Single Centre Experience with Hypoxic Ischemic Encephalopathy: Prognostic Factors and Development of a Prognostication Model

by

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Abstract

Hypoxic ischemic encephalopathy (HIE) continues to carry prognostic uncertainty despite therapeutic hypothermia (TH) becoming standard of care in high income nations. Prognostic factors have been identified with recent evidence relying on factors that are available later in a hospital admission such as brain magnetic resonance imaging (MRI). Further, most of the research utilizes a composite outcome of death or disability which makes it difficult to apply findings to patient-specific conversations at the bedside. In this thesis, we conducted a systematic review to identify early prognostic factors (those that can be identified in the first 72 hours) from randomized control trials (RCTs) of TH for neonatal HIE. This review identified pre-randomization, biochemical and clinical factors which were then used to guide model development from a cohort of infants with HIE in Edmonton, Alberta since 2006. We developed a regression model for early and late prediction of death in addition to a prediction model for significant/severe neurodevelopmental impairment (sNDI). The early prediction model included receipt of phenobarbital, hypotension receiving inotrope(s), severe HIE (as per Sarnat staging), chest compressions and perinatal sentinel event. The late prediction model for death included the above factors in addition to renal dysfunction. The prediction model for sNDI included receipt of phenobarbital, hypoglycemia, abnormal MRI, electrolyte abnormality and 10-minute Apgar score less than 5. Using the same cohort, classification and regression tree (CART) analysis was used to develop prediction models for death and sNDI. The CART models outperformed the logistic regression models for measures of sensitivity, specificity and negative predictive value, thereby providing a clinical picture of what survival and NDI-free survival would look like. According to the separate models, an infant who did not require inotropes for hypotension or receive phenobarbital would have a very low chance of death or sNDI. The findings from this

thesis will improve bedside conversations by decreasing prognostic uncertainty, allow for the identification of high-risk infants and ensure appropriate triage for neonatal follow-up.

Preface

This thesis is an original work by Nicole Anderson. No part of this thesis has been previously published. The research project, of which this thesis is a part, received ethics approval from the University of Alberta Research Ethics Board, Project Name “Single Centre Experience with Neonatal Hypoxic Ischemic Encephalopathy” No. Pro00103917, June 7, 2021.

Dedication

To the many NICU families who have trusted us with the care of their infants.

To my boys, Brooks and Griffin.

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Chapter 1. Introduction: Neonatal Hypoxic Ischemic Encephalopathy

1.1 Literature Review

1.1.1 History of Hypoxic Ischemic Encephalopathy (HIE) and Prognostication

Hypoxic ischemic encephalopathy which replaced the diagnosis of "perinatal or birth asphyxia" is the product of oxygen deprivation around the time of delivery leading to adverse neurological sequelae.[1] As early as the 1970s, Brown et al[2] described that when asphyxia occurs in association with subsequent neurological signs there may be long-term adverse outcomes. Sarnat and Sarnat[3] described three clinical stages as they relate to neonatal encephalopathy. In 1981, Nelson and Ellenberg[4] described a cohort of term infants with low 10-minute Apgar score, for a myriad of etiologies, and the association with cerebral palsy (CP) and neurodevelopmental impairment (NDI). In 1983, Bergman et al[5] published a cohort of infants who had seized during their neonatal course, 58% of whom were related to hypoxic-ischemic insult. Of these infants, poor prognostic markers were increased number of days of seizures, later onset of seizures, and tonic seizures.

1.1.2 Hypoxic Ischemic Encephalopathy: Epidemiology and Economic Impact

Hypoxic ischemic encephalopathy remains a major cause of death and disability worldwide. The incidence of HIE in the developed world ranges between 1-8/1000 live births.[6,7] Hypoxic ischemic encephalopathy is the single greatest contribution to disability worldwide and accounts for one-tenth of all disability adjusted life years.[8] In a systematic review, the proportion of cerebral palsy associated with intrapartum hypoxia and subsequent ischemic injury in term infants without congenital malformations was approximately 15%.[9] In 2003, the cost of

CP per person was calculate to be US $900 000.[10] A Denmark study looking at infants born from 1970-2000 had similar lifetime costs.[11] Globally, HIE contributes to one quarter of neonatal deaths.[12]

In Alberta, Canada, there are a total of 81 delivery sites with only two-level three neonatal intensive care units.[13] One in Edmonton, Alberta and the other in Calgary, Alberta. Each city also has a surgical NICU which may receive infants with HIE. The Northern Alberta Neonatal Program has a total of 136 beds and accepts neonates from northern Alberta, northern British Columbia, western Saskatchewan, Yukon, Northwest Territories and Nunavut. This catchment area has over 25,000 births per year with over 3,000 NICU admissions annually.

Provincial data from 2002-2016 shows that the rate of HIE was 2.28 per 1,000 births with 2.5 per 1,000 in urban hospitals and 1.35 per 1,000 in rural hospitals.[13] Rates of encephalopathy were similar in urban and rural births; urban hospitals being defined as serving more than or equal to 50,000 people. From 2006-2020, 436 neonates underwent therapeutic hypothermia in Edmonton, Alberta. Given that Edmonton was one of the centres involved in the CoolCap Trial[14], cooling was adopted early with long term follow-up in place to ascertain outcomes.

1.1.3 Pathophysiology and Definition of Hypoxic Ischemic Encephalopathy

Hypoxic ischemic encephalopathy is the result of reduced or absent oxygenation leading to decreased or lack of brain perfusion and subsequent findings of neurological injury. In some cases, the event is clear (i.e., placental abruption) but in other cases, less so. Evidence of hypoxic-ischemic sequelae include Apgar score of 5 or less at 10 minutes, continued need for resuscitation at 10 minutes after birth, metabolic acidosis (pH <7 within 60 minutes of birth) or base deficit (>16 mmol/L in a cord, venous or arterial sample).[6] There may be centre-to-centre

variation of this criteria. It is important to accurately identify possible HIE as subsequent treatment is time sensitive for optimal outcome.

If an infant meets criterion for hypoxia and ischemia as evidenced by clinical markers and laboratory data, a clinician performs a neurological examination to determine if there is evidence of brain injury or encephalopathy. Clinical seizure is one such example and, in some cases, predates the suspicion for HIE. Electrographic seizure and amplitude-integrated encephalography (aEEG) changes are also indicators of encephalopathy. Other signs of moderate or severe encephalopathy are in the domains of level of consciousness, spontaneous activity, posture, tone, primitive reflexes (suck and moro) and autonomic system (pupils, heart rate, respirations). The aforementioned clinical assessment comes from work done by Sarnat and Sarnat[3]. Hypoxic ischemic encephalopathy puts an infant at risk of significant morbidity and mortality.

Beyond meeting the clinical criteria, the American College of Obstetricians and the American Academy of Pediatrics recommends the diagnosis of HIE includes: (1) The presence of a sentinel event occurring immediately before or during labor and delivery, (2) the presence of fetal acidosis and low Apgar scores, (3) multiorgan injuring affecting the heart, liver or kidneys, (4) neuroimaging with magnetic resonance imaging (MRI) consistent with acute peripartum or intrapartum event and excluding other causes.[15] Further, the American Congress of Obstetricians and Gynecologists Task Force on Neonatal Encephalopathy and Cerebral Palsy highlight that before a connection can be made to an intrapartum event and subsequent cerebral palsy, there should be (1) evidence of metabolic acidosis in fetal umbilical cord arterial blood, (2) early onset of neonatal encephalopathy, (3) cerebral palsy of the spastic quadriplegic or dyskinetic type, and (4) exclusion of other etiologies such as infection or genetic disorders.

1.1.4 Therapeutic Hypothermia as the Standard of Care

Therapeutic hypothermia has become the standard of care for neonates with confirmed HIE since several large multicenter trials demonstrated both safety and efficacy of this treatment. In addition, several systematic reviews and meta-analyses have deemed this both a safe and efficacious standard of care.[16-21] As shown in animal models, cooling prevents secondary injury from reperfusion by downregulating the inflammatory cascade that ensues after a hypoxic event.[22-26] Seven sentinel cooling trials for neonatal HIE are frequently referenced in the literature (Table 1.1). Their inclusion criteria and protocols had subtle differences but the overall effect of cooling on the composite outcome of death and/or disability was 0.76 (0.69-.84), favoring hypothermia.[27] It should be noted that the definition for major disability has subtle differences among the trials. In general, NDI is defined as cerebral palsy (Gross Motor Functional Classification System 3-5), developmental delay (Bayley III or equivalent, Mental Developmental Index or MDI <70), blindness and/or sensorineural deafness. This is in line with the Canadian Neonatal Network (CNFUN) outcomes definitions as summarized in Table 1.2.

1.1.5 Outcomes Pre and Post Therapeutic Hypothermia Era

Prior to therapeutic hypothermia becoming the standard of care for neonatal HIE in industrialized nations, surviving infants with moderate encephalopathy had a neurodevelopmental impairment (NDI) rate of 6 to 21 percent while those with severe encephalopathy ranged from 42 to 100 percent.[28-32] Robertson and Finer[33] followed a cohort of 226 children with HIE in Alberta, twenty six children died (11.4%) and 19.0% were neurodevelopmentally impaired. This cohort was followed into school age; children with a history of moderate or severe encephalopathy performed lower in the domains of visual-motor

integration, receptive vocabulary as well as reading, spelling, and arithmetic subjects compared to those with mild encephalopathy or peer comparators.[34] Those who did not meet criteria for impairment displayed an intelligent quotient (IQ) that was approximately 10 points lower than an age-matched comparison group. The percentage of infants with a history of HIE who go on to develop CP is about 15 percent.[9] Beyond NDI, the mortality rates among infants with umbilical arterial pH less than 7.0 (as a proxy measure for HIE) were 4.3-9.5 percent.[9]

In a recent Cochrane systemic review and meta-analysis, therapeutic hypothermia reduced the outcomes of mortality and major NDI at 18 months of age with a risk ratio of 0.75 (95% confidence interbal [CI] 0.68-.83).[35] Though the advent of therapeutic hypothermia brought hope to clinicians and families involved in the care of infants with HIE, it is important to recognize that even with this treatment, more than 40 percent of infants either died or had NDI, this highlights the need for HIE prevention strategies and research on additional treatment adjuncts.

1.1.6 Early Predictors for Poor Outcome

Prediction research, which differs from aetiological research, aims to predict a future event. Aetiological research identifies causal variables referred to as risk factors.[36] There is HIE literature exploring predictors for poor outcome, death or disability as per the study definition, including clinical examination, biochemical values and other diagnostics including EEG and brain magnetic resonance imaging (MRI). The Apgar score which is given to infants at 1, 5, and 10 minutes after birth is done by assessing appearance, pulse, grimace, activity and respirations. There are studies that have looked at Apgar score in the setting of HIE.[37-41] Persistently low Apgar score at 10 minutes is associated with death or moderate/severe disability at 18 months

and 6-7 years of age. [38] Importantly, 1/5th of those with Apgar score of '0' at 10 minutes, survived without disability to school age. Modified Sarnat Staging is a tool used to denote severity of HIE based on a clinical examination for encephalopathy.[3] It is associated with neurodevelopmental outcome but a multicenter prospective trial did not show the Sarnat stage to be predictive of adverse outcome including death or moderate or severe disability[42]. More importantly, it seems to be the evolution of the clinical examination over time. An exam consistent with moderate HIE at 72 hours of age increased risk of death or disability at 18 months to an odds ratio of 60 (95% confidence interval 15-246).[43,44] Hemodynamic instability is reported in up to 77% of neonates with HIE.[45] Hypotension and receiving inotropes have independently been shown as risk factors for poor outcome[45]. The studies on heart rate variability are heterogenous so difficult to draw conclusions.[46]

With respect to aEEG, not only is the pattern important but also the timing and evolution. Therapeutic hypothermia also plays a role in the time to recovery on aEEG.[47] Several studies have found that a suppressed aEEG beyond 48 hours is associated with poor outcome.[48,49] Evoked potentials (EPs) are electrical responses to a sensory stimulation, including visual EPs, brainstem auditory EPs and somatosensory EPs. Evoked Potentials have been studied but are not routinely done in the clinical setting so difficult to draw concrete conclusions about their potential utility for prognostication.[46] Cerebral oxygenation, as measured by near infrared spectroscopy (NIRS), may be associated with short term MRI outcome but no long-term outcome data are available.[50,51] With respect to biochemical values, lactate has been studied as a predictor of short- and long-term outcomes. Lactate used in combination with creatine kinase, lactate dehydrogenase and uric acid may be used as a predictor of HIE severity.[52] There is also

literature supporting that the time to normalization of lactate may be an important consideration.[53]

In addition to identifying early prognostic factors, it is important to consider modifiable predictors of poor outcomes. Hypocarbia, hyperoxemia, hypo- or hyperglycemia and seizures have been studied. In two sentinel randomized control trials (NICHD and CoolCap), hypocarbia in the early phase of therapeutic hypothermia was linked with a higher risk of death or disability at 18 months.[54] CoolCap noted that carbon dioxide was inversely related to unfavorable outcome.[55] Hyperoxemia (partial pressure of oxygen (PaO2) >100 mmHg) during the first hour [56] or first 6 hours [57] was associated with a higher incidence of encephalopathy. Post hoc analysis of the CoolCap trial determined that the odds of an unfavorable outcome were 6.2 times greater among infants with at least one episode of hypoglycemia, 2.7 times greater if at least one episode of hyperglycemia and 3 times greater if at least one episode of any glucose derangement within the first 12 hours.[58] Seizures, which are not necessarily modifiable, have also been studied. It appears that it is not necessarily the presence of seizures but rather the total electrographic seizure burden, more than 40 minutes and a maximum hourly seizure burden of 13 minutes per hour, contributes to poor outcome.[59]

Several biomarkers that have been researched in the context of HIE have not gained clinical traction. These include serum, urinary and cerebral spinal fluid markers. For example, ubiquitin carboxyl-terminal esterase (UCHL1) is known to be released from neurons following cardiac arrest or brain injury.[60] Other serum biomarkers studied primarily in animal models include glial fibrillary acidic protein (GFAP), neuron-specific enolase and miR-199a which were sampled from cord blood specimens.[61,62] Urine S100B protein level and CSF biomarkers which are either cytokines or antioxidants are under academic interest.[63,64]

Generally, full EEG and/or brain MRI done early in the infant's course are not helpful as we expect EEG will change over time and brain MRI will not show patterns of injury if done too early. As such, these investigations are often not helpful when it comes to prognostication in the first 72 hours. A vignette-based study of Canadian subspecialists caring for infants with HIE identified that 85% of physicians use MRI results to aid in discussions around prognostication.[65] Similarly, these physicians agreed that MRI data can help guide decisions related to comfort care and gave the MRI result a weight of 25%. The vignettes that the physician participants were presented with had a case with MRI findings that are consistent with a poorer prognosis and another whereby the MRI findings are not as consistently reported in the context of poor outcome. This study supports that as perceived severity increases, so too does the certainty about outcome. However, we know that in the case of HIE, there is a great deal of prognostic uncertainty.[66]

1.1.7 Socioeconomic Impact on Neurodevelopmental Outcome

An entity that is not well described in HIE literature but warrants discussion is the impact of socioeconomic factors on an infant's development. As described by Daly et al[67], the three most common indicators of socioeconomic status are household income, education, and occupation. These factors are not always readily available and as such, a proxy can be utilized. The deprivation index was built from the combination of geographical units and socioeconomic indicators.[68] The six socioeconomic indicators are from six years of Canadian censuses. The indicators are as follows:

Material Indicators

1. The proportion of the population aged 15 years and over without a high school diploma or equivalent
2. The employment to population ratio for the population 15 years and over
3. The average income of the population aged 15 years and over

Social Indicators

4. The proportion of the population aged 15 and over living alone
5. The proportion of the population aged 15 and over who are separated, divorced, or widowed
6. The proportion of single-parent families

The indicators were selected because of their relationship with health status.[68] The small area units known as dissemination areas (DAs), which can be linked to postal codes, form the geographical component of the deprivation index. Postal codes are put into the model and assigned a quintile. The first quintile describes a materially and socially privileged DA while the last is a materially and socially deprived DA. The index is limited in a prospective cohort study as individuals may have moved from their initial address. In a population-based Canadian study, socioeconomic status measured by deprivation index, had little impact on adverse birth outcomes. However, low maternal education increased the likelihood of low birth weight in the neonate.[69] Other Canadian studies displayed an association between socioeconomic status with birth outcomes.[70,71]

1.1.8 Prognostic Uncertainty

In the Neonatal Intensive Care Unit (NICU), prognostication is difficult due to the uncertainty that often exists in addition to how and what we communicate with families.[66] There

is prognostic uncertainty that extends beyond the neonate's outcome but is also a product of uncertainty about the diagnoses, prognosis and at times the parent's role in medical decision making. When counselling families, a disease-specific population statistic is often applied to an individual neonate.[66] It is important to appreciate the sudden and acute nature of HIE, often in the setting of a normal pregnancy and with no antenatal lead up unlike other diagnoses (i.e., congenital heart disease or multiple congenital anomalies).

Krick et al[72] proposed a model of integrating prognostic uncertainty. The model depicts that as prognostic uncertainty increases, the zone of parental discretion increases. Parental discretion appreciates that parents can make difficult health care decisions based on their morals and values. There are some inherent assumptions to this model. Firstly, the model implies that where prognosis is "clear", the decision is more "black and white". Secondly, the model assumes that parents would want more decision-making ability in the face of prognostic uncertainty, but many families do not want to be the sole decision makers and rather opt for a shared decision-making model.[72] Lastly, the level of prognostic uncertainty is subjective, and some clinicians may be more comfortable communicating the certainty of the uncertainty than others.[66]

Interestingly, in a cohort of NICU parents, approximately 30% do not remember being given a neurologic prognosis. Of those that were given a prognosis, 24% recall that the prognosis was accurate and 46% recall that their child exceeded expectations.[73] Perhaps, the use of prognostic models would help reduce prognostic uncertainty.

1.1.9 Prognostic Tools for Hypoxic Ischemic Encephalopathy (HIE)

The Thompson Score was developed by Thompson et al[74] before the introduction of therapeutic hypothermia. The scoring system uses 9 signs (tone, level of consciousness,

fits/seizures, posture, moro-reflex, grasp-reflex, suck-reflex, respiratory pattern and fontanelle), scored from 0 to 3 where '0' is normal. The score has been validated for short- and long-term outcomes in the cooling era.[75,76] With respect to short term outcomes, a Thompson Score greater than 12 was associated with adverse outcome of death before discharge or severe epilepsy. When validation of the score for long term outcomes, Mendler et al[76] studied 36 infants with a primary outcome of survival without cognitive impairment as defined by general intelligent quotient (IQ) greater than 85. A Thompson-score greater than or equal to 11 was associated with an impaired IQ, but the specificity or ability of the score to identify patients with the outcome was only 61%. Specificity improved when the score was greater than 15 to 96%. Specificity is the test ability to accurately identify a patient without disease while sensitivity is the ability to identify those with disease.[77]

1.1.10 Composite Outcomes

A composite outcome is a study endpoint that includes multiple distinct components.[78] A review of neonatal trials displayed that the use of composite outcomes is less common than in adult trials[79], however, in the HIE literature it seems to be widespread. Statistically, a composite outcome will increase the prevalence of the primary outcome and study power and thus, the trial size can be smaller.[80] Clinically, the benefit of a composite outcome is really to address competing risks. For example, neonatal death would preclude the ability to assess for NDI. There are, inherently, issues with this approach, particularly in HIE.

It should be noted that the original cooling trials used composite outcome (see Table 1). By presenting death or major disability as a composite, you run the risk of false interpretation. Thus, if used, the risk of each individual component should be reported to avoid confusion and

false conclusions. As can be seen in Table 1.3, we have reported the composite outcome alongside death and disability to give a clearer depiction of the outcomes of interest. There are a few important things to point out, firstly, in most of the sentinel trials, the composite outcome is an accurate depiction of the overall benefits of therapeutic hypothermia. The composite outcome is typically an overestimate of one outcome and an underestimate of the other. In most of the trials, the risk ratio for disability was lower than that for death, an outcome that would be important to discuss with parents after the acute phase.

The other important element to consider is if the effect on death and disability is indeed continuous; in other words, does more "severe" HIE lead to death while less "severe" lead to disability? Statistics aside, it is important to understand the composite outcome when discussing prognostication with families. Work done by Janvier et al[81], highlight that outcome variables in neonatal research do not involve the parents as crucially important stakeholders and that the outcome of interest should reflect not only the functioning of the child but also the family and the interplay between the two.

1.2 Rationale, Research Question and Aims

1.2.1 Rationale

Despite over 20 years of data from randomized control trials and cohort studies there lacks clear identification of prognostic factors from a large cohort of neonates with HIE. Moreover, much of the research done uses a composite outcome of death or NDI which limits the ability to counsel families in the early stage of their infant's hospital course. A prognostication model developed from the cooling era is needed to inform early discussion with families, lessen prognostic uncertainty, guide acute care, and optimize follow-up of these infants.

1.2.2 Research Question and Aims

Research question: Using singe centre data for neonates with HIE, what are the early predictors (first 72 hours following birth) of death and NDI. Neurodevelopmental impairment is defined as CP (GMFCS 3-5), developmental delay (Bayley III or equivalent, Mental Developmental Index or MDI <70), blindness and/or sensorineural deafness. Further, can a prognostication model be built using this information to guide early discussions with families regarding prognostication and goals of care?

- Aim 1 (*Chapter 2*): Identify prognostic factors that have been identified in randomized control trials of therapeutic hypothermia for infants with HIE to guide subsequent data analysis.
    - Aim 1.1: Identify the effect direction and relative size of identified prognostic factors.
    - Aim 1.2: Complete bias analysis of the initial cooling trials.

- Aim 2 (*Chapter 3*): Identify prognostic factors for death or NDI from a single centre experience.
    - Aim 2.1: Describe the population using descriptive statistics.
    - Aim 2.2: Propose a logistic regression model that can guide early discussions related to outcomes in infants with HIE.

- Aim 3 (Chapter 4): Develop a prediction tool for poor outcome (death or NDI) in neonates with HIE using CART analysis.

- Aim 3.1: Compare the accuracy of the proposed models (logistic regression versus CART).

- Aim 4 (Chapter 5): Explore future directions for research with respect to HIE and prognostication.

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Table 1.1 A comparison of the Sentinel Cooling Trials for Neonates with HIE

Authors, year	Cooling Modality and Target Temperature (°C)	Number of Subjects; Total (Cooled)	Death or Major Disability at 18 Months, Risk Ratio (95% CI)
Azzopardi et al[82,83], 2009	Cooling blanket; rectal temperature 33-34	325 (163)	0.86 (0.68, 1.07)
Gluckman et al[14], 2005	Cooling cap; rectal temperature 34-35	234 (116)	0.82 (0.66, 1.02)
Gunn et al[84], 1998	Cooling cap with sequential randomization of rectal temp 34.5-36.5 depending on group)	22 (12)	1.26 (0.46, 3.44)
Jacobs et al[85], 2011	Refrigerated gel packs; rectal temp 33-34	221 (110)	0.75 (0.60, 0.94)
Shankaran et al[86], 2005	Cooling blanket; esophageal temperature 33-34	208 (102)	0.72 (0.54, 0.95)
Simbruner et al[87], 2010	Cooling mattress; rectal temperature 33-34	129 (64)	0.62 (0.46, 0.82)
Zhou et al[88], 2010	Cooling cap; nasopharyngeal temperature 34 +/- 0.2 C and rectal temperature 34.5-35	194 (100)	0.63 (0.44, 0.91)

Adapted from Tagin et al [20] and Zhou et al [88].

Table 1.2 Outcomes Definitions as per Canadian Neonatal Follow-up Network (CNFUN)

Impairments	**Neurodevelopmental Impairment (NDI)**	**Significant NDI**	**Severe NDI[89]**
Motor[90]	CP[a] with GMFCS[b] 1 or higher Bayley-III Motor Composite <85	CP with GMFCS 3,4 or 5 Bayley-III Motor Composite <70	CP with GMFCS 4 or 5 Not included
Cognitive	Bayley III[c] Cognitive Composite <85	Bayley-III Cognitive Composite <70	Bayley-III Cognitive Composite <55
Language	Bayley-III Language Composite <85	Bayley-III Language Composite <70	Bayley-III Language Composite <55
Hearing	Sensorineural/mixed hearing loss	Hearing aid or cochlear implant	Not included
Vision	Uni- or bilateral visual impairment	Bilateral visual impairment	Bilateral visual impairment

Adapted from CNFUN Annual Report 2021[91]

CP: Cerebral palsy; GMFCS: Gross motor functional classification score; Bayley III: Bayley Scale of Infant and Toddler Development Edition Three

Table 1.3 A Comparison of the Sentinel Cooling Trials Primary Outcome Reported as a Composite and Individual Outcomes (Death and Disability)

Authors, year	Death or major disability at 18 months, Risk Ratio (95% CI)	Death, Risk Ratio (95% CI)	Disability†, Risk Ratio (95% CI)
Azzopardi et al[82,83], 2009	0.86 (0.68, 1.07)	0.96 (0.66, 1.36)	0.74 (0.51, 1.09)
Gluckman et al[14], 2005	0.82 (0.66, 1.02)	0.87 (0.61, 1.25)	0.76 (0.47, 1.2)
Gunn et al[84], 1998	1.26 (0.46, 3.44)	0.83 (0.14, 4.90)	0.8 (0.06, 10.89)
Jacobs et al [85], 2011	0.75 (0.60, 0.94)	0.64 (0.43, 0.97)	0.87 (0.55, 1.38)
Shankaran et al[86], 2005	0.72 (0.54, 0.95)	0.68 (0.44, 1.05)	0.71 (0.44, 1.13)
Simbruner et al[87], 2010	0.62 (0.46, 0.82)	0.66 (0.44, 1.00)	0.47 (0.21, 1.02)
Zhou et al[88], 2010	0.64 (0.44, 0.91)	0.70 (0.42, 1.15)	0.48 (0.25, 0.95)

†*The definitions of major disability varied slightly among the studies:*

- *Azzopardi et al: One of MDI <70, GMFCS level 3-5 or bilateral cortical visual impairment*
- *Gluckman et al: GMFCS level 3-5, MDI <70 or bilateral cortical visual impairment*
- *Gunn et al: "severe handicap"-not well defined*
- *Jacobs et al: CP in which the child was not walking or unlikely to walk at 2 years of age, MDI <70, GMFCS 2-5, blindness and/or deafness requiring amplification*
- *Shankaran et al: MDI <70, GMFCS level 3-5, hearing impairment requiring hearing aids, or blindness*
- *Simburner et al: GMFCS level 3-5, Developmental Quotient <70, severe bilateral cortical visual deficit or any combination of the above*
  Zhou et al: GMFCS level 3-5 or Developmental Quotient <70

Chapter 2: A Systematic Review of Early Prognostic Factors for Neurodevelopmental Impairment and Mortality among Neonates with Hypoxic Ischemic Encephalopathy

2.1 Background

Hypoxic ischemic encephalopathy (HIE) is the result of reduced or absent oxygenation leading to decreased or lack of brain perfusion and subsequent findings of neurological injury. Therapeutic hypothermia (TH) has become the standard of care for neonates with confirmed HIE since several large randomized controlled trials (RCTs) demonstrated both safety and efficacy of this treatment.[1-8] As shown in animal models, hypothermia prevents secondary injury from reperfusion by downregulating the inflammatory cascade that ensues after a hypoxic event.[9-13]

Prior to TH becoming standard of care for neonatal HIE in high-income nations, surviving infants with moderate encephalopathy had a neurodevelopmental impairment (NDI) rate of 6-21% while those with severe encephalopathy ranged from 42-100%.[14-18] NDI is typically defined as cerebral palsy, cognitive deficits as measured by standardized testing, visual deficits and/or hearing loss. Beyond NDI, the mortality rates among infants with umbilical cord pH less than 7.1 (as a proxy measure for HIE) ranged from 4.3%-9.5%.[19] In a recent Cochrane systematic review and meta-analysis, TH reduced outcomes of mortality and major NDI at 18 months of age with a risk ratio of 0.75 (95% confidence interval (CI) 0.68-0.83).[20]

Several prognostic factors including clinical examination, biochemical values and other diagnostics including amplitude and full electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) exist in the literature. Most of which come from small, retrospective cohort studies of infants with HIE. There have been systematic reviews and meta-analyses of the original RCTs but to our knowledge this is the first review to identify post-hoc analysis from

RCTs to describe early prognostic factors. The identification of early prognostic factors (those that can be identified in the first 72 hours of age) may allow for early and crucial conversations with families of infants with HIE and resource allocation with respect to follow-up of these infants.

2.2 Methods

The methods for this systematic review have been previously published in a protocol, available at https://www.crd.york.ac.uk/prospero/. Registration number CRD42021276583.

2.2.1 Search Strategy

A comprehensive electronic search strategy was performed using MEDLINE via OVID, EMBASE and CINAHL using MeSH terms and keywords related to prognostic factors as per the Clinical Hedge database from the Health Information Research Unit at McMaster University.[21] The search identified any articles published between January 2005 and December 2021 that reported an early prognostic factor as it related to neurodevelopmental impairment or mortality in RCTs for TH. No language restrictions were made. Grey literature including conference abstracts and proceedings, were searched using Google Scholar. References of identified studies were reviewed to identify further eligible studies.

2.2.2 Eligibility Criteria

Articles were included if they satisfied 3 sets of criterioa; criteria for cooling, prognostic factor identification (as part of a RCT) and outcome measure. With respect to inclusion into the RCT neonates with HIE had to have been cooled within 6 hours of age and be greater than or

equal to 35 weeks gestation. For this review, a prognostic factor included any measure during the pre-, ante- or postnatal period. The articles included were secondary analyses of RCTs. Further, we wanted to identify early prognostic factors, factors that could be identified in the first 72 hours of age. The outcome of interest was NDI at a minimum age of 18 months, and mortality.

2.2.3 Data Extraction

All articles identified by the search strategies were screened on title and abstract after removal of duplicates for obvious exclusions. Potentially eligible articles identified in the screening phase underwent full-text review. Both screens were performed by 2 authors (N.A. and S.L.), if there was disagreement, the article was again reviewed and consensus achieved. If a decision could not be reached, the article was referred to a third reviewer (M.H.). For articles that met the preidentified inclusion criteria, data extraction was done by the first author (N.A.) using a data extraction form based on a modified Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist, CHARMS-PF (prognostic factor)[22]. Missing data was requested from study authors as necessary.

2.2.4 Risk-of-bias Assessment

We utilized the Quality in Prognostic Studies (QUIPS) tool to formally assess bias in the identified articles.[23] Briefly, QUIPS assesses the risk of bias in six domains: study participation, study attrition, prognostic factor measurement, confounding measurement and account, outcome measurement and analysis and reporting. See Table 2.3 of prompting items. Overall risk of bias was denoted as low, moderate, or high. ‘Low’ risk of bias if all domains ‘low’ or up to one ‘moderate’. High risk of bias if one or more domain deemed ‘high’ risk or 3 or more ‘moderate’

classifications. The remainder were considered moderate. Two reviewers (N.A. and S.L.) independently performed risk of bias assessment. A third reviewer (M.H.) settled differences in risk of bias assessment.

2.2.5 Data Synthesis and Reporting

The results are presented in accord with the Synthesis without Meta-Analysis (SWiM) guidelines.[24] A meta-analysis was not possible as there was high statistical and clinical heterogeneity across the studies. First, we present the flow of studies, characteristics, and risk of bias of the included studies. Second, we utilize an effect direction plot to represent the early prognostic factors and their impact on poor outcomes. Last, we provide a conceptual framework for prognostic factors described in the literature.

2.3 Results of Systematic Review

2.3.1 Flow of Studies and Study Characteristics

Our search resulted in 7,426 articles. Figure 2.1 is a flowchart of the study selection process. After removing duplicates, we screened the title and abstract of 3,447 articles. Of the relevant articles identified, 45 were excluded. The reasons for exclusion included incorrect study design (n=26), lack of an early prognostic factor (n=6), lack of a prognostic factor (n=4), an outcome measure other than mortality or NDI (n=6) and duplicate article (n=1). We did not identify any articles upon review of reference lists or grey literature.

Our review consisted of 19 studies. Most studies (n=12) were post-hoc analyses from the National Institute of Child Health and Human Development (NICHD) hypothermia trial.[6] The reminder analyses came from the Total Body Hypothermia for Neonatal Encephalopathy

(TOBY)[1,2], CoolCap[3] and South India Randomized Control Trial[25]. See Table 2.1 for study characteristics.

Six studies identified clinical prognostic factors[26-31] and five identified biochemical factors[25,32-35]. Eight studies were categorized as having identified pre-randomization variables (i.e., maternal characteristics)[31,36-42] and 4 studies investigated amplitude electroencephalogram (aEEG) as a prognostic factor for poor outcome[37,40,42,43], two of which were outside of the pre-randomization phase[40,43]. One study included MRI (outside of the 72 hour window) but was included as the focus was on perinatal sentinel event (PSE) defined as any of the following: umbilical cord problem (cord prolapse, knotted, torn, ruptured or compressed), uterine rupture, placental abruption, shoulder dystocia and major maternal hemorrhage, trauma, cardiorespiratory arrest, or seizures immediately preceding delivery.[41]

2.3.2 Risk of Bias Assessment

In this review, most studies were rated as 'low' or 'moderate' risk of bias using the QUIPS tool (Figure 2.2).[23] Given that all studies were post-hoc analysis of RCTs, the 'study participation' as defined by the QUIPS tool was 'low' risk of bias. Study attrition was difficult to assess as it was likely denoted in the original publication but may not have been explicitly stated in the subsequent analysis, albeit, dropout and loss to follow-up rates were low. This was where risk of bias was highest compared to other domains (see Figure 2.3). The measurement of prognostic factors was well described in most studies. Outcome measurement was reported in all studies, a product of the well-designed trials that these studies came from. Confounding variables were not consistently considered in the model development process of most studies, several

studies did not outline clear definitions and measurement of possible confounding variables. Overall, the statistical analysis and reporting had low risk of bias.

2.3.3 Early Prognostic Factors and Poor Outcome

See Table 2.1 for definitions of prognostic factors and poor outcome for each study. Clinical variables (i.e., neurological examination, Apgar score, etc.) were most frequently studied. The effect direction plot (Table 2.2) allows for representation of the prognostic factor of interest and the association, if any, with poor outcome.

2.3.4 Pre-Randomization Factors

One study assessed inborn versus outborn birth with outborn defined as infants requiring transport into a participating site.[39] For a composite outcome of death or moderate/severe disability, the adjusted odds ratio (OR) for outborn versus inborn was 0.81 (95% CI 0.29, 2.24) and 0.91 (95% CI 0.33, 2.45), respectively. The unadjusted P-value for interaction was 0.91. Two studies looked at a EEG, one of which was in combination with encephalopathy grade, aEEG background and Apgar score.[42] Pre-randomization neurological examination, Apgar score and maternal factors were combined in a model.[36] Shankaran et al[41] identified perinatal sentinel event as a pre-randomization variable. Infants with a PSE in this study had lower Apgar scores at 5 and 10 minutes and higher intubation rates. Outcomes were similar despite a higher frequency of basal ganglia injury on magnetic resonance imaging (MRI).

2.3.5 Biochemical Factors

The biochemical variables of interest included glucose derangement, neuronal biomarkers, urinary lactate to creatinine ratio and 2 studies of hypocarbia. Except for neuronal biomarkers, biochemical variables showed a trend of being associated with poor outcome. Glucose derangements showed an adjusted OR of 6.2 (95% CI 1.4, 27.3), 2.7 (95% CI 1.5, 4.9) or 3.0 (95% CI 1.6, 5.8) if hypoglycemic, hyperglycemia or both, respectively.[32] With respect to the hypocarbia models, not only was the severity of hypocarbia related to poor outcome but also the cumulative exposure to moderate hypocarbia (pCO2 <35 mmHg).[33,35] After adjustment for hypothermia treatment and encephalopathy severity, higher urinary lactate to creatinine ratio was associated with death or moderate/severe neurodevelopmental disability with an OR of 5.52 (95% CI 1.36, 22.42).[34]

2.3.6 Clinical Factors

Clinical variables included clinical seizures, persistent pulmonary hypertension (PPHN), elevated temperature, receipt of sedation-analgesia or anticonvulsants, temperature less than 32°C, grade and evolution of encephalopathy. Shankaran et al[31] used a neurological examination at less than 6 hours, during cooling and at discharge. Increased risk of death/disability was seen in infants who had more than 72 hours before their clinical examination improved. In another logistic regression model, encephalopathy grade 3 (versus 1 or 2) had an adjusted OR of 3.34 (95% CI 1.64, 6.93).[42]

Elevated temperatures were rank ordered for infants in control and TH groups. In the control group, the highest quartile of skin temperatures was associated with a 3.6-fold increase in death or moderate/severe disability. The OR of persistent pulmonary hypertension (PPHN) in the

cohort of infants from the NICHD trial was 1.9 (calculated, not reported) but when adjusted for severity of HIE, mortality was no longer significantly different.

2.3.7 Amplitude Electroencephalogram used for Prognostication

Prognostic factor analyses for aEEG were conducted in three studies. One of which interrogated the role of time to normal tracing and found that the OR of poor outcome increased by 1.23 or every hour delay in normalization.[43] The remaining two studies included aEEG as part of a logistic regression model. The predictive model developed by Wyatt et al[42] included both aEEG background (severely versus moderately abnormal) and presence of aEEG seizures, both of which were statistically significant.[42] When aEEG pattern was added to HIE severity in a different logistic regression model, aEEG pattern did not add predictive value.[40]

2.3.8 Conceptual Model from Systematic Review

See Figure 4 for a pictural representation of the factors that we identified in this review. Prognostic factors identified from this review were grouped into biochemical, clinical and 'other diagnostics' with a focus on data that would be available in the first 72 hours after birth.

2.4 Discussion

To our knowledge, this is the first systematic review to systematically identify prognostic factors from RCTs that are associated with increased risk of poor outcome in neonatal HIE within the first 72 hours after birth. Although the review contains a variety of prognostic factors, the primary outcome of interest was essentially the same. Poor outcome was defined by the reviewed studies and often was a composite of death or NDI. The two pre-randomization factors

that were associated with poor outcome were Apgar score at 10 minutes and clinical examination.[31,38] The biochemical factors including hypo/hyperglycemia, hypocarbia, urinary lactate to creatinine ratio showed an association with poor outcome as defined by the original study except for neuronal biomarkers which were not predictive.[25,32,34,35,44] Within this domain, we have identified potentially modifiable factors which should further work as we explore adjuvant treatment modalities. Clinical markers were the least reliable when it came to predictive abilities with temperature profile and evolution of encephalopathy showing an association with poor outcome, the remaining clinical variables did not have effect.[26-31] We suspect that the limited utility of what we identified as clinical factors may have been secondary to interrater variability. Interestingly, pre-randomization clinical examination had the highest odds ratio which supports that resource allocation to training providers to carry out this examination is vitally important.[40] Pre-randomization aEEG was associated with poor outcome in 2 studies[40,42] but its predictive ability only held in a normothermic group after randomization.[43]

Identifying these prognostic factors is important as it may guide earlier discussions with families concerning their infant's outcome. It is particularly helpful to have the prognostic factors associated with mortality or NDI from high quality RCTs during a time where many centers are cooling infants who would not have met initial inclusion criteria[45,46]. Though difficult to delineate with a composite outcome, recognition of prognostic factors associated with NDI may optimize resource allocation for follow-up of these infants. This will be particularly important as the neonatal community explores management of mild HIE and potentially risk stratification of these groups of infants.[47] By identifying key factors, we may reduce prognostic uncertainty and reduce the discretion that families may feel burdened by.[48,49]

Prognostic uncertainty remains a significant issue with neonatal HIE, particularly outside the clinical extremes. Early markers of poor prognosis may guide clinical decision making and, in some cases, appropriate redirection of care. Prognostication after the first hours to days may help clinicians optimize care and timely neonatal follow-up in multidisciplinary clinics. Previous systematic reviews identified the following prognostic tests: Spitzmiller et al[50] was a review on aEEG use in term neonates with HIE, Ramaswarmy et al[51] identified biochemical markers in serum, urine and cerebrospinal fluid and Thayyil et al[52] evaluated MRI and magnetic resonance spectroscopy (MRS). van Laerhoven et al[53] identified 13 prognostic tests of which the most promising included aEEG, EEG, visual evoked potentials, diffusion weighted MRI and MRS. More recently, four clinical tests were identified in systematic review to predict outcome in hypothermia-treated infants with HIE. These were MRI brain within 2 weeks of birth, multichannel EEG, aEEG and somatosensory evoked potentials.[54] Some of the prognostic tests identified in systematic reviews are available in the early days after birth but may not be feasible to collect in certain settings (i.e., MRS and somatosensory evoked potentials). The above reviews were done before and after TH became standard of care which is in contrast to our review which contains post-hoc analyses from the original RCTs that identified TH as an efficacious treatment[55]

This review has the benefit of strict inclusion criteria with respect to the original trial definition of hypoxia-ischemia and subsequent encephalopathy. The results from this systematic review come from high quality RCTs, with majority of studies having an overall risk of bias of low to moderate. As such, this review allows for a reliable depiction of early prognostic factors for neonatal HIE. This review highlights the importance of looking at the entire clinical picture and multiple domains. Further, there is value in the evolution of prognostic factors over time,

specifically, encephalopathy grade.[31] As access to more sophisticated testing improves, clinicians should be reminded that in some cases earlier prognostication may be of value. What has not yet been discussed is how clinicians communicate the relevance of various prognostic factors and their respective limitations with families and other healthcare practitioners. Clinical decision making, particularly in the setting of neonatal HIE, involves a comprehensive discussion around prognostication, uncertainty, family values and ultimately, shared decision making.[49,56-58]

2.4.1 Strengths and Limitations

This is the first systematic review of the literature which aims to identify 'early' prognostic factors in post hoc analysis of RCTs. One limitation of this review is that given the limited number of eligible studies and heterogeneity of prognostic factors, we were unable to provide a meta-analysis. Second, given that the inclusion criteria were for subjects who were part of an RCT, we limit the generalizability of our findings to modern day where the use of TH has become more standard in centres and milder cases of HIE are being cooled[59]. Studies on prognostic tests may become less generalizable as the population of infants who receive TH evolves. The strengths of this review include the comprehensive search strategy, independent evaluation of study eligibility, and risk of bias assessment by two reviewers. The included studies are post-hoc analyses of high quality RCTs and thus the criteria for therapeutic hypothermia was consistent. Moreover, the outcome definitions were similar and thus, despite several prognostic factors of interest, you can start to imagine how they may work together in a larger model. A practical limitation to using composite outcome is how we communicate two very different results (death and NDI) to families.

2.5 Systematic Review Conclusions

A number of pre-randomization (a model including maternal hypertension/pre-eclampsia, antepartum hemorrhage, base deficit of first gas, Apgar score at 5 min, posture, spontaneous activity and suck[36]; Apgar score at 10 minutes[38], evolution of encephalopathy[31], early amplitude EEG[40,42] and neurological examination/encephalopathy grade[40,42]), biochemical (hypo/hyperglycemia[32], hypocarbia[33,35] and urinary lactate to creatinine ratio[34]) and clinical (receipt of anticonvulsants[29], evolution of encephalopathy[31]) factors that can be identified early in the hospital course (<72h) should be used to guide conversations around prognosis. Given the use of TH as a standard of care in high-income countries for infants with HIE, this will not only inform communication with family but also resource allocation for neonatal follow-up programs. Moreover, early prognostic factors that may be associated with a poor outcome may guide a clinician to consider more aggressive management of 'modifiable' factors that are known to affect development. This is an area that needs more research. The infants included in these trials would have been considered 'moderate' or 'severe' as per trial inclusion criteria. As we consider the management of infants with mild HIE, it may become important to risk stratify based on early factors before consideration of cooling.

2.6 References

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Table 2.1 Included Studies Participant Numbers, Prognostic Factor of Interest and Poor Outcome Definition

Study	Original Trial	Participants [N (missing), n]	Prognostic Factor; Definition and Measure	Timing of Measurement	Outcome Measure at 18 months	Odds Ratio (95% CI)
Ambalavanan et al[36], 2006	NICHD	205 (34), 172	Maternal chronic hypertension/preeclampsia/eclampsia, antepartum hemorrhage, base deficit of first gas, Apgar score at 5 min, posture, spontaneous activity, suck	Pre-randomization	(A) Death or moderate/severe disability (MDI <70-84, GMFCS 2-5, hearing impairment requiring hearing aids or no amplification, blindness, seizure disorder)	Not reported
Azzopardi et al[37], 2014	TOBY Trial	325 (11), 314	aEEG	Pre-randomization	(B) Death or severe disability (MDI <70, GMFCS 3-5, bilateral cortical visual impairment)	Not reported
Basu et al[32], 2016	CoolCap	234 (24), 210	Hyperglycemia (>8.3), hypoglycemia (≤2.2) or normal	0,4,8,12 hours	See (B)	[a]Hypoglycemia: 2.1 (0.52, 8.3) [2]Hyperglycemia: 4.5 (1.7, 12.0)
Catherine et al[25], 2020	South India RCT	162 (7), 155	Serum levels using ELISA	0, 24 and 72 hours	Death or neurological abnormality (score of less than 70% in DASII)	Not reported
Kwon et al[26], 2011	NICHD	208 (0), 208	Clinical seizures were documented as subtle (ocular deviation, sucking, lip smacking), swimming, rowing, or bicycling movements; tonic/clonic, localized, multifocal, or generalized	Enrollment, enrollment-24 hours, 25-48h, 49-72h, 73h-discharge	See (A)	[b]1.76 (0.94, 3.29)
Lakshminrusimha et al[27], 2018	NICHD and IH Trial	303 (0), 303	Clinical signs consistent with PPHN and echocardiographic evidence of pulmonary hypertension (absence of structural heart disease, positive indication of elevated pulmonary arterial pressure and/or flattened ventricular septum)	Unclear	Survival to discharge	[c]1.52 (0.76, 3.02)

Laptook et al[38], 2009	NICHD	208 (20), 188	Apgar Score	1,5 and 10 min	See (A)	[d]1.45 (1.22, 1.72)
Laptook et al[28], 2008	NICHD	208 (12), 196	Esophageal and skin temperature; highest temperature quartile (35.7-39.3℃)	2-72 hours (varying intervals depending on allocation group)	See (A)	[e]4.0 (1.5, 11.2)
Lingappan et al[33], 2016	CoolCap	221 (25), 196	Carbon dioxide	0,4,8,12,24,48 and 72 h	See (B)	Not reported
Natarajan et al[29], 2018	NICHD	208 (0), 208	Receipt of sedation-analgesia and/or anticonvulsant medicaion	0,24,48 and 72 hours	See (A)	Sedation-analgesia factor count 0.93 (0.79, 1.10)[f]
Natarajan et al[39], 2012	NICHD	208 (3), 205	Inborn vs outborn status	Pre-randomization	See (A)	Outborn: 0.81 (0.29, 2.24)[g]
Oh et al[34], 2008	NICHD	58 (0), 58	urinary lactate to creatinine ratio	6-24 hours and repeated 48-72h	See (A)	5.52 (1.36, 22.4)[h]
Pappas et al[35], 2011	NICHD	208 (4), 204	Hypocarbia (minimum)	Pre-randomization, randomization, 4,8 and12h	See (A)	2.00 (1.10, 3.40)[i]
Shankaran et al[30], 2012	NICHD	102 (1), 101	Hypothermia (<32℃) (yes or no)	every 15 minutes for the first 4 hours, every hour for the next 8 hours and every 4 hours during the remaining period of cooling.	See (A)	Not reported
Shankaran et al[31], 2012	NICHD	208 (4), 204	Encephalopathy stage	6h, during cooling and at discharge	See (A)	Stage <6 hours 1.97 (0.75, 5.20) Stage at discharge 8.47 (1.76, 40.88)
Shankaran et al[40], 2011	NICHD	140 (32), 108	Encephalopathy stage and aEEG background pattern	During cooling, aEEg <9 hours of age	See (A)	Severe HIE 9.20 (3.19, 26.55)[j] Abnormal background aEEG 2.73 (0.73, 7.37)[j]
Shankaran et al[41], 2017	NICHD	136 (2), 134	Perinatal sentinel events	Pre-randomization	See (A)	1.11 (0.54, 2.28); *calculated*

Thoresen et al[43], 2010	None	74 (-), 74	aEEG; time to normalization	Every hour from start of recording until 6 hours after birth, then every 6 hours until start of rewarming	Death or 1 of MDI <70, GMFCS level 3-5 or no useful vision	Abnormal trace 1.70 (0.56, 3.78)
Wyatt et al[42], 2007	CoolCap	234 (16), 218	Encephalopathy grade, aEEG (background, electrical seizures), Apgar score at 5 minutes, birthweight	Pre-randomization	See (B)	Grade (3 vs 1 or 2) 2.27 (1.64, 6.93) aEEG (background) 2.06 (1.01, 4.17) aEEG (seizures) 1.96 (1.02, 3.74) Apgar score 0.90 (0.76, 1.06) Birthweight (100 g increments) 1.06 (1.01, 1.12)

EEG: Electroencephalogram; ELISA: enzyme-linked immunosorbent assay; GMFCS: Gross Motor Functional Classification Scale; IH:Induced Hypothermia; MDI: Mental Developmental Index; NICHD: National Institude of Child Health and Human Development; TOBY: Total Body Hypothermia for Neonatal Encephalopathy

[a]adjusted for birth weight, hypothermia therapy, Sarnat stage (3 vs 2), Apgar score at 5 min and first pH
[b]adjusted for hypothermia treatment and severe HIE
[c]adjusted for severeity of HIE (OR is for mortality alone)
[d]adjusted for birth weight, gestational age, gender, treatment group and outborn status
[e]adjusted for level of encephalopathy, gender, race and gestational age
[f]adjusted for severity of HIE, TH, center, anticonvulsant and pressor receipt and mechanical ventilation
[g]adjusted for study centre and HIE severity
[h]adjusted for TH and HIE severity
[i]adjusted for pH, level of encephalopathy, treatment group, time to spontaneous respiration and ventilator days
[j]adjusted for level of encephalopathy and cooling status

Table 2.2 Effect Direction Plot of Prognostic Factors and Association with Poor Outcome

		Effect Direction of Categorized Prognostic Factor on Poor Outcome (Death and/or Disability)			
Study, year	**Prognostic Factor(s)**	**Pre-Randomization**	**Biochemical**	**Clinical**	**Amplitude EEG**
Ambalavanan et al[36], 2006	Maternal chronic hypertension/preeclampsia /eclampsia,antepartum hemorrhage, base deficit of first gas, Apgar score at 5 min, Posture, spontaneous activity, suck	▲			
Azzopardi et al[37], 2014	Amplitude EEG	◄►			
Basu et al[32], 2016	Hypo/hyperglycemia		▲		
Catherine et al[25], 2020	Serum levels of neuronal biomarkers (S100 calcium-binding protein B and Neuron specific enolase)		◄►		
Kwon et al[26], 2011	Clinical seizures			◄►	
Lakshminrusimha et al[27], 2018	Persistent pulmonary hypertension			◄►*	
Laptook et al[38], 2009	Apgar scores at 10 Minutes	▲			
Laptook et al[28], 2008	Elevated temperature			▲**	
Lingappan et al[33], 2016	Hypocarbia		▲		
Natarajan et al[29], 2018	Receipt of SA and AC			◄►(SA) ▲ (AC)	
Natarajan et al[39], 2012	Inborn versus outborn	◄►			
Oh et al[34], 2008	Urinary lactate to creatinine ratio		▲		
Pappas et al[35], 2011	Hypocarbia		▲		
Shankaran et al[30], 2012	Temperature < 32°C			◄►	

Shankaran et al[31], 2012	Evolution of encephalopathy	▲	▲	
Shankaran et al[40], 2011	Early amplitude EEG and neurologic examination	▲		◄►†
Shankaran et al[41], 2017	Perinatal sentinel events and MRI	◄►		
Thoresen et al[43], 2010	Amplitude EEG	◄►		▲‡
Wyatt et al[42], 2007	Encephalopathy grade, aEEG background, Apgar Score	▲ (Grade) ◄► (Apgar) ▲ (aEEG)		

AC: anticonvulsants; EEG: electroencephalogram; MRI: magnetic resonance imaging; SA: sedation-analgesia

Effect direction: upward arrow ▲= increased association with defined outcome, sideways arrow ◄►= no change/mixed effects

*outcome of mortality alone

**Statistically significant for those randomized to normothermia group

†addition of aEEG pattern to HIE stage did not add to the predictive value

‡in normothermia group, not predictive in hypothermia group

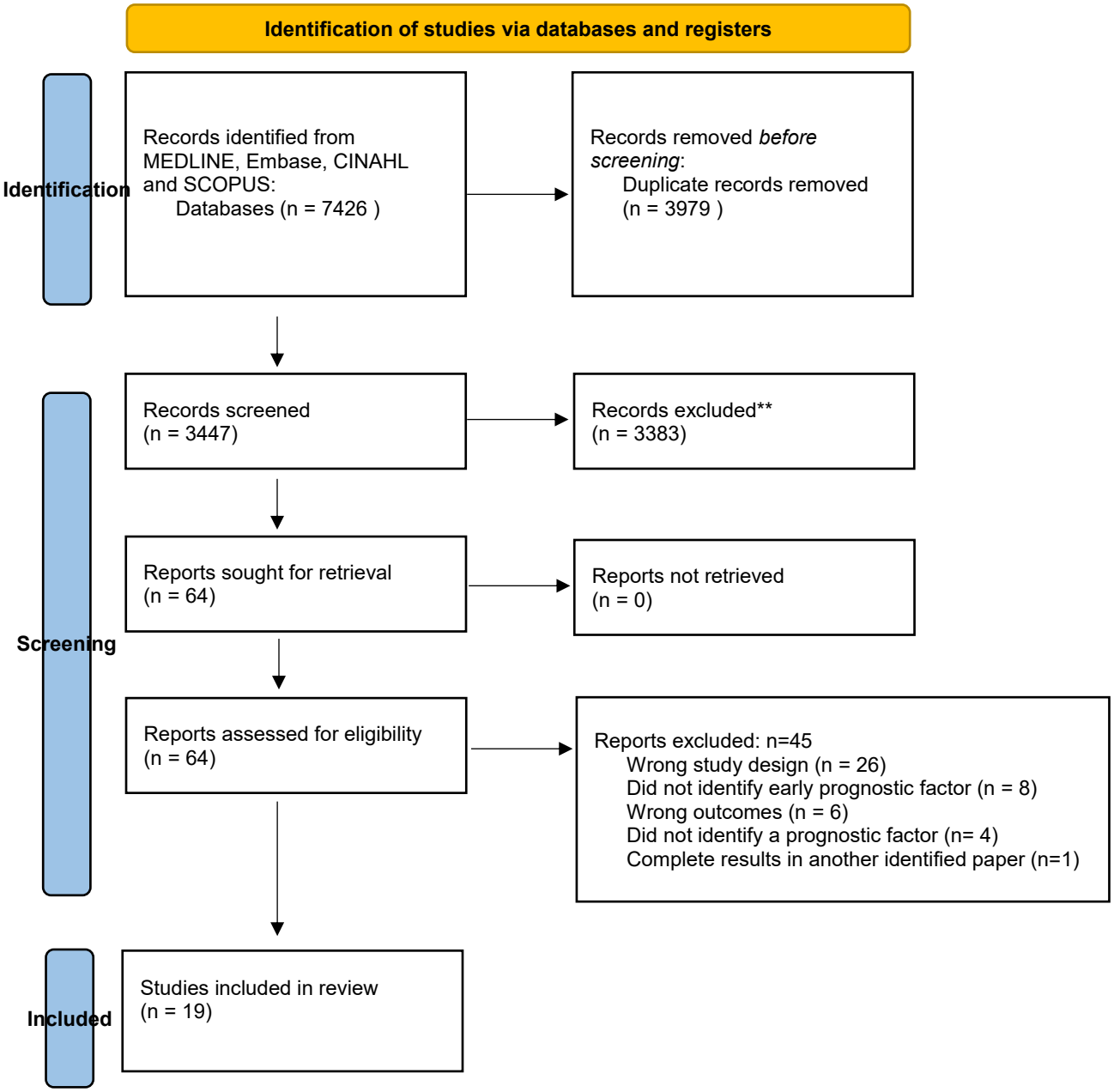

Figure 2.1 Flow chart of studies identified, screened, and included in the final review.

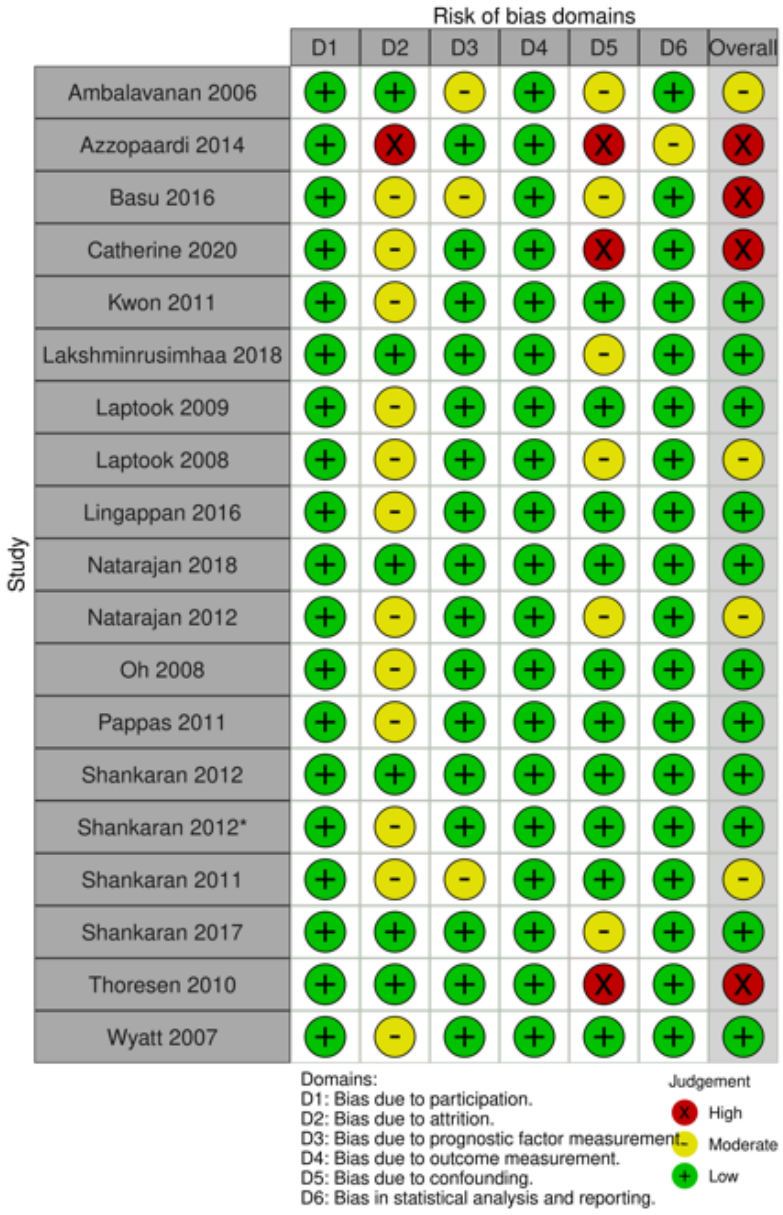

Figure 2.2 Overall and individual domain risk of bias assessment for the nineteen included studies.

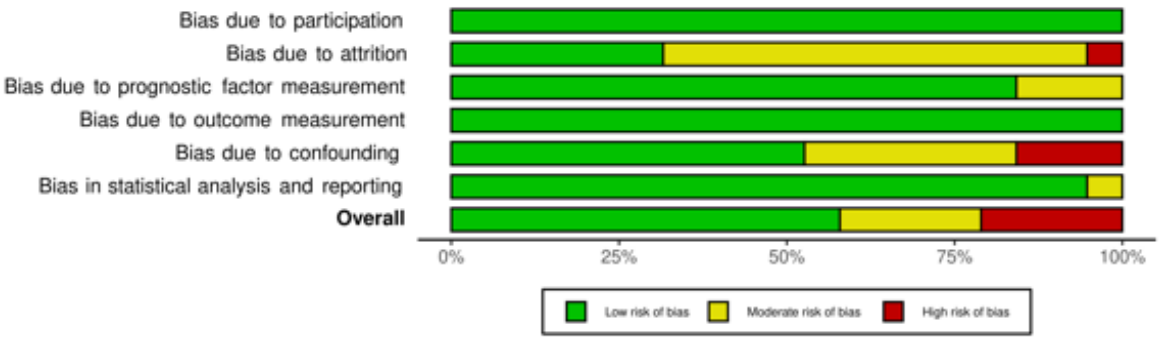

Figure 2.3 Risk of bias assessment summary based on individual bias domains from the nineteen included studies.

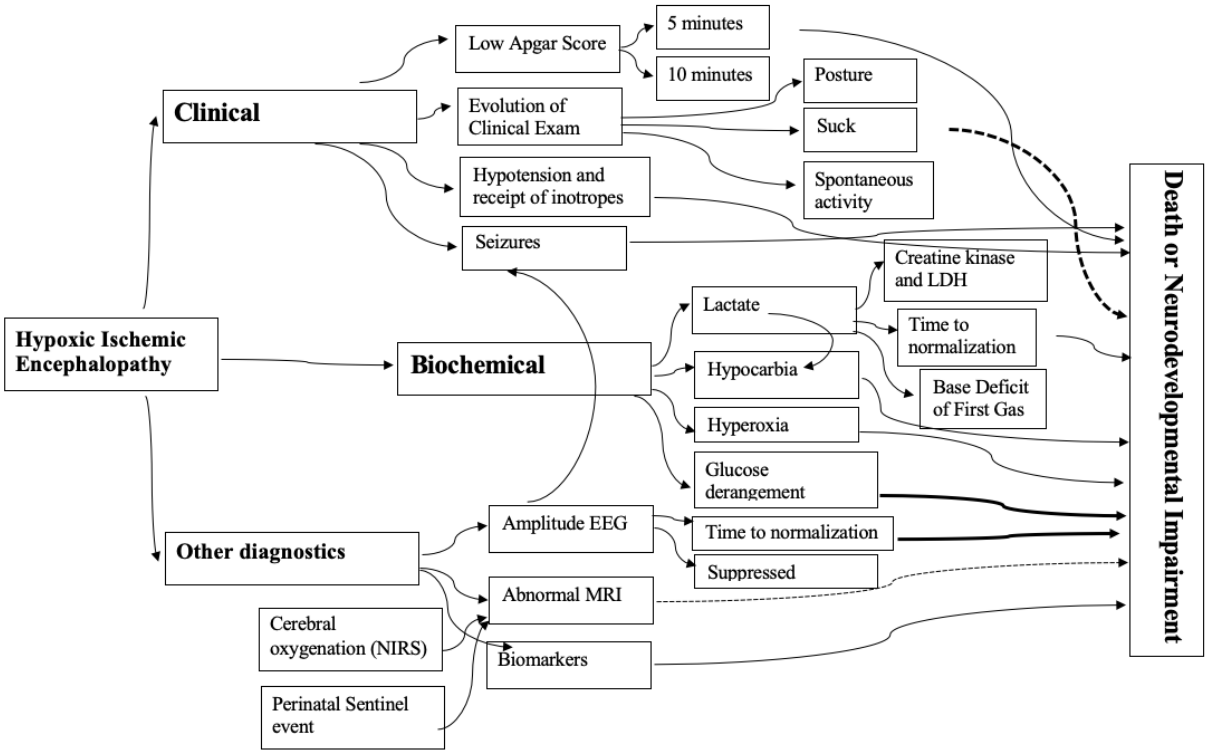

Figure 2.4 Conceptual model of early prognostic factors shown to be associated with death or neurodevelopmental impairment. Bolded line indicates an odds ratio >2.0 while the dashed line indicates a factor that would likely not be available in the first 72 hours.

Chapter 3. Identifying Prognostic Factors and Predicting Outcomes of Neonates Diagnosed with Hypoxic-Ischemic Encephalopathy in a Single Centre Cohort Study

3.1 Background

Our centre has a long history of providing therapeutic hypothermia (TH) and Edmonton, Alberta was one of the centres included in the CoolCap trial[1]. We have two Level-3 and one Level-2 NICU that provides therapeutic hypothermia for infants with HIE. These infants are from a large catchment area that includes Northern and Central Alberta, Northwest Territories, Yukon, and Nunavut. Since 2006 our centre has provided TH to over 436 infants who met criteria. Despite the mortality and morbidity associated with HIE, prognostic uncertainty remains a significant issue. There has been research to identify prognostic factors for poor outcome including clinical, biochemical, and other diagnostics (ie. amplitude encephalogram (EEG) and/or brain magnetic resonance imaging (MRI)) and much of this work comes from post-hoc analysis of the early cooling trials.[1-7] Generally, full EEG and/or brain MRI done early in the infant's course are not helpful as we expect EEG will change over time and brain MRI will not show patterns of injury if done too early. As such, these investigations are often not helpful when it comes to prognostication in the first 72 hours. Despite this, a vignette-based study of Canadian subspecialists caring for infants with hypoxic ischemic encephalopathy (HIE) identified that 85% of physicians use MRI results to aid in discussions around prognostication.[8] Given this, our aim was to use single centre data for neonates with HIE to identify early predictors of poor outcome and develop a prognostication model that can guide early discussions with family regarding goals of care and long-term outcome. The identification of candidate predictors was also guided by our systematic review (Chapter 2). Poor outcome was defined as mortality in the first year or

significant/severe neurodevelopmental impairment as defined by the Canadian Neonatal Follow-up Network (CNFUN).[9] The outcomes were not viewed as a composite endpoint but rather as two distinct entities.

There are prognostication models for outcomes in HIE in the literature, many of which include variables that would not be available in the early days of an infant's NICU course. A model that not only allows for early discussion in the setting of prognostic uncertainty but also looks at death and disability as separate outcomes is needed. Intentionally, we avoid the use of a composite outcome (ie. death or disability) as is often reported in the neonatal HIE literature. Though the use of a composite outcome may have statistical benefit, a review of neonatal trials displayed that the use of composite outcomes is less common than in adult trials.[10] Statistically, a composite outcome will increase the prevalence of the primary outcome and thus, the trial size can be smaller.[11] Clinically, the benefit of a composite outcome is really to address competing risks. For example, neonatal death would preclude the ability to assess for neurodevelopmental impairment. There are, inherently, issues with this approach, whereby, the more "severe" HIE would not necessarily cause death while less "severe" leads to disability. Parents with infants in the neonatal intensive care unit (NICU) do not view death and NDI as equivalent and it is important to consider outcomes that are important to the infant and family unit.[12]

3.2 Methods

Before conducting this study, we conducted a systematic review of prognostic factors for poor outcome (death or NDI) in HIE from randomized control trials (RCTs) (Chapter 2).

3.2.1 Study Design and Population

This was a prospectively assembled cohort study that retrospectively analyzed data from infants who underwent TH in Edmonton, Alberta, Canada since 2006. Eligibility criteria included a gestational age of ≥ 35 weeks, within 6 hours after birth and one of Apgar score ≤5 at 10 minutes, need for continued resuscitation at 10 minutes after birth, acidosis within 60 minutes after birth (umbilical cord pH or arterial pH <7.00) or base deficit ≥ 16 mmol/L in either an umbilical or peripheral blood sample within 60 minutes of birth. If the aforementioned criteria are met, the infant must meet criteria for neurological abnormality with at least one of lethargy, stupor or coma; hypotonia or hypertonia; abnormal reflexes including oculomotor or papillary abnormalities; absent or weak suck; or clinical seizures.[13] An amplitude EEG was done for clinical information but was not required for eligibility. Exclusion criteria for therapeutic hypothermia include major congenital abnormalities or birthweight <1800 g. Infants who met criteria for TH were cooled to a target rectal temperature of 33-34°C for 72 hours. This would often start with passive cooling (i.e., discontinuation of overhead warming device) before active cooling initiated in the NICU. Thereafter, the infant is warmed in a stepwise fashion. Management strategies with respect to ventilation, blood pressure support, management of seizures, electrolyte management and nutrition were dependent on the most responsible physician at the time of admission.

3.2.2 Subject and Hospital Characteristics

Data with respect to maternal and delivery history was collected in a standardized fashion. Maternal data included complications of labour; pre-eclampsia, eclampsia, maternal seizure, thyroid malfunction, gestational diabetes, prolonged rupture of membranes (PROM >18 hours)[14], pyrexia (≥ 37.6 in labour), antibiotic therapy and narcotic administration. Perinatal

sentinel event (PSE) was defined as one of core prolapse, cord knot, uterine rupture, placental abruption, shoulder dystocia, major maternal hemorrhage, trauma or cardiorespiratory arrest[15]. Method of delivery, delivery complications (antepartum hemorrhage, nuchal cord, head entrapment, true knot in cord, tear or rupture of cord, placental abruption, traumatic instrument delivery, shoulder dystocia, feto-maternal bleeding and ruptured uterus), Apgar scores and resuscitation details (need for oxygen, bag and mask ventilation, intubation, chest compressions or meconium suctioned). Biochemical data including first and highest lactate (mmol/L), renal failure (urine output <0.5 ml/kg/hr or serum creatinine >100 μmol/L within 1st 72 hours), AST >100 IU/L, ALT >100 IU/L, hyponatremia (<130 mmol/L), hypokalemia (<3.0 mmol/L) and hypoglycemia (<2.6 mmol/L), hypocalcemia (<1.0 mmol/L, ionized) and thrombocytopenia, for which patient was transfused with platelets, was collected. Documented clinical seizure and administration of phenobarbital or other anticonvulsants was also noted. Complications such as persistent pulmonary hypertension, sepsis, coagulopathy for which product was given and receipt of inotropes were also documented.

3.2.3 Measure of Socioeconomic Status

The Canadian Regional Deprivation Index, both material and social, were used as measures of socioeconomic status. The deprivation index uses socioeconomic indicators from 6 years of Canadian censuses.[16] Low income, education and a low employment to population ratio reflecting the material component and separated, divorced or widowed, living alone or in a single-parent family to develop a social quintile. Using postal code, each patient is assigned a quintile. Quintile 1 represents the most privileged dissemination area while quintile 5 represents the least.

3.2.4 Definition of Neurodevelopmental Impairment

The primary outcomes were death or neurodevelopmental impairment. These two separate outcomes were not analyzed as a composite but rather as two distinct endpoints. Definitions of neurodevelopmental impairment were as per the Canadian Neonatal Follow-up Network (CNFUN)[9]. Neurodevelopmental impairment (NDI) was defined as one or more of cerebral palsy (CP) with gross motor functional classification system (GMFCS) 1 or higher, Bayley III Motor Composite <85, Bayley-III Cognitive Composite <85, Bayley-III Language Composite <85, sensorineural/mixed hearing loss and/or uni or bilateral visual impairment. Significant NDI (sNDI) was defined as one or more of CP with GMFCS 3-5, Bayley III Motor Composite <70, Bayley-III Cognitive Composite <70, Bayley-III Language Composite <70, hearing aid or cochlear implant and/or bilateral visual impairment. Severe NDI was defined as one or more of CP with GMFCS 4 or 5, Bayley-III Cognitive Composite <55, Bayley-III Language Composite <55 and/or bilateral visual impairment. Trained members of the multidisciplinary team at a dedicated development centre assessed these infants in follow-up using standardized testing. All charts were reviewed in duplicate by a developmental pediatrician and neonatologists to capture infants that were either not seen or follow-up or whose developmental data had not been fully captured by our follow-up clinic. For example, infants who went on to receive a diagnosis of autism were classified as mild NDI in our cohort.

3.2.5 Statistical Analysis

Hospital characteristics (see section *3.2.2*) were described using frequencies and percentages for categorical data and means with standard deviations (SD) for continuous

variables. Univariate analysis was carried out using Chi-Square test for dichotomous variables and independent t-test for continuous variables. Logistic regression analysis was used to determine association between the variables of interest and the primary outcomes. Separate models were built using forward and backward selection for prediction of death and NDI. Associations between variables and outcomes are expressed as adjusted odd ratios (ORs) and 95% confidence intervals (CIs).

3.3 Results

3.3.1 Local Epidemiology

Since 2006, 472 infants underwent therapeutic hypothermia. As seen in Figure 3.1, our center is cooling more infants with a stable number of deaths and an overall decrease in the percentage of deaths for infants with HIE. The flow diagram (Figure 3.2) shows that 58 infants died. Of the 378 infants referred for follow-up, 305 infants were included in this analysis. Forty infants were lost to follow-up and 34 infants did not have standardized testing at the time of analysis (a product of COVID-19 related protocols and an increase in virtual visits). Table 3.1 shows the baseline characteristics for all neonatal patients that underwent therapeutic hypothermia. Within our cohort, 60.3% were male and the average birth weight and gestational age was 3.32 kg ± 0.630 kg and 38.5 weeks ± 1.90 weeks, respectively. Three hundred infants (68.8%) were considered outborn, defined as delivery outside of a center with a level 3 NICU. Seventy percent of infants were delivered by vaginal delivery, 20% of which required instrumentation. Approximately half of the cohort had documented maternal complications including gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), premature prolonged rupture of membranes, maternal infectious concerns (i.e., fever,

chorioamnionitis, need for antibiotics), maternal narcotics or maternal arrest. When comparing characteristics of infants' loss to follow-up versus those that were seen, there were no significant differences apart from a statistically significant difference with respect to males that were lost to follow-up (77.5% versus 59.5%, p-value 0.027). There were no differences with respect to material or social deprivation. Further, infants that met criteria for NDI were compared to those assigned a proxy NDI (did not have standardized testing) and there were no significant differences between these groups.

3.3.2 Incidence of NDI and their Hospital Characteristics

One hundred and eighty-six infants (61.0%) survived to hospital discharge and did not go on to receive an NDI diagnosis. Of the remaining infants, 16.8% and 21.8% went on to have NDI or significant/severe NDI (sNDI), respectively. Of those with sNDI, 31 children had cerebral palsy (CP) of which all but 3 had a GMFCS classification of 3 to 5. The 3 children that did not meet sNDI criteria based on their CP classification did so with sensorineural hearing loss and cognitive delays on standardized testing. Twenty-eight children with sNDI have either bilateral, unilateral, or mixed hearing loss. There were 15 patients that met criteria for visual impairment or blindness with sNDI. And 25 children with sNDI had cognitive impairment. Majority of the children met more than one criterion met for sNDI.

Compared to the cohort of children with sNDI, there were only 10 children with CP who met criteria for NDI. One child had SNHL. None of the children with NDI had visual concerns. Thirty-four children had cognitive impairment that met criteria for NDI. For all children with NDI (either mild, significant, or severe), the most common combination was cerebral palsy and cognitive impairment.

As seen in Table 3.2, infants who went on to be diagnosed with any classification of NDI were more likely to have c-section deliveries, a 10-minute Apgar score less than 5, be intubated and/or receive chest compressions. With respect to their hospital course, neurodevelopmentally impaired infants were statistically more likely to seize, receive phenobarbital, receive inotropes and have biochemical derangements (electrolytes abnormalities, thrombocytopenia, elevated liver function tests (LFTs), hypoglycemia and an elevated peak lactate).

3.3.3 Logistic Regression Models

Logistic regression analysis yielded parsimonious models, with the least number of variables that explained the most amount of variance in our data. Results of the separate regression models are seen in Tables 3.3 to 3.5. Five early predictors were associated with death (Table 3.3) including receipt of phenobarbital, hypotension receiving inotropes, severe HIE, chest compressions and PSE. The difference between the early and late prediction models for death is the addition of renal failure in the late model (Table 3.4). The prediction model for significant or severe NDI is seen in Table 3.5 and included receipt of phenobarbital, hypoglycemia, abnormal MRI, 10-minute Apgar score less than 5.

3.4 Discussion

In this single center longitudinal cohort study, we aimed to develop a prediction model to identify poor outcomes for infants with HIE. We intentionally avoided the use of a composite outcome to strengthen the ability to provide families with information on death or neurodevelopmental impairment, two very different outcomes. Looking at our cohort over time, more infants annually are being treated with TH while the number of deaths has remained

constant and thus, we have observed a decrease in the rate of death. Perhaps this is an indication that infants being treated with TH in recent years are "milder" cases or neonates that would not have met criteria for cooling in the initial randomized trials. A similar trend was suggested by Wood et al[17], over a 15-year period, the rate of neonatal asphyxia increased from 1.62 per 1000 live births in 2002 to 2.41 per 1000 births in 2016. Despite this increase, the neonatal deaths due to asphyxia remained constant, 1-2 per year. Again, without evidence that TH is more efficacious in recent years, there are either more infants with HIE or the infants being cooled are milder. To answer this question, one would also need to describe the cohort of pregnant women (i.e., maternal age, pregnancy complications etc) to gauge whether an increase in high-risk pregnancies is increasing rates of asphyxia in neonates. A systematic review and meta-analysis identified 13 cohort studies of infants who received TH for HIE[18]. They concluded that 22% (95% confidence interval: 16-27%) of infants who underwent TH were considered mild HIE. The authors of this review suggest that clinicians are using TH for mild HIE despite robust evidence to do so. As put forth by Chalak et al[19], neonatal encephalopathy is more dichotomous: those who do or do not qualify for TH. And though the initial data suggests there was no death or major disability for infants with mild HIE, we are learning more about this group and their potential to develop subtle developmental delays.[20-22] As more centers apply TH to infants with mild HIE there is a need to identify the subset of mild cases that will go on to develop NDI.

The early prediction model for death is intended to be used in the first 24 hours of an infant's NICU admission. A history of PSE was not a significant predictor of death in our cohort. But we felt that its general protective effect was important to include in the final model. This finding has been described previously and is likely explained by the anticipatory measures of the obstetrical and neonatal teams.[23] Shankaran et al[15] did not identify PSE to be associated with

death or disability but did find that infants with PSE were more likely to have basal ganglia and thalamus injury. In a retrospective cohort of 174 neonates in Switzerland, none of the perinatal risk factors were associated with severity of encephalopathy (Sarnat stage) on admission.[24] However, fetal distress on maternal admission was associated with neurological harm, as defined by lack of improvement in Sarnat staging during the first 4 days. In this study, fetal distress was defined as pathological cardiotocograph on admission or decreased fetal movement. Conversely, fetal distress during labor with no prior signs of distress was associated with neurological benefit. These findings are likely explained by the duration of hypoxia-ischemia.

Of all the markers for resuscitative needs, we chose to include chest compressions in the final model as it seemed the least subjective. Apgar score, despite being used worldwide, may lack interrater reliability.[25] The American Academy of Pediatrics and American College of Obstetricians and Gynecologists (ACOG) have suggested use of an 'Expanded-Apgar' score which essentially documents the interventions needed.[26] When used in combination with the traditioned Apgar score, it was more predictive of perinatal mortality.[27] The neurological exam as represented by HIE severity (grade 3 versus 1 or 2 as per Sarnat stage[28]) has been described in the literature.[29] The HIE stage at less than 6 hours was predictive of death or disability in an initial model but lost its significance when HIE stage at discharge was added to the model.[30] In a pre-cooling group, Sarnat stage in addition to presence of convulsions, severely abnormal EEG, cardiovascular failure and multiple organ dysfunction were associated with poor outcome.[31]

Some may argue that seizure (or a marker of seizure) and encephalopathy grade should not be in the same model as presence of seizure would indicate stage 2, at a minimum.[28] Interestingly, phenobarbital had a more significant adjusted odds ratio than seizure alone which is likely explained by the severity and cumulative seizure time. Total seizure burden,

independent of HIE severity and therapeutic hypothermia has been associated with poor outcome.[32] Natarajan et al[33] concluded that infants who were administered anticonvulsants had a higher rate of death or disability. In a large Canadian cohort of infants with HIE who were treated with hypothermia, hypotension treated with inotropes and renal failure were associated with risk of death and/or brain injury.[34] Renal failure was defined as urine output <0.5 milliliters per kilogram per hour (ml/kg/hour) and/or rising creatinine >100 millimoles per litre (mmol/L) at any time within the first 72 hours of life, a definition like ours. In a survey of centers in North America, Giesinger at al[35] identified 17 unique definitions of hypotension in the context of neonatal HIE. There are center and physician dependent practices that influence the administration of inotropes and will be an interesting variable to study in the future, particularly with the routine use of targeted neonatal echo in some centers.

The late prediction model for death includes renal dysfunction defined less than 0.5 ml/kg/hour of urine output for 72 hours after birth or a creatinine level greater than 100 mmol/L. In our cohort, 33.5% of infants with HIE who underwent therapeutic hypothermia met criteria for renal failure. In a prospective case-controlled study, 47.1% of infants with HIE had renal failure[36]. Notably, that cohort did not undergo therapeutic hypothermia but those with renal failure had higher mortality rates. Multiorgan dysfunction including renal, hepatic, hematologic and gastrointestinal is anticipated following asphyxia as blood shunts to the heart, adrenals and brain to preserve their function.[37,38]

The prediction model for significant or severe NDI includes biochemical markers including hypoglycemia and electrolyte abnormalities. Just over 20 percent of infants in our cohort had hypoglycemia, defined as blood sugar less than 2.6 mmol/l in the first 72 hours. This was higher than the infants enrolled in the CoolCap Study of which just under 10 percent were

hypoglycemia.[39,40] We suspect this is multifactorial but due to differing definitions, less than or equal to 2.2 mmol/L, in addition to the fact that not all infants in the CoolCap Study underwent TH. However, unfavorable outcome, death or disability, was 6.2 times greater if there was one episode of hypoglycemia. Parmentier et al[41] defined hypoglycemia as less than 2 mmol/L in the first 2 hours or less than 2.6mmol/L thereafter. In that cohort, 35.4% of infants had hypoglycemia and their brain injury scores on MRI were higher. Even with adjustment for HIE severity, infants with a history of hypoglycemia had lower intellectual quotients (IQs

Electrolyte abnormalities included hyponatremia, hypokalemia and hypocalcemia in the first 7 days. A retrospective cohort study identified a statistically significant difference in rates of hyponatremia in infants treated with TH, versus those who were not.[42] This finding may be due to vasoconstriction of skin vessels in response to cooling leading to fluid retention and hyponatremia.[43-45] There is also a likely element of dilutional hyponatremia due to oliguria or anuria which has been associated with worse prognosis.[36] Hypokalemia has been described in adult cooling literature with subsequent effect on the QT interval.[46] There is limited data on hypokalemia and the impact on myocardial repolarization in neonatal literature. In a cross sectional case-control study, 23.3% of babies with HIE had hypocalcemia.[47] After a neurological insult, there is movement of calcium in the cells, TH may mitigate this.[48] Electrolyte derangements in the setting of HIE are likely a representation of injury severity as well as reduced compensatory mechanisms with multiorgan dysfunction.

The model for sNDI also includes 10-minute Apgar score less than 5 and receipt of phenobarbital, both markers of clinical severity in the infant's course. In a cohort study of 129 infants, Apgar score at 1, 5 and 10 minutes, need for resuscitation, maternal age and infant birth weight in addition to first postnatal gas were predictors of developing HIE.[49] A secondary

analysis from the Optimizing Cooling Trial[49] showed that 50% of infants with a 10-minute Apgar score of 0 survived and 46% of those had no disability.[50] The Apgar score was more predictive when combined with other factors. Dalili et al[51] developed a sensitive and specific 'COMBINED'-Apgar (Continuous Positive Airway Pressure, Oxygen, Mask and Bag Ventilation, Intubation and Ventilation, Neonatal Chest Compressions, Exogenous Surfactant and Drugs) score which includes other resuscitative needs in addition to the traditional Apgar score at 1,5 and 10 minutes. This score was predictive for HIE but not necessarily severity and neurological outcome. In a study of 51 patients with HIE treated with head cooling, mechanical ventilation, Apgar score at 1 minute and advanced neonatal resuscitation defined as basic resuscitation plus endotracheal intubation, chest compression, and administration of epinephrine/volume, were statistically significant predictors of death in univariate analysis.[52] However, in multivariate regression, advanced neonatal resuscitation was the only factor that remained significant.

An MRI was considered abnormal if there was evidence of hypoxic injury. In a study of Canadian subspecialty physicians, neurological prognosis in neonatal HIE was guided heavily by MRI[8]. Of those that survived to hospital discharge 58.0% of infants had MRI findings of hypoxia-ischemia. This is comparable to other cohorts.[53-55] Not surprisingly, a significant association between injury severity on MRI and neurodevelopmental outcomes has been described.[56-58]

3.4.1 Study Limitations and Strengths

Our study has several limitations. First, the data used to develop prediction models was from a single center cohort which may have limited transferability to other centers. Albeit, our

large sample size hopefully gave an adequate representation. Second, as evidenced by the cases of HIE over time, our center, like others, may be cooling milder HIE cases. There were 41 infants (just under 10%) who were classified as 'mild' or modified Sarnat stage 1 but there is likely an element of indication creep being seen. Despite this, our modern population is likely a representation of what other centers is seeing and ultimately, the trend in total cases of HIE undergoing TH every year needs to be further probed. Third, the COVID-19 pandemic affected the ability to have standardized testing on every infant. As such, in some cases, a proxy NDI designation was given. This may have over or underestimated infants with NDI. Lastly, given the 14- year span of data collection, there were subtle changes to definitions of data collected and new data points that were collected on more recent infants but not included in the model as there were too many infants with missing data. Using a sample size calculation intended for use in observational studies with logistic regression modeling, Bujang et al[59] recommend a minimum sample size of 500. However, it is stated that a sample size less than 500 may be sufficient for medium to large effect size. As such, our sample size of 436 is sufficient for the research question at hand.

Before developing a prognostic model, predictors from a systematic review were identified, a strength of our study. Additionally, a significant strength of our study is the size of our cohort and completion of our dataset with minimal missing variables, a strength of a prospectively assembled cohort study design. Despite loss to follow-up being one of the inherent disadvantages of a cohort design, our follow-up rate in the neonatal follow-up clinic was high. Our cohort is likely an accurate representation of the infants being cooled in high income countries and will contribute to the literature around cooling in more mild cases. We have identified separate models for death and NDI in hopes to counsel families around these very

different outcomes early in the NICU course. Future research with respect to neonatal HIE should avoid the use of a composite outcome so that counselling with families can not only be more specific but allow for families to express their own beliefs and values as they relate to death and survival with NDI.

3.5 Conclusions

We identified predictive models for death (both early and late prediction) and sNDI for infants undergoing TH as treatment for HIE. Our prediction models include historical, clinical and biochemical information that is available to clinicians in the early days of an infant's NICU course. Importantly, we developed separate models for death and sNDI to respect the impact of these very different outcomes on a family unit. Further investigation is needed to validate these models with a future cohort. Further, more work is essential to determine how to use these models when communicating with families. It will be paramount to include family members as stakeholders as our research question evolves.

3.6 References

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Table 3.1 Hospital Characteristics of Neonatal Patients Treated with Therapeutic Hypothermia Who Survived to Hospital Discharge versus Those who Died

	Entire Cohort (N=436)*	Death (n=58)	Survived to hospital discharge (n=378)	p-value***
Male sex	263 (60.3)	31 (53.4)	232 (61.4)	0.251
Canadian Regional Deprivation Index; material				0.659
0: unassigned index	16 (4.00)	1 (1.90)	15 (4.30)	
1 (most privileged quintile)	67 16.6)	10 (18.9)	57 (16.2)	
2	73 18.1)	13 (24.5)	60 (17.1)	
3	89 (22.0)	10 (18.9)	79 (22.5)	
4	79 (19.6)	11 (20.8)	68 (19.4)	
5	80 (19.8) *of 404*	8 (15.1)	72 (20.5)	
Canadian Regional Deprivation Index; social				0.098
0: unassigned index	16 (4.00)	1 (1.90)	15 (4.30)	
1 (most privileged quintile)	70 (17.3)	12 (22.6)	58 (16.5)	
2	89 (22.0)	11 (20.8)	78 (22.2)	
3	89 (22.0)	6 (11.3)	83 (23.6)	
4	76 (18.8)	9 (17.0)	67 (19.1)	
5	64 (15.8) *of 404*	14 (26.4)	50 (14.2)	
Birthweight (g)	3319.8 (630)	3409.6 (667)	3306.0 (624)	0.244
Gestational age (weeks.days)	38.5 (1.9)	38.5 (2.06)	38.5 (1.9)	0.815
SGA**	73 (16.5)	7 (12.1)	66 (17.5)	0.306
Outborn	310 (71.1)	42 (72.4)	268 (70.9)	0.813
Maternal Complications	225 (51.6)	32 (55.2)	193 (51.1)	0.559
• **GDM**	43 (9.90)	5 (8.60)	38 (10.1)	0.733
• **PIH**	39 (8.90)	5 (8.60)	34 (9.00)	0.926
• **PPROM**	34 (7.80)	5 (8.60)	29 (7.70)	0.802
• **Maternal ID**	96 (22.0)	14 (24.1)	82 (21.7)	0.676
• **Maternal narcotics**	88 (20.2)	12 (20.7)	76 (20.1)	0.918
• **Maternal arrest**	4 (0.90)	2 (3.40)	2 (0.50)	**0.030**
Mode of Delivery				0.397
• **Vaginal delivery**	118 (27.1)	13 (22.4)	105 (27.9)	
• **Vaginal delivery requiring instrumentation**	84 (19.3)	8 (13.8)	76 (20.2)	
• **Emergency c-section**	222 (51.0)	35 (60.3)	187 (49.6)	
• **Elective c-section**	11 (2.50)	2 (3.40)	9 (2.4)	
Mode of Delivery (all caesarean sections)	233 (53.6)	37 (63.8)	196 (52.0)	0.093
Delivery Complications	329 (75.5)	44 (75.9)	285 (75.4)	0.939
• **Placental Abruption**	54 (12.4)	4 (6.90)	50 (13.2)	0.173
• **Uterine Rupture**	4 (0.90)	2 (3.40)	2 (0.50)	0.087
• **Fetal Heart Rate Abnormalities**	82 (18.8)	10 (17.2)	72 (19.0)	0.743
Perinatal Sentinel Event (PSE)	120 (27.5)	13 (22.4)	107 (28.3)	0.349
Time of delivery	285 (65.7)	38 (67.9)	247 (65.3)	0.712

5-minute Apgar Score (n=433)				**<0.001**
• **0-3**	251 (58.0)	49 (84.5)	204 (54.3)	
• **4-6**	153 (35.3)	8 (13.8)	144 (38.3)	
• **7-10**	29 (6.70)	1 (1.70)	28 (7.40)	
5 minute Apgar <5	323 (74.6)	53 (91.4)	270 (72.0)	**0.002**
10 minute Apgar <5	206 (48.7) *of 423*	44 (75.9)	162 (44.4)	**<0.001**
Intubated	295 (67.7)	51 (87.9)	244 (64.6)	**<0.001**
Received chest compressions	163 (37.4)	42 (72.4)	121 (32.0)	**<0.001**
Modified Sarnat Stage				**<0.001**
• **1**	41 (9.4)	1 (1.7)	40 (10.6)	
• **2**	354 (81.2)	38 (65.5)	316 (83.6)	
• **3**	41 (9.4)	19 (32.8)	22 (5.80)	
Did Not Complete 72 Hours of Therapeutic Hypothermia	369 (84.8)	56 (98.2)	10 (2.60)	**<0.001**
Age when target met (min)	275 (160)	202 (116)	286 (163)	**<0.001**
Seizures	104 (23.9)	14 (24.1)	90 (23.8)	0.956
Received inotropes	193 (44.9)	47 (85.5)	146 (38.9)	**<0.001**
Received Inhaled Nitric Oxide for Pulmonary Hypertension	21 (9.70) *of 217*	5 (27.8)	16 (8.00)	**0.007**
Oliguria/Renal failure	146 (33.5)	44 (75.9)	102 (27.0)	**<0.001**
Electrolyte abnormality	262 (62.5) *of 419*	47 (83.9)	215 (59.2)	**<0.001**
Thrombocytopenia	94 (21.6)	25 (43.1)	69 (18.3)	**<0.001**
Elevated LFTs	164 (37.6)	37 (63.8)	127 (33.6)	**<0.001**
Metabolic Acidosis	254 (58.8)	44 (77.2)	210 (56.0)	**0.002**
Sepsis	12 (2.80)	2 (3.40)	10 (2.70)	0.733
Hypoglycemia	90 (20.6)	14 (24.1)	76 (20.1)	0.480
Peak Lactate	11.8 (6.29) *of 409*	15.7 (6.89)	11.3 (6.01)	**<0.001**

**Cohort size 436 unless otherwise denoted*

***Definitions:*

- *Small for gestational age (SGA):*
- *Outborn: Infants born outside of a level 3 NICU site*
- *Maternal Complications: gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), premature prolonged rupture of membranes, maternal infectious concerns (ie, fever, chorioamnionitis, need for antibiotics), maternal narcotics or maternal arrest.*
- *Perinatal Sentinel Event: cord prolapse, cord knot, uterine rupture, placental abruption, shoulder dystocia, major maternal hemorrhage, trauma or cardiorespiratory arrest (ref: shankaran 2017)*
- *Time of delivery: Infants born between the hours of 1600 and 0800 whereby there is likely no neonatologist on site and there is reduced housestaff coverage*
- *Oliguria/renal failure: <0.5 ml/kg/hr for 72 hours after birth or creatinine >100 mmol/L*
- *Electrolyte abnormality: Hyponatremia (Na <130), hypokalemia (K<3.0) or hypocalcemia (<1.0) in first 7 days*
- *Thrombocytopenia: Platelet count <100 and received platelet transfusion*
- *Elevated LFTs: In the first 48 hours, AST or ALT >100*
- *Metabolic acidosis: pH <7 on two blood gases collected 6 hours apart*
- *Hypoglycemia: Blood sugar less than 2.6 in first 72 hours*

****p-value significant if <0.05*

Table 3.2 Hospital Characteristics of Neonatal Patients Treated with Therapeutic Hypothermia Who Survived to Hospital Discharge and were Diagnosed with Neurodevelopmental Impairment versus NDI-free Survival

	NDI Free survival ("good" outcome) (n= 186)	**Neurodevelopmental Impairment (NDI) (n=51)**	**p-value***	**Significant or severe NDI (SNDI) (n= 66)**	**p-value**	**p-value****
Male sex	113 (60.8)	35 (68.6)	0.304	32 (48.5)	0.191	0.758
Canadian Regional Deprivation Index; material			0.571		0.192	0.155
0: unassigned index	6 (3.50)	1 (2.00)		3 (4.90)		
1 (most privileged quintile)	27 (15.8)	6 (12.2)		9 (14.8)		
2	35 (20.5)	8 (16.3)		6 (9.80)		
3	36 (21.1)	13 (26.5)		16 (26.2)		
4	41 (24.0)	9 (18.4)		11 (18.0)		
5	26 (15.2)	12 (24.5)		16 (26.2)		
Canadian Regional Deprivation Index; social			0.812		0.730	0.934
0: unassigned index	6 (3.50)	1 (2.00)		3 (4.90)		
1 (most privileged quintile)	25 (14.6)	8 (16.3)		12 (19.7)		
2	43 (25.1)	13 (26.5)		10 (16.4)		
3	42 (24.6)	10 (20.4)		17 (27.9)		
4	35 (20.5)	8 (16.3)		13 (21.3)		
5	20 (11.7)	9 (18.4)		6 (9.80)		
Birthweight (g)	3308 (579)	3270 (604)	0.679	3244 (776)	0.546	0.380
Gestational age (weeks.days)	38.6 (1.77)	38.3 (1.79)	0.315	38.5 (1.88)	0.665	0.501
SGA* **	33 (17.7)	7 (13.7)	0.498	18 (27.3)	0.098	0.435
Delivery Hospital Level			0.053		0.761	0.250
0 (home or midwifery centre)	1 (0.50)	3 (5.90)		1 (1.50)		
1	50 (26.9)	16 (31.4)		16 (24.2)		
2	81 (43.5)	20 (39.2)		32 (48.5)		
3	54 (29.0)	12 (23.5)		17 (25.8)		
Outborn	132 (71.0)	39 (76.5)	0.437	49 (74.2)	0.611	0.420
Maternal	106 (57.0)	20 (39.2)	**0.024**	31 (47.0)	0.160	0.023
Complications	23 (12.4)	4 (7.80)	0.368	6 (9.10)	0.474	0.299
• **GDM**	17 (9.10)	3 (5.90)	0.458	7 (10.6)	0.727	0.860
• **PIH**	20 (10.8)	2 (3.90)	0.136	3 (4.50)	0.132	**0.046**
• **PPROM**	42 (22.6)	10 (19.6)	0.649	16 (24.2)	0.783	0.942
• **Maternal ID**	42 (22.6)	6 (11.8)	0.089	11 (16.7)	0.311	0.085
• **Maternal narcotics**	1 (0.50)	0	0.600	0	0.551	0.427
• **Maternal arrest**						
Mode of Delivery			**0.002**		0.378	**0.012**
	61 (32.8)	7 (13.7)		19 (29.2)		

• **Vaginal delivery**	46 (24.7)	7 (13.7)		11 (16.9(		
• **Vaginal delivery requiring instrumentation**	76 (40.9)	36 (70.6)		33 (50.8)		
• **Emergency c-section**	3 (1.60)	1 (2.00)		2 (3.10)		
• **Elective c-section**						
C-section	79 (42.5)	37 (73.5)	**<0.001**	35 (53.8)	0.113	**<0.001**
Delivery Complications	136 (73.1)	39 (76.5)	0.629	46 (69.7)	0.594	0.929
• **Abruption**	26 (14.0)	6 (11.8)	0.682	11 (16.7)	0.596	0.893
• **Uterine Rupture**	2 (1.10)	0	0.457	0	0.398	0.260
• **Fetal heart rate abnormality**	22 (11.8)	15 (29.4)	0.002	12 (18.2)	0.194	0.010
Perinatal Sentinel Event (PSE)	57 (30.6)	12 (23.5)	0.322	19 (28.8)	0.778	0.439
Time of delivery	124 (66.7)	23 (45.1)	**0.005**	47 (71.2)	0.497	0.227
5-minute Apgar Score (n=433)			0.060		0.104	**0.014**
• **0-3**	92 (49.5)	31 (62.0)		41 (63.1)		
• **4-6**	78 (41.9)	19 (38.0)		22 (33.8)		
• **7-10**	16 (8.60)	0		2 (3.10)		
5 minute Apgar <5	129 (69.4)	38 (77.6)	0.260	51 (78.5)	0.161	0.100
10 minute Apgar <5 (n=423)	72 (40.0)	22 (44.9)	0.537	38 (59.4)	**0.007**	**0.028**
Intubated	112 (60.2)	39 (76.5)	**0.032**	51 (77.3)	**0.013**	**0.003**
Received chest compressions	51 (27.4)	18 (35.3)	0.273	30 (45.5)	**0.007**	**0.014**
Modified Sarnat Stage			0.271		**0.022**	0.028
• **1**	26 (14.0)	3 (5.90)		3 (4.50)		
• **2**	151 (81.2)	46 (90.2)		55 (83.3)		
• **3**	9 (4.80)	2 (3.90)		8 (12.1)		
Did not complete 72 hours of TBC	183 (98.4)	50 (98.0)	0.864	1 (1.50)	0.956	0.949
Age when target met (min)	302 (169)	263 (142)	0.133	251 (146)	**0.031**	**0.016**
Seizures	33 (17.7)	13 (25.5)	0.215	27 (40.9)	**<0.001**	**<0.001**
Received Phenobarb	71 (41.8) of 170	28 (62.2) of 45	**0.014**	45 (81.8)	**<0.001**	**<0.001**
Received other anticonvulsants	8 (4.80) of 166	12 (27.9) of 43	**<0.001**	11 (40.0)	**<0.001**	**<0.001**
Received inotropes	57 (31.0)	32 (62.7)	**<0.001**	30 (46.2)	**0.027)**	**<0.001**
Oliguria/Renal failure	39 (21.0)	18 (35.3)	**0.034**	26 (39.4)	**0.003**	**0.002**
Electrolyte abnormality	87 (49.7)	37 (74.0)	**0.002**	54 (84.4)	**<0.001**	**<0.001**
Thrombocytopenia	24 (12.9)	15 (30.0)	**0.004**	20 (30.3)	**<0.001**	**<0.001**
Elevated LFTs	51 (27.4)	20 (39.2)	0.103	30 (45.4)	**0.007**	**0.006**
Metabolic Acidosis	120 (53.3)	21 (42.9)	0.184	46 (71.9)	**0.007**	0.239
Sepsis	0	2 (3.90)	0.007	5 (7.60)	**<0.001**	**<0.001**
Hypoglycemia	27 (14.5)	10 (19.6)	0.375	22 (33.3)	**<0.001**	**0.006**

Peak Lactate	10.7 (6.09)	11.3 (5.62)	0.100	14.0 (6.39)	**<0.001**	**0.005**

**p-value significant if <0.05*

** bivariate analysis of all NDI versus NDI free survival

***<u>Definitions</u>:*

- *Small for gestational age (SGA):*
- *Outborn: Infants born outside of a level 3 NICU site*
- *Maternal Complications: gestational diabetes mellitus (GDM), pregnancy induced hypertension (PIH), premature prolonged rupture of membranes, maternal infectious concerns (ie, fever, chorioamnionitis, need for antibiotics), maternal narcotics or maternal arrest.*
- *Perinatal Sentinel Event: cord prolapse, cord knot, uterine rupture, placental abruption, shoulder dystocia, major maternal hemorrhage, trauma or cardiorespiratory arrest (ref: shankaran 2017)*
- *Time of delivery: Infants born between the hours of 1600 and 0800 whereby there is likely no neonatologist on site and there is reduced housestaff coverage*
- *Oliguria/renal failure: <0.5 ml/kg/hr for 72 hours after birth or creatinine >100 mmol/L*
- *Electrolyte abnormality: Hyponatremia (Na <130), hypokalemia (K<3.0) or hypocalcemia (<1.0) in first 7 days*
- *Thrombocytopenia: Platelet count <100 and received platelet transfusion*
- *Elevated LFTs: In the first 48 hours, AST or ALT >100*
- *Metabolic acidosis: pH <7 on two blood gases collected 6 hours apart*
- *Hypoglycemia: Blood sugar less than 2.6 in first 72 hours*

Table 3.3 Early Prediction Model for Death after Hypoxic Ischemic Encephalopathy (n=387)

	Adjusted Odds Ratio (95% Confidence Interval)	Significance
Receipt of Phenobarbital[a]	7.53 (2.19, 25.9)	0.001
Hypotension Receiving Treatment[b]	3.87 (1.58, 9.45)	0.003
Severe HIE[c]	3.76 (1.67, 8.50)	0.001
Chest Compressions[d]	2.77 (1.30, 5.92)	0.008
Perinatal Sentinel Event (SPE)[e]	0.45 (0.19, 1.07)	0.071

[a] Administration of phenobarbital for suspected seizure.
[b] Inotropes given for hypotension,
[c] Stage 3 HIE as per modified Sarnat staging[28].
[d] chest compressions as part of delivery room resuscitation.
[e] Perinatal sentinel event (PSE) was defined as one of core prolapse, cord knot, uterine rupture, placental abruption, shoulder dystocia, major maternal hemorrhage, trauma or cardiorespiratory arrest[15].

Table 3.4 Late Prediction Model for Death after Hypoxic Ischemic Encephalopathy (n=387)

	Adjusted Odds Ratio (95% Confidence Interval)	**Significance**
Receipt of Phenobarbital[a]	6.55 (1.84, 23.3)	0.004
Hypotension Receiving Treatment[b]	2.92 (1.16, 7.34)	0.023
Severe HIE[c]	4.63 (1.94, 11.1)	<0.001
Chest Compressions[d]	2.13 (0.97, 4.70)	0.060
Perinatal Sentinel Event (SPE)[e]	0.46 (0.19, 1.11)	0.082
Renal Dysfunction[f]	3.73 (1.68, 8.31)	0.001

[a] Administration of phenobarbital for suspected seizure.
[b] Inotropes given for hypotension,
[c] Stage 3 HIE as per modified Sarnat staging[28].
[d] chest compressions as part of delivery room resuscitation.
[e] Perinatal sentinel event (PSE) was defined as one of core prolapse, cord knot, uterine rupture, placental abruption, shoulder dystocia, major maternal hemorrhage, trauma or cardiorespiratory arrest[15].
[f] Urine output <0.5 ml/kg/hr or serum creatinine >100 °µmol/L within 1st 72 hours.

Table 3.5 Prediction Model for Significant or Severe Neurodevelopmental Impairment versus Mild NDI or NDI Free Survival after Hypoxic Ischemic Encephalopathy (n=257)

	Adjusted Odds Ratio (95% Confidence Interval)	Significance
Receipt of phenobarbital[a]	3.49 (1.60, 7.61)	0.002
Hypoglycemia[b]	2.23 (1.05, 4.75)	0.037
Abnormal MRI[c]	2.97 (1.34, 6.52)	0.007
Electrolyte Abnormality[d]	2.21 (0.990, 4.92)	0.053
10-minute Apgar Score <5	1.84 (0.93, 3.64)	0.082

[a] Administration of phenobarbital for suspected seizure.
[b] Glucose <2.6 mmol/L
[c] Brain MRI finding secondary to ischemia/hypoxia.
[d] One or more of hyponatremia (<130 mmol/L), hypokalemia (<3.0 mmol/L), and/or hypocalcemia (<1.0 mmol/L, ionized).

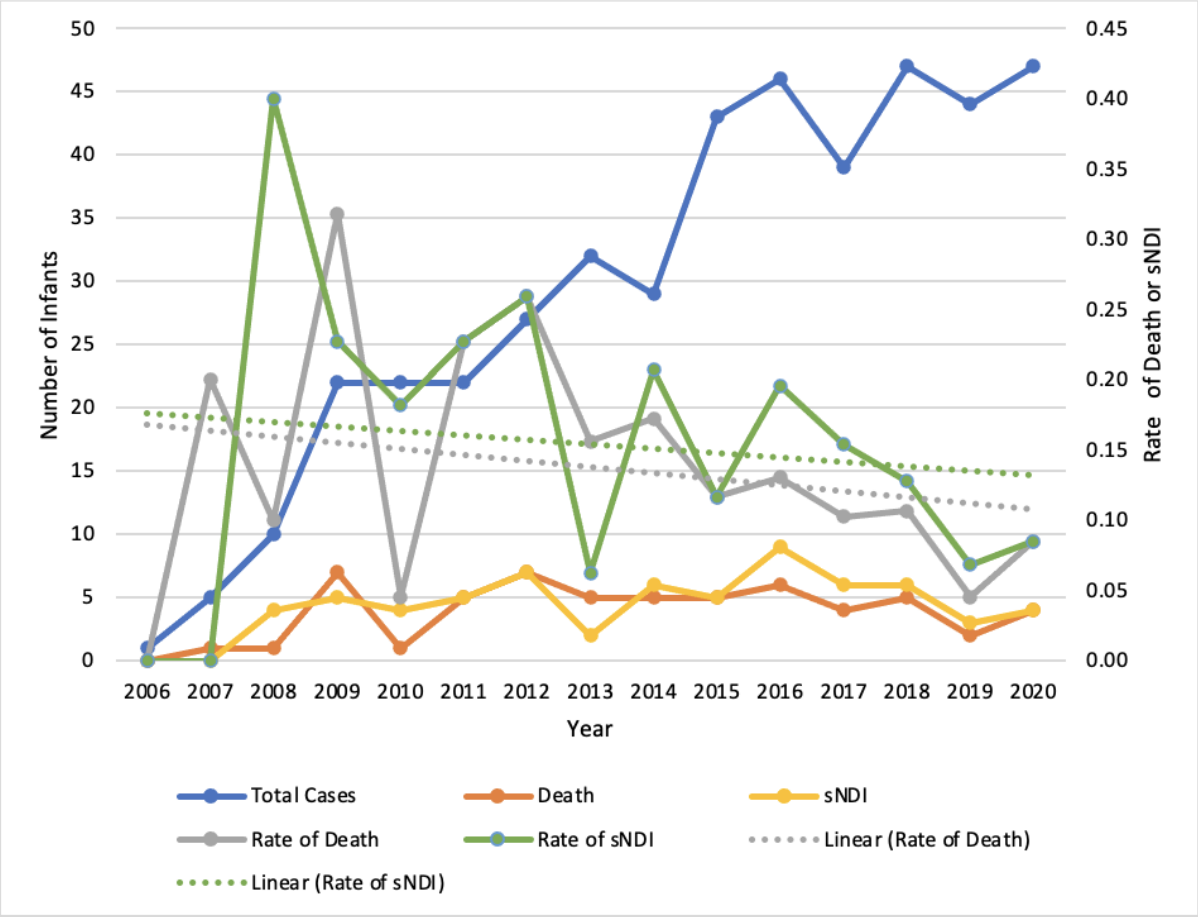

Figure 3.1 Total number of HIE cases treated with TH in Edmonton, Alberta from 2006-2020. Blue line represents all cases, orange line represents deaths per year and gray line is the rate of death per year (dotted line is the trendline). Yellow line represents sNDI cases per year and green line is the rate of sNDI per year (dotted line is the trendline).

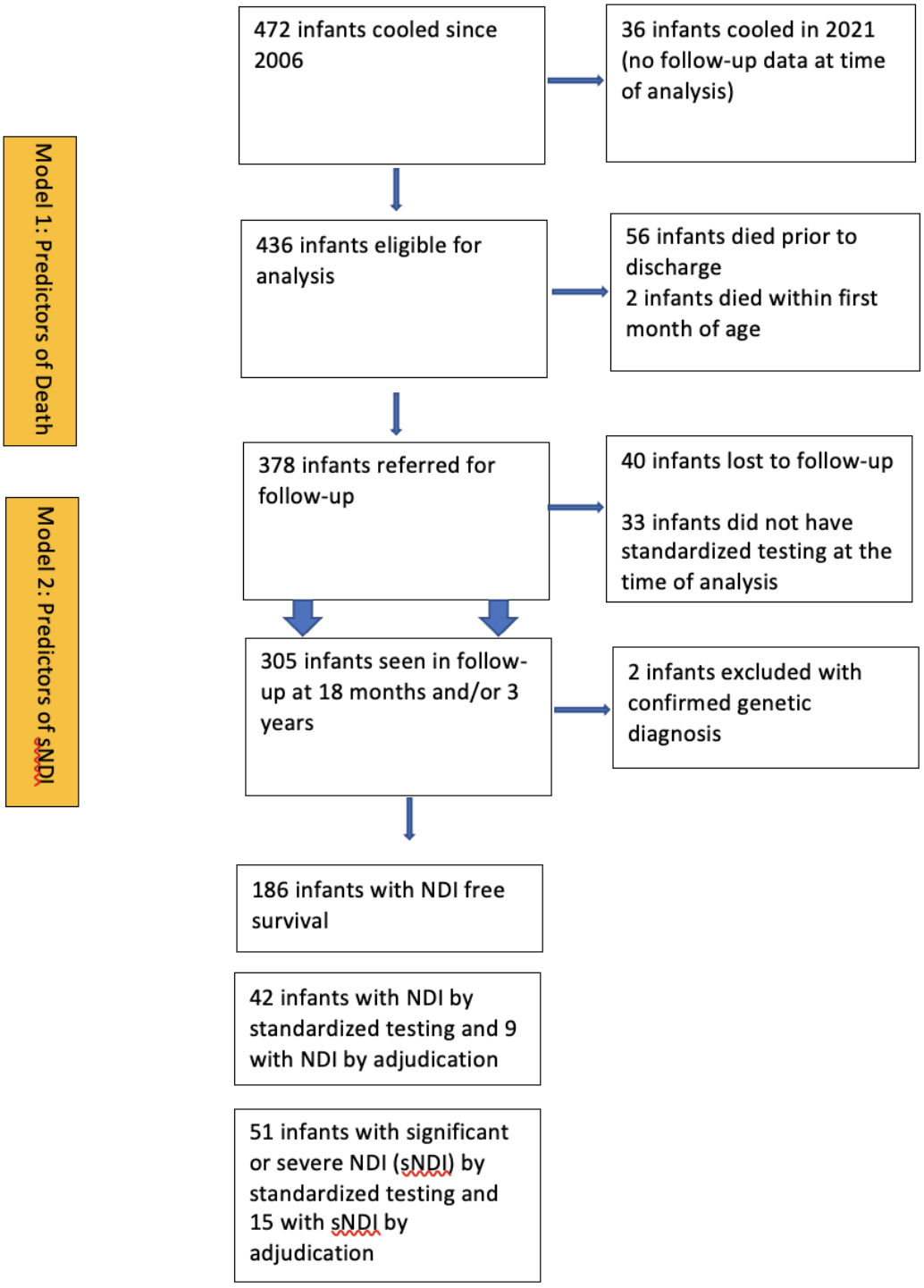

Figure 3.2 Number of Infants who Underwent Therapeutic Hypothermia and Subsequent Death, Loss to Follow-Up or Neurodevelopmental Impairment

Chapter 4: Development of a Prognostication Tool Using Classification and Regression Tree Analysis to Predict Poor Outcome for Infants with Hypoxic Ischemic Encephalopathy

4.1 Background

Hypoxic ischemic encephalopathy (HIE) remains a major cause of death and disability worldwide. The incidence of HIE in the developed world ranges between 1-8 /1000 live births.[1,2] HIE is the single greatest contribution to disability worldwide and accounts for one-tenth of all disability adjusted life years.[3] In a systematic review, the proportion of cerebral palsy associated with intrapartum hypoxia and subsequent ischemic injury in term infants without congenital malformations was approximately 15%.[4] Despite the mortality and morbidity associated with HIE, prognostic uncertainty remains a significant issue. There has been research to identify prognostic factors for poor outcome including clinical, biochemical, and other diagnostics (i.e., amplitude encephalogram (aEEG) and/or brain magnetic resonance imaging (MRI)) and much of this work comes from post-hoc analysis of the early cooling trials.[5-11] Generally, the predictive models that have been built predict a composite outcome of death or disability from factors that may not be available until after the cooling period. this, our aim was to use single centre data for neonates with HIE to identify early predictors of poor outcome, death, or disability as separate outcomes, and develop a model using classification and regression tree (CART) analysis.

Classification and regression tree analysis uses data mining methodology to provide a decision tree of several variables and their association with an outcome. CART can demonstrate which predictors are significant in a model or relationship that may be difficult to uncover in traditional regression techniques.[12-14] CART is an umbrella term that captures both classification and regression subtypes. Classification trees predict a discrete outcome while regression predicts

a numerical outcome.[12] The advantage of CART is its ability to describe complex relationships between predictor variables with the dependent variable in a visually pleasing tree diagram.[15] A classification analysis consists of four main components. The first component is a categorical outcome or dependent variable that we desire to predict. The second component is the predictor or independent variables. The third is the learning dataset and lastly, the test or future dataset, which consists of a new sample for whom we would like to make accurate predictions.[16] This strategy is gaining traction in health care research because of the ability to reveal hidden and unexplored relationships, in a ranked fashion, between variables.

4.2 Methods

This was a cohort study that used data from infants who underwent therapeutic hypothermia (TH) in Edmonton, as described in section 3.2. Infants who met criteria for cooling were immediately cooled to a target rectal temperature of 33-34°C for 72 hours. The current device used is the Blanketrol III™. Variables from the pre-TH period in addition to clinical and laboratory variables available during TH were included in development of these models (Table 4.1). The primary outcome was death within the first year of life or NDI. Definitions of NDI were as per the Canadian Neonatal Follow-up Network (CNFUN).[17,18] These definitions are outlined in section 3.2.

Prognostic algorithms were developed using CART analysis in SPSS. The growing method used was Chi Square Automatic Interaction Detection (CHAID). The maximum tree depth was specified to 3 with the minimum cases in the parent and child nodes of 100 and 50, respectively. The variables identified using stepwise selection for the regression models (Chapter 3), were used for CART development. Classification rates, holdout samples and cross-validation

were used as markers of model validity. Sensitivity, specificity, positive and negative predictive values were calculated for the logistic regression models, using a cut-off of 0.5 and the CART node that had the highest rate of the outcome (death or NDI).

4.3 Results

As seen in Figure 3.1, 436 infants underwent therapeutic hypothermia and were eligible for analysis. Fifty-eight infants died prior to 1 year of age. Of the 305 infants seen in follow-up at 18 months and/or 3 years, there were 186 infants with NDI-free survival. Sixty-six infants had significant or severe NDI. See Tables 3.1 and 3.2 for baseline characteristics. The CART models for early (first 24 hours) and late (24-72 hours) prediction of death are shown in Figure 4.1 and 4.2, respectively. The predictive variables in order of importance (earlier node on the decision tree) were hypotension receiving inotropic support, phenobarbital administration and need for chest compressions (Figure 4.1). The late prediction model (24-72 hours of age) had renal dysfunction, defined as oliguria (<0.5 ml/kg/hr for 72 hours after birth) or renal failure (creatinine >100 mmol/L) as the root node. Hypotension requiring inotropes was a decision node and administration of phenobarbital and chest compressions were terminal nodes. As seen in Table 4.2, both the early and late models for death had a risk estimate of 0.133 and standard error of 0.016. When cross validation was performed, both models had 100% accuracy of predicting survival but zero percent accuracy for predicting death. The highest percentage for death (37.1%) is seen in node 6, an infant with hypotension that received inotropic support and required chest compressions. In the late model, renal dysfunction and chest compressions led to the highest percentage of death (44.0%).

Figure 4.3 is a predictive model for significant or severe NDI (sNDI). The variables included are phenobarbital administration, abnormal MRI and 10-minute Apgar score less than 5. Compared to the models for death, this model did not perform as well with a risk estimate of 0.205 (standard error of 79.5 %). According to this model, the highest risk of sNDI is if an infant receives phenobarbital, has an abnormal MRI and a 10-minute Apgar score less than 5 (Node 5). Conversely, 92.1% of infants who did not receive phenobarbital had sNDI-free survival (Node 2).

As seen in Table 4.3, the CART models displayed improved sensitivity and specificity for predicting death and sNDI. With respect to positive predictive value (PPV), the logistic regression models performed better but when it came to negative predictive value (NPV), the CART outperformed.

4.4 Discussion

In this single center prospectively assembled cohort study, we aimed to develop a prediction model using CART that would identify poor outcome for infants with HIE. To our knowledge, these are the first CART models to identify predictors of death or disability as two separate entities rather than a composite outcome and the first models from the post-cooling era. A CART model proposed by Ambalavanan et al included pH of cord blood gases (cutoff of 6.70), spontaneous activity (none versus normal/decreased), base deficit of first postnatal arterial blood gas (cutoff if 18.5) and pCO2 of cord blood gas (cut off of 87).[19] For death alone, the variables included in the CART model were base deficit of first postnatal ABG and pH of cord blood gases. Their variables, guided by their initial logistic regression analysis, are largely markers of initial resuscitation. It should be noted, however, that their model was based on data

from infants who were randomized into either therapeutic hypothermia or not. The classification percentage for infants treated with TH was 82.0 %, lower than our classification rate of 86.7%.

Our predictor variables for death included hypotension that required inotropic support, receipt of phenobarbital and chest compressions. A varied list of variables that captures resuscitative needs, neurological injury, and end organ damage. When comparing to the logistic regression model (Table 3.3) for early prediction of death, the two variables that are not in the CART model are 'severe HIE' and perinatal sentinel event (PSE). Interestingly, the addition of renal failure into the late model for prediction of death did not improve the risk estimate or classification rate. In contrast, when renal failure was added to the logistic regression model (Table 3.4), it improved the R^2 value.

The CART model for sNDI (Figure 4.3) contained three of the five variables from the logistic regression model (Table 3.5); receipt of phenobarbital, abnormal MRI and 10-minute Apgar Score less than 5. The risk estimate, a measure of predictive accuracy, for this tree was higher than the estimates for the death models while classification, the number of cases classified correctly, was lower.

When comparing sensitivity, specificity, PPV and NPV, the CART models performed better in all domains except for PPV which was higher for the logistic regression models. The CART models were more sensitive rather than specific. Despite the use of these performance measures in prognostication research, there is limited literature on what elements would entail a "strong" prognostic test. The use of these measures allows for a comparison between the models developed. Compared to the CART model developed by Ambalavanan et al[19], our predictive models for death had a higher sensitivity and negative predictive value. According to Rector et al, "A prognostic test is used to predict a patient's likelihood of developing a disease or

experiencing a medical event".[20] The literature pertaining to predictive abilities of tests is mostly limited to screening tests and historically, a sensitive test is the goal for a good screening test. However, a prognostic model is different, especially one that attempts to predict the outcome of death or NDI. When speaking to a family about their infant's future, and utilizing the models we have developed, a high NPV, particularly as it pertains to the outcome of death is desirable. In contrast, a moderate PPV for the NDI model may be more desirable as the test would pick up a certain percentage of false positives for possible NDI.[21] For example, in the right clinical context, if a one-day old infant undergoing TH did not require inotropes for hypotension or received phenobarbital, you could reassure the family that the chance of death is extremely low (see Figure 4.1). Similarly, suppose that same infant is now 72 hours of age and does not have history of renal failure. In that case, you can be even more confident of the prognostic information you provided 2 days prior (using Figure 4.2). If the family of the same infant asks about sNDI you can explain that without receipt of phenobarbital, the chance of sNDI is less than 10%. This example demonstrates nicely a reassuring scenario and how you can use the models for both qualitative and quantitative information when providing prognostic information to families and other members of the multidisciplinary team.

4.4.1 Strengths and Limitations

A strength of this study was the large sample of infants with a relatively complete dataset of hospital variables. Given the size of our sample, we were able to utilize both a training and test dataset. The follow-up of our infants was done by trained clinicians in a standardized fashion and the follow-up rates were higher than the follow-up of rates very preterm infants in Canada[17] and other recent cohorts.[22,23]

As previously discussed, the data used to develop prediction models was from a single center cohort which may have limited transferability to other centers. Given the prospective study design, we were somewhat limited by the data collected. Albeit, based on the literature, except for postal codes, we felt that the data provided included the important maternal and infant variables. Postal codes were collected post-hoc. Given that none of the modes were 100% predictive, these models can be used for risk stratification and general discussion around prognostication but should not be definitive or the basis of decision making.

4.5 Conclusions

Using data from a prospectively assembled cohort of infants diagnosed with HIE, we developed CART models for prediction of death and sNDI. The models had high classification rates and outperformed logistic regression models (Chapter 3) when comparing sensitivity, specificity and negative predictive value. These models are from a single center cohort over the past 15 years. As such, the predictive value may be less so for future cohorts or populations from different centers. More research is needed with respect to how the information in these models can be used to communicate possible outcomes with families. Importantly, advancements in both obstetrical and neonatal care will necessitate ongoing model development, particularly as more research is being done around management of mild HIE.

4.6 References

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Table 4.1 Variables Collected on Infants who Underwent Therapeutic Hypothermia for Hypoxic Ischemic Encephalopathy

Category	**Variables**
Maternal/Delivery	Maternal data: complications of labour; pre-eclampsia, eclampsia, maternal seizure, thyroid malfunction, gestational diabetes, prolonged rupture of membranes (PROM >18 hours), pyrexia (≥ 37.6 in labour), antibiotic therapy and narcotic administration Delivery data: Method of delivery, delivery complications (antepartum hemorrhage, nuchal cord, head entrapment, true knot in cord, tear or rupture of cord, placental abruption, traumatic instrument delivery, shoulder dystocia, feto-maternal bleeding and rupture uterus)
Resuscitation	Apgar scores and resuscitation details (need for oxygen, bag and mask ventilation, intubation, chest compressions or meconium suctioned)
Biochemical	first and highest lactate, renal failure (urine output <0.5 ml/kg/hr or serum creatinine >100 umol/L within 1st 72 hours), AST >100 IU, ALT >100 IU, hyponatremia (<130 mmol/L), hypokalemia (<3.0 mmol/L) and hypoglycemia (<2.6 mmol/L), hypocalcemia (<1.0 ionized) and thrombocytopenia (given platelets)
Clinical	Ventilation needs, administration of inotropes, administration of antiepileptics, clinical seizures
Additional Diagnostics	aEEG, EEG, brain MRI
Complications	persistent pulmonary hypertension, sepsis, coagulopathy

Table 4.2 Performance Measure for CART Models (Figure 3.1-3.3)

Model	Risk Estimate	Standard Error	Classification (%)	Validation Risk Estimate (Standard Error)	
				Training (75%)	Test (25%)
Death by 1 year of Age (Early Model)	0.133	0.016	86.7	0.127 (0.018)	0.152 (0.034)
Death by 1 year of Age (Late Model)	0.133	0.016	86.7	0.131 (0.019)	0.138 (0.032)
Significant or severe NDI versus sNDI free survival	0.205	0.023	79.5	0.219 (0.027)	0.222 (0.049)

Table 4.3 Sensitivity, Specificity, PPV and NPV of the Logistic Regression and CART Models

	Model 1: Early Prediction of Death		Model 2: Late Prediction of Death		Model 3: Prediction of sNDI	
	Logistic Regression	CART	Logistic Regression	CART	Logistic Regression	CART
Sensitivity	0.239	0.672	0.217	0.569	0.236	0.803
Specificity	0.012	0.175	0.015	0.111	0.045	0.198
PPV	0.733	0.371	0.667	0.560	0.591	0.470
NPV	0.906	0.943	0.903	0.931	0.821	0.934

CART: Classification and Regression Tree; PPV: positive predictive value; NPV: negative predictive value

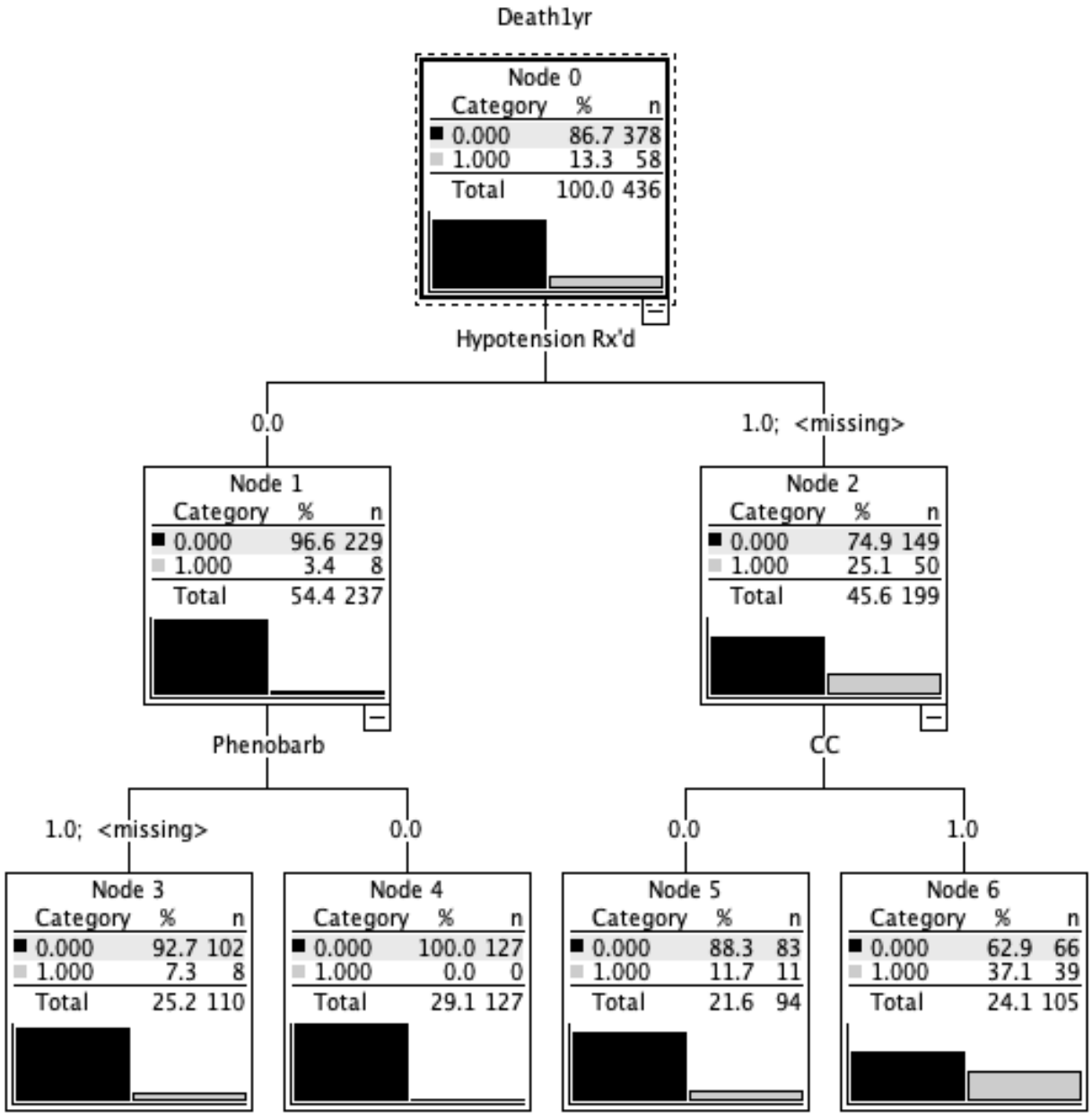

Figure 4.1 CART model for early prediction of death. In each node (rectangle), the category 0 or 1 refers to survival or death, respectively. 'Hypotension Rx'd' represents the administration of inotropes for hypotension, 'phenobarb' is simply whether an infant received phenobarbital and 'CC' represents chest compressions.

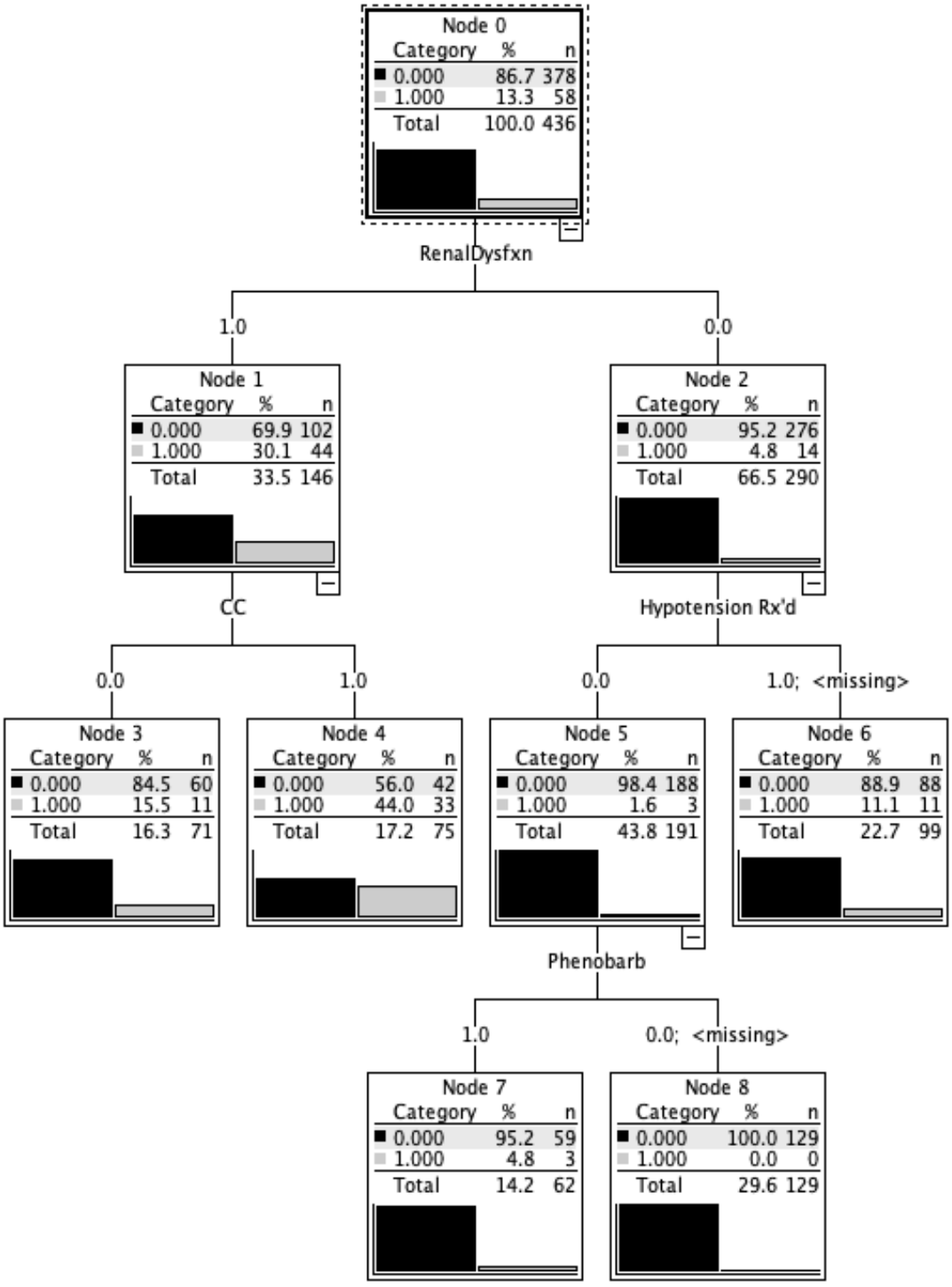

Figure 4.2 CART model for late prediction of death. In each node (rectangle), the category 0 or 1 refers to survival or death, respectively. 'Renal Dysfxn' represents renal dysfunction as defined by oliguria/renal failure (<0.5 ml/kg/hr for 72 hours after birth or creatinine >100 mmol/L), 'Hypotension Rx'd' represents the administration of inotropes for hypotension, 'phenobarb' is simply whether an infant received phenobarbital and 'CC' represents chest compressions.

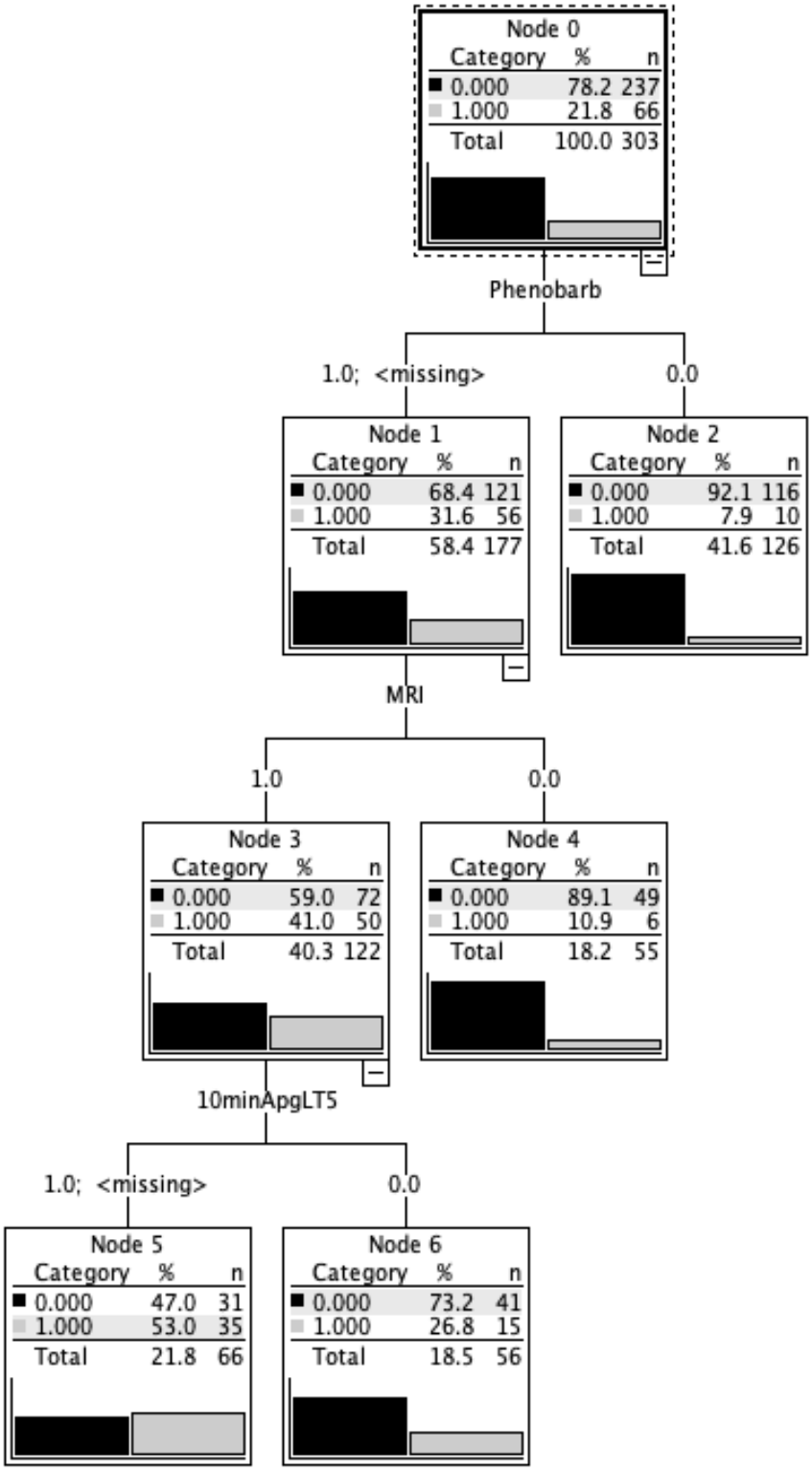

Figure 4.3 CART model for significant or severe NDI. In each node (rectangle), the category 0 or 1 refers to NDI-free/mild NDI survival or significant/severe NDI, respectively. 'Phenobarb' is simply whether an infant received phenobarbital, 'MRI' represents an abnormal MRI or not and '10minApgLT5' is whether an infant had a 10-minute Apgar score less than 5.

Chapter 5: Future Directions and Knowledge Translation

5.1 Overview of Study Results

This thesis aimed to develop a prognostication model from a large cohort of infants in the cooling era that can be used early in the neonatal intensive care unit (NICU) course to guide discussion with families, reduce prognostic uncertainty, optimize care and triage neonatal follow-up. To achieve our objectives, we conducted three studies. The first was a systematic review to identify prognostic factors from the original cooling randomized control trials (RCTs). The second study was a cohort study from our local database which aimed to describe the cohort of infants who underwent therapeutic hypothermia (TH) since 2006 as well as build a logistic regression model to identify prognostic factors for two distinct outcomes, death, or neurodevelopmental impairment (NDI). Lastly, using information from the cohort study, we built a classification and regression tree (CART) model to provide more quantitative information around prognostication. This final section will review results from the studies, their implications, and future directions of this research.

5.1.1 Results from Systematic Review

The systematic review in Chapter 2 identified early prognostic factors (those that could be identified in the first 72 hours of age) from RCTs investigating safety and efficacy of TH for neonatal hypoxic ischemic encephalopathy (HIE). We identified 19 studies, most of which were post-hoc analyses from the NICHD Hypothermia Trial[1]. The following variables demonstrated an association with outcome as defined by the original study as a composite of death or disability:

- Pre-randomization: A model including maternal hypertension/pre-eclampsia, antepartum hemorrhage, base deficit of first blood gas, Apgar score at 5 min, posture, spontaneous activity and suck[2]; Apgar score at 10 minutes[3], evolution of encephalopathy,[4] early amplitude electroencephalogram (EEG)[5,6] and neurological examination/encephalopathy grade[5,6].
- Biochemical: hypo/hyperglycemia[7], hypocarbia[8,9] and urinary lactate to creatinine ratio[10].
- Clinical: elevated temperature (if in normothermic group)[11], receipt of anticonvulsants[12], evolution of encephalopathy[4].

All but three studies in the review were deemed moderate to low risk of bias. Though we were not able to complete a meta-analysis given the heterogeneity of prognostic factors identified, the review allowed for a snapshot of variables that were associated with poor outcome from RCTs whereby the inclusion and exclusion criteria were strict. The findings from this review helped guide the logistic regression analysis in our cohort.

5.1.2 Results from Longitudinal Cohort study

5.1.2.1 Results from Logistic Regression

The aim of Chapter 3 was to describe the population of infant's who have undergone TH for neonatal HIE in our centre. Additionally, we built logistic regression models for death (early and late prediction) and significant/severe neurodevelopmental impairment (sNDI). A total of 472 infants made up our cohort of which 58 died and 305 had follow-up data. We postulate based on the number of infants undergoing TH over time in addition to the decline in rate of death and NDI, that over time, we are cooling milder cases. This is likely representative of the

modern-day cooling population and has been described in the literature[13]. Our models were made up of the following variables:

- Early Prediction Model for Death: receipt of phenobarbital, hypotension receiving inotrope(s), severe HIE (Sarnat stage 3[14]), chest compressions and perinatal sentinel event (PSE), which was protective.
- Late Prediction Model for Death: as above model with the inclusion of renal dysfunction.
- Prediction model for sNDI: receipt of phenobarbital, hypoglycemia, abnormal MRI, electrolyte abnormality and 10-minute Apgar score less than 5.

Like the findings from the systematic review, our longitudinal cohort identified important resuscitative, clinical, and biochemical variables that may be used to inform families of infants with HIE. The regression models provide a general sense of hospital variables that may be associated with poor outcome using an adjusted odds ratio. However, a logistic regression model fails to identify the complex and hierarchical interaction that may exist between the identified variables and the outcome of interest.[15] This is why classification and regression tree (CART) is gaining traction in health science research.[16-18]

5.1.2.2 Results from CART Analysis

In Chapter 4, we used our dataset to build CART models. The CART model for early (first 24 hours) prediction of death includes the variables of hypotension and subsequent inotrope use, receipt of phenobarbital and chest compressions at time of initial resuscitation. If an infant receives inotropes and has a history of chest compressions (node 6), approximately 40% of those infants died. Conversely, if there was no history of receiving inotropes and no phenobarbital

received (Node, 4 Figure 4.1), no infants died in our cohort. This trend is supported by a higher negative predictive value. The CART model for late prediction of death, which contains variables available in the first 72 hours, includes renal dysfunction, chest compressions at initial resuscitation, receipt of inotropes for hypotension and phenobarbital. If an infant did not have renal dysfunction, and did not receive inotropes or phenobarbital, then 100% of these neonates survived (Node 8, Figure 4.2). The CART model for sNDI included the following variables: receipt of phenobarbital, magnetic resonance imaging (MRI) (normal or abnormal) and 10-minute Apgar score less than 5. If an infant received phenobarbital but had a normal MRI, over 90% survived without sNDI (Figure 4.3 Node 2). If an infant received phenobarbital, had an abnormal MRI but 10-minute Apgar score was 5 or greater, 73% of infants had sNDI-free survival (Figure 4.3, Node 6).

5.2 Future Directions

5.2.1 Modern Day Infants Receiving Therapeutic Hypothermia

As discussed, we noticed a striking trend amongst our cohort over the past 15 years whereby there was a significant increase in the number of infants receiving TH with a declining rate of death and sNDI. Based on the unlikelihood of TH becoming more efficacious, we postulate that perhaps there has been a trend to apply TH to infants who would not have met the traditional criteria. This hypothesis is supported by a systematic review by Saw et al.[13] Not only do we need to take a closer look at our cohort in addition to maternal, pregnancy and obstetrical variables but we need to review other cohorts and centres. Future studies are needed to explore our hypothesis that there has been a tendency to utilize TH for milder cases of HIE.

5.2.2 Management of Infants with Mild HIE

Over the past few years, the neonatal community has questioned the management of infants with mild HIE, particularly as more evidence reports subtle neurodevelopmental concerns in this group.[19-21] Some also argue that a randomized trial is needed.[22] We question the ethical limitations to doing a RCT given the number of mild cases that are already being treated with TH. Perhaps a closer look at the mild cases that undergo TH and what characteristics, if any, influence decision making around management is needed. Further, a research question aimed at describing the evolution of mild cases, to determine characteristics that predict worsening from a neurological point of view to either moderate or severe encephalopathy may help guide the management of cases that do not meet traditional TH criteria initially.

5.2.3 Validation of Models

We have developed new prediction models using data from our cohort and applied internal validation methods (classification, holdout samples and cross-validation). The next step would be to evaluate model performance using another cohort or data that was not included in our analysis. This process is called external validation and requires that each individual in the new data set has a prediction from the original model which then gets compared to the observed outcome.[23] There has been interest from the HIE provincial (Alberta) group to use the data from Calgary, Alberta to expand and validate our model. Our model can then be adjusted as needed.

5.2.4 Use of Models in Clinical Setting

An important element of future research will require investigation of how the prognostic models be used in the clinical setting. Ideally, our aim is that these models can be used early

(first 72 hours) in the NICU course to communicate with families, decrease prognostic uncertainty and ensure infants at high risk of sNDI are seen in neonatal follow-up. More so, given the model performance, we hope that our models can be used to provide reassurance to families taking home an infant with HIE and their long term neurodevelopmental trajectory. Further studies should involve both members of the multidisciplinary team in addition to families of infants with HIE to understand how prognostic tools be used at the bedside. Krick et al[25] describe the varying experiences of families in the face of prognostic uncertainty and we do not expect a one-size-fits-all approach to these discussions. In an exploratory, qualitative study with parents who had infants with HIE, Craig et al[26] identified four areas by which parents of infants with HIE felt their expectations were not met. Two of which included intense fear around their infant's immediate survival and ongoing uncertainty about long-term prognosis. Using information from our models may help with both of those aspects.

5.3 Knowledge Translation

The Northern Alberta Neonatal Program continues to serve a high volume of infants and this research is a demonstration of the data that can be obtained to optimize patient care. We will continue to support the prospective collection of data for infants with HIE as well as other common neonatal conditions. The results from this cohort study will be disseminated through presentations and publications. We recognize that a key player in the knowledge translation process will be family members and we will include families as we consider ways to put our models into practice. We will begin by presenting our findings to the Family Advisory Committee (FACT) with the main objective of understanding how families would want this information presented to them in the acute stages of their NICU stay. As we develop further

research questions related to our prognostication models, we will ask families to be a part of the protocol development.

The NICU is an area where there are often conversations around prognostic uncertainty.[27] In our study, we aimed to identify prognostic factors associated with poor outcome for infants with HIE. Importantly, we separated the outcomes of death and sNDI rather than viewing them as a composite. We hope to see this distinction propagate throughout the neonatal research community. As we became comfortable with our dataset and the use of CART, we look forward to translating this form of analysis into other areas, particularly the preterm infant population.

5.4 Conclusion

This thesis aimed to identify early predictors of death and NDI, as two separate outcomes, for infants with HIE treated with TH in Edmonton, Alberta. In the systematic review, we identified prognostic factors from the original RCTs which effectively showed the benefit of TH for moderate/severe HIE. The heterogeneous nature of the factors identified allowed for a big picture understanding of the pre-randomization, biochemical and clinical characteristics that may lead to poor outcome. In the cohort study, whereby data was collected prospectively, we built both logistic regression and CART models for early/late prediction of death in addition to separate models for sNDI. The CART models, with their high negative predictive value, allowed us to consider patient characteristics that would confer a low risk of death or sNDI. External validation and careful implementation into practice are the next steps before assessing the model's ability to guide discussion with families, lessen prognostic uncertainty, optimize acute care and triage neonatal follow-up.

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Appendices

Appendix 1. MEDLINE Search Strategy

OVID Medline® ALL 1964 to March 19, 2021
Date searched: September 1, 2021
Results: 487
1. Hypoxia-Ischemia, brain/
2. (((hypoxi* or anoxi*) adj2 (ischemi* or ischaemi*) adj2 (encephalopath* or damage or injur*)) or HIE or neonatal asphyxia* or neonatal brain injur*).mp.
3. 1 or 2
4. (cooling or cooled or chill* or hypothermi*).mp.
5. Hypothermia, Induced/
6. 4 or 5
7. 3 and 6
8. (risk or incidence).sh. or exp mortality/ or follow-up studies.sh. or prognos*.tw. or predict*.tw. or course*.tw.
9. 7 and 8
10. Limit 9 to humans

Appendix 2. Data Collection Form: A Systematic Review of Early Prognostic Factors for Neurodevelopmental Impairment and Mortality among Cooled Neonates with Hypoxic Ischemic Encephalopathy

Notes:

- Record any missing information as unclear or not described
- Please record which page you found the information on

General Information

Study ID (first author name and year)	
Form completed by	
Study author contact details	
Publication type (ie. full report, abstract)	
Notes:	

Participants and Sample Size

Participant eligibility		Page #:
Participant description		
Total or head cooling		
Study dates		

Outcome(s) to be Predicted

Definition and method for measurement of outcome	.	
Was the same outcome definition (and method of measurement) used in all patients?		
Type of outcome (single or combined)		
Was the outcome assessed without knowledge of the candidate predictors? (blinded)		

Time of outcome occurrence or summary of duration of follow-up		

Prognostic factors (index and comparator prognostic factors)

Number and type of prognostic factors (eg. Obtained from demographics, patient history, physical examination, additional testing)		
Definition and method for measurement of prognostic factors		
Timing of prognostic factor measurement		
Were prognostic factors assessed blinded for outcome, and for each other (if relevant)?		
Handling of prognostic factors in the analysis (eg. Continuous, linear, non-linear)		

Sample Size

Was a sample size calculation conducted and, if so, how?		
Number of participants and number of outcomes or events		
Number of outcomes/events in relation to the number of candidate predictors (events per variable)		

Missing Data

Number of participants with any missing value (in the		

prognostic factors and outcomes)		
Number of participants with missing data for each prognostic factors of interest		
Details of attrition (loss to follow-up)		
Handling of missing data (eg. Complete case analysis, imputation, or other methods)		

Analysis

Modelling method (eg. Linear, Logistic, parametrics survival)		
How modelling assumptions were checked		
Method for selection of prognostic factors for **inclusion** in multivariable modelling (eg. All candidate prognostic factors considered, pre-selection of prognostic factors, retain only those significant from univariable analysis)		
Method for selection or exclusion of prognostic factors **during multivariable modelling** (eg. Full model approach, backward or forward selection) and criteria used (eg. P-value)		
Method of handling each continuous prognostic factor (eg. Dichotomisation, categorisation etc), including values of any cutpoints used and their justification; for nonlinear trends, the method of identifying non-linear relationships		

Results

Unadjusted and adjusted prognostic effect estimates (eg. Risk ratios, odds ratios, hazard ratios, mean difference) for each prognostic factor of interest, and the corresponding 95% confidence interval. Details of any non-linear relationships and whether modelling assumptions hold; in particular, for time-to-event outcomes, any evidence of non-proportional hazards for each prognostic factor of interest.		
For each extracted adjusted prognostic effect estimate of interest, the set of adjustment factors used		

Interpretation and Discussion

Interpretation of presented results		
Comparison with other studies, discussion of generalizability, strengths and limitations		

Adapted from Moons KG, de Groot JA, Bouwmeester W, Vergouwe Y, Mallett S, Altman DG, et al. Critical appraisal and data extraction for systematic reviews of prediction modelling studies: the CHARMS checklist. PLoS Med. 2014;11(10):e1001744.

Appendix 3. QUIPS Risk of Bias Assessment for Prognostic Factor Studies

Author and year of publication:

Study identifier:

Reviewer initials:

Domain	Issues to consider	Overall Risk of Bias (low, moderate or high)
Study Participation	▪ Inclusion and exclusion criteria are described ▪ Period of recruitment described ▪ Place of recruitment described ▪ The baseline study sample is described	
Study Attrition	▪ Reasons for loss to follow-up are provided ▪ Participants lost to follow-up are described ▪ No important differences between key characteristics and outcomes in participants who completed the study and those who did not	
Prognostic Factor Measurement	▪ A definition of prognostic factor is provided (ie. level, duration, method of measurement as appropriate) ▪ Method of prognostic factor measurement is adequately valid and reliable to limit misclassification ▪ Continuous variables are reported or appropriate cut points are used ▪ The method and setting of measurement of prognostic factor is the same ▪ adequate proportion of the study sample has complete data for prognostic factor variable ▪ appropriate methods of imputation are used for missing prognostic factor data	
Outcome Measurement	▪ a clear definition of outcome is provided including duration of follow-up and extend of the outcome ▪ the method of outcome measurement used is adequately valid and reliable to limit misclassification bias ▪ the method and setting of outcome measurement is the same for all participants	
Study Confounding	▪ important confounders are measured ▪ clear definitions of important confounders are provided	

	▪ measurement of all important confounders are adequately valid and reliable ▪ the method and setting of confounding measurements are the same for all study participants ▪ appropriate methods are used for missing confounder data ▪ important potential confounders are accounted for in the study design ▪ important potential confounders are accounted for in the analysis	
Statistical Analysis and Reporting	▪ There is sufficient presentation of data to assess the adequacy of the analysis ▪ The strategy for model building is appropriate and is based on a conceptual framework or model ▪ The selected statistical model is adequate for the design of the study ▪ There is no selective reporting of results	

OVERALL Risk of Bias (Circle): LOW MODERATE HIGH
Low: All domains 'low' OR up to one moderate risk of bias
High: One or more domain 'high' or 3 or more 'moderate' risk of bias
All other would be considered 'moderate'

Adapted from Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006;144:427-437, with the assistance of the QUIPS-LBP Working Group.