University of Alberta

Pre-school functional outcomes after neonatal cardiac surgery

by

Soreh Taghaddos

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Master of Science
in
Epidemiology

Department of Public Health Sciences

Fall 2011

Edmonton, Alberta

Dedication

I would like to dedicate this thesis to my kind mother, my dear father, my lovely husband and my beloved brother and sister.

Abstract

Title

Pre-school functional outcomes after neonatal cardiac surgery

Description

The objective of this study is to determine variables associated with four to five year functional outcomes in children undergoing complex cardiac surgery early in life.

This is a longitudinal follow-up study conducted between 2000 and 2005, consisting of 165 survivors of complex cardiac surgery at the age of 6 weeks or younger at the Stollery Children's Hospital in Edmonton, Alberta. Demographic characteristics as well as pre-operative, operative, post-operative and overall variables were recorded by trained pediatric nurses and used in the data analysis. When children were four to five years of age, parents completed the Adaptive Behavioral Assessment System II. The study focuses on the following four outcomes: ABAS-GAC (General Adaptive Composite of the Adaptive Behaviour Assessment System), and three broad categories of the children's assessed adaptation in Conceptual (functional academics, self-determination and communication skills), Social (leisure and social skills) and Practical (home living, health and safety, community use and self-care) domains.

Multivariate linear regression analysis revealed pre-operative plasma lactate, gender and mother's education were significantly associated with all of the four

outcomes in the study. The number of days ventilated was significantly associated with the Conceptual domain. Single Ventricle was associated with the Practical domain.

Acknowledgements

I would like to express my deepest gratitude to my lovely parents for their never-ending support and to my dearest lovely husband Amin for his help, support and warm companionship throughout my research process.

This research work would not have become a reality without the kind support of my supervisor, Dr. Irina Dinu. I am truly fortunate to have her as my advisor. Dr. Dinu guided me with patience and great insights throughout the whole dissertation process. I thank her and will be in her debt forever.

I would also like to thank Dr. Charlene Robertson and Gwen Alton for their insights and comments while reviewing my thesis. Many thanks go in particular to Gwen Alton for her important contributions in collecting and explaining the data. Without her knowledge and assistance this study would not have been successful. I also gratefully acknowledge The Registry and Follow-up of Complex Pediatric Therapies Program Group who made this research study possible. I am also grateful to my committee chair and examiner, Prof. Gian Jhangri, for his thoughtful review and valuable suggestions.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ABAS - Adaptive Behavioral Assessment System II

CHD – Congenital Heart Defect

CPB - Cardiopulmonary Bypass

DHCA - Deep hypothermic circulatory arrest

GAC - General Adaptive Composite

IQ - Intelligence Quotient

LOWESS – Locally-Weighted Scatter-plot Smoothing

MBTS - Modified Blalock-Taussig

PICU - Pediatric Intensive Care Unit

RVPA - Right Ventricle–to–Pulmonary Artery

SCH - Stollery Children's Hospital

SD – Standard Error

SES - Social Economic Status

VIF - Variance Inflation Factor

Chapter 1: Introduction

1.1 Rationale

Congenital heart defect (CHD) is a common form of birth defect in infants, with approximately more than a third of those afflicted undergoing complex paediatric therapies, such as open heart surgery in the first year of life (Shillingford and Wernovsky, 2004; Majnemer et al., 2009). The development of new techniques such as deep hypothermic circulatory arrest (DHCA) and cardiopulmonary bypass (CPB) has enabled an increasing number of survivors among those born with CHD (Shillingford and Wernovsky, 2004). However, these survivors are at risk for developing adverse neurodevelopmental and functional outcomes in the long term. Several studies have indicated these children are at risk for incidence of fine or gross motor delay, physical growth abnormalities, behaviour problems, learning difficulties, deficits in language skill and low-average intelligence quotient (IQ) (Shillingford and Wernovsky, 2004; Robertson et al., 2011; Rogers et al., 1995; Newburger, 1993; Mahle, 2001; Kern, 1998; Bellinger, 1995). Many CHD survivors face a range of problems when beginning their education, usually around five years of age.

There are just a few cohort studies prospectively following children undergoing complex cardiac surgery in the neonatal period with measurement of their developmental outcomes over time. It is crucial to investigate and identify the predictors of neurodevelopmental outcomes in these children at different stages of care, with the purpose of minimizing the development of these long-term adverse outcomes in future survivors. The longitudinal follow-up program "Complex Pediatric Therapies of Western Canada" was began in 1999 to follow children with CHD who received new life-saving treatments, mostly complex cardiac surgery, at six weeks of age and earlier. These children then were followed prospectively and assessed at two and five years of age for neurological and functional outcomes (Robertson et al., 2011). Developmental delays as well as some potentially modifiable variables for future care have been identified; however, many predictors at different stages of care remain unknown.

1.2 Purposes

The present study was initiated between 2000 and 2005 as part of the Western Canadian Pediatric Therapies Follow-up Program. The main purpose of this study is to determine potentially modifiable variables related to functional outcomes in four to five-year-old children with CHD who underwent infant complex cardiac surgery at six weeks of age or earlier. The ultimate objective of this study is to reduce the risk of developing adverse functional outcomes in such children, based on recognized risk factors.

1.3 Thesis organization

Following the Introduction, Chapter 2 will provide a comprehensive review of current research in the field and other studies related to the present study. Research methods and statistical analysis of the present study will be described in

Chapter 3. Chapter 4 will present the results of the statistical analysis. Discussion based on the results obtained from the statistical analysis and the strength of the present study will be shown in Chapter 5. Chapter 6 will offer a conclusion, including prospective for future studies.

Chapter 2: Literature Review

2.1 Relevant material in the literature

Complex cardiac surgery is one of the important neonatal life-saving therapies in children with complex cardiac defects. Long-term follow-up of infants after cardiac surgery began with only a few studies in the 1980s. Until the last decade, outcomes have focused on survival without giving information on morbidity.

As sustained progress on early diagnosis and developing technologies to repair complex defects has lead to an increasing number of survivors among children undergoing complex cardiac surgery, investigations of late sequelae and factors modifying their risks are emerging (Rudolph, 2001). Researchers have recognized that children surviving complex cardiac surgery are at risk for neurodevelopmental sequelae (Robertson et al., 2011). According to a study by Gaynor et al. (2007), patient characteristics such as the presence of genetic syndromes and low birth weight can significantly determine an adverse neurodevelopmental outcome. Infants with congenital heart disease may also have brain abnormality prior to cardiac surgery (Miller et al., 2007). Therefore, recognizing and understanding different neurological sequelae like physical, mental, visual, hearing, cognitive and behavioural outcomes can provide valuable information for care providers to counsel parents and present them with a realistic view of their infants' developmental outcomes after the surgical procedure (Sauve and Lee, 2006). Since these children are at risk for fine and gross motor delay, physical growth abnormality, behaviour problems, learning difficulties, deficits in language skill, and below-average intelligence quotients (IQ), early referral for developmental testing and outcome improvement is crucial (Shillingford and Wernovsky, 2004; Robertson et al., 2011).

Several follow-up studies for children who have undergone complex cardiac surgery early in their life are discussed below, including findings of potentially modifiable risk factors that play important roles in developing adverse long-term outcomes in these children (Robertson et al., 2011). Part A covers studies performed by investigators other than western Canadian researchers, and Part B discusses western Canadian studies, including the current study.

2.1.1 Studies other than western Canadian studies

Infants born with serious cardiac defects that entail early surgical intervention are at considerable risk for brain injury (Miller et al. 2007). Neurologic impairment is therefore significantly more prevalent in these children as compared to the normal population (Hövels-Gürich et al., 1997; Majnemer et al., 2009). The neurodevelopmental status of newborns and infants with congenital heart disease before and after open heart surgery was investigated by Limperopoulos and colleagues (2000). Based on their findings, neurobehavioural abnormalities in newborns and neurodevelopmental defects in infants are very common in these children, with no change in their neurodevelopmental status in most patients after surgery. Therefore, the researchers found a strong relationship between neurodevelopmental status in these children before and after surgery.

While neurodevelopmental abnormalities are common in children who have congenital heart disease and persist in most after open heart surgery, Robertson et al. conducted a study to assess neurodevelopmental outcome in one-year-old children who underwent infant cardiac surgery (Robertson et al., 2004a). According to their assessment, neurodevelopmental scores (consisting of mental and motor score) were significantly lower in the one-year-old children compared to preoperative scores, suggesting that children's ongoing progress should be monitored continuously. Continuous developmental examination early in life for children with congenital heart disease is also strongly recommended by other studies (Hövels-Gürich et al., 1997; Majnemer et al., 2009; Limperopoulos et al., 2000).

Emerging new surgical techniques has significantly increased the number of open heart surgery survivors. As a result, particular attention has been given to better understanding adverse long-term neurodevelopmental and functional outcomes. A study of infants with congenital heart defects who underwent open heart surgery, also conducted by Majnemer et al. (2009), evaluates infants prior to surgery, after surgery, around one year and five years later to observe their developmental outcome. Researchers first confirmed that neurodevelopmental abnormalities were common among the selected infants before surgery. Then, they proved that children with infant cardiac surgery had a higher chance of developmental delay, and as mentioned before, the researchers recommended surveillance after surgery. These developmental delays include gross and fine motor impairments such as poor balance, behaviour problems and specific cognitive challenges, and are associated with an inability to communicate, socialize and perform personal tasks. Significantly poor fine and gross motor skill, as well as acquired abilities and vocabulary in school-age children with newborn arterial switch operation was also confirmed by the Hövels-Gürich et al. (1997) study. These studies have revealed the increased incidence of delay in fine and gross motor, learning difficulties, deficits in language skill, and below-average intelligence quotients (IQ) (Dunbar-Masterson, 2001) in survivors of infant heart surgery. School performance, hyperactivity and inattention in school-age children were also investigated by Shillingford et al. (2008). They studied 5- to 10-year-old children who underwent newborn complex cardiac surgery and found levels of hyperactivity and inattention were three to four times higher in this group as compared to the normal population, and about half of the studied children were receiving remedial school services. They also had considerably increased parental reports of hyperactivity, inattention, learning difficulties, speech problems and developmental delay (Shillingford and Wernovsky, 2004).

A number of preoperative, intraoperative and postoperative factors have been found to be associated with long-term adverse neurological outcomes (Shillingford and Wernovsky, 2004). Identifying the modifiable predictors at each stage of care plays a great role in improving long term outcome results and significantly improving the child's quality of life (Robertson et al., 2004b). Genetic syndromes, low birth weight, duration of hospitalization after surgery, CPB and DHCA are some of the risk factors for neurodevelopmental sequelae (Gaynor et al., 2007; Newberger et al., 2003; Shillingford and Wernovsky, 2004).

Several studies were conducted to identify perioperative factors that play an important role in developing adverse long-term neurological outcomes in these children (Robertson et al., 2011).

In the study conducted by Shillingford and colleagues (2004), early diagnosis was reported as a preoperative factor that plays a great role in providing a more stable condition in children with congenital heart disease. Seizure, tone abnormalities, and feeding difficulties were reported in this study as postoperative factors significantly associated with long-term adverse neurodevelopmental outcomes. Surgical techniques such as CPB and DHCA are among the intraoperative risk factors mentioned in their study. Although these techniques have a major role in increasing the number of survivals, they are also risk factors for brain injury and neurological problems. The association between prolonged exposure to DHCA and neurodevelopmental outcomes was also confirmed by Majnemer and colleagues (2009). Moreover, significant inverse association was also found between children's intelligence and the duration of cardiopulmonary bypass procedures (Hövels-Gürich et al., 1997). In the study carried out by Limperopoulos et al. (2000), arterial oxygen saturations less than 85% and prolonged cardiopulmonary bypass in infants and longer circulatory arrest time in newborns were reported as significant risk factors for neurological abnormalities. The association between length of stay in hospital after newborn heart surgery and cognitive outcomes was also investigated in the Newburger et al. (2003) study. Children who underwent newborn heart surgery were re-assessed at eight years of age. According to the study's findings, children with longer postoperative lengths of stay had significantly lower full-scale IQ, verbal IQ and performance IQ, after adjusting for perioperative and sociodemographic variables.

As mentioned previously, significant association was found between prolonged CBP and longer DHCA procedures and neurological abnormalities in newborns; these are considered as key risk factors for brain injury and neurological problems (Shillingford and Wernovsky, 2004; Hövels-Gürich et al., 1997; Majnemer et al., 2009; Limperopoulos et al., 2000).

2.1.2 Western Canadian Complex Pediatric Therapies Follow-up

The longitudinal follow-up of Western Canadian Complex Pediatric Therapies Program was initiated in 1999 to follow children who received new life-saving treatments, mainly focusing on complex cardiac surgery (Robertson et al., 2011). Infants with congenital heart disease who underwent complex cardiac surgery at the age of six weeks or earlier at the Stollery Children's Hospital in Edmonton, Alberta, Canada were registered in the study. These children were followed prospectively and assessed for neurological outcomes at two and five years of age. Developmental delays as well as potentially modifiable risk variables were identified and published in various papers. The findings of this follow-up study are summarized below.

Adverse neurodevelopmental outcomes were investigated in these survivors and the relationship between these neurological abnormalities and preoperative, operative, and postoperative variables as outcome predictors was assessed (Robertson et al., 2004b). Identifying these modifiable predictors at each stage of care has a great effect on long-term outcome improvement. According to the study, the risk of adverse outcome was cumulative, with preoperative and potentially modifiable operative variables contributing the most significant effects. Genetic anomalies and intraoperative variables such as CPB and DHCA times have been found to be associated with motor and mental delays. In addition, among children with congenital heart disease, long-term adverse outcomes were more likely in those with hypoplastic left heart syndrome or underlying chromosomal defects.

Functional outcomes were assessed in survivors of early cardiac heart surgery after two years (Alton et al., 2010). The patients were appraised according to the Adaptive Behavioral Assessment System II (Harrison and Oakland, 2003). A delay on the General Adaptive Composite was found in these children as compared to normal children. Lower scores, compared to those measured in normal populations, for home living and self-care were also found. This has an adverse effect on feelings of independence and confidence in school-aged children.

Early childhood neurodevelopmental outcomes were evaluated in children at 18 to 24 months of age who underwent surgery for the complete repair of total anomalous pulmonary venous connection at six weeks of age or younger (Alton et al., 2007). The average developmental score was lower than that found in the normal population. Furthermore, high postoperative lactate level on day 1 of the study resulted in low motor scores later on. An association between socioeconomic status and mental outcome in these children was also found. This study recommended exploration of other potentially modifiable variables.

Neurodevelopmental outcomes were also assessed in two-year-old children who underwent infant cardiac surgery for interrupted aortic arch at less than six weeks of age (Joynt et al., 2009). This study measured neurodevelopmental outcomes, including mental and psychomotor indices, in survivors at 18 to 24 months of age. Longer durations of DHCA procedures was found to be associated with lower mental development score in 18 to 24-month-old children without a chromosomal abnormality who underwent infant cardiac surgery for an interrupted aortic arch.

The association between postoperative plasma lactate concentrations in infants after cardiac surgery and neurodevelopmental outcome was also investigated (Cheung et al., 2005). Plasma lactate concentrations in children who had CHD and underwent the intracardiac surgery were measured when the children were first discharged from hospital and then again 18 to 24 months later. According to the researchers' findings, serial lactate can significantly predict survival rate as well as adverse neurological outcomes in survivors after surgery. Moreover, a shorter time of return to 2 mmol/L or less of plasma lactate concentrations was linked to greater chances of survival and fewer long-term neurodevelopmental disorders in these patients.

The intermediate and operative outcomes of all neonates who underwent the arterial switch operation for transposition of great arteries were also explored. Children were assessed at 18 to 24 months for neurodevelopmental outcomes

(Freed et al., 2006) using the standardized outcome measure of the Bayley Scales of Infant Development II (Bayley, 2006). The Mental Development Index (MDI) and the Psychomotor Development Index (PDI) of these patients were assessed by this scale, with scores below 70 (two standard deviations) determining delayed mental or motor development. According to the results of Freed et al., mental and motor delay was more frequent in these children as compared to the normal population. A significant association between low gestational age and high preoperative lactate with mental and/or motor delay in children with arterial switch operation for transposition of great arteries was also found. More studies were strongly suggested for optimizing the set of potentially modifiable preoperative variables to further improve developmental outcomes.

Neurodevelopmental outcome was also evaluated in two-year-old children with deletion 22q11.2 who underwent infant complex cardiac surgery (Atallah et al., 2007). Mental and psychomotor development were assessed in these children and compared to those patients without deletion 22q11.2 who had the same surgery at the same centre at the same stage (less than six weeks of age), adjusting for cardiac lesion, socioeconomic status, and year of operation. The reported mortality rate was not significantly different from those patients without deletion 22q11.2. Mental and psychomotor delays were significantly more frequent in patients who underwent neonatal complex cardiac surgery and who were affected by deletion 22q11.2. Deletion 22q11.2 was found to be a significant predictor for adverse neurodevelopmental outcomes.

Two-year-old children with hypoplastic left heart syndrome undergoing the Norwood procedure at less than six weeks were examined in order to measure their developmental outcomes and the risk factors related to these outcomes (Atallah et al., 2008). Two methods, the modified Blalock-Taussig (MBTS) and the right ventricle–to–pulmonary artery (RVPA) shunt, used in the Norwood procedure, were compared in order to investigate the difference in survival, mental and psychomotor outcomes. Surgical practice changed from MBTS to RVPA shunt use in 2002. The analysis and reports were performed separately for the two groups, since they correspond to two consecutive surgical eras and therefore the outcome differences cannot be entirely attributed to the change in surgery type, but also to unidentified changes in practice over the years. The rate of survival was improved by two years of age, although it was found to be significantly higher in the RVPA era. Mental scores were not found to be different between the two surgical eras; however, psychomotor developmental outcome was better in the RVPA era. Modifiable and non-modifiable variables were compared between the two surgical eras. For instance, lower socioeconomic status and prolonged hospitalization at the time of the Norwood procedure resulted in lower mental scores in the MBTS era. Longer ventilation days and lower PaO2 before the Norwood procedure, and longer DHCA time during the procedure, were found to be associated with lower mental scores in RVPA era. In addition, boys were found to have lower psychomotor scores in the MBTS era. In the RVPA era, lower psychomotor scores were significantly associated with longer overall hospitalization and cardiopulmonary resuscitation before or after the procedure. Mortality by two years of age was associated with serum lactate after surgery in both MBTS and RVPA eras.

The association between neurodevelopmental outcome and use of sedation/analgesia drugs before or after cardiac surgery was also investigated in two-year-old children (Guerra, et al., 2011). No association between long-term adverse neurodevelopmental outcome and sedation/analgesia drugs was found.

Neurodevelopmental outcomes were evaluated in children at less than five years of age who had received cardiac extracorporeal life support (Lequier et al., 2008). Most survivors had neurodevelopmental problems. Single ventricle anatomy and lactate on admission to the pediatric intensive care unit (PICU) were found to be associated with mortality. Two potentially modifiable variables, “time for lactate to normalize on cardiac extracorporeal life support” and “highest inotrope score during 120 hours of life support,” were found to be associated with mental scores. Chromosomal abnormality was found to be a non-modifiable risk factor.

2.2 Focus on risk factors

Just a few of the previous studies have looked at the risk factors for functional outcomes in children who had infant cardiac surgery at six weeks of age or earlier. The main objective of the present study was to determine these risk factors and the potentially modifiable variables impacting functional outcomes.

Chapter 3: Methods

3.1 Study setting

The present study is part of a prospective inter-provincial longitudinal outcomes follow-up program which began in 1999 in the provinces of Alberta, Saskatchewan, Manitoba, British Columbia and corresponding northern territories (Robertson et al., 2011). In this program, infants less than six weeks of age who underwent complex cardiac surgery for congenital heart disease were identified at the time of surgery (Robertson et al., 2004b). For the present study, all survivors of complex cardiac surgery at six weeks of age or earlier who had no chromosomal abnormalities were registered in the study for prospective follow-up at the time of their surgery at the Stollery Children's Hospital in Edmonton, Alberta, between 2000 and 2005. Predefined demographic and periopertive variables were recorded prospectively (Robertson et al., 2011). Follow-up procedures were discussed with parents and written consent was obtained (Robertson et al., 2011). Institutional health research ethics boards also approved the project and database (Robertson et al., 2011). Compliance rate for registering children in the study was 99% at baseline, with follow-up of 100% at two years, and 96% at four years. (Sauve and Robertson, 2006)

3.2 Early childhood assessment

Outcomes were measured at 18-24 months and four to five years of age. At the time of assessment, patients' history of recurrent hospitalization, sicknesses, medicine used, and physical measurements were recorded by a research nurse

(Robertson et al., 2004b). In order to assess functional abilities and adaptive skills in these children, parents filled out the Adaptive Behavioral Assessment System II (ABAS) questionnaire at the time of assessment.

According to the manual of the Adaptive Behaviour Assessment System II written by Harrison and Oakland (2003),

> The ABAS-II is designed to evaluate whether an individual displays various functional skills necessary for daily living without the assistance of others. Thus, this instrument focuses on independent behaviours and measures what an individual actually does, in addition to measuring what he or she may be able to do. In addition, the ABAS-II focuses on behaviours an individual displays on his or her own, without assistance from others.

There are three broad composite domain areas of adaptive skills measured by ABAS: Conceptual (including communication skills, functional academics, and self-direction), Social (including social skills and leisure), and Practical (including home living, community use, health and safety, and self-care). Norm-referenced total scores, named the General Adaptive Composite (GAC) are also offered by the ABAS, and include three composite domain areas (containing nine skilled areas) and a motor skill area. There are age-based standard scores for the composite scores with a mean of 100 and standard deviation of 15. Each age-base skill area scaled score has a mean of 10 and standard deviation of 3. Scores less than 2 SD below the population mean indicate developmental delay in children.

A sample of 2100 children at birth to five years of age, according to race, gender and levels of disabilities, was taken in order to standardize ABAS-II (Harrison and Oakland, 2003). The adaptive domains of ABAS-II have average reliability coefficients of 0.91 to 0.98 with a test-retest of 0.70 to 0.90 (Harrison and Oakland, 2003). Internal consistency of 0.90 in all instrument scores confirms the validity of this test (Harrison and Oakland, 2003).

3.3 Case definition

All infants admitted at the Stollery Children's Hospital (SCH) between 2000 and 2005, and undergoing complex cardiac surgery for congenital heart disease at six weeks of age or earlier were included in the study. Patients with chromosomal abnormalities were excluded from the study.

3.4 Study population

This study is a subset of a prospective interprovincial longitudinal outcomes follow-up program beginning in 1999 in four western provinces of Canada (Robertson et al., 2011). Infants with life-threatening diseases, mainly congenital heart defects, and were treated with newly emerging health technologies, such as complex cardiac surgery, at less than six weeks and survived were registered in the Western Canadian Complex Pediatric Therapies Follow-up Program (Robertson et al., 2011).

3.5 Outcome variables used in the analysis of the study

At four to five years of age, children were assessed for functional outcomes. There were four continuous outcomes of interest: 1) General Adaptive Composite (GAC); 2) Conceptual (including communication skills, functional academics, and self-direction); 3) Social (including social skills and leisure); and 4) Practical (including home living, community use, health and safety, and self-care). These continuous outcomes were defined by four variables: 1) ABASGAC4, 2) ABAScon4, 3) ABASsocialCS4 and 4) ABASpractical4.

3.5.1 What are functional outcomes?

A range of physical, social, and behavioural factors are examined when assessing children for any developmental deficits. General health, vision, hearing, language use, language comprehension, performance skills, gross motor, fine motor, overall behaviour, social interaction, intellect, environment, quality of life, nutrition, and functional behaviour are the primary categories that should be checked when diagnosing children with neurodevelopmental problems (Harrison and Oakland, 2003). Functional or adaptive behaviour is one subset category of developmental examination in children.

Functional or adaptive behaviour can be assessed by evaluating personal independence and social care in children to see whether they meet the standard level, taking into account the children's age, level of development and cultural background (Harrison and Oakland, 2003). Real-life skills such as dressing, grooming, cleaning, safety and social skills such as making friends are some examples of independence and social-care. Strengths and weaknesses in children can also be identified by using the Adaptive Behaviour Assessment System. Identifying these strengths and weaknesses can play a great role in children's success in school and life (Harrison and Oakland, 2003).

3.6 Database and variables

Several different variables, such as demographic characteristics, preoperative, operative, post-operative and overall variables were recorded prospectively and used in the data analysis. Gender (male vs. female), birthgest (Birth gestation-completed, week), was mothtotaled4 (Mother's years of schooling at four years), was sv (Norwood/Single ventricle, yes/no), was preopO2lowest [Pre-operative lowest PaO2 (arterial blood gas)] and preopLactate [Pre-operative highest plasma lactate (mmol/L)] are some of the preoperative variables were recorded when the patients arrived at the Stollery Children's Hospital before the day of surgery. The study also included operative variables such as: ageTx (Age at treatment/surgery, days), was DHCA (Deep hypothermic circulatory arrest used, yes/no) and was CPB [Cardiopulmonary bypass time (min)]. POlowestPaO2 (Post-operative: overall lowest Pa02), POhighestinosc (Post-operative: overall highest inotrope score) and POhighestlact [Post-operative: overall highest plasma lactate (mmol/L)] are some post-operative variables were measured after surgery. Some variables also used at any time period: was allventd [All ventilated days (all pre-operative and post-operative)] and allhospdays (All hospialization days at the Stollery Children's Hospital).

3.7 Study design

In this prospective observational follow-up study, children who underwent complex cardiac surgery for congenital heart disease at six weeks of age or earlier and who had no chromosomal abnormalities enrolled in the study at the time of surgery at the Stollery Children's Hospital in Edmonton, Alberta between 2000 and 2005. Children were then followed for four to five years and assessed for functional outcomes. The ABAS scales were used in order to indicate functional delay in these children. Explanatory variables were screened for association with the outcomes in order to identify modifiable risk factors for functional outcomes.

3.8 Statistical analysis

3.8.1 Method: Multiple Linear Regression Model

Objective: To determine variables associated with four-year functional outcomes in children undergoing complex cardiac surgery early in life

According to Kleinbaum (2008) and Rossi (2010), regression analysis is a method mainly used to understand the relationship between a dependent or outcome variable and independent or explanatory variables, and to explore the forms of this relationship. Regression analysis is a helpful method for understanding how much the dependent variable will change when changing just one independent variable at a time and fixing other independent variables in the model. Statisticians commonly use regression analysis for prediction and forecasting as it can predict trends and future values. Beyond establishing the strength of the association between the dependent variable and each of the independent variables, linear regression can be used to determine the subset of the informative explanatory variables that can significantly predict the outcome variable in the model. Several regression techniques were developed to accommodate various outcome types. For example, linear regression is used for continuous outcomes such as scores; logistic regression is used for binary outcome such as delayed versus not delayed; Cox regression is used for survival data; and Poisson regression is used for count data such as number of daily hospital admissions.

Multiple linear regression is used when there is a dependent variable and more than one independent variables in the model. The term *linear* is explained by the fact that linear functions are used in modeling data and estimation of unknown model parameters. The goal of multiple regression is to determine the most important or most valid subset of predictor variables. Multiple regression can accommodate various types of outcomes. A multiple regression model with two predictor variables X1 and X2 can be written as: $Y=\beta0+\beta1X1+\beta2X2+\varepsilon$

There are three unknown parameters, also called regression coefficients, β0, β1 and β2 in the model. The regression coefficients are estimated from the data. The constant coefficient or intercept of the model is β0 and can be calculated as the mean of the response variable (Y) when all other covariates (Xs) in the model are zero. The other two regression coefficients can be interpreted as the adjusted mean difference of response variable (Y) corresponding to a unit increase in Xi when all other Xs in the model are held constant.

Statisticians prefer the multiple regression model with fewer independent variables in order to avoid collinearity and improve accuracy. The model also offers greater ease of interpretation and has a smaller sample size requirement. The multiple regression model includes statistically significant independent variables as well as non-significant but clinically important variables.

Occasionally, multiple regression analysis fails to elucidate the association between the covariates and the outcome variable due to the multicollinearity problem. Multicollinearity describes a situation in which predictor variables are highly correlated with each other. This problem generally occurs when predictor variables are strongly related to each other. This correlation does not affect the reliability of the model, although it may affect the accuracy of coefficient estimates of individual predictors. When two collinear variables are forced in the model at the same time, estimation may not be performed using the model as the results will be misleading.

Tolerance or Variance Inflation Factor (VIF) or the Pearson correlation coefficient is used to detect collinear independent variables. Tolerance less than 0.1 (corresponding to VIF greater than 10) or Pearson correlation greater than 0.7 indicates collinearity with other variables.

> Tolerance= 1- the proportion of variation in the independent variable explained by other independent variables.
>
> VIF= 1/tolerance

When a collinearity problem between two predictor variables arises, researchers must decide which variable to preserve. This choice is usually guided by the scientist, and is not a statistical decision.

After identifying the variables that should be included in the model, model selection is performed. Researchers should pick the appropriate model for the multiple regressions in order to select the best subset of predictor variables. There are several different selection techniques that can be applied for multiple regression analysis, such as backward elimination, forward selection, backward stepwise elimination, forward stepwise selection and purposeful selection. Each model is briefly described below.

3.8.2 Forward selection

Forward selection begins with a constant term as the current model and adds explanatory variables one at a time until no further addition improves the fit.

Step1: Consider all models obtained by adding one more variable to the current model. For each variable not included, calculate its potential contribution (extra sum of squares F statistic for testing its significance). Identify the variable with largest contribution.

Step 2: If the largest contribution (largest F) is greater than some user pre-specified threshold, add that explanatory variable to form a new current model.

Steps 1 and 2 are repeated until no additional explanatory variables can be added.

3.8.3 Backward elimination

Backward elimination begins with all independent variables as the current model and drops explanatory variables one at a time until further drops significantly weaken the fit.

Step 1: Calculate the partial F-statistic for every variable as though it were the last variable to enter and determine p-value for the F-statistic. Identify the variable with the highest p-value.

Step 2: If the highest p-value is greater than some user pre-specified threshold, drop that explanatory variable to form a new current model and re-compute the regression for remaining variables.

Steps 1 and 2 are repeated until none of the variables are dropped.

3.8.4 Forward stepwise selection

The forward stepwise selection procedure is similar to forward selection procedure except that each variable included at previous steps are considered for removal if the significance of this variable weakens in the presence of other variables chosen at the end of the current step.

3.8.5 Backward stepwise elimination

The backward stepwise elimination procedure is similar to backward elimination procedure except that each variable eliminated at previous steps is considered for re-entry if its significance increases in the presence of variables chosen at the end of the current step.

3.8.6 Purposeful selection

The present study employs the purposeful selection model for statistical analysis. The purposeful selection begins with a univariate analysis of each outcome variable and each predictor variable. Variables with p-value less than 0.15 alpha level in univariate regression and clinically important variables are candidates for the multiple model. Multiple regressions are then fit with all these variables. Except for clinically important variables that researchers wish to preserve in the model, variables not found significant at 0.05 alpha level will be removed at this stage. To checking the confounding effect of the removed variables on variables staying in the model, the variables should be removed one at a time, and remaining parameter estimates should be compared to the full model. If there is a change greater than 15% to 20%, they will be considered confounder variables and should be retained in the model.

3.8.7 Constructed model

In the present study, I began by identifying collinear predictors to identify a multiple regression model. The result of the collinearity test is given in Appendix A. Second, linear regressions were run for each of the continuous outcomes and each of the explanatory variables to determine variables significant at 0.15 alpha level. Tables 4.4-4.7 present the results of the linear regression tests.

Multiple regressions were fitted separately for each of the four continuous outcome variables and each set of the significant predictor variables in the univariate analysis, with the exception of multicollinear variables. Clinically important variables were also included in the model regardless of their p-values in the univariate analysis. Effect sizes, together with 95% confidence intervals and p-values of each predictor included in the multiple regressions for each outcome variables are reported separately in Tables 4.4-4.7.

An analysis of possible interactions (effect modifications) among predictors selected in the final multiple models for each outcome also was performed. No significant interaction effect was found in the model. Therefore, the multiple regression models consist of:

Systematic:

E (outcome variable) = $\beta 0 + \beta 1 \times X1 + \beta 2 \times X2 + \ldots + \mathcal{E}$

Random:

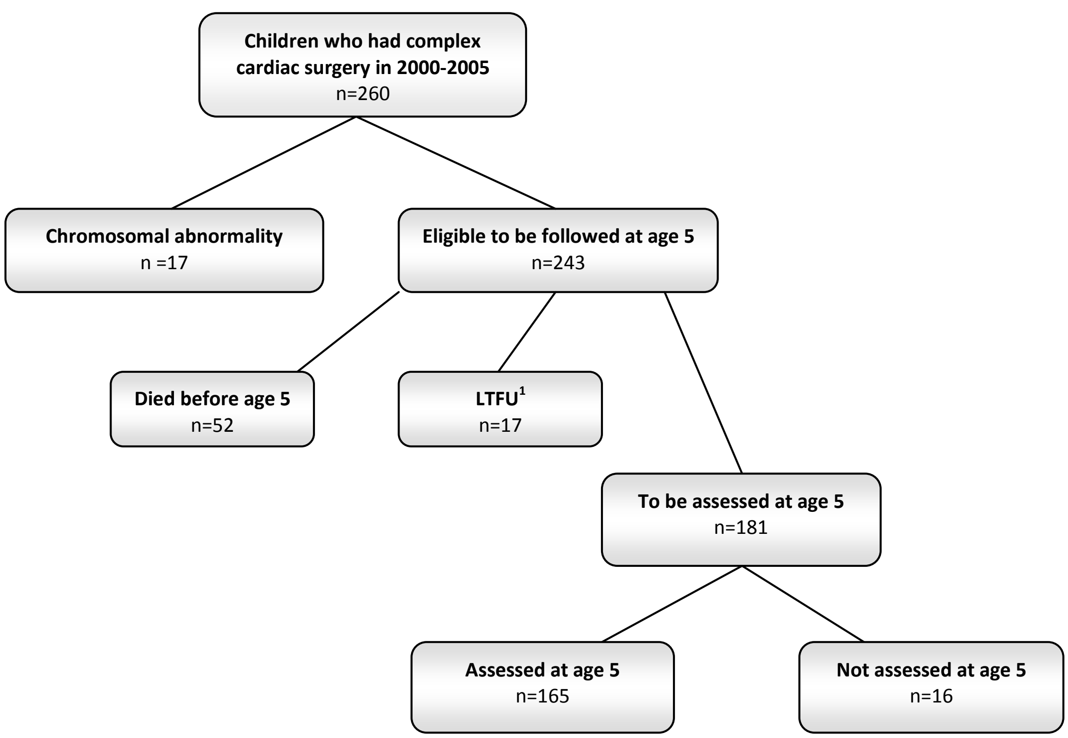
Outcome variable ~ Gaussian (E [outcome variable] , $\sigma 2$)

All statistical analysis was performed using statistical software SAS version 9.2 (SAS Institute, Cary, NC, USA) and SPSS version 16 (SPSS Inc., Chicago, Illinois, United States of America).

Chapter 4: Results

4.1 Description of the cohort study

Of the total 260 neonates who underwent complex cardiac surgery for CHD at six weeks of age or earlier between 2000 and 2005 and who were identified at the time of surgery, 17 had chromosomal abnormalities and were excluded from the study. Of the remaining 243 patients eligible for follow-up in the present study, 52 children died before age five, and 17 children were lost to follow-up, leaving 181 patients remaining for assessment at age five. Of the 181 patients, 165 children were assessed at age five in this study and 16 had not yet been assessed. The following flow chart (Figure 4.1) presents the cohort study recruitment.



[1]Lost to follow-up

Figure 4.1: Cohort study recruitment flow chart

4.2 Description of explanatory variables

Table 4.1 presents a detailed summary of demographic/preoperative, operative and post-operative variables. Continuous variables are shown as mean (SD) and dichotomous variables are presented as count (percentage %). In the study, among 165 registered patients, 104 (63%) were male and 61 (37%) were female infants. Children with single ventricle, 41 out of 165, represent approximately 25% of the patients. The average birth gestation in these infants was approximately 39 weeks (SD=1.8), and the average age at time of surgery was approximately 13 days following birth (SD=10.7). Mothers of these infants had on average 13 years of schooling (SD=2.8). The average arterial blood oxygen in these children before surgery was 37.5 mmHg (SD=15.6), increasing to 47.2 mmHg (SD=13.4) after surgery. Plasma lactate was 6.4 mmol/L (SD=3.3) after surgery as compared to 4.3 mmol/L (SD=4.5) before surgery. One hundred and thirteen (68.5%) patients required deep hypothermic circulatory arrest during surgery. The average cardiopulmonary bypass time during surgery was approximately 123.6 minutes (SD=64.5). Patient hospitalization time on average was around 34 days (SD=35.5), and the mean number of ventilation days at any time period was about 18 days (SD=17.5).

Table 4.1: Variables description of the cohort of 165 survivors of infant cardiac surgery

Preoperative/Demographic variables	**Categories**	**Mean or N (SD or %)**
Gender	Male	104 (63%)
	Female	61 (37%)
Single ventricle	Yes	41 (24.8%)
	No	124 (75.2%)
Birth gestation (weeks)		38.9 (1.8)
Mother's years of schooling		13.2 (2.8)
Lowest PaO_2 [arterial blood gas] (mmHg)		37.5 (15.6)
Highest plasma lactate (mmol/L)		4.3 (4.5)
Operative variables		**Mean or N (SD or %)**
Age at surgery (days)		12.8 (10.7)
Cardiopulmonary bypass time (min)		123.6 (64.5)
Deep hypothermic circulatory arrest used	Yes	113 (68.5%)
	No	52 (31.5%)
Post-operative variables		**Mean or N (SD or %)**
Highest inotrope score		18.3 (14.0)
Highest plasma lactate (mmol/L)		6.4 (3.3)
Lowest $Pa0_2$ (mmHg)		47.2 (13.4)
Any time period variables		**Mean or N (SD or %)**
All ventilated days		18.3 (17.5)
All hospitalization days		34.2 (35.5)

4.3 Description of outcome variables

A summary of outcome variables is presented in Table 4.2. Children's general adaptive composite score (GAC) of the ABAS at age 4 averaged to approximately 90 (SD=17), with only 23 (13.9%) children having functional delay, i.e. scores below 70. Mean scores for conceptual and social domains were around 93 (SD=17) and for practical were about 86 (SD=16). Only 15 (9.1%) children had delay in the conceptual domain, 10 (6.1%) in the social domain and 22 (13.3%) in the practical domain. Children had similar adaptive scores and showed very close rates of delay in all skill areas. The frequency of outcome delays (outcomes score<70) in these children is presented in Table 4.3.

Table 4.2: Description of outcomes in four- to five-year-old children undergoing infant cardiac surgery

Outcome	n	Minimum	Maximum	Mean	SD
ABAS[1]- GAC[2]	165	41	130	89.7	17.0
ABAS - conceptual	165	45	129	93.2	16.7
ABAS - social	165	48	130	93.9	17.1
ABAS - practical	165	35	127	85.8	16.2

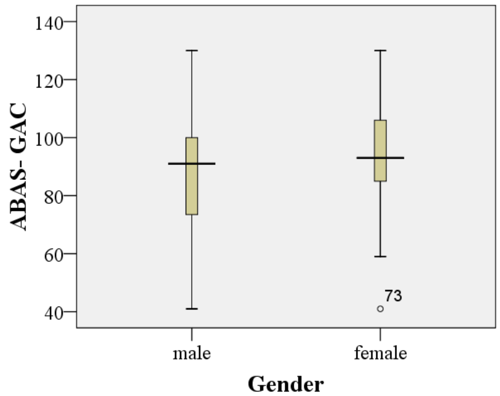
[1]ABAS: adaptive behavior assessment system
[2]GAC: general adaptive composite score of the ABAS

Table 4.3: Frequency of outcome delay (outcome score<70) in four- to five-year-old children undergoing infant cardiac surgery

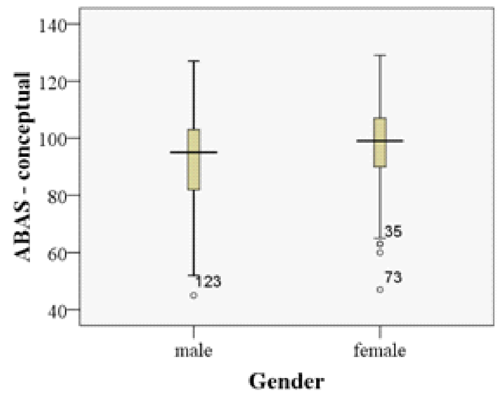
Outcome		n (%)
ABAS-GAC<70	Yes	23 (13.9%)
	No	142 (86.1%)
ABAS - conceptual,<70	Yes	15 (9.1%)
	No	150 (90.9%)
ABAS - social <70	Yes	10 (6.1%)
	No	155 (93.9%)
ABAS - practical<70	Yes	22 (13.3%)
	No	143 (86.7%)

4.4 Exploratory data analysis of outcomes versus explanatory variables

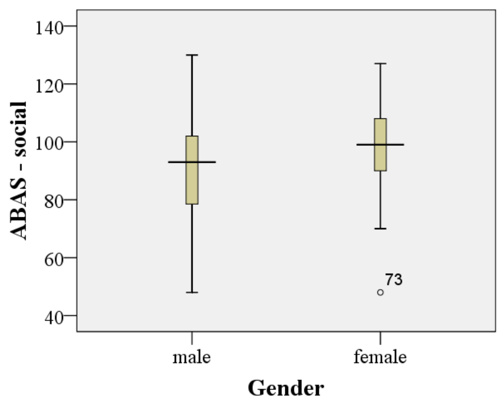
To describe the relationship between outcome variables and some of the most important explanatory variables, I used a side-by-side box plot for dichotomous variables and a scatter plot using lowess for continuous ones. The box plots presented in Figures 4.2 show the relationship between outcome variables and dichotomous variables of gender, DHCA and single ventricle. According to these plots, the median scores in males and females are almost similar; however, females had slightly higher scores compared to males. Outcome scores in patients who underwent DHCA were also similar to those patients who did not. In addition, patients with single ventricle heart had slightly lower scores than biventricular patients. The scatter plots presented in Figures 4.3 demonstrate the relationship between outcome variables and pre-operative plasma lactate. Outcome scores were decreased by increasing pre-operative plasma lactate; however, most patients had a low lactate score.



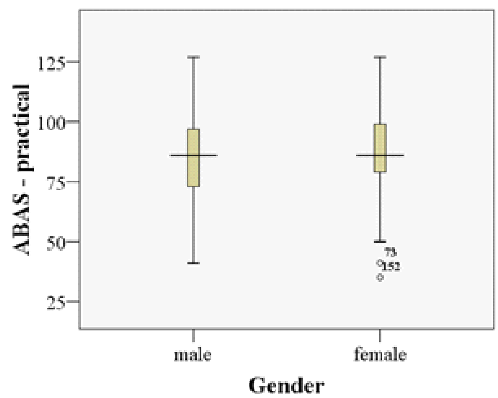
a) GAC score by gender



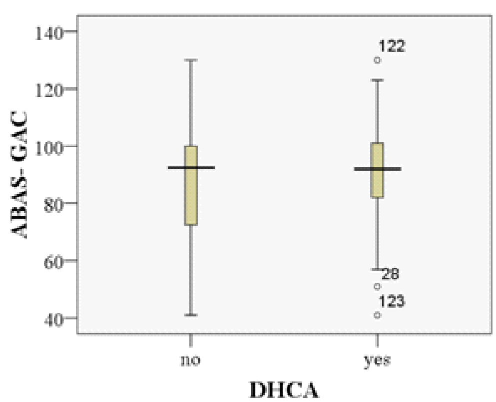
b) Conceptual score by gender



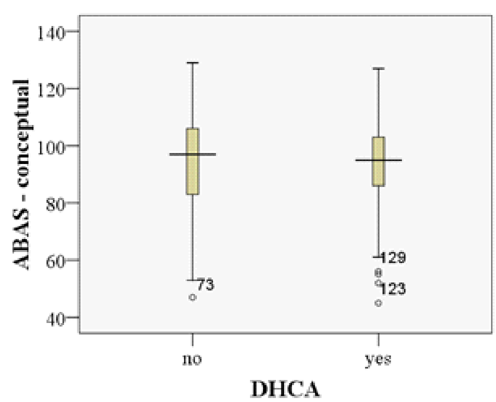
c) Social score by gender



d) Practical score by gender

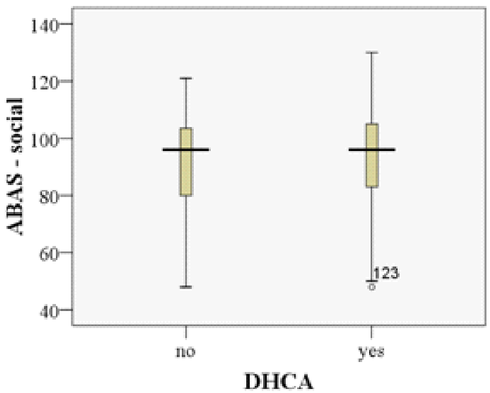


d) GAC score by DHCA

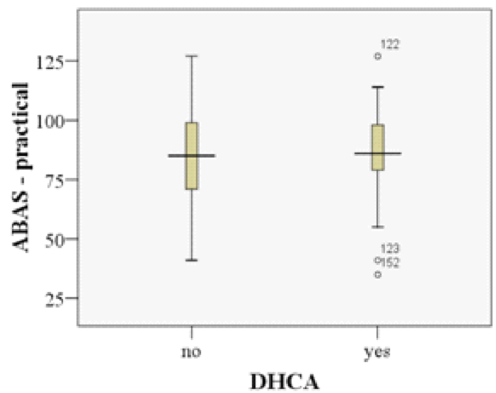


e) Conceptual score by DHCA

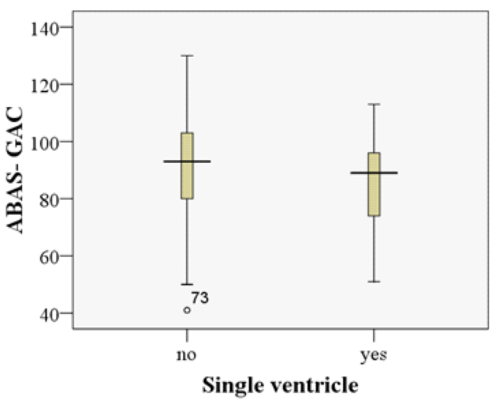
Figure 4.2: Side-by-side box plots of outcome variables by dichotomous predictors



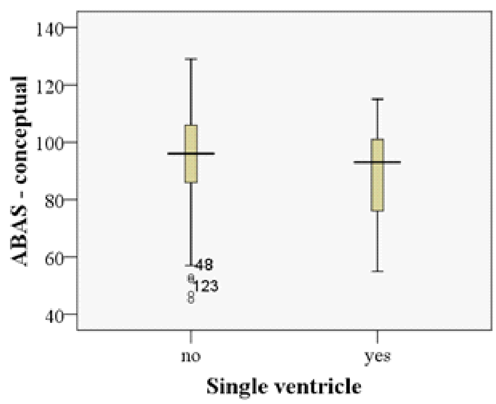
f) Social score by DHCA



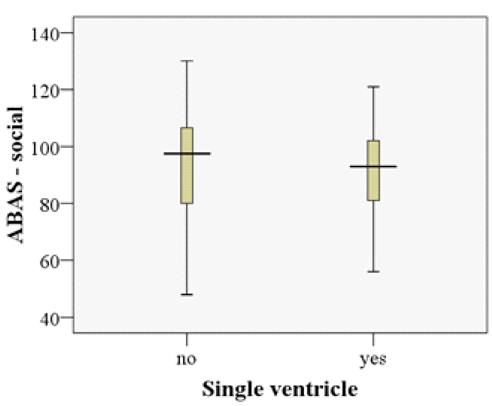
g) Practical score by DHCA



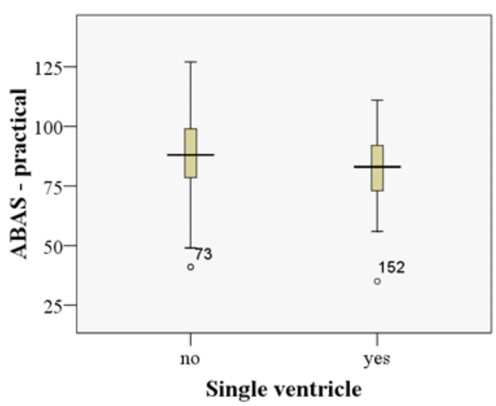
h) GAC score by single ventricle



i) Conceptual score by single ventricle

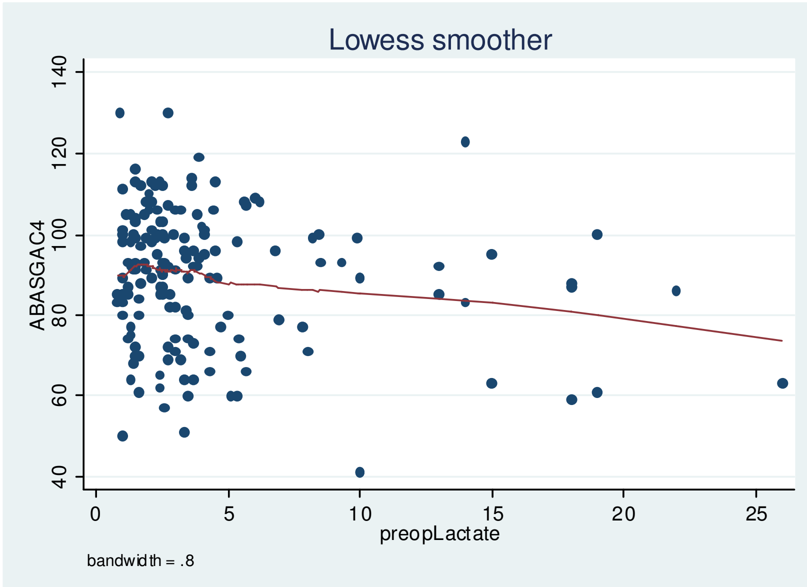


j) Social score by single ventricle

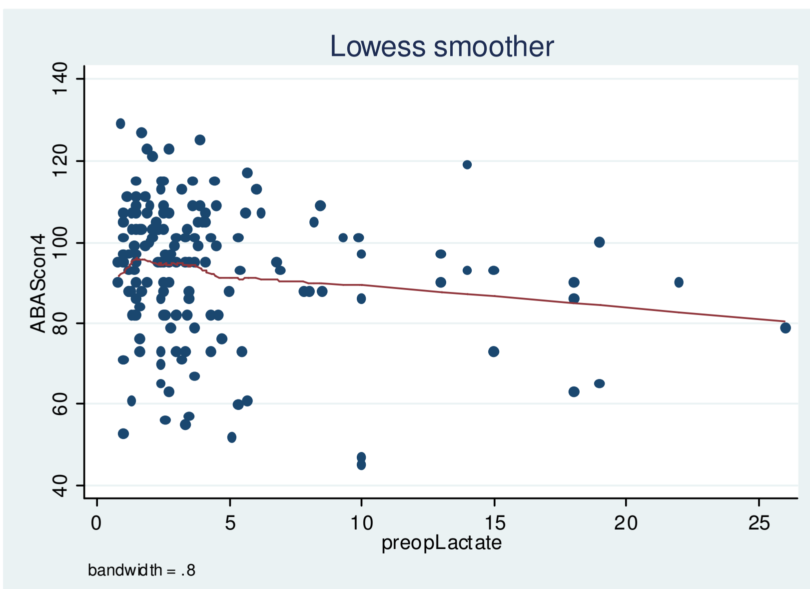


k) Practical score by single ventricle

Figure 4.2: Side-by-side box plots of outcome variables by dichotomous predictors (cont'd)

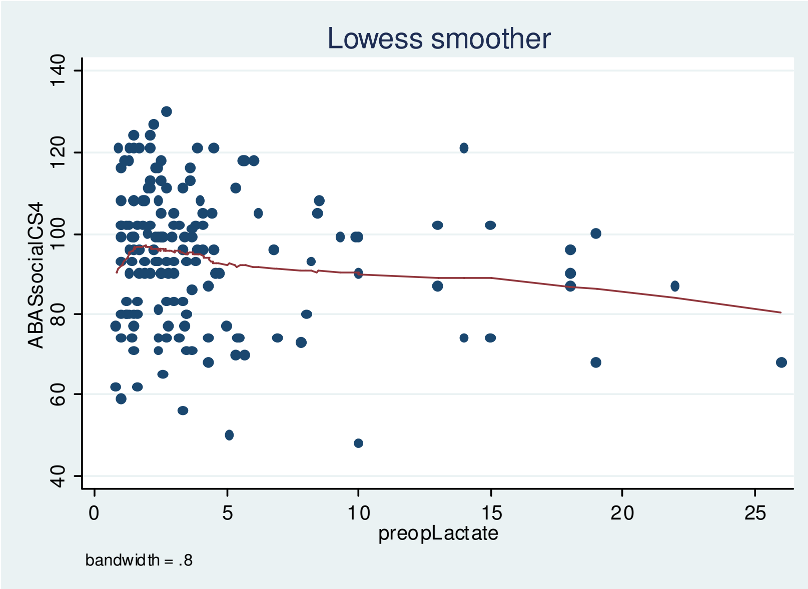


a) GAC score by pre-operative plasma lactate

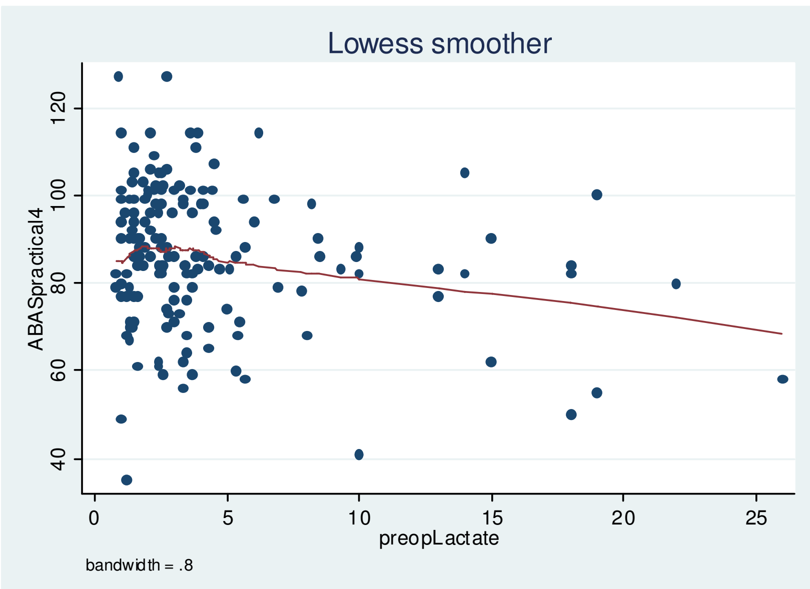


b) Conceptual score by pre-operative plasma lactate

Figure 4.3: Scatter plot of outcome variables by pre-operative plasma lactate with lowess smoother super-imposed



c) Social score by pre-operative plasma lactate



d) Practical score by pre-operative plasma lactate

Figure 4.3: Scatter plot of outcome variables by pre-operative plasma lactate with lowess smoother super-imposed (cont'd)

4.5 Risk factor analysis

Multiple linear regressions were used to assess the association between multiple risk factors and each of the four continuous outcomes. Purposeful selection method was chosen in the present study in order to select the best subset of predictor variables. As described before, first I should evaluated the correlation between all continuous independent variables. Therefore, a collinearity test was performed to identify the collinear variables (Appendix A). The predictor variables of "all hospitalization days at SCH" and "all ventilated days" as well as "single ventricle" and "post-operative lowest $Pa0_2$" were found to be multicollinear with Pearson correlation larger than 0.7. As per physician recommendation, "all ventilated days" and "single ventricle" were chosen to stay in the model.

Next, univariate analyses were carried out separately for each dependent outcome in the study and each of the explanatory variables. Except for the two variables "all hospitalization days at SCH" and "post-operative lowest $Pa0_2$" eliminated from the model due to a multicollinearity problem, all other variables with a p-value less than 0.15 alpha level were considered as significant candidates for the multiple linear regression models. The results of these analyses are presented in Tables 4.4-4.7 and discussed below.

According to the result of the univariate analysis for ABASGAC outcome, as demonstrated in Table 4.4, pre-operative highest plasma lactate (p=0.011), all ventilated days (p=0.024), single ventricle (p=0.105), post-operative highest plasma lactate (p=0.114), mother's education at four years (p=0.003) and gender (p=0.058) had p-values less than 0.15. Mother's education at four years and gender were the clinically important variables included in the four models, regardless of their p-values. However, both were significant in all bivariate data analysis except gender in relation to ABASpractical, which had a p= 0.38 and was not found to be significant. Two other variables, "hospitalization days at SCH" and "Post-operative lowest $Pa0_2$ (arterial blood gas)" were omitted from all models although they were significant, due to a multicollinearity problem.

For ABASconceptual outcome, as demonstrated in Table 4.5, all ventilated days (p=0.009), pre-operative highest plasma lactate (p=0.027), single ventricle (p=0.046), birth gestation (p=0.085), post-operative highest plasma lactate (p=0.107), post-operative highest inotrope score (p=0.126), age at treatment (p=0.133), mother's education at four years (p<0.001) and gender (p=0.020) had p-values less than 0.15.

For ABASpractical outcome, as demonstrated in Table 4.6, pre-operative highest plasma lactate (p=0.004), all ventilated days (p=0.030), single ventricle (p=0.039), post-operative highest plasma lactate (p=0.130) and mother's education at four years (p=0.043) had p-values less than 0.15. Furthermore, gender (p=0.376) as a clinically important variable was included in the model.

For ABASsocial outcome, as demonstrated in Table 4.7, pre-operative highest plasma lactate (p=0.025), all ventilated days (p=0.084), post-operative highest plasma lactate (p=0.144), mother's education at four years (p<0.001) and gender (p=0.029) had p-values less than 0.15.

Multiple regressions were fitted separately for each of the four continuous outcome variables and the corresponding subset of the predictor variables found significant in the univariate analysis. The results of multiple regression models selected by purposeful technique are presented in Tables 4.4-4.7.

According to Table 4.4, there was a significant relationship between ABASGAC with pre-operative plasma lactate [p=0.013 and 95% CI: (-1.28 , -0.16)], mother's education at four years [p=0.003 and 95% CI: (0.42 , 2.00)] and gender [p=0.031 and 95% CI: (0.51 , 10.84)] at the 0.05 alpha level. Considering the effect size of these covariates, the results can be interpreted in the following manner: when the amount of plasma lactate before surgery was increased by one unit, the General Adaptive Composite (GAC) score for children at four to five years of age who underwent complex cardiac surgery at less than six weeks of age decreased by 0.72-unit; this reduction was significant. Furthermore, females had a GAC score measuring 5.68 units more at four to five years of age than males, and this difference was statistically significant. Moreover, with each year increase in mother's education, the GAC score for children at four to five years of age was significantly improved by 1.21 units.

Therefore, the multiple regressions model was constructed as follows:

Systematic:

$E\ (ABASGAC) = \beta_0 + \beta_1 \times$ (pre-op lactate) $+ \beta_2 \times$ (mother's education) $+ \beta_3 \times$ (gender) $+ \varepsilon$

Random:

ABASGAC ~ Gaussian (E [ABASGAC], σ^2)

R-Squared for this model is 0.11, meaning that eleven percent of the variation in GAC score is explained by a model consisting of pre-op lactate, mother's education and gender.

Table 4.4: Univariate and multivariable linear regression for general adaptive composite in 165 four- to five-year-old children undergoing complex cardiac surgery at less than six weeks of age

Label	**Univariate regression**		**Multiple regression**	
	Effect size (95% CI)	**P-value[1]**	**Effect size (95% CI)**	**P-value[2]**
Mother's education at four years (year)	1.22 (0.41,2.03)	0.003	1.21 (0.42,2.00)	0.003
All hospitalization days at SCH	-0.11 (-0.18,-0.03)	0.004	-	-
Pre-op highest lactate (mmol/L)	-0.75 (-1.33,-0.17)	0.011	-0.72 (-1.28,-0.16)	0.013
All ventilated days [all pre-op and post-op]	-0.17 (-0.32,-0.02)	0.024	-	-
Post-op: overall lowest Pa02 (mmHg)	0.22 (0.03,0.42)	0.025	-	-
Female	5.21 (-0.17,10.59)	0.058	5.68 (0.51,10.84)	0.031
Norwood/Single ventricle	-4.97 (-11.00,1.06)	0.105	-	-
Post-op: overall highest lactate (mmol/L)	-0.64 (-1.43,0.15)	0.114	-	-
Age at Treatment/surgery - days	-0.17 (-0.42,0.07)	0.165	-	-
Birth gestation, completed (weeks)	0.97 (-0.47,2.41)	0.184	-	-
Post-op: overall highest inotrope score	-0.09 (-0.27,0.10)	0.369	-	-
DHCA[3] no/yes	2.24 (-3.41,7.88)	0.435	-	-
Cardiopulmonary bypass time (min)	-0.01 (-0.06,0.03)	0.473	-	-
Pre-op lowest PaO2 (mmHg)	0.05 (-0.12,0.22)	0.547	-	-

[1]P-value < 0.15 in univariate regression considered as significant candidates for the multivariate analysis

[2]P-value < 0.05 considered as significant predictors for ABASGAC

[3]DHCA: Deep hypothermic circulatory arrest

Table 4.5 shows the significant association between ABASconceptual with pre-operative plasma lactate [p=0.043 and 95% CI: (-1.09 , -0.02)], mother's education at four years [p<0.001 and 95% CI: (0.64 , 2.16)], all ventilated days [p=0.024 and 95% CI: (-0.29 , -0.02)] and gender [p=0.004 and 95% CI: (2.31 , 12.13)] at the 0.05 alpha level. The result of multiple regressions according to covariates' effect size can be interpreted in the following manner: when the amount of plasma lactate before surgery is increased by one unit, the conceptual score of children at four to five years of age who underwent complex cardiac surgery at less than six weeks of age decreased by 0.55-unit; this reduction was significant. Females showed conceptual scores that were 7.22 units higher than those of males at four to five years of age; this difference was also statistically significant. Furthermore, each one-year increase in mother's education level significantly improved the conceptual score of children at four to five years of age by 1.40 units; in addition, each day increase in ventilation reduced children's conceptual scores by 0.16-unit.

Therefore, the multiple regressions model was constructed as follows:

Systematic:

E (ABASconceptual) = $\beta_0 + \beta_1 \times$ (pre-op lactate) + $\beta_2 \times$ (mother's education) + $\beta_3 \times$ (gender) + $\beta_4 \times$ (all ventilated days) + $\mathcal{E}$

Random:

ABASconceptual ~ Gaussian (E [ABASconceptual], σ^2)

R-Squared for this model is 0.17, meaning that seventeen percent of the variation in conceptual score is explained by a model consisting of pre-op lactate, mother's education, gender and all ventilated days.

Table 4.5: Univariate and multivariable linear regression for conceptual score in 165 four- to five-year-old children undergoing complex cardiac surgery at less than six weeks of age

Label	**Univariate regression**		**Multiple regression**	
	Effect size (95% CI)	**P-value[1]**	**Effect size (95% CI)**	**P-value[2]**
Mother's education at four years (year)	1.53 (0.75,2.31)	0.001	1.40 (0.64,2.16)	0.001
All hospitalization days at SCH	-0.12 (-0.19,-0.05)	0.001	-	-
All ventilated days [all pre-op and post-op]	-0.19 (-0.34,-0.05)	0.009	-0.16 (-0.29,-0.02)	0.024
Post-op: overall lowest $Pa0_2$ (mmHg)	0.24 (0.05,0.43)	0.014		
Female	6.25 (1.01,11.49)	0.020	7.22 (2.31,12.13)	0.004
Pre-op highest lactate (mmol/L)	-0.64 (-1.22,-0.07)	0.027	-0.55 (-1.09,-0.02)	0.043
Norwood/Single ventricle	-5.98 (-11.86,-0.1)	0.046	-	-
Birth gestation, completed (weeks)	1.23 (-0.17,2.64)	0.085	-	--
Post-op: overall highest lactate (mmol/L)	-0.64 (-1.41,0.14)	0.107	-	-
Post-op: overall highest inotrope score	-0.14 (-0.33,0.04)	0.126	-	-
Age at Treatment/surgery - days	-0.18 (-0.42,0.06)	0.134	-	-
Cardiopulmonary bypass time (min)	-0.01 (-0.05,0.03)	0.555	-	-
Pre-op lowest PaO_2 (mmHg)	0.01 (-0.16,0.17)	0.914	-	-
DHCA[3] no/yes	-0.19 (-5.73,5.34)	0.945	-	-

[1]P-value < 0.15 in univariate regression considered as significant candidates for the multivariate analysis

[2]P-value < 0.05 considered as significant predictors for ABASconseptual

[3]DHCA: Deep hypothermic circulatory arrest

The regression result of ABASpractical is presented in Table 4.6. Based on the result, a significant relation was found between ABASpractical and pre-operative plasma lactate [p=0.004 and 95% CI: (-1.35 , -0.27)], mother's education at four years [p=0.047 and 95% CI: (0.01 , 1.53)] and single ventricle [p=0.026 and 95% CI: (-11.85 , -0.7)] and a not significant relation was found with the clinically important variable of gender [p=0.238 and 95% CI: (-1.98 , 7.94)] at the 0.05 alpha level. According to the covariates' effect size, an increase of one unit of plasma lactate before surgery caused a 0.81-unit decrease in the practical score of four-year-old children who underwent complex cardiac surgery at less than six weeks of age; this reduction was significant. Compared to males, females had a practical score that measured 2.98 units higher at four to five years of age, but this difference was not statistically significant. Furthermore, with each one-year increase in mother's education, the practical score of children at four to five years of age was significantly improved by 0.77-unit. Finally, single ventricle children (children with single heart ventricle) had significantly lower practical score, more precisely 6.31 units lower practical score at four to five years of age as compared to children with biventricular heart.

Therefore, the multiple regressions model was constructed as follows:

Systematic:

$E\ (ABASpractical) = \beta_0 + \beta_1 \times (\text{pre-op lactate}) + \beta_2 \times (\text{mother's education}) + \beta_3 \times (\text{gender}) + \beta_4 \times (\text{single ventricle}) + \varepsilon$

Random:

ABASpractical ~ Gaussian (E [ABASpractical], σ^2)

R-Squared for this model is 0.11, meaning that eleven percent of the variation in practical score is explained by a model consisting of pre-op lactate, mother's education, gender and single ventricle.

Table 4.6: Univariate and multivariable linear regression for practical score in 165 four- to five-year-old children undergoing complex cardiac surgery at less than six weeks of age

Label	Univariate regression		Multiple regression	
	Effect size (95% CI)	**P-value[1]**	**Effect size (95% CI)**	**P-value[2]**
Pre-op highest lactate (mmol/L)	-0.83 (-1.38,-0.28)	0.004	-0.81 (-1.35,-0.27)	0.003
Post-op: overall lowest $Pa0_2$ (mmHg)	0.24 (0.06,0.43)	0.010	-	-
All hospitalization days at SCH	-0.09 (-0.16,-0.02)	0.013	-	-
All ventilated days [all pre-op and post-op]	-0.16 (-0.30,-0.02)	0.030	-	-
Norwood/Single ventricle	-6.01 (-11.73,-0.2)	0.039	-6.31 (-11.85,-0.7)	0.026
Mother's education at four years (weeks)	0.81 (0.03,1.60)	0.043	0.77 (0.01,1.53)	0.046
Post-op: overall highest lactate (mmol/L)	-0.58 (-1.34,0.17)	0.130	-	-
Age at treatment/surgery - days	-0.15 (-0.38,0.09)	0.216	-	-
Female	2.33 (-2.85,7.50)	0.376	2.98 (-1.98,7.94)	0.238
DHCA[3] no/yes	1.80 (-3.58,7.19)	0.509	-	-
Post-op: overall highest inotrope score	-0.06 (-0.24,0.12)	0.514	-	-
Pre-op lowest PaO_2 (mmHg)	0.04 (-0.12,0.20)	0.616	-	-
Cardiopulmonary bypass time (min)	-0.01 (-0.05,0.03)	0.684	-	-
Birth gestation, completed (weeks)	0.15 (-1.23,1.53)	0.828	-	-

[1]P-value < 0.15 in univariate regression considered as significant candidates for the multivariate analysis

[2]P-value < 0.05 considered as significant predictors for ABASpractical

[3]DHCA: Deep hypothermic circulatory arrest

According to Table 4.7, there was a significant association between ABASsocial with pre-operative plasma lactate [p=0.028 and 95% CI: (-1.19 , -0.07)], mother's education at four years [p<0.001 and 95% CI: (0.60 , 2.18)] and gender [p=0.013 and 95% CI: (1.37 , 11.67)] at the 0.05 alpha level. The result of multiple regressions considering significant covariates' effect size can be interpreted in the following manner: by increasing plasma lactate before surgery by one unit, social scores of four-year-old children who underwent complex cardiac surgery at less than six weeks of age decreased by 0.63-unit; this reduction is significant. Females had a social score that was 6.52 units higher compared to males at four to five years of age; this difference is statistically significant. Furthermore, each one-year increase in mother's education was shown to improve the social score of four-year-old children by 1.39 units.

Therefore, the multiple regressions model was constructed as follows:

Systematic:

$E\,(\text{ABASsocial}) = \beta_0 + \beta_1 \times (\text{pre-op lactate}) + \beta_2 \times (\text{mother's education})$

$+\ \beta_3 \times (\text{gender}) + \mathcal{E}$

Random:

$\text{ABASsocial} \sim \text{Gaussian}\,(E\,[\text{ABASsocial}]\,,\ \sigma^2)$

R-Squared for this model is 0.13, meaning that thirteen of the variation in social score is explained by a model consisting of pre-op lactate, mother's education and gender.

Table 4.7: Univariate and multivariable linear regression for social score in 165 four- to five-year-old children undergoing complex cardiac surgery at less than six weeks of age

Label	Univariate regression		Multiple regression	
	Effect size (95% CI)	**P-value[1]**	**Effect size (95% CI)**	**P-value[2]**
Mother's education at four years (year)	1.39 (0.58,2.20)	0.001	1.39 (0.60,2.18)	0.001
Pre-op highest lactate (mmol/L)	-0.67 (-1.26,-0.08)	0.0251	-0.63 (-1.19,-0.07)	0.028
Female	6.01 (0.62,11.40)	0.0291	6.52 (1.37,11.67)	0.013
All hospitalization days at SCH	-0.08 (-0.15,-0.01)	0.032	-	-
All ventilated days [all pre-op and post-op]	-0.13 (-0.28,0.02)	0.084	-	-
Post-op: overall highest lactate (mmol/L)	-0.59 (-1.39,0.20)	0.144	-	-
Post-op: overall lowest Pa02 (mmHg)	0.13 (-0.06,0.33)	0.187	-	-
Age at Treatment/surgery - days	-0.15 (-0.40,0.10)	0.231	-	-
Pre-op lowest PaO_2 (mmHg)	0.08 (-0.08,0.25)	0.323	-	-
Birth gestation, completed (weeks)	0.65 (-0.80,2.10)	0.379	-	-
Norwood/Single ventricle	-2.35 (-8.44,3.75)	0.448	-	-
Cardiopulmonary bypass time (min)	-0.01 (-0.05,0.03)	0.509	-	-
DHCA[3] no/yes	1.78 (-3.89,7.46)	0.535	-	-
Post-op: overall highest inotrope score	-0.02 (-0.21,0.17)	0.840	-	-

[1]P-value < 0.15 in univariate regression considered as significant candidates for the multivariate analysis

[2]P-value < 0.05 considered as significant predictors for ABASsocial

[3]DHCA: Deep hypothermic circulatory arrest

4.6 Regression diagnostics

The proper regression model, after construction, should be confirmed by the goodness of fit of the model. There are different statistical tools for model validation, but generally graphical analysis of the pattern of residuals is a good method for this purpose. The normality assumption can be checked via a normal probability plot. A scatter plot of residuals against predicted values indicates the assumption of randomness and constant variance assumption for any errors.

Normal probability plots and scatter plots of residuals for all four outcomes showed the residuals of the four constructed models had normal distributions with constant variance. There was no indication of violating the normality and independence assumptions that were used to confirm the proper fit of the models.

Chapter 5: Discussion

5.1 Overview

Functional outcomes in four to five-year-old children who underwent complex cardiac surgery for congenital heart disease at less than six weeks of age and who had no chromosomal abnormalities were assessed in order to identify risk factors and potentially modifiable variables associated with these functional outcomes.

5.1.1 Statistical analysis in Outcomes Research after cardiac surgery in early infancy: current practice and recommendations

The findings of a comprehensive review of the statistical analysis sections of published studies on outcome research after cardiac surgery in early infancy are summarized below. Most studies assess associations between dichotomous predictors and continuous outcomes univariately, via a t-test (Bellinger, 2003; Bellinger, 1999). In the case of a continuous predictor, a dichotomization is performed, according to a pre-defined cut-off. Except for cases where the choice of the cut-off is motivated scientifically, searching for several cut-offs based only on statistical significance increases the type I error rate. Adjustments for multiple hypothesis testing are recommended. A common practice to avoid dichotomization is to perform a Pearson correlation for measuring the association between a continuous predictor and a continuous outcome. However, a Pearson correlation is not recommended beyond the exploratory phase of the analysis, for the reason that a high correlation does not necessarily correspond to a large effect.

Univariate regressions are better suited for understanding the association with a continuous outcome, providing an estimate of the effect size, confidence interval and significance value. Some studies adjust for demographic and/or clinical variables (Bellinger, 2003; Bellinger, 1999); however, we found that model building is rarely performed (Lequier, 2008; Atallah, 2008).

Model building is a comprehensive method that considers all details and provides a reliable result when there is a dependent variable and several (more than one) independent variables in a study. In this method, multicollinearity should be checked first. Multicollinearity describes a situation in which independent variables are strongly correlated with each other and some should be eliminated from the model. Reviewing some studies revealed that multicollinearity was not checked at the beginning of their analyses (Bellinger, 2003; Wernovsky, 2000; Rappaport, 1998; Bellinger, 1999). Next, after selecting the variables that should be included in the model, the best multiple regression model is identified in order to pick the best subset of independent (predictor) variables. This step was also not performed in some studies, which sought to determine the association between variables, such as the Bellinger (1999) study. Lastly, possible interaction among selected variables in the final multiple model should be checked. A number of studies also neglected to pay enough attention to the role of interactions in their model, or at least checking for interactions was not reported (Bellinger, 2003; Wernovsky, 2000; Rappaport, 1998; Bellinger, 1999; Lequier, 2008).

After constructing the proper regression model, the goodness of fit should be confirmed by different statistical tools for model validation, including normal probability plots and scatter plots of residuals. In most studies reviewed, the goodness of fit was not checked or at least was not reported in any particular section of findings (Bellinger, 2003; Wernovsky, 2000; Rappaport, 1998; Lequier, 2008; Atallah, 2008).

5.2 Identified risk factors for functional outcomes in four-year-old children undergoing congenital heart disease

5.2.1 Influence of gender on functional outcomes

Male children were identified in current study to have significantly lower functional abilities, as scored in the areas of GAC, conceptual, practical and social domains, when compared to female children. Being male has been reported to be associated with a lower psychomotor developmental index of infants at 18-24 months of age who survived Norwood surgery for hypoplastic left heart surgery (Blackwood et al., 2010).

5.2.2 Influence of pre-operative plasma lactate on functional outcomes

A significant association between high pre-operative plasma lactate with lower functional scores, in all domains, of four-year-old children was found in the present study. Increasing the amount of pre-operative plasma lactate has been found to influence increased risks of functional disabilities in these children. This finding is supported by other studies as well. For example, Freed et al. (2006) demonstrated a significant association between high pre-operative plasma lactate and mental and/or motor delay in children undergoing arterial switch operations for transposition of great arteries. In addition, according to the findings of Cheung et al. (2005), plasma lactate can significantly predict survival and also adverse neurological outcomes in survivors after cardiac surgery. Lequier et al. (2008) also found that lactate on admission to the pediatric intensive care unit is predictive of death. As a result, lower plasma lactate concentration indicates a greater chance of survival and fewer long-term neurodevelopmental disorders in these children.

5.2.3 Influence of mother's education on functional outcomes

Mother's education at four years significantly affects all domains of functional outcomes in these patients. Each year increase in mother's education significantly improves the functional abilities of four-year-old children. The effect of social economic status (SES) in these children was also previously studied. For instance, an association between socioeconomic status and mental outcome in children 18 to 24 months of age who underwent complete repair of total anomalous pulmonary venous connection at six weeks or younger was found in Alton et al. (2007) study. The significant relation of SES and mental outcomes in two-year-old children with hypoplastic left heart syndrome undergoing the Norwood procedure at less than six months was also found by Atallah et al. (2008). According to Wernovsky et al. (2000), there is also a strong relation between higher SES and higher IQ and performance in these children after Fontan operations. The relation between SES and IQ was also determined in the Forbess et al. (2002) study. This study found a significant association between lower SES and lower IQ scores in five-year-old children after congenital heart surgery.

5.2.4 Influence of number of days ventilated on functional outcomes

The number of ventilation days was found in the present study to have a significant relation to conceptual score in the studied children at four to five years. Longer ventilation time was a significant predictor of lower conceptual scores in four-year-old children. Other studies have also confirmed that ventilation time is a significant predictor of adverse neurodevelopmental outcomes. For example, Atallah et al. (2008) found a considerable association between longer ventilation time and lower mental score in two-year-old children with hypoplastic left heart syndrome undergoing the Norwood procedure at less than six months. The association between longer preoperative ventilation time and adverse neurodevelopmental outcome in 18-month-old survivors of complex heart surgery at less than six months was also determined in the Robertson et al. (2004b) study.

5.2.5 Influence of single ventricle heart defect on functional outcomes

The current study determined that there is a considerable relation between single ventricle anatomy and practical scores of children at four to five years. Single ventricle heart children had significantly lower practical scores at four to five years of age. Previously, single ventricle was found to be associated with mortality in children who had received cardiac extracorporeal life support (Lequier et al., 2008).

5.3 Strengths and limitations

This study is part of a larger cohort follow-up study which prospectively followed children who underwent complex cardiac surgery for CHD at less than six weeks of age. Children then were assessed at two and four to five years of age for neurological and functional outcomes. Therefore, data in this study were collected prospectively which ameliorates recall bias; it is the primary strength of this study. Second, there are a large number of children registered in the database, with the adequate length of follow-up and minimal loss to follow-up. Moreover this study offers an extensive geographic base, tracking children from across Western Canada who underwent complex cardiac surgery at the same centre. Finally, unique questionnaires were used to assess children; these questionnaires then were filled out by parents.

However, the results should be interpreted with caution due to several study limitations. First, this is an observational study; researchers had limited control over confounding factors and could only control recognized and measured factors, though this process made it unlikely that the researchers could adjust for unknown factors. Second, the questionnaires were filled out by parents who may be inclined to answer questions optimistically, which may affect the accuracy of the results. Third, since this is an observational study of a particular, defined group, results cannot be applied to the population at large.

Chapter 6: Conclusion

6.1 Summary

Based on the database provided for the present study, part of the Western Canadian Complex Pediatric Therapies Follow-up Program, pre-operative plasma lactate, gender and mother's education at four years were found significantly associated with all of the four domains of functional outcomes in the study. The number of days ventilated was significantly associated to the Conceptual domain, and single ventricle heart defect was associated with the Practical domain. This study used model building in order to construct a multivariable regression analysis. Pre-operative plasma lactate, which was found as an important modifiable risk factor for all four domains of functional outcomes in four-year-old children who underwent complex cardiac surgery for congenital heart disease at less than six weeks of age, should be kept low before surgery. Ultimately, we anticipate that the results of this study will add new knowledge for future targeted interventions that aim to reduce the burden of disease prior to school entry.

6.2 Future research

Alton et al. (2010) looked at functional outcomes in two-year-old children undergoing early cardiac surgery. However, the relationship between the functional outcomes of two- and four-year-old children has not been studied previously. The mean change in outcome from two years to four to five years of age, while adjusting for demographic variables, can be investigated via Generalized Estimating Equations. This is an advanced regression analysis technique that can accommodate correlations of these measures within children. Predicting outcomes at four to five years of age based on outcomes at two years and relevant demographic variables is also an important task with implications for counselling and resource allocation.

References

1. Alton, G.Y., Rempel, G.R., Robertson, C.M.T., Newburn-Cook, C.V., & Norris, C.M. (2010). Functional outcomes after neonatal open cardiac surgery: comparison of survivors of the Norwood Staged procedure and the Arterial Switch operation. Cardiol Young, 20(6):668-75.
2. Alton, G.Y., Robertson, C.M.T., Sauve, R.S., Divekar, A., Nettel-Aguirre, A., Seltzer, S., ...The Western Canadian Pediatric Therapies Follow-up Group (2007). Early childhood health, growth, and neurodevelopmental outcomes after complete repair of Total Anomalous Pulmonary Venous Correction at 6 weeks or younger. J Thorac Cardiovasc Surg, 133:905-11.
3. Atallah, J., Joffe, A.R., Robertson, C.M.T., Leonard, N., Blakley, P.M., Nettel-Aguirre, A., ...The Western Canadian Complex Pediatric Therapies Follow-up Group (2007). Two-year general and neurodevelopmental outcome after neonatal complex cardiac surgery in patients with deletion 21q11.2: a comparative study. J Thorac Cardiovasc Surg, 134:772-9.
4. Atallah, J., Dinu, I.A., Joffe, A.R., Robertson, C.M.T., Sauve, R.S., Dyck, J.D., ...The Western Canadian Complex Pediatric Therapies Follow-up Group (2008).Two-year survival and mental psychomotor outcomes after the Norwood Procedure: An analysis of the modified Blalock-Taussig shunt and right ventricle-to-pulmonary artery shunt surgical eras. Circulation, 118:1410-18.

5. Bellinger, D.C., Wypij, D., duPlessis, A.J., Rappaport, L.A., Jonas, R.A., Wernovsky, G., & Newburger, J.W. (2003). Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: The Boston Circulatory Arrest Trial. J Thorac Cardiovasc Surg, 126:1385-96.

6. Bellinger, D.C., Wypij, D., Kuban, K.C., Rappaport, L.A., Hickey, P.R., Wernovsky, G., ...Newburger, J.W. (1999). Developmental and neurological status of children at 4 years of age after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. 100:526-32.

7. Bellinger, D.C., Jonas, R.A., Rappaport, L.A., Wypij, D., Wernovsky, G., Kuban, K.C., ...Newburger, J.W. (1995). Developmental and neurologic status of children after heart surgery with hypothermic circulatory arrest or low-flow cardiopulmonary bypass. N Engl J Med., 332:549-55.

8. Blackwood, J., Joffe, A.R., Robertson, C.M.T., Dinu, I., Alton, G., Penner, K., …The Western Canadian Complex Pediatric Therapies Follow-up Group (2010). Association of Hemoglobin and Transfusion with Outcome After Operations for Hypoplastic Left Heart. Annals of Thoracic Surgery, 89:1378-84.

9. Cheung, P.Y., Chui, N., Joffe, R.A., Rebeyka, I.M., Robertson, C.M.T., & The Western Canadian Complex Pediatric Therapies Follow-up Group (2005). Post-operative lactate concentrations predict the outcome of infants aged 6 weeks or less after intracardiac surgery: a cohort follow-up to 18 months. J Thorac Cardiovasc Surg, 130:837-43.

10. Dunbar-Masterson, C., Wypij, D., Bellinger, D.C., Rappaport, L.A., Baker, A.L., Jonas, R.A., & Newburger, J.W. (2001). General health status of children with D-transposition of the great arteries after the arterial switch operation. Circulation, 104:I138-42.

11. Forbess, J.M., Visconti, K.J., Hancock-Friesen, C., Howe, R.C., Bellinger, D.C., Jonas, R.A. (2002). Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry. 106(Suppl I):I95-102.

12. Freed, D.H., Robertson, C.M.T., Sauve, R.S., Joffe, A.R., Rebeyka, I.M., Ross, D.B., ...The Western Canadian Complex Pediatric Therapies Follow-up Group (2006). Intermediate-term outcomes of the Arterial Switch operation for Transposition of the Great Arteries in neonates: alive but well? J Thorac Cardiovasc Surg, 132:845-52.

13. Gaynor, J.W., Wernovsky, G., Jarvick, G.P., Bernbaum, J., Gerdes, M., Zackai, E., ...Spray, T.L. (2007). Patient characteristics are important determinants of neurodevelopmental outcome at one year of age after neonatal and infant cardiac surgery. J Thorac Cardiovasc Surg, 113:1344-53.

14. Guerra, G.G., Robertson, C.M.T., Alton, G. Y., Joffe A.R., Cave, D.A., Dinu, I. A., ...The Western Canadian Complex Pediatric Therapies Follow-up Group (2011). Sedative and Analgesia Drugs and the Neurodevelopmental Outcomes of Neonates after cardiac surgery. Pediatric Anesthesia, 21(9): 932-941.

15. Harrison, P.L. & Oakland, T. (2003). Manual of the adaptive behaviour assessment system II. San Antonio, Texas: Psychological Corp, Harcourt Assessment Company.

16. Hövels-Gürich, H.H., Seghaye, M.C., Däbritz, S., Messmer, B.J., & von Bernuth, G. (1997). Cognitive and motor development in preschool and school-aged children after neonatal Arterial Switch Operation. J Thorac Cardiovas Surg, 114:578-85.

17. Joynt, C.A., Robertson, C.M.T., Cheung, P.Y., Nettel-Aguirre, A., Joffe, A.R., Sauve, R.S., ...The Western Canadian Complex Pediatric Therapies Follow-up Group (2009). Two-year neurodevelopmental outcomes of infants undergoing neonatal cardiac surgery for interrupted aortic arch: a descriptive analysis. J Thorac Cardiovasc Surg, 138:924-32.

18. Kern, J.H., Hinton, V.J., Nereo, N.E., Hayes, C.J., Gersony, W.M. (1998). Early developmental outcome after the Norwood procedure for hypoplastic left heart syndrome. Pediatrics, 102:1148– 52.

19. Kleinbaum, D.G., Kupper, L.L., Muller, K.E., Nizam, A. (2008). Applied Regression Analysis and other Multivariable Methods. 4th Edition. Toronto: Duxbury Press.

20. Lequier, L., Joffe, A.R., Robertson, C.M.T., Dinu, I.A., Wongswadiwat, Y., ...The Western Canadian Complex Pediatric Therapies Follow-up Group (2008). Two-year survival, mental and motor outcomes after cardiac extracorporeal life support at less than 5 years of age. J Thorac Cardiovasc, 36:976-83.

21. Limperopoulos, C., Majnemer, A., Shevell, M.I., Rosenblatt, B., Rohlicek, C., & Tchervenkov, C. (2000). Neurodevelopmental status of newborns and infants with congenital heart defects before and after open heart surgery. J Pediatr, 137:638-45.

22. Mahle, W.T., Coon, P.D., Wernovsky, G., Rychik, J. (2001). Quantitative echocardiographic assessment of the performance of the functionally single right ventricle after the Fontan operation. Cardiol Young, 11:399-406.

23. Majnemer, A., Limpropoulos, C., Shevell, M., Rohlicek, C., Rosenblatt, B., & Tchervenkov, C. (2009). A new look at outcomes of infants with congenital heart disease. Pediatric Neurology, 40(3):197-204.

24. Miller, S.P., McQuillen, P.S., Hamrick, S., Xu, D., Glidden, D.V., Charleton, N., ...Vigneron, D.B. (2007). Abnormal brain development in newborns with congenital heart disease. N Engl J Med, 357:1928-38.

25. Newburger, J.W., Jonas, R.A., Wernovsky, G., Wypij, D., Hickey, P.R., Kuban, K.C., ...Ware, J.H. (1993). A comparison of the perioperative neurologic effects of hypothermic circulatory arrest versus low-flow cardiopulmonary bypass in infant heart surgery. N Engl J Med, 329:1057 –64.

26. Newberger, J.W., Wypij, D., Bellinger, D.C., du Plessis, A.J., Kuban, K.C.K., Rappaport, L.A., Almirall, D., Wessel, D.L., Jonas, R.A., & Wernovsky, G. (2003). Length of stay after infant heart surgery is related to cognitive outcome at eight years. J Pediatr, 143:67-73.

27. Rappaport, L.A., Wypij, D., Bellinger, D.C., Helmers, S.L., Holmes, G.L., Barnes, P.D., ... Newburger, J.W. (1998). Relation of seizures after cardiac surgery in early infancy to neurodevelopmental outcome. Boston Circulatory Arrest Study Group, 97:773-9.

28. Rempel, G., Harrison, M.J., Williamson, D.L. (2009). Is ‘‘treat your child normally’’ helpful advice for parents of survivors of treatment of hypoplastic left heart syndrome? Cardiol Young, 19:135-44.

29. Robertson, A.F. (2003). Reflections on errors in neonatology: I. The “Hands-Off” years, 1920 to 1950. J Perinatol, 23:48-55.

30. Robertson, D.R., Justo, R.N., Burke, C.J., Pohlner, P.G., Graham, P.L., & Colditz, P.B. (2004a). Perioperative predictors of developmental outcome following cardiac surgery in infancy. Cardiol Young, 14:389-95.

31. Robertson, C.M.T., Joffe, A.R., Sauve, R.S., Rebeyka, I.M., Phillipos, E.Z., Dyck, J.D., ...The Western Canadian Pediatrics Therapies Follow-up Group (2004b). Outcomes from an interprovincial program of newborn open heart surgery. J Pediatr, 144:86-92.

32. Robertson, C. M. T., Sauve, R. S., Joffe, A.R., Alton, G.Y., Moddemann, D.M., Blakley, ...Rebeyka, I.M. (2011). The Registry and Follow-up of Complex Pediatric Therapies Program of Western Canada: A Mechanism for Service, Audit, and Research after Life-Saving Therapies for Young Children. Cardiol Res Pract, 2011:965740

33. Rogers, B.T., Msall, M.E., Buck, G.M., Lyon, N.R., Norris, M.K., Roland, J.M., Pieroni, D.R. (1995). Neurodevelopmental outcome of infants with hypoplastic left heart syndrome. J Pediatr, 126:496–8.

34. Rudolph, A.M. (2001). Congenital diseases of the heart: clinical-physiological considerations. 2nd ed. Futura PublishingArmonk, NY.

35. Rossi, R.J. (2010). Applied Biostatistics for the Health Sciences. Danvers, Massachusetts: John Wiley and Sons, Inc.

36. Sauve, R., & Lee, S.K. (2006). Neonatal follow-up programs and follow-up studies: Historical and current perspectives. Paediatr Child Health, 11(5):267-70.

37. Sauve, R., & Robertson, C.M.T. (2006). Follow-up of children who received complex invasive therapies early in life. Peadiatr Child Health, 11(5):287-90.

38. Shillingford, A.J., & Wernovsky, G. (2004). Academic performance and behavioral difficulties after neonatal and infant heart surgery. Pediatr Clin N Am, 51:1625-39.

39. Shillingford, A.J., Glanszman, M., Ittenbach, R.F., Clancy, R.R., Gaynor, J.W., & Wernovsky, G. (2008). Inattention, hyperactivity, and school-performance in a population of school-age children with complex congenital heart disease. Pediatrics, 121:e759-e767.

Wernovsky, G., Stiles, K.M., Gauvreau, K., Gentles, T.L., duPlessis, A.J., Bellinger, D.C., ... Newburger, J.W. (2000). Cognitive development after the Fontan operation. American Heart Association, 102:883-9.

Appendix A. Collinearity Test

The CORR Procedure

```
   14  Variables:    ageTx              gender             birthgest
was10preopO2lowest
                     preopLactate       was11CPB           was14DHCA
POlowestPaO2
                     POhighestinosc     POhighestlact      was27allventd
allhospdays
                     was34sv            was39mothtotaled4
```

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum	Maximum
ageTx	165	12.78788	10.69807	2110	1.00000	68.00000
gender	165	1.36970	0.48419	226.00000	1.00000	2.00000
birthgest	165	38.91515	1.81929	6421	31.00000	42.00000
was10preopO2lowest	165	37.53939	15.64449	6194	16.00000	96.00000
preopLactate	165	4.27273	4.44783	705.00000	0.80000	26.00000
was11CPB	165	123.61818	64.45877	20397	34.00000	529.00000
was14DHCA	165	0.68485	0.46599	113.00000	0	1.00000
POlowestPaO2	165	47.21212	13.39675	7790	22.00000	80.00000
POhighestinosc	165	18.29697	13.96881	3019	0	92.50000
POhighestlact	165	6.40000	3.30585	1056	1.50000	19.00000
was27allventd	165	18.18182	17.59097	3000	0	154.00000
allhospdays	165	34.20000	35.53051	5643	8.00000	286.00000
was34sv	165	0.24848	0.43345	41.00000	0	1.00000
was39mothtotaled4	165	13.07879	3.16033	2158	0	21.00000

Pearson Correlation Coefficients, N = 165
Prob > |r| under H0: Rho=0

	ageTx	gender	birthgest	was10preop O2lowest	preop Lactate	was11CPB
ageTx	1.00000	0.15649	-0.03884	0.20864	0.24292	0.04903
		0.0447	0.6204	0.0072	0.0017	0.5317

gender	0.15649	1.00000	-0.06800	-0.03293	0.01490	0.17218
	0.0447		0.3855	0.6746	0.8493	0.0270
birthgest	-0.03884	-0.06800	1.00000	-0.02302	-0.04844	-0.15278
	0.6204	0.3855		0.7692	0.5367	0.0501
was10preopO2lowest	0.20864	-0.03293	-0.02302	1.00000	-0.13945	0.06491
	0.0072	0.6746	0.7692		0.0740	0.4075
preopLactate	0.24292	0.01490	-0.04844	-0.13945	1.00000	0.00224
	0.0017	0.8493	0.5367	0.0740		0.9772
was11CPB	0.04903	0.17218	-0.15278	0.06491	0.00224	1.00000
	0.5317	0.0270	0.0501	0.4075	0.9772	

The CORR Procedure

Pearson Correlation Coefficients, N = 165
Prob > |r| under H0: Rho=0

	ageTx	gender	birthgest	was10preop O2lowest	preop Lactate	was11CPB
was14DHCA	-0.05019	0.06011	-0.09647	-0.08946	-0.09802	-0.16542
	0.5221	0.4431	0.2177	0.2532	0.2104	0.0337
POlowestPaO2	0.03959	-0.08737	0.05228	0.17584	0.01518	-0.02131
	0.6137	0.2645	0.5048	0.0239	0.8465	0.7859
POhighestinosc	-0.08265	-0.06456	-0.20331	0.17270	-0.01170	0.14133
	0.2912	0.4100	0.0088	0.0265	0.8814	0.0702
POhighestlact	-0.13741	0.05409	-0.13018	-0.08545	0.13351	0.18364
	0.0784	0.4902	0.0956	0.2751	0.0873	0.0182
was27allventd	0.04275	0.08155	-0.21901	-0.10611	0.08201	0.22080
	0.5856	0.2978	0.0047	0.1749	0.2950	0.0044

allhospdays	0.03212	0.07861	-0.20057	0.03320	0.00303	0.17060
	0.6822	0.3155	0.0098	0.6721	0.9692	0.0285
was34sv	-0.14241	0.05353	0.05010	-0.16376	-0.01512	-0.04089
	0.0680	0.4947	0.5228	0.0356	0.8471	0.6021
was39mothtotaled4	-0.05361	-0.04704	0.09556	0.12308	-0.05264	-0.12482
	0.4941	0.5485	0.2221	0.1153	0.5019	0.1102

Pearson Correlation Coefficients, N = 165
Prob > |r| under H0: Rho=0

	was14DHCA	POlowest PaO2	POhighestinosc	POhighestlact	was27allventd
ageTx	-0.05019	0.03959	-0.08265	-0.13741	0.04275
	0.5221	0.6137	0.2912	0.0784	0.5856
gender	0.06011	-0.08737	-0.06456	0.05409	0.08155
	0.4431	0.2645	0.4100	0.4902	0.2978
birthgest	-0.09647	0.05228	-0.20331	-0.13018	-0.21901
	0.2177	0.5048	0.0088	0.0956	0.0047
was10preopO2lowest	-0.08946	0.17584	0.17270	-0.08545	-0.10611
	0.2532	0.0239	0.0265	0.2751	0.1749
preopLactate	-0.09802	0.01518	-0.01170	0.13351	0.08201
	0.2104	0.8465	0.8814	0.0873	0.2950

1 11:57
Tuesday, January 18, 2011 3

The CORR Procedure

Pearson Correlation Coefficients, N = 165
Prob > |r| under H0: Rho=0

	was14DHCA	POlowest PaO2	POhighestinosc	POhighestlact	was27allventd
was11CPB	-0.16542	-0.02131	0.14133	0.18364	0.22080
	0.0337	0.7859	0.0702	0.0182	0.0044

```
  was14DHCA              1.00000    -0.28127           0.09081
0.30597          0.16771
                                     0.0003             0.2460
<.0001           0.0313

  POlowestPaO2          -0.28127     1.00000          -0.14955          -
0.30276         -0.27818
                          0.0003                        0.0552
<.0001           0.0003

  POhighestinosc         0.09081    -0.14955           1.00000
0.23740          0.37929
                          0.2460      0.0552
0.0021           <.0001

  POhighestlact          0.30597    -0.30276           0.23740
1.00000          0.24427
                          <.0001      <.0001            0.0021
0.0016

  was27allventd          0.16771    -0.27818           0.37929
0.24427          1.00000
                          0.0313      0.0003            <.0001
0.0016

  allhospdays            0.20381    -0.28058           0.32779
0.19466          0.71776
                          0.0086      0.0003            <.0001
0.0122           <.0001

  was34sv                0.35988    -0.76938           0.16498
0.29319          0.22995
                          <.0001      <.0001            0.0342
0.0001           0.0030

  was39mothtotaled4     -0.01202     0.04108          -0.10861          -
0.07850         -0.15601
                          0.8782      0.6003            0.1649
0.3162           0.0454

                          Pearson Correlation Coefficients, N = 165
                                  Prob > |r| under H0: Rho=0

                                  allhospdays       was34sv
was39mothtotaled4

              ageTx                   0.03212      -0.14241
-0.05361
                                       0.6822        0.0680
0.4941

              gender                  0.07861       0.05353
-0.04704
                                       0.3155        0.4947
0.5485

              birthgest              -0.20057       0.05010
0.09556
                                       0.0098        0.5228
0.2221

              was10preopO2lowest      0.03320      -0.16376
0.12308
```

	0.6721	0.0356	0.1153

The CORR Procedure

Pearson Correlation Coefficients, N = 165
Prob > |r| under H0: Rho=0

	allhospdays	was34sv	was39mothtotaled4
preopLactate	0.00303	-0.01512	-0.05264
	0.9692	0.8471	0.5019
was11CPB	0.17060	-0.04089	-0.12482
	0.0285	0.6021	0.1102
was14DHCA	0.20381	0.35988	-0.01202
	0.0086	<.0001	0.8782
POlowestPaO2	-0.28058	-0.76938	0.04108
	0.0003	<.0001	0.6003
POhighestinosc	0.32779	0.16498	-0.10861
	<.0001	0.0342	0.1649
POhighestlact	0.19466	0.29319	-0.07850
	0.0122	0.0001	0.3162
was27allventd	0.71776	0.22995	-0.15601
	<.0001	0.0030	0.0454
allhospdays	1.00000	0.33012	-0.21447
		<.0001	0.0057
was34sv	0.33012	1.00000	-0.00103
	<.0001		0.9896
was39mothtotaled4	-0.21447	-0.00103	1.00000
	0.0057	0.9896	