reduction in pulmonary microvascular development (Abman et al., 2017). Preterm birth introduces postnatal risks, thus continuing lung development arrest, and solidifying the pathway to BPD. While intrapersonal risks do not initiate the process of alveolar simplification or pulmonary microvascular development reduction, they continue the pathogenesis towards the development of BPD through premature delivery of the infant. Inflammation, infection, poor growth, and associated adverse events all contribute to the compounded risk for BPD (Abman et al., 2017).

Infants that have insults or risks in each of the stressors in this midrange theory are hypothesized to be at highest risk for BPD development when compared to preterm infants of the same age without similar risks. Following testing of this midrange theory,

it may be used to identify infants at risk and lead to risk reduction and treatment strategies that can be targeted towards these high-risk infants to prevent BPD. The following discussion describes in more detail all the stressors within the mid-range theory that are predicted to increase the likelihood of the pathogenesis of BPD. The NSM will be employed to describe and organize the stressors.

The normal line of defense represents the usual health state of the client system (i.e. patient) (Fawcett & Neuman, 2011). Testing this mid-range theory of BPD risk could lead to the development of interventions that could act as the flexible line of defense to decrease the risk of BPD. Infants with BPD have health ramifications that worsen as BPD severity increases. Some ramifications of more severe BPD include pulmonary hypertension, poor growth, and neurodevelopmental impairment (Abman et al., 2017). Therefore, grading is used to indicate the presence and types of BPD.

Extrapersonal Stressors

Extrapersonal stressors in the NSM are distal to the client (Fawcett & Neuman, 2011). In the mid-range theory, these stressors are represented by preconception factors and include genetic/epigenetic factors including sex of fetus, maternal sociodemographic factors, and allostatic load.

Sex

Male sex has been associated with BPD since its first identification (Northway et al., 1967). Data demonstrates diminished biosynthesis of androgen, a higher density of androgen receptors, a decreased metabolism of androgen, and decreased degradation of estrogen among male infants that developed BPD (Lal et al., 2018a). Furthermore, the male fetus has a delayed surfactant production secondary to these sex/hormonal based

differences, leading to increased resistance in the alveoli and control in the budding of the bronchioles during early fetal development (Shim, Cho, Kong, & Park, 2017). This knowledge provides insight into a sex-based hormonal mechanism increasing the risk for BPD among male infants.

Genetic/Epigenetic Risks

Genome-wide association studies (GWAS) and deoxyribonucleic acid (DNA) analysis have been used to identify genetic markers and/or variants that are associated with BPD (Ambalavanan et al., 2015). To date there have been no conclusive gene(s) identified that are associated with BPD. Further, genetic/epigenetic risk evaluations are not consistently performed for all infants with BPD. Due to lack of standardization in the incorporation of genetic/epigenetic evaluation in the routine care for infants with BPD, genetic/epigenetic variables were not measured in this study and will not be further discussed.

Race/Ethnicity and Preterm Birth

Preterm birth is the most significant risk factor for BPD. While the overall incidence of preterm birth in the United States (U.S.) is 10%, the incidence of preterm birth is 13% for Black Americans as compared to 9% for White Americans (CDC, 2016). The etiology of this significant health disparity may be due to a complex interaction of: 1) racism and allostatic load and 2) maternal access/utilization/quality of health care concerns (Alhusen, Bower, Epstein, & Sharps, 2016; Bediako, BeLue, & Hillemeier, 2015; Scott, Britton, & McLemore, 2019). Given the complexity of these issues each will be discussed separately.

Racism and Allostatic Load. Racism is defined as "unequal treatment stemming from skin color or other individual characteristics" (Alhusen et al., 2016, p. 2). Allostatic load is the effect(s) of chronic exposure to racism and the associated physiologic alterations, including impaired immune function and increased inflammation (Giurgescu et al., 2016; Olson et al., 2015). Biomarkers of allostatic load include cortisol, cytokines, interleukin-6, and C-reactive protein; each of these are inflammatory mediators (Olson et al., 2015). Among pregnant women, allostatic load is evidenced by an increase in preterm birth, pre-eclampsia, fetal growth restriction, inflammatory disease, and more (Alhusen et al., 2016; Giurgescu et al., 2016; Olson et al., 2015). Allostatic load has the capacity to perpetuate the significant health disparity experienced by Black Americans in immediate and subsequent generations through alterations in the inflammatory cascade (Olson et al., 2015).

Prematurity is the most consistent risk factor for BPD. The incidence of prematurity is higher among Black infants (CDC, 2016). However, the association of race/ethnicity and risk for BPD is inconsistent in the literature; there is literature supporting the role of race/ethnicity in BPD development as protective in Black neonates (Lapcharoensap et al., 2015), as well as a potential risk for BPD development (Janevic et al., 2018). The association between race/ethnicity, and BPD is complex and deserves further exploration.

Access/Utilization/Quality of Health Care. Access to health care is a complex process that ideally begins with preconception care. This is in relationship to the fetus' environment during pregnancy. While approximately 50% of births and care up to 60 days following birth are covered by public insurance in the United States, comprehensive

preconception care is not available to all pregnant women (Scott, Britton, & McLemore, 2019). Black women are more likely to be uninsured, thus are least likely to have access to preconception care. This makes them more likely to have ineffective management of any health conditions, should they arise, either during the pre-pregnancy or during pregnancy (Scott et al., 2019). Also, a result of their lack of insurance and access to healthcare they may be more likely to have under or undiagnosed chronic conditions for which they will not have received health education and/or treatment.

The relationship between early prenatal care and improved obstetric and neonatal outcomes, including reduction of preterm birth, have been well established (Daniels, Noe, & Mayberry, 2006). However, many barriers still exist to receiving prenatal care including lack of: 1) health insurance, 2) availability of providers, 3) time availability for the mothers to attend lengthy appointments, 4) transportation to the appointments, and 5) availability for the long wait times in clinics. These factors have all been reported as barriers to prenatal care especially for Black women (Scott et al., 2019; McLemore et al, 2018). Twenty-two percent of Black mothers enter prenatal care late, whereas 15% of White mothers have late entry (Bediako et al., 2015; Edmonds, Mogul, & Sheen, 2015; U.S. Department of Health and Human Services, 2013).

Once able to access prenatal care, the four other factors that decrease prenatal care, the availability of providers, transportation to prenatal care appointments, length of wait times, and insurance status, continue to impact prenatal care. Black mothers cited many barriers to accessing and maintaining prenatal care including; 1) insurance status; 2) understanding the Medicaid enrollment and eligibility; 3) lack of social support to attend prenatal care appointments; 4) transportation to appointments; 5) long wait times

in clinics; 6) ambivalence to pregnancy; 7) and having an unwanted pregnancy without access to providers to discuss health care options (Daniels, 2006; Edmonds et al., 2015).

Issues within the provider and women relationship continue to impact prenatal care for Black mothers. These issues include the lack of personal connection to their provider, lack of continuity of care with providers, and disrespectful actions by health care personnel. For example, Black mothers with public insurance perceived that clinic staff were less responsive and respectful of them as compared to mothers with private insurance (Salm, Mazul, Ngui, Bridgewater, & Harley, 2013). Public insurance was perceived as a barrier to quality health care by impacting mothers' options for hospitals and choice of providers (Salm et al., 2013; Scott et al., 2019). Women who had public insurance reported they felt they were viewed as less important by their providers and subsequently these impressions by providers was shown to lead to substandard care (Salm et al., 2013; Scott et al., 2019). Also, another research study found that Black and Hispanic mothers were more likely to give birth at poorer performing hospitals. Infants born at these poorer performing hospitals had higher morbidity and mortality rates as compared to infants born at higher performing hospitals (Howell et al., 2018).

Less access to health care does not only impact the number of appointments that Black mothers attend but also the prenatal education they receive due to a decrease in provider encounters. Many behavioral factors have been well established as causing an elevated risk for preterm birth especially in Black women. These behavioral factors include diabetes (Cabacungan, Ngui, & McGinley, 2012; Scott et al., 2019), hypertension (Cabacungan et al., 2012; Scott et al., 2019), sexually transmitted infections (STIs) (Cabacungan et al., 2012) pre-pregnancy obesity (Bediako et al., 2015), smoking

(Bediako et al., 2015), and inappropriate weight gain during pregnancy (Cabacungan et al., 2012). These conditions are impacted by the number of prenatal appointments and amount of education received. Access, utilization, and quality of health care are important contributing factors in preterm birth and potentially BPD development. However, these details are not available in the database that will be used for this research and they are not available in the Boston Children's Hospital medical records. Therefore, these data were not included in this research.

Interpersonal Stressors

Interpersonal stressors occur outside but proximal to the client (Fawcett & Neuman, 2011). Interpersonal stressors in this study's mid-range theory include prenatal inflammation, prenatal infection, and maternal vascular underperfusion.

Prenatal Inflammation

A systematic review of the literature identified several inflammatory biomarkers markers associated with the development of BPD. KL-6 is a high molecular weight mucinous glycoprotein expressed by alveolar type II cells and bronchiolar epithelial cells and is elevated in the setting of damage to the pulmonary epithelium and interstitium (Kim et al., 2008; Ogihara et al., 2006). Interleukin-8 (IL-8) is another inflammatory biomarker identified from the systematic review. IL-8 is a glycoprotein that regulates the innate immune response, the adaptive immune response, and the growth/differentiation of hematopoietic cells (Rocha et al., 2012). Biomarkers for fetal inflammation have been associated with chorioamnionitis, a bacterial infection of the fetal membranes that also leads to inflammatory changes present in the mother and the fetus. Biomarkers are not

routinely collected in the NICU, so they are not routinely reported in the database or the Boston Children's medical record and will not be a focus of this research.

Clinical methods to detect histologic chorioamnionitis were consistently performed according to the method outlined by Redline (2006), where a pathologic evaluation is completed to diagnose both maternal and fetal acute and chronic inflammation (Mestan et al., 2014). More specifically, for acute maternal inflammation, a neutrophil infiltration of the chorion, amnion, and at its most severe, necrotizing chorioamnionitis is evident (Redline, 2006). Chronic inflammation involves neutrophilic infiltration of the chorionic villi, intervillious space, and/or basal plate; this demonstrates inflammation with placental involvement (Redline, 2006). These biomarkers associated with chorioamnionitis are associated with damage to the lungs, immune system, and even growth/differentiation of hematopoietic cells (Kim et al., 2008; Ogihara et al., 2006; Rocha et al., 2012).

Prenatal Infection

Infection initiates an inflammatory process. Like antenatal inflammation, antenatal infection is a risk for BPD because of the resulting changes in lung surfactant composition, potentiation of the alveolar and vascular simplification, and contribution to the imbalance between pro and anti-angiogenesis (Thekkeveedu, Guaman, & Shivanna, 2017). Biomarkers for infection were represented by positive bacterial culture results and were associated with IL-8 (like inflammation). One bacterial organism associated with BPD is ureaplasma (Inatomi et al., 2012). In the literature, antenatal infection is clinically represented by chorioamnionitis. Histologic chorioamnionitis was described above. Clinical chorioamnionitis (CC) is diagnosed by one of two methods, either by

placental pathology or by maternal clinical signs and symptoms indicative of chorioamnionitis (American College of Obstetricians and Gynecologists, 2017; Arayici et al., 2014; Ballard et al., 2016; Kibel et al., 2016; Lee et al., 2011; Mestan et al., 2014; Redline, 2006; Solimon et al., 2017). Both diagnostic methods necessitate presence of a maternal fever (Arayici et al., 2014; Ballard et al., 2016; Kibel et al., 2016; Lee et al., 2011; Solimon et al., 2017). Depending on the source, either one or more of the following signs must be present for CC to be diagnosed: maternal tachycardia, fetal tachycardia, uterine tenderness, malodorous amniotic fluid, leukocytosis, and/or elevated C-reactive protein. The criteria from the American College of Obstetricians and Gynecologists (ACOG) uses the more conservative approach when diagnosing CC; maternal fever and at least one other clinical sign (Ballard et al., 2016; ACOG, 2017). Criteria for diagnosing histologic chorioamnionitis (HC) is based on a pathological exam of the placenta. When diagnosing HC there must be infiltration of neutrophils into the amniotic membranes, the umbilical cord, or the chorionic plate (Arayici et al., 2014; Durrmeyer et al., 2012; Lee et al., 2011; Redline, 2006; Solimon et al., 2017; Yum et al., 2018). HC and CC are diagnoses consistent with infection. HC and/or CC is acceptable to use to diagnose chorioamnionitis in clinical practice.

Maternal Vascular Underperfusion

Maternal vascular underperfusion (MVU) is defined by pathological changes to the placenta that can cause fetal growth restriction and increase risk for BPD and BPD associated pulmonary hypertension (Mestan et al., 2014; Mestan et al., 2017). The mechanism for BPD development among preterm infants whose mothers had hypertensive disorders is thought to be related to an imbalance of pro- and anti-

angiogenic factors. This disparity in angiogenic factors is believed to cause abnormal or insufficient vascular and alveolar pulmonary development (Dravet-Gounot et al., 2018).

There are many biomarkers associated with MVU identified from a systematic review of literature. Some of the biomarkers were the same as ones associated with inflammation and infection, such as KL-6 and cytokines. Other factors were unique to MVU were either pro or antiangiogenic (i.e., endothelin-1, fibroblast growth factor-10, and tumor necrosis factor) (Baumann et al., 2015; Janer, Andersson, Haglud, Karikoski, & Lassus, 2008; Kim & Kim, 2014; Kim et al., 2008; Kim, Shin, Kim, & Kim, 2018; Mohamed et al., 2014; Ogihara et al., 2006; Rocha et al., 2012.

MVU can be diagnosed clinically and/or pathologically. Clinically, MVU presents as maternal hypertensive disorders such as gestational hypertension, preeclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), and/or eclampsia [see Table 2] (ACOG, 2002; Solimon et al., 2017; Torchin et al., 2016). The criteria for diagnosing maternal hypertensive disorders was consistent across the literature and are the basis of the ACOG guidelines (ACOG, 2002). Criteria for pathologic evaluation of MVU was also consistent across all the studies specifically, vasculopathy of the parietal and basal decidua. MVU is graded as either mild or severe, depending on the number of lesions visualized (Redline et al., 2004). Maternal hypertensive disorders (chronic hypertension, gestational hypertension, preeclampsia, HELLP syndrome) are the empiric indicator for MVU in this research.

Fetal growth is associated with BPD thus birth weight is a critical measure to assess as it may be indicative of poor fetal growth (Charles et al., 2019). Further, fetal growth restriction (FGR) is associated with maternal vascular underperfusion, which is a

risk factor for BPD development. Infants with FGR experience a higher incidence and severity of BPD. FGR, small for gestational age, and intrauterine growth restriction are all synonymous in the literature and are defined as growth <10th percentile based on fetal growth curves (El Ayoubi et al., 2016; Nyp et al., 2015; Ozkan et al., 2012; Tsai et al., 2015). FGR will be used as the empiric indicator for this research.

Intrapersonal Stressors

These stressors are measured and/or occur postnatally within the premature infant. Infant characteristics include gestational age, birth weight, inflammation, infection, patent ductus arteriosus, and EUGR requiring interventions delivered in the NICU. These NICU interventions include doses of surfactant, number of transfusions of packed red blood cells, duration of mechanical ventilation.

Infant Characteristics

Infant characteristics associated with BPD include demographics such as gestational age and birth weight, postnatal inflammation and infection, patent ductus arteriosus, and EUGR.

Gestational Age. A hallmark of BPD is an arrest of lung development; the earlier the arrest, the less lung development has occurred at the time of birth. Further, the earlier the gestational age at birth, the earlier the exposure to oxygen and mechanical ventilation (Abman et al., 2017). This exposure to oxygen and mechanical ventilation injures vulnerable, underdeveloped lungs. Gestational age, measured in completed weeks of gestation, is inversely related to the incidence and severity of BPD and is multifactorial (Abman et al., 2017). This relationship is multifactorial.

The initial determination of gestational age commonly employed when confirming pregnancy, is based using either the date of the last menstrual period (LMP) and/or the estimate from a first trimester ultrasound (Binet et al., 2012; Dravet-Gounot et al., 2018; Mestan et al., 2014; Torchin et al., 2016; Tsai et al., 2015). The Ballard exam is a a systematic physical examination to assess preterm infants' gestational age. It was expanded in 1991 to include the assessment of gestational ages 20-44 weeks' (Ballard et al., 1991; Ozkan et al., 2012). This exam is most accurate when conducted in the first 96 hours of life and when compared with prenatal ultrasound, the New Ballard Score had a correlation of 0.97 and inter-rater reliability of 0.95 (Ballard et al., 1991). While the New Ballard is accurate, one limitation is that training is necessary to reliably complete the exam. Additionally, the results of the Ballard exam can be affected by issues such as sedating medications used during labor, sepsis, and neuromuscular disorders (Ballard et al., 1991). Clinically, the Ballard exam is useful to estimate gestational age when it is unknown, otherwise gestational age is most reliable when based on either LMP or ultrasound.

Birth Weight. According to the literature, infants born at lower birth weight have a higher risk for developing BPD. Further, infants with the lowest birth weights not only have a higher risk for BPD, but of also developing more severe forms of BPD (Dravet-Guonot et al., 2018; Guo et al., 2015). This relationship between BPD and lower birth weight is in part due to the association between low birth weight and maternal vascular underperfusion, and the relationship with an imbalance between pro and anti-angiogenic factors (Dravet-Guonot et al., 2018).

Fetal growth is a comprehensive and objective assessment of intrauterine growth. Fetal growth is estimated during pregnancy, and then finalized with birth weight. Poor fetal growth and low birth weight have many associated morbidities, including BPD (El Ayoubi et al., 2016; Nyp et al., 2015; Ozkan et al., 2012; Tsai et al., 2015). Infants with fetal growth restriction (FGR) experience a higher incidence and severity of BPD. FGR, small for gestational age (SGA), and intrauterine growth restriction (IUGR) are all defined as growth <10th percentile based on fetal growth curves. The Fenton Growth Chart (Fenton & Kim, 2013) is the most inclusive growth chart for preterm infants. Data for the Fenton Growth curve was formulated through a systematic review and meta-analysis from six developed countries among infants aged 22-36 weeks' gestation. Unique to this growth curve was synchronization with the World Health Organization (WHO) Growth Standard, which extended the growth chart through 50 weeks PMA. The WHO Growth Standard is an international standard for measuring the growth of full term, breastfed infants, living in countries with adequate nutrition, and it is the standard for growth assessment in the United States (The Centers for Disease Control and Prevention [CDC], 2010). Syncing the intrauterine growth curves with the WHO growth standard allows healthcare professionals to continue to monitor the growth of preterm infants based on the growth of full-term infants with optimal nutrition (CDC, 2010). Based on these details, the Fenton Growth Curve is the most comprehensive tool of growth measurement. Infants with a birth weight of <10th percentile, per the Fenton Growth Chart, will be considered to have FGR for this research.

Postnatal Inflammation. The systematic review of the literature identified many biomarkers associated with inflammation due to oxygen, oxidative stress, and exposure to

mechanical ventilation. For example, leukotriene E4 (LTE-4) is an inflammatory marker related to damage to the cell membrane in asthma (Joung et al., 2011), and oxidative stress was measured using 8-hydroxydeoxyguanosine (8-OHdG) (Joung et al., 2011). However, the most common reported biomarker was brain natriuretic peptide (BNP) or the inactive form of BNP, N-terminal-pro-BNP. BNP and N-terminal-pro-BNP measure the same physiologic process: measurement of ventricular stretch. Both BNP and N-terminal-pro-BNP are elevated in both BPD and BPD associated pulmonary hypertension due to hypoxia and chronic hypoxia and both are experienced by infants with BPD (Cuna et al., 2013; Cuna et al., 2014; Harris et al., 2018; Inoue et al., 2013; Kalra et al., 2014; Konig et al., 2016; Montgomery et al., 2016; & Rodriguez-Blanco et al., 2018). Finally, the association of inflammation, infection, and angiogenic factors was valuable to quantify. Neutrophil gelatinase-associated lipocalin (NGAL) was used to quantify the intersection of infection, inflammation, and angiogenic factors in sBPD development and found to be elevated in BPD (Capoluongo et al., 2008; Joung et al., 2011; Reicherzer et al., 2018; & Sarafidis et al., 2008).

Given the evidence of an association with inflammation and BPD, postnatal exposure to sources that could lead to inflammation were identified. The postnatal exposure(s) leading to inflammation originate from several sources including exposure to oxygen, need for mechanical ventilation (Inatomi et al., 2012; Klevebro et al., 2019; Mailaparambil et al., 2010; Oh et al., 2005; Ohlin et al., 2015; Rutkowska et al., 2019; Yum et al., 2018), and diagnosis of necrotizing enterocolitis (NEC), an inflammatory bowel infection [see Table 2] (Cuna et al., 2013; Cuna et al., 2014; Harris et al., 2018;

Inoue et al., 2013; Kalra et al., 2014; Konig et al., 2016; Montgomery et al., 2016; & Rodriguez-Blanco et al., 2018).

Premature lungs often lack the ability to adequately exchange gasses efficiently due to immature alveoli and lack of energy required to breathe. Therefore, mechanical ventilation is often required to assist premature infants with their work of breathing and gas exchange. However, there are side effects to mechanical ventilation including pressure and volume related trauma and oxygen toxicity. Each of these exposures incur a risk of inflammation (Abman et al., 2017; Laughon et al., 2011). When this inflammatory process is initiated there is disruption to alveolarization and vasculogenesis, which further interrupts adequate pulmonary growth (Mailaparambil et al., 2010). Oxygen exposure frequently changes during each day for a preterm infant in the NICU. Therefore, mechanical ventilation duration (total, non-invasive, and invasive) was the empirical indicator for this variable.

NEC was defined using Bell's Staging, the standardized assessment (Bell et al., 1978). NEC stage 2 includes: 1) perinatal stress, 2) signs of sepsis and gross gastrointestinal bleeding or abdominal distention, 3) abdominal radiograph demonstrating ileus, unchanging bowel loops, pneumatosis, and/or portal venous gas. Bell's Stage 3 included all criteria from stage 2 and: 1) signs of septic shock or marked gastrointestinal hemorrhage, and 2) evidence of pneumoperitoneum on radiograph (Bell et al., 1978). When measuring NEC as a variable, the studies only included patients with NEC ≥ stage 2 [see Table 2] (Bell et al., 1978). The empirical indicator for NEC was ≥ stage 2 (Bell et al., 1978). Mechanical ventilation duration (total, non-invasive, and invasive) and a

diagnosis of NEC ≥ Bell's stage 2 were the empirical indicators for postnatal inflammation.

Postnatal Infection. Methods that were used to measure infection consistently employed the results of bacterial cultures obtained from sites of the neonate that should be sterile (i.e., blood, spinal fluid, tracheal aspirates, and urine). A positive culture in any of these sites was considered evidence of an infection (Ballard et al., 2016; Dravet-Gounot et al., 2018; Durrmeyer et al., 2012; Guo et al., 2015; Klevebro et al., 2019; Lee et al., 2011; Ohlin et al., 2015; Solimon et al., 2017; Torchin et al., 2016). Clinical sepsis, where culture results were negative, but the patient demonstrated signs of an infection, is also a risk factor for sBPD (Hofer et al., 2013; Ohlin et al., 2015). Measurement of clinical sepsis was consistent between studies and included negative bacterial cultures. Infants were assessed as having an infection when they demonstrated three or more of the following clinical signs: respiratory compromise, cardiocirculatory compromise, neurological compromise, poor physical color, prolonged capillary refill time, and either hypothermia or hyperthermia. Yet another method of measuring inflammation in the preterm neonate was with the diagnosis of NEC ≥ stage 2 (Bell et al., 1978). When measuring NEC as a variable, the reviewed studies only included patients with NEC ≥ stage 2. For this study, there were two empiric indicators for postnatal infection: NEC ≥ Bell's stage 2 and/or positive blood, urine, spinal fluid, or tracheal aspirate cultures.

Patent Ductus Arteriosus (PDA). PDA is a normal prenatal shunt that allows blood flow to bypass the fetal lungs (United States National Library of Medicine, 2020). In full term infants the PDA typically closes by 72 hours of life, but closure of the PDA is delayed among preterm infants. Time to PDA closure is inversely related to gestational

age; the delay is significantly longer among very preterm infants. Therefore, a PDA is not considered an unexpected structural heart defect in preterm infants.

PDA closure requiring treatment is also more common among preterm infants (Benitz, 2016). In the systematic review of the literature, diagnosis of a PDA was associated with developing BPD (Dravet-Gounot et al., 2018; Demirel et al., 2009; Guo et al., 2015; Rutkowska et al., 2019; Torchin et al., 2016). Further, a PDA that required surgical closure was also associated with developing BPD (Durrmeyer et al., 2012; Mailaparambilel et al., 2010). PDA increases pulmonary pressure and the amount of fluid in the interstitium, which leads to pulmonary edema. This frequently leads to prolonged respiratory support or increased respiratory support needs. However, none of these identified risks play a causative role of BPD development. Instead they may be markers for severity of the infant's condition and the injury induced due to pulmonary edema (Clyman, 2013). PDA data was first classified as either present or not present (diagnosed by echocardiography). If an infant was diagnosed with a PDA, they would be further classified as either requiring no treatment or needing treatment to facilitate closure. Treatment for a PDA was either medical treatment and/or surgical treatment.

Extrauterine Growth Restriction. EUGR is consistently diagnosed by assessing growth at $< 10^{th}$ percentile for age according to the growth curve utilized (Ohlin et al., 2015). The association between EUGR and the development of BPD is related to higher energy demands and insufficient intake, leading to poor lung healing and growth (Klevebro et al., 2019).

The Fenton Growth Chart is a more comprehensive growth chart because: 1) thedata was derived from a systematic review and meta-analysis; 2) the data was

collected from six developed countries; 3) the data was examined on infants from 22 weeks' until 36 weeks' gestation; and 4) is synchronized with the WHO Growth Standard (Charles et al., 2019; Dravet-Gounot et al., 2018; Klevebro et al., 2019; Nyp et al., 2015; Fenton & Kim, 2013). The benefit of syncing with the WHO growth standard includes consistency of growth assessment, compares with full term peers, and does not necessitate the use of a different growth chart (CDC, 2010).

NICU Care and Interventions

Doses of Surfactant. Surfactant is a lipoprotein that reduces pulmonary surface tension (Halliday, 2008). Administration of exogenous surfactant has been standard of care to treat RDS since 1990 (NORD, 2004). Higher numbers of surfactant dosing are associated with the development of BPD among preterm infants (Dravet-Gounot et al., 2018; Guo et al., 2015; Hofer et al., 2013; Torchin et al., 2016). The relationship between BPD and surfactant dosing is likely multifactorial and includes prematurity, lack of surfactant, and arrested lung development (Bancalari & del Moral, 2001; Demirel et al., 2009). Empirical indicator for this variable was the total number of surfactant doses administered to the infant.

Transfusions. Higher number of packed red blood cell transfusions was associated with development of BPD (Demirel et al., 2009). There are several proposed mechanisms for this association including 1) damage from excessive heme oxygenase (a by-product from heme breakdown); 2) the role of transfusion-related acute lung injury (TRALI); and/or 3) an acute inflammatory response that negatively impacts the lungs (Zhang, Huang, & Lu, 2014). The empirical indicator for this variable was the total number of packed red blood cell transfusions found in all data sources (CHND, BCH

medical record, and/or outside medical record). While there are several types of blood components that are transfused, the systematic review of the literature focused on the association between BPD packed red blood cells. Therefore, packed red blood cells are the only blood component examined in this research and will be referred to as transfusions for the remainder of the study.

Duration of Mechanical Ventilation. Premature lungs often lack the ability to adequately exchange gasses efficiently due to immature alveoli and lack of energy required to do the work of breathing. Therefore, mechanical ventilation is often required to assist premature infants with their work of breathing and gas exchange. However, there are side effects to mechanical ventilation including pressure and volume related trauma, and oxygen toxicity. These side effects can incur a risk of inflammation (Abman et al., 2017; Laughon et al., 2011). Gentle forms of ventilation are a method to reduce pressure and volume-associated trauma but implementing these strategies have not led to a decrease in the incidence of BPD (Ehrenkranz et al, 2005; Jobe & Bancalari, 2001). Empirical indicators for this variable was the total duration of mechanical ventilation (in days) which included non-invasive ventilation duration (in days) and invasive ventilation duration (also in days).

Normal Line of Defense: Bronchopulmonary Dysplasia

The normal line of defense represents the usual health state of the client (Fawcett & Neuman, 2011). Testing this mid-range theory of BPD risk could lead to the development of a flexible line of defense by developing interventions that could decrease the risk of BPD. As the severity of BPD worsens, the abnormal pulmonary,

neurodevelopmental, and growth outcomes worsen (Abman et al., 2017; Ehrenkranz et al., 2006). A diagnosis of BPD has significant concomitant health, economic, and societal costs (Abman et al., 2017; Laughon et al., 2011), thus identification of those at risk is critical.

The most recent and applicable BPD risk assessment tool includes gestational age, birth weight, oxygen concentration, respiratory support, race/ethnicity, and sex. These components determine the probability of developing no BPD, mild BPD, moderate BPD, and severe BPD (combined types 1 and 2) (Laughon et al., 2011). To determine if the tool was more accurate on specific days of life, it was tested on multiple days (days 1, 3, 7, 14, 21, and 28) (Laughon et al., 2011). The tool was most accurate when used on day of life 28. While this risk assessment tool can be used, the variables of the tool do not include all of the variables from the mid-range theory.

Long term consequences of BPD can affect the infant, family, and society including physical, psychological, and economic impacts. The health ramifications of BPD on infants are significant and become more significant as the grading progresses from mild to severe. Some of these ramifications include pulmonary hypertension, poor growth, and neurodevelopmental impairment (Abman et al., 2017). Mothers of infants with BPD have poorer sleep quality, higher stress, and higher rates of depression (Feeley et al., 2014). Parents of infants with severe BPD perceive their infants' health-related quality of life as lower when compared to parents that have full term infants or preterm infants that do not have severe BPD (Brady, Zhang, Kirplani, & DeMauro, 2019). Finally, the economic impact of BPD is nebulous but incurs a greater cost than that of healthier preterm infants. There is no information on the long-term costs of BPD or the

costs associated with comorbidities such as neurodevelopmental impairment, poor growth, or pulmonary hypertension (Johnson, Patel, Jegier, Engstrom, & Meier, 2013; Lapcharoensap, Lee, Nyberg, & Dukhovny, 2018).

Conclusion

The mid-range theory, as guided by the NSM (see Figure 1), highlights extrapersonal, intrapersonal, and interpersonal stressors as represented by the empirical indicators discussed. These stressors were associated with the development of BPD in the systematic review of the literature. The next section of this dissertation includes a discussion of the study aims, hypotheses, and plan for post hoc analysis if there is sufficient sample size.

Study Aims and Hypotheses

Aim 1: To describe the sample of infants with BPD.

Aim 2: Examine the association of BPD development and the predictive variables, based on the developed mid-range theory.

Aim 2 Hypothesis 1: The presence of BPD will be higher among male infants, born at lower gestational ages, and born with lower birth weights.

Aim 2 Hypothesis 2: The presence of BPD will be higher for infants with fetal growth restriction, and whose mothers were diagnosed with hypertension and chorioamnionitis.

Aim 2 Hypothesis 3: The presence of BPD will be higher for infants with multiple doses of surfactant, multiple transfusions of packed red blood cells, and with a longer duration of mechanical ventilation.

Aim 2 Hypothesis 4: The presence of BPD will be higher for infants with multiple episodes of pneumonia, sepsis, meningitis, and urinary tract infections.

Aim 2 Hypothesis 5: The presence of BPD will be higher for infants with PDA, PDA requiring medical management, and PDA requiring surgical closure.

Aim 2 Hypothesis 6: The presence of BPD will be higher for infants with ≥ Stage 2 NEC.

Aim 2 Hypothesis 7: The presence of BPD will be higher among infants with extrauterine growth failure.

Post Hoc Analyses

Provided that the sample was large enough, and that missing data was not an issue, two post hoc analyses were conducted. The first sought to examine the association between BPD and race/ethnicity, as previous research studies have had conflicting results. The second post hoc analysis was to examine the association of each grade of BPD (no BPD, mild BPD, moderate BPD, severe BPD type 1, and severe BPD type 2) and the predictive variables within the mid-range theory.

CHAPTER III

METHODS

Study Design

This cohort study was a secondary analysis of data from the Children's Hospital Neonatal Database (CHND) as well as data collected from Boston Children's Hospital (BCH) medical records and medical records from other institutions that were previously entered into the BCH medical record. The data sought from this database were only from infants treated at Boston Children's Hospital, a referral center, and not a delivery hospital. To determine the outcome and grade of BPD, data regarding mechanical ventilation was required. Data of mechanical ventilation that was collected for the CHND was available beginning in 2010, therefore data analysis for this study included the years from January 2010 - January 2020. Study variables are described in Table 3. A data abstraction tool based on the mid-range theory (see Figure 1) is shown in Table 4. Further, a manual of definitions was employed to ensure consistency in operational definition characterizations (Vassar & Holtzmann, 2013).

Study Sample

The CHND was analyzed with the primary inclusion criteria of being an infant born at < 32 weeks' gestation. Exclusion criteria included inability to determine the

outcome of BPD and several conditions detailed in the section below (also see Table 5). These covariates were selected based on their potential confounding effect on the outcome of BPD.

Excluded Covariates

There are similar pulmonary signs and symptoms associated with BPD and congenital renal disease. In congenital renal disease the pulmonary signs are typically due to two major factors. The first factor is oligohydramnios (low amniotic fluid volume during pregnancy), which prevents normal fetal lung development. Enlarged kidneys is the second factor. Through their mass-effect, enlarged kidneys impede effective ventilation and is an additional etiology for abnormal pulmonary signs and symptoms found in infants with congenital renal disease (Rodriguez, 2014). Given these confounding factors, infants with congenital renal disease are generally excluded in BPD research. Infants with major congenital heart disease were also excluded. Depending on the physiology of the diagnosis, increased pulmonary blood flow can lead to abnormal pulmonary manifestations secondary to a cardiac etiology and not from pulmonary disease. Therefore, infants with major congenital heart disease were excluded. Finally, infants with neuromuscular disorders, metabolic disorders, and other major congenital anomalies were excluded from this research. Infants with these diagnoses frequently require mechanical ventilatory support due to poor muscular tone and/or abnormal neurologic function (Abman et al., 2017).

Ethical Considerations

The study design was a secondary analysis of deidentified CHND data. Other sources included data retrospectively collected from the BCH medical record and outside

hospital records. Institutional Review Board (IRB) approval was obtained from Boston Children's Hospital (IRB-P00035001) and the University of Massachusetts Boston (IRB Number 2020074). Data was electronically abstracted from CHND and entered into a REDCap database. Data for variables that were not included in the CHND were collected by a single data collector (the student PI) from the BCH medical record and/or the outside hospital record. When the data retrieval was completed, each research subject was assigned a unique identification number in REDCap. A log of subjects' medical record numbers and their identification numbers were stored in a separate file on a BCH computer behind the BCH firewall. The REDCap database was stored behind the BCH firewall in a password protected file. De-identified data was transferred in an Excel file.

Measures

As previously stated, data was obtained primarily from the CHND. When not available in the CHND, data was collected using the BCH medical record and/or the outside hospital records. Together they will be referred to as all data sources. If there was a discrepancy between the CHND and the BCH medical record the outside hospital record was reviewed to verify data accuracy.

Extrapersonal Stressor

Sex

Sex was documented in the database as either male, female, or unknown.

Race/Ethnicity

The variables for race were Asian, Black, White, American Indian, Native Pacific Islander, other, and unknown. The variables for ethnicity include Hispanic, non-Hispanic, and unknown.

Interpersonal Stressors

Interpersonal risks comprised the prenatal environment and included inflammation, infection, and MVU variables.

Prenatal Inflammation and Infection

When risk factors for BPD development were examined in a recent systematic review, inflammation and infection were often found in concert. Clinically, inflammation was represented by chorioamnionitis. As previously discussed, chorioamnionitis can be diagnosed histologically and/or clinically. The database did not differentiate between histologic or clinical chorioamnionitis. Rather, chorioamnionitis was either diagnosed or not diagnosed for each subject. The empiric indicators for these variables were either yes (present) or no (not present).

Maternal Vascular Underperfusion

Placental pathology was not collected as part of the data in the CHND. The database did identify whether the mother had clinical evidence of MVU represented by maternal chronic hypertension, gestational hypertension, HELLP syndrome, and/or preeclampsia. The empiric indicators for this variable was either yes (present) or no (not present).

Fetal Growth Restriction

Fetal growth restriction was assessed by plotting the birth weight on the Fenton growth chart (Fenton & Kim, 2013) and any infant with a birth weight less than 10^{th} percentile considered to have fetal growth restriction, and was entered as "yes" during data collection. If the birth weight was > 10^{th} percentile based on gestational age, then "no" was entered in the data collection tool.

Intrapersonal Stressors

Intrapersonal stressors included infant characteristics (gestational age, birth weight, patent ductus arteriosus, and extrauterine growth failure) and NICU interventions. The NICU interventions included doses of surfactant, number of transfusions, duration of mechanical ventilation.

Infant Demographics

Infant demographics that increase risk of BPD included gestational age, and birth weight.

Gestational Age and Birth Weight. Gestational age was measured using completed weeks of gestation. Birth weight was measured in grams.

Postnatal Inflammation. Risks for inflammation were represented by duration of mechanical ventilation, due to oxidative stress, and with NEC. Duration of mechanical ventilation was measured in number of days. NEC was measured as yes if the infant was diagnosed with NEC (see Table 2) and if they have findings on radiograph consistent with ≥ Bell's Stage 2 (Bell et al., 1978). Data for NEC was categorized in the database by the location of its occurrence, referring hospital or BCH. Medical and surgical NEC fulfilled the requirements for Bell's stage ≥ 2, so both variables were included in the analysis as "yes" if diagnosed an "no" if they were not diagnosed

Postnatal Infection. Laboratory samples indicative of infection were positive cultures. Positive blood cultures are considered diagnostic for bacteremia. Positive urine cultures were diagnostic for urinary tract infections. Positive cerebral spinal fluid cultures. were indicative of meningitis. Per the CHND. Pneumonia was diagnosed if the following were demonstrated: 1) worsening gas exchange as evidenced on blood gasses;

2) worsening appearance of the lungs on chest radiographs obtained at two different time points; and 3) a combination of several other signs and symptoms (fever and elevated white blood cell count, for example). Each diagnosis of infection was measured as separate occurrences and the cumulative number of infections was used for analysis.

Patent Ductus Arteriosus. The CHND collected multiple variables for PDA. This first included either if there is a diagnosis of PDA determined during hospitalization or if there is no diagnosis made during hospitalization. If a diagnosis of a PDA was determined, using echocardiography, it was further defined into other variables which included no treatment, medical treatment, or surgical treatment. The variables collected for this research were: 1) PDA diagnosis (yes or no), 2) treatment required for management of the PDA, if any; and 3) what type of treatment(s) were required.

Extrauterine Growth Failure. If available, the CHND collected weights at several time points for infants born < 32 weeks (i.e., at birth, 28 days of life, 36 weeks PMA, 40 weeks PMA, and 44 weeks PMA). If the infant remained in the NICU at BCH, the 50-week weight was collected, using data from the BCH medical record. Consistent with assessing for FGR, EUGR was measured with a yes if the infant was assessed as $<10^{th}$ percentile in weight for their gestational age, or no if they were not $<10^{th}$ percentile for age (Fenton & Kim, 2013). Given that subjects are admitted and discharged from BCH at different time points, the last weight collected was used to determine whether a subject was EUGR.

NICU Interventions

Doses of Surfactant. The CHND collected whether a subject received surfactant, or not as their surfactant variable. The other data sources were searched for the precise

number of surfactant doses. For the purposes of this research, the total number of surfactant doses was used as the empirical indicator for this variable

Transfusions. The CHND did not include data regarding transfusions. Therefore, other data sources were searched for the number of transfusions administered. Due to the wide range in the number of transfusions administered, the transfusions were grouped into equal proportional groupings for the analysis: 1) group one received zero transfusions, 2) group two received either one or two transfusions, 3) group three received between three to six transfusions, and 4) group four received more than six transfusions. A fifth group was added to account for the infants with missing transfusion data.

Duration of Mechanical Ventilation. Duration in mechanical ventilation was measured in total days. To further categorize mechanical ventilation data, the total duration of mechanical ventilation was separated into non-invasive and invasive mechanical ventilation (total days).

Normal Line of Defense

BPD Diagnosis and Grading

BPD diagnosis was determined using the diagnostic criteria developed in 2000 [see Table 1] (Jobe & Bancalari, 2001). For this research, a diagnosis of BPD was established based on oxygen requirement at 28 days of life and respiratory support requirements at 36 weeks ± 2 weeks.

Data Analysis

An ‘a priori’ p value for statistically significant findings was set at 0.05. Power was set as 0.80. Statistical analysis as completed using IBM SPSS Statistics 27.

Aim 1

The first aim was to describe the infants in the study. To describe the study sample and determine the distribution of the sample's data, a univariate analysis of each concept was conducted. Gestational age and birth weight were not normally distributed, so the median and interquartile range were reported. For race and ethnicity and sex, frequency and percentage were reported.

Aim 2

To examine the bivariate association of BPD development (yes or no) and the predictive variables, Chi-square test was used to examine the association between BPD and the categorical variables (fetal growth restriction, chorioamnionitis, maternal vascular underperfusion, patent ductus arteriosus, treatment of patent ductus arteriosus, NEC, and extrauterine growth restriction). Wilcoxon Signed Ranks was used to test the association between BPD and the continuous variables (doses of surfactant, number of transfusions, duration of mechanical ventilation, episodes of infection). Bivariate analysis and multivariate binary logistic regression were conducted to determine the association between the outcome variable of BPD and the independent variables.

Post Hoc Analyses

Two post hoc analyses were planned, but due to insufficient representation of all the race/ethnicity categories, only one was performed. Examining the association between development of BPD and race/ethnicity had been conflicting in the literature (Janevic et al., 2018). Therefore, the first post hoc analysis was planned to explore the relationship between race, ethnicity, and BPD. However, there was insufficient

representation of all race/ethnicity categories so this post hoc analysis could not be performed.

The second post hoc analysis was to explore the relationship between the risk factors and each grade of BPD (see Table 1). There were many infants in this sample that were diagnosed with BPD, so this analysis could be performed. To examine the association of race, ethnicity, and each grade of BPD (see Table 1) and the categorical predictive variables, use of Chi-square test was planned. Wilcoxon Signed Ranks test was planned to test the association between race, ethnicity, and each grade of BPD and continuous variables. Predictive variables with $p < 0.05$ from the bivariate analysis was entered into multinomial logistic regression, with the dependent variables as each grade of BPD (see Table 1).

CHAPTER IV

RESULTS

The purpose of this study was to examine the extrapersonal, interpersonal, and intrapersonal stressors as identified in a systematic review that is predicted to affect the development of BPD. The organization of the risk factors and analysis of this study was guided by the NSM (2011), a holistic systems approach. The specific aims of this study were to (1) describe the sample of infants with BPD in the BCH CHND and (2) examine the association of BPD development and the predictive variables, based on the mid-range theory (see Figure 1).

Describing the Sample

Between 2010 and 2020, there were 645 infants born at < 32 weeks' gestation admitted to the NICU at BCH and entered into the CHND. After identification in the CHND, their medical records were screened following inclusion/exclusion criteria (see Table 5). Infants were excluded if they were diagnosed with major congenital anomalies (n=122), the presence of congenital renal disease (n=11), neuromuscular disorders (n=2), and a metabolic disorder (n=1), or if the diagnosis of BPD could not be determined (n=54), After screening for inclusion/exclusion criteria a final sample of 455 infants remained (see Figure 2).

Description of the sample of infants from the CNHC, born at <32 weeks' gestation was completed to address Aim 1.

Frequency and percentages were used to summarize race, ethnicity, sex, FGR, chorioamnionitis, MVU, transfusions, PDA, and NEC (Table 6 and 8). Infant weights (measured in grams), gestational ages (measured in weeks), non-invasive mechanical ventilation (measured in days), invasive mechanical ventilation (measured in days), and total mechanical ventilation (measured in days) were not normally distributed, thus median and interquartile ranges were calculated (see Table 6). Infection frequency and percentage are presented in Table 7.

Extrapersonal Stressors

As depicted in Table 6, the ethnicity of the infant was unknown for 133 records, and race was unknown for 96 records. Of those infants with known race and ethnicity, the majority were white non-Hispanic, or Latino. There were more male infants than female infants in the sample.

Interpersonal Stressors

Most pregnancies in this sample were not affected by FGR, chorioamnionitis, or MVU (see Table 6).

Intrapersonal Stressors

Gestational Age and Birth Weight

The majority of infants in the sample were born at younger gestational ages and had lower birth weights. The median gestational age for subjects was 26 weeks, with a median birth weight of 820 grams (see Table 6).

Infections

Type of infection and total infections in each subject (see Table 7) was as follows: blood stream infections were diagnosed most frequently (27%), followed by pneumonia (25.1%), urinary tract infections (13.2%), and meningitis (6.2%). When examined as total number of infections per each subject, the median was 1 with IQR 0, 1; approximately half of all subjects had at least one infection (50.8%).

Patent Ductus Arteriosus and Necrotizing Enterocolitis

Greater than half of the subjects were diagnosed with a PDA, and the majority required medical and/or surgical treatment. There was also a group of infants that required both medical and surgical treatment (see Table 8).

NEC was diagnosed in approximately one-third of study sample requiring medical and/or surgical management, with the majority requiring surgical treatment (see Table 8).

NICU Interventions Required to Treat Infant Characteristics

Surfactant. The majority of infants received surfactant (77%), with a range of 0-4 doses. Most of the subjects received one dose of surfactant.

Transfusions. All data sources for each subject were searched for a history of receiving transfusion. Of the total sample of 455 infants, data for 314 subjects was obtained. For a more meaningful analysis because of missing data, transfusion groups were created (see Table 9). Group one had zero transfusions (n=78), group two (n= 74) were transfused either once or twice, group three (n=86) received between three to six transfusions, group four (n=76) had ≥ 7 transfusions. There were 141 subjects for whom the exact number of transfusions could not be determined despite searching all the data

sources, A fifth transfusion group was created to include these subjects with missing transfusion data.

Mechanical Ventilation. The days of non-invasive mechanical ventilation, invasive mechanical ventilation, and total mechanical ventilation were not normally distributed due to a subset of the subjects with significantly longer duration of mechanical ventilation (see Table 6). Of those subjects requiring mechanical ventilation: the median for non-invasive ventilation was 25 days, invasive ventilation 32 days, and the total duration of mechanical ventilation had a median of 63 days.

Normal Line of Defense

Of the 455 subjects included in this study, 83.7% were diagnosed with BPD with the majority diagnosed with Severe BPD [type 1 or 2] (see Table 10).

Bivariate Analysis of BPD Development and the Predictor Variables

Aim two examined the association between BPD and the predictor variables in the study. The hypotheses were that BPD was associated with the predictive variables. Further, it was hypothesized that variables from more than one stressor (extrapersonal, interpersonal, and intrapersonal) would increase the risk for BPD.

First, bivariate analysis between each predictive variable and the development of BPD were conducted. Variables with statistically significant ($p < 0.05$) associations with BPD development were then entered into binary logistic regression analysis.

BPD Diagnosis and the Association with Race, Ethnicity, and Sex

Race, as a combined variable including all variables of races, did not have a statistically significant relationship with BPD diagnosis ($X^2 = 11.33$, df 8, $N = 455$, $p = 0.18$). There were seven categories within the race variable: White, Black/African

American, Asian, Native American, Native Hawaiian, other, and unknown. For all of the categories, Chi-Square analyses were performed to determine if a statistical association with BPD existed (see Table 11). Only White (*n = 218*, $p < 0.01$) and other (*n = 49*, $p = 0.01$) were statistically significant.

The majority of subjects were not Hispanic, and this variable was found not to have a statistically significant relationship with BPD ($X^2 = 5.79$, *df* 2, $N = 322$, $p = 0.06$). While there were more male subjects, there was no statistically significant association between BPD and sex ($X^2 = 1.21$, *df* 1, $N = 455$, $p = 0.27$).

BPD and the Association with Chorioamnionitis, MVU, and FGR

Chi-Square tests were used to examine associations between the diagnosis of BPD and chorioamnionitis, MVU, and FGR (see Table 12). Of these conditions, FGR was the only variable to have a statistically significant relationship with BPD ($X^2 = 7.38$, *df 2*, $N = 81$, $p = 0.03$).

BPD Diagnosis and the Association with Gestational Age and Birth Weight

Table 13 depicts the bivariate analysis of the intrapersonal stressors with BPD. Using Wilcoxon Signed Ranks test for both, subjects born at lower gestational age were more likely to develop BPD ($p < 0.01$), as were infants with lower birth weights ($p < 0.01$).

BPD Diagnosis and the Association with Surfactant, Transfusions, and Mechanical Ventilation

The association between surfactant administration, transfusions, and duration of mechanical ventilation were all continuous variables, so they were analyzed using the Wilcoxon Signed Ranks. Each of the variables were statistically associated with BPD

(see Table 13). More doses of surfactant administered was associated with the development of BPD ($p < 0.01$). The number of transfusions varied from 0-41, so they were grouped into four equal groups (group 1 with n=78, group 2 with n=74, group 3 with n=86, and group 4 with n=76). There were 141 missing data for transfusions, which were grouped into a fifth group. Higher number of transfusions and BPD has a statistically significant association ($p < 0.01$). The longer the duration of mechanical ventilation was associated with BPD development ($p < 0.01$). This association was also true for invasive and non-invasive ventilation duration.

BPD Diagnosis and the Association with Postnatal Infections

Risk for BPD and its association with pneumonia, blood stream infection, meningitis, and urinary tract infections were analyzed using Wilcoxon Signed Ranks (see Table13). Neither blood stream infections nor meningitis were statistically significant. Pneumonia was associated with the development of BPD ($p < 0.01$), as was urinary tract infections ($p<0.01$). Furthermore, the association between total number of infections and BPD was also tested and demonstrated that increased number of infections was associated with development of BPD ($p < 0.01$).

BPD Diagnosis and the Association with PDA

The association between BPD and diagnosis of a PDA was analyzed using Chi-Square test and was found to be statistically significant ($X^2 = 56.26$, df 2, N= 455, $p < 0.01$). This group was further analyzed, looking at the four variables associated with a diagnosis of a PDA: 1) no treatment, 2) medical treatment, 3) surgical treatment, or 4) medical and surgical treatment. PDA diagnosis was examined as a categorical and interval level variable (see Table 13). PDA diagnosis was examined as interval since each

increasing treatment category has more implications for the infant (no treatment, medical treatment, surgical treatment, and both medical and surgical treatment). The association between BPD and no treatment for their PDA was not statistically significant. However, the other three groups did demonstrate statistically significant results. First, the two methods of treatment were analyzed. Medical treatment was associated with the development of BPD (X^2 = 36.6, *df* 1, *N* = 455, p < 0.01), as was surgical management (X^2 = 19.45, *df* 1, *N*= 455, p<0.01). Finally, the association between BPD and both medical and surgical management was evaluated and found to be associated with the development of BPD (X^2 = 12.07, *df* 1, *N* = 455, p < 0.01). Finally, all variables of PDA were combined, and its association with BPD was tested. The combined variable was associated with BPD (X^2 = 62.79, *df* 5, *N* = 455, p < 0.01) with a medium effect (phi = 0.44).

BPD Diagnosis and the Association with NEC

The association between a diagnosis of Stage ≥ 2 NEC and BPD was analyzed using Chi-Square test. The diagnosis of Stage ≥ 2 NEC and BPD was statistically significant (X^2 = 20.02, *df* 2, *N* = 455, p < 0.01). Treatment of Stage ≥ 2 NEC and the association with BPD was analyzed: 1) medical treatment, 2) surgical treatment, and 3) medical and surgical treatment. Like PDA, NEC diagnosis was examined as a categorical and interval level variable (see Table 13). NEC diagnosis was examined as interval since each increasing treatment category has more implications for the infant (medical treatment, surgical treatment, and both medical and surgical treatment). The association between BPD and medical management was statistically significant (X^2 = 3.95, *df* 1, *N* = 455, p = 0.05). The association between surgical management and BPD development was

also statistically significant (X^2 = 13.88, *df* 1, *N* =455, p < 0.01). Finally, management with medical and surgical treatment was also found to be statistically significant (X^2 = 4.06, *df* 1, *N* = 455, p = 0.04)

BPD Diagnosis and the Association with EUGR

The Independent -Sample Mann-Whitney U Test was used to analyze the association with weight (in grams) and BPD at 28 days of life, 36 weeks' gestation, 40 weeks' gestation, 44 weeks' gestation, and 50 weeks' gestation. However, there was a significant amount of missing data from each category. The association between EUGR and BPD development was assessed using data from the last available weight using the Chi-Square test. EUGR and the development of BPD was found to be statistically significant (X^2 = 20.19, *df* 2, *N* = 455, p < 0.01).

Correlation Matrix

A correlation matrix was performed to demonstrate if there were significant correlations between the independent variables in this study. Findings demonstrated many correlated independent variables in the study (see Table 14). There were multiple correlated variables.

Binary Logistic Regression

The bivariate analysis of the predictor variables demonstrated that there were significant variables in each of the extrapersonal, interpersonal, and intrapersonal stressors. Extrapersonal stressors with p< 0.05 included variables of White and Other. Ethnicity did not have a statistically significant relationship with development of BPD. Of the interpersonal stressors, only FGR was statistically significant. Finally, of the

intrapersonal stressors, many were statistically significant and evaluated further in the regression analysis.

Table 15 depicts the results from the binary logistic regression. While variables from the extrapersonal, interpersonal, and intrapersonal stressor categories were entered into the analysis, only intrapersonal stressors remained statistically significant. Lower birth weight was associated with development of BPD (OR 0.99, p = 0.04; 95% CI [0.993, 1.00]). Patients that received more doses of surfactant were more likely to develop BPD (OR 2.49, p <0.03; 95% CI [1.1, 5.77]). Finally, patients that were on mechanical ventilation for longer duration were more likely to develop BPD (OR 1.2, p < 0.01; 95% CI [1.12, 1.27]).

Post Hoc Analysis

The role of race/ethnicity and the development of BPD was not further examined since there was an insufficient representation of Black/African American, Asian, Native American, Native Hawaiian races in the sample.

The majority of infants in this study were diagnosed with BPD (n=381, 83.7%). More than half of those with BPD had Severe Type 1 or 2 BPD (see Table 10). The post hoc analysis examining grades of BPD and the predictive variables was conducted. First, a bivariate analysis was performed using Chi-square test to examine the association between BPD grade and the categorical variables. Wilcoxon Signed Ranks test was used to test the association between BPD grade and the continuous variables.

Bivariate Analysis of the Predictive Variables and Grades of BPD Severity

Chi-Square was used to analyze the categorical variables (see Table 16). Among the variables of race, White (X^2 =12.58, *df*, 4, *N* =455 , p = 0.01) and Asian (X^2 = 17.73,

df 4, *N* = 455, p < 0.01) were significantly associated with worsening severity of BPD. The combined sample category was also statistically significant (X^2 = 57.715, *df* 32, *N* = 455, p < 0.01). Among the interpersonal stressors, only FGR was statistically significant (X^2 = 29.07, *df* 4, *N* = 455, p < 0.01), with a medium effect (see Table 17). All variables of PDA and NEC were statistically associated with severe grade of BPD (X^2 = 89.34, *df* 16, N = 455, p < 0.01; X^2 = 39.25, *df* 16, *N* = 455, p < 0.01). PDA had a large effect size and NEC had a medium effect size. EUGR was also statistically significant with a medium effect size (X^2 =26.916, *df* = 4, *N* = 455, p < 0.01). Table 18 represents these results.

Continuous variables were analyzed using Wilcoxon Signed Ranks. Birth weight and gestational age were both statistically significant (U = -18.4, p < 0.01; U = -18.51, p < 0.01). Doses of surfactant was statistically significant (U = 17.03, p < 0.01). Total days of mechanical ventilation is a continuous variable (U = -18.237, p < 0.01). Total infections and transfusion groups were also statistically significant (U = -17.724, p < 0.01; U = -7.13, p < 0.01).

Multinomial Logistic Regression Analysis

Multinomial logistic regression was conducted in the post hoc analysis. The outcome variable was categorized into five categories: no BPD, mild BPD, moderate BPD, severe BPD (type 1), and severe BPD (type 2). Independent variables with p < 0.05 from the bivariate analysis (see Tables 16, 17, and 18) were entered into the multinomial regression analysis. Based on this analysis race, FGR, gestational age, birth weight, doses of surfactant, total days of mechanical ventilation, total infections, transfusion

groups, all variables of PDA, all variables of NEC, and EUGR were statistically significant and entered into the multinomial logistic regression analysis.

Table 19 depicts the significant relationships with mild BPD included total days of mechanical ventilation (OR = 1.16, $p < 0.01$; 95% CI [1.1, 1.24]), total infections (OR 0.36, $p = 0.03$; 95% CI [0.14, 0.9]), and NEC variables (OR = 2.17, $p = 0.03$; 95% CI [1.09, 4.35]). Table 20 demonstrates the variables with significant relationships to moderate BPD. These include doses of surfactant (OR = 2.48 $p = 0.04$; 95% CI [1.04, 5.89]), total days of mechanical ventilation (OR 1.15, $p < 0.01$; 95% CI [1.09, 1.22]), total infections (OR 0.36, $p = 0.04$; 95% CI [0.14, 0.94]), and PDA variables (OR 3.35, $p = 0.01$; 95% CI [1.27, 8.84]).

Table 21 demonstrates the statistically significant findings for Severe (Type 1) BPD and the predictive variables. Variables with a statistically significant association with Severe Type 1 BPD include gestational age, birth weight, doses of surfactant, total days of mechanical ventilation, and all variables of PDA. Finally, Table 22 depicts the association between Severe (Type 2) BPD and the predictive variables. Of the variables entered in the multinomial logistic regression analysis, six were statistically significant. The variables associated with development of Severe (Type 2) BPD included gestational age, doses of surfactant, total duration of mechanical ventilation, and all variables of PDA.

The only variable that was consistent across all grades of BPD was total duration of mechanical ventilation. Total infections were associated with mild and moderate BPD. As the grade of BPD worsens, more variables were statistically significant. For moderate, severe type 1, and severe type 2 BPD doses of surfactant, PDA was associated with the

development of BPD. Finally, gestational age was associated with severe type 1 and 2 BPD.

CHAPTER V

DISCUSSION

Introduction

The sample in this study (n = 455) was treated at a Level IV NICU. All infants treated in this NICU were transferred to the facility due to need for a higher level of care such as a surgical procedure or a complication related to their preterm birth. This is a select sample of preterm infants and they are among the most complex infants cared for in the NICU. The purpose of this chapter is to interpret the findings of this research in context of contemporary knowledge of BPD and the mid-range theory, which was developed using the NSM (Fawcett & Neuman, 2011). The findings provide an opportunity to improve future practice and research. Limitations to this research study are also discussed.

Extrapersonal Stressors

The male fetus has delayed surfactant production due to hormonally based differences which leads to an increase resistance in the alveoli and control in the budding of the bronchioles during early fetal development (Shim et al., 2017). While male sex has historically been a risk factor for the development of BPD (Abman et al., 2017), this was not the case in this study. Perhaps the findings from this research demonstrate that there

is a moderating effect due to other conditions, such as PDA or NEC that change this long-established relationship.

Ethnicity was not statistically associated with BPD development, however approximately one-third of subjects' ethnicities were not reported. While the race variables of White and other were associated with BPD development in bivariate analysis, this relationship was not demonstrated in binary logistic regression analysis. If there had been more subjects with race and ethnicity reported, there may have been different results.

Interpersonal Stressors

Interpersonal stressors included chorioamnionitis, MVU, and FGR. In the bivariate analysis, only FGR had a significant relationship with BPD. Given the association found in the literature between chorioamnionitis and MVU, the measures were examined in this sample. Maternal hypertensive disorders were the empirical indicator for MVU, consistent with the literature (Mestan et al., 2014; Mestan et al., 2017). However, other signs of MVU may include placental insufficiency, and reversal end diastolic flow, and chronic placental insufficiency Mestan et al., 2014; Mestan et al., 2017). As these conditions impact placental blood flow, and may impact fetal lung development they should be included as variables in future research. Finally, it should be noted that sufficient representation in this category of stressors may have been underrepresented since MVU and chorioamnionitis are not typical indications for transfer to BCH, which is a Level IV referral center and not a birth center.

Intrapersonal Stressors

Gestational Age and Birth Weight

Generally, BPD incidence and severity increases as gestational age and birth weight decreases. Gestational age was significantly associated with severe BPD (type 1), and severe BPD (type 2). Birth weight was associated with a diagnosis of BPD, as well as severe BPD (type 1). These findings are consistent with past research findings (Dravet-Guonot et al., 2018; Guo et al., 2015).

Surfactant

Exogenous surfactant is administered to preterm infants to bridge the gap in time between birth and when endogenous surfactant production is sufficient to facilitate adequate ventilation and oxygenation. The timing of endogenous production varies depending on factors such as gestational age, maternal conditions, male sex (Dravet-Gounot et al., 2018; Guo et al., 2015; Hofer et al., 2013; Shim et al., 2017; Torchin et al., 2016). Objective indications for an initial surfactant dose are prematurity and symptoms of RDS (see Table 2). Repeated doses can be administered (depending on formulation) several more times within the first days of life for continued signs of RDS including high oxygen requirements and high mean airway pressure. The additional doses facilitate ventilation and oxygen needs of the premature infant (Polin & Carlo, 2014). In this study sample, reported increased doses of surfactant were associated with a higher likelihood of a BPD diagnosis, and specifically with moderate, severe type 1, and severe type 2 BPD. This is consistent with previous research (Dravet-Gounot et al., 2018; Guo et al., 2015; Hofer et al., 2013; Shim et al., 2017; Torchin et al., 2016).

The findings from this research suggest that the relationship between exogenous surfactant and BPD is more complex than surfactant deficiency alone. Perhaps the requirement of exogenous surfactant dosing is less due to surfactant production deficiency and is instead a signal for the "new BPD", or maldevelopment of the lungs and pulmonary microvasculature. Finally, a need for more surfactant dosing may also represent an inflammatory or infectious etiology which prevents endogenous surfactant production (Abman et al., 2017).

Transfusions

Transfusions are postulated to be associated with BPD through several mechanisms including 1) damage from excessive heme oxygenase; 2) the role of transfusion-related acute lung injury (TRALI); and/or3) an acute inflammatory response that negatively impacts the lungs (Zhang, Huang, & Lu, 2014). The majority of subjects received at least one transfusion, and transfusions was associated with BPD development. The role of transfusions in BPD can be examined in two ways. The first way is examining those infants that receive more transfusions; they are generally more ill than those that did not require multiple transfusions. The infants that require more transfusions are more likely to have had surgical conditions, were unable to tolerate enteral feedings, and had less iron intake. Whether BPD is caused by transfusions or a mark of infants with more complicated conditions are at higher risk for BPD remains to be researched.

Mechanical Ventilation

Mechanical ventilation has been associated with BPD since 1967 (Northway et al., 1967), and was again demonstrated in this sample. The use of mechanical ventilation

is a necessity to support the ventilation and oxygenation of preterm infants, but also incurs risks of oxidative injury, barotrauma, and volutrauma (Abman et al., 2017). Infants requiring a longer duration of mechanical ventilation may be a signal of maldevelopment in utero, that is then exacerbated by the treatment itself, and other conditions causing inflammation and/or infection.

Patent Ductus Arteriosus

Diagnosis of PDA was made in 62.4% of the infants in this study. It is considered a natural finding in all infants, with higher incidence and longer duration of patency among preterm infants. Consistent with other research (Dravet-Gounot et al., 2018; Demirel et al., 2009; Guo et al., 2015; Rutkowska et al., 2019; Torchin et al., 2016), the findings of this study demonstrate a relationship between PDA diagnosis and development of BPD, including the development of severe grades of BPD. Common practice is to treat a hemodynamically significant PDA, using guidance from echocardiography and clinical examination. Indications for treatment include a large PDA that is not responsive to medical interventions and/or a symptomatic PDA that causes hypotension and increased O2 requirement and increased ventilatory support.

However, waiting for signs and symptoms to occur before treating the PDA may permit insidious pulmonary damage caused by overcirculation. Instead of waiting for signs of a hemodynamically significant PDA prior to echocardiography, closer surveillance, such as echocardiography and/or brain natriuretic peptide (BNP) measurement should be considered. More research is needed to determine when a PDA is no longer a naturally occurring condition and becomes harmful. The findings from this

research suggest that the impact of the PDA and its role in the development of BPD among premature infants deserves further exploration.

Necrotizing Enterocolitis and Infections

Pneumonia, urinary tract infections, and total number of infections were associated with the development of BPD in the bivariate analysis, but not in the binary logistic regression analysis. Total infections were associated with the development of mild and moderate BPD in the post hoc analysis. Subjects with NEC were more likely to develop BPD. Demonstrating the role of inflammation and infection in the development of BPD. Infection and NEC surveillance must continue as standard of care. Further, if infections and/or NEC are diagnosed, early BPD detection and risk reduction must be employed.

Clinical sepsis, where the bacterial culture results were negative, but the patient demonstrated signs of an infection, has been highlighted as a risk for BPD (Hofer et al., 2013; Ohlin et al., 2015). Perhaps inclusion of cases of clinical sepsis would be useful in future research to explore the role of its associated inflammation.

Extrauterine Growth Restriction

EUGR is defined as weighing < the 10^{th} percentile for age (Ohlin et al., 2015), and this variable was associated with BPD in bivariate analysis but not in binary logistic regression, nor in multinomial regression analysis. While reviewing the last weight, which was used to determine EUGR, only those weights that were in the < 10^{th} percentile classified EUGR. However, there were subjects whose weights decelerated significantly over the time between birth and the final assessment. There are two considerations for

discussion: 1) what are the reasons for the decelerations in growth, and 2) is there a more comprehensive assessment to categorize extrauterine growth restriction?

Growth restriction is an imbalance of metabolic demands and nutritional intake. Conditions associated with high metabolic demands include respiratory distress, infections, NEC, PDA, and more. Nutritional intake is in the form of parenteral and/or enteral nutrition, however providing nutritional intake to meet the dynamic needs of NICU patients is a challenge. The balance between metabolic demands and intake needs further exploration in the future. Comparing outcomes, using growth to define the groups, would aid in delineating the role of growth in outcomes, specifically the development of BPD.

Next, the most appropriate measure for EUGR deserves further exploration. As an example, if an infant is born in the 75th percentile and then their weight decelerated to the 15th percentile they were not classified as having EUGR based on the measurement selected. However, this represents a significant deceleration in growth. Failure to thrive (FTT) is defined as a weight decline of ≥ 2 major percentiles on the growth chart at separate points of assessment (Cole & Lanham, 2011). FTT is not a commonly applied definition for preterm infants; instead EUGR is more common. However, examining weight over time rather than only a one-time assessment could be an important area for future examination as it may be a better indicator of overall wellness in this population.

Conclusion

This research was framed using the NSM, a holistic systems approach (Fawcett & Neuman, 2011). A systematic review of the literature was conducted to explore the risk factors for BPD. These risk factors were categorized into each of the NSM stressors:

extrapersonal, interpersonal, and intrapersonal (see Figure 1). Initially there were 15 variables (with subcategories) that were proposed to be associated with the development of BPD.

BPD diagnosis and each grade of BPD were associated with total duration of mechanical ventilation. As severity of BPD increased, other variables increased risk including gestational age, birth weight, and PDA. Variables that were associated with BPD in bivariate analysis, but not in the regression analysis, deserve further exploration in future research.

Implications

The "new BPD" is characterized by an arrest in lung development, simplified alveoli, and a reduction in pulmonary microvasculature (Abman et al., 2017). The development of this "new BPD" is multifactorial, demonstrated in the results of this research. Pediatric research has demonstrated a complex relationship between physiologic and psychologic stressors and the development of chronic diseases and conditions (Hornor, 2016). There were multiple stressors from the intrapersonal stressors that reflect risk(s) early in postnatal life (i.e., lower birth weight, gestational age, and need for surfactant dosing). This research demonstrates that there is ongoing evolution of the risks in the development of BPD. Multiple surfactant doses may be an early signal for the "new BPD" rather than being indicative of profound surfactant deficiency. Perhaps infants that require multiple doses of surfactant could benefit from early BPD reduction efforts, such as steroid administration. Also, infants with infections and/or NEC could benefit from early BPD reduction measures such as steroid administration. Finally, systematic surveillance for PDA may lead to improved diagnosis of infants with early

signs of cardiovascular alterations, such as stretching of chambers. Perhaps infants with these signs would benefit from early closure, thus reducing risk for BPD.

Risks Without an Association with BPD

Classically BPD diagnoses are more likely among male infants. This was not the case in this study cohort. Since the sample of subjects were transferred to BCH, they may not represent the total population of preterm infants. While they may represent a segment of NICU patients, these results may not be generalized to all preterm patients. Fetal growth restriction was measured using birth weight, but perhaps there is a more comprehensive measure such as decelerations in growth. MVU and chorioamnionitis were not associated with BPD in any of the analyses. For MVU, it is possible that maternal hypertension does not provide direct measure of MVU. Abnormal fetal doppler findings such as decreased, absent, or reversed umbilical artery end diastolic blood flow may provide a more direct measure of MVU for it is a sign of placental vascular dysfunction with consequences to the fetus (Mestan et al., 2014; Mestan et al., 2017; Taglauer et al., 2018). Coupling maternal hypertension and abnormal fetal doppler may provide improved insight into the impact of MVU on the developing fetus, including its risk for development of BPD. Further, arrest in fetal growth with abnormal fetal doppler findings have been proposed as indicative of FGR without including weight (Torchin et al., 2016). Chorioamnionitis impacts pregnancies that result in preterm deliveries more than full term deliveries, with increasing incidence as gestation decreases (Fowler & Simon, 2020). Chorioamnionitis impacted 12.5% of pregnancies in this study, however the true impact is proposed to be between (8-50%) (Fowler & Simon, 2020). Clinical chorioamnionitis was used to determine chorioamnionitis for this study, but histologic

chorioamnionitis could have led to a more comprehensive determination of the impact of chorioamnionitis on BPD diagnosis. Given that the subjects in the CHND are transferred from outside hospitals, histologic diagnosis of chorioamnionitis may not be entered into the CHND. Perhaps future studies can examine histologic and clinical chorioamnionitis in relation to BPD. While the transfusions were positively associated with BPD diagnosis and higher grade of BPD, it did not continue to have a statistically significant association in the regression analyses. Transfusions may be related to comorbidities.

Limitations

There are several limitations to this study. The data in this study was obtained retrospectively and employed secondary analysis of the CHND. Despite an extensive review of all data sources, there was missing data. Missing data specifically impacted transfusions, race, and ethnicity variables. BCH was not the birth hospital, rather infants were transferred to BCH for management of other conditions such as NEC, PDA, and extreme prematurity. Therefore, the population treated at BCH is not generalizable to the total population of premature infants. This is a sample at a Level IV center, so results may only be generalized to other preterm patients cared for at Level IV NICUs.

Future research

This research revealed several opportunities for future research. Measurement of EUGR was based the Fenton Growth Chart the most consistent measure in the literature (Fenton & Kim, 2013). However, there may be a superior method such as examining not only the weight on a growth chart at a single point, but rather pattern of weight gain or loss. Perhaps using the definition of FTT (weight decline of ≥ 2 major percentiles on the growth chart at separate points of assessment) would be more meaningful (Cole &

Lanham, 2011). Examining MVU more comprehensively, such as patterns of placental blood flow and maternal hypertension would be more comprehensive to fully assess MVU. Finally, testing an updated risk assessment tool that includes the additional variables from this research may lead to more comprehensive diagnosis of each grade of BPD.

Professional Practice Implications

The purpose of this research was to examine the risk factors for BPD as identified in the developed mid-range theory (see Figure 1). With such significant health, economic, and societal costs, identifying infants at risk and targeting interventions to reduce BPD are critical (Abman et al., 2017; Laughon et al., 2011). The normal line of defense represents the usual health state of the client (Fawcett & Neuman, 2011). Findings from this research can be used to implement surveillance and/or preventative management for BPD, thus establishing the Normal Line of Defense for these fragile infants.

The most recent and applicable BPD risk assessment tool includes gestational age, birth weight, sex, race/ethnicity, postnatal day (maximum of 28 days), ventilator type, and oxygen requirement (Laughon et al., 2011). These risk assessment variables were validated through this research however the addition of number of surfactant administrations, diagnosis of NEC, number of postnatal infections, and presence of PDA may help to more accurately predict the development and severity of BPD.

The Normal Line of Defense

Improving the survival and health of infants has been a national focus since 1963, Despite improvements in preterm infant survivability, BPD continues to be a formidable

threat. Identification of infants through a BPD risk assessment is critical so risk reduction efforts can be implemented thus improving the health of preterm survivors.

This research demonstrated the need to add several variables to the current risk assessment tool including surfactant administration, a diagnosis of NEC, postnatal infections, and PDA. Further, understanding the stressors and identifying infants at risk may lead to risk reduction and treatment strategies that can be targeted to prevent BPD. Risk reduction strategies such as early postnatal steroid administration (Clauss et al., 2020) could be implemented for infants that require more than one dose of surfactant and those with postnatal infection(s). Further, the role of PDA and incorporating early systematic surveillance to the care for preterm infants requires examination. Opportunities exist to intervene earlier if damage from over circulation into the lungs can be diagnosed prior to the onset of significant injury. These risk reductions strategies described, provide just a couple examples of the treatment strategies for BPD prevention. With innovation and research perhaps these strategies will be replaced with more advantageous methods of prevention not long into the future.

Appendix 1

Table 1 Criteria for Diagnosis of Bronchopulmonary Dysplasia

Table 1
Criteria for diagnosis of bronchopulmonary dysplasia (BPD)

	Definition	Subcategories	Incidence
Bronchopulmonary Dysplasia (BPD)	Varying severity. Generally defined as any O2 requirement at 28 days of life for infants born <32 weeks gestation. It is diagnosed at 36 weeks corrected GA (Abman et al., 2016)	Mild: O2 treatment at least 28 days, in room air at 36 weeks or at discharge*	Mild 30.3%
		Moderate: O2 treatment at least 28 days and < 30% O2 at 36 weeks or discharge*	Moderate 30.2%
		Severe (type 1): O2 treatment at least 28 days and on ≥30% O2 or nasal CPAP/HFNC at ≥ 36 weeks CGA	Severe 16.4%
		Severe (type 2): O2 treatment at least 28 days and on mechanical ventilation at ≥ 36 weeks CGA	

Abman et al., 2017

Note: 23.1% of infants born <32 weeks' gestation have no BPD

CPAP (continuous positive airway pressure) and HFNC (high flow nasal cannula)

*whichever occurs first

Table 2 Operational Definitions

Table 2 *Operational Definitions*	
Extrauterine growth restriction (EUGR)	Weight less than 10th percentile for age
Necrotizing enterocolitis	A disorder of ischemic necrosis of the intestine, predominantly found in very preterm infants. Stage 1: signs of sepsis, feeding intolerance, abdominal distention, occult blood in the stool Stage 2: signs from Stage 1 plus abdominal radiographs demonstrating rigid bowel loops, pneumatosis, portal venous gas Stage 3: signs from Stage 1 and 2 plus signs of shock and abdominal radiographic evidence of bowel perforation
Neurodevelopmental impairment	Represents a wide variety of manifestations such as cerebral palsy, cognitive delay, and more.
Patent ductus arteriosus (PDA)	A ductus arteriosus is a vascular connection shunting blood from the lungs to the systemic vascular system in the fetus. A PDA occurs when this fails to close postnatally.
Postmenstrual age (PMA)	Gestational age plus time elapsed at birth
Pulmonary hypertension	Elevated pulmonary pressure and manifesting with hypoxia. Can develop among infants with BPD. Associated with more complex hospitalizations, higher costs, and increased risk for morbidity.
Respiratory distress syndrome (RDS)	A syndrome found in preterm infants related to surfactant deficiency, leading to increased work of breathing and varying respiratory support requirements.
Surfactant	A soapy substance that reduces surface tension in the lungs. It is deficient in preterm infants due to lung immaturity, leading to Respiratory Distress syndrome.

Abman et al., 2017; Bell et al., 1978; Glass et al., 2015

Figure 1 Conceptual – Theoretical – Empirical Model

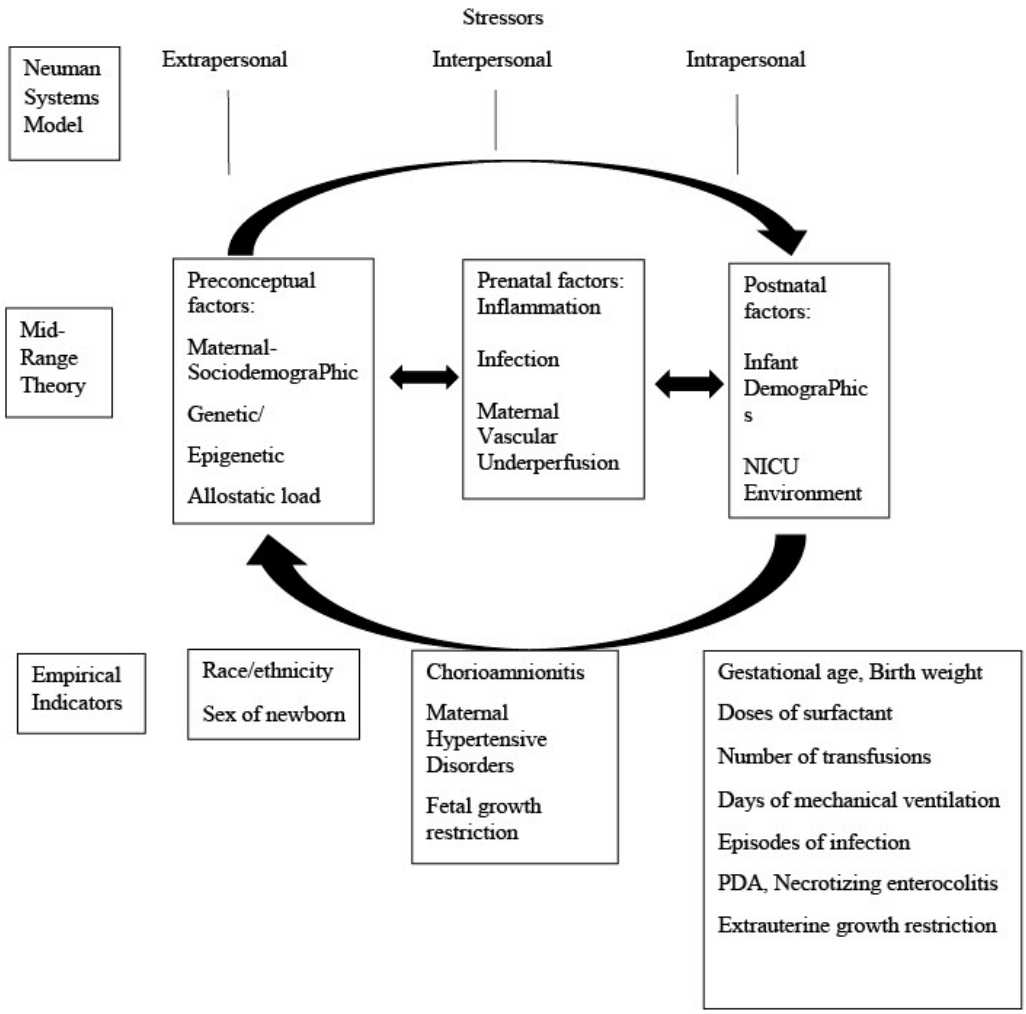

Table 3 Study Variables

Table 3 *Study Variables*		
Category	Variables	Description
Extrapersonal stressors (Socio-demographic)	Race and ethnicity	Black mothers are more likely to experience preterm births (CDC, 2016), but the role of race/ethnicity and the development of BPD is conflicting.
	Sex	Male infants have an increased risk for developing BPD (Northway et al., 1967; Lal et al., 2018a).
Interpersonal stressors (Prenatal risks)	Inflammation	Prenatal inflammation is evidenced by inflammatory changes in the placenta (Redline, 2006). Chorioamnionitis is a maternal infection that causes inflammatory changes in the placenta (Kim et al., 2008; Ogihara et al., 2006; Rocha et al., 2012).
	Infection	Chorioamnionitis is a prenatal infectious process that increases risk for BPD (Arayici et al., 2014; Ballard et al., 2016; Kibel et al., 2016; Lee et al., 2011; Mestan et al., 2014; Solimon et al., 2017).
	Maternal vascular underperfusion	Maternal hypertensive disorders cause maternal vascular underperfusion and increase the risk for BPD and BPD associated pulmonary hypertension (Mestan et al., 2014; Mestan et al., 2017; Solimon et al., 2017; Torchin et al., 2016).
		Fetal growth restriction is defined as fetal growth at < 10^{th} percentile for gestational age, fetal growth restriction is associated with maternal vascular underperfusion. It is defined using birth weight, and it is related to the development of BPD (Charles et al., 2019).
Intrapersonal stressors (Postnatal risks)	Infant demographics	There is an increased risk for development of BPD as gestational age decreases (Binet et al., 2012; Dravet-Gounot et al., 2018; Mestan et al., 2014; Torchin et al., 2016; Tsai et al., 2015).
		Lower birth weights are associated with BPD development (Dravet-Guonot et al., 2018; Guo et al., 2015).
	Inflammation	Mechanical ventilation and oxygen exposure contribute to inflammatory changes and increase the risk for BPD (Inatomi et al., 2012; Klevebro et

		al., 2019; Mailaparambil et al., 2010; Oh et al., 2005; Ohlin et al., 2015; Ozkan et al., 2012; Rutkowska et al., 2019; Yum et al., 2018).
		Necrotizing enterocolitis is an inflammatory bowel infection and is associated with BPD development (Janevic et al., 2018; Ozkan et al., 2012).
	Infection	Postnatal infections are represented by positive bacterial cultures from blood, spinal fluid, tracheal aspirates, and/or urine (Ballard et al., 2016; Dravet-Gounot et al., 2018; Durrmeyer et al., 2012; Guo et al., 2015; Klevebro et al., 2019; Lee et al., 2011; Ohlin et al., 2015; Solimon et al., 2017; Torchin et al., 2016). A diagnosis of necrotizing enterocolitis will also be considered an infection (Bell et al., 1978).
	Doses of surfactant	Higher doses of surfactant is associated with a risk for BPD development ((Dravet-Gounot et al., 2018; Guo et al., 2015; Hofer et al., 2013; Torchin et al., 2016).
	Transfusions of packed red blood cells	Higher volume of packed red blood cell transfusions is associated with an increased risk for BPD development (Demirel et al., 2009)
	Patent ductus arteriosus (PDA)	Presence of a PDA, and whether medical or surgical closure is required, is associated with an increased risk for BPD (Dravet-Gounot et al., 2018; Demirel et al., 2009; Guo et al., 2015; Rutkowska et al., 2019; Torchin et al., 2016).
	Extrauterine growth restriction	Postnatal growth measured at < 10^{th} percentile for gestational age is associated with development of BPD ((Ohlin et al., 2015).

Table 4 Data Abstraction Tool

Table 4 *Data Abstraction Tool*			
Socio-demographic	Ethnicity	Hispanic	Yes
			No
			Unknown
	Race	Select:	Asian
			Black
			White
			American Indian
			Native Alaskan
			Native Pacific Islander
			Other
			Unknown
Interpersonal stressors (Prenatal risks)	Fetal growth restriction (< 10th percentile for age using Fenton & Kim, 2013)	Select	Yes
			No
	Chorioamnionitis	Select	Yes
			No
	Maternal hypertensive disorder (MVU)	Select	Yes
			No
Intrapersonal stressors (Postnatal)	Gestational age	Completed weeks	
	Birth weight	Weight (grams)	
	Sex	Select	Male
			Female
			Unknown
	Doses of surfactant*	Number	
	Number of transfusions*	Number	
	Duration of mechanical ventilation	Number of days Key date of 36 weeks (if	

	(days collected starting in 2010 and minutes in 2016)	admitted prior to key date) look at support on that date, and that gives diagnosis) If < 32 weeks and admitted after key date, they need to be on respiratory support for > 28 days and if they meet that criteria, the days of ventilation are counted. Cut off at 36 weeks ± 2 weeks.	
	Episodes pneumonia*	Number	
	Episodes of blood stream infection*	Number	
	Episodes of meningitis*	Number	
	Episodes of urinary tract infections*	Number	
	Patent ductus arteriosus	Diagnosis of PDA	Yes
			No
		If Yes PDA:	No treatment
			Medical treatment
			Surgical treatment
	Necrotizing enterocolitis ≥ Bell's Stage 2 (Bell et al., 1978)	Diagnosis of NEC	Yes
			No
		If Yes NEC	Medical NEC
			Surgical NEC: Drain placement or Open abdomen
			Recurrent NEC
	Weight*	28 days (grams)	
		36 weeks (grams)	

		40 weeks (grams)	
		44 weeks (grams)	
		50 weeks (grams)	
	Extrauterine growth restriction (Fenton & Kim, 2013)	Select	Yes
			No
	Diagnosis of BPD	Select	Yes
			No
		Grading (select)	None
			Mild
			Moderate
			Severe Type 1
			Severe Type 2

*Denotes data that may be obtained in the Boston Children's Medical Record

Table 5 Inclusion and Exclusion Criteria

Table 5

Inclusion and Exclusion Criteria

Inclusion	Exclusion
Birth at < 32 weeks' gestation	Major congenital anomalies (excluding PDA)
	Congenital renal disease
	Outcome of BPD cannot be determined based on data
	Neuromuscular disorders
	Metabolic disorders

Figure 2 PRISMA Diagram

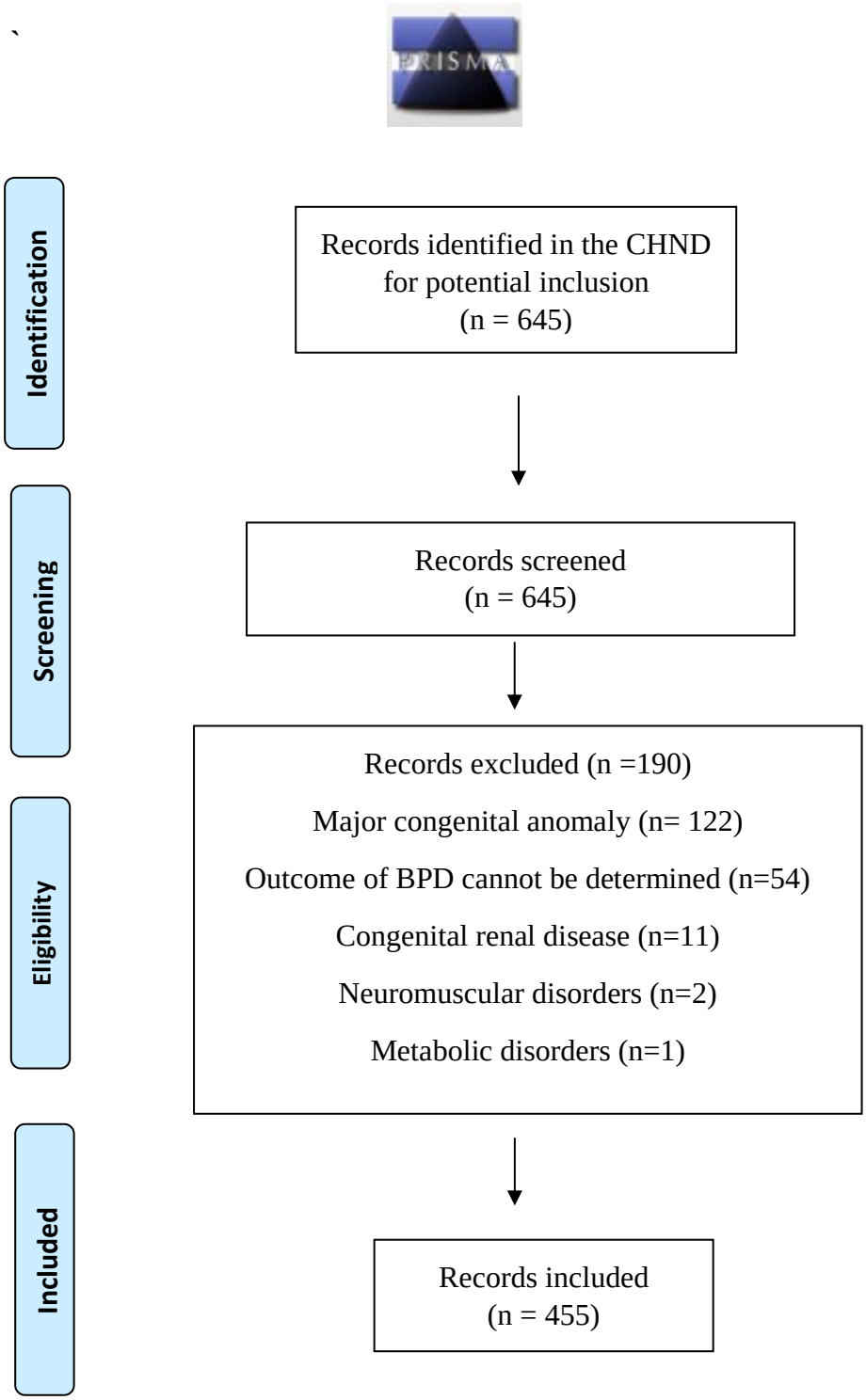

Table 6 Description of the Sample

Table 6 *Description of the Sample*		
Variable	Frequency (n)	Percentage (%)
Sex		
Male	284	62.4
Female	171	37.6
Ethnicity		
Hispanic or Latino	48	10.5
Not Hispanic or Latino	274	60.2
Unknown	133	29.2
Race		
White	218	47.9
Black/African American	78	17.1
Asian	18	4
Native American/Alaskan	1	0.2
Native Hawaiian/Pacific Islander	0	0
Other	49	10.8
Unknown	96	21.1
Fetal growth restriction		
Yes	81	17.8
No	369	81.1
Missing	5	1.1
Chorioamnionitis		
Yes	57	12.5
No	394	86.6
Missing	4	0.9
Maternal vascular underperfusion		
Yes	116	25.5
No	336	73.8
Missing	3	0.7
Variable	Median	Interquartile Range
Gestational age (completed weeks)	26	25, 28
Birth weight (grams)	820	650, 1090
Mechanical ventilation		
Non-invasive mechanical ventilation (days)	25	10, 44
Invasive mechanical ventilation (days)	32	8, 61
Total mechanical ventilation (days)	63	25, 91

Table 7 Infections

Table 7 *Infections*		
Number of infections	Frequency (n)	Percent (%)
Pneumonia		
0	341	74.9
1	73	16
2	33	7.3
3	5	1.1
6	1	0.2
Missing	2	0.4
Blood stream infection		
0	332	73
1	99	21.7
2	19	4.2
3	3	0.7
Missing	2	0.4
Meningitis		
0	427	93.8
1	25	5.5
2	1	0.2
Missing	2	0.4
Urinary tract infections		
0	395	86.8
1	47	10.3
2	11	2.4
Missing	2	0.4
Total infections		
0	224	49.2
1	119	26.2
2	66	14.5
3	30	6.6
4	13	2.9
9	1	0.2
Missing	2	0.4

Table 8 PDA and NEC Diagnoses

Table 8 *PDA and NEC Diagnoses*		
Variable	Frequency (n)	Percentage (%)
PDA diagnosis		
Yes	284	62.4
No	169	37.1
Unknown	2	0.4
PDA medical treatment		
Yes	194	42.6
No	261	57.4
PDA surgical treatment		
Yes	101	22.2
No	354	77.8
PDA medical and surgical treatment		
Yes	65	14.3
No	390	85.7
NEC diagnosis		
Yes	151	33.2
No	303	66.6
Unknown	1	0.2
NEC medical treatment		
Yes	72	15.8
No	383	84.2
NEC surgical treatment		
Yes	99	21.8
No	356	78.2
NEC medical and surgical treatment		
Yes	20	4.4
No	435	95.6

Table 9 Transfusion Groups

Table 9 *Transfusion Groups*				
141 missing		BPD		
Transfusion groups	Group	No	Yes	Total
	Group 1 0 (78)	45	33	78
	Group 2 1-2 (74)	16	58	74
	Group 3 3-6 (86)	6	80	86
	Group 4 7 and > (76)	1	75	76
Total		68	246	314

Table 10 BPD Diagnosis and Grading

Table 10 *BPD Diagnosis and Grading*		
Variable	Frequency (n)	Percentage (%)
BPD diagnosis		
Yes	381	83.7
No	73	16.3
Grade		
Mild	70	15.4
Moderate	54	11.9
Severe (type 1)	168	36.9
Severe (type 2)	90	19.8

Table 11 Bivariate Analysis of the Extrapersonal Stressors and BPD

Table 11

Bivariate Analysis of the Extrapersonal Stressors and BPD

	BPD Diagnosis			
	Yes	No		
Variable	n (%)	n (%)	X^2(df)	p value
Race				
White	172 (78.9)	46 (21.1)	7.19 (1)	<0.01
Asian	14 (77.8)	4 (22.2)	0.49 (1)	0.49
Black/African American	68 (87.2)	10 (12.8)	0.82 (1)	0.37
Other	47 (10.3)	2 (0.4)	5.98 (1)	0.01
Unknown	84 (87.5)	12 (12.5)	1.27 (1)	0.26
Native Alaskan	1 (100)	0 (0)	0.2 (1)	0.66
Ethnicity			5.79 (2)	0.06
Hispanic/Latino	46 (95.8)	2 (4.2)		
Not Hispanic/Latino	225 (82.1)	49 (17.9)		
Unknown	110 (82.7)	23 (17.3)		
Sex			1.21 (1)	0.27
Female	139 (81.3)	32 (18.7)		
Male	242 (85.2)	42 (14.8)		

There were zero Native Hawaiian/Pacific Islander

Row percentage was reported here.

Race categories are not mutually exclusive

Table 12 Bivariate Analysis of the Interpersonal Stressors and BPD

Table 12

Bivariate Analysis of the Interpersonal Stressors and BPD

	BPD Diagnosis			
	Yes	No		
Variable	n (%)	n (%)	X^2(df)	p value
Chorioamnionitis	51	6	1.76 (2)	0.42
Maternal vascular underperfusion	100	16	0.53 (2)	0.53
Fetal growth restriction	76	5	7.48 (2)	0.03

Table 13 Bivariate Analysis of the Intrapersonal Stressors and BPD

Table 13 *Bivariate Analysis of the Intrapersonal Stressors and BPD*					
Continuous Variables					
Variable	Median	IQR	SD	*Z*	p value
Gestational age (weeks)	26	25, 28	2.93	-18.52	<0.01
Birth weight (grams)	820	650, 1090	348.38	-18.4	<0.01
Non-invasive MV (days)	25	10, 44	23.37	-17.37	<0.01
Invasive MV (days)	32	8, 60.8	44.34	-16.62	<0.01
Total days MV (days)	63	29, 91	46.85	-18.22	<0.01
Total infections	1	0, 1	1.14	-13.7	<0.01
	Median	IQR	*SE*	*U*	p value
Surfactant	1	1, 2	931.74	7.2	<0.01
Categorical Variables					
	BPD Diagnosis				
	Yes	No			
Variable	n (%)	n (%)	X^2(df)	p value	
Transfusions			89.16	<0.01	
0 transfusions	33	45			
1-2 transfusions	58	16			
3-6 transfusions	80	6			
≥ 7 transfusions	75	1			
NEC categories			21.73	<0.01	
No NEC	240	63			
Medical NEC	46	6			
Surgical NEC	75	4			
Medical and Surgical NEC	20	0			
PDA categories			60.41	<0.01	
No PDA	45	9			
PDA, no treatment	115	56			
Medically treated PDA	122	7			
Surgically treated PDA	35	1			
Medically and surgically treated PDA	64	1			
Extrauterine growth restriction	228	24	20.2	<0.01	

U is standardized test statistic

Mechanical ventilation (MV)

Table 14 Correlation Matrix

Table 14

Correlation Matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13
GA	1												
BW	.76**	1											
Surf	-.35**	-.32**	1										
Trans	-.33**	-.31**	.24**	1									
Total MV	-.58**	-.58**	.38**	.45**	1								
PNA	-.23**	-.27**	.17**	.20**	.53**	1							
BSI	-.22**	-.17**	.05	.17**	.13**	.02	1						
Men.	-.05**	.00	-.00	.04	.02	-.01	.17**	1					
UTI	-.11**	-.15**	.09	.22**	.25**	.05	.21**	.02	1				
Total Inf	-.31**	-.31**	.17**	.3**	.49**	.66**	.65**	.31**	.52**	1			
Trans Grps	-.63**	-.54**	.31**	.63**	.65**	.29**	.29**	.1	.29**	.46**	1		
NEC All	-.28**	-.2**	.08	.29**	.14**	-.03	.28**	.03	.23**	.22**	.47**	1	
PDA All	-.4**	-.33**	.21**	.16**	.24**	.12*	.04	-.06	.07	.11*	.32**	.12**	1

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

Table 15 Binary Logistic Regression Analysis of the Predictive Variables and BPD

Table 15

Binary Logistic Regression Analysis of the Predictive Variables and BPD

	Univariate Logistic Regression		Multivariate Logistic Regression	
Independent Variables	OR (95% CI)	*P value*	OR (95% CI)	*P value*
Gestational age (weeks)	0.39 (0.32, 0.48)	<0.01	1.29 (0.741, 2.25)	0.37
Birth weight (GA)	0.99 (0.99, 0.99)	<0.01	0.99 (0.99, 1)	0.04
FGR	3.4 (1.34, 8.81)	0.01	0.59 (0.07, 5.09)	0.64
Doses of surfactant	3.86 (2.57, 5.79)	<0.01	2.49 (1.07, 5.77)	0.03
Total days of mechanical ventilation	1.18 (1.13, 1.23)	<0.01	1.19 (1.11, 1.27)	<0.01
Total infections	2.31 (1.59, 3.37)	<0.01	0.45 (0.19, 1.03)	0.06
EUGR	3.21 (1.89, 5.44)	<0.01	0.89 (0.24, 3.29)	0.87
Transfusion groups	1.8 (1.47, 2.19)	<0.01	0.89 (0.67, 1.18)	0.43
Race: population	1.16 (1.04, 1.29)	0.01	8979712 (0.00)	0.99
PDA (categorical)	7.2 (4,05, 12.78)	<0.01	1.55 (0.37, 6.45)	0.55
PDA (interval)	5.71 (2.99, 10.88)	<0.01	2.57 (0.84, 7.86)	0.09
NEC (categorical)	3.37 (1.72, 6.6)	<0.01	2.1 (0.27, 16.08)	0.48
NEC (interval)	1.77 (1.27, 2.74)	<0.01	1.66 (0.75, 3.7)	0.22

Model fit for binary logistic regression was X^2 292.77, *df* 18, $p < 0.01$

Table 16 Bivariate Analysis of Extrapersonal Stressors by BPD Grade

Table 16

Bivariate Analysis of Extrapersonal Stressors by BPD Grade

	BPD Grade						
	None	Mild	Moderate	Severe (type 1)	Severe (type 2)		
Variable	n (%)	n (%)	n (%)	n (%)	n (%)	X^2 (*df*)	*p* value
Race						57.72 (32)	<0.01
White	45 (61,6)	36 (51.4)	29 (53.7)	76 (45.2)	32 (35.6)	12.58 (4)	0.01
Black	10 (13.7)	12 (17.1)	9 (16.7)	25 (14.9)	22 (24.4)	4.6 (4)	0.33
Asian	4 (5.5)	0 (0)	0 (0)	14 (8.3)	0 (0)	17.73 (4)	<0.01
Other	0 (0)	0 (0)	0 (0)	1 (0.6)	0 (0)	1.71 (4)	0.79
Unknown	12 (16.4)	14 (20)	8 (14.8)	35 (20.8)	27 (30)	6.58 (4)	0.16
Ethnicity						*9.54 (8)*	0.29
Hispanic or Latino	2 (2.7)	8 (11.4)	6 (11.1)	20 (11.9)	12 (13.3)		
Not Hispanic or Latino	49 (67.1)	40 (57.1)	27 (50)	104 (61.9)	54 (60)		
Unknown	22 (30.1)	22 (31.4)	21 (38.9)	44 (26.2)	24 (26.7)		
Sex						4.72 (4)	0.32
Male	42 (57.5)	39 (55.7)	31 (57.4)	111 (66.1)	61 (64.2)		
Female	31 (42.5)	31 (44.3)	23 (42.6)	57 (33.9)	29 (32.2)		

Table 17 Bivariate Analysis of Interpersonal Stressors by BPD Grade

Table 17

Bivariate Analysis of Interpersonal Stressors by BPD Grade

	BPD Grade							
	None	Mild	Moderate	Severe (type 1)	Severe (type 2)			
Variable	n (%)	n (%)	n (%)	n (%)	n (%)	X^2 (*df*)	Phi	*p* value
Chorioamnionitis	6	11	7	15	18	10.37 (8)	0.15	0.24
Maternal vascular underperfusion	16	15	43	43	31	7.62 (8)	0.13	0.47
Fetal growth restriction	5	5	4	40	27	29.07 (4)	0.25	<0.01

Table 18 Bivariate Analysis of Intrapersonal Stressors and BPD Grade

Table 18

Bivariate Analysis of Intrapersonal Stressors and BPD Grade

Variable	Median	IQR	SD	*Z*	p value			
Gestational age (weeks)	26	25, 28	2.39	-18.51	<0.01			
Birth	820	650, 1090	348.38	-18.4	<0.01			
Total MV (days)	63	29	91	-18.22	<0.01			
Total infections	1	0, 1	1.14	-17.72	<0.01			
	BPD Grading							
	None	Mild	Moderate	Severe Type 1	Severe Type 2			
	n (%)	n (%)	n (%)	n (%)	n (%)	X^2 (df)	phi	p value
Surfactant						95.52 (16)	0.46	<0.01
0 doses	35	17	5	17	6			
1 dose	31	33	33	71	36			
2 doses	3	16	12	63	32			
3 doses	2	2	3	11	10			
4 doses	0	0	0	3	3			
Transfusion groups						185.22 (16)	0.64	<0.01
0 transfusions	45	15	8	9	1			
1-2 transfusions	16	13	14	27	4			
3-6 transfusions	6	14	13	40	13			
≥ 7 transfusions	1	7	8	30	30			
NEC categories						39.25 (16)	0.29	<0.01
No NEC	62	39	43	106	53			
Medical NEC	6	6	6	25	9			
Surgical NEC	4	20	4	30	21			
Medical and Surgical NEC	0	5	1	7	7			
PDA categories						89.34 (16)	0.44	<0.01
No PDA	8	9	9	19	9			
PDA, no treatment	56	38	13	41	23			

Medically treated PDA	7	14	19	56	33			
Surgically treated PDA	1	4	4	20	7			
Medically and surgically treated PDA	1	5	9	32	18			
EUGR	24	33	30	108	60	26.92 (4)	0.24	<0.01

Table 19 Multinomial Regression Analysis of Predictive Variables and Mild BPD

Table 19

Multinomial Regression Analysis of Predictive Variables and Mild BPD

	Univariate Multinomial Regression		Multivariate Multinomial Regression	
Independent Variables	OR (95% CI)	p value	OR (95% CI)	p value
Race: White	1.12 (0.55, 2.28)	0.75	0.75 (0.23, 2.46)	0.64
Race: Other	0.16 (0.03, 0.8)	0.03	0.31 (0.03, 3.52)	0.35
FGR	0.96 (0.26, 3.46)	0.94	2.22 (0.22, 22)	0.5
Gestational age	0.45 (0.36, 0.56)	<0.01	1.08 (0.61, 1.89)	0.79
Birth weight	0.99 (0.99, 0.99)	<0.01	0.99 (0.99, 1)	0.13
Doses of surfactant	2.47 (1.5, 4.04)	<0.01	1.89 (0.83, 4.34)	0.13
Total days of mechanical ventilation	1.16 (1.11, 1.21)	<0.01	1.16 (1.1,1.22)	<0.01
Total infections	1.51 (0.93, 2.44)	0.1	0.36 (0.14, 0.9)	0.03
Transfusion (0)	0.19 (0.06, 0.66)	<0.01	1.06 (0.13, 8.92)	0.96
Transfusions (1-2)	0.19 (0.06, 0.66)	<0.01	1.46 (0.2, 10.72)	0.71
Transfusions (3-6)	0.56 (0.14, 2.22)	0.4	2.29 (0.22, 24.35)	0.49
Transfusions (>7)	1.67 (0.17, 16.81)	0.67	2.03 (0.05, 84.54)	0.49
PDA (interval)	3.27 (1.61, 6.65)	<0.01	2.06 (0.77, 5.56)	0.15
PDA (categorical)	0.36 (0.18, 0.74)	<0.01	0.64 (0.18, 2.3)	0.49
NEC (interval)	2.06 (1.44, 2.95)	<0.01	2.17 (1.09, 4.35)	0.03
NEC (categorical)	0.22 (0.1, 0.49)	0.22	0.28 (0.05, 1.44)	0.13
EUGR	0.55 (0.28, 1.08)	0.08	1.79 (0.44, 7.32)	0.41

For entire model: X^2 629.59 (df 84), p<0.01. Goodness-of-Fit X^2 1715.85 (PDA and NEC categorical)

X^2 611.67 (df 64) p< 0.01. Goodness-of-Fit X^2 7422 (df 1672) p<0.01) PDA and NEC interval)

Table 20 Multinomial Regression Analysis of Predictive Variables and Moderate BPD

Table 20

Multinomial Regression Analysis of Predictive Variables and Moderate BPD

	Univariate Multinomial Regression		Multivariable Multinomial Regression	
Independent Variables	OR (95% CI)	p value	OR (95% CI)	p value
Race: White	0.98 (0.45, 2.11)	0.95	0.86 (0.24, 3.04)	0.82
Race: Other	0.14 (0.03, 0.72)	0.02	0.23 (0.02, 2.95)	0.26
FGR	0.92 (0.24, 3.65)	0.92	2.44 (0.22, 26.88)	0.47
Gestational age	0.4 (0.32, 0.51)	<0.01	1.05 (0.57, 1.93)	0.87
Birth weight	0.99 (0.99, 0.99)	<0.01	0.99 (0.99, 1)	0.11
Doses of surfactant	3.45 (2.05, 5.8)	<0.01	2.48 (1.04, 5.89)	0.04
Total days of MV	1.17 (1.12, 1.22)	<0.01	1.15 (1.09, 1.22)	<0.01
Total infections	1.44 (0.86, 2.39)	0.17	0.36 (0.14, 0.94)	0.04
Transfusion (0)	0.08 (0.02, 0.3)	0.67	1.44 (0.15, 14)	0.75
Transfusion (1-2)	0.4 (0.11, 1.43)	0.16	2.84 (0.35, 23.43)	0.33
Transfusion (3-6)	0.99 (0.24, 4.13)	0.98	3.28 (0.29, 36.39)	0.33
Transfusion (>7)	3.64 (0.35, 37.46)	0.28	4.1 (0.09, 188.17)	0.47
PDA (categorical)	0.01 (0.04, 0.22)	<0.01	0.16 (0.04, 5.9)	0.01
PDA (interval)	5.91 (2.96, 11.81)	<0.01	3.35 (1.27, 8.84)	0.02
NEC (categorical)	0.69 (0.28, 1.74)	0.44	1.2 (0.21, 6.9)	0.84
NEC (interval)	1.22 (0.79, 1.89)	0.37	0.92 (0.42, 2.02)	0.84
EUGR	0.39 (0.19, 0.81)	0.01	0.95 (0.22, 4.05)	0.94

Table 21 Multinomial Regression Analysis of Predictive Variables and Severe (Type 1) BPD

Table 21

Multinomial Regression Analysis of Predictive Variables and Severe (Type 1) BPD

	Univariate Multinomial Regression		Multivariable Multinomial Regression	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Race: White	1.67 (0.94, 2.98)	0.08	1.27 (0.36, 4.47)	0.71
Race: Other	0.31 (0.07, 1.42)	0.13	0.9 (0.07, 11.49)	0.94
FGR	0.24 (0.9, 0.63)	<0.01	1.02 (0.1, 10.28)	0.98
Gestational age	0.38 (0.31, 0.47)	<0.01	2.07 (1.13, 3.79)	0.02
Birth weight	0.99 (0.99, 0.99)	<0.01	0.99 (0.99, 0.99)	0.01
Doses of surfactant	4.79 (3.05, 7.51)	<0.01	2.61 (1.09, 6.23)	0.03
Total days of MV	1.22 (1.17, 1.28)	<0.01	1.23 (1.16, 1.31)	<0.01
Total infections	2.44 (1.62, 3.68)	<0.01	0.44 (0.17, 1.11)	0.08
Transfusion (0)	0.02 (0.01, 0.05)	<0.01	0.42 (0.04, 4.14)	0.45
Transfusion (1-2)	0.14 (0.05, 0.41)	<0.01	0.88 (0.11, 7.21)	0.91
Transfusion (3-6)	0.54 (0.15, 1.88)	0.33	1.34 (0.13, 14.39)	0.81
Transfusion (>7)	2.42 (0.27, 21.64)	0.43	1.34 (0.03, 59.75)	0.88
PDA (categorical)	0.01 (0.05, 0.19)	<0.01	0.19 (0.05, 0.73)	0.02
PDA (interval)	6.44 (3.33, 12.47)	<0.01	3.77 (1.39, 10.2)	<0.01
NEC (categorical)	0.3 (0.15, 0.62)	<0.01	0.49 (0.09, 2.76)	0.42
NEC (interval)	1.67 (1.18, 2.38)	<0.01	1.51 (0.72, 3.16)	0.28

EUGR	0.27 (10.15, 0.49)	<0.01	1.61 (0.37, 7.13)	0.53

Table 22 Multinomial Regression Analysis of Predictive Variables and Severe (Type 2) BPD

Table 22

Multinomial Regression Analysis of Predictive Variables and Severe (Type 2) BPD

	Univariate Multinomial Regression		Multivariable Multinomial Regression	
Variable	OR (95% CI)	p value	OR (95% CI)	*p value*
Race: White	2.66 (1.38, 5.11)	<0.01	1.85 (0.46, 7.52)	0.39
Race: Other	0.41 (0.08, 2.04)	0.28	1.13 (0.08, 16.58)	0.93
FGR	0.17 (0.06, 0.47)	<0.01	0.6 (0.05, 7.27)	0.69
Gestational age	0.35 (0.28, 0.44)	<0.01	2.34 (1.21, 4.5)	0.01
Birth weight	0.99 (0.99, 0.99)	<0.01	0.99 (0.99, 1)	0.06
Doses of surfactant	5.98 (3.67, 9.73)	<0.01	3.07 (1.21, 7.79)	0.02
Total days of mechanical ventilation	1.26 (1.21, 1.32)	<0.01	1.27 (1.19, 1.35)	<0.01
Total infections	4.22 (2.72, 6.52)	<0.01	0.55 (0.21, 1.46)	0.23
Transfusion (0)	0.00 (0.00, 0.02)	<0.01	0.32 (0.01, 7.05)	0.47
Transfusion (1-2)	0.03 (0.01, 0.13)	<0.01	0.45 (0.04, 5.02)	0.51
Transfusion (3-6)	0.26 (0.07, 0.99)	0.05	0.97 (0.08, 11.83)	0.98
Transfusion (>7)	2.42 (0.27, 21.64)	0.43	2.3 (0.05, 107.95)	0.67
PDA (categorical)	0.1 (0.05, 0.21)	<0.01	0.16 (0.04, 0.7)	0.02
PDA (interval)	6.55 (3.35, 12,84)	<0.01	4.75 (1.69, 13.34)	<0.01
NEC (categorical)	0.25 (0.12, 0.55)	<0.01	0.49 (0.08, 3.12)	0.46
NEC (interval)	1.95 (1.37, 2.78)	<0.01	1.84 (0.85, 3.9)	0.12
EUGR	0.25 (0.13, 0.47)	<0.01	2.34 (0.44, 12.36)	0.32

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