

2019

# Developing a predictive mortality risk algorithm for preterm neonates requiring surgical intervention at Boston Children's Hospital

---

<https://hdl.handle.net/2144/36609>

*"Downloaded from OpenBU. Boston University's institutional repository."*

BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**DEVELOPING A PREDICTIVE MORTALITY RISK ALGORITHM FOR  
PRETERM NEONATES REQUIRING SURGICAL INTERVENTION AT  
BOSTON CHILDREN'S HOSPITAL**

by

**MICHAEL ROMANO**

B.A., Boston University, 2015

Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Science

2019

© 2019 by  
MICHAEL ROMANO  
All rights reserved

Approved by

First Reader

---

Judith D. Saide, Ph.D.  
Associate Professor of Physiology & Biophysics

Second Reader

---

Izabela C. Leahy, MS, BSN, RN  
Executive Director Department of Anesthesiology, Critical Care & Pain  
Medicine at Boston Children's Hospital

**DEVELOPING A PREDICTIVE MORTALITY RISK ALGORITHM FOR  
PRETERM NEONATES REQUIRING SURGICAL INTERVENTION AT  
BOSTON CHILDREN'S HOSPITAL**

**MICHAEL ROMANO**

**ABSTRACT**

**Introduction:** Preterm infants have high mortality rates worldwide (Blencowe et al., 2013). The leading causes of infant mortality in the United States are preterm birth, low birth weight, and birth defects (Ely, Driscoll, & Matthews, 2018). The aim of this study is to compare demographics and patient characteristics between surviving and deceased neonates who had fewer than 39 weeks of gestation and required surgical intervention at Boston Children's Hospital (BCH), and to report clinical characteristics among the deceased population. By identifying significant prognostic factors of mortality in this patient population, a future predictive mortality risk algorithm can be developed.

**Methods:** After IRB approval, data was obtained from electronic medical records. All patients born before 39 weeks of gestation from 2013-2018 and had a surgical procedure at BCH within the first thirty days of life were included. Demographic characteristics were compared between survivors and deceased patients, and clinical variables are presented among deceased neonates. Statistical testing was done by the Wilcoxon rank sum test and Fisher's exact test.

**Results:** 653 patients were included in the dataset, 56 of whom were deceased, an 8.6% mortality rate. The median gestational age of the deceased and surviving patients was not statistically different, 35 weeks and 36 weeks respectively ( $p=0.076$ ). In addition, there was no significant difference between the ratio of males to females between the two groups ( $p=0.234$ ). However, mortality rates were significantly different across gestational age categories ( $p=0.015$ ) between deceased and surviving patients. In addition, lower birth weight ( $p=0.009$ ) and higher ASA classification (an anesthesia preoperative physiological assessment score) ( $p<0.001$ ) were both independently associated with significantly higher mortality rates. Due to time constraints, only a descriptive analysis could be done on certain clinical variables among the deceased population. Among the deceased group, 62.5% of the surgical procedures were cardiac-related. The median maximum intraoperative lactate value for the entire deceased population was 6.5 mmol/L (IQR: 4.3–8.7). The median age at death was 46 days (IQR: 25-109), and 58.9% of all deceased patients had their care redirected to comfort measures only. Nearly half of the deceased population (27/56; 48.2%) had at least one CPR (cardiopulmonary resuscitation) event. Future analysis will compare these factors against the surviving patients to determine if a significant association with mortality exists.

**Discussion:** The mortality of preterm infants occurs at a high rate. While there were no significant differences between the deceased and surviving groups in terms of gender distribution or gestational age, lower birth weight and higher ASA classification were both independently associated with significantly higher mortality rates; this suggests that

the deceased patients were smaller and had more complex medical histories than the surviving group. The majority of deceased patients underwent cardiac-related procedures and most had CPR performed at least once. Further investigation of the entire study population is necessary. A better understanding of the factors that contribute to preterm infant mortality could help families and health professionals to make complex decisions about medical interventions.

**Conclusion:** Additional analysis is needed to further identify and better understand patterns in premature neonate mortality at Boston Children's Hospital.

## TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
ABSTRACT.....	iv
TABLE OF CONTENTS.....	vii
LIST OF TABLES.....	ix
LIST OF FIGURES.....	x
LIST OF ABBREVIATIONS.....	xi
INTRODUCTION.....	1
<b>Infant and Neonatal Mortality</b> .....	1
<b>Prematurity</b> .....	3
<b>Risk Factors of Preterm Pregnancy</b> .....	6
<b>Preterm Mortality and Morbidity</b> .....	8
<b>Improvements in Neonatal Care</b> .....	12
<b>Mortality Risk Assessment Tools</b> .....	13
SPECIFIC AIMS.....	18
METHODS.....	19
<b>Statistical Analysis</b> .....	21

RESULTS.....	23
DISCUSSION.....	26
APPENDIX.....	36
LIST OF JOURNAL ABBREVIATIONS.....	38
REFERENCES.....	39
VITA.....	44

## LIST OF TABLES

Table	Title	Page
1	Comparisons of Global Neonatal Mortality and Infant Mortality in 2017	2
2	Prevalence of Preterm Birth by Gestational Age in the United States; 2015	5
3	Prognostic Factors Used in Several Popular Illness Severity Scoring Systems	17
4	Research Variables of Interest	20
5	Gestational Age Categories	21
6	A Comparison of Patient Characteristics and Demographics Between Deceased and Surviving Patients	24
7	Descriptive Statistics of the Deceased Group	25
8	Emergency Drug Dose Recommendation guidelines	30

## LIST OF FIGURES

Figure	Title	Page
1	Preterm mortality rate by gestational age of neonates born in the United States	9
2	Major and minor morbidity prevalence by gestational age	11

## LIST OF ABBREVIATIONS

ASA.....	American Society of Anesthesiologists
BCH.....	Boston Children’s Hospital
CPAP.....	Continuous Positive Airway Pressure
CPR.....	Cardiopulmonary Resuscitation
CRIB.....	Clinical Risk Index for Babies
ICS.....	Infant Coma Scale
IFS.....	Infant Face Scale
IL-6.....	Interleukin 6
PGCS.....	Pediatric Glasgow Coma Scale
PPROM.....	Preterm Premature Rupture of Membranes
SNAP.....	Score for Neonatal Acute Physiology
SNAPPE.....	Score for Neonatal Acute Physiology-Perinatal Extension
TNF.....	Tumor Necrosis Factor

## INTRODUCTION

### **Infant and Neonatal Mortality**

The neonatal period, defined as the first 28 days of life, is an extremely vulnerable time period corresponding to the highest risk of infant mortality (UNICEF, WHO, World Bank Group, & United Nations, 2018). Globally, the neonatal mortality rate was 18 deaths per 1000 births, with approximately 2.5 million neonatal deaths in 2017 alone (“Neonatal mortality,” 2018). Of the 2.5 million neonatal deaths that occurred, roughly 1 million deaths were on the first day of life, and a subsequent 1 million deaths occurred within the next six days (“Neonatal mortality,” 2018). While neonatal mortality is very high, there have been significant reductions in neonatal mortality over the last thirty years. In 1990 the global neonatal mortality rate was 37 deaths per 1000 births with 5 million neonatal deaths that year (UNICEF et al., 2018). From 1990 to 2017, the global neonatal mortality rate and total number of neonatal deaths have both decreased by approximately 50%.

Total infant mortality is usually broken down into neonatal (age 0-28 days) and post-neonatal (age 29-364 days) periods (Ely et al., 2018). Data from the United States in 2017 indicate that the neonatal and post-neonatal mortality rates were 3.88 and 1.99 deaths per 1000 births respectively, corresponding to a total infant mortality rate of 5.87 per thousand births (Ely et al., 2018). Comparison of the neonatal mortality rate with the total infant mortality rate reveals that neonates made up two-thirds of all infant deaths in the United States (Table 1). While the United States has seen a ten percent decline in

neonatal mortality from 2007 to 2011, there have not been significant changes in either neonatal or post-neonatal mortality rates from 2011 to 2016 (Ely et al., 2018).

**Table 1. Comparisons of Global Neonatal Mortality and Infant Mortality in 2017. Table amended from UNICEF et al., 2018**

<b>Region</b>	<b>Infant Mortality Rate (deaths per 1000 births)</b>	<b>Neonatal Mortality Rate (deaths per 1000 births)</b>	<b>Neonatal proportion of Infant deaths (%)</b>
Africa	51	27	53%
Europe	8	5	63%
South-East Asia	29	21	72%
United States	6	4	66%
Global	29	18	62%

Just as the neonatal and post-neonatal mortality rates are significantly different, so too are the leading causes of death for each respective group. For neonates in the United States, the top three causes of death in 2016 were low birth weight, congenital malformations, and maternal complications (Ely et al., 2018). For post-neonatal infants the top three causes of death in 2016 were congenital malformations, sudden infant death syndrome, and unintentional injuries (Ely et al., 2018). When we look at risk factors associated with neonatal mortality, we find that prematurity is associated with over 50% of all neonatal deaths (Blencowe et al., 2013). In 2010, one million neonatal deaths were

the direct result of prematurity and another 800,000 deaths were the indirect result of preterm birth, with or without intrauterine growth restriction, resulting from complications such as infection (Howson, Kinney, McDougall, & Lawn, 2013). The impact of prematurity as a serious risk factor in neonatal health is also not confined to developing countries. In almost all middle and high-income countries in the world, the direct and indirect consequences of preterm birth are the leading cause of neonatal death (Blencowe et al., 2013).

### **Prematurity**

The World Health Organization (WHO) defines preterm or premature birth as being born alive before completing 37 weeks of gestation (“Preterm birth,” 2018). Globally, it is estimated that 41,000 infants are born preterm each day (Platt, 2014). While more specific estimates of the extent and prevalence of preterm birth has been difficult to assess across the world, estimates by the WHO in recent years have shed new light on prematurity’s pervasive effects (Howson et al., 2013). In the landmark report, *Born too Soon: The Global Action Report on Preterm Birth*, WHO et al. showed for the first time the country-specific estimates of prematurity with reliable trend data showing that rates of prematurity are increasing worldwide (World Health Organization, March of Dimes, The Partnership for Maternal, Newborn & Child Health, & Save the Children, 2012). While the global preterm birth rate was estimated to be 11.1% in 2010, there are significant variations in this rate depending on the geographic region and country (Blencowe et al., 2013). The areas of Southern Asia and Sub-Saharan Africa have the

highest preterm birth rate (12.8%), making up 60% of all global preterm births (Blencowe et al., 2013). While not as high, the United States, in comparison, had a 12.0% preterm birth rate in 2010 and accounted for 42% of all preterm births in developed countries (Blencowe et al., 2012). Estimates for preterm birth show a consistent increase in the preterm birth rate over time. Trends of preterm birth from 1990 to 2010 show a consistent increase in the number of preterm births per year, with an estimated 19.4% increase in developed countries over that time (Blencowe et al., 2012). In the United States however, there has been a slight decline in recent years. Reaching as high as 12.8% in 2006, the preterm birth rate in the United States as of 2015 has gone down to 9.62% (Purisch & Gyamfi-Bannerman, 2017).

In developing countries human viability, defined as the gestational age at which the chance of survival is 50%, is 23-24 weeks (Glass et al., 2015). To better categorize preterm patients, prematurity has been classified by the extent of gestation before birth: extremely preterm (<28 weeks' gestation), very preterm (28 weeks to 31 weeks 6/7 days), moderately preterm (32 weeks to 33 weeks 6/7 days), and late preterm (34 weeks to 36 weeks 6/7 days) (Schonhaut, Armijo, & Pérez, 2015).<sup>1</sup> While this 37 week cutoff formally defines prematurity, it is known that babies born at 38 and 39 weeks' gestation still have higher mortality and morbidity risks than babies born at 40 weeks (Blencowe et al., 2013). In the United States, the majority of preterm births are in the late preterm

---

<sup>1</sup> The written notation for gestational age was used based on past studies and is consistent with current literature (e.g. 31 weeks 6/7 days refers to 31 weeks and 6 days old).

period, and represent 71.4% of all preterm births (Table 2) (Purisch & Gyamfi-Bannerman, 2017).

**Table 2. Prevalence of Preterm Birth by Gestational Age in the United States; 2015. Table amended from Purisch & Gyamfi-Bannerman, 2017**

<b>Gestational Age Category</b>	<b>Number of Weeks</b>	<b>% of all Preterm Births</b>	<b>% of all Births</b>
Late Preterm	34 to 36 6/7 weeks	71.4%	6.87%
Moderate Preterm	32 to 33 6/7 weeks	12.2%	1.17%
Early Preterm	<32 weeks	16.4%	1.58%

The types of premature birth broadly fall into two sub-types: spontaneous preterm birth and provider-initiated preterm birth (Blencowe et al., 2013). Sometimes referred to as an iatrogenic preterm birth, the use of obstetric intervention commonly occurs when the risk of continuing the pregnancy is greater than the risks, to either mother or child, of preterm birth (Platt, 2014). Some common conditions that require immediate delivery regardless of gestational age include: acute fatty liver of pregnancy, chorioamnionitis, and eclampsia (Chescheir & Menard, 2012). Furthermore, Chescheir et al. evaluated various “soft” risk factors that may result in iatrogenic preterm birth between 34 and 38 weeks and found several associated conditions such as oligohydramnios, small fetus for gestational age, well-controlled gestational diabetes, prior uterine scarring, and pregnancy

associated hypertension. While the American College of Obstetrics and Gynecology has recommended against elective iatrogenic birth before 39 weeks, a large multicenter study found that over one-third of all elective cesarean births were done before this 39 week recommendation (Chescheir & Menard, 2012). While this is more common in developed countries, it is not as prevalent in developing nations such as Africa where the rates of cesarean sections are less than 5% (Blencowe et al., 2012). Spontaneous preterm birth can be further subdivided into two subtypes: preterm premature rupture of the membranes (PPROM) and spontaneous preterm birth with intact membranes (Goldenberg, Culhane, Iams, & Romero, 2008).

### **Risk Factors of Preterm Pregnancy**

While the specific etiology of preterm birth remains relatively unknown, there are several identifiable risk factors that increase the odds of preterm birth: prior spontaneous preterm birth, short cervix, non-Hispanic, black race, multiple gestations, and uterine anomalies (Purisch & Gyamfi-Bannerman, 2017). Additional risk factors mentioned by Räsänen et al include: advanced maternal age, smoking, obesity, genital infections, primiparity, and assisted reproductive technology (Räsänen, Gissler, Saari, Kramer, & Heinonen, 2013).

Because many of the etiologic risks of preterm birth are associated with systemic and/or pathologic inflammation, recent studies have looked at genetic variants of genes associated with inflammatory response in both genome-wide association assays and whole exome sequencing (Strauss et al., 2018). Oros et al observed distinctly different

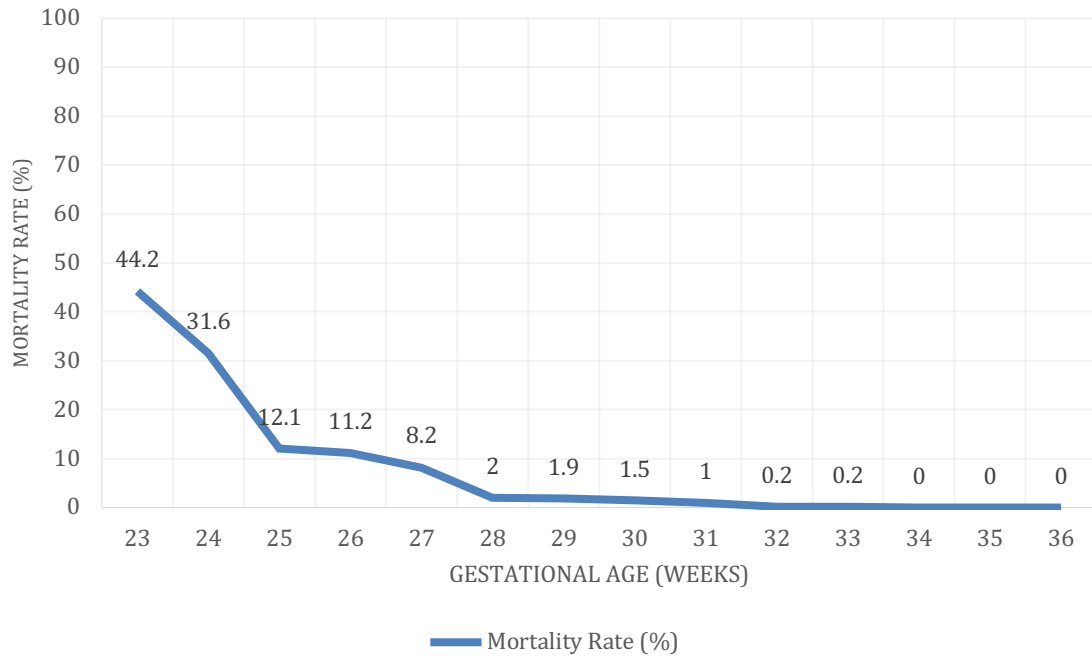
gene expression patterns that were indicative of inflammation in the placentas of suspected preterm patients. They showed a positive correlation between preterm birth and gene expression of known cytokine inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF $\alpha$ ) based on placental and umbilical cord blood samples (Oros et al., 2017). Furthermore, recent studies by Zhang et al have shown three specific loci (EBF1, EEFSEC, and AGTR2) to be associated with preterm birth and gestational duration in a large scale genome association assay of European mothers (Zhang et al., 2017).

While there have been many strides in the advancement of neonatal care to improve health outcomes, there still exist health disparities and known mortality risk differences depending on factors such as race and ethnicity. As stated previously, non-Hispanic black mothers have a higher risk of spontaneous preterm birth. In fact, data from 2012 to 2014 in the United States showed preterm birth rates of non-Hispanic Black women to be 48% higher compared to those of other racial groups (Purisch & Gyamfi-Bannerman, 2017). Several studies comparing preterm birth rates by race/ethnicity have shown disparities even when researchers controlled for confounders such as socioeconomic factors (Purisch & Gyamfi-Bannerman, 2017). Looking at this further, Manuck et al. concluded that these disparities for non-Hispanic Black women were not the result of one specific factor, but rather a more complex multifactorial relationship between several factors including maternal education, differences in biomarkers, genetic variation, and differing microbiomes of non-Hispanic black women as compared to non-Hispanic white women (Manuck, 2017).

Several studies have looked at possible genetic, epigenetic, or biomarkers associated with these preterm birth disparities in non-Hispanic Black women. In a review by Purisch et al, several groups found that the TNF-2 allele of the TNF $\alpha$  gene was associated with higher spontaneous preterm birth in non-Hispanic black women as compared to non-Hispanic white women (Purisch & Gyamfi-Bannerman, 2017). Additional research has shown racial differences in DNA methylation, leading to further investigation into the effects of epigenetics. In one such study, Salihu et al looked at 42 CpG sites on 20 genes consistently reported in the literature to be associated with preterm birth. Their results showed that three CpG sites on the TNFAIP8 and PON1 genes had significantly different rates of methylation in non-Hispanic black versus non-Hispanic white individuals (Salihu et al., 2016).

### **Preterm Mortality and Morbidity**

Several studies have previously shown an increase in mortality as gestational age at birth decreases. While many of these studies used older data from smaller cohorts, a recent population-based analysis by Manuck et al. has provided an updated analysis of preterm outcomes (Manuck et al., 2016). The aforementioned study looked at data from 25 hospitals in 2008-2011 that included a cohort of 115,502 pregnant women, of which 8334 deliveries met inclusion criteria. Their results showed a total neonatal mortality rate of 1.4%, or 199 neonatal deaths in 8334 births, and a rapid decline in mortality rate with each increasing week of gestation (Figure 1).



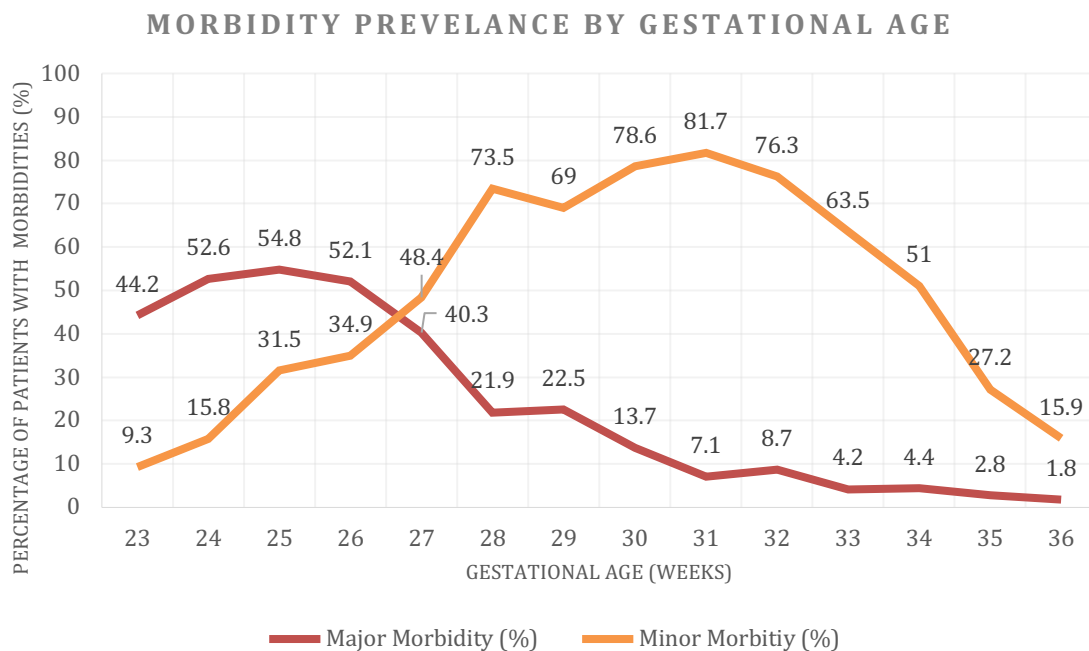
**Figure 1: Preterm mortality rate by gestational age of neonates born in the United States. Figure based on data from Manuck et al., 2016**

While preterm prognostic assessment is largely driven by gestational age at birth, many other factors may contribute to preterm neonatal mortality such as birth weight and sex (Delorme et al., 2016). Examining a cohort of over 1.5 million births in the province of Ontario, Canada, Ray et al. analyzed the combined effects of severe small for gestational age (SGA) births (<5% percentile) and preterm births to see how mortality rates differed (Ray, Park, & Fell, 2017). Their results showed a significantly higher mortality rate for patients born 23-28 weeks with severe SGA as compared to those without severe SGA, in addition to higher mortality rates in males versus females, even after accounting for possible confounding demographic factors (Ray et al., 2017).

Additionally, several studies have looked at how neonatal mortality rates differ depending on the specific cause of preterm birth: preterm birth with intact membranes, PPRM, and indicated preterm birth (also known as provider initiated). Chen et al. analyzed a data set of 3 million births. They found that there was a higher risk of neonatal mortality in patients born after 28 weeks gestation with PPRM and indicated preterm birth as compared to those with preterm labor and intact membranes (Chen, Feresu, & Barsoom, 2009). In another large scale US data cohort, Kamath-Rayne et al. found similarly higher risk of post-neonatal (age 29-364 days) mortality for PPRM and indicated preterm births (Kamath-Rayne, DeFranco, & Chen, 2013). Further work by Delorme et al. refined these “causes” of preterm birth into more granular disease specific causes such as placental abruption, hypertensive disorder with or without fetal growth restriction, and fetal growth restriction without hypertensive disorder (Delorme et al., 2016). To test for the risk of in-hospital mortality and to compare these groups, a model was built that included possible confounding prognostic factors. Statistical analysis showed that fetal growth restriction with or without hypertension was associated with a higher risk of neonatal death (3.0 and 2.3 adjusted odds ratios, respectively) (Delorme et al., 2016).

In terms of morbidity, infants born preterm are at a greater risk of several short- and long-term complications. In fact, several studies have shown that as the survival rate of extremely preterm neonates has increased, so too has the incidence of many acute and chronic morbidities (Glass et al., 2015). In the aforementioned study by Manuck et al, the prevalence of major morbidities (intraventricular hemorrhage grade III/IV, seizure,

hypoxic ischemic encephalopathy, necrotizing enterocolitis stage II/III, bronchopulmonary dysplasia, or persistent pulmonary hypertension) and minor morbidities (hypotension, intraventricular hemorrhage grade I/II, necrotizing enterocolitis stage I, respiratory distress syndrome, and/or hyperbilirubinemia requiring treatment) differed based on gestational age (Manuck et al., 2016). Analysis showed that extremely preterm infants had high rates of major morbidities which decreased with each subsequent week of gestation, while minor morbidities gradually increased and ultimately peaked at 81.7% prevalence around 31 weeks' gestation (Figure 2).



**Figure 2: Major and minor morbidity prevalence by gestational age. Major morbidities include: intraventricular hemorrhage grade III/IV, seizures, hypoxic ischemic encephalopathy, necrotizing enterocolitis stage II/III, bronchopulmonary dysplasia, or persistent pulmonary hypertension. Minor morbidities include: hypotension, intraventricular hemorrhage grade I/II, necrotizing enterocolitis stage I, respiratory distress syndrome, and/or hyperbilirubinemia requiring treatment. Figure based on data from Manuck et al., 2016**

Several longer-term chronic morbidities associated with prematurity include increased risk of cerebral palsy, neurodevelopmental abnormalities, cognitive developmental delay, hearing impairment, severe visual impairment (retinopathy of prematurity), and chronic lung disease (Glass et al., 2015).

### **Improvements in Neonatal Care**

Over the last forty to fifty years, the advancement in neonatal and maternal treatment has dramatically decreased mortality and morbidity, and has improved outcomes, especially in preterm patients (Glass et al., 2015). The development of neonatal intensive care units, maternal-neonatal transport systems, and the increased use of antenatal corticosteroids for fetal lung maturation, tocolytic drugs to delay delivery, or magnesium sulfate for neuroprotection have all been paramount (Manuck et al., 2016; McIntire & Leveno, 2008). The use of exogenous surfactant led to reductions in mortality risk and became pivotal in the management of neonates suffering from respiratory distress syndrome (Suresh & Soll, 2003). Furthermore, studies investigating chronic lung disease in premature patients has led to the understanding of the harmful effects of postnatal steroids (Glass et al., 2015). While early results showed that postnatal steroids improved chronic lung disease outcomes and facilitated extubation following, steroid usage came at the expense of several adverse effects including but not limited to hyperglycemia, hypertension, and gastrointestinal bleeding (Halliday, 2017).

One specific field of medicine which has contributed a great deal to improved neonatal outcomes is anesthesiology. Preterm newborns are especially vulnerable during

anesthesia due to their immature organ system growth (McCann & Soriano, 2014). The development of breathing circuits, artificial airways, and the Apgar score to assess breathing and identify the need for resuscitation efforts are just a few of these advancements (Glass et al., 2015). Additionally, the shift from endotracheal intubation and mechanical ventilation to continuous positive airway pressure (CPAP) allowed patients to continue spontaneous breathing without the need for intubation and, thereby, reduced the risk of lung damage from mechanical ventilation (Roberts, Badgery-Parker, Algert, Bowen, & Nassar, 2011).

In terms of surgical innovation, there has been a rapid growth in minimally invasive surgery in neonates as a way to make smaller incisions, speed up postoperative healing, and lessen postoperative pain (McCann & Soriano, 2014). The miniaturization of common surgical tools has made laparoscopic and thoracoscopic surgical procedures much more feasible for common surgical procedures such as Nissen fundoplication, pyloromyotomy, and patent ductus arteriosus occlusions (Rothenberg, Chang, & Bealer, 2004).

### **Mortality Risk Assessment Tools**

When caring for extremely sick preterm neonates, clinicians and parents are faced with countless difficult medical decisions. As a way to help medical teams make such complex decisions, various predictive risk assessment tools based on several prognostic factors have been developed over the years in an effort to quantify mortality risk and

illness severity (Figure 3). The following is a summary of current assessment tools and their use-cases.

The Clinical Risk Index for Babies (CRIB) was first developed in 1993, and was based on a cohort of 812 infants weighing less than 1500 grams and born less than 31 weeks' gestation across several UK hospitals ("The CRIB (clinical risk index for babies) score," 1993). Statistical modeling was based on six prognostic factors assessed within the first 12 hours of life (birth weight, gestation, congenital malformation, base deficit, and minimum/maximum  $\text{FiO}_2$ ) to predict mortality ("The CRIB (clinical risk index for babies) score," 1993). One of the main benefits of CRIB is the fact that it can be quickly and easily calculated as compared to other more complex assessment tools (Dorling, Field, & Manktelow, 2005).

In the United States in 1993, Richardson et al. published a similar mortality risk assessment scoring system, called the Score for Neonatal Acute Physiology (SNAP), based on a cohort of low birth weight patients from three Boston area hospitals (Richardson, Gray, McCormick, Workman, & Goldmann, 1993). The SNAP score is similar to CRIB but differs in several key ways. First, SNAP's model design and framework was based on current adult and pediatric mortality risk assessment tools, the Acute Physiology and Chronic Health Evaluation (APACHE) and the Physiological Strain Index (PSI) respectively (Richardson, Gray, et al., 1993). Second, SNAP includes many more prognostic factors (28 in total) which are measures of organ physiology derangement during the first 24 hours of life (Richardson, Gray, et al., 1993). Lastly, during the model design process these 28 prognostic factors were weighted by expert

opinion as opposed to the statistical modeling used in CRIB (Dorling et al., 2005). As a way to correlate the SNAP illness severity score to mortality, Richardson et al. expanded on their work to produce the SNAP-Perinatal Extension (SNAP-PE) which, in conjunction with birth weight and SNAP score, was able to estimate neonatal mortality (Richardson, Phibbs, et al., 1993).

While the SNAP and CRIB assessment scores both became widely validated and their use became more prevalent in neonatal intensive care units, they were not without their faults. In the early 2000s, second-generation assessment scoring systems brought about several key and important changes to both SNAP and CRIB.

The SNAP-II was first published by Richardson et al. in 2001, promising a simplified scoring system based on an updated cohort of patients (Richardson, Corcoran, Escobar, & Lee, 2001). While the original SNAP score requires 28 prognostic factors, the new SNAP-II requires only 6 (mean blood pressure, lowest temperature,  $PO_2/FiO_2$  ratio, lowest serum pH, multiple seizures, and urine output). Additionally, a big change to SNAP-II was that data from patients was only collected within the first 12 hours of life, as compared to 24 hours in the original SNAP score, in an effort to eliminate treatment bias (Richardson et al., 2001). While the original SNAP score utilized clinical weighting for its prognostic factors, the SNAP-II score introduced statistical modeling to help Richardson et al. eliminate factors that were not correlated with mortality or were redundant (Richardson et al., 2001). Just as with SNAP, the SNAP-II was extended to produce the SNAPPE-II, which gives clinicians a predicative mortality risk assessment (Dorling et al., 2005).

In 2003 the CRIB II was introduced as an updated assessment tool for determining neonatal mortality risk. The new score eliminated prognostic factors such as  $\text{FiO}_2$  and introduced new variables such as sex and temperature at admission (Parry, Tucker, Tarnow-Mordi, & UK Neonatal Staffing Study Collaborative Group, 2003). Because  $\text{FiO}_2$  is not a true physiological measurement, and its value is determined by the medical care team, Parry et al. chose to remove this variable to reduce the risk of treatment bias. By removing  $\text{FiO}_2$ , adding additional variables, and validating the model with a more recent cohort of patients, the score was intended to give improved results as compared to the original CRIB score. (Parry et al., 2003).

While these second-generation systems offer simplified scoring, making it easier to use in clinical practice, and were validated on an updated cohort of patients, they are not without limitations. With both CRIB II and SNAPPE-II, since all prognostic factors are taken within the first 12 hours of life, they have limited effectiveness for assessing mortality risk later in life. In addition, these scoring systems fail to include any information on potential surgical interventions a patient might have had. For these reasons, and more that will be expanded on later, the current set of standard illness severity scoring systems and mortality risk assessments tools are not applicable to all cohorts of patients, and there exists an opportunity to develop a novel scoring system more suited towards a high-risk cohort of preterm neonatal patients who undergo a surgical procedure.

**Table 3: Prognostic Factors Used in Several Popular Illness Severity Scoring Systems**

<p><b><u>CRIB:</u></b>            Birth weight            Gestation            Congenital Malformation            Base deficit            Minimum FiO<sub>2</sub></p>	<p><b><u>SNAP:</u></b>            Mean blood pressure            Heart rate            Respiratory rate            Temperature            PO<sub>2</sub>            PO<sub>2</sub>/FiO<sub>2</sub>            PCO<sub>2</sub>            Oxygenation index            Hematocrit            White blood cell count            Immature total ratio            Absolute neutrophil count            Platelet count            Blood urea nitrogen            Creatinine            Urine output            Indirect bilirubin            Direct bilirubin            Sodium            Potassium            Calcium (ionized)            Calcium (total)            Glucose            Serum bicarbonate            Serum pH            Seizure            Apnea</p>
<p><b><u>CRIB II:</u></b>            Birth weight            Gestation            Sex            Maximum base deficit            Admission temperature</p>	
<p><b><u>SNAP-PE:</u></b>            Initial SNAP score            Birth weight            Small for gestational age            Apgar at 5 minutes</p>	<p><b><u>SNAP-II:</u></b>            Mean blood pressure            Lowest temperature            PO<sub>2</sub>/FiO<sub>2</sub> ratio            Serum pH            Multiple seizures            Urine output</p>
<p><b><u>SNAPPE-II:</u></b>            Initial SNAP-II score            Birth weight            Small for gestational age            Apgar at 5 minutes</p>	

## **SPECIFIC AIMS**

The specific aim of this study is to compare various patient demographic and clinical characteristic variables between deceased and surviving preterm neonates who had at least one surgical procedure at Boston Children's Hospital within the first 30 days of life. Using a combination of descriptive and inferential statistics, we hope to identify trends in mortality and/or morbidity for this patient population of preterm neonates. We hope to use these results to develop a multivariable logistic regression model to better predict mortality risk depending on the severity and number of different demographic and clinical characteristics identified in the study. While current mortality risk assessment tools exist, none are applicable to this cohort of preterm surgical neonates. In addition,, there have been substantial advancements in medical technology and provider education that necessitate the need for new mortality risk assessment tools. By creating a new predictive mortality risk model more suited towards this cohort of patients, this assessment tool could be used in the future to help assist clinicians and families make complex medical decisions about necessary or justifiable potential medical treatment options.

## METHODS

After IRB approval, medical records were obtained from Boston Children's Hospital (BCH) electronic medical record, PowerChart, for patients matching the following criteria:

- Date of birth ranging from 2015 to 2018
- Gestational age at birth less than 39 weeks
- Had at least one surgical procedure at BCH within the first 30 days of life

Patient demographic information in addition to lab values and clinical information in regards to the surgical procedure was obtained (Table 4). All data was pulled from patient's electronic medical records at BCH by IT staff in the Department of Anesthesiology, Critical Care and Pain Medicine, with the exception of "Number of Cardiopulmonary Resuscitation (CPR) Attempts" and "End of Life Care Redirected", which was obtained via manual chart review by research staff. For clinical lab values such as pH, pO<sub>2</sub>, pCO<sub>2</sub> and base excess, these values were taken from patient records 24 hours prior to surgery. In addition, patients' medication use while at BCH was pulled from electronic medical records (see Appendix for complete medication lists).

**Table 4: Research Variables of Interest**

<b>Patient Demographics</b>	Gender Weight Gestational Age
<b>Clinical Variables</b>	Procedure Type Cardiac/Non-Cardiac ASA Status 1 to 5 Lactate Values Number of CPR Attempts End of Life Care Redirected? (Y/N) Age of Death Acid Base Disorder: pH, pO <sub>2</sub> , pCO <sub>2</sub> , base excess, bicarbonate Airway Assessment: Ventilator Use (Y/N) Blood Products Medication Usage: Bronchodilators Emergency Resuscitation Vasopressors/Inotropic Agents

“Medication usage” will be assessed by detailing if a patient got a medication from one of four categories based on the “Emergency Drug Dose Recommendation” guidelines of BCH (Boston Children’s Hospital, 2016). At the time of writing, acid base disorder, airway assessment, and medication usage data are not available as these data are still in the process of being retrieved from patient records by BCH IT staff. Additionally, patients’ gestational age was categorized based on previous, known guidelines from the WHO and American Academy of Pediatrics (AAP) (Table 5) (“Preterm birth,” 2018; Schonhaut et al., 2015).

**Table 5: Gestational Age Categories**

<b>Category</b>	<b>Gestational Age (weeks)</b>
Extremely Preterm	< 28 Weeks
Very Preterm	28 Weeks 0 Days to 31 Weeks 6/7 Days
Moderate Preterm	32 Weeks 0 Days to 33 Weeks 6/7 Days
Late Preterm	34 Weeks 0 Days to 36 Weeks 6/7 Days
Early Term	37 Weeks 0 Days to 38 Weeks 6/7 Days

A univariate analysis of patient demographics was done between deceased and surviving patient groups. For the clinical variables of interest, a set of descriptive statistics was performed, as data from the surviving group were not available.

### **Statistical Analysis**

Due to the non-normality of the sample and the relatively small sample size, the Wilcoxon rank sum test was used as opposed to the Student's t-test for comparing two independent groups of continuous variables. The non-parametric Wilcoxon rank sum test provides a more conservative estimate in this regard. In addition, descriptive statistics such as medians and interquartile ranges were calculated and presented for all continuous variables.

When analyzing the categorical variables of the data set, Fischer's exact test was used to assess the distribution of the categorical variables between the deceased and surviving patient groups. Due to the relatively small sample size in certain categories of certain variables, the more conservative non-parametric Fischer's exact test was chosen instead of a Chi square test, which relies on making distribution assumptions with regard to the specific categories of a categorical variable.

## RESULTS

A total of 653 patients were included in the dataset, 56 of whom were deceased, an overall 8.6% mortality rate. Median gestational age of the deceased and surviving patient groups was 35 and 36 weeks respectively ( $p=0.076$ ). In the deceased patient group, 64% of patients were male, 36% female. In the surviving group 54% of the survivors were male, 46% female. ( $p=0.234$ ).

Mortality rates were statistically different across gestational age categories ( $p=0.015$ ), and there were significant differences in mortality rate based on ASA classification ( $p<0.001$ ) between deceased and surviving patient groups. Patient weight was also found to be statistically different between deceased and surviving patient groups ( $p=0.009$ ).

Of the 56 patients in the deceased group, 62.5% of the surgical procedures were cardiac related cases. (Data for surgeries for the surviving group is not yet available.) The median age of death for patients in the deceased group was 46 days (interquartile range 25-109) and the median lactate value for the deceased patient group was 6.5 mmol/L (interquartile range 4.3-8.7). At the time of writing, data from surviving patients on these variables and the clinical variables that follow are not yet available. In addition, 60% of the patients in the deceased group had one surgical procedure and 51.8% had no CPR attempts. Lastly, 58.9% of patients in the deceased group had their care ultimately redirected to comfort measures only.

**Table 6: A Comparison of Patient Characteristics and Demographics Between Deceased and Surviving Patients**

Characteristic	Deceased	Survivors	P
<b>N</b>	56	597	
<b>Gestational Age (weeks)</b>	35 (33, 38) [24, 38]	36 (34, 38) [24, 38]	0.076
<b>Extremely Preterm</b> <28 Weeks	9 (16.1%)	84 (14.1%)	0.015* <sup>2</sup>
<b>Very Preterm</b> 28 Weeks 0 Days to 31 Weeks 6/7 Days	4 (7.1%)	24 (4.0%)	
<b>Moderate Preterm</b> 32 Weeks 0 Days to 33 Weeks 6/7 Days	10 (17.9%)	36 (6.0%)	
<b>Late Preterm</b> 34 Weeks 0 Days to 36 Weeks 6/7 Days	12 (21.4%)	173 (29.0%)	
<b>Early Term</b> 37 Weeks 0 Days to 38 Weeks 6/7 Days	21 (37.5%)	280 (46.9%)	
<b>Weight (kg)</b>	2.2 (1.5, 2.9) [0.7, 3.8]	2.6 (1.9, 3.2) [0.6, 4.5]	0.009*
<b>ASA</b>			<0.001*
<b>I</b>	0 (0%)	11 (1.8%)	
<b>II</b>	0 (0%)	73 (12.2%)	
<b>III</b>	7 (12.5%)	206 (34.5%)	
<b>IV</b>	44 (78.6%)	299 (50.1%)	
<b>V</b>	5 (8.9%)	7 (1.2%)	
<b>Gender</b>			0.234
<b>Female</b>	20 (35.7%)	272 (45.6%)	
<b>Male</b>	36 (64.3%)	324 (54.4%)	

Values are presented as n (%) for categorical data or median (IQR) [range] for continuous data.

P values comparing survivors and deceased patients are computed using the Wilcoxon rank sum test or Fisher's exact test as appropriate.

\*Statistically significant.

<sup>2</sup> The *p*-value for this test is comparing mortality rates by gestational age to assess if any differences in mortality rates exist between gestational age categories

**Table 7: Descriptive Statistics of the Deceased Group**

<b>Characteristic</b>	<b>Frequency</b>
<b>Procedure Type</b>	
<b>Cardiac</b>	35 (62.5%)
<b>Non-Cardiac</b>	21 (37.5%)
<b>Age of Death (days)</b>	46 (25, 109) [1, 1342]
<b>Lactate (mmol/L)</b>	6.5 (4.3, 8.7) [1.3, 15]
<b>End of Life Care Redirected</b>	33 (58.9%)
<b>Number of procedures</b>	
<b>1</b>	33 (60%)
<b>2</b>	14 (25.5%)
<b>3</b>	5 (9%)
<b>4</b>	3 (5.5%)
<b>Number of CPR Events</b>	
<b>0</b>	29 (51.8%)
<b>1</b>	16 (28.6%)
<b>2</b>	10 (17.9%)
<b>3</b>	0 (0%)
<b>4</b>	0 (0%)
<b>5</b>	1 (1.8%)

Values are presented as n (%) for categorical data or median (IQR) [range] for continuous data.

## DISCUSSION

The significance and impact of prematurity is a worldwide phenomenon with pervasive effects, even in developed countries like the United States (World Health Organization et al., 2012). With advances in neonatal care, minimally invasive surgery, and anesthesia of the neonatal patient, there have been decreases in neonatal mortality and morbidity over the past twenty years (Glass et al., 2015). However, even with today's advances in medical knowledge, technology, and provider training, preterm neonates still remain an incredibly fragile and at-risk patient population. The use and prevalence of illness severity scoring systems and mortality risk assessment tools at NICUs around the country provide added information to clinicians and medical teams faced with countless complex medical decisions (Dorling et al., 2005). The two most popular mortality risk assessment systems, CRIB II and SNAPPE-II, were first developed and validated based on cohorts of patients from the late 1990s and have been since independently validated on cohorts of patients from the mid 2000s (Reid, Bajuk, Lui, Sullivan, & NSW and ACT Neonatal Intensive Care Units Audit Group, PSN, 2015). However, these assessment tools have limited application to our cohort of patients, chiefly because they fail to consider inherent surgical risk amongst other limitations. While it is important to realize that no one score can capture the prognosis and mortality risk of a neonate, there are certainly specific areas where improvements can be made to better predict mortality risk in today's preterm neonate.

One area of improvement is to develop a mortality risk assessment model based on an entirely new cohort of patients from more recent data. While there have been some validation studies of CRIB II and SNAPPE-II on more recent patient populations, the cohorts used in these recent validation studies have not been representative of the patient population at BCH (Reid et al., 2015). More specifically, both CRIB II and SNAPPE-II failed to factor in any prognostic factors that might be associated with mortality for patients undergoing surgery, a requisite criterion for inclusion in this study. Moreover, while SNAPPE-II and CRIB II have seen validation in newer cohorts of patients, the original model design was done on cohorts of patients from the 1990s. This means possible prognostic factors might have been eliminated in the original model design by Richardson et al. and Parry et al., respectively, due to the lack of significant association with mortality because of limited knowledge and a different prognostic assessment of neonatal patient outcomes by clinicians at the time. Another important limiting factor in the usefulness of SNAPPE-II and CRIB II is the fact that both use prognostic factors taken from patients within the first 12 hours of life. This could affect the accuracy and effectiveness of SNAPPE-II and CRIB II to estimate neonatal mortality (Dorling et al., 2005). In the deceased group of this study the median age of death is 46 days. Therefore, the lack of data past 12 hours might limit the accuracy of SNAPPE-II and CRIB II to predict mortality in this cohort.

While the model design process has not yet begun, the current set of results provides some interesting talking points and consideration of possible prognostic factors to include in a future predictive risk assessment model. The first point to note is that

mortality occurs at a high rate. The mortality rate of our cohort is 8.6%, which is considerably higher than the United States preterm mortality rate of 1.4% from 2016 (Manuck et al., 2016). The results of this study also show several prognostic factors that have significant associations with mortality. Mortality rate varied significantly with gestational age ( $p=0.015$ ), a finding that is consistent with past literature by Manuck et al. (Manuck, 2017). Results also showed significantly different mortality rates based on birth weight ( $p=0.009$ ), as with past studies (Ray et al., 2017). The last prognostic factor that had a significant effect on mortality rate between deceased and surviving patients was ASA classification ( $p<0.001$ ), which is a physical classification system used to categorize patients by physiological status and can be helpful for determining operative risk (Doyle & Garmon, 2018). These results are expected, as one might assume patients with a more compromised physiological state would carry a greater risk of mortality intraoperatively and postoperatively. No other illness severity score or mortality risk assessment tool to our knowledge has included ASA classification as a risk factor in developing a model in the neonate population. One interesting area of note is that these results showed no statistically significant difference in mortality rate based on gender ( $p=0.234$ ), unlike several past studies describing a higher mortality risk for males as compared to females (Ray et al., 2017). One possible explanation for the lack of significance is the limited number of patients in the deceased group. While the deceased group had a greater proportion of males to females as compared to the surviving group (64.3% versus 54.4% respectively) the sample size of 56 patients in the deceased group limited the statistical significance of this finding.

Descriptive statistics of clinical variables were performed in the deceased group. At the time of writing, however, comparable data from our surviving group was not available. Therefore, no statistical comparisons could be performed to determine if there were any significant associations with mortality. A clinical variable that one might expect to be associated with mortality risk is lactate levels. Lactate is a common lab value that can be used as a prognostic indicator for total illness severity, and, in fact, the median lactate value 24 hours prior to surgery in the deceased cohort is 6.5 mmol/L, which is considered a high value ( $>4$  mmol/L) (Andersen et al., 2013). In addition, nearly half (48.2%) of patients in the deceased group had at least one CPR event, and roughly 40% had more than one procedure, both possible prognostic factors for mortality based on the increased physiological stress and compromised health of neonates requiring multiple interventions to sustain life.

Ongoing research for this study has been focused on three specific areas of analysis prior to developing a statistical model: pre-operative ventilation, patient medications, and acid-base disorders. It is known that preterm neonates are born with immature organ systems, especially a compromised respiratory system (Roberts et al., 2011). While advances in care such as antenatal corticosteroids and postnatal surfactant have improved outcomes, the need for mechanical ventilation to sustain life prior to surgery was estimated to be a significant prognostic factor when building a neonatal mortality risk model (Glass et al., 2015). While many different types and modes of mechanical ventilation exist, it was difficult to ascertain these specifics with enough clarity given the data on hand from patient records. For that reason, future analysis on

mechanical ventilation will be limited to whether or not a patient was on any type of mechanical ventilation 24 hours prior to their surgical procedure.

The second current area of analysis is identifying and categorizing patient blood products and medications that could possibly be associated with mortality risk (see Appendix for full list of medications). Four specific categories of treatments from BCH's "Emergency Drug Dose Recommendation" guidelines were chosen to be investigated to determine if there was any association with neonatal mortality: blood products, bronchodilators, emergency resuscitation, and vasopressors/inotropic agents (Figure 4) (Boston Children's Hospital, 2016).

**Table 8: Emergency Drug Dose Recommendation guidelines taken from Boston Children's Hospital, 2016**

BLOOD PRODUCTS	EMERGENCY RESUSCITATION
Albumin 5% 10 - 20 mL/kg = 0.5 - 1 g/kg	<b>Amiodarone</b> (shock-refractory VF/pulseless VT): 5 mg/kg (MAX 300 mg) IV/IO bolus; may repeat x 2 up to 15 mg/kg (MAX 2.2 g/day)
Albumin 25% 2 - 4 mL/kg = 0.5 - 1 g/kg (MAX 25 g/dose)	<b>Atropine</b> 0.02 mg/kg/dose (MAX 1 mg) IV/IO/ET*, repeat x1 PRN
Cryoprecipitate 1 unit/10 kg	<b>Calcium CHLORIDE</b> 10% (100 mg/mL) 20 mg/kg = 0.2 mL/kg (MAX 2000 mg) IV/IO, slowly (CVL STRONGLY PREFERRED, MUST DILUTE)
FFP 10 - 15 mL/kg	<b>Calcium GLUCONATE</b> 10% (100 mg/mL) 100 mg/kg = 1 mL/kg (MAX 2000 mg) IV/IO, slowly (CVL PREFERRED)
Packed red cells 10 mL/kg will raise Hct ~ 10%	<b>Dextrose</b> 0.5 - 1 g/kg IV/IO (D50W 1 - 2 mL/kg; D25W 2 - 4 mL/kg; D10W 5 - 10 mL/kg) To make D25W, mix equal volumes of D50W with sterile water or 0.9%NS
Platelets 1 unit/10 kg will raise count ~ 50,000	<b>Epinephrine</b>
BRONCHODILATORS	<i>Cardiac arrest or severe bradycardia requiring CPR:</i> IV/IO: Standard dose ( <b>1:10,000</b> ), 0.01 mg/kg (= 0.1 mL/kg) Q 3 - 5 min (MAX 1 mg) ET: <b>1:1,000</b> , 0.1 mg/kg (= 0.1 mL/kg) Q 3 - 5 min
<b>NEBULIZED:</b>	<i>Severe hypotension/pre-arrest state (not during CPR):</i> IV/IO: Diluted formulation ( <b>1:100,000</b> ), 0.001 mg/kg (= 1 mCg/kg = 0.1 mL/kg), repeat as needed to achieve desired HR/BP
<b>Albuterol</b> intermittent (0.5%); <10kg: 0.25 mL; 10-30kg: 0.5 mL, ≥30kg: 1 mL, INH Q20min x 3; then Q1-6hr ± PRN <i>continuous inhalation:</i> 0.5 mg/kg/hr* (usual MAX 20 mg/hr)	<i>Anaphylaxis:</i> IM: ( <b>1:1,000</b> ), 0.01 mg/kg (= 0.01 mL/kg) (MAX 0.5 mg = 0.5 mL) Epi-Pen®: 0.3 mg IM (≥30 kg) Epi-Pen Jr.®: 0.15 mg IM (10 - 29kg)
<b>Ipratropium</b> 0.25 - 0.5 mg INH Q20min x 3 then Q4-6hr	<b>Lidocaine</b>
<b>Racemic epinephrine</b> (2.25%) 0.25 - 0.5 mL INH Q1hr ± PRN	<i>Cardiac arrhythmias:</i> 1 mg/kg IV/IO/ET* (MAX 100 mg) <i>Pre-intubation:</i> 2 mg/kg IV/IO (MAX 200 mg)
INTRAMUSCULAR:	<b>Magnesium sulfate</b> (torsades de pointes) : 25 - 50 mg/kg IV/IO (MAX 2000 mg; MUST DILUTE)
<b>Epinephrine</b> (1:1,000) 0.01 mg/kg/dose=0.01 mL/kg/dose (MAX 0.5 mL) IM x1	<b>Sodium bicarbonate</b> 1 mEq/kg IV/IO slowly Infants/Children/Adults: 8.4% (1 mEq/mL) = 1 mEq/kg = 1 mL/kg Neonates: 4% Neut® (0.5 mEq/mL) = 1 -2 mEq/kg = 2 - 4 mL/kg
INTRAVENOUS:	*Increase ET doses by 2 times
<b>Terbutaline</b> * 10 mCg/kg IV x1 over 10 min then 0.4 - 6 mCg/kg/min IV	
<b>Magnesium sulfate</b> 40 - 50 mg/kg (MAX 2000 mg) IV over 20 min	
*Suggested total β <sub>2</sub> -agonist MAX hourly dose = 20 mg/hr	
VASOPRESSORS AND INOTROPIC AGENTS	
<b>DOBUTAMINE</b> 2.5 - 20 mCg/kg/min IV	
<b>DOPAMINE</b> 2.5 - 20 mCg/kg/min IV	
<b>EPINEPHRINE</b> 0.05 - 1 mCg/kg/min IV	
<b>Milrinone</b> Neonates: 25 mCg/kg IV x1 (Load), then 0.25 - 0.5 mCg/kg/min IV; Infants/Children: 50 mCg/kg IV x1 (Load), then 0.25 - 0.75 mCg/kg/min IV	
<b>NOREPINEPHRINE</b> 0.05 - 1 mCg/kg/min IV	
<b>Phenylephrine</b> 0.1 - 0.5 mCg/kg/min IV	
<b>Vasopressin (for shock)</b> 6-30 milliunits/kg/hr IV (MAX 0.4 units/min)	

Lastly, work is being done to analyze this cohort of patients for potential acid-base disorders, given their arterial pH, pO<sub>2</sub>, pCO<sub>2</sub>, base deficit, and bicarbonate concentration 24 hours prior to surgery. Signs of metabolic acidosis can be the result of neonatal asphyxia (due to impaired blood gas exchange) leading to brain damage, encephalopathy and respiratory complications (Low, Lindsay, & Derrick, 1997).

Unfortunately, at the time of writing, patient data on ventilation status, medication usage, and acid base disorders is not yet available. BCH IT data analysts are still in the process of retrieving this information from PowerChart patient records, and the level of completeness for all patients in the cohort is unknown. For this reason, the statistical model design portion of the study has not yet begun, as current work is focused on finishing the complete list of potential prognostic factors of neonatal mortality to include in the future model. Although a statistical mortality risk model has not yet been developed, it is important to understand how to develop such a model, what important factors to consider when building a model, and ways to test a model's performance and validity for robustness.

Logistical regression is a common analysis tool used to create a statistical model to calculate mortality risk, and has been used in SNAPPE-II, CRIB II, and other mortality risk assessment studies (Dorling et al., 2005). By incorporating the strongest predictors of mortality, logistic regression allows one to generate a direct probability model, with no assumptions about the variables, on a specific binary outcome (mortality in this case) (Harre, Lee, & Pollock, 1988). To identify the strongest predictors of mortality, univariate analysis of possible prognostic factors is done. While several significant

prognostic patient characteristics and demographics have been identified in this cohort, further univariate analysis needs to be performed on future ventilation use and medication category data to identify any predictive effect on mortality. Afterwards, a multivariable logistic regression can be generated using a statistical software package (e.g. STATA) to calculate the beta coefficients of each covariate and identify the 3 to 4 strongest independent predictors of mortality. Using this model, one can calculate a predictive probability of mortality for each unique covariate pattern of prognostic factors (Harre et al., 1988). The next step after creating a logistic regression model and predictive risk algorithm is to assess its performance and validation.

There are several key performance measures that are commonly analyzed in mortality risk assessment models: accuracy, calibration, and discrimination (Medlock, Ravelli, Tamminga, Mol, & Abu-Hanna, 2011). Firstly, accuracy is a measure of the effectiveness to correctly predict an actual outcome (Dorling et al., 2005). In a systematic review of 41 developmental studies, Medlock, et al. found that the most common ways that accuracy was assessed were: negative predictive value, positive predictive value, specificity and sensitivity (Medlock et al., 2011). Second, calibration is a measure of how a model's predictive probability can accurately assess the actual probability, and it is commonly assessed using the Hosmer-Lemeshow goodness of fit test (Medlock et al., 2011). Lastly, discrimination refers to the ability of a model to accurately differentiate patients with the same outcomes, and it is frequently measured using the area under the receiver operator curve (AUC) (Dorling et al., 2005). All of these performance measures can be calculated using a statistical software package, and they are commonly used in

literature as a basis of comparison to determine which model does a better job at predicating mortality (Dorling et al., 2005; Reid et al., 2015).

After testing the performance of any future predictive mortality risk model, the next step would be to validate the model. Validation would most likely be done on a cohort of patients from a comparable children's hospital with similar resources, provider training, and high-risk patient population to BCH as a way to see how well the model accurately predicts mortality in a new dataset. Importantly, validating the model on a prospective (as opposed to retrospective) cohort of patient would further add to the robustness of the model to accurately predict future outcomes (Dorling et al., 2005). Validating the model on several cohorts of prospective neonates would also show the reproducibility of the model to assess consistent and accurate mortality risk on new groups of unique patients.

While the conclusions of this study are still far off, the data collected so far provide a good opportunity to look at the project critically and to assess the current limitations and areas of improvement for future work. A total of 653 patients met the inclusion criteria for this study, which presents a possible limitation to the robustness of our model design, especially when considering that the base cohorts used in the design of SNAPPE-II and CRIB II had several thousand patients from multiple clinical sites (Parry et al., 2003; Richardson et al., 2001). Improvements in the future could easily be made by expanding the data set to a larger time period (currently only patients born from 2015 to 2018 were investigated) and also including patients from multiple clinical sites to get a more representative patient cohort. Other areas of improvement include expanding the

scope of clinical lab values analyzed, beyond just lactate. While lactate data was used as a representative of total illness severity, a similar study examining prognostic factors of surgical neonates by Manchada et al. examined additional lab values such as: white blood cell count, platelets, and c-reactive protein (Manchanda, Sarin, & Ramji, 2012). Looking at c-reactive protein in particular is likely to be a useful data point, given the fact that it is commonly used as a sign of infection, sepsis, septic shock, and organ dysfunction (Castelli et al., 2004). Other variables to consider, that were not included in this analysis, are urine output and creatinine levels. Both elevated levels of creatinine and decreased urine output are known prognostic factors for neonatal renal failure (Chevalier, Campbell, & Brenbridge, 1984). To assess for neurological derangement, future studies could add information from either the pediatric Glasgow Coma Scale (PGCS) or the Infant Comas Scale (ICS), both of which have shown to be good assessments of pediatric mental status (Ahn, Sohn, & Lee, 2010; Jain & Iverson, 2018). Another alternative for assessing neurologic injury is the CHOP Infant Coma Scale, or Infant Face Scale (IFS), which was shown to be good reliable index for brain injury severity and hypoxemia/ischemia in a 2000 study by Durham et al. (Durham et al., 2000). Lastly, one potential area for improvement would be to add Apgar scores at 5 minutes to the analysis. SNAPPE-II includes 5 minute Apgar scores in its assessment criteria, and several past studies have shown Apgar at 5 minutes to be strongly associated with neonatal and infant death (Iliodromiti, Mackay, Smith, Pell, & Nelson, 2014).

In conclusion, while several current neonatal mortality risk and illness severity scoring systems currently exist, there are several key ways in which these can be updated

with modern standards to be more representative in today's current medical landscape and more applicable to a cohort of preterm neonates undergoing surgery. The main failure of these scoring systems is the reliance on data solely from the first 12 hours of life and the lack of data for a surgical cohort, severely limiting its potential effectiveness in a patient population such as that at BCH. Analyzing a cohort of 653 patients has identified several key demographic and patient characteristics that are associated with mortality: gestational age, weight, and ASA classification. While preliminary work has begun on evaluating many of the clinical variables of interest, more analyses are required to understand the significance of these variables and all the factors as a whole, and to start the processes of building a logistic regression model and validating its performance and reliability to assess mortality risk.

## APPENDIX

**Table 9: A Complete List of Medications in the Methods Discovery**

1/2 Normal Saline 500 mL	Clindamycin mg
Acetaminophen mg IV	Clindamycin mg IV
Acetaminophen mg PO	Clonidine mcg
Acetaminophen mg PR	Clonidine mcg Caudal
Acyclovir (Zovirax) mg	Concentrated Platelets mL
Adenosine mg	Cryoprecipitate mL
Adenosine mg IV	Crystalloid mL
Albumin 5% mL	D10 1/2 Normal Saline mL
Albuterol- Nebulizer mL Inhalation	D10 Normal Saline mL
Albuterol- Puff (90 mcg per puff) puff Circuit	D25 mL
Albuterol- Puff (90 mcg per puff) puff Inhalation	D5- Sodium Bicarbonate mL
Albuterol- Puff (90 mcg per puff) puff Nebulizer	D5 1/2 Normal Saline mL
Aminocaproic Acid mg	D5 1/4 Normal Saline mL
Aminocaproic Acid mg IV	D5 Lactated Ringers 500 mL mL
Amiodarone mg	D5 Lactated Ringers mL
Ampicillin mg IV	D5 Normal Saline mL
Antithrombin III units	D50 mL
Atropine mg	D5W 1/2 Normal Saline mL
Atropine mg IM	Dexamethasone mg IV
Atropine mg IV	Dexmedetomidine mcg
Autologous Blood mL	Dexmedetomidine mcg IV
Basiliximab (Simulect) mg	Dextrose (g) g IV
Bumetanide mg	Dextrose 10% Water mL
Bupivacaine 0.1% mL	Dextrose 5% Water mL
Bupivacaine 0.125% + epi 1/200k mL Caudal	Dopamine mcg
Bupivacaine 0.125% mL	Ephedrine mg IV
Bupivacaine 0.125% mL Caudal	Epinephrine mcg
Bupivacaine 0.125% mL Epidural	Epinephrine mcg Intrathecal
Bupivacaine 0.125% mL Peripheral Nerve Block	Esmolol mg
Bupivacaine 0.25% mL Caudal	Esmolol mg IV
Bupivacaine 0.25% mL Epidural	Etomidate mg IV
Bupivacaine 0.25% mL Peripheral Nerve Block	Factor VIIa mg
Bupivacaine 0.5% Isobaric mL Intrathecal	Factor VIII (Human) IU
Bupivacaine 0.75% D8.25 mL Intrathecal	Factor VIII IU
Calcium Chloride mg IV	Fenoldopam mcg
Calcium Gluconate mg	Fentanyl mcg
Calcium Gluconate mg Circuit	Fentanyl mcg Circuit
Calcium Gluconate mg Intrathecal	Fentanyl mcg IM
Calcium Gluconate mg IV	Fentanyl mcg IV
Cefazolin mg Circuit	Fluconazole (Diflucan) mg
Cefazolin mg IV	Fresh Frozen Plasma mL
Cefepime mg	Furosemide mg
Cefotaxime mg IV	Furosemide mg Circuit
Cefoxitin mg IV	Furosemide mg IV
Cell Saver Washed PRBC mL	Gentamicin mg
Cell Saver mL	Glycopyrrolate mg IV
Chloroprocaine 1.5% mL	Heparin units
Chloroprocaine 1.5% mL Caudal	Heparin units Circuit
Chloroprocaine 1.5% mL Epidural	Heparin units IV
Chloroprocaine 3% mL	Hydralazine mg
Chloroprocaine 3% mL Caudal	Hydralazine mg IV
Chloroprocaine 3% mL Epidural	Hydrocortisone mg IV
Cisatracurium mg	Hydromorphone mg IV
Cisatracurium mg IV	ICU Fluid- See CHAMPS for Details mL

Insulin units	Phenylephrine mcg
Insulin units IV	Phenylephrine mcg Circuit
Intralipid 20% mL	Phenylephrine mcg IV
Isoflurane % Inhalation	Piperacillin/Tazobactam(Zosyn) mg
Isoproterenol mcg	Piperacillin/Tazobactam(Zosyn) mg Circuit
Ketamine mg	Piperacillin/Tazobactam(Zosyn) mg IV
Ketamine mg IV	Plasma-Lyte mL
Labetalol mg IV	Platelets mL
Lactated Ringers mL	Potassium Chloride (KCl) mEq
Lidocaine 1% + epi 1/200k mL Caudal	Potassium Chloride (KCl) mEq IV
Lidocaine 1% mL Epidural	Procainamide mg
Lidocaine 1% mL Inhalation	Procainamide mg IV
Lidocaine 1% mL IV	Propofol mg
Lidocaine 1% mL Topical	Propofol mg IV
Lidocaine 1.5% with epi 1/200k (Test Dose) mL Epidural	Prostaglandin E1 (Alprostadil) mcg
Lidocaine 2% + epi 1/200k mL Caudal	Protamine mg IV
Lidocaine 2% Jelly Application Topical	Pump Blood mL
Lidocaine 2% mL Topical	Ranitidine mg IV
Lidocaine mg	Recovered Cardioplegia Circuit Volume mL
Lidocaine mg IV	Remifentanil mcg
Lidocaine mg Topical	Remifentanil mcg IV
Lipids mL	Rocuronium mg
Magnesium Sulfate mg IV	Rocuronium mg Circuit
Mannitol g Circuit	Rocuronium mg IM
Meropenem mg IV	Rocuronium mg IV
Methylprednisolone mg Circuit	Ropivacaine 0.1% mL
Methylprednisolone mg IV	Ropivacaine 0.1% mL Caudal
Midazolam mg	Ropivacaine 0.1% mL Epidural
Midazolam mg Circuit	Ropivacaine 0.1% mL Peripheral Nerve Block
Midazolam mg IV	Ropivacaine 0.2% mL Caudal
Milrinone mcg	Ropivacaine 0.2% mL Epidural
Milrinone mcg IV	Ropivacaine 0.2% mL Peripheral Nerve Block
Morphine mg	Salvaged Red Cells mL
Morphine mg IV	Sodium Bicarbonate mEq
Neostigmine mg IV	Sodium Bicarbonate mEq Circuit
New Fluid mL	Sodium Bicarbonate mEq IV
New Medication- mg Infusion mg	Special Fluids- See CHAMPS for Details mL
New Medication- mg mg IV	Succinylcholine mg IM
New Medication- mL Infusion mL	Succinylcholine mg IV
Nicardipine mcg	Sucrose mL PO
Nitric Oxide ppm Circuit	Sufentanil mcg
Nitric Oxide ppm Inhalation	Sugammadex mg IV
Nitroglycerin mcg	Tranexamic Acid mg
Nitroglycerin mcg IV	Tranexamic Acid mg Circuit
Nitroprusside mcg	Tranexamic Acid mg IV
Nitroprusside mcg Circuit	Unasyn mg
Norepinephrine mcg	Unasyn mg IV
Norepinephrine mcg IV	Vancomycin mg
Normal Saline mL	Vancomycin mg IV
Octreotide mcg	Vasopressin units
Ondansetron mg IV	Vasopressin units IV
Oxacillin mg	Vecuronium mg
Packed Red Blood Cells mL	Vecuronium mg Circuit
Pancuronium mg IV	Vecuronium mg IV
Pantoprazole mg IV	Vitamin K mg IM
Parenteral Nutrition mL	Vitamin K mg IV
Phentolamine mg Circuit	Whole Blood mL

## LIST OF JOURNAL ABBREVIATIONS

BMC .....	BioMed Central
NCHS .....	National Center for Health Statistics
PLOS .....	Public Library of Science
UNICEF .....	United Nations Children’s Fund
WHO.....	World Health Organization

## REFERENCES

- Ahn, Y.-M., Sohn, M., & Lee, S.-M. (2010). [Evaluation of mental status in high-risk neonates using infants coma scale]. *Journal of Korean Academy of Nursing*, 40(4), 561–570. <https://doi.org/10.4040/jkan.2010.40.4.561>
- Andersen, L. W., Mackenhauer, J., Roberts, J. C., Berg, K. M., Cocchi, M. N., & Donnino, M. W. (2013). Etiology and therapeutic approach to elevated lactate. *Mayo Clinic Proceedings*, 88(10), 1127–1140. <https://doi.org/10.1016/j.mayocp.2013.06.012>
- Blencowe, H., Cousens, S., Chou, D., Oestergaard, M., Say, L., Moller, A.-B., ... Lawn, J. (2013). Born Too Soon: The global epidemiology of 15 million preterm births. *Reproductive Health*, 10(Suppl 1), S2. <https://doi.org/10.1186/1742-4755-10-S1-S2>
- Blencowe, H., Cousens, S., Oestergaard, M. Z., Chou, D., Moller, A.-B., Narwal, R., ... Lawn, J. E. (2012). National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet (London, England)*, 379(9832), 2162–2172. [https://doi.org/10.1016/S0140-6736\(12\)60820-4](https://doi.org/10.1016/S0140-6736(12)60820-4)
- Boston Children's Hospital. (2016, June). Emergency Drug Dosage Recommendations. Boston Children's Hospital.
- Castelli, G. P., Pognani, C., Meisner, M., Stuani, A., Bellomi, D., & Sgarbi, L. (2004). Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Critical Care*, 8(4), R234. <https://doi.org/10.1186/cc2877>
- Chen, A., Feresu, S. A., & Barsoom, M. J. (2009). Heterogeneity of preterm birth subtypes in relation to neonatal death. *Obstetrics and Gynecology*, 114(3), 516–522. <https://doi.org/10.1097/AOG.0b013e3181b473fc>
- Chescheir, N., & Menard, M. K. (2012). Scheduled deliveries: avoiding iatrogenic prematurity. *American Journal of Perinatology*, 29(1), 27–34. <https://doi.org/10.1055/s-0031-1285830>
- Chevalier, R. L., Campbell, F., & Brenbridge, A. N. A. G. (1984). Prognostic Factors in Neonatal Acute Renal Failure. *Pediatrics*, 74(2), 265–272.
- Delorme, P., Goffinet, F., Ancel, P.-Y., Foix-L'Hélias, L., Langer, B., Lebeaux, C., ... Kayem, G. (2016). Cause of Preterm Birth as a Prognostic Factor for Mortality. *Obstetrics and Gynecology*, 127(1), 40–48. <https://doi.org/10.1097/AOG.0000000000001179>

Dorling, J. S., Field, D. J., & Manktelow, B. (2005). Neonatal disease severity scoring systems. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, *90*(1), F11–F16. <https://doi.org/10.1136/adc.2003.048488>

Doyle, D. J., & Garmon, E. H. (2018). American Society of Anesthesiologists Classification (ASA Class). In *StatPearls*. Treasure Island (FL): StatPearls Publishing. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK441940/>

Durham, S. R., Clancy, R. R., Leuthardt, E., Sun, P., Kamerling, S., Dominguez, T., & Duhaime, A. C. (2000). CHOP Infant Coma Scale (“Infant Face Scale”): a novel coma scale for children less than two years of age. *Journal of Neurotrauma*, *17*(9), 729–737. <https://doi.org/10.1089/neu.2000.17.729>

Ely, D. M., Driscoll, A. K., & Matthews, T. J. (2018). Infant Mortality by Age at Death in the United States, 2016. *NCHS Data Brief*, (326), 1–8.

Glass, H. C., Costarino, A. T., Stayer, S. A., Brett, C., Cladis, F., & Davis, P. J. (2015). Outcomes for Extremely Premature Infants. *Anesthesia and Analgesia*, *120*(6), 1337–1351. <https://doi.org/10.1213/ANE.0000000000000705>

Goldenberg, R. L., Culhane, J. F., Iams, J. D., & Romero, R. (2008). Epidemiology and causes of preterm birth. *Lancet (London, England)*, *371*(9606), 75–84. [https://doi.org/10.1016/S0140-6736\(08\)60074-4](https://doi.org/10.1016/S0140-6736(08)60074-4)

Halliday, H. L. (2017). Update on Postnatal Steroids. *Neonatology*, *111*(4), 415–422. <https://doi.org/10.1159/000458460>

Harre, F. E., Lee, K. L., & Pollock, B. G. (1988). Regression Models in Clinical Studies: Determining Relationships Between Predictors and Response. *JNCI: Journal of the National Cancer Institute*, *80*(15), 1198–1202. <https://doi.org/10.1093/jnci/80.15.1198>

Howson, C. P., Kinney, M. V., McDougall, L., & Lawn, J. E. (2013). Born Too Soon: Preterm birth matters. *Reproductive Health*, *10*(Suppl 1), S1. <https://doi.org/10.1186/1742-4755-10-S1-S1>

Iliodromiti, S., Mackay, D. F., Smith, G. C. S., Pell, J. P., & Nelson, S. M. (2014). Apgar score and the risk of cause-specific infant mortality: a population-based cohort study. *Lancet (London, England)*, *384*(9956), 1749–1755. [https://doi.org/10.1016/S0140-6736\(14\)61135-1](https://doi.org/10.1016/S0140-6736(14)61135-1)

Jain, S., & Iverson, L. M. (2018). Glasgow Coma Scale. In *StatPearls*. Treasure Island (FL): StatPearls Publishing. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK513298/>

- Kamath-Rayne, B. D., DeFranco, E. A., & Chen, A. (2013). Subtypes of Preterm Birth and the Risk of Postneonatal Death. *The Journal of Pediatrics*, *162*(1), 28-34.e2. <https://doi.org/10.1016/j.jpeds.2012.06.051>
- Low, J. A., Lindsay, B. G., & Derrick, E. J. (1997). Threshold of metabolic acidosis associated with newborn complications. *American Journal of Obstetrics and Gynecology*, *177*(6), 1391–1394. [https://doi.org/10.1016/S0002-9378\(97\)70080-2](https://doi.org/10.1016/S0002-9378(97)70080-2)
- Manchanda, V., Sarin, Y. K., & Ramji, S. (2012). Prognostic Factors Determining Mortality in Surgical Neonates. *Journal of Neonatal Surgery*, *1*(1). Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4420309/>
- Manuck, T. A. (2017). Racial and ethnic differences in preterm birth: A complex, multifactorial problem. *Seminars in Perinatology*, *41*(8), 511–518. <https://doi.org/10.1053/j.semperi.2017.08.010>
- Manuck, T. A., Rice, M. M., Bailit, J. L., Grobman, W. A., Reddy, U. M., Wapner, R. J., ... Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. (2016). Preterm neonatal morbidity and mortality by gestational age: a contemporary cohort. *American Journal of Obstetrics and Gynecology*, *215*(1), 103.e1-103.e14. <https://doi.org/10.1016/j.ajog.2016.01.004>
- McCann, M. E., & Soriano, S. G. (2014). Progress in anesthesia and management of the newborn surgical patient. *Seminars in Pediatric Surgery*, *23*(5), 244–248. <https://doi.org/10.1053/j.sempedsurg.2014.09.003>
- McIntire, D. D., & Leveno, K. J. (2008). Neonatal Mortality and Morbidity Rates in Late Preterm Births Compared With Births at Term. *Obstetrics & Gynecology*, *111*(1), 35. <https://doi.org/10.1097/01.AOG.0000297311.33046.73>
- Medlock, S., Ravelli, A. C. J., Tamminga, P., Mol, B. W. M., & Abu-Hanna, A. (2011). Prediction of Mortality in Very Premature Infants: A Systematic Review of Prediction Models. *PLoS ONE*, *6*(9). <https://doi.org/10.1371/journal.pone.0023441>
- Neonatal mortality. (2018, March). Retrieved February 1, 2019, from <https://data.unicef.org/topic/child-survival/neonatal-mortality/>
- Oros, D., Strunk, M., Breton, P., Paules, C., Benito, R., Moreno, E., ... Schoorlemmer, J. (2017). Altered gene expression in human placenta after suspected preterm labour. *Placenta*, *55*, 21–28. <https://doi.org/10.1016/j.placenta.2017.04.025>
- Parry, G., Tucker, J., Tarnow-Mordi, W., & UK Neonatal Staffing Study Collaborative Group. (2003). CRIB II: an update of the clinical risk index for babies score. *Lancet (London, England)*, *361*(9371), 1789–1791. [https://doi.org/10.1016/S0140-6736\(03\)13397-1](https://doi.org/10.1016/S0140-6736(03)13397-1)

Platt, M. J. (2014). Outcomes in preterm infants. *Public Health*, *128*(5), 399–403. <https://doi.org/10.1016/j.puhe.2014.03.010>

Preterm birth. (2018, February 19). Retrieved November 12, 2018, from <http://www.who.int/news-room/fact-sheets/detail/preterm-birth>

Purisch, S. E., & Gyamfi-Bannerman, C. (2017). Epidemiology of preterm birth. *Seminars in Perinatology*, *41*(7), 387–391. <https://doi.org/10.1053/j.semperi.2017.07.009>

Räsänen, S., Gissler, M., Saari, J., Kramer, M., & Heinonen, S. (2013). Contribution of risk factors to extremely, very and moderately preterm births - register-based analysis of 1,390,742 singleton births. *PloS One*, *8*(4), e60660. <https://doi.org/10.1371/journal.pone.0060660>

Ray, J. G., Park, A. L., & Fell, D. B. (2017). Mortality in Infants Affected by Preterm Birth and Severe Small-for-Gestational Age Birth Weight. *Pediatrics*, *140*(6), e20171881. <https://doi.org/10.1542/peds.2017-1881>

Reid, S., Bajuk, B., Lui, K., Sullivan, E. A., & NSW and ACT Neonatal Intensive Care Units Audit Group, PSN. (2015). Comparing CRIB-II and SNAPPE-II as mortality predictors for very preterm infants. *Journal of Paediatrics and Child Health*, *51*(5), 524–528. <https://doi.org/10.1111/jpc.12742>

Richardson, D. K., Corcoran, J. D., Escobar, G. J., & Lee, S. K. (2001). SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *The Journal of Pediatrics*, *138*(1), 92–100.

Richardson, D. K., Gray, J. E., McCormick, M. C., Workman, K., & Goldmann, D. A. (1993). Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. *Pediatrics*, *91*(3), 617–623.

Richardson, D. K., Phibbs, C. S., Gray, J. E., McCormick, M. C., Workman-Daniels, K., & Goldmann, D. A. (1993). Birth weight and illness severity: independent predictors of neonatal mortality. *Pediatrics*, *91*(5), 969–975.

Roberts, C. L., Badgery-Parker, T., Algert, C. S., Bowen, J. R., & Nassar, N. (2011). Trends in use of neonatal CPAP: a population-based study. *BMC Pediatrics*, *11*, 89. <https://doi.org/10.1186/1471-2431-11-89>

Rothenberg, S. S., Chang, J. H. T., & Bealer, J. F. (2004). Minimally Invasive Surgery in Neonates: Ten Years' Experience. *Pediatric Endosurgery & Innovative Techniques*, *8*(2), 89–94. <https://doi.org/10.1089/1092641041360931>

Salihu, H. M., Das, R., Morton, L., Huang, H., Paothong, A., Wilson, R. E., ... Marty, P. J. (2016). Racial Differences in DNA-Methylation of CpG Sites Within Preterm-

Promoting Genes and Gene Variants. *Maternal and Child Health Journal*, 20(8), 1680–1687. <https://doi.org/10.1007/s10995-016-1967-3>

Schonhaut, L., Armijo, I., & Pérez, M. (2015). Gestational Age and Developmental Risk in Moderately and Late Preterm and Early Term Infants. *Pediatrics*, 135(4), e835–e841. <https://doi.org/10.1542/peds.2014-1957>

Strauss, J. F., Romero, R., Gomez-Lopez, N., Haymond-Thornburg, H., Modi, B. P., Teves, M. E., ... Schenkein, H. A. (2018). Spontaneous preterm birth: advances toward the discovery of genetic predisposition. *American Journal of Obstetrics & Gynecology*, 218(3), 294-314.e2. <https://doi.org/10.1016/j.ajog.2017.12.009>

Suresh, G. K., & Soll, R. F. (2003). Exogenous surfactant therapy in newborn infants. *Annals of the Academy of Medicine, Singapore*, 32(3), 335–345.

The CRIB (clinical risk index for babies) score: a tool for assessing initial neonatal risk and comparing performance of neonatal intensive care units. The International Neonatal Network. (1993). *Lancet (London, England)*, 342(8865), 193–198.

UNICEF, WHO, World Bank Group, & United Nations. (2018). *Levels and Trends in Child Mortality: Report 2018*. Retrieved from <https://data.unicef.org/resources/levels-and-trends-in-child-mortality/>

World Health Organization, March of Dimes, The Partnership for Maternal, Newborn & Child Health, & Save the Children. (2012). *Born too Soon: The Global Action Report on Preterm Birth* (No. 9789241503433). Retrieved from [http://www.who.int/maternal\\_child\\_adolescent/documents/born\\_too\\_soon/en/](http://www.who.int/maternal_child_adolescent/documents/born_too_soon/en/)

Zhang, G., Feenstra, B., Bacelis, J., Liu, X., Muglia, L. M., Juodakis, J., ... Muglia, L. J. (2017). Genetic Associations with Gestational Duration and Spontaneous Preterm Birth. *New England Journal of Medicine*, 377(12), 1156–1167. <https://doi.org/10.1056/NEJMoa1612665>

## VITA

