A SIMPLIFIED RISK PREDICTION MODEL USING ELECTRONIC MEDICAL RECORD DATA FOR PEDIATRIC AND ADULT PATIENTS WITH CONGENITAL HEART DISEASE UNDERGOING CARDIAC SURGERY

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Dedication

I dedicate this dissertation to my dearest family:

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To my big brother, Kevin, for being my role model and caring for me all along;

To my dear sister, Hui, for your complete unselfishness to all of us;

To my husband, Michael, and our beloved fur kids, Junior and Blackie,
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我亲爱的爸爸妈妈 - 养育之恩，无以回报；

我亲爱的哥哥，姜雷 - 这么多年做**我的榜**样和所有的照顾；

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我的先生，Michael, **和我**们心爱的猫宝宝，Junior **和** Blackie - **你**们是我生活**中最好的祝福**。

Abstract

Background: Vasoactive-inotrope score (VIS) has recently been proposed as a surrogate marker of illness severity after cardiac surgery for pediatric patients with congenital heart disease (CHD). However, it has not been validated in an exclusively pediatric population as a robust outcome predictor in the early postoperative period. Furthermore, as a result of advances in the treatment of CHD, the majority of these children now survive to adulthood when they will require additional surgical intervention. However, there are no risk prediction tools for these adult patients with CHD; and pediatric and adult non-CHD cardiac risk scores perform poorly in this population. A simple yet robust risk prediction tool is crucial to support clinical decision making and optimize quantity and quality of life for both pediatric and adult CHD patients undergoing cardiac surgery.

Objectives: This research aims to 1) externally validate VIS risk predictive performance of early outcome in pediatric CHD patients after cardiac surgery; 2) propose a simplified VIS Index model with robust predictive performance of early postoperative mortality and morbidity by incorporating both the magnitude and duration of inotrope support required for pediatric CHD patients after cardiac surgery; 3) evaluate whether the proposed VIS Index has strong discriminative performance of early mortality and morbidity outcome for adult CHD patients after cardiac surgery.

Methods: Automated data capture of the electronic medical record (EMR) system was utilized in conjunction with retrospective clinical chart review. A total number of 244 infant CHD patients and 243 adult CHD patients undergoing cardiac surgery at the Mayo

Clinic Rochester, MN were included in the study. Inotrope and vasoactive dose values were collected at 15-minute intervals for the first 96 hours after cardiac Intensive Care Unit (ICU) admission. Demographic and clinical data were collected from both Mayo Clinic institutional Society of Thoracic Surgeons database and clinical chart review. Maximum vasoactive inotrope support (maxVIS) values were calculated and VIS postoperative temporal characteristics were further assessed to evaluate their relationship with early mortality and morbidity. The logistic regression model with generalized estimating equation methodology was applied to address the correlated outcomes from the same patient. The maxVIS model was validated on pediatric CHD patients. A simplified VIS index model incorporating both the magnitude and duration of inotrope support was developed with superior predictive performance of early mortality and morbidity for both pediatric and adult CHD patients following cardiac surgery. The area under the curve (AUC) of the receiver operating characteristic (ROC) curves was used to evaluate the discriminative performance; Hosmer-Lemeshow (H-L) test was used to assess the goodness of fit of the model.

Results: The maxVIS model proposed by recent research was externally validated in our institution to exhibit good predictive ability (H-L test, P = 0.791) and discriminate reasonably well between CHD patients with high- and low-risk for early mortality and morbidity (AUC = 0.77, 95% CI: 0.72 to 0.82). The new VIS index risk prediction model shows superior discriminative performance over the existing maxVIS model for pediatric CHD patients undergoing cardiac surgery (AUC = 0.84, 95% CI: 0.78 to 0.88; H-L test,

P = 0.725). A high VIS index is strongly associated with a poor clinical outcome compared to a low VIS index. Patients with a VIS index of 6 have an estimated risk of 98% (95% CI: 85% to 100%) of having a poor outcome after cardiac surgery, compared with a risk of 20% (95% CI: 11% to 34%) for patients with a VIS index of 1. Furthermore, both maxVIS model and VIS index model presents robust predictive performance for adult CHD patients after cardiac surgery with the VIS index model consistently showing superior discriminative performance over the maxVIS model for early postoperative mortality and morbidity (MaxVIS model AUC = 0.82, 95% CI: 0.76 to 0.88; VIS index model AUC = 0.88, 95% CI: 0.82 to 0.93). Adult CHD patients with a VIS index of 6 have an estimated risk of 95% (95% CI: 72 % to 99%) of experiencing a poor clinical outcome during early postoperative period, compared with a risk of 6% (95% CI: 3% to 11%) for patients with a VIS index of 1.

Conclusions: The maxVIS model is a strong predictive tool of early mortality and morbidity for CHD patients undergoing cardiac surgery. The VIS index we proposed is a more robust, yet much simpler tool to predict early postoperative mortality and morbidity for both pediatric and adult CHD patients after cardiac surgery. More importantly, this is the first analysis evaluating the correlation between VIS and poor clinical outcomes in adult CHD patients undergoing cardiac surgery. The findings of this research will facilitate earlier detection of high risk patients to direct clinical interventions and preventative measures that will improve outcome for pediatric and adult CHD patients after cardiac surgery.

Table of Contents

List of Tables

List of Figures

CHAPTER ONE: INTRODUCTION

1.1 Background

Infants undergoing congenital heart surgery (CHS) with cardiopulmonary bypass (CPB) are at increased risk for significant postoperative morbidity and mortality compared with other age groups (1). With the advancement of operative techniques and improvement in perioperative management, mortality rates have significantly decreased (1), which has allowed the focus of outcomes research to shift from preventing mortality to decreasing morbidities. There has been ongoing research into early postoperative markers that are prognostic of illness severity and short-term outcome for this patient population. An ideal early outcome measure would be easily measured, reproducible, and, most importantly, independently correlated with other measures of short- and long-term outcomes (2).

Vasoactive-inotrope score (VIS) has been proposed as a marker of illness severity after cardiac surgery for pediatric patients with congenital heart disease (CHD). However, it has not been externally validated in the pediatric population as a robust outcome predictor in the early postoperative period. On the other hand, advances in treatment of CHD have resulted in most patients surviving to adulthood, yet risk prediction tools do not exist for adult patients with CHD; and pediatric CHD and adult non-CHD cardiac risk scores perform poorly in the adult CHD population. A simple yet robust risk prediction tool is crucial to support clinical decision making and optimizing quantity and quality of life for both pediatric and adult CHD patients undergoing cardiac surgery.

Given the large-scale deployment of the electronic medical record (EMR) systems, there has been a subsequent increase in interest in using these systems for clinical research, also known as secondary use of EMR data. The EMR system provides an innovative and simplified resource for automated collection of perioperative clinical variables relevant to predicting both pediatric and adult CHD outcomes. In this research project, we extracted data from the EMR system at the Mayo Clinic in Rochester, MN for pediatric and adult CHD patients to validate the predictive performance of VIS on both pediatric and adult CHD patients. In the ICU setting, receiving high levels of vasoactive support during the immediate postoperative period after cardiac surgery could be an indicator compromised physiologic functioning which may in turn lead to increased likelihood of morbidity and mortality. Therefore we hypothesize that the amount of vasoactive support received postoperatively is a good predictor of adverse clinical outcomes in early postoperative period in both pediatric and adult CHD patients following cardiac surgery. Furthermore, we hypothesize that a simplified VIS index which takes into account magnitude and duration of inotrope support would be a robust tool to predict poor short-term outcomes for both pediatric and adult CHD patients at risk.

1.2 Dissertation Aims

The purpose of this research is to utilize an EMR automated data capture system to assess the association between inotropic and vasoactive support required by patients

after cardiac surgery with early postoperative mortality and morbidity outcomes for both pediatric and adult CHD patient populations. It addresses three specific aims:

1. Externally validate the risk predictive performance of the maximum VIS (maxVIS) model proposed in the pediatric literature to predict early morbidity and mortality in pediatric CHD patients undergoing CHS;
2. Propose a simplified VIS Index model with superior predictive performance for early postoperative mortality and morbidity by incorporating both the magnitude and duration of inotrope support required after pediatric cardiac surgery;
3. Evaluate and compare the discriminative performance of the existing maxVIS model and the proposed VIS Index model for predicting early adverse outcomes in adult CHD patients after cardiac surgery.

1.3 Significance of the Work

In summary, this project has several significant features that stand to impact both clinical and health informatics research. First, this research provides a successful example of secondary use of EMR data to perform clinical research. In addition, this work provides a proof of concept that with cross-functional collaboration efforts, EMR data provides a feasible approach for answering important clinical research questions aimed at improving the quality and efficiency of patient care. Secondly, this project provides evidence that the VIS is a robust surrogate outcome marker for accurately predicting important postoperative morbidities after cardiac surgery for both pediatric and adult

CHD patients. Such a measure will support physician clinical decision making to guide the choice and timing of a variety of diagnostic and therapeutic interventions for patients recovering from cardiac surgery, some of which are highly invasive with potentially high risks. Finally, the predictive score we proposed, known as the VIS index, has additional benefit over the traditional VIS by being quick and simple to calculate. The VIS index has promise for being easily translated to the patient bedside as a clinical decision support tool to help identify high risk patients and facilitate early intervention for optimizing patient outcomes.

CHAPTER TWO: BACKGROUND AND LITERATURE REVIEW

2.1 CHD Outcome Research

Congenital heart disease (CHD) is a type of defect or malformation in one or more structures of the heart or blood vessels that occurs before birth. According to the American Heart Association, CHD is the most common cause of infant death from birth defects; over 24 percent of infants who die from a birth defect have a heart defect (3). Some CHDs can be treated with medication alone, but many require one or more surgical procedures for correction. While most CHD patients live beyond the surgery, many experience short-term challenges such as low blood pressure, prolonged time on mechanical ventilation and long-lasting effects such as neurologic deficits. Patients with congenital or acquired heart disease comprise a major diagnostic category for admissions to large pediatric intensive care units (PICUs) across the country, compromising 30% to 40% or more of admissions in many centers (4). The average length of stay in the PICU after congenital heart surgery (CHS) for infants is 3.5 to 7 days depending on the type of surgery and complexity of their heart defect (elective vs. nonelective) (5). Therefore, a critical need remains to identify and quantify clinical factors during the early postoperative period that are indicative of illness severity and short-term outcome. Such outcome measures would be particularly useful to practitioners trying to decide between various diagnostic and therapeutic options for CHD patients recovering from cardiac surgery, some of which are highly invasive with potentially high risks. It will also provide clinical decision support for clinicians to counsel families on their child's

likelihood of recovery from surgery. Therefore, a robust severity of illness and surrogate marker for acute outcomes would be a tremendous advance for improving patient care, and most importantly, outcomes following CHD surgery.

Advances in surgical management for CHD over the past two decades have resulted in dramatic reductions in operative mortality. As a result, mortality rate, the traditional measure used to study outcomes post pediatric cardiac surgery, is becoming less relevant. The focus of perioperative management has now turned to comparing the effectiveness of clinical management, decision-making tools and interventions that promise to reduce morbidity for children after CHD surgery. The impact of the immediate postoperative morbidity on long-term outcomes for hospital survivors is significant. The cumulative effect of these morbidities can lead to decreased longitudinal quality of life as a result of impaired neurodevelopment outcomes, and increased and continued healthcare expenditures (6). Thus, surrogate outcome measures that accurately predict important postoperative events leading to morbidity are becoming increasingly relevant necessities. Despite this need, widely applicable, validated surrogate outcome markers that can be applied in clinical practice to accurately predict important postoperative morbidities after pediatric cardiac surgery have not been established.

2.2 Existing Risk Adjustment Systems

2.2.1 Pediatric CHD Patient Population

Because each congenital heart defect is a rare condition, assessing the quality of care based on crude outcomes is problematic. In the past decade a few risk adjustment systems have been developed. Two of these systems, the Risk Adjustment in Congenital Heart Surgery-1 (RACHS-1) method and the Aristotle Complexity Score have been validated in the pediatric CHD patient population and are utilized to establish preoperative risk for CHD-related surgical procedures. Both systems were based on multi-institutional efforts, and both were derived in large part from subjective probability, or expert opinion with the goal of measuring and adjusting for the surgical complexity of pediatric cardiac operations.

Risk Adjustment Classification for Congenital Heart Surgery (RACHS-1)

The RACHS-1 score was created to allow for meaningful comparison and evaluation of in-hospital mortality between institutions and within groups of children undergoing surgery for CHD (7). It was developed by a panel of 11 clinically and statistically experienced pediatric surgeons and cardiologists and published in January 2002. The data used to develop the resulting score system RACHS-1 were 4,370 procedures performed in 1996 in 32 hospitals that belonged to the Pediatric Cardiac Care Consortium and 3,646 American hospital discharge datasets of 1994 and 1995. Each panel member was provided with a list of 207 surgical procedures drawn from both *Current Procedural Terminology 4* and International Classification of Diseases, Ninth

Revision, Clinical Modification *(ICD-9-CM)* codes. Members were asked to group procedures with similar risks of in-hospital death. After rounds of panel meetings, six mortality risk groups were defined by the panel with category 1 has the lowest odds for death (e.g., ostium secundum atrial septal defect closure), and category 6 has the highest odds for death (e.g., stage-1 Norwood operation). The RACHS-1 classification was later validated in 2 independent populations and was found to have a good group-wise but a low individual predictive ability for mortality and length of stay in ICU (8, 9). The main strength of the RACHS-1 method, as the developers of the method point out is that it has the ability to incorporate relatively rare procedures. This ability is especially important because surgery for CHD in the pediatric age group is characterized by extreme diversity. However, the developers of the RACHS-1 method also cautioned about the intended use of the tool. It was derived and validated "to provide risk adjustment for comparison of in-hospital mortality. No assumption can be made about the method's performance for other outcomes, such as morbidity or late mortality" (7). A surgical risk adjustment tool is essential because cardiac populations from different hospitals demonstrate "marked differences in the percentage of malformation complexity" (9). This imbalance is likely the result of referral patterns that triage more complex patients from smaller hospitals to large tertiary centers with established pediatric cardiac surgical programs and support systems. The RACHS-1 score has been utilized in the databases of The European Association for Cardio-Thoracic Surgery and The Society of Thoracic Surgeons (STS) since 2006. This scoring system is well validated and widely accepted in pediatric

clinical research as the risk adjustment tool of choice for surgical complexity in both the United States and abroad (8, 9, 10).

The Aristotle Complexity Score

The Aristotle Basic Complexity Score (ABC score) expresses the case complexity of congenital heart surgery procedures based on three components: the potential for mortality, the potential for morbidity, and the technical difficulty of the procedure. The ABC score was created at a time when objective data from large congenital databases for complexity adjustment were unavailable. Therefore the grading of individual procedures was subjectively determined and represents the consensus opinion of an international surgeon panel composed of 50 surgeon experts. The score ranges 1.5 to 15 for groups of procedures. The higher the score, the more complex the surgical procedure is in terms of the potentials of the three components. Since 2002, this methodology has been used by both the Society of Thoracic Surgeons (STS) and the European Association of Cardiothoracic Surgery (EACTS) in their yearly analysis and reporting of outcomes for a current aggregate of more than 80,000 operations (11-14). The accuracy of the ABC score with respect to mortality and morbidity (prolonged postoperative length of hospital stay) was later objectively validated in a large study with two multi-institution databases. In this study, O'Brien and colleagues show that the ABC score discriminates between low-risk and high-risk congenital procedures (with a C-statistic of 0.70 for mortality and 0.67 for prolonged hospital LOS) and can be used in the context of risk-adjustment and complexity-adjustment. Although an overall positive correlation existed between the

ABC score and outcomes, there was not a perfect one-to-one increasing relationship between the ABC score of a procedure and its empirically determined potential for mortality and morbidity (15). As it is for the RACHS-1 score system, the ABC score has also been utilized in the databases of the EACTS and the STS since 2006.

The Aristotle Comprehensive Complexity Score (ACC score) is an extension of the Basic Aristotle score for complexity adjustment. It includes 10 additional data points that can be assigned based on procedure and patient related variables. The ACC score has been used by numerous investigators to analyze the outcomes from complex procedures (16-18).

Al-Radi and colleagues compared the predictive performance of the RACHS-1 score and the ABC score on 13,675 congenital cardiac surgeries performed on children (age < 18 years) between July 1, 1982 and June 30, 2004 at one institution (19). Their study results found that the RACHS-1 score had higher predictive performance for in-hospital mortality and length of stay than the ABC score. They further confirmed that both scoring methods are better characterized as a method of risk stratification than as risk prediction since it is difficult to expect that knowing little else than the procedure, one can accurately predict the outcome.

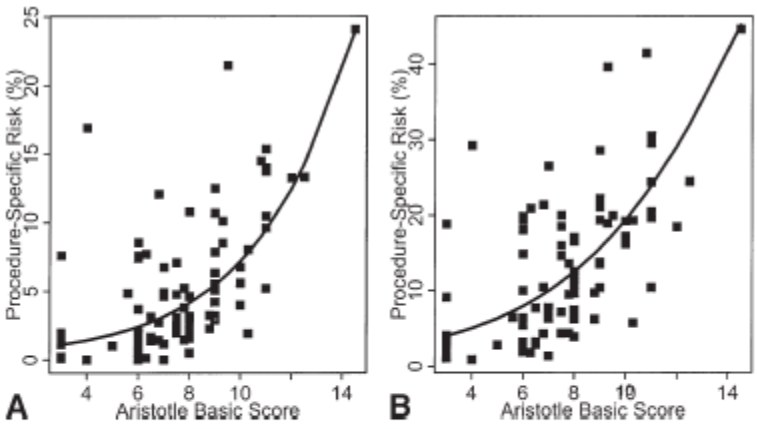


Fig 1. Relationship between the Aristotle Basic Complexity (ABC) score and risk of (A) mortality and (B) postoperative length of stay exceeding 21 days. Square dots represent the actual observed rate of the outcome for the 83 individual procedures with adequate (N ≥ 50) sample sizes. The overlaid solid line represents the estimated relationship between the ABC score and the outcome as determined by logistic regression.

Note. Reprinted from "Accuracy of the aristotle basic complexity score for classifying the mortality and morbidity potential of congenital heart surgery operations" by O'Brien SM, Jacobs JP, Clarke DR, et al. 2007, Ann Thorac Surg, 84(6):2027-37

STS-EACTS Congenital Heart Surgery Mortality Categories

In 2009, a new score based upon 77,294 procedures from the STS database and EACTS congenital database between 2002 and 2007 was presented as an alternative to the RACHS-1 system and the Aristotle Score (20). Procedure-specific mortality rate estimates were calculated for 148 types of operative procedures using a Bayesian model that adjusted for small denominators. Operations were sorted by increasing risk and grouped into five categories (the STAT Mortality Categories) that were designed to minimize within-category variation and maximize between-category variation. The main advantage of this score system is that it was developed using patient data and statistical

models instead of expert opinion. The authors of this score system compared its discriminative performance of predicting mortality with RACHS-1 score and the ABC score. The STS-EACTS categories had a c-index value of 0.812 from the receiver operating characteristic (ROC) curve, compared with a c-index value of 0.802 for RACHS-1 score and 0.795 for ABC score (20). However, the high degree of discrimination of the STS-EACTS categories on mortality risk was not able to be re-produced in a different study. Vijarnsorn et al. (21) performed a risk analysis of hospital mortality using the RACHS-1 score, the ABC score and the STS-EACTS categories on 230 pediatric patients who underwent CHS at a tertiary cardiac center in Thailand in 2009. With an overall mortality discharge rate of 6.1% in this patient population, the c-index of the ROC curve of the RACHS-1 score, the ABC score, and the STS-EACTS categories was reported as 0.78, 0.74, and 0.67, respectively, with STS-EACTS categories having the lowest discrimination on mortality. Besides the study Vijarnsorn et al. conducted, no other studies have been performed to further validate the STS-EACTS categories in other institutions since it was first proposed in 2009.

2.2.2 Adult CHD Patient Population

Despite the fact that the size of the adult CHD population has now surpassed the pediatric CHD population with half of all CHD-related mortality occurring in adulthood, no risk stratification models are available for adult congenital cardiac surgery. The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is often used to

perform risk assessment for all types of adult cardiac surgery but was mainly developed with coronary artery bypass patients (22). Gameren and colleagues compared the predictive ability of the RACHS-1 score, the ABC score, the STS-EACTS score and the EuroSCORE score in predicting adult CHD mortality. None of the scores performed well (Table 1). The Comprehensive Aristotle score plus age performed the best but only predicted mortality 76% of the time (22).

The under-performance of these risk stratification tools is not surprising. Surgical procedures performed in adult CHD patients are a unique combination of pediatric and adult cardiac surgical interventions. In the Gameren study of 963 adult CHD patients, there were no patients that could be classified as RACHS-1 categories 5 and 6, with only 6 patients in category 4. Surgical procedures for these categories are performed during infancy and are not relevant to the cardiac anatomy of the adult CHD survivors. Similar discrepancies in patient distribution were seen for the other complexity scores.

Table 1. Discrimination of Existing Risk Scores – Adult CHD Patients

Score	Thirty-day mortality		One-year mortality	
	c-index	95% CI	*c*-index	95% CI
Logistic EuroSCORE [13]	0.59	0.45–0.72	0.67	0.56–0.78
Age	0.67	0.54–0.80	0.66	0.56–0.76
RACHS-1	0.60	0.45–0.75	0.59	0.47–0.70
RACHS-1 + age	0.69	0.54–0.84	0.66	0.56–0.77
Basic Aristotle	0.60	0.44–0.76	0.56	0.44–0.68
Basic Aristotle + age	0.70	0.53–0.86	0.64	0.53–0.76
STS–EACTS	0.60	0.44–0.76	0.57	0.46–0.68
STS–EACTS + age	0.69	0.54–0.84	0.67	0.57–0.77
Comprehensive Aristotle	0.66	0.54–0.79	0.65	0.54–0.75
Comprehensive Aristotle + age	0.76	0.62–0.90	0.74	0.65–0.84

RACHS: Risk Adjustment in Congenital Heart Surgery; STS: Society of Thoracic Surgeons; and EACTS: European Association for Cardiothoracic Surgery.

Note. Reprinted from "Risk stratification for adult congenital heart surgery," by M. van Gameren, L. M. Putman, J. J. M. Takkenberg, and A. J. J. C. Bogers. 2011, Eur J Cardiothorac Surg, 39(4): 490 – 494.

2.3 The Vasoactive Inotrope Score

The primary objective of currently existing scoring systems is to adjust for the complexity of the surgical procedures. Because these scores do not provide any information about patient-specific factors such as age and co-morbidities, they are not intended as a predictive measurement for operative mortality for a given patient. Therefore, current research is focusing on investigating early postoperative markers that are prognostic of illness severity and short-term outcome for pediatric CHD patients undergoing CHS. The inotropic score (IS) and vasoactive inotrope score (VIS) have recently gained popularity as a predictor for morbidity and mortality in this patient population. The idea of an IS system was initially described in a study by Wernovsky and colleagues (23) to quantify

the amount of cardiovascular support received by neonates after the arterial switch operations. Although this inotropic score and various adaption have subsequently been used in clinical research as a measurement of illness severity in CHD patients (24, 25), there remains limited data to support the use of this clinical marker as an outcome predictor in the early postoperative period. More recently, Gaies and colleagues (26) proposed expanding the inotropic score to include the additional vasoactive medications of milrinone, vasopressin, and norepinephrine, and named the expanded score the vasoactive-inotrope score (VIS). In their validation study, they presented VIS as a surrogate of a combined mortality-mortality outcome measure in infants after cardiac surgery. Their results showed that higher maximum VIS in the first 48 hours after operation was associated with postoperative morbidity and mortality for infants up to 6 months old who had cardiac surgery that required cardiopulmonary bypass (CPB). They further proposed that VIS may serve as a surrogate mortality-morbidity outcome measure that can be used in clinical outcomes studies for this population. However, as the authors stated, the performance of VIS needs to be further determined by independent clinical research efforts that are designed to validate their single institution findings. External validation of the VIS would confirm a valuable surrogate outcome measure that would guide diagnostic and therapeutic decision-making for patients recovering from CHS. Gaies' VIS validation study had some additional limitations. First, the authors only examined the first 48 postoperative hours. As a result, Inotrope usage beyond 48 hours was not examined despite the fact that prolonged Inotrope dependence beyond 48 hours

is a clinically plausible risk factor for poor outcomes. Secondly, inotropes, vasopressors, and vasodilator agents in the construction of the score are equally weighted, potentially risking the loss of discriminating power. For example, vasopressin tends to be utilized clinically for only the sickest patients, whereas milrinone is almost universally utilized no matter how smooth the clinical course is. Lastly, the classification algorithm the authors proposed required cutoff value determination of VIS values at each 24-hour interval, therefore was not easy to be applied in the clinical practice.

Adult with CHD make up a second population of patients in need of validated surrogate outcome measures to guide clinical decision-making. Advances in treatment of children with CHD have resulted in decreased childhood operative mortality to such a degree that there are now more adults living with CHD than children (27-29). With more than 95% of individuals with CHD surviving to adulthood, the adult CHD population now exceeds 1 million with an estimated growth rate of 5% per year (30, 31). Identifying patients with highest risk for adverse outcome earlier in the CHD trajectory is the crucial next step for preventing morbidity and mortality in these adult CHD survivors. Risk prediction tools specific to adult with CHD are virtually non-existent; and pediatric CHD and adult non-CHD cardiac risk scores perform poorly in the adult CHD population. Validated, relevant risk estimates of key outcomes after surgery are crucial for making difficult choices about timing and appropriateness of surgical intervention aimed at optimizing quantity and quality of life. This gap in our clinical and investigative tool set

hampers clinical management and high-quality research in the adult cardiac intensive care setting.

2.4 Electronic Medical Record (EMR) Automated Data Capture

In the past decades there have been numerous studies conducted in the pediatric critical care area as researchers and physicians try to understand how information collected in the PICU, such as physiologic variables, inotropic requirements, and laboratory data could be used as potential markers to predict immediate and long-term outcome. Knowledge of clinical risk factors would inform clinical decision making by enabling early recognition and modification of management strategies that can decrease the likelihood of adverse outcomes and improve the overall quality of care. Until recently detailed investigation of the thousands of relevant clinical data points have been limited by the sheer cost and time that would be required to complete data collection of this magnitude. However, the increasing adoption of electronic medical record (EMR) systems provides a novel opportunity to obtain this valuable data by automated capture with high efficiency and often improved accuracy than traditional manual data collection methods. The ability to collect these large datasets provides its own unique challenges. Automated data capture of the EMR produces datasets whose size and complexity have grown exponentially. Effective utilization of these data for research presents a new challenge for physicians, clinical researchers, informaticians and biostatisticians in patient care and/or research in the intensive care setting.

Early adoption of the EMR at the Mayo Clinic and recognition of its value to support research led to the formation of The Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) group. METRIC investigators at the Mayo Clinic have established a partnership with IBM to collaboratively develop a sophisticated data warehouse, Mayo Clinic Life Sciences System (MCLSS), which contains a near real-time normalized replicate of Mayo Clinic's EMR. This warehouse is developed from multiple original clinical data sources, including highly annotated, full-text clinical notes, laboratory tests, diagnostic findings, demographics, and related clinical data from the year 2000 onward. Mayo Clinic's EMR data are extracted, transformed, and loaded into MCLSS using IBM's WebSphere Commerce Analyzer, creating DB/2 Universal Database structures of Mayo Clinic's normalized clinical data. Clinical patient data are mapped to standard medical terminologies using LexGrid (Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN) natural language processing technology. The MCLSS also provides approved users with a query-building took called the *Data Discovery and Query Builder* (DDQB). The DDQB allows users to identify administrative, demographic, laboratory, and diagnostic data of interest within the EMR. The MCLSS/DDQB automated data collection approach has been validated in the adult population for calculating illness severity scores such as APACHE, collection of comorbid conditions, history of present illness, and diagnosis for the 5 years preceding the event of interest (32). Furthermore, the superior accuracy of this approach has been

demonstrated through comparison of this automated method with traditional manual data collection methods.

The METRIC group has combined epidemiologic population based studies with informatic data collection tools to facilitate the development and validation of prediction tools that reliably identify high risk patients within the first few hours of admission for a variety of diagnoses. These tools have also been utilized to measure the compliance and change in outcome following practice modifications to ensure that outcome benefits persist beyond the initial research investigation. Over the past three years, Dr. Sheri Crow, a pediatric ICU intensivist at Mayo Clinic, has collaborated with the METRIC investigators and the Mayo Clinic Department of Medical Informatics to develop infrastructure to perform automated EMR data capture for neonatal and pediatric critical care patients. This process, entitled the Minnesota Congenital Heart Network (MCHN) datamart, has involved extensive manual review of EMR data variables acquired by automated data capture to establish programming that reliably generates accurate data variables specific to the neonatal and pediatric patient. The MCHN data collection infrastructure was completed in the summer of 2012. Rapidly accessible data including vital signs at 15 minute intervals, mechanical ventilation settings, vasopressor doses, fluid type, infusion rates, comprehensive medication lists, time of medication administration, fluid intake and hourly output totals, and laboratory results are just a sampling of the data accessible through the MCHN extension of the METRIC automated data capture system.

2.5 Research Objective

In summary, the risk prediction tools that are currently well-validated and well-adopted for the pediatric CHD patients, the RACHS-1 method and the ABC method, were created to allow for meaningful comparison and evaluation of in-hospital mortality between institutions and within groups of children undergoing surgery for CHD. Therefore they are better characterized as a method of risk stratification than as risk prediction; for adult CHD patients, robust, well-validated risk prediction tools currently do not exist; and pediatric CHD and adult non-CHD cardiac risk scores perform poorly in the adult CHD population. The VIS has been proposed as a marker of illness severity after cardiac surgery for pediatric CHD patients but has not been externally validated as a robust outcome predictor in the early postoperative period. No research has been carried out to evaluate the predictive performance of VIS on adult CHD patients.

As part of the biostatistical core support for the MCHN project, this dissertation aims to:

1. Demonstrate the feasibility and efficacy of EMR automated data capture feature for evaluating the association between patient critical care management strategies and clinical outcomes;
2. Validate the VIS as a robust predictor of early mortality and morbidity outcomes for both pediatric and adult CHD patients after cardiac surgery;
3. Develop a simplified VIS prediction model that can be used as a clinical decision support tool for CHD patients following cardiac surgery in order to reduce early

postoperative adverse outcomes and improve quantity and quality of life for CHD survivor.

CHAPTER THREE: METHODS

3.1 Overview

This project includes two patient populations, infants 0-12 months of age and adult patients (≥ 18 years old) with CHD who had cardiac surgery at the Mayo Clinic in Rochester, MN. Figure 1 summarizes the overall flow chart of the project.

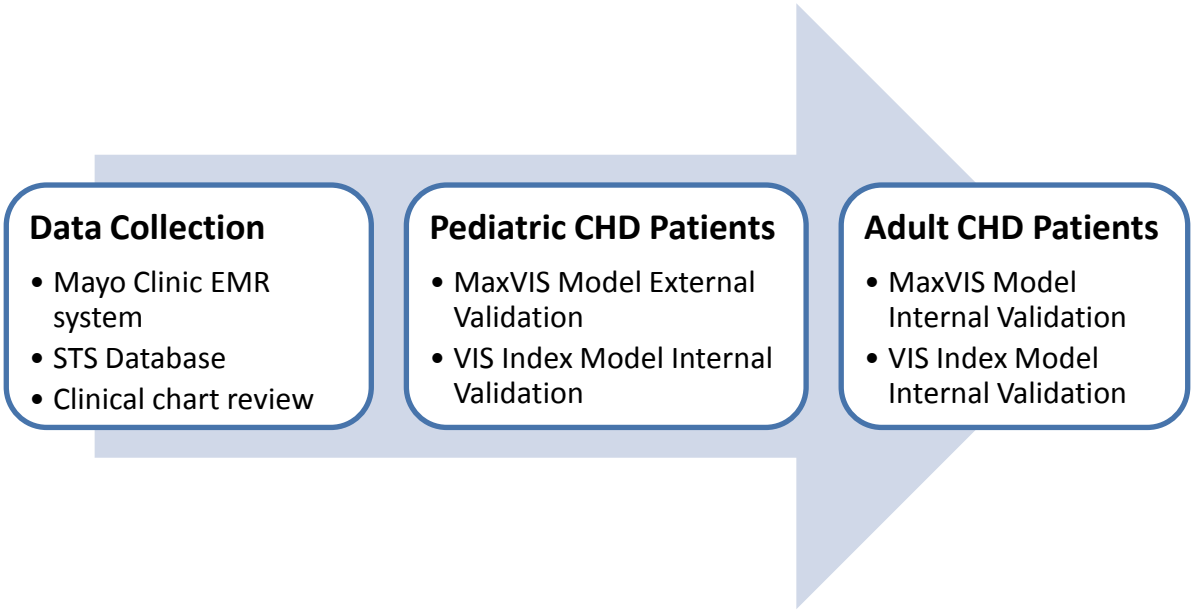


Figure 1. VIS predictive model project flow chart

3.2 Data Sources and Patient Population

For both pediatric and adult CHD patient populations, the EMR system at the Mayo Clinic in Rochester, MN was the data source for this study. The automated data capture system, the MCHN datamart, was used to collect vasoactive medication data and all hemodynamic variables including heart rate and blood pressure. Electronic clinical

data has only been consistently available at the Mayo Clinic since 2002. As a result, only patients admitted after 2002 were queried from MCHN datamart to optimize the comprehensiveness of data available through automated capture.

Preoperative patient characteristics were identified in advance as candidate predictors from both clinical experience of the principle investigator of the study and established demographic characteristics consistently reported in the congenital heart disease literature. Table 2 summarizes the data source of each variable. For pediatric patients, Mayo Clinic institutional STS CHS database was used to obtain demographic and clinical data including age at the time of surgery, gender, weight, operative procedure, cardiopulmonary bypass (CPB) time, aortic cross clamp time, and circulatory arrest times. Patient intubation and extubation dates were obtained through manual clinical chart review. Patients were categorized using the Risk Adjustment in Cardiac Surgery (RACHS-1) classification system based on their operative procedure by a health care provider trained in critical care management. For adults CHD patients, demographic and clinical data including age, body mass index (BMI), year of surgery, diabetic status, RACHS-1 score, prior sternotomy status (if patients had prior sternotomy procedure at the Mayo Clinic or other institutions), aortic cross clamp time and circulatory arrest times were obtained from manual chart extraction. For both pediatric and adult patient populations, ICU admission and discharge data as well as death outcome data were retrieved both electronically from MCHN datamart and manual chart review.

Table 2. Data Source Summary

Variable	Pediatric CHD Patients			Adult CHD Patients		
	Manual	ADC	STS DB	Manual	ADC	STS DB
Age at surgery			X	X		
Gender			X	X		
Weight			X	X		
BMI*				X		
Diabetic status*				X		
Operative procedure			X	X		
CPB time			X	X		
Aortic-cross clamp time			X	X		
Circulatory arrest time			X	NA		
Intubation/extubation date	X			X		
RACHS-1 score	X			X		
vasoactive medication		X			X	
ICU admission/discharge date/time	X	X		X	X	
Death outcome	X	X		X	X	

CHD, congenital heart disease; ADC, automated data capture; STS, Society of Thoracic Surgeons; BMI, body mass index; CPB, cardiopulmonary bypass; RACHS-1, Risk Adjustment in Congenital Heart Surgery-1; ICU, intensive care unit.

* BMI and diabetic status only apply to adult CHD patients.

The collection and study of this data was approved by the Mayo Clinic Institutional Review Board. The research project includes three IRB protocols as listed below. The first protocol outlines the global data collection initiative for the MCHN project and grants the author of this dissertation the permission to access and work with Mayo Clinic EMR data; and the second and third protocols are to evaluate pediatric and adult CHD patients, respectively, by using the EMR data.

1. Protocol 09-001966, Minnesota Congenital Heart Network Data Collection Initiative;

2. Protocol 09-001747, Defining the Perioperative Hemodynamic Profile of Children Undergoing Congenital Cardiac Surgery;
3. Protocol 11-008522, Risk Factors for Post-Surgical Morbidity and Mortality in Adult Congenital Heart Disease Patients.

We took the following approaches to ensure the accuracy and quality of the data retrieved through MCHN data mart system:

1. Confirmed the accuracy of electronically extracted data for ICU admission, discharge data, and death outcome data with manual chart review for all patients;
2. Performed descriptive statistical analysis and graphical data exploration to identify outlier vasoactive medication data followed by manual chart review of vasoactive outliers;
3. Established clinically appropriate vasoactive dose ranges for each inotropic medications and any dose value that was outside of this range was manually reviewed. Table 3 summarizes the dose range of each vasoactive medication.

Table 3. Summary of Vasoactive Dose Range

Vasoactive Agent	Unit	Range
Dopamine	µg/kg/min	> 0 – 20
Dobutamine	µg/kg/min	> 0 – 20
Epinephrine[1]	µg/kg/min	> 0 – 0.3
Milrinone[2]	µg/kg/min	> 0 – 1.0
Vasopressin	U/kg/min	0.002 – 0.08
Norepinephrine	µg/kg/min	> 0 – 0.8

1. Most patients should be in the range of 0.05 to 0.15 µg/kg/min. However, technically it could go as high as 0.8.
2. Most patients should be in the range of 0.25 to 0.75 µg /kg/min.

For vasoactive medication data, once dose values were identified as potentially inaccurate through descriptive statistics and data range check, manual review of the patient chart was performed and the values from the manual chart review were then used.

3.3 Statistical Analysis

3.3.1 Outcome Variables

The overall operative mortality rate has dramatically declined in the last decade (3% for pediatric CHD patients and 3 to 4% for adult CHD patients) due to advances in surgical technique and perioperative management (31, 33). As a result, current outcomes research has shifted focus beyond preventing mortality to decreasing morbidities in both populations. To reflect this paradigm shift, our investigation utilized a composite dichotomous outcome variable for early mortality and major morbidity which is referred to as “poor outcome” for this project. Mortality was determined by comparing patient hospital discharge data and death date. Early mortality was defined as in-hospital death or death within 90 days of hospital discharge. Morbidity outcomes were pre-specified based on literature review and the clinical practice of the investigators. For pediatric CHD patients, the most common early morbidity outcomes reported in the literature review were used and included the following clinical outcomes during the ICU stay following cardiac surgery: low cardiac output syndrome, acute kidney injury (AKI), prolonged ICU length of stay (LOS) and prolonged postoperative mechanical ventilation. Patients with AKI were identified using the pediatric RIFLE (risk, injury, failure, loss, end stage)

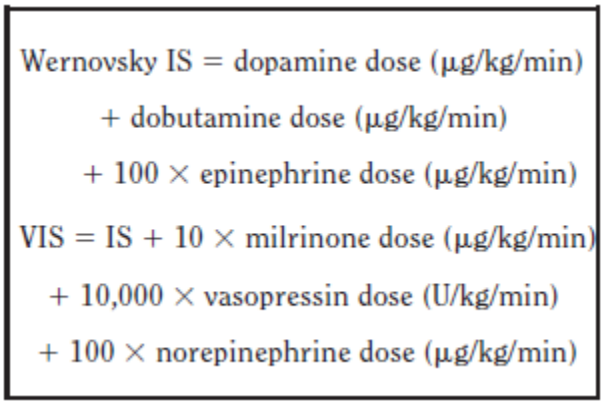
criteria (34). Low cardiac output syndrome was defined using the well-accepted PRIMACORP milrinone study definition of clinical signs or symptoms of decreased perfusion, metabolic acidosis and/or escalating pharmacologic support of blood pressure (≥100% over baseline) (35). ICU length of stay was accurately calculated using ICU admission and discharge time stamps retrieved from the MCHN datamart. Length of mechanical ventilation was determined from the time of ICU admission to the time of the extubation when ventilator measurements stopped being recorded in the medical record. The definition of prolonged ICU LOS and prolonged mechanical ventilation was based on both clinical practice at the Mayo Clinic and previous research (23), in which the 75th percentile was used as the cutoff value to define prolonged ICU LOS and prolonged mechanical ventilation, respectively.

For adult CHD patients, early morbidity includes any of the following clinical outcomes during ICU stay following cardiac surgery: renal failure, reoperation for bleeding, sternal wound infection, stroke, pneumonia, prolonged ICU LOS and prolonged postoperative mechanical ventilation. Determination of renal failure, reoperation for bleeding, sternal wound infection, stroke and pneumonia were retrieved from the patient clinical chart. The 75th percentile of ICU LOS was used to establish the cutoff value for defining prolonged ICU LOS. A significant difference in outcome characteristics between the pediatric and adult patient populations was that the adult patients spent much shorter time on mechanical support. In fact, 80% adult patients were on mechanical support for less than or equal to one day. As opposed to pediatric patients who had a

median value of 3 days on mechanical support (ranges 1 to 36 days). Therefore in the adult CHD patient population we defined prolonged mechanical ventilation as ventilation >=5 days based on previous research that had been published for the same patient population (31). A poor outcome occurred if a patient experienced early mortality or any of the morbidity events. The poor outcome variable was used to determine the best predictors in validating maxVIS model and developing the new model. In additional, due to the small incidence of complication related outcomes, which includes renal failure, reoperation for bleeding, sternal wound infection, stroke and pneumonia, a second composite outcome variable, complication related outcome variable, defined as the occurrence of any of these morbidity outcomes was also assessed in the analysis. Finally, each of these early outcomes was also assessed separately for their relationship with VIS.

3.3.2 Inotrope Score and Vasoactive–Inotrope Score

The following inotropic and vasoactive medications were included in this study: dopamine, dobutamine, epinephrine, norepinephrine, milrinone, and vasopressin. The inotropic score (IS) was calculated as described by Wernovsky (23) and the vasoactive-inotropic score (VIS) was calculated as described by Gaies et al. (26):



Note. Reprinted from "Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass," by Gaies MG, Gurney JG, Yen AH et al., 2010, *Pediatr Crit Care Med*, 11:234–238.

The IS and VIS were calculated on an hourly interval for the first 96 hours after CICU admission. If the patient did not receive milrinone, vasopressin or norepinephrine during his or her inotropic administration, these values were set to be zero in calculating VIS. In this case, VIS has the same value as IS. The maximum VIS values at 12-hour and 24-hour intervals were calculated and graphically presented to determine the optimal dose interval for VIS predictive performance.

3.3.3 Statistical Models

Baseline characteristics and clinical outcomes were described using medians with 25th and 75th percentiles for continuous variables and frequencies and proportions for categorical variables. Descriptive data were compared using the Wilcoxon rank–sum test for continuous and a Pearson χ^2 or Fisher's exact test for categorical variables. Descriptive statistics and graphic figures were applied to explore the basic characteristics

of the patients and inotropic use at each time interval. Multivariable logistic regression was performed to evaluate the predictive performance of maxVIS on early mortality and morbidity outcomes. Given that some patients had two different encounters in the same study population, the logistic regression model was fitted with generalized estimating equation (GEE) methodology to address the correlated outcomes from the same patient. An exchangeable correlation structure was used to apply the GEE methodology. This methodology assumes that pair-wise correlations between encounters from the same patient are equal, whereas encounters from different patients are independent. Potential confounding variables including year of surgery, age, RACHS-1 score, cardiopulmonary bypass (CPB) time, clamp time were included in the model. Year of surgery was included in the model to adjust for changes in surgical procedures and patient care over time that may affect mortality rate over the past 10 years. Because of the diverse complexity of the surgeries and the modest cohort size for both patient populations, the number of patients in each RACHS category is not evenly distributed. For instance, there is only one pediatric patient with RACHS-1 score of 5, and one adult patient with RACHS-1 score of 6. The sparseness in certain RACHS score category could potentially affect the validity of statistical model estimates when RACHS score was assessed as a potential confounding variable. Therefore, for both patient populations, RACHS-1 score was dichotomized into RACHS-1 subgroup 1 to 3 (lower surgical risk) and RACHS-1 subgroup 4 to 6 (higher surgical risk) based on their relative risk categories. To assess the potential correlation between different age group and risk of outcomes, we also classified

age into different categories based on our study of interest. For pediatric CHD patient, age was classified into age group of 0 to 1 months, 1 to 6 months and 6 to 12 months old. For adult CHD patients, age was classified into age group of 18-30, 31-50, 51-65 and ≥65 years old. For adult CHD patients, number of prior sternotomy, BMI, and diabetic status were also assessed in the model. Prior sternotomy status was assessed as a potential confounding factor based on the clinical knowledge that patient risk for poor outcome increases as the number of sternotomies increases (31). A backward elimination strategy with a statistical significance level of 5% was used to exclude statistically insignificant confounding covariates from the model. The multivariate mixed-effects model with repeated measures was performed to calculate the estimated marginal mean values of maxVIS within each time interval. This approach was to ensure the VIS values were calculated after controlling poor clinical outcome and other significant covariates.

3.4 Predictive Performance Measurements

The accuracy of predictive models is most commonly assessed in terms of their discrimination and calibration performance. Discrimination refers to the ability to distinguish high-risk subjects from low-risk subjects, and is commonly quantified by the ROC curve. The overall strength of association is summarized by the area underneath the curve, often called the concordance AUC. The AUC is the probability of concordance between outcomes and predictions. Published AUC criteria suggest that ≥ 0.7 is acceptable, ≥0.8 is good, and ≥ 0.9 is excellent (36). Calibration refers to how well the

predicted probabilities of outcome from the model agree with the observed outcome. It is generally assessed using the Hosmer-Lemeshow (H-L) χ^2 test (37). It is a statistical test for goodness of fit for logistic regression models. The test assesses whether or not the observed event rates match expected event rates in subgroups of the model population. For each prediction model, the H-L goodness-of-fit test specifically categorizes subjects into 10 groups according to quintiles of their associated predicted probability of mortality, and the observed and expected outcomes were compared using a χ^2 statistic. Models for which expected and observed event rates in subgroups are similar are called well calibrated.

For this project, the AUC with 95% confidence interval (CI) was calculated after adjusting significant confounding variables to assess the performance of different VIS models in discriminating poor clinical outcomes, and H-L χ^2 test was used to assess the goodness of fit of the model. The observed and predicted log odds plots were created to ascertain whether the risk model predicted clinical outcomes correctly.

In addition, odds ratio (OR) with 95% CIs was calculated after adjusting for significant covariates for each outcome variable to assess the association between poor clinical outcomes and VIS values.

All statistical analyses were performed with SAS statistical software version 9.2 (38). All statistical tests were two-sided with α level set at 0.05 for statistical significance.

3.5 MaxVIS Model Validation - Pediatric CHD Patients

In general, there are two forms of validation of a clinical predictive model. The first, internal validation, is done in the context of an individual study, for example by splitting the study data set into one data set to train or build the model (training set) and one data set to test performance (test set, also called the validation set). The appealing feature of internal validation is its convenience, as it does not require collection of data beyond the original study. However, when the sample size is small, accurate estimation of the internal validity of a predictive model could be problematic. External validation consists of assessing model performance on one or more data sets collected by different investigators from different institutions. External validation is a more rigorous procedure necessary for evaluating whether the predictive model will generalize to populations other than the one on which it was developed. Gaies et al. proposed the maxVIS prediction model with patients admitted to the cardiothoracic intensive care unit (CICU) after CHS at University of Michigan School of Medicine (26). In this project, we opt to externally validate the maxVIS model with patients admitted to the pediatric ICU after CHS at Mayo Clinic in Rochester, MN.

Gaies and colleagues applied the following algorithm in classifying patients based on their IS/VIS values during the first 24 and subsequent 24 hours postoperatively based on their clinical experience (Table 4).

They reasoned that in their institution, a patient who requires moderate cardiovascular support on return to the intensive care unit is typically receiving

vasoactive infusions at dosages that would result in a VIS of approximately 15. Thus, they set scores in this range as the midpoint in the classification scheme for the first 24 hours and reasoned that most patients would be on lower doses during the second 24 hours. Patients were assigned to the highest classification group achieved during either the first or subsequent 24-hour periods (i.e., a patient with a group 4 score at 24 hours and a group 3 score at 48 hours was classified as group 4 support).

We took a similar approach in deriving maxVIS score in order to evaluate if the predictive performance of maxVIS during the first 48 hours postoperatively was reproducible in our institution. Specifically, we performed the following steps:

1. Only the first 48 hours VIS dose values were evaluated;
2. The maximum VIS within the first 24 hours and the subsequent 24 hours were calculated and patients were assigned to the highest VIS score based on their maxVIS value at each 24-hour period. For example, a patient with a VIS score of 4 during the first 24 hours and a VIS score of 3 during the subsequent 24 hours was assigned to a VIS score of 4.

We examined the descriptive summary of maxVIS values at each 24-hour time interval and applied the same classifying algorithm to group patients into different risk category. Discriminative performance of this maxVIS classification model was then evaluated for both primary composite outcome and each individual outcome with the

statistical techniques as described in section 3.4 after controlling for significant covariates.

Table 4. Classification System Based on Inotropic Score

Group[a]	IS or VIS in First 24 hrs	IS or VIS 24–48 hrs
1	<10	<5
2	10–14	5–9
3	15–19	10–14
4	20–24	15–19
5	≥25	≥20

IS, inotrope score; VIS, vasoactive–inotropic score.

[a]Group assignment based on highest support level in either time period. (Example: Patient with maximum IS 22 in first 24 hrs and 14 in the subsequent 24 hrs would be classified as group 4).

Note. Reprinted from "Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass," by Gaies MG, Gurney JG, Yen AH et al., 2010, *Pediatr Crit Care Med*, 11:234–238

3.6 VIS Index Model Development - Pediatric CHD Patients

The second aim of this research is to further examine the VIS predictive performance by investigating additional characteristics of VIS and to develop a more robust yet simple predictive model of poor clinical outcome. One of the main study interests of this research is to understand the relationship between longer duration of high VIS exposure and increased risk of poor clinical outcome and to quantify such association if there is any. In validating the maxVIS classification model as described in section 3.3, we discovered that the overall VIS values at our institution are slightly lower than what were reported in other institutions possibly due to the fact that physicians at

different hospitals practice differently in administrating inotropic and vasoactive agents to patients. This could cause potential issue of reproducibility and reusability of the prediction model in other institutions. Therefore, in proposing the new model, instead of classifying patients into different risk groups based on their VIS values at each 24-hour period, we took a simplified approach by taking the cumulative maxVIS values during the postoperative period. Specifically, we examined the following two characteristics of VIS values:

1. The postoperative temporal characteristics of VIS dose values up to 96 hours. This is to assess if taking VIS dose values at 24-hour time intervals is appropriate without losing significant clinical information and to identify the optimal time point at which VIS values have significantly changes over time;
2. The correlation between the duration of staying on high doses of inotropic support and early postoperative adverse outcomes.

To assess the postoperative temporal characteristics of VIS dose values, simple data exploration including data plots over time and descriptive summary were used. The median, 25^{th} and 75^{th} percentile of VIS values on the hourly interval across all patients were calculated and plotted over the first 96 hours postoperatively. Furthermore, to evaluate by what time point the VIS values do not change significantly over time any more after adjusting for poor clinical outcome, the multivariate mixed effect model was applied with duration on VIS for up to 96 hours as the fixed effect, patients as random

effect and VIS values as response variable. The VIS on the hourly interval was treated as a categorical variable. Age, RACHS-1 score, CPB time and cross clamp time were assessed as potential confounding variables and were included in the model with a backward elimination approach with significant level of 0.05.

In addition, to assess if taking the maxVIS values on a 24-hour time interval is appropriate, we further examined the difference of maxVIS dose values on 12-hour period within each 24-hour interval, i.e. we compared the maxVIS dose values between 0-12 hour and 12-24 hours, and between 24-36 hours and 36-48 hours, etc. The estimated marginal means of maxVIS values within each 12-hour time interval were compared after adjusting for subject random effect and controlling for poor clinical outcome and other significant covariates.

The assessment of maxVIS temporal characteristics shows that maxVIS values were significantly correlated with time up until 66 hours postoperatively. After 66 hours on vasoactive support, the maxVIS values do not change significantly over time any more. Therefore in developing the new prediction model, we only consider the VIS values during the first 72 hours postoperatively.

3.6.1 Weighted Cumulative maxVIS Score

The predictive model we proposed takes into account the cumulative effect of maxVIS value over time by summing the maxVIS values at each 24-hour time interval postoperatively. Furthermore, we considered the impact of duration of inotropic support

by including a weight if a patient was on inotropic support for longer than 48 hours. Based on the initial data exploration, we found that the number of patients without any poor clinical outcome who still required inotropic support after 48 hours postoperatively decreased by more than 50%. However, the number of patients with at least one poor clinical outcome who were still on vasoactive support only decreased by 10% after 48 hours. Therefore, a weighting factor was introduced in the prediction model to account for the correlation between the longer duration of vasoactive support and the higher incidence of poor outcomes. To determine the optimal weight, we first calculated the odds ratio of experiencing a poor clinical outcome for patients who received vasoactive support longer than 48 hours compared to those who were on vasoactive support less than 48 hours. We then developed the first model with the odds ratio estimate as the weighting factor on maxVIS value during the 48-72 hour period. We also developed a second model with a weight of 2 because it was simple and intuitive to apply in clinical practice. We then compared the discrimination characteristics of the two models. The AUC results of the ROC from the two models did not show any significant difference. Therefore we chose a weight of 2 in proposing the final weighted cumulative maxVIS model for simplicity and ease of use in clinical practice. We first calculated the cumulative maxVIS score as follows:

$$Cumulative\ maxVIS\ score = maxVIS_1 + maxVIS_2 + 2 \times maxVIS_3$$

$maxVIS_i$, i = 1, 2, 3 are the maxVIS values at each 24-hour time period, respectively.

3.6.2 VIS Index Predictive Model

We proposed our prediction model, VIS index, by converting the cumulative maxVIS score to simple integer scores based on both clinical knowledge and the distribution of the cumulative maxVIS values so that the risk model can be easily applied in clinical practice. We assessed the validity of this conversion by calculating the correlation between the predicted log odds from the original model and the simplified model. To examine whether the VIS index risk model is appropriate for patients with different types of morbidity events, we evaluated the model discrimination, calibration, strength of association, and predicted vs. observed risk for both the composite poor outcome and each individual morbidity event. The predictive performance of VIS index was not separately evaluated for mortality due to the small incidence of death events.

We applied the statistical methods described in section 3.4 to evaluate the overall predictive performance of the VIS index model.

3.6.3 Assessment of Duration of High VIS

We further investigated the association of duration of patient receiving high doses of inotropic support with the clinical outcome. We hypothesized that a sick patient with a high risk of developing any poor outcome could be on high dose of vasopressors as soon as he was admitted to ICU. Therefore we sought to examine if the VIS index model adequately address such prognostic correlation. The descriptive statistic summary of VIS values at each 24-hour time interval shows that most patients received highest doses

during the first 24 hours and lower doses thereafter, and patients with a poor clinical outcome have significantly higher maxVIS values than those patients who do not have any poor clinical outcome. Therefore we used the mean maxVIS value within each 24-hour period for patients with a poor clinical outcome as the cut-off values to define high VIS values. Then for each patient, the maxVIS value on the hourly interval was compared with the high VIS value and the cumulative duration of a patient staying on high VIS was calculated. We identified those patients who were on high inotropic support for at least 1 hour during the first 72-hour postoperative period and evaluated the correlation between poor clinical outcome, the VIS index and longer duration on high doses of inotropic support.

3.7 VIS Index Model Development – Adult CHD Patients

The last aim of this research is to investigate if the maxVIS model and the VIS index model based on the pediatric CHD patient population also apply to the adult CHD patient population. We took the same approach in developing maxVIS model and the VIS index model for pediatric CHD patients as described in section 3.5 and 3.6 for the adult CHD patients. We examined the postoperative temporal characteristics of VIS dose values up to 96 hours and assessed the correlation between the duration of staying on high doses of inotropic support and early postoperative adverse outcomes. The maxVIS model includes the maxVIS values during the first 48-hour postoperative period. Patients

were classified into one of the risk groups based on their maxVIS values during the first 24-hour and subsequent 24-hour postoperative period. The VIS index model takes into account the weighted cumulative effect of maxVIS value over time by summing the maxVIS values at each 24-hour time interval postoperatively. We compared model discrimination and calibration of the maxVIS model and the VIS index model on the composite poor outcome as well as each individual morbidity outcome using AUC and H-L test. We calculated the strength of association, and predicted vs. observed risk for the VIS index model. We then proposed the final risk prediction scoring system based on the VIS index model.

CHAPTER FOUR: RESULTS

4.1 EMR Data Quality Assurance

One of the biggest challenges in utilizing EMR data capture system in clinical research is the assurance of data quality. As the vasopressor doses were entered by operating room (OR) nurses and then captured in the EMR system, two types of data errors were encountered and addressed in this project. The first type was data inconsistency due to human error. For example, one OR nurse may use “unit/min” as the unit for epinephrine dose for a few hours to a few days after one patient was admitted to the ICU. Later when another OR nurse needed to refill an epinephrine order for the patient, he/she may use the unit "unit/kg/hour" for the epinephrine dose. Because of the inconsistency in vasopressor units, the dose values could differ dramatically. The second issue was data inaccuracy due to a “system fluke”, i.e. when the vasopressor doses was changed, the system became “confused” in the transition and captured erroneous values at the same time point. Figure 2 shows a snapshot of such data values.

We took the approaches described in section 3.1 to address both of these data issues manually and programmatically and to ensure the study data used in this project were complete, accurate and consistent.

	A	B	C	D	E
1	ChnlD	Med	Unit	DoseDate	doseValue
193	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 09:00	3.7267
194	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 09:02	3.7267
195	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 09:02	3.5887
196	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 09:15	3.5887
197	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 09:30	3.5887
198	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 09:45	3.5887
199	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 09:45	3.4507
200	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 10:00	3.4507
201	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 10:09	3.4507
202	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 10:15	25
203	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 10:27	25
204	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 10:45	3.3126
205	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 11:00	3.3126
206	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 11:15	3.3126
207	405f11c7-57ff-4f4c-b97e-4b6b293f6ade	Dopamine	mcg/kg/m	02/20/2003 11:30	3.3126

Figure 2. Snapshot of vasopressor dose data with “system fluke”

4.2 Results – Pediatric CHD Patients

4.2.1 Patients Characteristics

Two hundred forty-four infants age of 0 to 12 months admitted to the pediatric intensive care unit (PICU) after CHS between November 2002 and September 2011 were included with complete demographic, clinical and inotropic-vasoactive data. Eleven patients had two separate admissions with a median value of 134 days apart between the two encounters (range from 80 days to 246 days). The two admissions from these 11 patients were treated as two independent admissions and specific statistical technique was applied to adjust the inter-correlation within subjects. Therefore a total number of 255 encounters were included in the pediatric patient data analysis. The demographic, baseline clinical and operative data are shown in Table 5 and Table 6. Overall 78%

pediatric patients have a RACHS-1 score of 1 to 3. The 75th percentile of ICU LOS and duration on mechanical ventilation was 12 days and 6 days, respectively. These two values were used to define prolonged ICU LOS and prolonged mechanical ventilation.

Table 5. Pediatric Patient Characteristics – Categorical Variables

Characteristic	n (%)
Age at surgery	
0-1 months	62 (24.3%)
1-6 months	122 (47.8%)
6-12 months	71 (27.8%)
Gender	
Female	106 (41.6%)
Male	143 (56.1%)
RACHS-1 category	
1-3	199 (78.0%)
4-6	56 (22.0%)

RACHS-1, Risk Adjustment in Congenital Heart Surgery.

Table 6. Pediatric Patient Characteristics – Continuous Variables

Characteristics	n	Mean ± SD	Median	75th percentile	Range
Age (days)	255	127±98.2	122	192	0-362
Aortic crossclamp time (mins)	247	53±26.9	48	70	0-169
CPB time (mins)	255	98±44.5	85	120	22-247
ICU LOS (days)	255	12±13.9	8	12	1-111
Length of mechanical ventilation (days)	255	5±5.2	3	6	1-36

CPB, cardiopulmonary bypass; ICU, intensive care unit; LOS, length of stay.

One hundred and forty-five patients experienced a poor clinical outcome (57%), including 7 deaths either in-hospital or within 90 days of hospital discharge (3%). Early mortality rate is lower than what was reported in the initial VIS study (3% vs. 12%) and this is consistent with the lower RACHS scores observed in our study. All 7 patients with

early mortality outcome also had at least one of the morbidity events - five patients developed low cardiac output syndrome, three patients had prolonged ICU LOS, and three patients had prolonged mechanical ventilation. Ninety-five patients (37%) had a prolonged ICU LOS (≥12 days), 71 (28%) patients had a prolonged mechanical ventilation (≥6 days) and 86 (34%) patients had low cardiac output syndrome. Because all three patients who had AKI also had low cardiac output syndrome, and because the incidence of this outcome is small, the association of VIS with AKI was not evaluated separately in this project.

Table 7. Summary of Outcome Variables - Pediatric CHD Patients

Clinical Outcome	n (%)
Composite mortality and morbidity	145 (57%)
Mortality[1]	7 (3%)
Prolonged ICU LOS	95 (37%)
Prolonged mechanical ventilation	71 (28%)
Low cardiac output syndrome	86 (34%)
Acute Kidney Injury	3 (1%)

ICU, intensive care unit; LOS, length of stay.
1. Mortality is in-hospital death or death within 90 days of hospital discharge.

4.2.2 Vasopressor Characteristics

Vasoactive Administration

The postoperative use of vasoactive agents is summarized in table 8. All pediatric CHD patients in our institution received milrinone (100%), and epinephrine was the second most widely used vasopressor (92.9%). No patients received either dobutamine or norepinephrine during the first 96-hour postoperative period.

Table 8. Postoperative Use of Vasoactive Agents - Pediatric CHD Patients

Vasoactive Agents	n(%)
Dopamine	39 (15.3%)
Epinephrine	237 (92.9%)
Milrinone	255 (100%)
Vasopressin	35 (13.7%)

VIS Temporal Characteristics

We examined the temporal characteristics of VIS values during the first 96-hour postoperative period. The scatter plot in Figure 3 presents the VIS values for each patient by composite outcome; the series plot in Figure 4 presents the median, 25^{th} and 75^{th} percentile of VIS values of all patients by composite outcome; the box plot in Figure 5 presents the distribution of maxVIS values at 12-hour interval by composite poor outcome. These graphical presentations of VIS temporal pattern show that overall maxVIS values are higher for those patients with at least one poor clinical outcome than those patients without any poor outcome. The median maxVIS values within the first and the second 24-hour period are 12 (range, 1-48) and 9 (range, 2-37) for patients with a poor outcome, compared to 8 (range, 1-34) and 5 (range, 1-14), respectively, for patients without any poor outcome (Table 9). For both outcome groups, maxVIS values are higher during the first 24 hours than the subsequent postoperative period for patients with and without any poor outcome, and the values stay relatively stable after 48 hours. Figure 6 shows that the number of patients receiving inotropic support during the first 48-hour postoperative period is consistent between the two outcome groups. However, the number

of patients without any poor clinical outcome who still required inotropic support after 48 hours postoperatively decreased by 57 percentage points, compared to 16 percentage points decrease among patients who had at least one poor clinical outcome.

Table 9. MaxVIS Value Summary by Outcome - Pediatric CHD Patients

Time Interval	n (%)	Mean (SD)	Median (range)
Poor clinical outcome: Yes			
0 – 24 hrs	145 (100%)	14.3 (8.39)	12 (1-48)
24 – 48 hrs	137 (94.4%)	10.5 (6.38)	9 (2-37)
48 – 72 hrs	113 (78.1%)	9.2 (5.69)	8 (1-32)
72 – 96 hrs	87 (60.0%)	9.0 (5.55)	8 (1-29)
Poor clinical outcome: No			
0 – 24 hrs	110 (100%)	8.7 (4.35)	8 (1-34)
24 – 48 hrs	94 (85.5%)	5.5 (3.09)	5 (1-14)
48 – 72 hrs	31 (28.2%)	5.5 (2.49)	5 (2-11)
72 – 96 hrs	15 (13.6%)	4.9 (2.53)	5 (2-11)

SD, standard deviation.

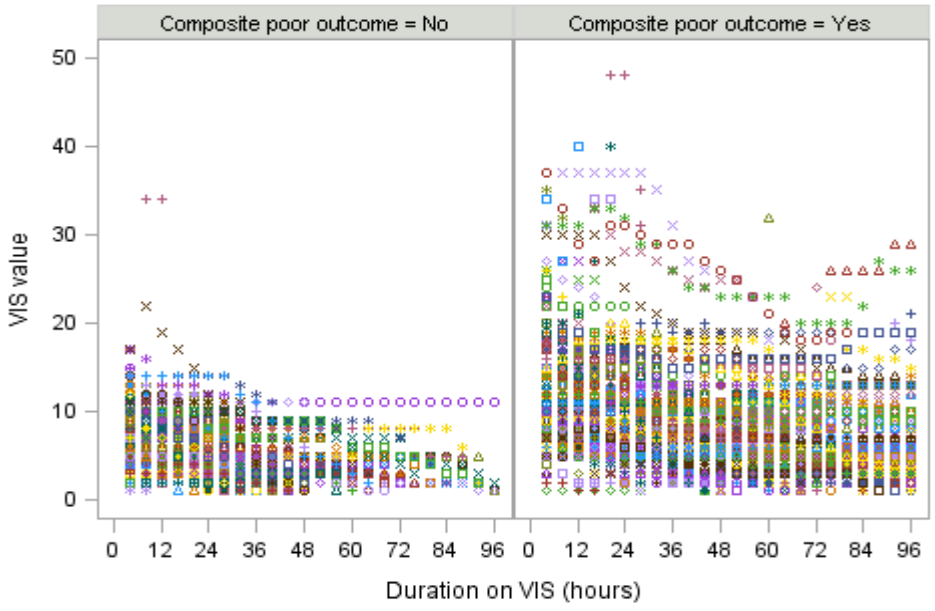


Figure 3. Series Plot of VIS values by outcome - Pediatric CHD patients

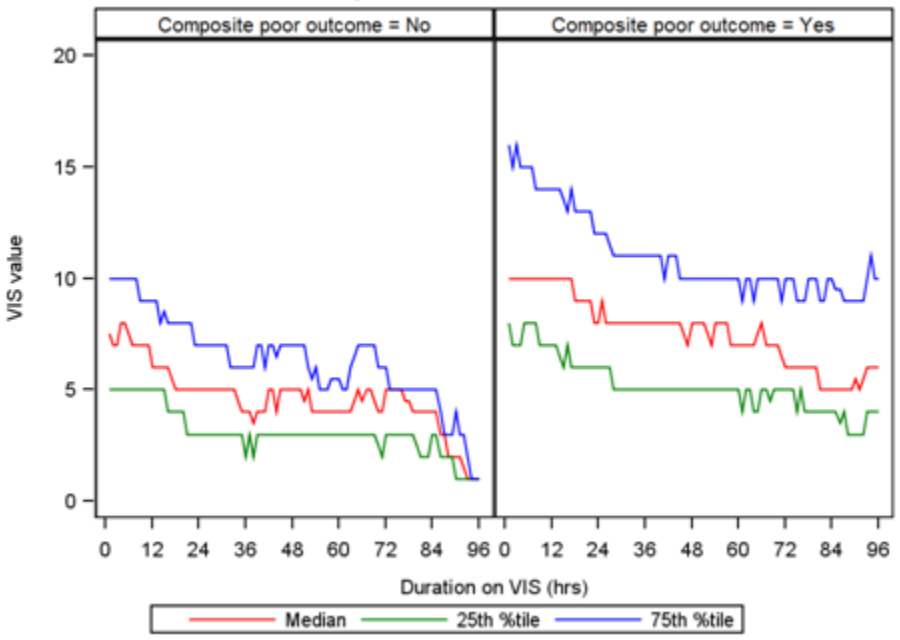


Figure 4. Series Plot of maxVIS values by outcome - Pediatric CHD patients

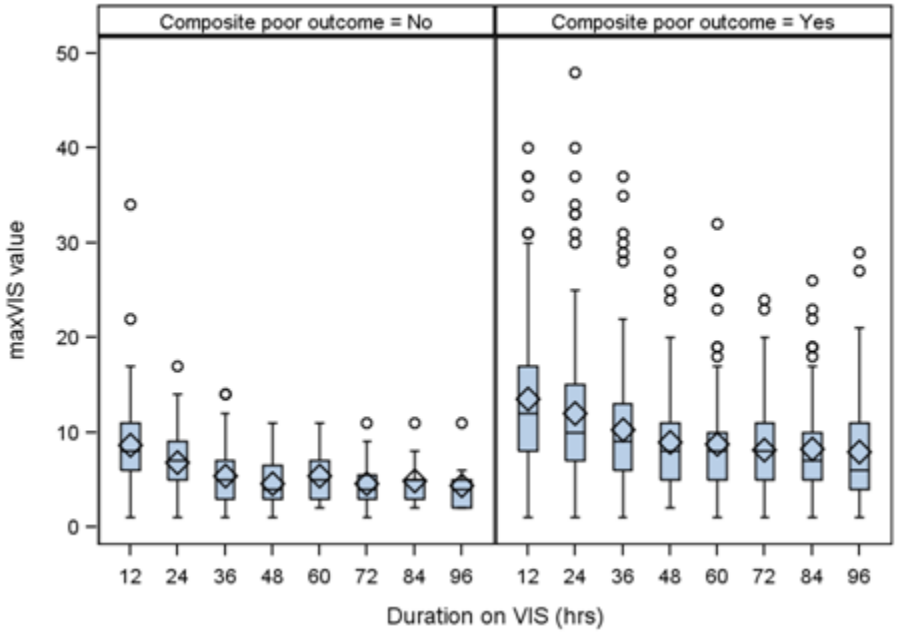


Figure 5. Boxplot of maxVIS values by outcome - Pediatric CHD patients

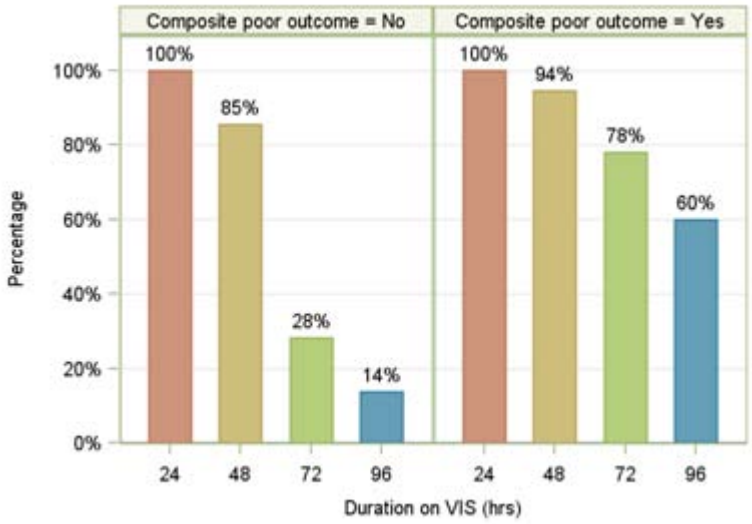


Figure 6. Frequency of VIS values within each 24-hour period - Pediatric CHD patients. Percentage is based on the total number of patients in each outcome group

Optimal Time Interval of VIS

The pair-wise comparisons of maxVIS values between the first and the second 12 hours within each 24-hour period are shown in Table 10. The maxVIS values show statistically significant difference between the first 12-hour and the second 12-hour interval during the first 24-hour postoperative period (estimated marginal mean difference 1.7; $P = 0.0064$). No significant difference was found between the two 12-hour intervals during the subsequent 24-96 hour period. Since 100% patients received vasoactive support during the first 24-hour postoperative period, and the maximum VIS values during this period was used in the VIS prediction model, we concluded that it was

appropriate to use a 24-hour interval in calculating VIS values without losing any significant clinical information.

Table 10. MaxVIS Value Pair-wise Comparison - Pediatric CHD Patients

Time Interval	LS Mean* (95% CI)	Mean Difference	p value
0 – 24 hrs			
0 – 12 hrs	12.0 (11.3, 12.8)	1.7	0.0064
12 – 24 hrs	10.4 (9.6, 11.1)		
24 – 48 hrs			
24 – 36 hrs	8.7 (7.9, 9.5)	1.5	0.1252
36 – 48 hrs	7.1 (6.3, 7.9)		
48 – 72 hrs			
48 – 60 hrs	6.4 (5.5, 7.3)	1.1	0.3476
60 – 72 hrs	5.3 (4.4, 6.2)		
72 – 96 hrs			
72 – 84 hrs	4.7 (3.8, 5.7)	0.5	0.7563
84 – 96 hrs	4.3 (3.3, 5.2)		

* LS mean is the estimated marginal mean value of maxVIS after controlling for poor clinical outcome
CI, confidence interval.

Optimal Duration on VIS

The estimated marginal mean of maxVIS values is 6.8 (95% CI: 5.7 to 7.9) at 48-72 hours and 5.4 (95% CI: 4.0 to 6.8) at 72-96 hours after controlling for poor clinical outcome (Table 11). The mean difference between these two 24-hour internals is 1.4 (95% CI: 0.04 to 2.8) and considered insignificant. The results from the multivariate mixed effect model in assessing the correlation between maxVIS values and duration on VIS further confirms VIS temporal characteristics exhibited in the graphical plots. The maxVIS values were significantly correlated with duration on VIS up until 66 hours postoperatively after adjusting for poor clinical outcome and controlling for age group

and RACHS score. Therefore, we considered the first 72 hours postoperatively of VIS values in developing VIS index model.

Table 11. MaxVIS Value Summary - Pediatric CHD Patients

Time Interval	n (%)	LS Mean*	95% CI
0 – 24 hrs	255 (100%)	12.3	11.5 – 13.2
24 – 48 hrs	231(91%)	8.7	7.8 – 9.6
48 – 72 hrs	144 (56%)	6.8	5.7 – 7.9
72 – 96 hrs	102 (40%)	5.4	4.0 – 6.8

* LS mean is the estimated marginal mean value of maxVIS after controlling for poor clinical outcome
CI, confidence interval.

Duration of High VIS

As Table 9 shows, patients experiencing a poor clinical outcome have a mean maxVIS value of 14.3 during the first 24 hours, and 10.5 and 9.2 during the subsequent 24-48, and 48-72 hour postoperative period. Therefore we chose maxVIS value of 15 during the first 24 hours and 10 during the subsequent 24-72 hour period as the cutoff value in defining high VIS. There are a total number of 92 patients with duration on high inotropic support for at least 1 hour during the first 72-hour postoperative period. Seventy-eight of them experienced at least one poor outcome, which accounts for 53.8% of all patients with a poor outcome. There is strong correlation between poor clinical outcome and longer duration on high volume of inotropic support (Wilcoxon rank sum test P= 0.0004) as shown in Table 12.

Table 12. Duration on High VIS by Outcome – Pediatric CHD Patients

Poor Outcome	Duration on High VIS (hrs)			
	n(%)*	Mean (SD)	Median (range)	Wilcoxon rank sum p value
Yes	78 (53.8%)	33.7 (22.76)	34.0 (1.0 – 72.0)	0.0004
No	14 (12.7%)	10.6 (8.02)	8.5 (1.0 – 28.0)	

VIS, vasoactive–inotropic score; SD, standard deviation.
* The denominator for percentage calculation is the total number of patients in each outcome group.

4.2.3 MaxVIS Model Validation

Confounding Factors of Poor Clinical Outcomes

The correlation of confounding factors for each outcome variable is presented in Table 13. Age group was significantly correlated with the composite poor outcome (χ^2 statistics = 8.55, P = 0.0139). RACHS-1 categories with dichotomized values of 1-3 and 4-6 did not show any significant correlation with either composite poor outcome or individual outcome variable. This could be due to the low mortality rate (3%) of the pediatric patients in our study. CPB time and cross clamp time were significantly correlated with prolonged mechanical ventilation but not with any other outcomes. This finding is consistent with what other clinical studies have reported, i.e. cardiac surgery with CPB can result in systemic inflammatory response, impaired immune reaction, and organ dysfunction in children, which leads to longer duration on mechanical support (39-41). None of the confounding variables were found to be significantly correlated with mortality. This could be due to the small incidence of the event (7 deaths within 90 days of discharge).

Table 13. Confounding Variables Summary - Pediatric CHD Patients

Clinical outcome	Variable	Wald Chi-square value	p-value
Composite poor outcome			
	RACHS-1 group	0.1573	0.6916
	Age group	8.5501	**0.0139**
	Year of surgery	0.2914	0.5893
	CPB time (mins)	0.7150	0.3989
	Aortic xclamp time (mins)	1.0436	0.3070
Mortality[1]			
	RACHS-1 group	0.1015	0.7500
	Age group	3.0464	0.2180
	Year of surgery	0.8551	0.3551
	CPB time (mins)	0.0006	0.9813
	Aortic xclamp time (mins)	0.1640	0.6855
Prolonged ICU LOS			
	RACHS-1 group	0.6821	0.4089
	Age group	5.7769	0.0557
	Year of surgery	0.0022	0.9622
	CPB time (mins)	2.4365	0.1185
	Aortic xclamp time (mins)	1.5861	0.2079
Prolonged mechanical support			
	RACHS-1 group	0.0000	0.9961
	Age group	3.4747	0.1760
	Year of surgery	0.0128	0.9100
	CPB time (mins)	5.5337	**0.0187**
	Aortic xclamp time (mins)	4.9250	**0.0265**
Low cardiac output syndrome			
	RACHS-1 group	0.7970	0.3720
	Age group	1.3299	0.5143
	Year of surgery	1.4090	0.2352
	CPB time (mins)	0.4377	0.5083
	Aortic xclamp time (mins)	0.0543	0.8157

RACHS-1, Risk Adjustment in Congenital Heart Surgery; CPB, cardiac-pulmonary bypass; ICU, intensive care unit; LOS, length of stay.
RACHS-1 group: RACHS 1-3 and 4-6; Age group: 0-1 month, 1-6 months and 6-12 months.
1. Mortality is in-hospital death or death within 90 days of hospital discharge.

MaxVIS Classification Model

In the sentinel study Gaies et al. conducted, they reasoned that a patient who requires moderate cardiovascular support after being admitted to the ICU typically receives vasoactive infusions at dosages that would result in a VIS of approximately 15.

Therefore they assigned a risk score of 3 as the median score in the classification scheme for patients with a VIS value between 15 and 20 during the first 24-hour postoperative hours. In order to externally validate the maxVIS model, we first examined the maxVIS values for our patient population. Within our study population, patients who experienced a poor clinical outcome had a mean maxVIS value of 14.3 during the first 24 hours, and 10.5 during the subsequent 24-48 hour postoperative hours (Table 9). Overall the maxVIS values in our study were consistent with those reported in Gaies' study. Therefore, we applied the same algorithm used by Gaies et al to classify patients into different risk categories. (Table 4).

MaxVIS Model Performance – Discrimination and Calibration

The performance characteristics of maxVIS prediction model for each poor clinical outcome are show in Table 15. The H-L test result and ROC area suggest maxVIS has good calibration and reasonable discrimination for the composite mortality and morbidity (H-L test: P = 0.692, AUC = 0.771, 95% CI: 0.718 to 0.824). The performance is consistent for all other individual morbidity outcomes as well. In the original study which maxVIS model was developed, the authors reported AUC value of 0.83 (95% CI: 0.76 to 0.90) for composite outcome of mortality and morbidity. Our study result is consistent with the original finding for the predictive ability of maxVIS and suggests that maxVIS during the first 48 hours postoperatively may be used to stratify pediatric CHD patients into risk groups for treatment management after CHS.

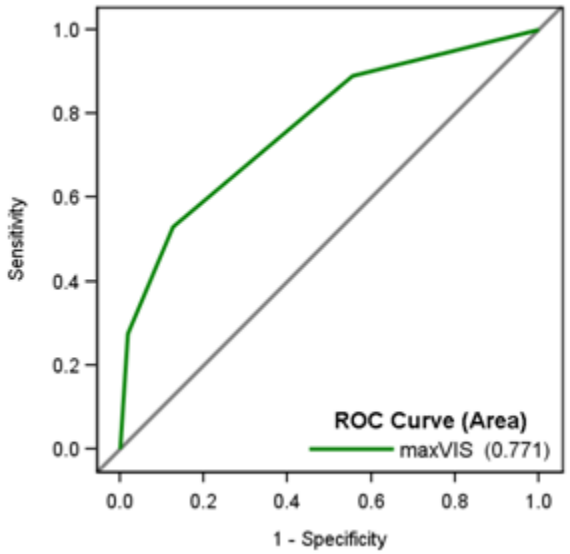


Figure 7. MaxVIS model ROC curve for composite poor outcome - Pediatric CHD patients

Table 15. Performance Characteristics of MaxVIS Model - Pediatric CHD Patients

Clinical Outcome	AUC[1]	95% CI	H-L p-value
Composite poor outcome	0.771	(0.717, 0.824)	0.791
Mortality[2]	0.766	(0.515, 1.000)	0.239
Prolonged ICU LOS	0.771	(0.713, 0.829)	0.284
Prolonged mechanical ventilation	0.804	(0.748, 0.859)	0.113
Low cardiac output syndrome	0.717	(0.655, 0.780)	0.290

AUC, area under the curve; CI, confidence interval; H-L, Hosmer-Lemeshow test;
ICU, intensive care unit; LOS, length of stay;
1. Adjusted for significant covariates for each outcome.
2. Mortality is in-hospital death or death within 90 days of hospital discharge.

4.2.4 VIS Index Model

VIS Index Model Development

In developing the VIS index prediction model, we first applied the algorithm as described in Methods Section 3.6 and calculated the weighted cumulative maxVIS over each 24-hour period during the first 72-hour postoperative period. The cumulative VIS score is a continuous variable with value ranges from 2 to 124 for patients with a poor clinical outcome and from 1 to 58 for patients without any poor outcome (Table 16). Figure 8.1 presents the predicted log odds ratio of cumulative VIS value ranges from 0 to 120. As the predicted risk has the most significant increase with cumulative VIS value ranges from 0 to 60 and reaches to asymptote of 100% as cumulative VIS value > 60, we also created the predicted log odds ratio plot with cumulative VIS value ranges from 0 to 60 as shown in Figure 8.2.

Table 16. Cumulative MaxVIS Values by Outcome - Pediatric CHD Patients

Poor Outcome	n	Mean	SD	Median (range)	25th %tile	75th %tile
Yes	145	38.6	24.06	34 (2 – 124)	20	53
No	110	16.4	11.19	14 (1 – 58)	8	21

SD, standard deviation.

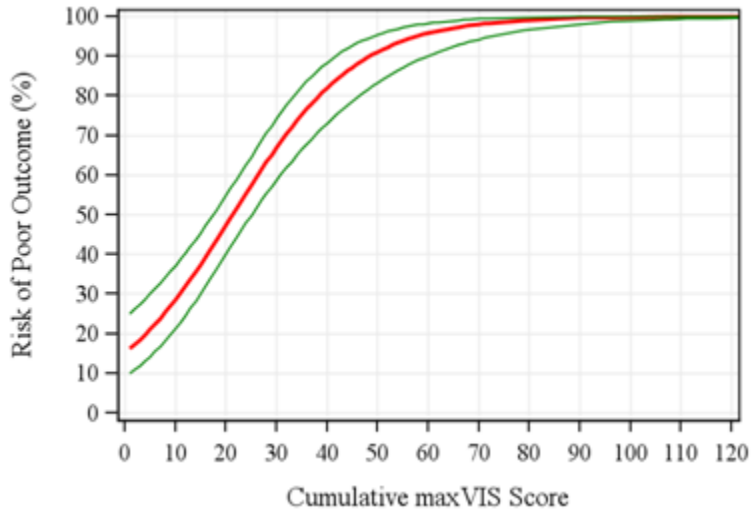


Figure 8.1. Predicted risk plot of cumulative maxVIS score with range 0 to 120 - Pediatric CHD patients

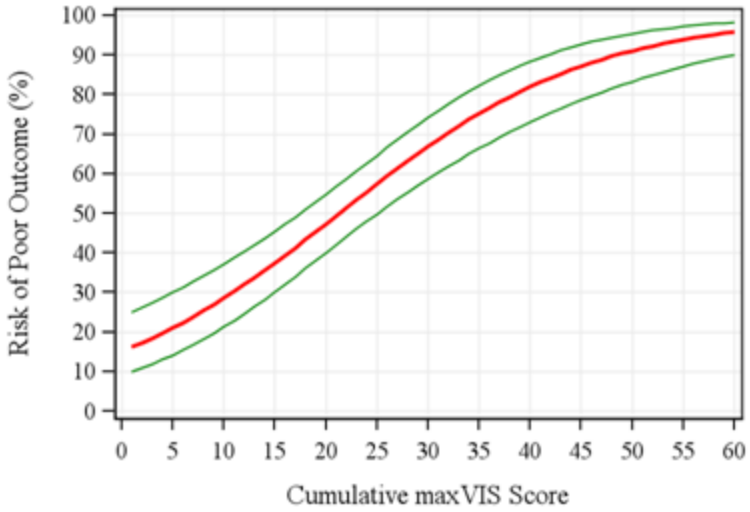


Figure 8.2. Predicted risk plot of cumulative maxVIS score with range 0 to 60 - Pediatric CHD patients

We then incorporated both clinical judgment and statistical results to convert the cumulative VIS values to simple integer scores for ease of use in clinical practice. As

both Figure 8.1 and 8.2 show that the predicted risk of experiencing a poor outcome is less than 30% with a cumulative maxVIS value $\leq$ 10; and the predicted risk increases to greater than 90% at cumulative maxVIS value of 50 and continues to increase towards an asymptote of 100% as cumulative maxVIS value increases. Thus, we assigned an integer score of 1 for cumulative VIS value $\leq$ 10 and applied a scale factor of 10 for any cumulative VIS value between 10 and 50, and assign a maximum integer score for any cumulative maxVIS value greater than 50. We reasoned that a risk of 90% vs. a risk of 95% of experiencing a poor clinical outcome is equally serious from a clinical perspective. The resulting simple score system, the VIS index, has discrete integer values ranges from 1 to 6 (Table 17). This conversion resulted in little loss of predictive accuracy; the correlation between the predicted log odds before and after the simplification is 0.994.

Table 17. VIS Index Conversion Table - Pediatric CHD Patients

Cumulative maxVIS value	VIS Index
1–10	1
11–20	2
21–30	3
31–40	4
41-50	5
> 50	6

VIS, vasoactive-inotrope score.

VIS Index Model Discrimination and Calibration

The VIS index model presents good discrimination and excellent calibration consistently for both the composite poor outcome and each individual morbidity outcome (Table 18). For the composite poor outcome, the AUC was 0.835 (95% CI: 0.780 to 0.880), and there is close agreement between predicted and observed poor outcome rate (H-L test, $P = 0.725$). Death with 90 days of discharge has the lowest AUC with largest confidence interval due to the small incidence of the event. The VIS index also presents very similar discrimination and calibration for prolonged ICU LOS and prolonged mechanical support outcome.

Table 18. VIS Index ROC Curve - Pediatric CHD Patients

Clinical Outcome	AUC[1]	95% CI	H-L p-value
Composite poor outcome	0.835	(0.780, 0.880)	0.725
Mortality[2]	0.685	(0.462, 0.908)	0.383
Prolonged ICU LOS	0.840	(0.786, 0.893)	0.853
Prolonged mechanical ventilation	0.846	(0.794, 0.898)	0.900
Low cardiac output syndrome	0.736	(0.674, 0.797)	0.109

AUC, area under the curve; CI, confidence interval; H-L, Hosmer-Lemeshow test;
ICU, intensive care unit; LOS, length of stay.
1. Adjusted for significant covariates for each outcome.
2. Mortality is in-hospital death or death within 90 days of hospital discharge.

We further compared the predictive performance of the VIS index model with the original maxVIS model. As shown in Figure 9 and Table 19, VIS index model demonstrates a stronger discriminative performance than the original maxVIS model for the composite poor outcome as well as each individual morbidity outcome but death within 90 days of discharge. The difference of AUC between the maxVIS model and the

VIS index model is 0.064 (95% CI: 0.026 to 0.102, *P* value = 0.0009) for the composite poor outcome. Overall AUC was the highest for the prediction of prolonged mechanical ventilation, and was the lowest for the prediction of death within 90 days of discharge due to the small number of incidence of this outcome.

Table 19. ROC Curve of MaxVIS and VIS Index Model - Pediatric CHD Patients

Clinical outcome	maxVIS Model		VIS Index Model	
	AUC[1]	95% CI	AUC[1]	95% CI
Composite poor outcome	0.771	(0.717, 0.824)	0.835	(0.786, 0.884)
Mortality[2]	0.766	(0.515, 1.000)	0.685	(0.462, 0.908)
Prolonged ICU LOS	0.771	(0.713, 0.829)	0.840	(0.786, 0.893)
Prolonged mechanical ventilation	0.804	(0.748, 0.859)	0.846	(0.794, 0.898)
Low cardiac output syndrome	0.717	(0.655, 0.780)	0.736	(0.674, 0.797)

AUC, area under the curve; CI, confidence interval; H-L, Hosmer-Lemeshow test; VIS, vasoactive-inotrope score; ICU, intensive care unit; LOS, length of stay;

1. Adjusted for significant covariates for each outcome.
2. Mortality is in-hospital death or death within 90 days of hospital discharge.

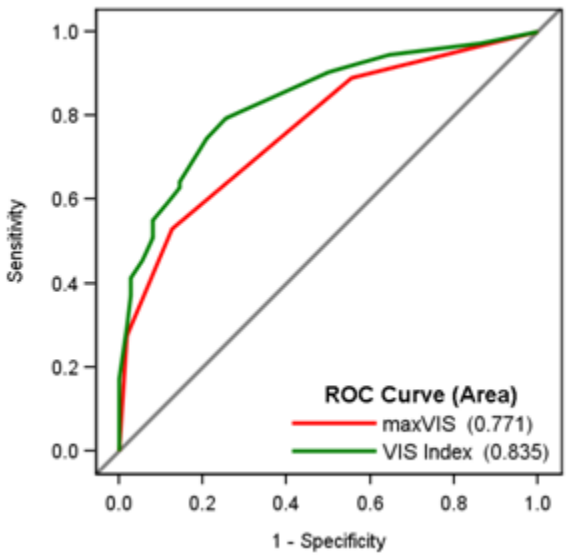


Figure 9. ROC curve of composite poor outcome - Pediatric CHD patients

VIS Index Model Correlation with Duration on High VIS

As we presented in Section 4.2.2, there is strong correlation between poor clinical outcome and longer duration on high doses of vasoactive support (Table 12). To confirm that the VIS index sufficiently addresses such correlation, we examined the relationship between the VIS index and duration on high VIS. As Figure 10 shows, a high VIS index is strongly correlated with longer duration on high VIS. Out of 92 patients who had at least one hour on high vasoactive support, 64 (69.6%) of them had a VIS index value of 5 or 6. This result further confirms that the VIS index incorporates both the duration and magnitude of Inotrope and vasoactive support. It is derived from the maxVIS values of the first 72-hour postoperative period; it also reflects the high dosage of vasoactive support a patient receives. Therefore it can be utilized any time after patients' ICU admission. For example, a sick patient could be on high vasoactive support as soon as he was admitted to ICU after cardiac surgery, which would result a high VIS index immediately during the first 24 hours in ICU and indicate he was on high risk of developing poor outcome.

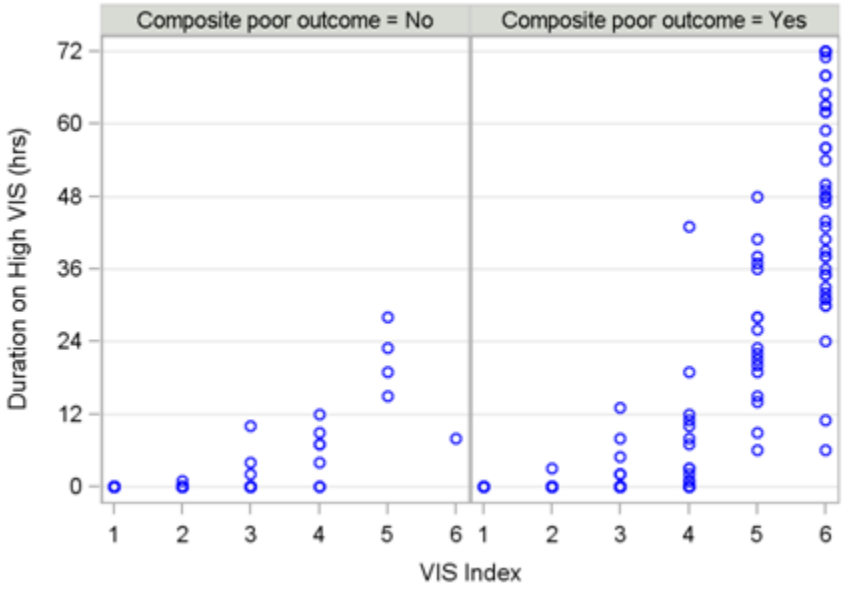


Figure 10. VIS index and duration on high VIS - Pediatric CHD patients

VIS Index Model Risk Prediction Performance

Table 20 present predicted risk of any poor clinical outcome associated with VIS index. The relationship between the observed outcome and the predicted outcome by the VIS index model is illustrated graphically in Figure 11. Overall the predicted risk of having a poor clinical outcome is consistent with the observed outcome for both composite poor outcome and each individual outcome. The predicted risk of experiencing a poor outcome ranges from 20% to 98%, with the lowest risk of 20% (95% CI: 11.3% to 33.9%) with a VIS index of 1 and the highest risk of 98% (95% CI: 85.3% to 99.7%) with a VIS index of 6. There is a slight drop in risk prediction for prolonged mechanical support at VIS index of 4. This could be due to the small incidence of this event at this

index value. The risk plots for each individual poor outcome demonstrate that VIS index is consistent and robust in predicting each outcome event.

Table 20. VIS Index Risk Score – Pediatric CHD Patients

VIS index	Risk of Poor Outcome (%)	95% CI
1	20.4	11.3 – 33.9
2	39.4	28.8 – 51.1
3	65.1	50.0 – 77.8
4	71.4	52.4 – 85.0
5	81.0	58.9 – 92.7
6	97.7	85.3 – 99.7

VIS, vasoactive-inotrope score; CI, confidence interval.

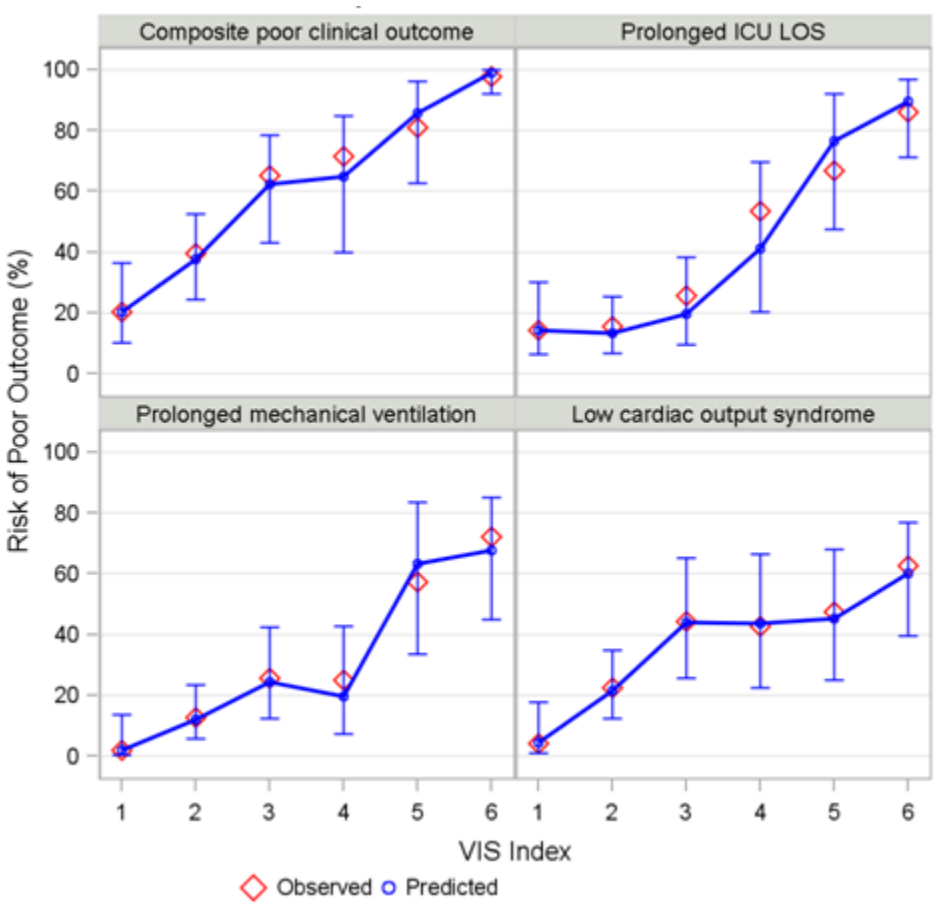


Figure 11. VIS index predicted risk of poor clinical outcomes - Pediatric CHD patients
Composite poor outcome includes mortality and any of the following morbidity events: prolonged ICU LOS, prolonged mechanical ventilation, and low cardiac output syndrome.

VIS Index Model Strength of Association with Risk

As Table 20 shows, the risk for a patient to experience a poor outcome increases from 39.4% (95% CI: 28.8%-51.1%) to 65.1% (95% CI: 50%-77.8%) as the VIS index changes from 2 to 3. We reasoned that from a clinical perspective, a VIS index value that indicates a risk of poor outcome greater than 50% should trigger physician awareness that

the patient may require close monitoring and possibly additional clinical care. Therefore, we chose a VIS index of 3 as the cutoff value to compare the strength of association of VIS index with risk of poor clinical outcome. The results based on multivariate logistic regression model after adjusting for significant confounding factors for each outcome are presented in Table 21. Overall high VIS index (VIS index $\geq$ 3) was strongly associated with poor outcomes with OR of 5.6 (95% CI: 3.1– 10.2; $P < .0001$). On average, patients in the high VIS category were also more likely than those in the low VIS category to experience prolonged ICU LOS (OR: 4.7; 95% CI: 2.5–9.1; $P < .001$), prolonged mechanical support (OR: 5.6; 95% CI: 2.5–12.3; $P < .001$), and low cardiac output syndrome (OR: 5.8; 95% CI: 3.2–10.6; $P < .001$). The association of VIS index with early mortality was not estimated due to the small incidence of events.

Table 21. Association of High VIS Index with Outcome – Pediatric CHD Patients

Clinical Outcome	n (%)	OR*	95% CI	*P* value
Composite poor outcome	145 (56.9%)	5.6	(3.1, 10.2)	<.001
Prolonged ICU LOS	95 (37.3%)	4.7	(2.5, 9.1)	<.001
Prolonged mechanical ventilation	71 (27.8%)	5.6	(2.5, 12.3)	<.001
Low cardiac output syndrome	86 (34.0%)	5.8	(3.2, 10.6)	<.001

OR, odds ratio; CI, confidence interval.

* Adjusted for significant covariates for each outcome.

4.3 Results - Adult CHD Patients

4.3.1 Patients Characteristics

Two hundred forty-three adult patients age 18 years and older admitted to the cardiac ICU following cardiac surgery between November 2002 and September 2011 were included with complete demographic, clinical and inotropic-vasoactive data. Four patients had two separate admissions with the admission dates range from 88 days to 1512 days apart. The two admissions from these 4 patients were treated as two independent admissions and a specific statistical technique was applied to adjust the inter-correlation within subjects. The demographic, baseline clinical and operative data are shown in Table 22 and Table 23. The median age of patients was 33 years (18 – 83 years) with 42.9% are in the age group of 31 – 50 years old and 38.1% are in the age group of 18 – 30 years old. There were slightly more female patients than male patients (58.7% vs. 41.3%). The majority of patients had a RACHS-1 score of 1 to 3 (92.7%), which may reflect why these CHD patients survived into their adulthood. 55.5% patients had one prior sternotomy, either at the Mayo Clinic or another institution. The median BMI is 25 (ranges 15 – 44) with 42.1% patients had a normal BMI range of 18.5 – 25. The 75^{th} percentile of ICU LOS and duration on mechanical ventilation was 4 days and 1 day, respectively. This is a significant difference from the pediatric patient population, which has 12 days and 6 days for the 75^{th} percentile of ICU LOS and duration on mechanical ventilation. This finding could be easily explained by the fact that in general the adult patients have much better recovery ability than the pediatric patients.

Table 22. Adult Patients Characteristics – Categorical Variables

Characteristic	n (%)
Age at surgery (years)	
18-30	94 (38.1%)
31-50	106 (42.9%)
51-65	35 (14.2%)
>=65	12 (4.9%)
Gender	
Male	102 (41.3%)
Female	145 (58.7%)
BMI	
Underweight (<18.5)	15 (6.1%)
Normal (18.5 - <25)	104 (42.1%)
Overweight (25 - <30)	83 (33.6%)
Obese (>=30)	45 (18.2%)
Number of prior sternotomy	
1	137 (55.5%)
2	71 (28.7%)
3	24 (9.7%)
4	13 (5.3%)
5	2 (0.8%)
Diabetic status at surgery	
Yes	15 (6.1%)
No	232 (93.9%)
RACHS-1 category	
1-3	229 (92.7%)
4-6	18 (7.3%)

BMI, body mass index; RACHS-1, Risk Adjustment in Congenital Heart Surgery.

Table 23. Adult Patients Characteristics – Continuous Variables

Characteristics	n	Mean ± SD	Median	75th percentile	Range
Age (years)	247	37±14.5	33	47	18-83
BMI (kg/m^2)	246	26±5.6	25	29	15-44
ICU Length of Stay (days)	247	4±8.0	2	4	1-77
Length of mechanical ventilation (days)	247	2±7.1	1	1	0-77
Aortic crossclamp time (mins)	212	52±45.4	44	80	0-189

BMI, body mass index; ICU, intensive care unit; SD, standard deviation.

The patient outcome results are summarized in Table 24. Sixty-two patients experienced a poor clinical outcome (25%), including 8 deaths occurred either in-hospital

or within 90 days of hospital discharge (3%). Fifty patients (20%) had a prolonged ICU LOS (≥4 days) and 22 (9%) patients had a prolonged mechanical ventilation (≥5 days). Thirty-eight patients (15%) had at least one complication related morbidity event (renal failure, re-operation for bleeding, sterna wound infection, stroke or pneumonia). All eight patients with early mortality also experienced at least one morbidity event with seven of them had prolonged ICU LOS, five patients had prolonged mechanical ventilation, five patients had renal failure, three patients had re-operation for bleeding, two patients had stroke and two patients had pneumonia.

Table 24. Summary of Outcome Variables – Adult CHD Patients

Clinical Outcome	n (%)
Composite mortality and morbidity	62 (25%)
Complication-related morbidity[1]	38 (15%)
Mortality[2]	8 (3%)
Prolonged ICU LOS	50 (20%)
Prolonged mechanical ventilation	22 (9%)
Renal failure	18 (7%)
Re-operation for bleeding	8 (3%)
Sternal wound infection	7 (3%)
Stroke	5 (2%)
Pneumonia	21 (9%)

ICU, intensive care unit; LOS, length of stay.

1. Complication-related morbidity includes any of the following morbidity events: renal failure, re-operation for bleeding, sternal wound infection, stroke and pneumonia.

2. Mortality is in-hospital death or death within 90 days of hospital discharge.

4.3.2 Vasopressor Characteristics

Vasoactive Administration

The postoperative use of vasoactive agents for adult CHD patients is summarized in table 25. Epinephrine was the most widely used vasopressor on adult CHD patients (79.8%), and milrinone was the second most widely used vasopressor (70.4%). Only 5 patients (2%) received dobutamine, and 7 patients (2.8%) received norepinephrine during the first 96-hour postoperative period.

Table 25. Postoperative Use of Vasoactive Agents – Adult CHD Patients

Vasoactive Agents	n(%)
Dobutamine	5 (2.0%)
Dopamine	91 (36.8%)
Epinephrine	197 (79.8%)
Milrinone	174 (70.4%)
Vasopressin	44 (17.8%)
norepinephrine	7 (2.8%)

VIS Temporal Characteristics

The VIS values for adult CHD patients during the first 96-hour postoperative period exhibit very consistent temporal characteristics as those for pediatric CHD patients. The scatter plot in Figure 12 shows overall VIS values are higher for those patients with at least one poor clinical outcome than those patients without any poor outcome. Figure 13 displays the median, 25^{th} and 75^{th} percentile of maxVIS values of 247 ICU encounters over time by poor clinical outcome. The box-plot of maxVIS at 12-hour

interval by composite poor outcome is shown in Figure 14. The graphical presentation of VIS temporal pattern shows that maxVIS values are higher during the first 24 hours than the subsequent postoperative period for patients with and without any poor outcome, and the values stay relatively stable after 24 hours. Compared to the pediatric CHD patients, the adult patients received slightly higher dosage of vasoactive agents if they had a poor outcome at early postoperative period; the median maxVIS value is 17.5 (ranges 5 to 39) during the first 24 hour period and 12 (ranges 3 to 31) during the subsequent 24 hours for adult patients who experienced a poor outcome; compared with a median maxVIS value of 12 (ranges 1 to 48) and 9 (ranges 2-37), respectively, for the pediatric patients who had a poor outcome. Moreover, the amount of vasoactive support adult CHD patients received tend to stabilize much faster than the pediatric patients and had much shorter duration on vasoactive support if they did not experience any poor outcome. After 48 hours, only 12% of those patients who did not have any poor outcome were still requiring vasoactive support, comparing to 79% patients who did experience at least one poor outcome (Figure 15).

Table 26. MaxVIS Value Summary by Outcome - Adult CHD Patients

Time Interval	n (%)	Mean (SD)	Median (range)
Poor clinical outcome: Yes			
0 – 24 hrs	62 (100%)	17.4 (7.72)	17.5 (5-39)
24 – 48 hrs	59 (95%)	12.7 (5.80)	12 (3-31)
48 – 72 hrs	50 (81%)	12.6 (7.75)	11.5 (1-44)
72 – 96 hrs	43 (69%)	11.3 (6.14)	10 (1-30)
Poor clinical outcome: No			
0 – 24 hrs	185 (100%)	9.7 (4.53)	9 (2-32)
24 – 48 hrs	107 (58%)	6.9 (4.08)	6 (1-19)
48 – 72 hrs	23 (12%)	6.0 (2.92)	6 (1-12)
72 – 96 hrs	6 (3.2%)	2.7 (1.75)	2 (1-6)

SD, standard deviation.

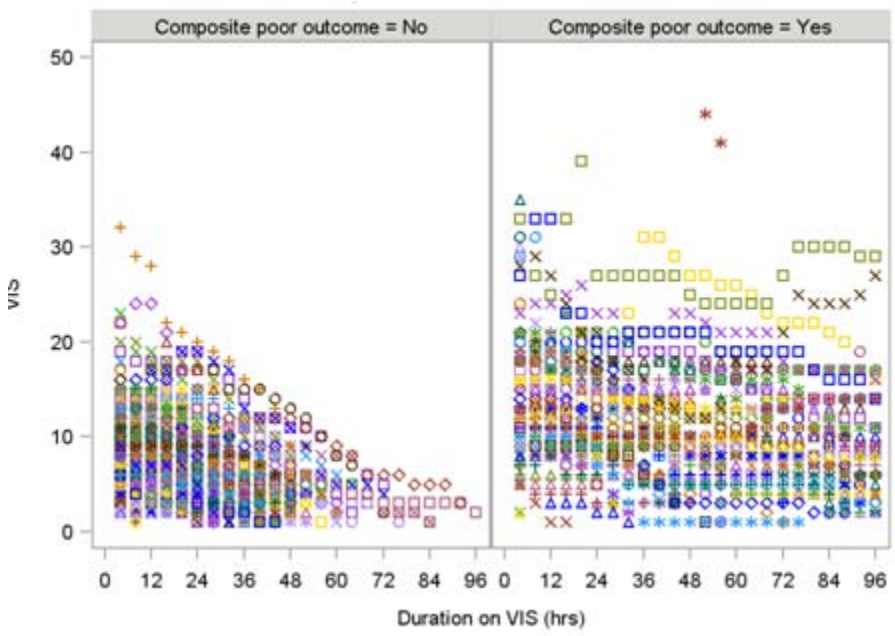


Figure 12. Scatter plot of maxVIS during the first 96-hour postoperative period by outcome - Adult CHD patients

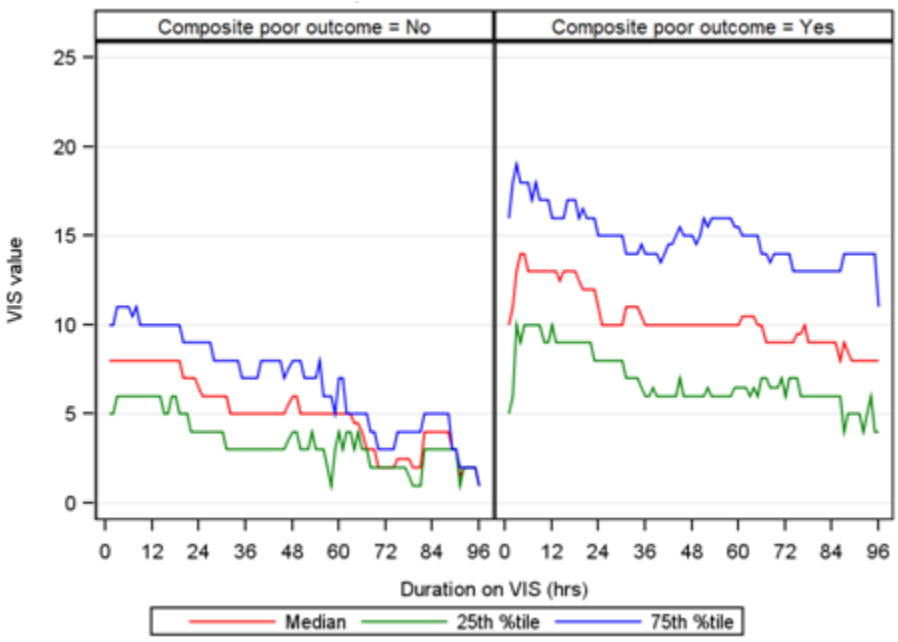


Figure 13. Series plot of maxVIS during the first 96-hour postoperative period by outcome - Adult CHD patients

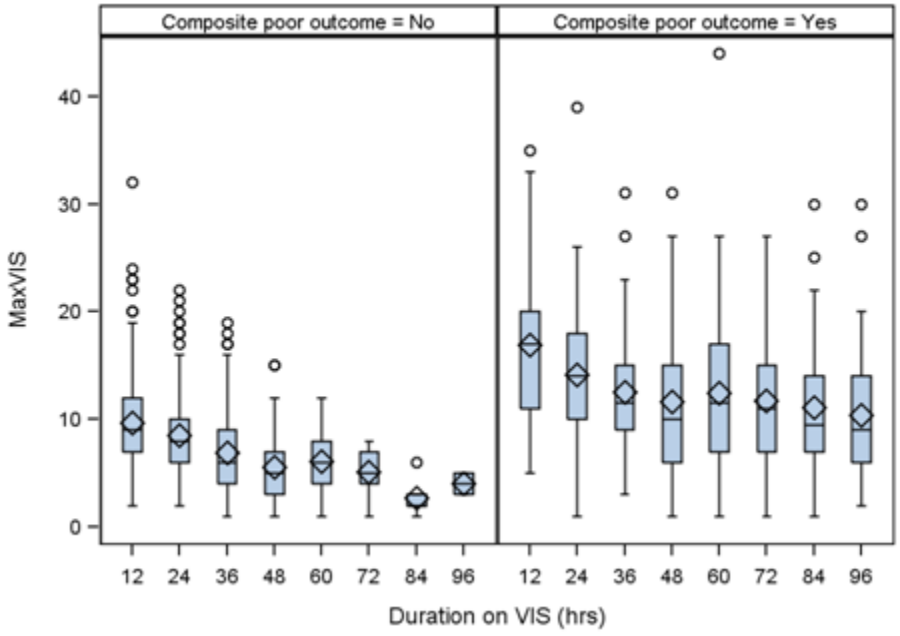


Figure 14. Boxplot of maxVIS during the first 96-hour postoperative period by outcome - Adult CHD patients

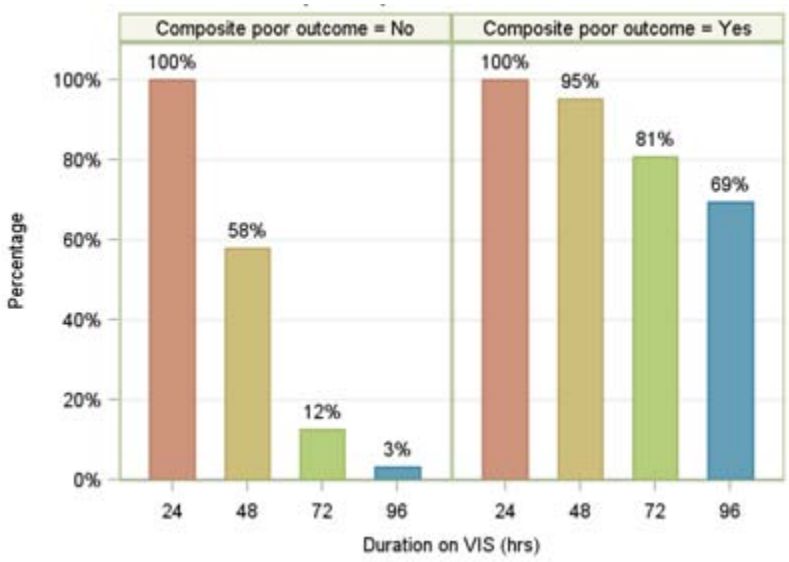


Figure 15. Frequency of VIS values within each 24-hour period - Adult CHD patients
Percentage is based on the total number of patients in each outcome group

Optimal Time Interval of VIS

The pair-wise comparisons of maxVIS values between the first and the second 12 hours within each 24-hour period are shown in Table 27. The maxVIS values show statistically significant difference between the first 12-hour and the second 12-hour interval during the first 24-hour postoperative period (estimated marginal mean difference 1.8; $P = 0.0094$). No significant difference was found between the two 12-hour intervals during the subsequent 24-96 hour period. We applied the same justification as for the pediatric patients and reasoned that since 100% patients received vasoactive support during the first 24-hour postoperative period, and the maximum VIS values during this period was used in the VIS prediction model, it was appropriate to take 24-

hour interval in calculating VIS values without losing any significant clinical information.

Table 27. MaxVIS Value Pair-wise Comparison - Adult CHD Patients

Time Interval	LS Mean* (95% CI)	Mean Difference	p value
0 – 24 hrs			
0 – 12 hrs	14.3 (12.9, 15.7)	1.8	0.0094
12 – 24 hrs	12.5 (11.1, 13.9)		
24 – 48 hrs			
24 – 36 hrs	10.1 (8.6, 11.5)	1.9	0.3606
36 – 48 hrs	8.2 (6.7, 9.7)		
48 – 72 hrs			
48 – 60 hrs	8.3 (6.8, 9.9)	0.9	0.9621
60 – 72 hrs	7.4 (5.8, 9.0)		
72 – 96 hrs			
72 – 84 hrs	6.5 (4.9, 8.2)	0.5	0.9889
84 – 96 hrs	6.0 (4.3, 7.7)		

CI, confidence interval.

* LS mean, least square mean, is the estimated marginal mean value of maxVIS after controlling for poor clinical outcome.

Optimal Duration on VIS

The estimated marginal mean of maxVIS values is 7.9 (95% CI: 6.5 to 9.4) at 48-72 hours and 5.2 (95% CI: 3.1 to 7.3) at 72-96 hours after controlling for poor clinical outcome (Table 28). The mean difference between these two 24-hour internals is 2.7 (95% CI: 0.76 to 4.7). The results from the multivariate mixed effect model in assessing the correlation between maxVIS values and duration on VIS further confirms VIS temporal characteristics exhibited in the graphical plots. The maxVIS values were significantly correlated with duration on VIS up until 76 hours postoperatively after

adjusting for poor clinical outcome. Therefore, we considered the first 72 hours postoperatively of VIS values in developing VIS index model.

Table 28. MaxVIS Value Summary - Adult CHD Patients

Time Interval	n (%)	LS Mean*	95% CI
0 – 24 hrs	247 (100%)	14.1	12.8 – 15.3
24 – 48 hrs	166(67%)	9.7	8.5 – 11.0
48 – 72 hrs	73 (30%)	7.9	6.5 – 9.4
72 – 96 hrs	49 (20%)	5.2	3.1 – 7.3

CI, confidence interval.

* LS mean, least square mean, is the estimated marginal mean value of maxVIS after controlling for poor clinical outcome.

Duration of High VIS

As Table 26 shows, patients who experienced at least one poor clinical outcome have a mean maxVIS value of 17.5 during the first 24 hours, and 12.7 and 12.6 during the subsequent 24-48, and 48-72 hour postoperative period. Therefore we chose maxVIS value of 20 during the first 24 hours and 15 during the subsequent 24-72 hour period as the cutoff value in defining high VIS. There are a total number of 41 patients who received high VIS for at least 1 hour during the first 72-hour postoperative period and 30 of them experienced at least one poor outcome, which accounts for 48.4% of all patients with a poor outcome. There is strong correlation between poor clinical outcome and longer duration on high volume of inotropic support (Wilcoxon rank sum test P= 0.0436) as shown in Table 29.

Table 29. Duration on High VIS by Outcome – Adult CHD Patients

Poor Outcome	Duration on High VIS (hrs)			
	n(%)*	Mean (SD)	Median (range)	Wilcoxon rank sum p value
Yes	30 (48.4%)	26.6 (23.76)	25.0 (1.0 – 71.0)	0.0436
No	11 (5.9%)	8.6 (10.27)	7.0 (1.0 – 37.0)	

VIS, vasoactive–inotropic score; SD, standard deviation.
* The denominator for percentage calculation is the total number of patients in each outcome group.

4.3.3 MaxVIS Model

Confounding Factors of Poor Clinical Outcomes

The correlation of potential confounding factors with composite poor outcome variable is presented in Table 30. None of these factors, RACHS categories with dichotomized values of 1-3 and 4-6, year of surgery, age group, prior sternotomy status, aortic cross clamp time, circulatory arrest times, BMI, and diabetes status were found significantly correlated with either the composite poor outcome or each individual outcome variable. Therefore, these covariates were not included in the final model.

Table 30. Confounding Variables for Composite Outcome - Adult CHD Patients

Variable	Wald Chi-square value	p-value
RACHS-1 group	0.6536	0.4188
Age group	1.6459	0.6490
BMI	1.7130	0.1906
Diabetes status	0.8646	0.3525
Year of surgery	0.3462	0.5563
Prior sternotomy status	0.1667	0.6831
Aortic xclamp time (mins)	3.3360	0.0678
Circulatory arrest time (mins)	1.2020	0.2729

RACHS-1, Risk Adjustment in Congenital Heart Surgery; BMI, body mass index.
RACHS-1 group: RACHS 1-3 and 4-6; Age group: 18-30, 31-50, 51-65 and ≥65 years old.

MaxVIS Classification Model

We took the same approach to classify adult CHD patients into different risk groups based on their maxVIS values in the first 48 hours postoperative period as the pediatric patients. Adult patients who experienced a poor clinical outcome had a mean maxVIS value of 17.4 during the first 24 hours, and 12.7 during the subsequent 24-48 hour postoperative period (Table 26). We applied the same algorithm in classifying patients into different risk categories as the pediatric patients, i.e. patients were assigned to the higher classification group achieved during either the first or the second 24-hour postoperative periods based on their maxVIS values during each interval (Table 4).

MaxVIS Model Discrimination and Calibration

The performance characteristics of maxVIS prediction model for adult CHD patients are shown in Table 31. The H-L test result and ROC area suggest maxVIS has good calibration and reasonable discrimination consistently for both the composite outcome and each individual morbidity outcome. Mortality has the highest AUC value with narrow 95% CI (AUC = 0.916, 95% CI: 0.856 to 0.976). All eight adult patients who experienced either in-hospital death or death within 90 days of hospital discharge have a maxVIS value >=3.

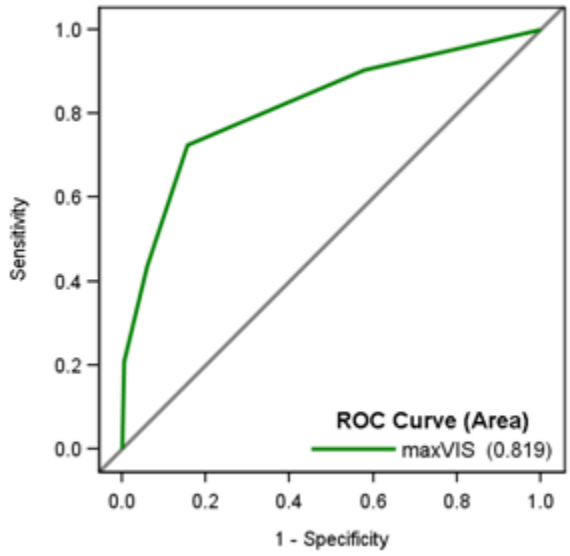


Figure 16. MaxVIS model ROC curve for composite poor outcome - Adult CHD patients

Table 31. Performance characteristics of maxVIS Model - Adult CHD Patients

Clinical Outcome	AUC	95% CI	H-L P value
Composite poor outcome	0.819	(0.755, 0.883)	0.205
Complication-related morbidity	0.761	(0.672, 0.850)	0.793
Mortality[1]	0.916	(0.856, 0.976)	0.529
Prolonged ICU LOS	0.851	(0.790, 0.912)	0.064
Prolonged mechanical ventilation	0.835	(0.747, 0.924)	0.435
Renal failure	0.856	(0.790, 0.922)	0.133
Re-operation for bleeding	0.694	(0.462, 0.925)	0.175
Sternal wound infection	0.642	(0.488, 0.797)	0.088
Stroke	0.793	(0.641, 0.944)	0.552
Pneumonia	0.718	(0.595, 0.840)	0.830

AUC, area under the curve; CI, confidence interval; H-L, Hosmer-Lemeshow test;
ICU, intensive care unit; LOS, length of stay.

1. Mortality is in-hospital death or death within 90 days of hospital discharge.

4.3.4 VIS Index Model

VIS Index Model Development

Since the adult CHD patients VIS values exhibited very consistent pattern as the pediatric CHD patients, we calculated the same weighted cumulative maxVIS values during the first 72-hour period in developing VIS index model with the adult CHD data. We took the same approach in converting the cumulative maxVIS values into simple integer scores as we did for the pediatric CHD patient population. We evaluated the predicted log odds ratio of cumulative VIS values as shown in Figure 17.1 and Figure 17.2. Figure 17.1 is the predicted log odds ratio of cumulative VIS value ranges from 0 to 120. As the predicted risk has the most significant increase with cumulative VIS value ranges from 0 to 70 and reaches to > 90% as cumulative VIS value > 70, we also created the predicted log odds ratio plot with cumulative VIS value ranges from 0 to 70 as shown in Figure 17.2.

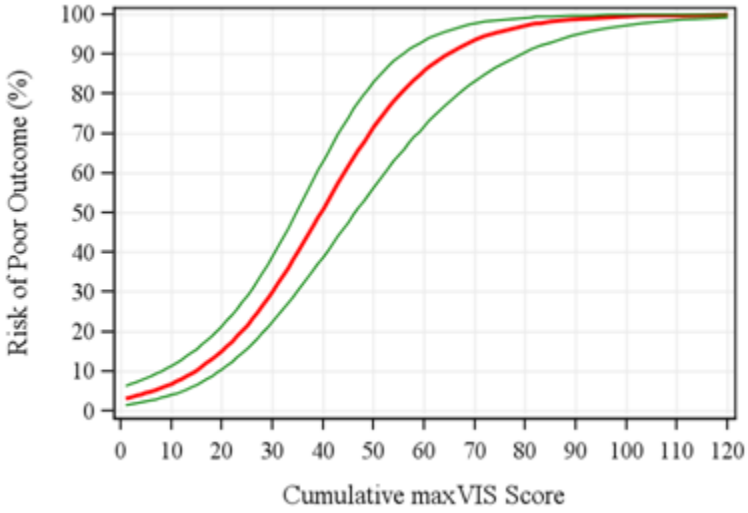


Figure 17.1. Predicted risk plot of cumulative maxVIS score with range 0 to 120 – Adult CHD patients

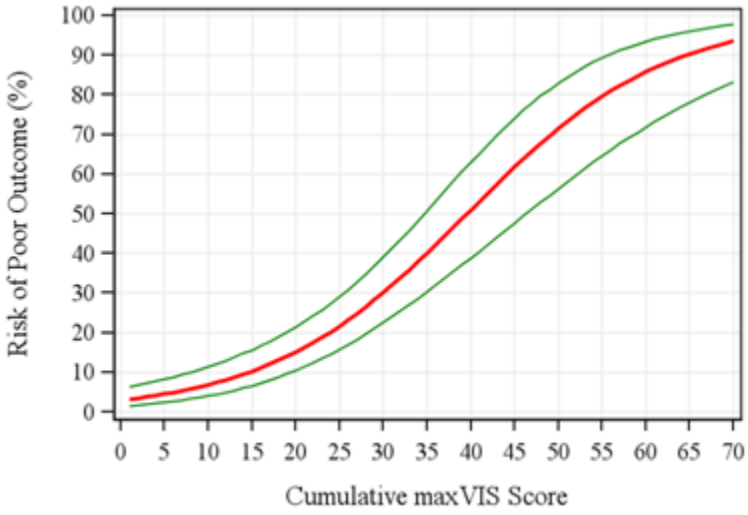


Figure 17.2. Predicted risk plot of cumulative maxVIS score with range 0 to 70 – Adult CHD patients

As both figures show that the predicted risk of experiencing a poor outcome is less than 20% with a cumulative maxVIS value≤ 2 0; and the predicted risk increases to

about 85% at cumulative maxVIS value of 60 and continues to increase towards an asymptote of 100% as cumulative maxVIS value increases. Thus, we assigned an integer score of 1 for cumulative VIS value ≤ 20 and applied a scale factor of 10 for any cumulative VIS value between 10 and 60, and assign a maximum integer score for any cumulative maxVIS value greater than 60. This scale of the conversion is slightly different from pediatric patients. However, the resulting VIS index score is consistent and the predictive accuracy was persevered well at this conversion; the correlation between the predicted log odds before and after the simplification is 0.990. The final VIS index model for the adult CHD patients is presented in Table 32.

Table 32. VIS Index Conversion Table - Adult CHD Patients

Cumulative maxVIS value	VIS Index
1–20	1
21–30	2
31–40	3
41–50	4
51–60	5
> 60	6

VIS, vasoactive-inotrope score.

VIS Index Model Discrimination and Calibration

The VIS index model presents good calibration and discrimination consistently for both the composite poor outcome, complication related morbidity outcome and each individual morbidity outcome (Table 33). For the composite poor outcome, the AUC was 0.876 (95% CI: 0.822 to 0.929), and there is close agreement between predicted and

observed poor outcome rate (H-L test, P = 0.140). Several complication-related events that included re-operation for bleeding (3%), sternal wound infection, and stroke (3%), had relatively wide 95% CI for the AUC. This finding was likely due to the small number of incidences of each event.

Table 33. VIS Index ROC Curve - Adult CHD Patients

Clinical Outcome	AUC	95% CI	H-L p-value
Composite mortality and morbidity	0.876	(0.822, 0.929)	0.140
Complication-related morbidity	0.826	(0.753, 0.900)	0.127
Mortality[1]	0.967	(0.946, 0.987)	0.948
Prolonged ICU LOS	0.911	(0.862, 0.959)	0.150
Prolonged mechanical ventilation	0.914	(0.852, 0.976)	0.398
Renal failure	0.922	(0.880, 0.965)	0.137
Re-operation for bleeding	0.801	(0.596, 1.000)	0.295
Sternal wound infection	0.617	(0.401, 0.833)	0.953
Stroke	0.846	(0.755, 0.937)	0.103
Pneumonia	0.775	(0.672, 0.879)	0.126

AUC, area under the curve; CI, confidence interval; H-L, Hosmer-Lemeshow test;
ICU, intensive care unit; LOS, length of stay.
1. Mortality is in-hospital death or death within 90 days of hospital discharge.

Further evaluations were completed to compare the predictive performance of the VIS index model with the maxVIS model. As shown in Figure 18 and Table 34, the VIS index model demonstrates a stronger discriminative performance than the maxVIS model for the composite poor outcome, complication-related morbidity, as well as each individual morbidity event. The difference of AUC between the maxVIS model and the VIS index model is 0.067 (95% CI: 0.019 to 0.094, P value = 0.0029) for the composite poor outcome. Overall AUC was the highest for the prediction of mortality, and was the

lowest for the prediction of sternal wound infection. This result is consistent with what we found in the pediatric patient population.

Table 34. MaxVIS and VIS Index Model ROC Curve of - Adult CHD Patients

Clinical outcome	maxVIS Model		VIS Index Model	
	AUC	95% CI	AUC	95% CI
Composite poor outcome	0.819	(0.755, 0.883)	0.876	(0.822, 0.929)
Complication-related morbidity	0.761	(0.672, 0.850)	0.826	(0.753, 0.900)
Mortality[1]	0.916	(0.856, 0.976)	0.967	(0.946, 0.987)
Prolonged ICU LOS	0.851	(0.790, 0.912)	0.911	(0.862, 0.959)
Prolonged mechanical ventilation	0.835	(0.747, 0.924)	0.914	(0.852, 0.976)
Renal failure	0.856	(0.790, 0.922)	0.922	(0.880, 0.965)
Re-operation for bleeding	0.694	(0.462, 0.925)	0.801	(0.596, 1.000)
Sternal wound infection	0.642	(0.488, 0.797)	0.617	(0.401, 0.833)
Stroke	0.793	(0.641, 0.944)	0.846	(0.755, 0.937)
Pneumonia	0.718	(0.595, 0.840)	0.775	(0.672, 0.879)

AUC, area under the curve; CI, confidence interval; H-L, Hosmer-Lemeshow test; VIS, vasoactive-inotrope score; ICU, intensive care unit; LOS, length of stay.

1. Mortality is in-hospital death or death within 90 days of hospital discharge.

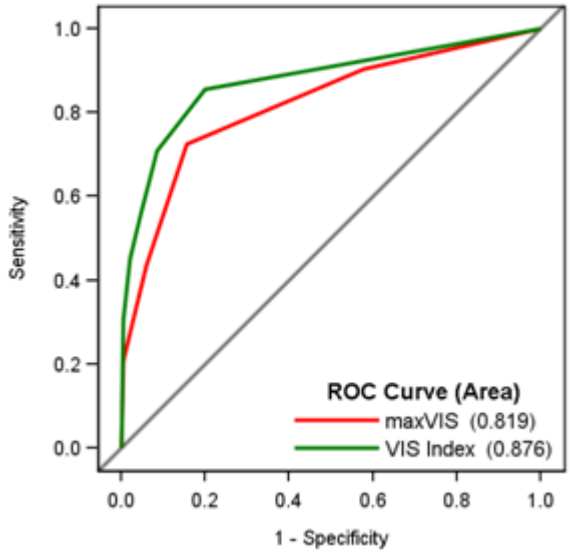


Figure 18. ROC curve of composite poor outcome - Adult CHD patients

VIS Index Model Correlation with Duration on High VIS

Figure 19 shows that a high VIS index is strongly correlated with longer duration on high VIS. Out of 41 patients who had at least one hour on high vasoactive support, 29 (70.7%) of them had a VIS index value of 5 or 6. This finding is consistent with what we observed in the pediatric patient population. Among 92 pediatric patients who spent at least one hour on high dosage of vasoactive support, 64 (69.6%) of them had a VIS index value of 5 or 6. This result further confirms that although the VIS index is based on the maxVIS values of the 72-hour postoperative period, it also reflects the high dosage of vasoactive support a patient receives and can be utilized any time after patients ICU admission.

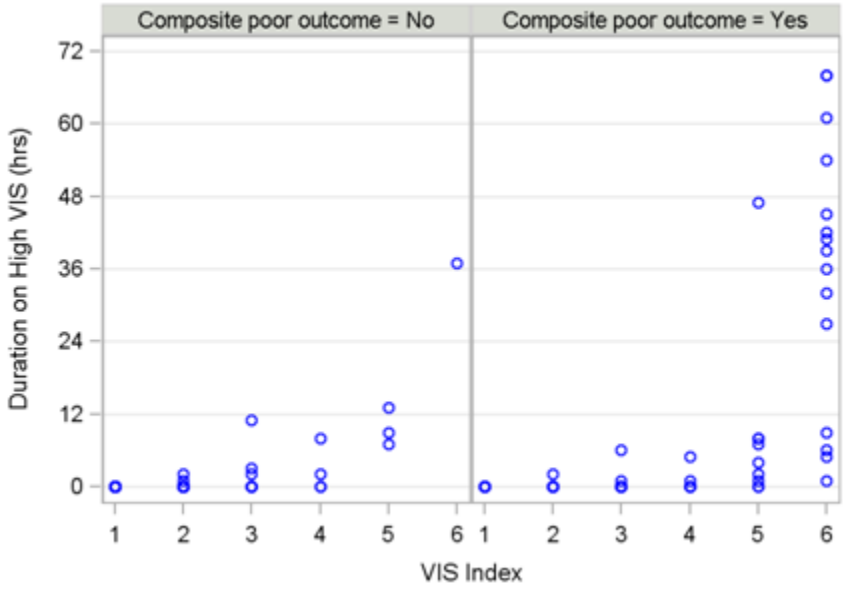


Figure 19: VIS index and duration on high VIS - Adult CHD patients

VIS Index Model Risk Prediction Performance

Table 35 presents the predicted risk of a composite poor clinical outcome using the VIS index. The relationship between the observed risk and the predicted risk based on the VIS index model is illustrated graphically in Figure 20. Overall the predicted risk of having a poor clinical outcome is very consistent with the observed risk for the composite poor outcome, complication related morbidity, prolonged ICU LOS, and prolonged mechanical support. The predicted risk of experiencing a poor outcome ranges from 5.7% to 95%. A VIS index of 1 predicts the lowest risk of poor outcome at 5.7% (95% CI: 3.0% to 10.6%) and a VIS index of 6 designates the highest risk category with a 95.0% (95% CI: 71.8% to 99.3%) risk for poor clinical outcome. The risk plots of complication related morbidity and prolonged ICU LOS demonstrate very similar positive correlation between VIS index and the predicted risk. Patients with a VIS index of 6 would have a predicted risk > 90% for prolonged ICU LOS, and > 60% for developing complication related morbidity. However, the VIS index is less sensitive for predicting prolonged mechanical support. The predicted risk for experiencing prolonged mechanical support is well below 20% when the VIS index value is within the 1 to 5 range. The validation of VIS index for this outcome was limited by the small number of patients (n=22) who had prolonged mechanical ventilation in our study cohort. Further validation with a larger patient sample size will be required prior to using the VIS index as a predictor for this outcome measure. The 95% confidence interval was relatively wide for the predicted risk of each outcome. We postulate that this finding is due to the relatively small incidence of

the events at each index value. This issue is discussed further in the Discussion section. Figure 19 demonstrates that the VIS index is a consistent and robust predictor of composite poor outcome and individual morbidity.

Table 35. VIS Index Risk Score – Adult CHD Patients

VIS index	Risk of Poor Outcome (%)	95% CI
1	5.7	3.0 – 10.6
2	30.0	16.4 – 48.3
3	55.6	33.0 – 76.0
4	60.0	29.7 – 84.2
5	75.0	44.8 – 91.7
6	95.0	71.8 – 99.3

VIS, vasoactive-inotrope score; CI, confidence interval.

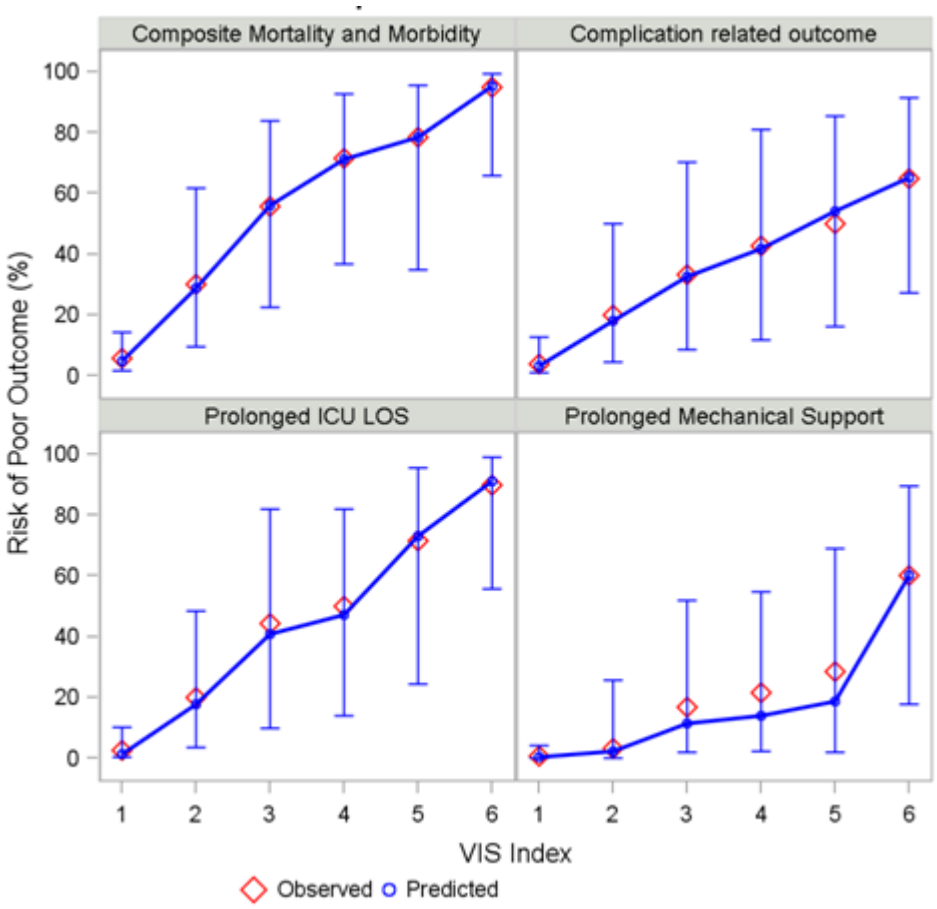


Figure 20: VIS index predicted risk of poor clinical outcomes - Adult CHD patient

VIS Index Model Strength of Association with Risk

The final VIS index prediction model for the adult CHD patients has the same score of 1-6 indicating the risk of poor outcomes as the pediatric patients and the risk associated with each score is consistent between the two patient populations. The predicted risk increases from 30% (95% CI: 16.4% to 48.3%) at VIS index value of 2 to 55.6% (95% CI: 33.0% to 76.0%) at VIS index of 3. Therefore we applied the same algorithm to assess the strength of association between VIS index and poor clinical

outcomes for the adult patients as we did for the pediatric patients, i.e. we chose a VIS index of 3 as the cutoff value to define high VIS. The results of strength of association for selected outcomes are presented in Table 36. The association of VIS index with early mortality and prolonged mechanical ventilation was not estimated due to the small incidence of mortality, and the VIS index cutoff value of 3 used in defining high vasoactive support does not apply to prolonged mechanical support based on the predicted risk plot (Figure 20). Overall high VIS index (VIS index $\geq$ 3) was strongly associated with a poor outcome (OR: 26.7; 95% CI: 12.4 – 57.4; $P < .0001$). Patients in the high VIS category were also more likely than those in the low VIS category to experience prolonged ICU LOS (OR: 36.7; 95% CI: 15.7 – 85.9; $P < .0001$) and complication related morbidity (OR: 11.2; 95% CI: 5.1 – 24.2; $P < .0001$).

Table 36. Association of High VIS Index with Outcome – Adult CHD Patients

Clinical Outcome	n (%)	OR	95% CI	*P* value
Composite poor outcome	62 (25.1%)	26.7	(12.4, 57.4)	<.0001
Complication-related morbidity	38 (15.4%)	11.2	(5.1, 24.2)	<.0001
Prolonged ICU LOS	50 (20.2%)	36.7	(15.7, 85.9)	<.0001

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; LOS, length of stay.

4.4 VIS Index Clinical Decision Support Application

We proposed the final VIS index risk prediction model that can be developed as a clinical decision support tool to facilitate the decision-making process of patient care after CHD patients are admitted to the ICU following cardiac surgery (Table 35 and Table 36). The VIS index models are consistent in predicting the risk of poor clinical

outcomes for both pediatric and adult CHD patients. The color grids indicate the degree of risk with light green color indicating the lowest risk and maroon color indicating the highest risk of developing adverse outcomes following cardiac surgery. We illustrated the application of the VIS index prediction tool with a few real-life examples that could be encountered in a typical cardiac ICU setting (Figure 21).

Table 35. VIS Index Risk Prediction Table - Pediatric CHD patient

VIS index	Risk of Poor Outcome (%)	95% CI (%)
1	20	11 – 34
2	39	29 – 51
3	65	50 – 78
4	71	52 – 85
5	81	59 – 93
6	98	85 – 100

Table 36. VIS Index Risk Prediction Table - Adult CHD patient

VIS index	Risk of Poor Outcome (%)	95% CI (%)
1	6	3 – 11
2	30	16 – 48
3	56	33 – 76
4	60	30 – 84
5	75	45 – 92
6	95	72 – 99

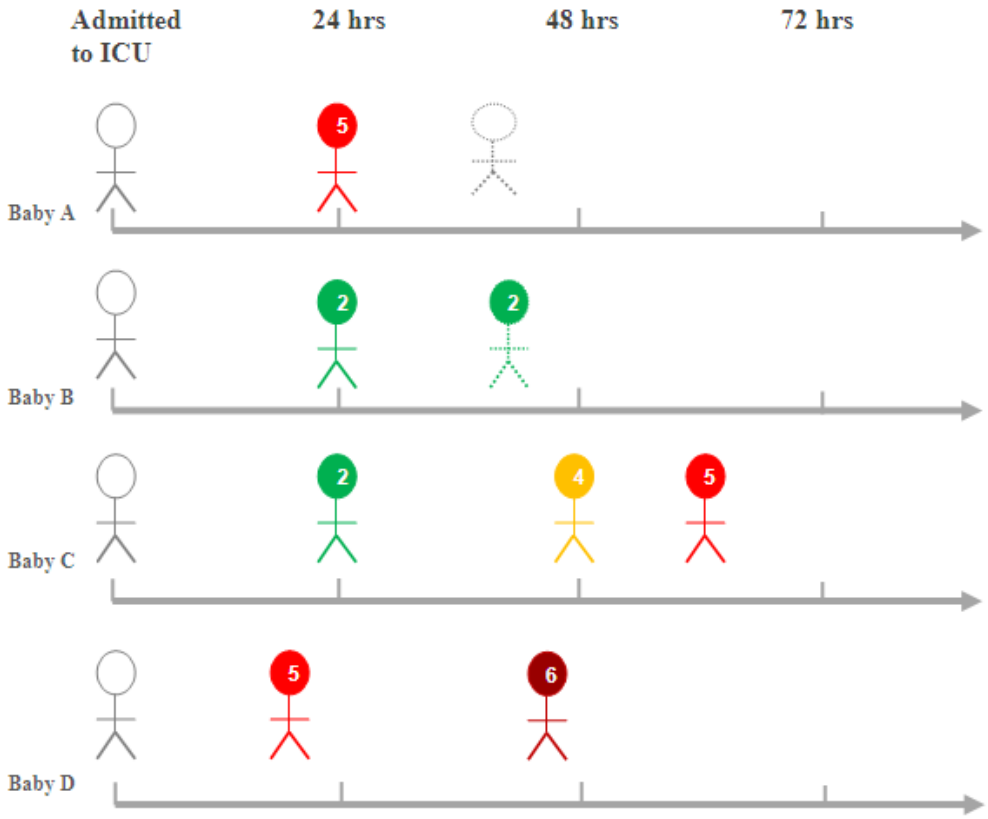


Figure 21. VIS index prediction tool application illustration
The number associated with each patient is the VIS index value; the color corresponds to the risk level. The patient with solid line indicates he stayed in the ICU during the first 72-hour postoperative period; the patient with dotted line indicated he was either discharged from the ICU or deceased.

Baby A had a VIS index value of 5 during the first 24 hours after he was admitted to the pediatric ICU following cardiac surgery, which indicates he was at high risk of developing adverse outcome. Then at around the 40th hour after staying in the ICU, he was deceased.

Baby B had a VIS index value of 2 during the first 24 hours after he was admitted to the pediatric ICU following cardiac surgery, which implies he was at low risk of

developing an adverse outcome. Then at around the 40th hour after staying in the ICU, he was discharged from the ICU with better medical condition. At the time of ICU discharge, his VIS index value stayed at 2.

Baby C had a VIS index value of 2 during the first 24 hours after he was admitted to the pediatric ICU following cardiac surgery. However, at 48 hours in the ICU, his VIS index increased to 4, which categorized him into moderate risk group. Therefore, this patient condition should get close monitoring and appropriate medical procedures should be taken at physician's decision. Then at around 60th hours in the ICU, his VIS index increased to 5. This patient should definitely be put under special monitor to minimize the possible adverse outcome.

Baby D had a VIS index value of 5 at around 20th hours after being admitted to the ICU following cardiac surgery. Therefore he should be under close monitoring as a high risk patient. Then at around 40th hours in the ICU, his VIS index increased to 6. This indicates he is in the highest risk of developing a poor outcome.

CHAPTER FIVE: DISCUSSION

5.1 Study Overview

This research has several pioneering characteristics that will advance CHD research and ultimately inform clinical bedside management for patients after cardiac surgery. To our knowledge, this is the first study to evaluate the temporal characteristics of vasoactive support following cardiac surgery; it is the first study to derive and validate a predictive scoring system of early postoperative mortality and morbidity that apply to pediatric and adult CHD patients.

The specific strengths and novelty of this project are as follows:

1. Data collection from the EMR using automated data retrieval. This study provides a "proof of concept" that the EMR system, specifically, the MCHN automatic data capture system used for our study, is a feasible approach to answer important clinical research questions that will improve the quality and efficiency of patient care. We were also able to determine the optimal time intervals required to collect inotrope doses to facilitate reliable prediction of clinical outcomes. This knowledge enables centers without automated EMR capabilities to reduce the frequency of data collection without missing clinically significant intervals that would change study outcomes. This information alone will reduce the cost and time required to conduct high impact perioperative studies, increasing the feasibility and likelihood of follow up independent multicenter evaluations of ours and future findings.

2. Large patient samples. Due to the unique nature of congenital heart disease, and the low mortality rates, sufficient patient sample size has always been a significant obstacle to congenital heart disease research. The Mayo Clinic has the advantage of being a high volume congenital cardiac program with sufficient patient numbers to support high impact congenital heart disease research investigations.

3. Simplified yet robust early mortality and morbidity prediction tool. The VIS index prediction tool we proposed is robust in predicting both mortality and early morbidity events for both pediatric and adult CHD patients after cardiac surgery; it is also simple to calculate and easy to be implemented as a clinical decision support tool in the EHR system. This feature is particularly useful to physicians trying to decide between various diagnostic and therapeutic options for optimal patient care.

5.2 EMR Data Collection

The data collection process took about a year for both pediatric and adult patient data. The biggest challenge and requirement for utilizing EMR data for research is to validate the data quality. Rigorous steps must be taken to review the data output manually for completeness, accuracy and consistency. The actual data extraction process from the MCHN datamart is outside the scope of this research project. However, we

would like to highlight a few key steps that were taken in collaboration with the MCHN database team to confirm data quality assurance:

1. Patient ICU admission and discharge dates were available for retrieval from three sources and compared for accuracy: 1) the MCHN datamart, 2) clinical chart review and 3) the STS database (pediatric patients only). In mapping the admission and discharge date with the date patients received vasoactive support, we found that the MCHN datamart dates had improved accuracy over the STS database after cross-checking with manual clinical chart review. In addition, the MCHN datamart includes both date and time stamps, compared to a date stamp alone in the STS database. Therefore, we extracted the ICU admission and discharge date from the MCHN datamart and cross-checked them manually with the patient clinical chart. In case of discrepancy, the dates in the patient clinical chart were used.

2. Since the MCHN datamart is essentially an automated data capture system of Mayo Clinical EMR system, the data stored inevitably had duplicate issue between the archived data and the current data during new data "dumping" process i.e. each time the EMR undergoes a new query, the collected data returned may be a duplicate of data that was already archived within the datamart storage system on previous data collection events. This causes some duplicate records in the vasopressor medication data during the process of updating data mart with newly collected data from the EMR system. The MCHN data

management team programmatically removed any completely duplicate records during the data cleaning process.

3. After exploring the data through graphical presentation and simple descriptive summary, we identified outlier vasoactive medication doses and clinical data variables. These data were then manually checked with the patient's clinical chart by a health care provider trained in critical care management. In case of discrepancy, manual chart review results were used. This process highlights the challenge of ensuring data quality when utilizing EMR data for clinical research. Although the automated data capture enhances the efficiency of the data collection process compared to traditional manual data collection, the data quality can still be affected by both human and system errors as described in section 4.1.

5.3 Research Methods

Logistic Regression Model vs. Cox Proportional Model

Both logistic regression and Cox proportional hazards models are used widely in longitudinal epidemiologic studies for analyzing the relationship between several risk factors and a time-related dichotomous event. However, the Cox model is mainly used to model time to the development of a particular symptom or to relapse after remission of a disease, as well as to the time to event. In our study, we were not interested in "When" an event will occur. Instead, we are interested in "If" the event of interest will occur if a patient has a high VIS index. For example, the mortality outcome in our study is death

within 90 days of ICU discharge for pediatric and adult CHD patients. We are not interested in *when* death occurred, but *if* death occurred for a patient with a high VIS index value. Furthermore, although the outcomes of interests in our study are time-related, they are not time-dependent. For example, we estimate the correlation between VIS index and renal failure after CHD patients undergo cardiac surgery. We want to know *if* renal failure occurs after the surgery, not *when* renal failure will occur. Therefore, the logistic regression model was applied in this study.

Generalized Estimating Equations (GEE) Methodology

In evaluating the correlation between outcome measures and maxVIS at each time interval, GENMOD procedure with a logistic link function in SAS was applied to account for correlated outcome measures due to repeated measures (time intervals) on the same subject. In addition, since 11 pediatric patients and 5 adult patients have two encounters in this study, the same procedure was also applied to model the logistic regression after adjusting for correlated outcomes within subjects. However, the standard logistic regression model without GEE methodology gives almost identical results in terms of parameter estimates and odd ratio estimates as the logistic model with GEE. This could be due to the small number of patients with such correlated relationships. It also suggests that the correlation between different encounters for these patients with multiple admissions is negligible. Therefore it is legitimate to treat multiple encounters from the same patient as independent events in this study.

VIS Index Model Development

In developing the VIS index prediction model, we strived for a balance between applying good statistical principles and achieving usefulness in clinical practice. We firmly believe that a good predictive model should be both statistically robust, valid, and clinically useful. With this in mind we needed to determine an optimal weighting factor that would account for the correlation between longer duration on vasoactive support and poor clinical outcome, Instead of applying anodds ratio estimate for the weight based on a logistic regression model output,we compared the discriminative performance of different weight options including a weight value of 2. This valueseemed simple and intuitive to use in clinical practice. The results of ROC AUC were strikingly similar with a weight of 2 vs. a weight of 4.6 (the odds ratio for a pediatric CHD patient to have a poor outcome with longer duration on vasoactive support). Maintaining simplicity for the VIS index calculation improves the likelihood for establishing a generalized predictive model that will be applicable to heterogeneous populations at other institutions.

Another good example of our attempt to ensure the VIS index model both clinically useful and statistically robust was reflected in finalizing the VIS index model with simple integer scores. A common practice in developing risk score systems in clinical research is to convert the parameter estimates from the statistical modeling into integer scores for the ease of use in clinical practice. A few approaches for making the conversion include finding a scale factor required for the transformation via a grid search (39) and multiplying the regression coefficient by a fixed number and rounding it to the

nearest integer (40). For this conversion we incorporated both clinical knowledge and the statistical modeling results. For example, for the pediatric CHD patients, when the cumulative maxVIS value is ≤ 10, the risk of experiencing a poor outcome during the early postoperative period is less than 30%; and when the cumulative maxVIS value is ≥ 50, the risk of experiencing a poor outcome is more than 90%. Therefore we assigned the lowest VIS index of 1 to patients with a cumulative maxVIS value ≤ 10 and a highest VIS index of 6 to patients with a cumulative maxVIS value > 50. We took the same approach for adult CHD patients as the adult data presents very consistent characteristics as the pediatric data. We then assessed the converted model by calculating the correlation between the predicted log odds from the original and simplified models to show that our clinical judgment regarding the score conversion was legitimate.

Cut-off Value Determination

A common but much overemphasized practice in predictive modeling is to seek optimal cut-points in the prediction. Although cut-off values are needed in the final stages of a model to provide guidelines in clinical practice for medical decision making, we believe models that provide a continuous score provide potentially useful information, particularly for subjects near the threshold. That is why we took a cumulative approach in calculating maxVIS over time, instead of finding a cut-off value at each 24-hour time interval as proposed in the sentinel study. At the final stage of defining VIS index model, we chose to convert the cumulative VIS values into *continuous* integer scores to classifying patients into distinct groups for ease of use in clinical practice. We performed

statistical analysis to ensure such conversion would result in little loss of predictive accuracy.

On the other hand, when the measurement is on a continuous scale, it is implausible that there exists a fixed threshold at which risk abruptly changes. Therefore, when we do need to determine a crystal clear cutoff value in order to assess the strength of association between the VIS index and early mortality and morbidity, we incorporated clinical judgment and chose VIS index value of 3 as the optimal cutoff which corresponds to 65% risk (95% CI: 50% to 78%) of experiencing a poor clinical outcome for pediatric CHD patients and 56% risk (95% CI: 33% to 76%) for adult CHD patients. We reasoned that a VIS index value that indicates a risk of poor outcomes greater than 50% should trigger physician awareness that the patient may require close monitoring and possibly additional clinical care.

5.4 Research Results

Vasoactive Medication Use

Dobutamine was included in the original IS formula. However, in today's era, milrinone has largely replaced dobutamine use. This clinical trend was observed in both pediatric and adult CHD patient populations in our study with only 3 pediatric patients and 5 adult patients received dobutamine. All three administration of dobutamine for the pediatric patients occurred after the first 96 hours postoperative hours. For pediatric CHD patients, milrinone was the most widely used vasopressor (100%), followed by

epinephrine (92.9%) at our institution. This is significantly different from what was seen in the original VIS study, in which milrinone was administrated to only 62% of pediatric CHD patients, and epinephrine was used in 55% of the patients. On the other hand, only 15% pediatric patients received dopamine, compared to 87% in the original VIS study. For the adult CHD patients, epinephrine was the mostly used vasopressor (79.8%), followed by milrinone (70.4%). The administration of vasopressin presents similar pattern between the two patient populations with 13.7% pediatric patients and 17.8% adult patients received vasopressin, lower than that in the original VIS study on pediatric patients (32%). The difference in each individual vasopressor administration between the two independent institutions and between the two populations highlights a key issue, i.e. universal agreement is lacking among cardiac intensivists regarding the optimal use of inotropic and vasoactive medications in patients undergoing cardiac surgery. Evidenced-based literature to support any single pattern of vasopressor and inotropic administration in the post-operative setting is non-existent. This heterogeneity in clinical management highlights the importance of developing validated predictive scoring tools like the VIS index and to improve the clinician's ability to compare and apply research findings generated from diverse practice settings. This issue is further discussed in Study Limitation section.

RACHS-1 Score

RACHS-1 score was not significantly correlated with the composite poor outcome or the individual morbidity outcomes for either the pediatric or adult CHD patients. As a

matter of fact, it was the first variable removed from the logistic regression model when using the backward elimination strategy for all outcome measures. This differed from the initial Gaies maxVIS validation study, in which the RACHS-1 score was the only significant confounding factor in the association between maxVIS and poor outcome for pediatric patients. This discrepancy could be due to the difference in patient samples. Our pediatric population had less proportion of patients undergoing complex operations (22% patients had a RACHS-1 score of 4 to 6, compared to 37% patients in the original maxVIS study) and lower mortality rate (3% vs. 12% in the original maxVIS study). Furthermore, out of 199 patients in the lower surgical risk categories (RACHS-1 score of 1 to 3), 48.2% of them experienced at least one poor outcome. RACHS-1 score was created as a method of risk stratification of in-hospital *mortality* and was not intended to predict different *morbidity* outcomes between patients. Therefore, it is not surprising to observe some inconsistency in the RACHS-1 score relationship with poor outcome between institutions and patient populations. A clearer understanding of the association between RACHS-1 category and morbidity require further investigation that would ideally include multi-centered data.

It was not surprising that RACHS-1 score was not significantly correlated with the poor clinical outcomes for adult CHD patients. As we presented in Section 2, previous studies have shown that RACHS-1 score does not have good risk stratification performance for adult CHD patients. RACHS-1 scoring was created based on different categories of surgical procedures. The majority of these procedures is performed

exclusively during childhood and therefore is not relevant to the surgical interventions being performed in adult CHD survivors. The limited relevance of the RACHS-1 score is further evidence for the urgent need of a robust, well-performing risk prediction model that is truly based upon and designed for the adult CHD patient population.

VIS Index Predictive Model

The specific strengths and novelty of the VIS index prediction tool are as follows:

1. The VIS index demonstrates substantial improvement in predicting poor outcomes over the traditional maxVIS score. It is simpler to calculate and easy to use compared to the original maxVIS score, therefore enhancing its application in the real ICU setting to advance patient care.
2. The VIS index model exhibits robust and consistent performance in predicting overall poor clinical outcome as well as individual morbidity outcomes for both pediatric and adult CHD patients following cardiac surgery, despite morbidity is significantly different in these two populations. It provides one score system (VIS index 1 to 6) to indicate the risk of early mortality and morbidity after cardiac surgery.
3. The VIS index model was derived after adjusting for significant confounding variables we identified in this study. Therefore, it can be used as an independent evaluation tool to predict risk of poor clinical outcome. This is a valuable asset for the bedside clinician, whose access to key clinical information, such as the

RACHS score, is not readily available to identify high risk patients and guide clinical decision making. Furthermore, it also incorporates the duration on high doses of vasoactive support so although the model is based on the first 72-hour postoperative period, it is effective in predicting poor outcome risk as soon as the patients get admitted to the ICU after cardiac surgery.

Risk Score Future Updates

The VIS index score is derived based on the patient data from 2002 through September 2012. The year that the surgical operation was performed was included in the model but was not significantly correlated to the outcome. Therefore the results should be relevant to the clinical practice and for operations performed in the current cardiac surgical era. However, we suggest that the VIS index model be re-evaluated every few years to ensure that it reflects changes to the clinical practice as critical care management continues to evolve.

5.5 Study Limitations

There are a few limitations to consider in this research. Automated data capture of the EMR was utilized only for collecting the vasoactive medication data and patient ICU admission and discharge dates. All other clinical data was collected through manual chart review. Data quality has the potential to be impacted by both system and human errors as described in Section 4.1. To reduce error, data was consistently audited for accuracy by comparing the results from EMR automated data collection with manual chart review.

This was a time-consuming, labor-intensive effort. As the MCHN project continues to develop, a major priority is refining approaches for improving the data collection process to ensure its comprehensiveness and accuracy.

A second limitation is that this study is based on a patient population from a single institution. Therefore, even with modest patient sample size, the results may not be representative or generalizable to all patient populations. Furthermore, some of the outcome measures only occurred in a small number of patients. This resulted in significant variability in some of the individual outcome measures. This limitation was especially obvious when we estimated the predicted risk for individual morbidity events with low incidence rates at each VIS index value. Therefore, more research using multi-centered data for large patient populations is needed to validate the reliability and predictive capability of VIS index.

Thirdly, for the pediatric patient population, we only included infants aged less than one year old. This age range was chosen as these patients represent one of the higher risk categories for experiencing death from congenital heart disease. In addition, this population was most comparable to the pediatric patient population studied in the original VIS validation by Gaies et al. It is not known if VIS would be as robust in predicting mortality and morbidity in older children undergoing cardiac surgery.

Fourthly, in validating the current maxVIS model for the pediatric CHD patient population, we found that the overall VIS dose values at our institution are slightly lower than what was described in previous study. This difference demonstrates the diversity of

congenital heart disease management between institutions. VIS dose values are likely to be highly institution dependent as physicians at different institutions will have different approaches and preferences for administrating vasoactive agents to post-operative patients. Hoffman and colleagues demonstrated in a randomized, placebo-controlled trial that prophylactic administration of milrinone may prevent the onset of low cardiac output syndrome in patients undergoing repair or palliation of biventricular congenital heart disease (41). The use of milrinone is now common in many PICUs. However, there have been few studies performed to guide selection of other commonly used vasopressors such as norepinephrine and vasopressin. In addition, within-institution variability can be significant. It is not uncommon for different clinicians to have a "favorite" combination of vasopressors, and as a result they will use these combinations for the majority of their patients. Even if clinicians within the same practice apply similar vasopressor combinations, the variability in practice between institutions can still be significant. All these variations in the clinical practice of inotropic and vasoactive administration could potentially affect the cutoff values used in defining "high" vs. "low" VIS.

Finally, the VIS index predictive probability was based on a composite outcome variable including mortality and multiple morbidities. The list of morbidities in our study is extensive but not comprehensive. In the absence of validated surrogate outcomes for long term morbidity, studies have reported alternative acute outcome measures such as time to first negative fluid balance, cardiac arrest, need for mechanical circulatory support and peak lactate levels. These parameters were not included in this study. Thus

the VIS index predictive performance on adverse outcome is limited to the morbidity measures included in this study, and their relationship to other early and late outcomes warrants further investigation.

CHAPTER SIX: CONCLUSION

6.1 Study Overview

In this project, we successfully utilized the EHR automated data capture system to assess VIS predictive performance for early adverse outcome in both pediatric and adult CHD patients after cardiac surgery at the Mayo Clinic, Rochester, MN. The project provides a "proof of concept" that the EMR system, specifically, the MCHN automatic data capture system used for our study, is a feasible approach to answer important clinical research questions that will improve the quality and efficiency of patient care. The results of this project provide strong evidence that both infants and adults requiring high levels of vasoactive support during the early postoperative period have an increased likelihood of morbidity and mortality and suggest that a high VIS is a surrogate marker of illness severity after cardiac surgery for both infants and adult CHD patients. We externally validated the maxVIS model predictive performance of early postoperative adverse outcome in pediatric CHD patients. This validation further confirms that maxVIS is a promising surrogate marker of severity of illness despite the heterogeneity in vasoactive administration at different institutions. We were also able to determine the optimal time intervals for collecting inotrope doses to reliably predict clinical outcomes. This knowledge enables centers without automated EMR capabilities to reduce the frequency of data collection requirements without missing clinically significant intervals that would change study outcomes. Finally we proposed a robust, yet simplified VIS index model that outperforms the original maxVIS model for predicting early mortality and morbidity for both pediatric and adult CHD patients. The VIS index strengthens the traditional

inotrope score's ability to predict poor outcome by incorporating dose magnitude and duration of inotrope support into the equation and could be used as an illness severity score to lead to improved clinical care and guide therapeutic decision making.

6.2 Contribution to Health Informatics and CHD Clinical Research

This project is an important contribution to outcome analysis in CHD clinical research. First of all, we are able to externally validate VIS as a promising severity of illness scoring system with large CHD patient sample size. Secondly, the VIS index prediction tool we proposed is robust for both pediatric and adult CHD patients after cardiac surgery, for both overall poor clinical outcome and individual morbidity outcomes evaluated in this study. Therefore it could be particularly useful for physicians trying to decide between various diagnostic and therapeutic options for patients recovering from cardiac surgery. Thirdly, our research findings suggest that the VIS index prediction tool could be a useful addition to the field as a highly sensitive, easily generated index of severity of illness.

From clinical informatics perspective, this project represents a real example of secondary use of EMR data for clinical research and proves that with cross-functional collaboration efforts, EMR data can contribute significantly to these investigations. Moreover, the VIS index prediction model can be easily developed and implemented in the EMR system as a clinical decision support tool.

6.3 Future Study Directions

We propose a few suggestions for the future research directions. First, as more patient data is stored in the EMR system, the MCHN automated data capture system will continue to develop in complexity and comprehensiveness. The ongoing accumulation of new patient data within the MCHN system can be added to this current analysis for an updated VIS model. In addition, continued improvement of the MCHN data capture system will continue to add additional clinical data, such as diagnosis, ICU order sets, and a variety of other clinical measures.. As the clinical data available within the MCHN datamart through automated data capture grows, the requirements for manual chart review can be expected to decrease for both the pediatric and adult CHD patients. Secondly, future research is needed to determine whether the findings we presented in this project are reproducible in other institutions and to identify what other clinical factors during the early postoperative period independently predict clinical outcomes of interest in CHD patients following cardiac surgery. Multi-centered and adequately powered studies would be ideal to externally validate the VIS index performance in both pediatric and adult CHD patient populations. This will enable the validation of VIS index predictive performance on more comprehensive morbidity outcome events for both pediatric and adult CHD patients. Thirdly, future research could address the relative importance of different vasoactive/inotropic medications, and evaluate each individual vasopressin relationship with outcome measures. Hemodynamic data is also available in the MCHN data mart. Further analysis can be carried out to assess the association among

patient hemodynamic profile, the VIS score, and the clinical outcome. Finally, a clinical decision support system incorporating the VIS index prediction model could be readily implemented in the EHR system to facilitate optimal decision-making and improve the quality of patient care for CHD patients after cardiac surgery.

Reference

1. Jacobs JP, Jacobs ML, Mavroudis C, Lacour-Gayet FG, Tchervenkov CI. Executive Summary: The Society of Thoracic Surgeons Congenital Heart Surgery Database - Sixth Harvest–(2002–2005). The Society of Thoracic Surgeons (STS) and Duke Clinical Research Institute (DCRI), Duke University Medical Center, Durham, North Carolina, United States, Spring 2006 Harvest.
2. Kane RL: Approaching the Outcomes Question. In: Understanding Health Care Outcomes Research. Kane RL (Ed). Sudbury, MA, Jones and Bartlett Publishers, 2004, pp 1–14.
3. American Heart Association. Congenital Cardiovascular Defects — Statistics. Web. 18 July 2011. http://www.heart.org
4. Wessel D: Managing low cardiac output syndrome after congenital heart surgery. *Crit Care Med* 2001; 29:S220-30
5. Gillespie M, Kuijpers M, Van Rossem M, Ravishankar C, Gaynor JW, Spray T, Clark B 3rd: Determinants of intensive care unit length of stay for infants undergoing cardiac surgery. *Congenit Heart Dis* 2006; 1(4):152-60
6. Newburger JW, Wypij D, Bellinger DC, et al. Length of stay after infant heart surgery is related to cognitive outcome at age 8 years. J Pediatr 2003; 143:67–73.
7. Jenkins KJ, Gauvreau K, Newburger JW, et al: Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002; 123:110–118.
8. Larsen SH, Pedersen J, Jacobsen J, Johnsen SP, Hansen OK, Hjortdal V. The RACHS-1 risk categories reflect mortality and length of stay in a Danish population of children operated for congenital heart disease. Eur J Cardiothorac Surg. 2005;28:877-81.
9. Boethig D, Jenkins KJ, Hecker H, Thies WR, Breymann T. The RACHS-1 risk categories reflect mortality and length of hospital stay in a large German pediatric cardiac surgery population. Eur J Cardiothorac Surg. 2004;26:12-7.
10. Allen SW, Gauvreau K, Bloom BT, Jenkins KJ. Evidence-based referral results in significantly reduced mortality after congenital heart surgery. Pediatrics 2003; 112 (1 Pt 1): 24–28.

11. Jacobs JP, Jacobs ML, Maruszewski B, et al. Current status of the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons Congenital Heart Surgery Database. Ann Thorac Surg 2005;80:2278-2283discussion 2283–4.
12. Jacobs JP, Jacobs ML, Mavroudis C, Lacour-Gayet FG, Tchervenkov CI. Executive Summary: The Society of Thoracic Surgeons Congenital Heart Surgery Database - Sixth Harvest–(2002–2005). The Society of Thoracic Surgeons (STS) and Duke Clinical Research Institute (DCRI), Duke University Medical Center, Durham, North Carolina, United States, Spring 2006 Harvest.
13. The European Association for Cardiothoracic Surgery (EACTS) Congenital Database. Available at: http://www.eactscongenitaldb.org. Accessed December 17, 2006.
14. Maruszewski B, Zdzislaw Tobota A. An update on the database and data verification 2006 Presented at the European Congenital Heart Surgeons Association Meeting, Stockholm, Sweden; September 9.
15. O'Brien SM, Jacobs JP, Clarke DR, et al. Accuracy of the aristotle basic complexity score for classifying the mortality and morbidity potential of congenital heart surgery operations. Ann Thorac Surg. 2007; 84(6):2027-37.
16. Sinzobahamvya N, Photiadis J, Kumpikaite D, et al. Comprehensive Aristotle score: implications for the Norwood procedure. Ann Thorac Surg 2006; 81: 1794–1800.
17. Miyamoto T, Sinzobahamvya N, Kumpikaite D, et al. Repair of truncus arteriosus and aortic arch interruption: outcome analysis. Ann Thorac Surg 2005; 79: 2077–2082.
18. Atrip JH, Campbell DN, Ivy DD, et al. Birth weight and complexity are significant factors for the management of hypoplastic left heart syndrome. Ann Thorac Surg 2006; 82:1252–1257; discussion 1258–9.
19. Al-Radi OO, Harrell FE, Caldarone CA, McCrindle BW, et al. Case complexity scores in congenital heart surgery: A comparative study of the Aristotle Basic Complexity score and the Risk Adjustment in Congenital Heart Surgery (RACHS-1) system. J Thorac Cardiovasc Surg 2007;133:865-74.
20. O'Brien SM, Clarke DR, Jacobs JP, Jacobs ML, Lacour-Gayet FG, Pizarro C, Welke KF, Maruszewski B, Tobota Z, Miller WJ, Hamilton L, Peterson ED,

Mavroudis C, Edwards FH. An empirically based tool for analyzing mortality associated with congenital heart surgery. J Thorac Cardiovasc Surg 2009;138(5):1139-53.

21. Vijarnsorn C, Duangmanee L, Kritvikrom D, et al. Surveillance of Pediatric Cardiac Surgical Outcome Using Risk Stratifications at a Tertiary Care Center in Thailand. Cardiology Research and Practice, vol. 2011, Article ID 254321, 9 pages. doi:10.4061/2011/254321.
22. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg 1999;16(1):9-13.
23. Wernovsky G, Wypij D, Jonas RA, et al. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of lowflow cardiopulmonary bypass and circulatoryarrest. Circulation 1995; 92:2226-2235
24. Basaran M, Sever K, Kafali E, et al: Serum lactate level has prognostic significance after pediatric cardiac surgery. J Cardiothorac Vasc Anesth 2006; 20:43–47.
25. Gruenwald CE, McCrindle BW, Crawford-Lean L, et al. Reconstituted fresh whole blood improves clinical outcomes compared with stored component blood therapy for neonates undergoing cardiopulmonary bypass for cardiac surgery: A randomized controlled trial. J Thorac Cardiovasc Surg 2008; 136: 1442–1449.
26. Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, Charpie JR, Hirsch JC (2010) Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med 11:234–238.
27. Dearani JA, Mavroudis C, Quintessenza JA, Deal BJ, Backer CL, Fitzgerald P, et al. Surgical advances in the treatment of adults with congenital heart disease. Curr Opin Pediatr. 2009;21:565-72.
28. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, et al. Task force 1: the changing profile of congenital heart disease in adult life. J Am Coll Cardiol. 2001;37:1170-5.
29. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. Am Heart J. 2004;147:425-39.

30. Dearani JA, Connolly HM, Martinez R, Fontanet H,Webb GD. Caring for adults with congenital cardiac disease: successes and challenges for 2007 and beyond. Cardiol Young. 2007;17(Suppl 2):87-96.
31. Holst KA, Dearani JA, Burkhart HM, Connolly HM, Warnes CA, Li Z, Schaff HV. Risk factors and early outcomes of multiple reoperations in adults with congenital heart disease. Ann Thorac Surg 2011; 92:122-8.
32. Herasevich V, Pickering BW, Dong Y, Peters SG, Gajic O. Informatics Infrastructure for Syndrome Surveillance, Decision Support, Reporting, and Modeling of Critical Illness. Mayo Clin Proc. 2010;85(3):247-254
33. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ (2010) Changing mortality in congenital heart disease. J Am Coll Cardiol 56(14):1149–1157.
34. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007 May;71(10):1028-35.
35. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, Bailey JM, Akbary A, Kocsis JF, Kaczmarek R, Spray TL, Wessel DL. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003;107:996–1002.
36. Murphy-Filkins R, Teres D, Lemeshow S, Hosmer DW. Effect of changing patient mix on the performance of an intensive care unit severity-of-illness model: how to distinguish a general from a specialty intensive care unit. Crit Care Med. 1996;24:1968–1973.
37. Hosmer DW, Lemeshow S. Goodness of fit tests for the multiple logistic regression model. Commun Stat. 1980;A9:1043–1069.
38. SAS, Version 9.2. SAS Institute Inc., Cary, NC
39. Ambler G, Omar RZ, Royston P, Kinsman R, Keogh BE, Taylor KM. Generic, simple risk stratification model for heart valve surgery. Circulation. 2005; 112:224–231.
40. Barker GM, O'Brien SM, Welke KF, Jacobs ML, Jacobs JP, Benjamin DK Jr, Peterson ED, Jaggers J, Li JS. Major infection after pediatric cardiac surgery: a risk estimation model. Ann Thorac Surg. 2010 Mar;89(3):843-50

41. Hoffman TM, Wernovsky G, Atz AM, et al. Effcacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003; 107:996–1002