Outcomes of children receiving in-hospital resuscitation

By

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Graduate department of Institute of Medical Science
University of Toronto

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ABSTRACT

Outcomes of children receiving in-hospital resuscitation, Master of Science, 2009,
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Introduction: This thesis prospectively evaluated the cognitive and functional outcomes and health-related quality of life of children admitted urgently to a Pediatric Intensive Care Unit (PICU) at the Hospital for Sick Children.

Methods: The primary outcome was the Vineland Adaptive Behavioural Scale (VABS-2) measured at 1-month and secondary outcomes were health-related quality of life, daily functioning, and caregiver perceptions.

Results: 56 children and 66 caregivers were enrolled; 42 (75%) patients and 49 (74%) caregivers completed the 1-month assessment. Children in the PICU had a mean VABS-2 score of 85(±25). Daily functioning outcomes did not significantly change from baseline to 1-month. In comparison to baseline, children had significantly reduced health-related quality of life at 1-week but no significant change was found at 1-month.

Discussion: Children surviving PICU have significant cognitive morbidity and reduced health-related quality of life that is exacerbated by more intense modes of resuscitation and increasing severity of illness.
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*Note: Outcome measures excluded due to copyright restrictions*
LIST OF ABBREVIATIONS

AHA – American Heart Association
ALS – Advanced Life Support
ARF – Acute Renal Failure
CA – Cardiac Arrest
CCCU – Cardiac Critical Care Unit
CPR – Cardiopulmonary Resuscitation
CPB – Cardiopulmonary Bypass
ECMO – Extracorporeal Membrane Oxygenation
ELSO – Extracorporeal Life Support Organization
HRQoL – Health-related Quality of Life
HUI-3 – Health Utilities Index (III)
ICU – Intensive Care Unit
LOS – Length of Stay
NIH – National Institutes of Health
NRCPR – National Registry of Cardiopulmonary Resuscitation
PCPC – Pediatric Cerebral Performance Category
PedsQL-4 – Pediatric Quality of Life Inventory (IV)
PELOD – Pediatric Logistic Organ Dysfunction
PEWS – Pediatric Early Warning System
PICU – Paediatric Intensive Care Unit
PIM – Pediatric Index of Mortality
POPC – Pediatric Overall Performance Category
PRISM – Pediatric Risk of Mortality
ROSC – Return of Spontaneous Circulation
ROSV - Return of Spontaneous Ventilation
SOI – Severity of Illness
THAPCA – Therapeutic Hypothermia after Pediatric Cardiac Arrest
VABS-2 – Vineland Adaptive Behavioural Scale (II)
VAS – Visual Analogue Scale
PREFACE

This thesis is organized into fifteen chapters. Chapter one describes the rationale and objectives of the study. Chapter two evaluates the literature on paediatric critical illness, resuscitation and factors affecting survival in critically ill children. Chapter three evaluates literature on health-related quality of life and assessment of morbidity. Longitudinal outcome assessment in children is described in chapter four. Chapter five evaluates the literature on caregiver satisfaction and factors potentially influencing satisfaction. Chapter six presents the study hypotheses. Chapter seven describes the methodology, design and analytic plan evaluated. Results of the patient population are presented in chapter eight. Results of the ratings of neurocognitive functioning, daily functioning and health-related quality of life are presented in chapter nine, ten and eleven respectively. Chapter twelve describes the factors that were significantly associated with the primary and secondary outcomes. Chapter thirteen presents the results of caregiver perceptions. Chapter fourteen discusses the findings of the study in the context of paediatric critical care, highlights the strengths and limitations of the study, and discusses the implications and future directions. Chapter fifteen presents the conclusions.
RESEARCH AIMS
CHAPTER 1
PURPOSE AND OBJECTIVES

The primary rationale for providing paediatric ICU (PICU) care to critically ill children is neurologically intact survival. Each year, over ten thousand children are cared for in the 15 major PICUs in Canada. To date, population level assessments of outcome have focused on mortality, or in-ICU morbidity such as organ dysfunction.\(^1\) Cognitive morbidity and health-related quality of life following PICU admission has not been well studied.\(^2\) With improving survival following PICU admission—now at more than 95%—it is imperative that evaluations of the effectiveness of PICU care include cognitive and health-related quality of life assessments. As a prelude to a larger cross-sectional study, and as part of a resuscitation research program focused on children urgently admitted to PICU, this thesis project evaluated neurocognitive and health-related quality of life outcomes in children urgently admitted to a PICU.

In children surviving urgent admission to a paediatric ICU from a hospital ward, we described:


BACKGROUND
CHAPTER 2
PAEDIATRIC CRITICAL ILLNESS, RESUSCITATION, AND FACTORS AFFECTING SURVIVAL

Urgent admission to the ICU is not a benign phenomenon. The use of multiple invasive therapies with potentially fatal complications may ultimately save lives. However, these may also provide many opportunities for acquired cognitive morbidity and reduced quality of life.\(^3\)-\(^8\)

2.1 Critical Illness in Children

The evolution of critical illness in hospitalized children is common,\(^9\) and is associated with adverse outcomes including cardiopulmonary arrest and mortality despite ICU admission (Table 2.1).\(^10\)-\(^16\) Resuscitation treatments including circulatory, respiratory, renal, hepatic, endocrine and/or metabolic therapies are provided in the ICU, with the intent of supporting organ systems, preventing organ failure, saving life and ultimately preserving neurologic function and health-related quality of life.

Each year in Canada, over 10,000 children receive care in a Paediatric ICU (PICU). Data from 5 PICUs show that 5,413 (50\%) of 10,825 admissions (2 years) were classified as urgent, defined as twelve hours or less. Children admitted urgently to a PICU from hospital inpatient areas are at increased risk for adverse outcomes compared with children admitted to a PICU from other sources.\(^11\),\(^17\),\(^18\)
TABLE 2.1: Adverse outcomes of critical illness

<table>
<thead>
<tr>
<th>Study</th>
<th>Years studied</th>
<th>Duration</th>
<th>n</th>
<th>Age (years)</th>
<th>Duration of stay (days)</th>
<th>PICU mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flori 2005</td>
<td>1996-2000</td>
<td>4 yrs</td>
<td>320</td>
<td>5.8 ± 5.6</td>
<td>14.9 ± 17.8</td>
<td>72 (22%)</td>
<td>Mortality greater in patients with presenting 2 or more nonpulmonary organ system failures in comparison to 1 or less [60 (47%) vs. 11 (6%)]</td>
</tr>
<tr>
<td>Alhual 2007</td>
<td>1988-1992, 2000-2004</td>
<td>8 yrs</td>
<td>164</td>
<td>1.3 (3.4); 2.6 (7.7)</td>
<td>n/a</td>
<td>28 (35%) from 1988-1992; 18 (21%) from 2000-2004</td>
<td>Tidal volume significantly associated with reduced mortality</td>
</tr>
<tr>
<td>De Mos 2006</td>
<td>1997-2002</td>
<td>5.5 yrs</td>
<td>91</td>
<td>4.0</td>
<td>10</td>
<td>68 (75%)</td>
<td>In-ICU cardiac arrest associated with high in-hospital mortality and subsequent morbidity in survivors</td>
</tr>
<tr>
<td>Van Litsenborg 2005</td>
<td>1997-2002</td>
<td>5.5 yrs</td>
<td>80</td>
<td>0-18</td>
<td>n/a</td>
<td>52 (65%)</td>
<td>Fewer than 2 of 5 children receiving ECMO survived to hospital discharge</td>
</tr>
<tr>
<td>Bateman 2008</td>
<td>2004-2005</td>
<td>6 mths</td>
<td>986</td>
<td>28d-18yrs</td>
<td>n/a</td>
<td>n/a</td>
<td>The burden of anemia, blood loss, and transfusions in the PICU population are significant</td>
</tr>
</tbody>
</table>
Amongst children urgently admitted to a PICU from hospital wards, children admitted following calls for immediate assistance (code blue calls) have twice the risk of ICU mortality compared with children who are admitted following an urgent ICU consultation.\textsuperscript{19}

Clinical deterioration preceding ICU admission may take many forms, including increasing need for respiratory or circulatory support, near cardiac arrest requiring immediate pre-emptive medical attention by a code-blue or medical emergency team, or actual cardiopulmonary arrest requiring cardiopulmonary resuscitation. Evidence shows that the nature of resuscitation can affect outcomes,\textsuperscript{20-27} however the outcomes observed are both a consequence of the resuscitation provided and the underlying severity of illness that lead to the resuscitation.

\textbf{2.2 Resuscitation of critically ill children}

ICU technologies can be used to support failing organ systems and can increase survival rates in critically ill children. Conventional and other forms of mechanical ventilation, pharmacologic and mechanical circulatory support, and renal replacement therapies are frequently used. Complications or unsuccessful therapy can result in death or chronic morbidity.

\textbf{Mechanical Ventilation:} Between 50\% and 75\% of patients admitted to the PICU receive mechanical ventilation. Seventy-five percent of children cared for by the critical care medicine program at the Hospital for Sick Children are mechanically
ventilated at some point during their ICU stay. Acute complications of ventilation include ventilator induced lung injury, pneumothorax, ventilator associated pneumonia, and complications of drug therapy used to support mechanical ventilation.\textsuperscript{12, 28, 29} The duration and nature of ventilation are associated with acquired morbidity.\textsuperscript{10, 12, 30}

**Extracorporeal Membrane Oxygenation (ECMO):** ECMO is an alternative treatment to cardiorespiratory failure, a means to support circulation while resting the heart, which gives the myocardium an opportunity to recover adequate contractility.\textsuperscript{31} ECMO helps to prevent multi-organ system failure and acquired brain injury by supporting the systemic circulation. With the ECMO pump, the systemic ventricular workload may be reduced which prevents myocardial ischemia. This potentially improves myocardial oxygen supply. The most significant aspect in successful cardiopulmonary resuscitation of paediatric patients is considered to be the prompt establishment of an adequate cardiac output.\textsuperscript{32} ECMO may be used pre-emptively to provide respiratory and circulatory support in critically ill patients who are refractory to aggressive application of therapies, before cardiopulmonary arrest. Alternatively, it can be used as a curative therapy for refractory cardiopulmonary arrest. Pre-emptive ECMO has been recommended in sepsis guidelines since 2002,\textsuperscript{33} and is commonly used following surgery for congenital heart disease.\textsuperscript{34}

The Extracorporeal Life Support Organization (ELSO)—an international consortium of healthcare professionals and scientists dedicated to developing and
evaluating novel therapies for support of failing organ systems—maintains a registry of the use of ECMO in active ELSO centres. According to the ELSO registry data, ECMO is used nearly 1000 times per year in critically ill children. The Critical Care Medicine Program at the Hospital for Sick Children treats 70-80 children each year with mechanical circulatory support. ECMO is associated with high mortality and coarsely assessed but significant morbidity, some of which is directly related to the treatment provided. Complications of ECMO include micro-emboli, stroke, intracranial haemorrhage and organ dysfunction. Each of these can result in cognitive morbidity, functional impairment or death. Delayed ECMO is associated with increased mortality. Early institution following neonatal cardiac surgery may be life-saving and/or associated with morbidity.

Cardiopulmonary resuscitation (CPR): According to the Utstein guidelines, basic CPR is “an attempt to restore ventilation, using expired air inflation of the lungs and circulation and using external compressions of the chest wall”. This definition does not include the use of bag-valve-mask devices with invasive airway maneuvers. Advanced CPR is “the addition of invasive maneuvers to restore effective ventilation and circulation...these maneuvers include interventions such as bag-valve-mask ventilation, endotracheal intubation, or needle cricothyrotomy”. Advanced CPR includes administration of endotracheal or intravenous medication or use of cardiopulmonary bypass. The return of palpable, spontaneous central pulses in a cardiac arrest patient, regardless of their duration, refers to the ‘Return of spontaneous circulation’ (ROSC). The ROSC is not an indicator that chest
compressions should be discontinued as it may still be considered necessary.\textsuperscript{47} The return of spontaneous respiratory effort in a previously apneic child, excluding agonal or gasping respirations refers to the ‘Return of spontaneous ventilation’ (ROSV).\textsuperscript{46} Start-stop CPR interval refers to the time from initiation of basic CPR to either onset of sustained ROSC or termination of efforts. Data suggests that failure to respond to 25-minutes of pre-hospital advanced life support (ALS) predicts death or severe neurological impairment.\textsuperscript{13, 46, 48, 49} Therefore, it has been suggested that the duration of CPR effort may provide valuable insight on how long CPR efforts should be continued.\textsuperscript{46}

CPR is provided to 1-3\% of hospitalized children, and is associated with 27\% survival in a recent series of 880 cases from the National Registry of Cardiopulmonary Resuscitation (NRCPR).\textsuperscript{49} Interruption to cerebral blood flow and hypoxemia are associated with neurologic injury. In a retrospective study of 91 children with in-ICU cardiac arrest, it was found that all survivors had abnormal Pediatric Cerebral Performance Category (PCPC) scores or Pediatric Overall Performance Category (POPC) scores at hospital discharge and 12 months after in-ICU cardiac arrest.\textsuperscript{13} Mortality, following in-ICU arrest, may be lower in younger children.\textsuperscript{50} Cardiopulmonary resuscitation plus ECMO may be associated with poor cognitive and functional outcomes at 2-3 years (n=8 survivors).\textsuperscript{51} Other studies describe 60-70\% short-term mortality.\textsuperscript{52, 53}
2.3 Factors potentially affecting outcomes of critical illness in children

In general, survival following PICU admission has improved over the last decades to the 95-96% currently reported.\textsuperscript{54} The factors influencing outcome of critically ill children are multi-factorial and include:

[1] \textbf{Baseline illness (primary diagnosis)}

Children with chronic and complex diseases are at increased risk for in-hospital clinical deterioration and are over-represented in the ICU.\textsuperscript{55-59} In chronically ventilated patients, underlying diagnosis is a major determinant of outcomes,\textsuperscript{60} however the outcomes are frequently described in terms of disposition as a proxy for function, without considering quality of life.\textsuperscript{61} Studies have shown prolonged ICU stay and higher mortality rates in children with ventilator-associated pneumonia,\textsuperscript{62} bone marrow transplant,\textsuperscript{63} hypoplastic left heart syndrome (HLHS),\textsuperscript{64} hemophagocytic lymphohistiocytosis (HLH),\textsuperscript{65} hyperglycemia,\textsuperscript{66} and acute kidney injury.\textsuperscript{67}

[2] \textbf{Acute Severity of illness}

Acute Severity of illness (SOI) on ICU admission is highly correlated with ICU survival in children,\textsuperscript{68,69} and adults.\textsuperscript{70} In critically ill children, the SOI at PICU admission may be related to functional outcomes as assessed by the PCPC and POPC.\textsuperscript{71} Increased SOI may necessitate a longer PICU stay. Longer PICU stay is associated with cognitive morbidity,\textsuperscript{72} and increased mortality.\textsuperscript{55}
SOI assessments are widely accepted within the ICU for quality assessments, controlling for SOI in clinical studies, and studies of ICU resource utilization and management.\(^68\) Until recently, the Pediatric Risk of Mortality (PRISM) score—a physiology based predictor for paediatric patients—was the only SOI assessment in the PICU.\(^68\) The Pediatric Index of Mortality (PIM) score was introduced later which analyzes the condition of the patient directly upon arrival in the PICU.\(^73\) Organ dysfunction occurring while in the ICU is also highly correlated to ICU-mortality,\(^1\) and is assessed using the Canadian-developed Pediatric Logistic Organ Dysfunction (PELOD) score.\(^1\) Unlike the PRISM system, developed to be a predictive marker, the PELOD system was designed to be an outcome measure.\(^1\) Furthermore, PRISM includes parameters related to different organ dysfunctions but does not separate each dysfunction.\(^1\) The PELOD score describes the number and severity of organ dysfunctions during the child’s stay in the PICU, independent of cause.\(^1\)

Acute renal failure (ARF), functional failure of kidneys, is common among critically ill patients with significant morbidity and mortality.\(^74,75\) A recent study (2009) showed that increased duration of ECMO support in paediatric patients is associated with the development of ARF and a significant decrease in the odds of survival.\(^76\) A study evaluating the prevalence of ARF in adults in the ICU showed that prevalence of ARF is associated with a high mortality rate.\(^77\)

Hypoxemia and oxygenation index have shown to be predictors of outcome.\(^30\) A study conducted at the Hospital for Sick Children showed that severity of oxygenation
failure at any point during acute hypoxemic respiratory failure is significantly associated with mortality rate and number of days on mechanical ventilation.\(^{30}\)

[3] **Interventions**

Less severe forms of critical illness require less intense forms of resuscitation. These include urgent intubation, mechanical ventilation, circulatory support with inotropes and administration of intravenous fluids to restore circulation. Acquired morbidity in the ICU can follow drug administration,\(^{78-80}\) transfusion,\(^{16}\) mechanical ventilation,\(^{12,81}\) monitoring, anticoagulation,\(^{36}\) and other therapies.

The type of resuscitation treatment required is an important factor.\(^{13,82}\) Urgent treatment of impending respiratory failure with mechanical ventilation, circulatory and/or respiratory failure with ECMO, and absent circulation during cardiac arrest all provide reduced cerebral perfusion/oxygenation. The aggressiveness of these treatments has important implications for morbidity, increasing the probability for acquired brain injury.

The most severely ill children suffer cardiopulmonary arrest. The outcome of treated cardiopulmonary arrest in hospitalized children is poor. Data from the NRCPR study (JAMA 2006)—a prospective American Heart Association (AHA) funded registry, with voluntary contributions from 150 paediatric institutions—found 27% hospital survival.\(^{49}\) Sixty-five percent of survivors had ‘good’ neurologic outcome, defined as a PCPC score of 3 or less.\(^{49}\) Thus, children who had ‘moderate’ disability identifiable from medical record review were classified as having ‘good’ outcome.
Several studies showed that patients who received more than 2 doses of standard-dose epinephrine did not survive.\textsuperscript{83-86} Termination of resuscitation has been recommended if there is no ROSC after 2 doses of epinephrine. These studies conflict with DeMos’ study (2006) where number of epinephrine boluses given during cardiac arrest was not significantly associated with ICU or hospital survival.\textsuperscript{13} In studies where there has been documented long-term survival after >2 doses of epinephrine, most were severely neurologically impaired.\textsuperscript{87-90}

Duration of therapy is an important predictor for future outcomes. In Young and Seidel’s (1999) review, twelve studies correlated duration of CPR and outcome.\textsuperscript{83} Eight reports demonstrated that continuing CPR longer than 20 to 30 minutes in normothermic patients did not produce additional survivors whereas four reports noted that majority of survivors underwent CPR for 15 minutes or less.\textsuperscript{84-87, 91-98} Prolonged periods of low flow (>30 minutes) are unlikely to result in survival and may increase the relative risk of neurologically impaired survival.\textsuperscript{87, 88, 99-101}

CPR is associated with decreased cerebral flow and thus neurologic injury. Although post-resuscitation interventions such as haemodialysis, ECMO, and sedation have sequelae including intracranial haemorrhage, stroke and behavioural changes, other modes of post-resuscitation support including inotropes are less likely to have neurologic sequelae.
[4] **Timing of treatment**

One study illustrated that urgent PICU admission following urgent PICU consultation was associated with 14% mortality, with mortality increasing to 28% if the PICU admission followed an immediate call for medical assistance (a code blue call).\(^\text{19}\) Early application of ICU interventions to treat patients with evolving critical illness have been associated with improved outcome.\(^\text{20, 25, 102, 103}\) Increasing interest and application of early interventions to improve patient outcome include earlier identification and referral of children and adults with evolving critical illness, from Bedside PEWS, Medical Emergency Teams, and other ICU expertise.\(^\text{104-106}\) This may improve survival but does not necessarily equate to improved cognitive or functional outcomes. These interventions may be improving timeliness of admission to ICU and thus improving the outcomes of care, by permitting intubation and other resuscitation to be delivered in the controlled ICU environment.\(^\text{107}\) Conversely, earlier ICU admission may simply be shifting the site of clinical deterioration, and the true determinant of outcome may instead be the severity of illness.

[5] **Other risk factors**

Age may be an important predictor.\(^\text{83}\) More than half of paediatric cardiac arrest cases occurred in patients before age two, which represents a disproportionate distribution in a paediatric population.\(^\text{91, 108-110}\) Data showing differences in survival by age may be confounded by cause of cardiac arrest. As an example, cardiac arrests in infants are predominantly patients with Sudden Death Infant Syndrome (SIDS).\(^\text{83}\) Other risk
factors identified include: cause of the arrest, patient location at the time of the arrest and length of stay in hospital prior to ICU admission.\textsuperscript{111-113}

\textbf{[6] Nature of the ICU}

The nature of the PICU itself can affect patient outcomes. A study evaluating changes of outcomes within a single ICU over a 10-year period showed that increased ICU activity is significantly associated with prolonged severity-adjusted survival.\textsuperscript{114} Another study comparing the efficiency of open ICUs with closed ICUs showed that ICU and hospital length of stay and days on mechanical ventilation were lower in closed ICUs.\textsuperscript{115} A recent study (2007) showed that patients with acute lung injury in a closed-model ICU have reduced mortality.\textsuperscript{116}

A systematic review by Kane et al (2007) examined nursing staff patterns and their effects on patient outcomes and showed a significant association between nurse staffing and hospital-related mortality, failure to rescue and other patient outcomes.\textsuperscript{117} This review suggests that higher quality of hospital care, effective nurse retention strategies and implementation of collaborative evidence-based medicine lead to better patient outcomes.
CHAPTER 3
OUTCOMES BEYOND PICU SURVIVAL

Classically, the outcome of PICU admission has been assessed by ICU survival. There are relatively few studies evaluating cognitive or functional outcomes or quality of life after PICU. A recent systematic review identified 27 studies including 3,444 PICU survivors. The authors concluded that: [1] distinct sequelae in patients interfere with quality of life, [2] small numbers, methodological limitations and quantitative and qualitative heterogeneity hamper the interpretation of data, and [3] further well-designed prospective studies evaluating outcomes of critical illness are warranted.

3.1 Health-related Quality of Life

Health-related quality of life (HRQoL) is an important health outcome in adults and children. The original World Health Organization (WHO) definition of quality of life was “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” has evolved into a health-related concept that includes four essential domains: disease state and physical symptoms, functional status, psychological functioning and social functioning.

A prospective study (Knoester et al, 2008) evaluated 81 of 142 eligible children at 3 and 9 months after discharge over 3 years. They found worse motor functioning and HRQoL compared with the general population and this did not improve between
3 and 9 month assessments.\textsuperscript{8} The remaining four studies reporting HRQoL outcomes are of children admitted 9-17 years ago (Table 3.1). A Dutch study of 254 patients admitted to a PICU in 1991 used the Health Utilities Index and found that 25\% of children improved and 25\% had worsened from baseline.\textsuperscript{7} In an Indian study of 150 critically ill children reported at 1-year, 25\% of children were worse than baseline.\textsuperscript{5} An Australian study of 432 patients, treated between 1992-1994, reported 59\% of survivors had ‘good’ health-related quality of life and 11\% had ‘unfavourable’ outcome.\textsuperscript{4} Duration of ICU stay, comorbidities and severity of illness on ICU admission explained 33\% of the variability in HRQoL measurements.\textsuperscript{4} A subsequent study in the same hospital evaluated 3-year outcomes study of children admitted to an Australian PICU in 1995, and found 16.4\% of children had ‘poor’ HRQoL—defined as a Health State Utilities (HSU) Index of 0.29 or less.\textsuperscript{3}

Evaluations of cognitive outcomes in children with congenital heart disease have described considerable variability in outcome.\textsuperscript{121, 122} A recent study of 88 children with complex congenital cardiac disease showed significant morbidity: at 1 year of age, 65\% had neuromuscular abnormality, 11\% had sub-normal neurodevelopment and 48\% had psychomotor development scores of less than 70.\textsuperscript{123} In one single centre study of 26 children with hypoplastic left heart syndrome (HLHS) treated with heart transplantation, 39\% scored more than one standard deviation lower than the mean on the Vineland Adaptive Behaviour Scale.\textsuperscript{124} Other studies of children receiving chronic ventilation and following trauma show significant issues with HRQoL.\textsuperscript{125, 126}
TABLE 3.1: Studies reporting Health-related Quality of Life after PICU admission

<table>
<thead>
<tr>
<th>Study</th>
<th>Years studied</th>
<th>Duration of the study</th>
<th>n</th>
<th>Age</th>
<th>Duration of stay (days)</th>
<th>QoL measure</th>
<th>% 'Abnormal'</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemke 1995</td>
<td>1992</td>
<td>3 years</td>
<td>468</td>
<td>55m</td>
<td>4.4</td>
<td>MAHSC(^1)</td>
<td>27%</td>
<td>Favorable outcomes were observed even with large numbers of patients with pre-ICU health impairments</td>
</tr>
<tr>
<td>Morrison 2002</td>
<td>1992-1994</td>
<td>24 months</td>
<td>432</td>
<td>2.3 yrs</td>
<td>n/a</td>
<td>RAHC Measure of function (CRS+FRS)(^2)</td>
<td>40%</td>
<td>Children with poor outcomes are more likely to have significant comorbidities or a malignant diagnosis</td>
</tr>
<tr>
<td>Taylor 2003</td>
<td>1995</td>
<td>2-6 years</td>
<td>1032</td>
<td>19.3 m</td>
<td>1.1</td>
<td>MGOS(^3) HUI-1(^4)</td>
<td>16% MGOS 16% HUI-1</td>
<td>Majority of Children survive with good functional outcome and quality of life</td>
</tr>
<tr>
<td>Jayashree 2003</td>
<td>1999-2000</td>
<td>1 year</td>
<td>150</td>
<td>5.7 yrs</td>
<td>5.7</td>
<td>MAHSC(^1)</td>
<td>15%</td>
<td>Improvement could be seen in 4 domain specific parameters</td>
</tr>
<tr>
<td>Knoester 2008</td>
<td>2002-2005</td>
<td>9 months</td>
<td>81</td>
<td>5.8 yrs</td>
<td>5.0</td>
<td>TAPQOL-PF(^5) TACQOL-PF(^6) TACQOL-CF(^7)</td>
<td>Worse HRQOL(^8) than normal controls found on several domains</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HRQoL did not change significantly from 3 - 9 months</td>
</tr>
</tbody>
</table>

\(^1\) Multiattribute Health Status Classification
\(^2\) Royal Alexandra Hospital for Children Measure of Function (Clinical Rating Scale + Family Rating Scale)
\(^3\) Modified Glasgow Outcome Score
\(^4\) Health Utilities Index – Mark 1
\(^5\) TNO-AZL Preschool Children Quality of Life Questionnaire (ages 1 - 6 years)
\(^6\) TNO-AZL Children’s Quality of Life Questionnaire – Parent Form (ages 6 - 12 years)
\(^7\) TNO-AZL Children’s Quality of Life Questionnaire – Child Form (ages 8 - 16 years)
\(^8\) Health-Related Quality of Life
3.2 Longitudinal assessment of morbidity in other populations

Longitudinal outcomes have been studied in critically ill adults,\textsuperscript{127,128} adults following cardiac arrest,\textsuperscript{129} premature neonates,\textsuperscript{130} paediatric populations following trauma and traumatic brain injury, malignancy, and congenital malformation.\textsuperscript{131-136} A recent review suggested that long term outcomes research in adult critical care was still ‘in its infancy’.\textsuperscript{137} Current adult post-ICU studies are now beginning to evaluate HRQoL as a longitudinal measure.\textsuperscript{138} Studies that have evaluated these long-term outcomes show that survival of critical illness in adults and premature neonates is associated with significant morbidity as observed over several years following ICU admission.\textsuperscript{127,139} A Dutch study of adult ICU patients found low pre-admission HRQoL, which reduced following ICU discharge.\textsuperscript{140}

There are have been many studies evaluating long-term neonatal cognitive and functional outcomes in neonatal ICU survivors,\textsuperscript{130,141-143} showing speech and other problems at 3 years in 13\%,\textsuperscript{144} and 48\% functional impairment using the Vineland Adaptive Behaviour scale.\textsuperscript{130} Other long term studies of randomized clinical trials included assessments of respiratory function at 8-11 years of age,\textsuperscript{145} and development at school age.\textsuperscript{146}
CHAPTER 4
OUTCOME ASSESSMENT IN CRITICALLY ILL CHILDREN

International recommendations by the American Academy of Pediatrics, the American Heart Association (AHA), and the European Resuscitation Council suggest that survival be reported after admission to the ICU, general ward, rehabilitation unit, and/or discharge from hospital.\textsuperscript{47} Survival should also be reported 6 months after resuscitation, 1 year after resuscitation and longer at appropriate intervals. At a minimum, survival should be reported 24 hours after resuscitation.

In-ICU outcomes for children have been primarily assessed using organ dysfunction.\textsuperscript{1} The best validated measure for organ dysfunction in the PICU is the PELOD score.\textsuperscript{1} Cognitive function following ICU discharge is recognized as an increasingly important measure of the success of PICU.\textsuperscript{147} Coarse measures of functional outcomes (Pediatric Cerebral Performance Category and Pediatric Overall Performance Category) are recommended in the Utstein guidelines for reporting outcomes of CPR,\textsuperscript{148} however current National Institutes of Health (NIH) funded paediatric resuscitation trials are using the Vineland Adaptive Behaviour Scale as a primary outcome measure.\textsuperscript{149}
4.1 Assessment of cognitive and functional outcomes

4.1.1 Ratings of cognitive functioning

The Vineland Adaptive Behavioural Scale II (VABS-2) provides a parental rating of cognitive functioning from newborns to young adults. The scale is administered to parents/caregivers of the critically ill child. It can be completed in 20-60 minutes and is composed of 4 domains. Each domain comprises of 2 to 3 sub-domains. Domains include Communication (receptive, expressive, and written), Daily Living Skills (personal, domestic, and community), Socialization (interpersonal relations, play/leisure time, and coping skills) and Motor Skills (gross motor and fine motor).

The measure provides an overall adaptive behaviour composite score and a score for each domain. Its basal and ceiling criteria allow for a focused evaluation of each child’s skill level within a specific sub-domain and domain. VABS-2 scores are strongly correlated with other adaptive measures (Behaviour Assessment System for Children and Adaptive Behaviour System Assessment) and intelligence measures (Wechsler Intelligence Scales for Children and Wechsler Adult Intelligence Scale), and has been previously used to measure functional outcomes in studies of acquired neurological deficits and neuro-developmental disorders.

Scores of 85 or less are regarded as ‘moderately-low’ functioning, and scores of 70 and below can be used to represent ‘poor’ outcome.
4.1.2 Functional Assessment

Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC) scales describe the outcomes of paediatric intensive care by quantifying cognitive impairment and overall functional morbidity. Both of these outcomes have been shown to be associated with length of PICU stay, total hospital charges, discharge care needs and the Pediatric Risk of Mortality (PRISM) Score. The PCPC and POPC are recommended in the Utstein cardiac arrest reporting guidelines and are reliable, valid and easily utilized measures to quantify morbidity in critically ill children. Studies have demonstrated a significant relationship between PCPC scores and the Stanford-Binet Intelligence Quotient and the Bayley Mental Developmental Index and between POPC scores and the Bayley Psychomotor Developmental Index and the Vineland Adaptive Behaviour Scale scores. It is important to note that the PCPC and POPC are coarse assessment tools and may overlook subtle yet important abnormalities. However, they can be considered effective in baseline assessments and as ongoing assessments of functional outcomes.

4.2 Assessment of Health-related Quality of Life

HRQoL assessments can be used to indicate health status, measure response to treatment, identify psychological risk, predict outcomes and evaluate disease progression.
Utility is a distinct type of HRQoL assessment to gauge preferences for health states. Elicitation of preferences can be determined directly by using a rating scale, such as the visual analogue scale (VAS), or either of the more complex time trade-off and standard gamble techniques. Preferences can also be deduced indirectly through validated questionnaires such as the Health Utilities Index (HUI). Both assess HRQoL through multiple attributes. Preference-based measures of HRQoL have a special role in economic evaluations of health interventions, as preferences for diverse health states can be integrated into quality-adjusted life years (QALY). The QALY is a standardized outcome measure endorsed by provincial and national agencies. Calculation of the area under the curve of repeated utility measurements over time, allows calculation of the number of QALYs. One quality adjusted life year is equivalent to one year in perfect health and a utility of zero represents death. The QALY can be also used to compare the cost-effectiveness of different interventions in different patient populations.

The issue with HRQoL measurements in children is the use of preference-based HRQoL measures—measures providing a single number (or index) representing the net aggregate impact of physical, emotional and social functioning on quality of life—is less well-developed than in adults. Children represent a population with unique measurement challenges. These include children’s understanding of the questions being asked, using parents as proxies, time perceptions problems, assessing children’s cognitive functioning as it may be dynamic over time and their severity of
disease.\textsuperscript{156-159} Also, HRQoL assessments for children are more recent developments and as a result, there is less experience with them.\textsuperscript{157}

\textbf{4.2.1 Health Utilities Index}

The Health Utilities Index is a generic health status instrument,\textsuperscript{160} which has been used to evaluate diverse North American populations,\textsuperscript{161} and has been incorporated into the National Population Health Survey and the National Health Longitudinal Survey of Children and Youth, allowing the generation of norms for all age groups. The first version of the HUI (HUI-1) was developed to evaluate outcomes for very-low birth weight infants and specifically address the global morbidity burden of childhood cancer.\textsuperscript{162-164} HUI-2 was developed to apply to various groups with a wide range of predicted global morbidity burdens.\textsuperscript{165} HUI-3 was developed to address some of the drawbacks of HUI-2, to be applicable in clinical and general population studies and to have structural independence among the attributes.\textsuperscript{165}

The HUI-3 uses multi-attribute utility theory to derive utilities for diverse health states. This multi-attribute system provides a holistic description of patients, facilitating the examination of multiple sequelae and varying levels of severity.\textsuperscript{160} The HUI-3 consists of 8 attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. Each attribute of the HUI-3 consists of 5 to 6 levels. The organization of attributes by level of functioning is referred to as the HUI classification system. The HUI-3 can be used to summarize an individual’s health status. A multi-attribute utility function is used to assign pre-determined weights to each level of
each attribute. The weighted attribute values are then combined to derive a single utility using a scoring formula. The HUI has been successfully used in paediatric populations and is considered to be reliable in children 4-18 years of age.\textsuperscript{160,166}

4.2.2 Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) is an extensively validated multi-attribute quality of life instrument that can assess HRQoL in children from 2-18 years of age.\textsuperscript{167} It distinguishes between healthy children and children with acute and chronic health conditions and distinguishes disease severity within a chronic health condition. It is responsive to clinical change over time. The PedsQL-4 is a 23-item measure that consists of four multidimensional scales: Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items) and three summary scores: physical health, psychosocial and total.\textsuperscript{167} The PedsQL-4 parent proxy-report (ages 2–18) has demonstrated internal consistency reliabilities for the four multidimensional scales and for the total score (23 items; Cronbach’s alpha =0.90).\textsuperscript{168,169} The PedsQL has been used in populations with cerebral palsy, diabetes, rheumatic conditions, heart disease, respiratory disease, traumatic brain injury and malignancy.\textsuperscript{132,135,136,167,170-176}

4.2.3 Visual Analogue Scale

Visual Analogue Scale (VAS) including the rating scales such as the ‘feeling thermometer’,\textsuperscript{177} is another method by which preferences for health states can be measured. The VAS was originally used for the measurement of pain relief but it is
widely used to elicit an individual’s health value function either through measuring
their preferences for specific health states or through evaluating their own health-
related quality of life.\textsuperscript{178-184} In VAS ratings, subjects use a graphic to rate global quality
of life on a linear VAS that was anchored on death (0.0) and perfect health (1.0).\textsuperscript{183,185}
This results in a global rating of quality of life on a 0.0 to 1.0 scale, which can be
directly converted into a utility value or by use of a power function.\textsuperscript{186} The use of a
power function to convert the VAS into a measured HUI-3 utility value (utility value=
VAS\textsuperscript{0.559}) has an r\textsuperscript{2} of 0.77, suggesting that VAS may be a useful adjunct to quality of life
measurement in critically ill children.\textsuperscript{186}
CHAPTER 5
CAREGIVERS OF CRITICALLY ILL CHILDREN

The ICU setting is considered to be a stressful environment by parents/caregivers that is characterized by frequent uncertainty, risk of patient mortality, and busy clinicians.\(^\text{187}\) It is recommended that healthcare providers communicate adequately with family members and involve families during decision making to ease their stress.\(^\text{187}\) Strong communication between family and healthcare providers foster the family’s adjustment to their child’s illness.\(^\text{188}\) Poor communication contributes to inaccurate expectations, compounds fear, increases stress for families and decreases their involvement and overall satisfaction during their ICU stay.\(^\text{188}\)

5.1 Caregiver satisfaction

Measuring family satisfaction is related to perceived perceptions of the caregivers.\(^\text{189}\) Satisfaction is considered to be an important method for assessing one aspect of the quality of care in the ICU,\(^\text{187,190}\) and may help identify the burden for caregivers of critically ill children.\(^\text{191,192}\) A study in Brazil found that the most important factors promoting family satisfaction were accessibility of ICU doctors, concordance (between family and healthcare providers) about patient’s treatment options, and demonstration of empathy for family emotions.\(^\text{188}\) A study surveying the family members of patients who died in the ICU found that 83\% of family members were
satisfied during their ICU stay.\textsuperscript{193} A 2007 study noted that families of patients dying in the ICU reported higher satisfaction with their ICU experience than the families of survivors.\textsuperscript{187} This could be due to increased communication by healthcare providers with family members of dying children and allowing for family to be increasingly involved in decision making at the end-of-life.

Satisfaction measures allow for an in-depth understanding of the perceived care of critically ill children by their family members.\textsuperscript{194} A 2005 systematic review on satisfaction instruments showed that most satisfaction rating scales use Likert-type scales.\textsuperscript{194} The authors of this review reported that Likert scales may cause difficulties for interpretation due to neutral choices being the most frequent responses.

\section*{5.2 Factors potentially influencing satisfaction}

\subsection*{5.2.1 Caregiver presence}

In 2000, the American Heart Association and other national organizations endorsed a guideline that recommended parents be given the option to be present during their child’s invasive procedure and/or resuscitation.\textsuperscript{195-198} Studies have demonstrated many positive benefits of family presence, such as increased family understanding of the child’s situation, facilitating closure and healing, helping families see that everything was done to save their loved one, and calming effect for both family and child.\textsuperscript{195,199-205} Many healthcare providers, however, are not in favour of family being present due to concerns of family interfering with the resuscitation procedure,
increasing stress on healthcare providers, decreasing effectiveness of resuscitation team members, requiring additional staff resources, compromising teaching opportunities and increasing risk of litigation.199-206

5.2.2 Caregiver anxiety and post-traumatic stress

Parents are continually distressed when their child is hospitalized due to shock, uncertainty and loss of control.207 One study showed that caregiver restrictions on overnight stay caused systematic disruption of family supports and routine, contributing to increased stress and anxiety.207 Another study showed that caregiver anxiety was independently associated with one patient-related factor, mechanical ventilation, and two family-related factors, Catholic religion and gender.208 A Greek study showed that early anxiety responses predicted the development of post-traumatic stress symptoms with women exhibiting higher levels of distress and more symptoms related to post-traumatic stress than men.209 This was consistent with other studies that showed that bereaved and non-bereaved participants had high rates of post-traumatic stress and complicated grief,210 and that severe post-traumatic stress was associated with increased rates of anxiety and depression and decreased quality of life for caregivers.211
HYPOTHESES
CHAPTER 6

HYPOTHESES

6.1 Primary hypotheses

We evaluated the following primary hypotheses:

[1] Children surviving PICU have significant cognitive morbidity and reduced health-related quality of life

[2] The use of more intense resuscitation therapies is associated with worse cognitive and functional outcomes and reduced health-related quality of life

[3] Increasing severity of illness during ICU stay is associated with worse cognitive and functional outcomes and reduced health-related quality of life

6.2 Secondary hypotheses

We evaluated the following secondary hypotheses:

[4] Caregivers are generally satisfied with their interaction with healthcare providers and are involved in the decision making for treatment options
METHODOLOGY
CHAPTER 7
METHODS

7.1 Design

A prospective observational study of a cohort of children urgently admitted to PICU from hospital ward.

7.2 Setting

Eligible patients were in either the Paediatric Intensive Care Unit (PICU) or the Cardiac Critical Care Unit (CCCU) at the Hospital for Sick Children in Toronto, Ontario, Canada. The PICU has 18 beds and 1100 annual admissions and the CCCU has 18 beds and 800 annual admissions. The study began on May 2008 with enrolment ending in December 2008.

7.3 Population

Eligible children were:

[1] Ages greater than or equal to 1 month and less than or equal to 18 years at ICU admission. The outcomes used in the study were validated across the neurodevelopmental ages.
[2] Either urgently admitted to one of the ICUs of the Critical Care Medicine Program (PICU or CCCU) at the Hospital for Sick Children from a non-ICU inpatient area or placed on ECMO in the ICU or had a cardiac arrest in the ICU, if they were not urgently admitted to the ICU.

We studied children one month and older in order to permit accurate baseline assessments.

We excluded patients:

[1] Who did not survive over 24 hours after admission due to morbidity being the primary focus of the study

[2] Admitted from the operating room after an elective procedure

[3] Less than one month of age and over 18 years of age at ICU admission

[4] Who had non-English speaking caregivers

[5] Whose caregivers were identified as likely to engage (or engaged) in medico-legal proceedings as determined by the critical care research nurses and ICU staff physicians

7.4 Definitions and representations

| **Urgent ICU admission** | Admission with less than 6 hours notice from the decision to admit to the ICU. |
In-ICU ECMO

Patients that were physiologically unstable and treated with mechanical circulatory/respiratory support, either to prevent a cardiac arrest or treat a patient who was having or had a cardiac arrest.\(^{139}\)

In-ICU cardiac arrest

Children who have had a cardiac arrest. \textit{Cardiac arrest} was defined as the cessation of cardiac mechanical activity that is confirmed by the absence of signs of circulation which implies, but is not limited to, lack of responsiveness, lack of movement, lack of breathing, and the absence of a pulse.\(^{84}\)

Health-related Quality of Life

The perceived physical and mental health of the patient over time by caregivers of the patient.

Intensity of resuscitation

Represented by the durations of mechanical ventilation, epinephrine dosage, haemodialysis, cardiopulmonary arrest, ECMO and cardiopulmonary bypass.

Severity of Illness

Represented by the PELOD score, minimum transcutaneous oxygen saturation, minimum venous oxygen saturation and length of ICU stay.

7.5 Outcomes

7.5.1 Primary outcome

The primary outcome was the adaptive behaviour composite score from the Vineland Adaptive Behavioural Scale (VABS-2) at 1-month post ICU admission. The VABS-2 provided an extensive global assessment of neurocognitive functioning. The VABS-2 population mean is 100 with a standard deviation of 15. Scores of 70 and below were described as a ‘poor’ outcome.\(^{150}\) This scale was based solely on information completed by the caregiver and therefore no direct observation or monitoring of the child was required by a healthcare provider for accurate completion of this measure.
The VABS-2 was not assessed at baseline or 1-week due to possible respondent burden for caregivers of critically ill children.

7.5.2 Secondary outcomes

[1] Health-related Quality of Life was assessed with the HUI-3, PedsQL-4 and VAS. These three scales are reliable and have been validated in paediatric populations.\textsuperscript{160, 175, 183} The HUI-3 and VAS was assessed at baseline, 1-week and 1-month. The PedsQL-4 was assessed at 1-month. Children represented a population with unique HRQoL measurement challenges. The use of repeated measurements with a number of validated and accepted instruments and a consistent respondent was thus employed to overcome these limitations.

[2] Functional Outcomes were assessed with the PCPC and POPC at baseline and 1-month. These measures are recommended by the Utstein guidelines for reporting outcomes of paediatric resuscitation.\textsuperscript{46} The PCPC and POPC do not allow for detailed measurements nor do they detect subtle changes in functioning or cognition. They were included to assess daily functioning and to enable comparisons with the VABS-2 and the predictive in-ICU variables.

[3] Caregiver perceptions were assessed at 1-month using a self-designed and pre-tested caregiver perceptions form. Pre-testing was performed by physicians, nurses and parents to determine the overall flow, timing and face-validity of the measure. The survey consisted of 4 questions inquiring on (i) caregiver satisfaction with healthcare providers, (ii) caregiver presence during resuscitation, (iii) caregiver
involvement in deciding treatment options, and (iv) caregiver reflections on events if they were to be re-enacted. A comments section was included for descriptive purposes. Completion of this form took approximately 10 minutes and was completed by two caregivers of the child, when feasible (Table 7.1).

**TABLE 7.1: Schedule of assessments for primary and secondary outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Questionnaire</th>
<th>Baseline</th>
<th>1-week</th>
<th>1-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive</td>
<td>VABS-2</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>HRQoL</td>
<td>HUI-3</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PedsQL-4</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Functional</td>
<td>PCPC</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>POPC</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceptions</td>
<td>Caregiver perceptions</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Outcomes were assessed at baseline, 1-week and 1-month. The PCPC, POPC, HUI-3 and VAS were assessed at baseline. The HUI-3 and VAS were assessed at 1-week. The VABS-2, PCPC, POPC, HUI-3, VAS, PedsQL-4 and caregiver perceptions were assessed at 1-month.
7.6 Predictive factors

Fourteen factors that were potentially predictive of outcome were assessed:

**Patient demographics and baseline characteristics:**

[1] Baseline neurologic state was assessed by parents on the PCPC measure at baseline

[2] Reason for admission was assessed by grouping baseline disease and reason for ICU admission and classifying them as one of 5 categories: respiratory, circulatory, neurological, oncological and other. This was performed after consultation with a critical care expert due to the complexities of this classification in a modest sample size drawn for a quaternary referral centre population.

[3] Age (in months) of child

[4] Sex of child

**Severity of Illness (assessed daily):**

[5] Daily Pediatric Logistic Organ Dysfunction Score (dPELOD) – obtaining one score per ICU day

[6] Minimum transcutaneous oxygenation saturation – obtaining the minimum arterial oxygenation per ICU day

[7] Minimum (mixed) venous oxygen saturation – obtaining the minimum venous oxygenation per ICU day
[8] Length of Stay (LOS) in the ICU

Intensity of resuscitation (assessed daily):

In-ICU interventions: [9] mechanical ventilation (yes/no), [10] epinephrine dosage (yes/no), and [11] haemodialysis (yes/no)


7.7 Study procedures

7.7.1 Eligibility, approach and consent

Eligible patients were identified by daily screening of recently admitted ICU patients. Charts of eligible patients were examined by a research team member and later confirmed by trained research nurses. A responsible physician or another health care provider directly involved with the patient’s care (e.g. the bedside nurse) approached parents/guardians (while in the ICU) at an appropriate time to make sure if it is okay to have a discussion about the study with a member of the study team. If parents/guardians agreed, a member of the study team discussed the purpose, description, confidentiality, harms and benefits of the research study and provided them with a consent form. If parents/guardians were willing to participate, the consent form was signed by the parent/guardians and the member of the study team. A copy of the consent form was given to parents/guardians, another copy was placed
in the patient’s medical chart and the original consent form was placed in the research office.

7.8 Measurements

7.8.1 Baseline

Following consent, caregivers completed the following assessments: PCPC, POPC, HUI-3 (if child was 4-18 years of age) and VAS. The reason for ICU admission, baseline disease, age and gender were collected by direct abstraction from the patient medical records.

7.8.2 During ICU admission

An ICU day was defined as beginning at 7:00am and ending at 6:59am the following day. Each day the child was in the ICU, a member of the study team documented the use of mechanical ventilation, administration of epinephrine, the use of haemodialysis, the duration of cardiac arrest in minutes, ECMO in hours, cardiopulmonary bypass in minutes, the minimum transcutaneous oxygenation saturation, the minimum (mixed) venous oxygen saturation and the daily PELOD score for the given ICU day.

At or before ICU discharge, the caregivers of the child were contacted to arrange meetings for the 1-week assessment. Efforts were made to coordinate the 1-month follow up with a hospital visit, if feasible. Caregivers were given a contact phone number at the research office.
7.8.3 One week after-ICU admission

The 1-week assessment was comprised of two HRQOL questionnaires: HUI-3 and VAS, both completed by the parent-caregiver. Completion was either in-person if respondent was in the hospital, by telephone (if preferred by the respondent) or by mail. The 1-week package was completed in approximately 10 minutes. The outcomes were ideally assessed within 1-2 days of the 1-week date.

7.8.4 One month after-ICU admission

The 1-month assessment was comprised of 7 questionnaires: VABS-2, PCPC, POPC, HUI-3, PedsQL-4, VAS, and caregiver perceptions rating forms. Each questionnaire was completed by the parent-caregiver. Completion was either in-person if the respondent had reason to be in the hospital, by telephone (if preferred by the respondent) or by mail. Completion required 45-60 minutes. The outcomes were ideally assessed within 1 week of the 1-month date.

7.9 Data management

Measurement of each predictive factor was given one score per patient for his/her entire ICU stay. The scores for the variables were assessed as follows: [1] PCPC score at baseline, [2] total compression duration in minutes, [3] number of days in the ICU, [4] number of days on mechanical ventilation, [5] PELOD score for the entire ICU stay, [6] number of days that epinephrine was administered, [7] number of days on

7.10 Analyses

7.10.1 Descriptive analyses

Demographics: the number of children that were screened, approached and enrolled was reported. Children that died, withdrew, completed 1-week, were lost to follow-up and completed 1-month was reported.

Predictive factors: The mean, standard deviation, median and interquartile range of the predictive factors were reported in a tabular format. The predictive factors with greater variability were illustrated graphically.

Primary outcome: VABS-2 was presented graphically to illustrate sample distribution. Mean, standard deviation, median and interquartile range was calculated and the proportion of children with a poor outcome—defined as an adaptive behavioural score of 70 and below—was reported.

Secondary outcomes: The PCPC, POPC, HUI-3, VAS, caregiver satisfaction and caregiver involvement were illustrated graphically. The means were compared in
relation to time for the PCPC, POPC, HUI-3 and VAS. The mean, standard deviation, median and interquartile range was reported for the PedsQL. The means, medians, and interquartile range were reported for caregiver satisfaction with healthcare providers, caregiver involvement in making decisions and caregiver decisions if events were to be re-enacted.

7.10.2 Primary regression analysis

Multivariable regression analysis was performed to evaluate factors potentially associated with VABS-2 at one month post-ICU admission. The primary regression model consisted of three steps: [1] performing bivariate analyses with the predictive factors to evaluate its effect on the VABS-2, [2] forcing clinical relevant variables—baseline PCPC score and compression duration (in mins), and [3] performing a backward multivariable regression using the factors that were significant with a p<0.2 in step 1 and the factors in step 2.

In step 1, linear regression was performed on variables [1] to [12], t-test on variable [13] and analysis of variance on variable [14] (Data Management, Table 7.2). Predictive factors that were significant with a p-value of ≤0.2 were carried on to step 3, backward multivariable regression, with the clinically relevant variables in step 2 forced into each step.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Type of data</th>
<th>Expected range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>Categorical</td>
<td>1-6</td>
</tr>
<tr>
<td>Compression duration</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>ICU days</td>
<td>Continuous</td>
<td>1-71</td>
</tr>
<tr>
<td>Mechanical ventilation (days)</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>PELOD score</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>Epinephrine (days)</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>Hemodialysis (days)</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (hours)</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>ECMO (hours)</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>Continuous</td>
<td>0-100</td>
</tr>
<tr>
<td>(minimum)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous oxygen sat. (days below 40)</td>
<td>Continuous</td>
<td>0-71</td>
</tr>
<tr>
<td>Age (months)</td>
<td>Continuous</td>
<td>1-288</td>
</tr>
<tr>
<td>Gender</td>
<td>Dichotomous</td>
<td>male, female</td>
</tr>
<tr>
<td>Reason for admission category</td>
<td>Categorical</td>
<td>respiratory, circulatory, neurological, oncological, other</td>
</tr>
</tbody>
</table>
Backward multivariable regression began with the saturated model. Variables with the highest associated p-value were eliminated in an iterative process until the final model consisted of variables that were significant with a p≤0.05. These factors were considered to be significantly associated with the VABS-2. Post-regression multicollinearity analysis was performed to detect collinearity between the significant predictive factors. A variance inflation factor (VIF) of less than 10 was considered to be low collinearity.

7.10.3 Secondary analyses

Regression analyses of secondary outcomes

Health-related quality of life outcomes: HUI-3, PedsQL-4 and VAS, and functional outcomes: PCPC and POPC, were evaluated with bivariate and backward multiple variable regression using the same steps as the primary regression analysis. Post-regression multicollinearity analyses were performed to detect collinearity between the significant predictive factors.

Repeated measures analyses

Time intervals of the PCPC and the POPC were each analyzed using paired sample t-tests. Time intervals of the HUI-3 and VAS were each analyzed using repeated measures ANOVA. The Tukey-Kramer adjustment was performed to detect significant differences between time intervals.
**Respondents vs. Non-respondents**

An independent samples t-test was performed to test the difference in baseline scores of PCPC, POPC, HUI-3 and VAS between respondents at 1-month and non-respondents at 1-month.

**Correlation analyses**

The relationships between related outcomes: the VABS-2 and PCPC, POPC, PedsQL-4, VAS and HUI-3 were evaluated using correlation analyses as were the relationships between the HRQoL measures. A correlation coefficient of 0.5 was considered to be a ‘high’ correlation (after consultation with a statistician).

**Caregiver perceptions analyses**

The caregiver perceptions rating form was described according to caregivers’ satisfaction with their interaction with healthcare providers, their presence during what they perceived as a resuscitation treatment, their involvement in deciding the treatment and their reflections over the decisions that were made. The satisfaction and involvement ratings of caregivers present during the resuscitation of their child were compared to caregivers not present during the resuscitation. Correlation analyses were performed to observe the relationship between ratings of neurocognitive functioning and ratings of caregiver satisfaction and caregiver involvement. A correlation coefficient of 0.5 was considered to be a ‘high’ correlation. Concordance was evaluated when two caregivers completed the form.
7.11 Sample Size and Feasibility

Approximately 400 children older than 1 month are urgently admitted to the Critical Care Program at the Hospital for Sick Children each year. There are 50-60 code blue events and 60-70 children treated with ECMO, many of whom have been urgently admitted to the ICU. Given 50% recruitment and retention of eligible patients, we anticipated that we would enrol 55-60 children within 6 months of starting the study. Given the anticipated 15% mortality, enrolment of 55-60 children over 6 months would allow 45-50 ICU-survivors to be studied. Analyses were performed with recognition that evaluation of 14 variables in a sample size of 50 ICU survivors may be underpowered.
RESULTS
CHAPTER 8
DEMOGRAPHICS

Patients were screened on 87 days over a 24 week period, beginning in May 2008 and ending in December 2008. There were 172 eligible patients. The study team were asked not to approach 24 children due to competition with other studies or due to concerns about caregivers being overwhelmed. Consent discussion occurred with parents/guardians of 86 patients: 30 (35%) declined and 56 (65%) patients and 66 parents/guardians were enrolled in the studies of patient outcomes and caregiver perceptions respectively. Of the 56 patients, 48 (86%) completed the 1-week, 2 withdrew from the study, 5 died, 14 (25%) were lost to follow-up and 42 (75%) completed the 1-month assessment. The results of caregiver perceptions study are reported in chapter 13.

Of the 56 enrolled patients, the mean age was 74 months (6 years and 2 months) with a standard deviation of 67 months (Figure 8.1). Thirty-five (63%) patients were male and 21 (37%) were female. The reason for admission was classified as follows: 21 (38%) respiratory, 15 (27%) neurological, 13 (23%) circulatory, 3 (5%) oncological and 4 (7%) other.

Pediatric Cerebral Performance Category (PCPC) score at baseline was recorded in 54 (96%) patients with a median of 1.0 (IQR: 1.0-2.0). The total length of ICU stay for the combined population was 550 days with a median of 6.5 days (IQR:
3.0-14.0) (Figure 8.2). The total number of days on mechanical ventilation for the combined population was 312 days with a median of 2.0 (IQR: 0.0-8.0) (Figure 8.3). Each patient was given a PELOD score for their entire ICU stay; median: 21.0 (IQR: 20.0-36.0) (Figure 8.4). The minimum transcutaneous oxygen saturation was recorded for each child during their entire ICU stay; median: 86.0 (IQR: 73.0-93.0) (Figure 8.5). Fourteen children (25%) had a documented venous saturation. Two children (3 days) had a venous saturation less than 40.

From 56 patients, two patients had a cardiac arrest for a total of 3 episodes and a total duration of 55 minutes. Two children were on cardiopulmonary bypass for a total of 2 episodes and a total duration of 164 minutes. Two children were on ECMO for a total of 2 episodes and a total duration of 115 hours. Epinephrine was administered in 4 children for a total of 19 days. No patients received haemodialysis during the study. Therefore, it was excluded for the univariate, bivariate and backward multivariable regression analyses (Table 8.1).
FIGURE 8.1: Age Distribution

From 56 enrolled patients, the mean age was 74 months (6 years and 2 months) with a standard deviation of 67 months.
The total ICU stay for the sample of 56 children was 550 days. The median was 6.5 days (IQR: 3.0-14.0).
FIGURE 8.3: Mechanical Ventilation

56 children were mechanically ventilated for a total of 312 days. The median was 2.0 (IQR: 0.0-8.0).
Each patient was given a PELOD score for their entire ICU stay. The mean was 21.0 (IQR: 20.0-36.0).
The minimum transcutaneous oxygen saturation was recorded for each child during their ICU stay. The median was 86.0 (IQR 73.0-93.0).
TABLE 8.1: Univariate analyses of predictive factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Lower quartile</th>
<th>Upper quartile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>73.5</td>
<td>67.1</td>
<td>50.5</td>
<td>14.0</td>
<td>136.5</td>
</tr>
<tr>
<td>PCPC Baseline</td>
<td>1.6</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>ICU days</td>
<td>9.8</td>
<td>9.0</td>
<td>6.5</td>
<td>3.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Mechanical ventilation days</td>
<td>5.6</td>
<td>7.6</td>
<td>2.0</td>
<td>0.0</td>
<td>8.0</td>
</tr>
<tr>
<td>PELOD score</td>
<td>26.4</td>
<td>13.9</td>
<td>21.0</td>
<td>20.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>78.6</td>
<td>19.8</td>
<td>86.0</td>
<td>73.0</td>
<td>93.0</td>
</tr>
<tr>
<td>Venous oxygen sat.</td>
<td>0.1</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Compression duration</td>
<td>1.0</td>
<td>6.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>2.9</td>
<td>18.9</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ECMO</td>
<td>2.1</td>
<td>11.2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.3</td>
<td>1.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

An ICU day was defined as beginning at 7:00am and ending at 6:59am the following day. Each day, a member of the study team documented the compression duration, the ICU day number, use of mechanical ventilation, PELOD score, use of epinephrine, use of haemodialysis, duration of cardiopulmonary bypass, duration of ECMO, minimum transcutaneous oxygen saturation and the minimum venous oxygen saturation. Each factor was then given one score per patient for his/her entire ICU stay and were assessed as follows: [1] PCPC score at baseline, [2] total compression duration in minutes, [3] number of days in the given ICU stay, [4] number of days on mechanical ventilation, [5] PELOD score for the entire ICU stay, [6] number of days that epinephrine was administered, [7] number of days on haemodialysis, [8] total minutes on cardiopulmonary bypass, [9] total hours on ECMO, [10] minimum transcutaneous oxygen saturation for the entire ICU stay, [11] number of days venous saturation was below 40.
CHAPTER 9
RATINGS OF NEUROCOGNITIVE FUNCTIONING

The Vineland Adaptive Behaviour Scale (VABS-2) was assessed on 40 patients. Thirty-six (90%) measures were appropriately scored. The VABS-2 had a mean: 84.8, SD: 24.9, median: 86 and IQR: 67-100 (n=36) (Figure 9.1). Ten (28%) patients had a poor outcome, score of 70 and below.

9.1 Association between VABS-2 and predictive factors

In the bivariate analyses of the VABS-2 and the 14 predictive factors, 7 factors were significantly associated with decreasing the VABS-2 at 1-month (p<0.2): [1] greater PCPC score at baseline (p=<0.001), [2] longer compression duration (p=0.120), [3] longer ICU stay (p=0.009), [4] greater number of days on mechanical ventilation (p=0.006), [5] longer duration of ECMO (p=0.119), [6] lower transcutaneous oxygen saturation (p=0.006) and [7] greater number of venous oxygen saturation days that were less than 40 (p=0.132) (Table 9.1).

The backward multivariable regression model eliminated the following factors in each subsequent step (in order): number of days venous oxygen saturation was less than 40 (exit p=0.800), total ECMO hours (exit p=0.832), days on mechanical ventilation (exit p=0.356) and length of ICU stay (exit p=0.414).
Factors that were significantly associated with decreasing VABS-2 at 1-month were greater PCPC score at baseline (p=<0.001, regression coefficient -12.44), longer compression duration (p=0.021, regression coefficient -1.14) and lower minimum transcutaneous oxygen saturation (p=0.025, regression coefficient +0.39). Therefore, for every point increase on the PCPC score, there was a reduction of 12.44 on the VABS-2. For every minute added to the compression duration, VABS-2 decreased by 1.14. For every increase of one percent in the transcutaneous oxygen saturation, VABS-2 increased by 0.39. The adjusted r² of this model was 0.494 (n=36) (Table 9.1).

Post-regression multicollinearity analyses showed low collinearity (VIF of less than 10) between PCPC score, compression duration and transcutaneous oxygen saturation in its association with VABS-2 (Table 9.2).

9.2 Relationship between VABS-2 and secondary outcomes

The VABS-2 was significantly correlated with daily functioning: PCPC (r=-0.681, p=<0.001, n=35) and POPC (r=-0.566, p=<0.001, n=35). The VABS-2 was significantly correlated with one HRQoL outcome: VAS (r=+0.481, p=0.003, n=36) and was not significantly correlated with HUI-3 (r=+0.188, p=0.503, n=15) and PedsQL-4 (r=+0.279, p=0.234, n=20) (Table 9.3).
36 (90%) VABS-2 measures at 1-month were successfully scored. The mean VABS-2 was 85(±25) (compared to the population mean of 100(±15)).
TABLE 9.1: Backward multivariable regression: VABS-2

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Bivariate p-value</th>
<th>Multivariable exit p-value</th>
<th>Regression Coefficient</th>
<th>Final p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC baseline</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-12.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compression duration</td>
<td>0.120</td>
<td>-</td>
<td>-1.14</td>
<td>0.005</td>
</tr>
<tr>
<td>ICU days</td>
<td>0.009</td>
<td>0.414</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.006</td>
<td>0.356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PELOD score</td>
<td>0.258</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.521</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>0.957</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>0.119</td>
<td>0.832</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>0.006</td>
<td>-</td>
<td>+0.39</td>
<td>0.025</td>
</tr>
<tr>
<td>Venous oxygen sat.</td>
<td>0.132</td>
<td>0.800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.950</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.401</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for admission</td>
<td>0.889</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with the VABS-2 one month after ICU admission. The regression coefficients are not standardized units of measure. Significant variables are marked with grey highlight.
### TABLE 9.2: Multicollinearity of predictive factors in VABS-2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t-value</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>-12.437</td>
<td>3.125</td>
<td>-3.98</td>
<td>&lt;0.001</td>
<td>1.169</td>
</tr>
<tr>
<td>Compression duration</td>
<td>-1.141</td>
<td>0.377</td>
<td>-3.03</td>
<td>0.004</td>
<td>1.024</td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>+0.390</td>
<td>0.165</td>
<td>2.36</td>
<td>0.025</td>
<td>1.168</td>
</tr>
</tbody>
</table>

A variance inflation factor (VIF) is a method of detecting the severity of multicollinearity. A VIF of 10 or greater illustrates that the variable may be correlated with another variable, which requires further investigation.

PCPC score at baseline, total compression duration in minutes and minimum transcutaneous oxygen saturation were not significantly correlated with one another.
TABLE 9.3: Correlation between VABS-2 and secondary outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>VABS-2</th>
<th>r-value</th>
<th>p-value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC</td>
<td></td>
<td>-0.681</td>
<td>&lt;0.001</td>
<td>35</td>
</tr>
<tr>
<td>POPC</td>
<td></td>
<td>-0.566</td>
<td>&lt;0.001</td>
<td>35</td>
</tr>
<tr>
<td>HUI-3</td>
<td></td>
<td>+0.188</td>
<td>0.503</td>
<td>15</td>
</tr>
<tr>
<td>PedsQL-4</td>
<td></td>
<td>+0.279</td>
<td>0.234</td>
<td>20</td>
</tr>
<tr>
<td>VAS</td>
<td></td>
<td>+0.481</td>
<td>0.003</td>
<td>36</td>
</tr>
</tbody>
</table>

Correlational analyses were performed with the VABS-2 and PCPC, POPC, HUI-3, PedsQL and VAS. VABS-2 was significantly correlated with PCPC, POPC and VAS. Significant correlations are marked with grey highlight.
CHAPTER 10
DAILY FUNCTIONING

The Pediatric Cerebral Performance Category (PCPC) and the Pediatric Overall Performance Category (POPC) assessed daily functioning for ages 0-18.

10.1 Pediatric Cerebral Performance Category

The PCPC at 1-month was assessed in 39 (70%) patients. The PCPC score did not significantly change from baseline to 1-month (1.65 to 1.77, p=0.57) (Figure 10.1). At 1-month, 8 (21%) children had poor daily functioning, a PCPC score of 3 or less.

10.1.1 Association between PCPC and predictive factors

In the bivariate analyses of the PCPC and the 14 predictive factors, 10 factors were significantly associated with increasing PCPC at 1-month (p<0.2): [1] greater PCPC score at baseline (p=<0.001), [2] longer compression duration (p=0.039), [3] longer ICU stay (p=0.001), [4] greater number of days on mechanical ventilation (p=<0.001), [5] greater PELOD score (p=0.033), [6] greater number of days on epinephrine (p=0.137), [7] longer duration of ECMO (p=0.017), [8] lower transcutaneous oxygen saturation (p=0.006), [9] greater number of days that venous oxygen saturation was less than 40 (p=0.017) and [10] younger age (p=0.199) (Table 10.1).
The backward multivariable regression model eliminated the following factors in each subsequent step (in order): minimum transcutaneous oxygen saturation (exit \( p=0.353 \)), age (exit \( p=0.340 \)), number of days venous oxygen saturation was less than 40 (exit \( p=0.490 \)), PELOD score (exit \( p=0.455 \)), length of ICU stay (exit \( p=0.284 \)), total ECMO hours (\( p=0.227 \)) and number of days on epinephrine (exit \( p=0.160 \)).

Factors that were significantly associated with increasing PCPC score at 1-month were greater PCPC score at baseline (\( p<0.001 \), regression coefficient +0.58), longer compression duration (\( p=0.010 \), regression coefficient +0.04) and greater number of days on mechanical ventilation (\( p=0.006 \), regression coefficient +0.05). Therefore, for every point increase on the PCPC score at baseline (a worse score), the PCPC score at 1-month increased by 0.58. For every 25 minutes increase in compression duration, PCPC score at 1-month increased by 1. For every additional 20 days on mechanical ventilation, PCPC score at 1-month increased by 1. The adjusted \( r^2 \) of this model was 0.604 (\( n=39 \)) (Table 10.1).

Post-regression multicollinearity analyses showed low collinearity (VIF of less than 10) between PCPC score, compression duration and mechanical ventilation days in its association with PCPC score at 1-month (Table 10.2).

**10.1.2 PCPC respondents vs. non-respondents at 1-month**

There was no significant difference in PCPC baseline scores between respondents at 1-month and non-respondents at 1-month (1.67 to 1.60, \( p=0.82 \)).
The PCPC at 1-month was assessed in 39 (70%) patients. The PCPC did not significantly change from baseline to 1-month (p=0.57).
**TABLE 10.1: Backward multivariable regression: PCPC**

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Bivariate p-value</th>
<th>Multivariable exit p-value</th>
<th>Regression coefficient</th>
<th>Final p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC baseline</td>
<td>&lt;0.001</td>
<td>-</td>
<td>+0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compression duration</td>
<td>0.039</td>
<td>-</td>
<td>+0.04</td>
<td>0.010</td>
</tr>
<tr>
<td>ICU days</td>
<td>0.001</td>
<td>0.284</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>&lt;0.001</td>
<td>-</td>
<td>+0.05</td>
<td>0.006</td>
</tr>
<tr>
<td>PELOD score</td>
<td>0.033</td>
<td>0.455</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.137</td>
<td>0.160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>0.328</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>0.017</td>
<td>0.227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>0.006</td>
<td>0.353</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous oxygen sat.</td>
<td>0.017</td>
<td>0.490</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.199</td>
<td>0.340</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.263</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for admission</td>
<td>0.672</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with the PCPC one month after ICU admission. The regression coefficients are not standardized units of measure. Significant variables are marked with grey highlight.
TABLE 10.2: Multicollinearity of predictive factors in PCPC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t-value</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>+0.581</td>
<td>0.136</td>
<td>4.28</td>
<td>&lt;0.001</td>
<td>1.305</td>
</tr>
<tr>
<td>Compression duration</td>
<td>+0.043</td>
<td>0.016</td>
<td>2.72</td>
<td>0.010</td>
<td>1.137</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>+0.052</td>
<td>0.018</td>
<td>2.95</td>
<td>0.006</td>
<td>1.379</td>
</tr>
</tbody>
</table>

A variance inflation factor (VIF) is a method of detecting the severity of multicollinearity. A VIF of 10 or greater illustrates that the variable may be correlated with another variable, which requires further investigation.

PCPC score at baseline, total compression duration in minutes and number of days on mechanical ventilation were not significantly correlated with one another.
10.2 Pediatric Overall Performance Category

The POPC at 1-month was assessed and scored in 40 (71%) patients. The POPC did not significantly change from baseline to 1-month (1.91 to 2.30, p=0.13) (Figure 10.2).

10.2.1 Association between POPC and predictive factors

In the bivariate analyses of the POPC and the 14 predictive factors, 7 factors were significantly associated with increasing POPC at 1-month (p<0.2): [1] greater PCPC score at baseline (p=<0.001), [2] longer ICU stay (p=0.001), [3] greater number of days on mechanical ventilation (p=0.004), [4] greater PELOD score (p=0.007), [5] longer duration of ECMO (p=0.072), [6] lower transcutaneous oxygen saturation (p=0.011), and [7] greater number of days venous oxygen saturation was less than 40 (p=0.078) (Table 10.3).

The backward multivariable regression model eliminated the following factors in each subsequent step (in order): number of days venous oxygen saturation was less than 40 (exit p=0.853), minimum transcutaneous oxygen saturation (exit p=0.591), PELOD score (exit p=0.076), total ECMO hours (exit p=0.125), and days on mechanical ventilation (exit p=0.185).

Factors that were significantly associated with increasing POPC score at 1-month were greater PCPC score at baseline (p=<0.001, regression coefficient +0.66) and longer ICU stay (p=0.007, regression coefficient +0.05). Therefore, for every point increase on the PCPC score at baseline (a worse score), POPC score at 1-month
increased by 0.66. For every additional 20 days in the ICU, POPC score at 1-month increased by 1. Compression duration was not significantly associated with the POPC score at 1-month in the final regression model (p=0.126). The adjusted $r^2$ of this model was 0.443 (n=40) Table 10.3).

Post-regression multicollinearity analyses showed low collinearity (VIF of less than 10) between PCPC score at baseline, compression duration and length of ICU stay in its association with POPC score at 1-month (Table 10.4).

10.2.2 POPC respondents vs. non-respondents at 1-month

There was no significant difference in POPC baseline scores between respondents at 1-month and non-respondents at 1-month (1.98 to 1.71, p=0.47).

10.3 Relationship between daily functioning and HRQoL

The PCPC was significantly correlated with the POPC ($r=+0.746, p<0.001, n=39$) and the three HRQoL measures: HUI-3 ($r=-0.571, p=0.013, n=18$), PedsQL-4 ($r=-0.533, p=0.011, n=22$) and VAS ($r=-0.350, p=0.029, n=39$).

The POPC was significantly correlated with the PCPC ($r=+0.746, p<0.001, n=39$) and the three HRQoL measures: HUI-3 ($r=-0.871, p<0.001, n=19$), PedsQL-4 ($r=-0.641, p=0.001, n=22$) and VAS ($r=-0.415, p=0.008, n=40$).
The POPC at 1-month was assessed in 40 (71%) patients. The POPC did not significantly change from baseline to 1-month ($p=0.13$).
### TABLE 10.3: Backward multivariable regression: POPC

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Bivariate p-value</th>
<th>Multivariable exit p-value</th>
<th>Regression coefficient</th>
<th>Final p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC baseline</td>
<td>&lt;0.001</td>
<td>-</td>
<td>+0.66</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compression duration</td>
<td>0.257</td>
<td>0.126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU days</td>
<td>0.001</td>
<td>-</td>
<td>+0.05</td>
<td>0.007</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.004</td>
<td>0.185</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PELOD score</td>
<td>0.007</td>
<td>0.076</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.573</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>0.269</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>0.072</td>
<td>0.125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>0.011</td>
<td>0.591</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous oxygen sat.</td>
<td>0.078</td>
<td>0.853</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.465</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.589</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for admission</td>
<td>0.249</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with the POPC one month after ICU admission. The regression coefficients are not standardized units of measure. Significant variables are marked with grey highlight.
### TABLE 10.4: Multicollinearity of predictive factors in POPC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t-value</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>+0.664</td>
<td>0.171</td>
<td>3.88</td>
<td>&lt;0.001</td>
<td>1.089</td>
</tr>
<tr>
<td>Compression duration</td>
<td>+0.033</td>
<td>0.021</td>
<td>1.57</td>
<td>0.126</td>
<td>1.039</td>
</tr>
<tr>
<td>ICU days</td>
<td>+0.051</td>
<td>0.018</td>
<td>2.89</td>
<td>0.007</td>
<td>1.094</td>
</tr>
</tbody>
</table>

A variance inflation factor (VIF) is a method of detecting the severity of multicollinearity. A VIF of 10 or greater illustrates that the variable may be correlated with another variable, which requires further investigation.

PCPC score at baseline, total compression duration in minutes and number of days in the ICU were not significantly correlated with one another.
CHAPTER 11
HEALTH-RELATED QUALITY OF LIFE

Health Utilities Index (HUI-3), Pediatric Quality of Life Inventory (PedsQL-4) and the Visual Analogue Scale (VAS) assessed health-related quality of life (HRQoL).

11.1 Health Utilities Index

The HUI-3 at 1-month was assessed and scored in 19 of 29 children aged 4-18. HUI-3 significantly decreased from baseline to 1-week (0.84 to 0.57, p=0.02, n=21). There was no significant change from baseline to 1-month (0.84 to 0.70, p=0.33, n=19), or from 1-week to 1-month (0.57 to 0.70, p=0.43, n=19) (Figure 11.1).

11.1.1 Association between HUI-3 and predictive factors

In the bivariate analyses of the HUI-3 and the 14 predictive factors, 5 factors were significantly associated with decreasing HUI-3 at 1-month (p<0.2): [1] longer ICU stay (p=0.001), [2] greater number of days on mechanical ventilation (p=0.165), [3] greater PELOD score (p=0.138), [4] lower transcutaneous oxygen saturation (p=0.166), and [5] reason for admission (p=0.135) (Table 11.1). Compression duration, number of days on epinephrine, duration of cardiopulmonary bypass, duration of ECMO and number of days venous oxygen saturation was less than 40 were reported as zero. Therefore, they were not included in the regression model.
The backward multivariable regression model eliminated the following factors in each subsequent step (in order): PELOD score (exit p=0.930), minimum transcutaneous oxygen saturation (exit p=0.834), and days on mechanical ventilation (exit p=0.665).

Factors that were significantly associated with decreasing HUI-3 score at 1-month were greater PCPC score at baseline (p=0.042, regression coefficient -0.11), longer ICU stay (p=<0.001, regression coefficient -0.03) and being admitted for reasons other than respiratory (p=0.003, regression coefficient +0.06 circulatory, -0.15 neurological, -0.54 oncological, +0.003 other). Therefore, for every point increase on the PCPC score at baseline, the HUI-3 score at 1-month decreased by 0.11. For every additional day in the ICU, HUI-3 score at 1-month decreased by 0.02. In comparison to respiratory patients, the HUI-3 score at 1-month increased by 0.06 for circulatory patients, decreased by 0.15 for neurological patients, decreased by 0.54 for oncological patients and increased by 0.003 for every other category of admissions. The adjusted r² of this model was 0.883 (n=19, Table 11.1).

Post-regression multicollinearity analyses showed low collinearity (VIF of less than 10) between PCPC score at baseline, length of ICU stay and reason for admission in its association with the HUI-3 score at 1-month (Table 11.2).
11.1.2 HUI-3 respondents vs. non-respondents at 1-month

There was no significant difference in HUI-3 baseline scores between respondents at 1-month and non-respondents at 1-month (0.90 to 0.74, p=0.11).
FIGURE 11.1: HUI-3 Distribution

The HUI-3 at 1-month was assessed in 19 (66%) patients. The HUI-3 significantly changed from baseline to 1-week ($p=0.02$) but not from baseline to 1-month ($p=0.33$) or 1-week to 1-month ($p=0.43$).
### TABLE 11.1: Backward multivariable regression: HUI-3

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Bivariate p-value</th>
<th>Multivariable exit p-value</th>
<th>Regression coefficient</th>
<th>Final p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC baseline</td>
<td>0.393</td>
<td>-</td>
<td>-0.11</td>
<td>0.042</td>
</tr>
<tr>
<td>ICU days</td>
<td>0.001</td>
<td>-</td>
<td>-0.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.165</td>
<td>0.665</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PELOD score</td>
<td>0.138</td>
<td>0.930</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>0.166</td>
<td>0.834</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.382</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.796</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for admission</td>
<td>0.135</td>
<td>-</td>
<td>+0.06 (circ)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.15 (neuro)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.54 (onco)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+0.003 (other)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.00 (resp)</td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with the HUI-3 one month after ICU admission. (circ) – circulatory; (neuro) – neurological; (onco) – oncological; (resp) – respiratory

The regression coefficients are not standardized units of measure. Significant variables are marked with grey highlight.
**TABLE 11.2: Multicollinearity of predictive factors in HUI-3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t-value</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>-0.108</td>
<td>0.048</td>
<td>-2.27</td>
<td>0.042</td>
<td>1.291</td>
</tr>
<tr>
<td>ICU days</td>
<td>-0.027</td>
<td>0.004</td>
<td>-7.07</td>
<td>&lt;0.001</td>
<td>1.136</td>
</tr>
<tr>
<td>Admission (Circulatory)</td>
<td>+0.059</td>
<td>0.129</td>
<td>0.46</td>
<td>0.653</td>
<td>2.280</td>
</tr>
<tr>
<td>Admission (neurological)</td>
<td>-0.157</td>
<td>0.115</td>
<td>-1.36</td>
<td>0.199</td>
<td>2.678</td>
</tr>
<tr>
<td>Admission (Oncological)</td>
<td>-0.547</td>
<td>0.145</td>
<td>-3.78</td>
<td>0.003</td>
<td>2.045</td>
</tr>
<tr>
<td>Admission (Respiratory)</td>
<td>-0.003</td>
<td>0.115</td>
<td>-0.02</td>
<td>0.981</td>
<td>3.203</td>
</tr>
</tbody>
</table>

A variance inflation factor (VIF) is a method of detecting the severity of multicollinearity. A VIF of 10 or greater illustrates that the variable may be correlated with another variable, which requires further investigation.

PCPC score at baseline, total compression duration in minutes, number of days in the ICU and reason for admission categories were not significantly correlated with one another. The reported number of cases for total compression duration was zero. Therefore, it was not included in the model.
11.2 Pediatric Quality of Life Inventory

The PedsQL-4 at 1-month was assessed and scored in 23 of 36 children aged 2-18. PedsQL-4 at 1-month had a mean: 53.3, SD: 26.0, median: 57.0 and IQR: (40-64) (Figure 11.2).

11.2.1 Association between PedsQL-4 and predictive factors

In the bivariate analyses of the PedsQL-4 and the 14 predictive factors, 7 factors were significantly associated with decreasing PedsQL-4 at 1-month (p<0.2): [1] longer compression duration (p=0.040), [2] longer ICU stay (p=0.003), [3] greater number of days on mechanical ventilation (p=0.006), [4] greater PELOD score (p=<0.001), [5] greater number of days on epinephrine (p=0.040), [6] longer duration of ECMO (p=0.040), and [7] lower transcutaneous oxygen saturation (p=0.020) (Table 11.3). Compression duration, number of days on cardiopulmonary bypass and total ECMO hours were zero. Therefore, they were not included in the regression model.

The backward multivariable regression model eliminated the following factors in each subsequent step (in order): length of ICU stay (exit p=0.329) and days on mechanical ventilation (exit p=0.542).

Factors that were significantly associated with decreasing PedsQL-4 score at 1-month were greater PELOD score (p=0.027, regression coefficient -0.69) and lower transcutaneous oxygen saturation (p=0.036, regression coefficient +0.54). Therefore, for every point increase in the PELOD score, the PedsQL-4 score at 1-month decreased
by 0.69. For every point increase in the minimum transcutaneous membrane oxygen saturation, the PedsQL-4 score at 1-month increased by 0.54. PCPC score at baseline (p=0.906) and compression duration (p=0.056) were not significantly associated in predicting the PedsQL-4 at 1-month. The adjusted $r^2$ of this model was 0.602 (n=23, Table 11.3).

Post-regression multicollinearity analyses showed low collinearity (VIF of less than 10) between PCPC score at baseline, compression duration, PELOD score and minimum transcutaneous oxygenation saturation in its association with the PedsQL-4 score at 1-month (Table 11.4).
FIGURE 11.2: PedsQL-4 Distribution

The PedsQL-4 at 1-month was assessed in 23 (64%) patients. The PedsQL-4 had a median 57.0 (IQR: 40-64).
## TABLE 11.3: Backward multivariable regression: PedsQL-4

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Bivariate p-value</th>
<th>Multivariable exit p-value</th>
<th>Regression coefficient</th>
<th>Final p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC baseline</td>
<td>0.653</td>
<td>0.906</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression duration</td>
<td>0.040</td>
<td>0.056</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU days</td>
<td>0.003</td>
<td>0.329</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.006</td>
<td>0.542</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PELOD score</td>
<td>0.001</td>
<td>-</td>
<td>-0.69</td>
<td>0.027</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.040</td>
<td>no data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>0.040</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>0.020</td>
<td>-</td>
<td>+0.54</td>
<td>0.036</td>
</tr>
<tr>
<td>Venous oxygen sat.</td>
<td>0.685</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.993</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.951</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for admission</td>
<td>0.797</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with the PedsQL-4 one month after ICU admission. The regression coefficients are not standardized units of measure. Significant variables are marked with grey highlight.
TABLE 11.4: Multicollinearity of predictive factors in PedsQL-4

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t-value</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>+0.480</td>
<td>4.006</td>
<td>0.12</td>
<td>0.906</td>
<td>1.132</td>
</tr>
<tr>
<td>Compression duration</td>
<td>-0.872</td>
<td>0.426</td>
<td>-2.04</td>
<td>0.056</td>
<td>1.218</td>
</tr>
<tr>
<td>PELOD score</td>
<td>-0.685</td>
<td>0.284</td>
<td>-2.42</td>
<td>0.027</td>
<td>1.342</td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>+0.538</td>
<td>0.237</td>
<td>2.27</td>
<td>0.036</td>
<td>1.315</td>
</tr>
</tbody>
</table>

A variance inflation factor (VIF) is a method of detecting the severity of multicollinearity. A VIF of 10 or greater illustrates that the variable may be correlated with another variable, which requires further investigation.

PCPC score at baseline, total compression duration in minutes, PELOD score and minimum transcutaneous oxygen saturation were not significantly correlated with one another.
11.3 Visual Analog Scale

The VAS at 1-month was assessed in 41 (73%) of children aged 0-18. VAS significantly decreased from baseline to 1-week (75 to 61, p=0.006, n=49). It did not significantly change from baseline to 1-month (75 to 69, p=0.48, n=41) or from 1-week to 1-month (61 to 69, p=0.17, n=41) (Figure 11.3).

11.3.1 Association between VAS and predictive factors

In the bivariate analyses of the VAS and the 14 predictive factors, 5 factors were significantly associated with decreasing VAS at 1-month (p<0.2): [1] greater PCPC score at baseline (p=0.181), [2] longer compression duration (p=0.048), [3] longer duration of ECMO (p=0.018), [4] older age (p=0.104), and [5] reason for admission (p=0.026) (Table 11.5).

The backward multivariable regression model eliminated the following factors in each subsequent step (in order): age (exit p=0.669) and total ECMO hours (exit p=0.164).

Factors that were significantly associated with decreasing the VAS score at 1-month were greater PCPC score at baseline (p=0.040, regression coefficient -5.88), longer compression duration (p=0.024, regression coefficient -0.89) and being admitted for reasons other than respiratory (p=0.014, regression coefficient -2.48 circulatory, +7.93 neurological, -11.37 oncological, -40.25 other). Therefore, for every point increase on the PCPC score at baseline, the VAS score at 1-month decreased by
5.88. For every additional minute of compression, the VAS score at 1-month decreased by 0.89. In comparison to respiratory patients, the VAS score at 1-month decreased by 2.48 for circulatory patients, increased by 7.93 for neurological patients, decreased by 11.37 for oncological patients and decreased by 40.25 for every other category of admissions. The adjusted $r^2$ of this model was 0.411 (n=41, Table 11.5).

Post-regression multicollinearity analyses showed low collinearity (VIF of less than 10) between PCPC score at baseline, compression duration, and reason for admission in its association with the VAS score at 1-month (Table 11.6).

**11.3.2 VAS respondents vs. non-respondents at 1-month**

There was no significant difference in VAS baseline scores between respondents at 1-month and non-respondents at 1-month (72.73 to 79.67, p=0.35).

**11.4 Relationship between HRQoL outcomes**

Correlation analyses between the HRQoL measures showed that the VAS was significantly correlated with the PedsQL-4 ($r=+0.509$, $p=0.013$) and was not significantly correlated with the HUI-3 ($r=+0.249$, $p=0.305$). The PedsQL-4 was significantly correlated with both VAS ($r=+0.509$, $p=0.013$) and HUI-3 ($r=+0.751$, $p=0.001$) (Table 11.7).
The VAS at 1-month was assessed in 41 (73%) patients. The VAS significantly changed from baseline to 1-week (p=0.006) but not from baseline to 1-month (p=0.48) or 1-week to 1-month (p=0.17).
**TABLE 11.5: Backward multivariable regression: VAS**

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Bivariate p-value</th>
<th>Multivariable exit p-value</th>
<th>Regression coefficient</th>
<th>Final p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC baseline</td>
<td>0.181</td>
<td>-</td>
<td>-5.88</td>
<td>0.040</td>
</tr>
<tr>
<td>Compression duration</td>
<td>0.048</td>
<td>-</td>
<td>-0.89</td>
<td>0.024</td>
</tr>
<tr>
<td>ICU days</td>
<td>0.257</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>0.814</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PELOD score</td>
<td>0.911</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>0.643</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass</td>
<td>0.501</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO</td>
<td>0.018</td>
<td>0.164</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>0.711</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venous oxygen sat.</td>
<td>0.673</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.104</td>
<td>0.669</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.821</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reason for admission</td>
<td>0.026</td>
<td>-</td>
<td>-2.48 (circ) +7.93 (neuro) -11.37 (onco) -40.25 (other) 0.00 (resp)</td>
<td>0.014</td>
</tr>
</tbody>
</table>

(circ) – circulatory; (neuro) – neurological; (onco) – oncological; (resp) – respiratory. Factors associated with the VAS one month after ICU admission. The regression coefficients are not standardized units. Significant variables are in grey highlight.
### TABLE 11.6: Multicollinearity of predictive factors in VAS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>t-value</th>
<th>p-value</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>-5.875</td>
<td>2.748</td>
<td>-2.14</td>
<td>0.040</td>
<td>1.075</td>
</tr>
<tr>
<td>Compression duration</td>
<td>-0.894</td>
<td>0.379</td>
<td>-2.36</td>
<td>0.024</td>
<td>1.122</td>
</tr>
<tr>
<td>Admission (Circulatory)</td>
<td>+37.765</td>
<td>13.554</td>
<td>2.79</td>
<td>0.009</td>
<td>5.066</td>
</tr>
<tr>
<td>Admission (neurological)</td>
<td>+48.177</td>
<td>13.146</td>
<td>3.66</td>
<td>0.001</td>
<td>5.026</td>
</tr>
<tr>
<td>Admission (Oncological)</td>
<td>+28.875</td>
<td>17.303</td>
<td>1.67</td>
<td>0.104</td>
<td>1.952</td>
</tr>
<tr>
<td>Admission (Respiratory)</td>
<td>+40.250</td>
<td>13.127</td>
<td>3.07</td>
<td>0.004</td>
<td>5.444</td>
</tr>
</tbody>
</table>

A variance inflation factor (VIF) is a method of detecting the severity of multicollinearity. A VIF of 10 or greater illustrates that the variable may be correlated with another variable, which requires further investigation.

PCPC score at baseline, total compression duration in minutes and reason for admission categories were not significantly correlated with one another.
TABLE 11.7: Correlation between HRQoL outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>HUI-3</th>
<th>PedsQL-4</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r-value</td>
<td>p-value</td>
<td>n</td>
</tr>
<tr>
<td>HUI-3</td>
<td>+1.000</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>PedsQL-4</td>
<td>+0.751</td>
<td>+1.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

Correlation analyses showed that VAS was significantly correlated with PedsQL-4 and not significantly correlated with HUI-3. PedsQL-4 was significantly correlated with HUI-3 and VAS. Significant correlations are marked with grey highlight.

A greater PCPC score at baseline was significantly associated with a lower VABS-2, greater PCPC, greater POPC, lower HUI-3 and lower VAS score at 1-month. Longer compression duration was significantly associated with lower VABS-2, greater PCPC and lower VAS score at 1-month. A greater number of days in the ICU was significantly associated with a greater POPC and lower HUI-3 score at 1-month. A greater number of days on mechanical ventilation was significantly associated with a greater PCPC score at 1-month. A greater PELOD score was significantly associated with a lower PedsQL-4 score at 1-month. Lower transcutaneous oxygenation saturation was significantly associated with a lower VABS-2 and PedsQL-4 score at 1-month. In comparison to respiratory patients at 1-month, circulatory patients had a greater HUI-3 and lower VAS scores, neurological patients had lower HUI-3 and greater VAS scores, oncological patients had lower HUI-3 and VAS scores and other category of admissions had higher HUI-3 and lower VAS scores (Table 12.1).
Although clinically interrelated, we found that baseline characteristics, resuscitation intensity and illness severity factors were independently associated with worse neurocognitive and functional outcomes, and reduced health-related quality of life.
TABLE 12.1: Factors predictive of outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>VABS-II</th>
<th>PCPC</th>
<th>POPC</th>
<th>HUI</th>
<th>PedsQL</th>
<th>VAS</th>
<th>Associated outcomes per factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCPC Baseline</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>5</td>
</tr>
<tr>
<td>Compression duration</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>ICU days</td>
<td></td>
<td></td>
<td>×</td>
<td>×</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Daily PELOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Transcutaneous oxygen sat.</td>
<td>×</td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Reason for admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>×</td>
<td>2</td>
</tr>
<tr>
<td>Factors associated per outcome</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Sixty-six parents/guardians of the 56 patients were enrolled in the caregiver perceptions study (chapter 8). Forty-nine (74%) caregivers of 42 patients completed the caregiver perceptions questionnaire at 1-month.

**13.1 Satisfaction and involvement**

Caregivers rated their satisfaction with healthcare providers favourably with a mean: 89, median: 94, IQR: 83-99 (n=49) on a scale from 0 (not satisfied) to 100 (completely satisfied) (Figure 13.1). Involvement in decision-making was rated a mean: 69, median: 87, IQR: 52-98 (n=49) on a scale from 0 (not involved) to 100 (completely involved) (Figure 13.2).

**13.2 Future decisions**

If events were to be re-enacted, 4 (9%) caregivers reported that they would have stopped treatment earlier, 7 (15%) would have wanted to be more present, 15 (31%) would have wanted to interact more with healthcare team and 10 (21%) would have wanted to more involved in choosing treatment options (Figure 13.3).
49 (74%) caregivers completed the question, “how satisfied were you with your interaction with the healthcare providers” on a 100mm scale from 0 “not satisfied” to 100 “completely satisfied”. The median was 94 (IQR: 83-99).
49 (74%) caregivers completed the question, “how involved were you in deciding what major treatment would be best for your child” on a 100mm scale from 0 “not involved” to 100 “completely involved”. The median was 87 (IQR: 52-98).
49 (74%) caregivers completed the question, “if things were re-done, would you have wanted things to be done differently, (1) being present during resuscitation, (2) interaction with healthcare providers, (3) being involved in choosing treatment options.
13.3 Caregiver presence

21 (57%) of caregivers reported being present in what they perceived as a resuscitation procedure. When comparing caregivers present to caregivers not present, there was no significant difference in satisfaction with healthcare providers (88 to 89, p=0.788) and no significant difference in involvement in decision-making for treatment options (77 to 59, p=0.170) (Table 13.1).

13.4 Relationship with neurocognitive functioning

The VABS-2 was not significantly correlated with caregiver satisfaction with healthcare providers (r=+0.065, p=0.708, n=36) and caregiver involvement in deciding treatment options (r=+0.015, p=0.930, n=36).

13.5 Caregiver concordance

There was a significant difference between caregiver 1 and caregiver 2 in their ratings of satisfaction with healthcare providers (mean 95 to 88, p=0.018, n=7). There was no significant difference between caregiver 1 and caregiver 2 in their ratings of involvement in decision-making for treatment options (mean 70 to 65, p=0.790).
TABLE 13.1: Caregiver presence

<table>
<thead>
<tr>
<th></th>
<th>Present</th>
<th>Not-present</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>21 (57%)</td>
<td>16 (43%)</td>
<td></td>
</tr>
<tr>
<td>Caregiver satisfaction (mean/100)</td>
<td>88</td>
<td>89</td>
<td>0.788</td>
</tr>
<tr>
<td>Involvement with treatment decisions (mean/100)</td>
<td>77</td>
<td>59</td>
<td>0.170</td>
</tr>
</tbody>
</table>

When comparing caregivers present and caregivers not present, there were no significant difference in caregiver satisfaction with healthcare providers and caregiver involvement with treatment decisions.
INTERPRETATION
CHAPTER 14
DISCUSSION

This study evaluated neurocognitive, functional and health-related quality of life outcomes in children surviving urgent admission to a university affiliated paediatric ICU. The present results provide information about intensity of resuscitation, duration of resuscitation and the severity of illness that are associated with subsequent cognitive outcomes and health-related quality of life of children admitted to the PICU. They provide insight into caregiver perceptions during their child’s PICU stay.

14.1 Results in relation to hypotheses

We considered how the results related to the study hypotheses:

14.1.1 Children surviving PICU have significant cognitive morbidity and reduced health-related quality of life.

The study identified clinically significant cognitive morbidity and reduced health-related quality of life in children surviving PICU. The mean (standard deviation) adaptive behaviour score for the study population was 85 (±25), more than one standard deviation below the ‘normal’ population mean of 100 (±15).\(^{150}\) This is lower than the 96 (± 14) in children with inflicted traumatic brain injury and 116 (±20) in children with non-inflicted traumatic brain injury and, \(^{213}\) 89 (±18) in children with
hypoplastic left heart syndrome (HLHS),\textsuperscript{124} and higher than 82 (±22) reported in young adults with autism.\textsuperscript{214} Thus, in comparison to some sub-populations with severe illnesses, neurocognitive functioning was relatively poor in this sample, but similar to other populations.

In this study, neurocognitive functioning was directly associated with compromised neurologic state at baseline. It seems logical that a child's post-ICU outcome is directly related to his/her pre-ICU status. Importantly, we found that one intensity of resuscitation factor and one severity of illness (SOI) factor were also associated with reduced neurocognitive functioning during children's ICU stay. These additional factors are thus associated with the development of acquired brain injury during a child's ICU stay.

Children surviving PICU had reduced health-related quality of life (HRQoL) one month after PICU admission. The mean HUI-3 score of 0.70 (±0.32) at 1-month was lower than the 0.87 (±0.26) reported in adolescents with extremely low birth weight,\textsuperscript{215} and higher than the 0.58 (±0.32) reported in children with hydrocephalus.\textsuperscript{216} The mean PedsQL-4 score of 53 (±26) and median score of 57 (IQR: 40-64) at 1-month was lower than the median score of 67 (IQR: 50-84) reported in children with sickle cell disease,\textsuperscript{217} and the mean score of 70 (±19) reported in children with cancer,\textsuperscript{218} and higher than the mean score of 51 (±18) reported in children with cerebral palsy.\textsuperscript{172} The mean VAS score of 69 (±21) at 1-month was lower than 75 (±21) reported in children with chronic arthritis,\textsuperscript{219} and 72 (±15) reported in
adults with metabolic syndrome, and higher than 59 (±15) reported in patients with haemophilia. In the population studied, reduced health-related quality of life was associated with a compromised neurologic state at baseline (post-ICU outcome directly related to pre-ICU status), reason for ICU admission, more intense modes of resuscitation, and greater severity of illness.

14.1.2 The use of more intense resuscitation therapies is associated with worse cognitive and functional outcomes and reduced health-related quality of life

There were two patients receiving chest compressions in this sample. Their reduced cognitive functioning and health-related quality of life had a significant effect on the whole population suggesting that CPR duration is a major determinant of acquired morbidity. This study’s poor neurocognitive outcome for 47% of patients and reduced health-related quality of life is consistent with Young and Seidel’s review (1999) of 40% poor neurocognitive outcome reported for children receiving cardiopulmonary resuscitation, and 16.4% poor quality of life reported for children in an Australian PICU. The median PCPC score of 1.77 in this study at 1-month was consistent with the score of 2 reported for paediatric in-ICU cardiac arrests, and the 79% of children with ‘good’ neurologic outcome (defined as a PCPC score of 1-2) in this study was higher than that reported in 63% of paediatric patients who had a cardiac arrest. Study of greater number of children will increase the precision of this effect.

Mechanical ventilation was significantly associated with worsening of daily functioning outcome. This is consistent with reported outcomes for ventilated
children with acute lung injury that showed an increased risk of mortality with mechanical ventilation.\textsuperscript{10, 12, 30}

Extracorporeal membrane oxygenation (ECMO) was not significantly associated with neurocognitive outcome or health-related quality of life. This is not consistent with other studies that reported that longer duration of ECMO in children was associated with higher risk of mortality.\textsuperscript{222, 223} It is also not consistent with studies that reported acceptable/favourable outcomes for ECMO: a paediatric study that reported no severe neurologic outcome and improved survival in paediatric patients with heart disease after cardiopulmonary arrest,\textsuperscript{32} and an adult study that reported acceptable neurologic outcomes in adults with prolonged CPR rescue by ECMO.\textsuperscript{224}

Epinephrine dosage, haemodialysis and cardiopulmonary bypass did not show any significant association with neurocognitive, functional or health-related quality of life outcomes. This is not consistent with studies that showed that the use of cardiopulmonary bypass with operations was associated with lower neurodevelopmental outcome in newborns with congenital heart defects,\textsuperscript{225} the increase in dosages of epinephrine in children was associated with severe neurologic impairment,\textsuperscript{83} and the use of haemodialysis in infants was associated with significant morbidity and mortality.\textsuperscript{226}

The non-significant associations with ECMO, epinephrine, haemodialysis and cardiopulmonary bypass with neurocognitive and health-related quality of life
outcomes may be due to the low (or zero) reported number of cases/episodes for these factors, limiting the power of the analyses. A larger sample size may demonstrate clinically significant associations.

14.1.3 Increasing severity of illness during ICU stay is associated with worse cognitive and functional outcomes and reduced health-related quality of life

Increasing severity of illness (SOI) was significantly associated with worse cognitive and functional outcomes and reduced health-related quality of life. One SOI factor, lower transcutaneous oxygen saturation, was significantly associated with worse cognitive outcome, and one SOI factor, longer ICU stay, was significantly associated with worse functional outcome. Three SOI factors: longer ICU stay, lower transcutaneous oxygen saturation and greater PELOD score, were associated with reduced health-related quality of life.

In previous studies, the PELOD score has been primarily used to assess morbidity in children.\(^1\) When comparing to other populations, the median PELOD score of 21 in our study was higher (worse) than 10 reported for children with sepsis,\(^{227}\) 18 reported for children in a PICU in Pakistan,\(^{228}\) and 12 reported for ventilated children in Australia and New Zealand.\(^{229}\) The PELOD score demonstrates that the contribution of different organ dysfunctions increases the risk of mortality.\(^1\) Considering that the most common cause of ICU morbidity is related to the development of physiological dysfunction remote from the site of the baseline
disease, our finding of reduced health-related quality of life in children is consistent of biological processes.

**14.1.4 Caregivers are generally satisfied with their interaction with healthcare providers and are involved in the decision making for treatment options**

Caregivers were highly satisfied with their interaction with healthcare providers, mean 89 out of a 100. This is consistent with other studies that reported 80 out of a 100 for family satisfaction of survivors in the ICU and 87 out of a 100 for family satisfaction of non-survivors in the ICU, and 83-85 reported for families’ interaction with physicians in an adult ICU. Caregivers reported moderate levels of involvement in decision making, mean 69 out of a 100, but we are unable to identify if caregivers were satisfied with their involvement. Future evaluations must address caregiver satisfaction of involvement in decision-making.

It is notable that the difference in satisfaction rates was not significantly associated with caregiver presence. However, this could be attributed to the limited sample size. For instance, a large difference was observed between parents present and not present (mean 77 to 59 out of a scale of 100), yet it was not a significant difference (p=0.17). A larger sample size may show an effect by increasing the power of the analyses.
14.2 Relationship between outcome measures

The Vineland Adaptive Behaviour Scale (VABS-2) demonstrated a significant relationship with both the daily functioning measures, Pediatric Cerebral Performance Category (PCPC) and Pediatric Overall Performance Category (POPC). This is closely linked with Fiser et al (2000) that reported a significant relationship with the VABS and POPC. VABS-2 was also significantly correlated with the Visual Analog Scale (VAS) but not with the Health Utilities Index (HUI-3) and the Pediatric Quality of Life (PedsQL-4). This may be due to the limited sample size of 19 patients reported for HUI-3 and 23 patients for PedsQL in comparison to 41 patients reported for VAS. Correlation of these measures demonstrated internal consistency and reinforced the validity of the measures. Additionally, future studies utilizing a similar model may want to streamline the ‘outcome package’ by utilizing measures that capture the entire population group.

14.3 Limitations

The generalizability of the results of this study may be limited due to sampling constraints, design limitations, biases due to parental-reported measures and non-respondents, and data documentation errors.
[1] Generalizability to centres

All patients in this study were sampled from the Hospital for Sick Children, a tertiary/quaternary academic health science centre. This institution is one of the largest tertiary care centres that provide more specialized care of severely ill children than the general population. This may limit generalizability to similar centres.

[2] Sample size

The findings of the study should be interpreted with caution due to the comparatively small sample size that limits the power of the analyses, as well as the ability of its model to demonstrate all significant clinical effects. Subsequent evaluations using a similar model will thus require larger sample sizes.

[3] Recruitment and response rate

We had consent discussion with approximately half of the eligible patients and families and recruited 65% of them. Therefore, we may not have had a representative sample for the PICU population. It is important to note that competition with other studies in the PICU and many caregivers being overwhelmed impacted the recruitment rate greatly.

The lower response rate (75%) at 1-month assessments may introduce error and reduce reliability of the results. Although, efforts were made to increase response rates of non-respondents through phone call, mail and e-mail reminders, it nonetheless raises the issue of non-respondent bias—differences between
respondents and non-respondents—that may ultimately produce biased conclusions. However, it is important to note that the comparisons between the baseline scores of respondents and non-respondents at 1-month showed no significant differences in any outcomes. A sampling bias was also introduced due to missing patients treated with more intense modes of resuscitation and perhaps excluding non-English participants. The inability of recruiting patients treated with more intense modes of resuscitation was either due to requests by healthcare providers to not ask the sickest patients or due to competition with other research studies within the ICU. Non-English participants were excluded due to outcome measures being primarily in English and our inability of obtaining translators. Additionally, we were unable to obtain any outcomes of children who did not survive PICU admission. Under-representation of these three groups causes an inherent bias and limits the true generalizability of the PICU population. Sampling methods used may have exacerbated the under-representation as caregivers that can be accessed more easily were approached.

[4] Limited ability to demonstrate causality

Although the study identified important associations between independent variables and outcomes of interest, its prospective observational non-interventional design limits the extent to which conclusions of causality can be supported. However, it is important to note that our findings are based upon a model that is grounded in an established conceptual framework that studied similar and different populations.
The reliance on parental-reported outcomes

All outcome measures assessed in this study were parental-reported measures completed by the caregivers. This may create potential reporting biases where caregivers inflate/deflate certain answers due to misconstrued perceptions about their child’s outcomes. However, it is important to note that all these instruments have demonstrated strong psychometric properties that have been employed and validated in previous research studies.13, 49, 160, 175, 176, 186, 213, 220, 231

The caregiver perceptions form, on the other hand, was not a validated measure. There were few questions and the content was of limited nature, limiting the conclusions drawn from that aspect of the study. In addition, there was inability to obtain the ratings of both caregivers in the caregiver satisfaction and caregiver involvement section, limiting the power of the analyses of caregiver concordance.

Pre-ICU variables

The timing of treatment was not assessed in this study and has previously shown to have important implications in paediatric outcomes in the ICU.232 Future studies using a similar model should study pre-ICU variables including severity of illness and resuscitation treatments.

Data documentation errors

The possibility of data documentation errors must be acknowledged. There is a possibility that some of the predictive factors could have been documented or
calculated incorrectly, affecting the accuracy of the results. However, it is important to note that this limitation is applied to all studies of similar design.

14.4 Strengths

Despite the limitations, there are many strengths to the work constituting this thesis. The primary focus of this study was assessing morbidity—neurocognitive and health-related quality of life outcomes. The majority of previous work in this area used mortality as their primary outcome. Considering that the goal of resuscitation is to improve survival with good neurologic outcome, this study demonstrates that evaluating the long-term outcomes of neurocognitive functioning and health-related quality of life may be more relevant than survival rates.

The use of the Vineland Adapative Behaviour Scale (VABS-2) for primary outcome provided an extensive measure that assessed neurocognitive functioning. Previous studies utilized the PCPC and POPC scales—coarse assessment measures—as its primary cognitive outcome; these measures may overlook subtle yet important abnormalities or changes in neurocognitive functioning. Using three health-related quality of life measures allowed us to capture all age groups in the population and permitted correlations that reinforced the validation of these measures.

Although sample size limited the association of some predicted factors with outcomes of interest, it was still able to show clinically significant associations with
several factors: baseline neurologic state, two intensity of resuscitation factors and three severity of illness factors.

The prospective observational design performed in the study limited the recall bias as the answers were not affected by the parent/caregiver’s memory. A longitudinal evaluation generated an additional strength by excluding time-invariant unobserved individual differences by virtue of observing the temporal order of events. Using repeated measures further aids in keeping the variability low and keeps the validity of the results higher.

This study also demonstrated the feasibility by its moderate enrolment rate of 65% (for the caregivers that were approached) and its moderate to good follow-up rate of 75% one month after ICU admission. The 90% completion rate of the VABS-2, our primary outcome, was a successful rate as well.

It is important to note that this was the first study to evaluate caregiver presence with satisfaction. Although conclusive results were not found, it provides a model for future studies to evaluate this area.

14.5 Clinical implications

The work arising from this thesis study has made important contributions to studying outcomes in a paediatric ICU setting and has several implications. This project provided current-era data on the cognitive and health-related quality of life outcomes
of critically ill children treated within an institution in Canada. The detailed data may be of immediate value to clinicians describing prognosis to families, and may better inform pre-emptive resuscitation decision-making by the identified predictors of poor and favourable outcomes. As a result, this provides more specific information for families, possibly improving informed consent and decision-making, and potential for improved quality of care.

This study identified vulnerable populations and identified several factors associated with worse neurocognitive outcome, poor daily functioning and reduced health-related quality of life. These include diminished neurological state prior to a child’s ICU stay, more intense modes of resuscitation, and greater severity of illness. It is important to recognize the contribution of these factors and evaluate it further in future studies.

This study also describes the importance of studying neurocognitive and health-related quality of life outcomes as primary measures in reporting outcomes of children receiving in-hospital resuscitation. The establishment of feasibly measured, consistent set of neurocognitive, functional and health-related quality of life outcomes for children treated in the PICU may be of use to other studies of critically ill children by permitting comparisons across sub-populations of critically ill children.

Although caregiver satisfaction has been studied previously, there are no studies comparing caregiver satisfaction to neurocognitive functioning or health-
related quality of life. This study provided a template to implement a design to study these variables in future studies.

14.6 Future research

Future work should address some of the limitations of this study, including: (i) larger sample size, (ii) multicentre evaluation and (iii) additional time measurements (including data of up to 2 years), as is frequently performed in neonatal,\textsuperscript{130} paediatric,\textsuperscript{132} adolescent,\textsuperscript{131} and adult studies.\textsuperscript{128}

Continuation of this study by obtaining the neurocognitive and health-related quality of life outcomes of children at 6 months, 1 year and 2 years after urgent ICU admission is currently underway to evaluate the long-term effects of children undergoing resuscitation in the PICU. The patients who participated in this study are being followed and assessed repeatedly up to two years following their admission date. These individuals have consented to the repeated assessments when they were first approached in the ICU. Additionally, we are addressing the issue of sample size by continually enrolling new patients.

Future work should also investigate the effects of pre-ICU variables, using the Bedside Paediatric Early Warning System (PEWS) score,\textsuperscript{233} and accordingly assess these factors with neurocognitive, functional and health-related quality of life outcomes. Future evaluations should design a more extensive measurement to assess caregiver perceptions by tighter cross-linkage of satisfaction, presence and
involvement factors of parents/caregivers with the cognitive outcomes and health-related quality of life of children.
CONCLUSIONS
CHAPTER 15
CONCLUSIONS

After evaluating neurocognitive and functional outcomes, and health-related quality of life in children following in-hospital resuscitation, we found that outcomes were relatively poor in children one month after ICU admission. Although the small sample size for the study underpowered the analyses to show the many significant effects, the study still demonstrated a few clinically relevant associations. Neurologic state at baseline and compression duration was the most significant determinants of reduced neurocognitive functioning and health-related quality of life. After adjusting for baseline state that affects post-ICU outcomes, this study found that more intense modes of resuscitation and increasing severity of illness were independently associated with the development of acquired brain injury and reduced health-related quality of life. Improved understanding of the effects of these factors—as well as the other non-significant factors—associated with these outcomes is warranted. In addition, an evaluation of the clinical impact of these results is necessary.

The study demonstrated moderate to good feasibility and provides a model for future studies to evaluate cognitive and health-related quality of life outcomes in children resuscitated in the ICU. Future work should evaluate a larger sample size in a multicentre longitudinal design in order to observe the long-term outcomes and to define all relevant effects of the factors with greater precision. This will be important
to healthcare providers for prognostication and evaluation of new treatments and procedures, to identify areas amenable to improvement, to assess the impact of interventions designed to improve the outcomes of hospitalized children as they move beyond the PICU admission, and to potentially improve informed decision-making for parents-caregivers.
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validity across age subgroups using the PedsQL 4.0 Generic Core Scales. **Health Qual Life Outcomes.** 2007;5:2.


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222. Alsoufi B, Al-Radi OO, Gruenwald C, Lean L, Williams WG, McCrindle BW, Caldarone CA, Van Arsdell GS. Extra-corporeal life support following cardiac


APPENDIX A: Identifiers form

Longitudinal evaluation of the outcomes of children receiving in-hospital resuscitation

Baseline
Caregiver 1

Child ID

Date: d m y

Child ID
HSC ID

First Caregiver Name
(Caregiver 1):

Last name
First name

Eligibility

Has the child signed the consent form
OR
has this parent signed the consent form?

If the answer is "NO" to the above question(s), then we are unable to continue this part of the study. Please STOP here. Thank you.

If the answer to the above question(s) is "YES", then please proceed to complete the study. Thank you in advance.

Child Information (**filled out by staff**)

Age (in months)

Gender (circle one) | Male | Female

Primary Diagnosis

Reason for ICU admission

Investigators: Dr. Christopher Parshuram
Shanil Ebrahim

Contact: Department of Critical Care Medicine (416) 813-4919
### Caregiver 1
Please fill out the following information:

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;23</th>
<th>24-33</th>
<th>34-43</th>
<th>44+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Address</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(Street, City, Province, Postal Code)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary address (If applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Street, City, Province, Postal Code)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contact Details</th>
<th>Home Phone:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Business Phone:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mobile Phone:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Email</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Longitudinal evaluation of the outcomes of children receiving in-hospital resuscitation

Child ID
HSC ID

Second Caregiver Name (if applicable)
(Caregiver A)

Last name
First name

Eligibility

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has the child signed the consent form?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>has this parent signed the consent form?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the answer is "NO" to the above question(s), then we are unable to continue this part of the study. Please STOP here. Thank you.

If the answer to the above question(s) is "YES", then please proceed to complete the study. Thank you in advance.

Investigators:  Dr. Christopher Parshuram
                Shanil Ebrahim
Contact:        Department of Critical Care Medicine (416) 813-4919
## Caregiver A (if applicable)

Please fill out the following information:

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Gender**
(Please circle one)

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;23</td>
<td>24-33</td>
</tr>
</tbody>
</table>

**Age (years)**

**Primary Address**
(Street, City, Province, Postal Code)

**Secondary address**
(If applicable)
(Street, City, Province, Postal Code)

**Contact Details**

<table>
<thead>
<tr>
<th>Home Phone:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Business Phone:</td>
</tr>
<tr>
<td>Mobile Phone:</td>
</tr>
</tbody>
</table>

**Email**
APPENDIX B: In-ICU daily data collection

Longitudinal evaluation of the outcomes of children receiving in-hospital resuscitation

Start of this ICU Day: dd/mm/yy

ICU Day: 7 am – 6:59 am

Data Collection sheet

Please fill out the following information for the child:

<table>
<thead>
<tr>
<th>ICU day #</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily PELQD Score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Epinephrine? Any:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Infusion:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Compression duration:</td>
<td>mins</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cardiopulmonary bypass (OR):</td>
<td>mins</td>
<td></td>
</tr>
<tr>
<td>ECMO hours:</td>
<td>hrs</td>
<td></td>
</tr>
<tr>
<td>Transcutaneous oxygen saturation</td>
<td>(minimum)</td>
<td></td>
</tr>
<tr>
<td>Venous saturation (minimum during 24hr period) [from superior venous system [RASV]]</td>
<td>(minimum)</td>
<td></td>
</tr>
</tbody>
</table>

Version date: May 12th, 2008
APPENDIX C: Caregiver perceptions form

Longitudinal evaluation of the outcomes of children receiving in-hospital resuscitation

2 Year
Caregiver A

Child ID

Date: 

Please answer all the questions. Answer questions ‘1’ and ‘3’ by marking ‘|’ on the horizontal line:

1) How satisfied were you with your interaction with the health care providers (e.g. doctors, nurses, etc)?

| Not Satisfied | Completely Satisfied |

For the following questions (2 and 3), the general term “resuscitation” will refer to cardiopulmonary resuscitation (CPR), cardiorespiratory resuscitation and extracorporeal membrane oxygenation (ECMO). These are actions that are carried out to restore the breathing and circulation in a patient.

2) Were you present in the room during the resuscitation or part of the resuscitation?

| YES | NO | N/A |

3) How involved were you in deciding what major treatment (e.g. resuscitation, operations, etc.) would be best for your child?

| Not Involved | Highly Involved |
Longitudinal evaluation of the outcomes of children receiving in-hospital resuscitation

2 Year
Caregiver A
Child ID

Date: \( \text{d} \text{ m} \text{ y} \)

If things were re-done, would you have wanted things to be done differently?
(For each question below, please circle an answer)

<table>
<thead>
<tr>
<th></th>
<th>Stopping treatment</th>
<th>Earlier</th>
<th>Later</th>
<th>No Change</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Being present (during resuscitation)</th>
<th>More</th>
<th>Less</th>
<th>No Change</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Interact with health care providers (e.g. Doctors, nurses, etc.)</th>
<th>More</th>
<th>Less</th>
<th>Same</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>c</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Being involved in choosing the treatment options</th>
<th>More</th>
<th>Less</th>
<th>Same</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>d</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

Comments:

_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________
_________________________________________________________________________