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Utility of Competing Risks in Analyzing Outcomes of Repair of Congenital Heart Defects

David A. Ashburn M.D.
John W. Kirklin Research Fellow
Congenital Heart Surgeons Society Data Center
Division of Cardiovascular Surgery
Hospital for Sick Children
Toronto, Ontario

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Abstract

Background and Objectives: Analysis of outcomes in patients with congenital heart disease often involves endpoints that are subject to competing risks. This thesis seeks to describe the concept of competing risks, to apply competing risks methodology to the analysis of multiple simultaneous time-related outcomes after congenital heart surgery, and to demonstrate the generation of clinically relevant competing risks models from which therapeutic inferences can be made.

Methods: Two cohorts of patients at risk for end-points subject to competing risks were analyzed. Competing risks methodology was used to quantify the cumulative incidence of 1) death and definitive repair states in a multi-institutional cohort of neonates with pulmonary atresia and intact ventricular septum (PAIVS)(n=408), and 2) hospital mortality and discharge in adults after congenital cardiac operations (n=1351). Parametric hazard function modeling with multivariable regression analysis was used to demonstrate the time-related migration from the initial state into each defined end-state and to determine risk factors for each end-state. The multivariable parametric competing risks model was solved for various permutations of risk factors to demonstrate the impact of risk factors on the cumulative incidence of end-states over time.

Results: In neonates with PAIVS, competing risks revealed the prevalence of end states 15 years after entry were: 2-ventricle repair, 33%; Fontan, 20%; 1.5 ventricle repair, 5%; heart transplant, 2%; death before reaching definitive repair, 38%, and alive without definitive repair, 2%. Multivariable analysis revealed characteristics of neonates (demographic and morphologic) and institutional protocols predict type of definitive repair. After adjusting for patient characteristics, competing risks elucidates institutional protocols and illustrates that a morphologically driven institutional protocol emphasizing both 2-ventricle and Fontan pathways may in part mitigate negative impact of unfavorable morphology.

Among adults undergoing congenital heart surgery, competing risks demonstrated the actual prevalence of hospital mortality was 4.5% and hospital

discharge was 95.5% with 9 day median LOS. Multivariable analysis identified patient and procedural variables impacting hospital mortality and time to discharge. Creation of a single competing risks model allows simultaneous analysis of hospital mortality and LOS and illustrates the impact of risk factors on early hospital outcomes. For example, valve replacement increases risk-adjusted mortality (4.1% vs. 1.2%) and LOS (9.4d vs. 7.9d). The model suggests that in a dedicated center with at least moderate volume, adult congenital heart surgery may be performed with similar risk-adjusted results as other areas of adult cardiac surgery.

Conclusions: Competing risks methodology is useful in analyzing outcomes after congenital heart surgery when patients are at simultaneous risk for experiencing one of multiple outcome events. When analyzed in the parametric hazard function domain, clinically relevant multivariable models that demonstrate the impact of important risk factors on outcomes can be generated.

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Introduction

Clinical outcomes research provides the data upon which the evidence-based practice of medicine is built. Goals of outcomes research include elucidation of natural and modified history of diseases, determination of optimal therapies, and provision of data useful in counseling patients and their families. The field of outcomes research has burgeoned, and a vast amount of resources are utilized in defining outcomes in essentially all disciplines of medicine.

Many outcomes of interest in clinical medicine are broadly defined as events which occur over time after an identifiable starting point. Examples include myocardial infarction after diagnosis of coronary artery disease, recurrence of cancer after surgical resection, and death after surgical repair of a congenital heart defect. Unfortunately, time-related outcomes such as these are often analyzed in the medical literature using methods that do not account for the time domain over which they occur.

In contrast, the section of biostatistics known as survival analysis is based upon the time domain, or distribution of discrete times-to-event, over which an outcome event occurs within a study population. By incorporating the time domain, survival techniques provide a more descriptive and precise understanding of the prevalence of a time-related outcome and its modulating risk factors. Despite its name, survival analysis may be applied to any time-related outcome, not just survival and death. Although survival analysis has been traditionally applied to single-event outcomes, techniques that allow modeling of more complex multiple-

event outcomes have been introduced yet remain underutilized in the medical literature.[1,2]

Objectives

The goals of the present thesis are to describe the concept of competing risks methodology, to demonstrate the application of competing risks to the analysis of time-related outcomes among patients undergoing surgical correction of congenital heart defects, and to illustrate the mechanistic advantages and usefulness of competing risks in generating clinically relevant models.

Background Information

Single- Versus Multiple-Event Outcomes

The most common application of survival analysis is the modeling of a single-event outcome (i.e. a single end-point) within a patient population over time. In its simplest and most traditional form, actuarial estimation (either life table method or Kaplan-Meier product-limit method) is used to define the prevalence of a single defined outcome event across time after an identifiable common starting point within a defined group of patients.[3,4] Death after surgical repair of a complex congenital heart defect is a good example. There is a single failure event - death - which occurs over follow up time after an identifiable common starting point - surgical repair - in a defined group of patients - children with a complex congenital heart defect.

Unless all patients in the cohort are followed up until their death (i.e. complete follow-up), there will be two categories of patients at the time of their last follow-up as shown in Figure 1: those who remain alive at last follow-up some time after surgical repair (the default state) and those who have died at some time after surgical repair (the end-state). Actuarial analytic techniques estimate the prevalence of the single end-state, death, across time by “censoring” those children remaining in the default state, alive after repair, at the time of their last follow-up. Censoring is a mathematical concept in which subjects are included in the overall at-risk cohort until the time of their last known follow-up, after which they are removed from the denominator (or at-risk cohort). In a single-event analysis, risk

factor determination may follow using methodology such as Cox proportional hazards modeling.[5]

It is not uncommon that a cohort of patients may be at simultaneous risk of experiencing any one of multiple mutually exclusive, or competing, outcome events. Consider the investigator wishing to characterize the prevalence of reoperation over time among children after surgical repair of a complex heart defect. Although initially appearing to be a single-event outcome (reoperation), the investigator finds that some children died during follow-up after surgical repair but prior to undergoing a reoperation (Figure 2A). In this scenario, there are two different, mutually exclusive events occurring over time after surgical repair - reoperation and death occurring before reoperation. Thus, patients may be in one of three categories, or states: alive after surgical repair (default state), reoperated after surgical repair (end-state), or dead after surgical repair but before reoperation (second end-state). Stated another way, after surgical repair of a complex congenital heart defect, a child is at simultaneous risk of requiring reoperation or of dying prior to requiring a reoperation.

How the investigator statistically handles the children who died prior to a reoperation may have an important impact on the reported results regarding prevalence of reoperation and its risk factors.[6,7] Applying single-event analytic techniques to multiple-event data such as this represents an attempt at conceptual and mechanistic oversimplification and may have profound ramifications on the accuracy of the reported results. Because actuarial techniques can only incorporate one censored state and one end-state, an attempt to analyze multiple-event

outcomes using actuarial methods requires that the extra end-state(s) be grouped either into the censoring state or into the end-state of interest.

In our example of reoperation after surgical repair of a complex heart defect, patients who die after surgical repair but prior to requiring reoperation may be grouped into the default state and censored at the time of their death (Figure 2B). The resulting actuarial event-free curve estimates the proportion free from reoperation across time for the cohort in which the competing risk of death has been *artificially* eliminated by censoring. By decreasing the denominator - the at-risk population - through censoring of patients who have died without reoperation, this maneuver artificially inflates the estimates of the percentage of children who will actually require reoperation.[6,7] The magnitude of this artificial inflation is directly proportional to the number of patients dying before reoperation. In an acknowledgement of this limitation, several authors have shown that the practice of simply censoring competing outcome events is inadequate and may lead to non-plausible results.[7-11]

Another work-around option is to group patients who die prior to requiring reoperation into the defined end-state with patients undergoing reoperation (Figure 2C). The resulting survival curve is generally stated to demonstrate prevalence of "survival free of reoperation". Although commonly appearing in the literature, grouping of different mutually exclusive outcomes into one end-state should be avoided. Once multiple end-states are combined into a single end-state, the risk or prevalence of one particular end-state cannot be precisely characterized. In addition, risk factor determination for a combined end-state may be misleading, as

each individual mutually exclusive end-state in the combined group may have a separate set of modulating factors.

Competing Risks. Competing risks methodology should be used to analyze scenarios in which there are multiple mutually exclusive end-points. In contrast to the overestimates of prevalence resulting from actuarial analysis of multi-state data, competing risks methodology provides an *actual* estimate of prevalence of each of multiple end-states (ie cumulative incidence). In our reoperation example above, reoperation and death occurring prior to a reoperation are different outcome events potentially driven by different factors. They should be considered as two separate mutually exclusive end-states in a competing risks manner (Figure 2D). In competing risks, patients remain in the default state until migrating into one of the two defined end-states – reoperation or death occurring before reoperation. Competing risks allows censoring of the default state while also accurately and simultaneously accounting for *each* of multiple outcome events.

Competing Risks in the Medical Literature

The theory and practical application of competing risks methodology originated in France in the 1760s during the smallpox scourge. By recording and analyzing survival rates and various causes of death during this period, French scientist and mathematician Daniel Bernoulli surmised that one could calculate the rate of migration from the transient state of being alive to any one of multiple end-states of being dead from various causes (smallpox, dysentery, murder, etc).[12] Utilizing this groundwork for competing risks, he demonstrated to the French Royal

Academy of Sciences the impact that eliminating smallpox related deaths would have on overall survival as well as on death rates due to other causes.[13]

In the current era, competing risks methodology has primarily been utilized in the medical literature to address two general areas. The first is isolating and quantifying death by one specific cause from death by other causes, just as Bernoulli separated death by smallpox from death by other causes. In cancer outcomes research, competing risks has been used to differentiate cancer-related mortality from other-cause mortality.[14-16] To define the impact of cancer treatment on overall survival, researchers must isolate cancer-related death from death by other competing causes. This is particularly true for aging populations in which death by other competing causes such as myocardial infarction, stroke, or infection is common. Additionally, analogous to Bernoulli's calculations, as cancer-related mortality decreases other-cause mortality increases.

The second area of utilization of competing risks methodology in medical outcomes research is analyzing non-fatal outcome events. In these scenarios, death is a major competing event that may affect the interpretation of results as described earlier. Perhaps the best example is evaluation of prosthetic implant durability.[8-10,17] A prosthetic device may fail and require replacement during the lifetime of the patient in whom it was implanted. Conversely, the patient may die at some point in time after prosthesis insertion but before failure and replacement of the prosthesis. These two events - prosthesis failure and patient death prior to prosthesis failure - are competing risks and should be analyzed as such. Because of the competing risk of death, Schwarzer and colleagues showed that competing

risks methodology provides more accurate analysis of joint prosthesis failure than does actuarial analysis.[9] They concluded that accounting for the competing risk of death is mandatory to generate the actual prevalence of prosthesis replacement. Indeed, comparisons of efficacy of various point prostheses should be based on actual prevalence of failure - not based on prevalences artificially inflated by censoring at the time of death.

In the field of adult cardiac surgery, competing risks has been applied to outcomes of heart valve prostheses. In evaluating the durability of prosthetic heart valves, a researcher wishes to determine the probability that a given valve will fail during a patient's lifetime. Given the competing risk of death occurring before prosthesis failure, competing risks methodology has been used by Grunkemeier and colleagues and McGiffin and colleagues to quantify actual valve failure rates among various types of prostheses.[8,10,17] More recently, Blackstone and Lytle have used competing risks methodology to analyze the impact of interim death on the rate of reintervention among variously aged patients undergoing different strategies of coronary artery bypass grafting.[18]

Competing Risks in Congenital Heart Disease

The phenomenon of competing risks, or being at simultaneous risk for one of multiple mutually exclusive outcome events, is particularly representative of children born with congenital heart malformations. At any given time, children may be at risk of experiencing one of a myriad of important events such as various forms of definitive surgical correction, various stages of palliative surgery, heart

transplantation, reoperation, or death. As survival for children born with complex heart disease has improved, so has the diversity and complexity of their outcomes increased.

Children born with hypoplastic left heart syndrome are an example. These children undergo an initial complex palliative operation known as the Norwood operation followed generally by two subsequent operations aimed at definitive palliation. However, the observed outcomes after the initial palliation (Norwood operation) are not straightforward. Using a competing risks analysis, Ashburn and colleagues quantified the prevalence of five defined end-states at any time after the Norwood operation: subsequent staged palliation, alive without further staged palliation, death prior to subsequent staging, conversion to two-ventricle repair, and heart transplantation.[19] Only through competing risks methods can the actual prevalence of multiple end-states over time be determined. Despite the growth in outcomes research and the increasing complexity of time-related outcomes among children with congenital heart defects, there are few reports in pediatric cardiac literature utilizing competing risks methodology.

Jacobs and colleagues from the Congenital Heart Surgeons Society utilized competing risks methodology to compare the proportion of neonates born with hypoplastic left heart syndrome achieving various definitive end-points after either heart transplantation or staged surgical reconstruction via the Norwood operation.[20] McGiffin and colleagues from the Pediatric Heart Transplant Study Group utilized competing risks methods to define the prevalence of the following end-states across time after listing for heart transplant in children: death prior to transplantation,

transplantation, removal from the waiting list, or remaining on the list awaiting transplantation.[21] By accounting for each of these competing outcomes, they showed that competing risks methods provide a more accurate depiction of the actual proportion of patients experiencing an outcome after listing.

The remainder of the present thesis aims to demonstrate how competing risks methodology can be applied to the analysis of outcomes among patients undergoing surgical correction of congenital heart defects and to illustrate the mechanistic advantages and usefulness in generating clinically relevant models. Two studies utilizing parametric hazard function modeling, multivariable risk factor determination with risk-adjustment, and synthesis within the competing risks domain are presented.

The first study examines the prevalence and determinants of definitive end-states among children born with pulmonary atresia and intact ventricular septum (PAIVS).[22] This multi-institutional study conducted by the Congenital Heart Surgeons Society highlights multivariable parametric hazard function modeling, competing risks depiction of end-states over years of follow-up, and the use of risk-adjusted time-related models to draw inferences related to institutional protocols.

The second study defines early outcome measures - mortality and length of stay - as competing risks after surgery for adults with congenital heart disease.[23] A multivariable parametric competing risks model of these outcomes is built, and risk factors for each outcome measure are determined within a single parametric model. This study highlights the usefulness of a single competing risks model to simultaneously predict death and length of stay as well as to illustrate the risk-

adjusted impact of various demographic, anatomical, and surgical factors on surgical mortality and length of stay.

Definitive End-States in Children with Pulmonary Atresia and Intact Ventricular Septum

Introduction

Pulmonary atresia with intact ventricular septum (PAIVS) is a congenital heart defect characterized by absence of communication between the right ventricle and pulmonary trunk or left ventricle. The lesion is morphologically heterogeneous with a varying degree of right ventricular and tricuspid valve hypoplasia.[24] Aberrations of coronary circulation are common, ranging from cameral-coronary sinusoids and fistulae to right-ventricle-dependent coronary circulation.[25]

A prior report from the Congenital Heart Surgeons Society (CHSS) examined various morphologic substrates and optimal initial palliative pathways for the initial 171 neonates with PAIVS enrolled in their multi-institutional study.[26] Since that report an additional 237 neonates were enrolled, and the present cohort includes all 408 neonates. We undertook this multi-institutional analysis to 1) determine the proportion of neonates reaching defined end-states, 2) identify factors predictive of each end-state, and 3) sythesize these in a way that would reveal which factors are associated with a greater proportion of neonates reaching definitive repair.

Patients and Methods

Patients. From January 1987 to April 1997, 408 neonates with PAIVS admitted to a CHSS institution within 30 days after birth were prospectively enrolled

in a multi-institutional study. PAIVS was defined as no communication between the right ventricle (RV) and pulmonary trunk and absence of ventricular septal defect (VSD) as determined by echocardiographic, catheterization, or surgical findings. Neonates were managed at 33 member institutions with a median enrollment of 10 neonates per institution (range 1 to 41 neonates). Mean birth weight was 3.1 $\pm$ 0.6 kg.

Median tricuspid valve Z score was –1.2 (range –5.4 to 6.0). Of 334 neonates for whom RV size was known, it was small for age in 303 (91%) and moderately or severely so in 49% (Table 1). Tricuspid valve Z score and RV size were moderately correlated (r=.60, *P*<.001). RV-coronary artery fistulae were present in 126 (31%). RV-dependent coronary circulation, defined as supply of a major portion of left ventricle from only the RV through fistula(e), was present in 19 (5%) neonates. Coronary aberrations were observed primarily in association with moderate or severe hypoplasia of right heart structures.[26]

Morphology. Morphologic data were obtained by independent review of pre-intervention echocardiograms and catheterizations as previously described.[26] A subjective grade for RV size was assigned based on available combined information from catheterization, echocardiography, and surgery. Normal-for-age cavity size was assigned a value of 0, extreme hypoplasia –5, and intermediate degrees –1 through –4. For enlargement, a similar scheme was used with +5 denoting the most extreme enlargement.

Data Collection. Participation in the study and submission of patient information was voluntary and confidential. Parental consent was obtained in a

manner consistent with individual institutional policy. Ethics approval for the CHSS Data Center is obtained annually from the Hospital for Sick Children in Toronto. Admission, diagnostic, interventional, and surgical records were abstracted into a comprehensive database by CHSS members and staff.

Follow-up. The physician, family, or guardian of each child not known to have died has been contacted annually to ascertain clinical status and any intervening problems, procedures, or operations. After most recent cross-sectional follow-up in 2002, current data (within 1 year of this analysis) were available for 373 (91%) children. For all neonates, follow-up time from the date of first hospital admission was median 5.8 years (range 1 day to 15.6 years). For surviving patients, median follow-up was 10.3 years (range 1 day to 15.6 years). For neonates without current data (n=35, 9%), median follow-up was 3.4 years (range 1 day to 9.1 years).

***Data Analysis*.** All analyses were performed using SAS statistical software (version 8; SAS Institute, Inc; Cary, NC). Data are presented as frequencies, medians with range, or means ± SD as appropriate.

***End-states*.** Beginning at the common identifiable starting point of initial hospital admission, neonates with PAIVS are alive with a mixed (parallel or non-series) circulation and are at simultaneous risk of attaining one of multiple definitive end-states over time. In addition to the initial, or default, state of surviving with mixed circulation and without definitive repair, the following mutually exclusive end-states were designated: 2-ventricle repair, 1.5-ventricle repair (biventricular repair with superior cavopulmonary connection), 1-ventricle repair (completed Fontan

operation with or without fenestration), primary heart transplantation, and death prior to attaining a definitive repair. Definitive repair was defined as complete separation of systemic and pulmonary circulations (no extra-cardiac shunts and no intra-cardiac right-to-left shunt at the atrial level), such that children having a fenestrated 2-ventricle repair were not considered definitively repaired until the intra-atrial shunt was known to be closed – either surgically or spontaneously.[26]

***Prevalence of End-states*.** Non-risk-adjusted freedom from each state was estimated non-parametrically using the Kaplan-Meier method. Individual rates of transition from the initial state of mixed circulation to each competing end-state were estimated by multi-phase parametric modeling of the underlying hazard functions as described by Blackstone and colleagues[27] Using competing risks methodology, the individual hazard functions were integrated to yield the actual proportion of the initial neonatal cohort reaching each defined end-state at any given time after initial hospital admission.[1]

Risk Factors for End-states. Demographic and morphologic factors associated with each end-state were sought by multivariable regression of each hazard model. Variable selection was primarily by bootstrap bagging. In bootstap bagging, the analytic process of variable selection is subjected to repeated resampling and reanalysis, and those variables that are consistently selected (ie selected in > 50% of resamples) are considered reliable.[28,29] Bootstrap bagging nearly perfectly balances the probability of selecting risk factors that are not reliable (type I error) and falsely rejecting a covariate that is a reliable risk factor (type II error).[30] For the bootstrap step, randomly selected data sets (n=200) of identical

size as the original data set were analyzed by automated stepwise regression with an inclusion criterion of $P \leq .05$. For the aggregation step, cluster analysis was used to identify risk factors occurring in 50% or more of the analyses, with the most commonly occurring mathematic transformation (if applicable) selected. These factors were entered into the final model, and those with $P \leq .05$ were retained. Frequency of identifying factors (percentage of bootstraps in which variable is selected as a risk factor) according to the bagging analysis is a measure of the reliability of each risk factor retained in the final mode. For each selected risk factor, the reliability term, the *P* value, and the parameter estimate with its standard error are reported. Parameter estimates signify contribution of a variable to the overall model, and their interpretation is affected by increments of measurement and, where applicable, mathematical transformations.

Impact of Institution. After adjusting for the retained patient factors, institutions associated with each end-state were identified in similar manner. To further assess institutional outcomes, the competing risks model containing patient factors was repeated – entering each institution identified as a "risk factor" for 2-ventricle repair, for Fontan operation, and for death before definitive repair. Adjusting the outcomes of each institution based on the level of risk it managed allows a fair comparison among institutions. Nomograms of individual institutional 5-year outcomes based on the morphologic spectrum (TV *Z* score with concordant RV size adjustment) of PAIVS were constructed.

Concept of Hazard and its Modulating Factors

"Risk" is commonly used in the literature to convey the likelihood or probability that a specified event, usually a negative outcome, will occur. In its purest sense, risk is actually a rate - the rate at which at-risk patients experience designated outcomes over a defined time interval. In survival analysis, hazard is defined as the instantaneous rate at which patients migrate from the initial default state into a defined end-state. Thus, hazard is equivalent to instantaneous risk. When multiple competing end-states exist, there are individual competing hazards that define the rate of migration from the initial state into one of the competing end-states.

***Analogy of Enzyme Kinetics*.** The manner in which an initial cohort of patients migrates over time into one or more defined end-states is comparable to enzyme kinetics. During an enzymatic reaction, an enzyme converts substrate into a given product (Figure 3A). The enzymatic reaction proceeds from time=0 at a defined quantifiable rate. The reaction rate may vary over time as defined by the rate law – a mathematical equation quantifying the speed at which substrate is converted into products. The rate of reaction may increase or decrease in response to modulating factors such as heat, light, solution pH, or concentration (Figure 3B). If additional non-interacting enzymes are added to the solution, each enzyme *competes* with the other enzymes to convert substrate to specific products (Figure 3C). Although occurring in the same solution, each of the three independent enzymatic reactions has a unique rate law and unique modulating factors. Depending on the modulating factors present, changes in the reaction rate of one

enzyme may impact the availability of substrate and reaction rate of the other enzymes. Therefore, the proportions of the various products across time after the reactions begin are dependent upon the combination of various modulating factors present.

"Kinetics" of Competing Risks. Analogous to enzyme kinetics in which competing enzymes convert substrate into various products, neonates born with PAIVS may migrate into one of several competing end-states after initial hospital admission (Figure 4). Estimating the prevalence of each end-state actuarially with censoring of other end-states results in gross overestimation of the prevalence of end-states (Figure 5). Competing risks methodology overcomes this limitation.[7]

At time=0, all neonates are alive at the time of admission. Thereafter, they may migrate over time into a defined end-state: 2-ventricle repair, 1.5-ventricle repair, 1-ventricle repair, heart transplant, or death before reaching a definitive repair. The instantaneous rate, or *hazard*, of migration into each end-state is unique, may vary over time, and may be quantified by a time-dependent mathematical equation known as the *hazard function*. The hazard function for migration into each end-state is independent and may increase or decrease in response to a unique set of modulating, or risk, factors. In short, each of the competing end-states has its own unique hazard function as well as a unique set of risk factors which modulate (either increase or decrease) the hazard of achieving that end-state. The proportions of neonates in each definitive end-state across time after initial admission are dependent upon the combination of various modulating factors present.

***Generating Models of Time-Related Hazard*.** Modeling of the underlying hazard functions defining the rates of migration into each end-state was performed using methods introduced by Blackstone and colleagues.[27] The premise of their methodology is that the instantaneous hazard curve plotted across time (or hazard function) can be broken down into one, two, or all of three distinct phases of risk - early, constant, and late. An early hazard phase includes a peak in risk at (ie asymptotic) or near time=0 with progressive decline in risk over the time of follow-up. As its name implies, a constant phase of hazard is one-dimensional and does not vary over time, indicating that a population is always at a finite level of risk for a given outcome. Lastly, a late hazard phase describes progressively increasing risk as time proceeds.

Blackstone's approach is fully parametric, meaning that the researcher defines a mathematical equation that quantifies underlying hazard throughout follow-up time. The overall hazard function is modeled by incorporating one of or a combination of the above defined component phases. The magnitude and shape of the early phase is defined by 5 parameters (1 scaling parameter, 4 shaping parameters) and the late phase by 5 parameters (1 scaling parameter, 4 shaping parameters). For a constant phase, only a single parameter (1 scaling parameter) is needed to define the magnitude of risk. Therefore, a full hazard model with 3 phases may have up to 11 parameters (3 scaling parameters, 8 shaping parameters).

Once a parametric model of hazard is generated, the hazard function can be applied back to the original cohort of patients just as a rate law defines the kinetics

of an enzymatic reaction. The result is a parametric survival curve that may be compared to a non-parametric curve (the Kaplan-Meier survival curve) to assess goodness of fit.

Because each hazard phase is separate and has different “kinetics”, each phase also has its own unique set of modulating factors. Covariates are regressed against each hazard phase in a given hazard function, and significant risk factors are determined as described earlier.

With the hazard function for each end-state identified, a parametric model that simultaneously quantifies the prevalence of each end-state is generated. This competing risks model is obtained by integrating the hazard functions as they compete for subjects remaining in the default state. By incorporating phase-specific risk factors of each hazard function, an overall parametric model that defines the actual prevalences of each end-state and the impact of risk factors on them is generated.

The parametric multivariable competing risks model can be applied to individual patients or a cohort of patients to predict the likelihood of achieving each of the various definitive end-states, to illustrate the impact of single factors or combinations of factors on outcomes, and to draw inferences regarding the various management strategies studied.

***Advantages of the Fully Parametric Model*.** The parametric approach has several advantages over non-parametric and semi-parametric models often used in survival analysis. The parametric model breaks down a complex hazard function into multiple less complex components. The resulting overall model provides a

flexible family of models which is mathematically robust. Also, this decomposition into component phases allows the model for each phase to be simplified to its most basic form (with as few parameters used as needed to fit the data), resulting in parsimony between model structure and the number of parameters. Also, risk may be graphically portrayed with visualization of the effects of risk factors.

A commonly used approach to risk factor selection is the Cox proportional hazards model. The Cox model is an overall analysis across the entire observation period and does not consider various phases of risk. Therefore, the Cox model often fails to reveal the influence of transient risk factors. Thus, risk factors operative during discrete periods of follow-up may be missed. While the parametric approach allows a more specific focus on the risk factors for the events within a specific phase, the Cox proportional hazards model provides general risk factors averaged over the entire follow-up period. Because risk factors are considered phase-specific and not necessarily influential across the observation period, the parametric model does not depend upon the assumption of proportional hazards. In fact, the ability to seek out non-proportional hazard is important in defining clinically important trends. For example, it is clinically relevant to distinguish factors associated with early, or operative, mortality from the factors associated with death occurring years after an operation.

In contrast to non-parametric estimation, semi-parametric procedures (such as PROC LIFEREG in the SAS statistical system, SAS Institute, Cary, NC) attempt to model survival data by incorporating a single defined hazard distribution. Multiple distributions (or phases) cannot be accommodated, leading to similar limitations as

for the Cox model. By incorporating multiple phases of hazard, the parametric procedure allows generation of a model more closely approximating the observed pattern(s).

***Model Completion*.** With risk factors for each migration identified, a parametric, or mathematical, multivariable equation incorporating each hazard function and the impact of its risk factors can be generated. The parametric equation can be applied to individual patients or a cohort of patients to predict the likelihood of achieving each of various definitive end-states and to illustrate the impact of single factors or combinations of factors on outcomes.

Results

For all 408 neonates, survival at 1 month, 6 months, 1 year, 5 years, and 15 years after initial hospital admission was 80%, 70%, 68%, 60%, and 58%. Risk factors for death at any time were similar to those described below for death occurring before reaching a definitive repair. There was improvement in overall survival across the study period. Holding other factors constant, predicted 5-year overall survival for neonates enrolled in 1987, 1992, and 1997 was 49%, 63%, and 79% respectively.

Prevalence, timing, and factors predictive of end-states. Prevalence of neonates reaching a definitive end-state was 49%, 89%, 96% and 98% at 1, 5, 10, and 15 years after initial hospital admission (Figure 6A). The hazard functions, or Instantaneous rates, of reaching each end-state at any given time after entry are

shown in Figure 6B. Incremental risk factors for each end-state are listed in Table 2.

Completed 2-ventricle repair (n=120). The prevalence of completed 2-ventricle repair was 13%, 28%, and 33% at 1, 5, and 15 years after admission. The hazard function revealed two major phases. An early phase, starting near the time of admission and extending to 3 months, represented 25 neonates with favorable morphology. The subsequent late hazard phase included 95 children, rises beyond 2 months, and spans the remainder of the study period. It corresponds to the wide timeframe for closing extra- and intra-cardiac shunts.

Fontan operation (n=76). The prevalence of Fontan repair was 1%, 19%, and 20% at 1, 5, and 15 years after admission. There is a single hazard phase for Fontan operation peaking at 3 years.

Other definitive repairs (n=31). The 15-year prevalence of 1.5-ventricle repair and cardiac transplantation was 5% and 2% respectively.

Death before definitive repair (n=149). The prevalence of death before definitive repair was 31%, 36%, and 38% at 1, 5, and 15 years after admission and was heavily concentrated around the time of first admission. For neonates not reaching a definitive repair within the first two years of life, there was an ongoing late hazard for death.

Predicted pathway. From patient factors in Table 2, the multivariable competing risks model was solved for each neonate in the dataset to predict whether 1- or 2- ventricle repair pathway was most probable for each neonate. Predicted pathway was 2-ventricle for 246 (60%) neonates and 1-ventricle for 162

(40%). Management protocol matched predicted protocol in 315 (77%) neonates. For neonates managed different from their predicted pathway, an increased prevalence of death before reaching definitive repair was observed (54% versus 31%, *P*<.001).

Impact of institution. A competing risks model was constructed for each institution identified as a "risk factor" for one or more end-states. Nomograms illustrating the risk-adjusted 5-year prevalence of end-states for representative institutions favoring 2-ventricle, Fontan, and both 2-ventricle and Fontan pathways are shown in Figure 7. Institutions favoring 2-ventricle repair on average achieved a higher prevalence of 2-ventricle repair at the cost of higher pre-repair mortality (Table 3). Such institutions may improve outcomes by more aggressive application of Fontan pathway in children with less favorable morphology (Figure 7A).

The single institution favoring Fontan repair achieved good survival at the cost of fewer 2-ventricle repairs, even for more favorable morphology (Table 3). Such institutions may improve outcomes by applying 2-ventricle repair to children with favorable morphology (Figure 7B).

Two institutions applied both 2-ventricle and Fontan pathways in a morphologically dependent manner (Figure 7D) to achieve comparably excellent survival and higher prevalence of 2-ventricle and Fontan repairs with few remaining unrepaired at 5 years (Table 3).

High-risk institutions, with the exception of Institution H, demonstrated a reticence toward "committing" to either a 2-ventricle or Fontan pathway as indicated

by the high prevalence of children alive without a definitive repair at 5 years as compared to low-risk factor institutions (Figure 7C).

Discussion

PAIVS is a rare lesion, and most previous reports include small numbers of children treated at a single institution.[31-37] A unique aspect of our study made possible by the large unselected population of neonates accrued by CHSS institutions is consideration of various mutually exclusive end-states achieved in these neonates. By accounting for multiple simultaneous outcome events, competing risks methods allow 1) determination of the actual prevalence of each end-state over time after entry, 2) multivariable definition of patient-related factors associated with the distribution of end-states, and 3) demonstration of risk-adjusted impact of institution on the prevalence of end-states.

Though variable, reported survival in neonates with PAIVS has improved over time. In an earlier era, reported 5-year survival among 135 neonates admitted between 1970 and 1989 was less than 50% with 25% of children determined to be suitable for definitive repair.[38] The overall 5-year survival in our multi-institutional study was 60%, with adjusted 5-year mortality for neonates admitted in later years of 79%. The proportion reaching definitive repair at 5 years was 52%. Our data are similar to a national Swedish study of 84 children born between 1980 and 1999.[39] Several recent reports have documented outstanding survival ranging from 76% to 98% at 5 years.[33,36,37] Despite excellent survival, the proportion undergoing definitive repair in these studies was 55% to 72%.

The morphologic spectrum of PAIVS requires different management protocols with the goal of maximizing the number of neonates reaching appropriate definitive repair. From the institutional findings of this study, we infer that surgical protocol based upon individual risk factors present may optimize outcomes. Findings of this and the initial CHSS study show that the decision process must begin at the time of initial admission.[26]

Our study demonstrates that an optimal protocol emphasizes 2-ventricle pathway for favorable morphology and Fontan pathway for unfavorable morphology. Such a protocol results in 1) higher proportion of neonates reaching a "definitive" repair, 2) earlier completion of "definitive" repair, and 3) lower proportion of pre-repair attrition. We have shown that such a protocol at least in part mitigates the negative impact of hypoplastic right heart structures on survival. Selecting a Fontan pathway for children with marginal or severe anatomy should not be considered a failure of therapy.[35,40] The benefits of selective management are supported by several previous reports.[36,37]

The method of risk-adjustment deserves further explanation. Multivariable analysis of patient factors identified important variables in predicting the prevalence of each end-state, with the weight of each factor determined from the overall data. In contrast to risk-stratification, institutions associated with a comparably high prevalence of one or more end-states were identified *after* adjusting for important patient variables (ie institutions predisposed to a particular end-state after consideration of their patient population). This method allows "fair" comparison of outcomes from different institutions based on different levels of risk managed by

each institution. The recently emerging technique of multi-level modeling may prove to be useful in determining institutional impact on outcomes.[41-43] Multi-level analysis examines data involving nested sources of variability such that lower level, or individual order, risk factors (eg patient weight or age) nested within higher level, or group order, risk factors (eg institution) may be simultaneously determined. However, multi-level modeling has not yet been applied in the time-domain of survival analysis in the medical literature.

While we and others have shown that tricuspid valve (TV) size is a primary determinant of the type of repair likely to be achieved, our analysis reveals that there are other variables to be considered. We demonstrated that both TV Z score and right ventricle (RV) size are important determinants of achieving a 2-ventricle repair - either early or late. Because TV diameter and RV size were only moderately correlated, the inference is that adequacy of both structures should be considered when determining candidacy for 2-ventricle repair.[34] In addition to TV size, TV morphology is an important factor determining suitability for 2-ventricle repair.[44] Surrogated by RV enlargement and severe tricuspid regurgitation in this study, associated Ebstein malformation imposes a high risk of death and not achieving 2-ventricle repair. There are instances in which size of the RV and TV suggest potential for 2-ventricle repair, but TV dysplasia precludes reaching that outcome. Additionally, valves with an acceptable Z score may have stenotic dysplasia with thickened knobby leaflets and abnormal chordal attachments making them irreparable. Because TV replacement in young children is undesirable, valve

closure (often with a patch) and proceeding to Fontan operation may be the best option.

We did not find aberrations of coronary circulation to be specific risk factors for death, a finding supported by other studies.[36,37] When considered in the context of improving overall survival, this finding lends further evidence that the most unfavorable morphologic subsets of neonates with PAIVS can be managed successfully. Because multiple patient-related factors determine the appropriate protocol, management decisions should be made after careful delineation of presenting characteristics for each neonate.

In conclusion, we observed improving overall survival across the span of the study. Further, we estimate that definitive repair could be achieved in 85% of neonates within 3-5 years after admission. Based on factors predicting repair pathway, we expect that 50% of neonates will be suitable for 2-ventricle repair, and 35% will be more appropriately managed on a Fontan pathway.

Single Model Determination of Hospital Length-of-Stay and Mortality for Congenital Heart Surgery in Adults

Introduction

For the first time in history, the number of adults with congenital heart disease (ACHD) exceeds the number of children with congenital heart disease.[45] There are currently an estimated 1 million adults living with congenital heart disease in the US and over 120,000 in Canada.[45,46] Because the expected survival into adulthood of children born with congenital heart disease has risen to 90%, the population of ACHD will likely continue to expand over the next two decades.[47] Many in this population have had prior surgical repair and are likely to fair well without further surgical intervention. Others who initially present as adults or who develop late sequelae subsequent to a prior repair may require cardiac surgery. The proportion of ACHD patients that will require cardiac surgery is unknown; however, specialists meeting at the 32nd Bethesda Conference suggested that 55% of the ACHD population is at increased risk of premature death, reoperation, or other major complications.[48]

At present, there are a small number of centers with dedicated ACHD surgical services. The demand for ACHD surgery will increase as the population of ACHD grows in number, complexity, and age. Comprehensive reports from dedicated ACHD surgical services are few.[49,50] Herein, we review the experience in cardiac surgery for ACHD at the Toronto Congenital Cardiac Center for Adults (TCCCA) with a focus on factors that affect early outcomes. Using a novel

application of competing risks, a single model is utilized to determine both mortality and length-of-stay, define factors associated with each outcome, and simultaneously demonstrate the risk-adjusted impact of various factors on measures of early outcomes.

Patients and Methods

Patients. From September 1973 to December 2001, 1286 adults with congenital heart disease underwent 1351 operations. Congenital heart surgeons based at the Hospital for Sick Children performed all operations. A comprehensive team of specialists at TCCCA dedicated to ACHD provided patient care at all levels. All operations were grouped into one of six classes: primary repair of left-to-right shunt lesions (n=304,23%); primary repair of obstructive or valvular lesions (n=438, 32%); reoperation for late residual lesions (n=337, 25%); late definitive repair of non-simple defects (n=141, 10%); palliative surgery (n=109, 8%); and miscellaneous (n=22, 2%) (Appendix 1).

Data collection. Diagnostic, surgical, and early outcome data were retrieved from the Cardiovascular Surgery Database (CVSDB) maintained by the Division of Cardiac Surgery at the Hospital for Sick Children.[51] Two measures of early outcome are considered in this report: hospital mortality and length of hospital stay (LOS). Hospital mortality is defined as death occurring before hospital discharge.

Data analysis. The goals of this analysis include defining the prevalence and timing of death and discharge after surgery in ACHD and determining the factors associated with each outcome. Time to operative death or discharge was

considered. All time-related analyses were truncated at 120 days because no events in this series occurred thereafter. All analyses were performed using SAS statistical software, version 8 (SAS Institute, Inc., Cary, NC). Descriptive data are defined as frequencies, medians with ranges, and means with standard deviations as appropriate.

Because patients are at simultaneous risk of mortality and hospital discharge in the early postoperative period, a competing risks analysis was used to determine the true prevalence and timing of each outcome. After surgical repair of congenital heart disease, adults may migrate into one of two mutually exclusive end-states. At time=0, all patients are alive in hospital. Thereafter, they migrate over time into an end-state - either hospital death or discharge (Figure 8). Each end-state has its own unique hazard function as well as a unique set of modulating factors. Both the prevalence and timing of death and discharge after surgery are dependent upon the combination of modulating factors present.

Non-risk-adjusted non-parametric estimates of freedom from death and discharge were plotted using Kaplan-Meier methods.[3] As demonstrated in the PAIVS example earlier in this thesis, actuarial estimation of competing events grossly overestimates the prevalence of each end-state due to censoring of the competing end-state(s).[6,7] In the present analysis, actuarial estimates of the 60-day prevalence of hospital discharge of 98% and hospital mortality of 29% sum to 127% (Figure 9). Clearly, the sum of “actual” prevalences of hospital discharge and mortality cannot exceed 100% (each patient may experience only one of the two mutually exclusive end-states).

The hazard function, or instantaneous risk plotted over time, for death and discharge was modeled using a parametric approach that elucidated the number of hazard phases, the shape of the hazard function, and estimated the characteristic parametric equation.[27] The hazard functions were then synthesized using competing risks methodology to yield the proportion of patients reaching the defined states of operative death and discharge across the post-operative period.[1,2] The competing risks model was confirmed using non-parametric multiple decrement analysis. [2]

Demographic, diagnostic, and surgical factors associated with each outcome were sought from the variables listed in Table 4 by multivariable regression of the hazard models. Significance criteria for variable selection included $P<0.15$ for entry into the regression and $P<0.10$ for retention in the model. Numerous transformations of continuous variables and interactions of interest were explored. Because of the 29 year span of the study period, all models were adjusted for time since the ACHD program started. This time variable attempts to account for changes in outcomes resulting from era effects secondary to changes in management protocols, technologic advancements, or longitudinal learning. Parameter estimates reported for significant covariates represent the contribution of a variable to the overall model. Increment of variable measurement and mathematical transformation affect interpretation of the contribution and are specified where applicable. To better help the reader understand the risk-adjusted impact of significant factors on outcomes, the multivariable competing risks model

was solved for various permutations of risk factors and their resultant predicted hospital mortality rates and median LOS reported (Figure 10).

Results

Trends in Surgical Volume. Since adult congenital cardiac surgery began at the TCCCA in 1973, there has been an average annualized rate of growth of 7.5% in ACHD surgical volume. As shown in Figure 11, the greatest increase in volume has occurred in patients with primary repair of obstructive or valvular lesions and those with late residual lesions presenting for reoperation.

Measures of early outcomes. The competing risks model reveals the proportion of patients who have died, been discharged, or remain alive in hospital throughout the post-operative period for all 1351 operations (Figure 12). For example, at 7 days, 3% have died, 23% have been discharged, and 74% remain alive in hospital. By 60 days after surgery, most outcomes have been determined with 4% dying prior to discharge and 96% being discharged. Overall, there were 60 operative deaths resulting in a non-risk-adjusted operative mortality rate of 4.4%. The risk-adjusted operative mortality rate has declined over the study period from 4.5% in 1980 to 2.5% and 1.7% in 1990 and 2001, respectively. Median LOS for discharged patients was 9 days.

Hospital mortality. Incremental risk factors for in-hospital death are noted in Table 5 and include late definitive repair of non-simple defects, palliative surgery, valve replacement other than pulmonary valve, and the need for reoperation during

the same admission. Primary repair of left to right shunt lesions was associated with reduced risk. To illustrate the impact of these risk factors, predicted mortality rates were generated using the multivariable competing risks model (Table 6). Also, higher annual surgical volume was associated with reduced operative risk. The predicted risk-adjusted mortality rate drops below 2% when clinical volume exceeds 50-55 operations per year (Figure 13).

Length-of-Stay. Incremental factors associated with time to discharge are listed in Table 7. To illustrate the impact of these risk factors, predictions of median LOS were made using the multivariable model (Table 8). Of note, repair of late residual lesions was associated with reduced length of stay. We believe this finding is attributable to the considerable experience we have acquired in reoperations in patients with prior tetralogy of Fallot repair, most of which involve reconstruction of the right ventricular outflow tract with a pulmonary valve prosthesis. Also, higher surgical volume was found to reduce median LOS although the impact was of lower magnitude than for mortality.

Impact of Era. The model was also adjusted for era-effect and demonstrates improved outcomes by quantifying the decrease in hospital mortality and shortened length-of-stay across the period of the study (Tables 7 and 8). The inference is that the impact of elucidated risk factors in more recent years has resulted from increasing institutional and surgeon experience.

Discussion

Adult congenital cardiac surgery is a growing discipline with increasing clinical relevance. However, there remains little data regarding outcomes after surgery for congenital heart disease in adult patients. Mott and colleagues reported 112 ACHD operations performed between 1995 and 2000 at a pediatric hospital.[50] They reported an operative mortality of 6%, and no risk factors were characterized. Dore and colleagues detailed early outcomes after adult congenital heart surgery in 307 patients between 1991 and 1994.[49] Operative mortality was 7% with cyanosis, increasing number of prior cardiac operations, and increasing age as risk factors for death. In a series covering a much wider time period, we found that increasing age and number of prior cardiac operations were associated with a longer length-of-stay but not higher hospital mortality. The inference is that the impact of such factors in complex patients on hospital mortality can be mitigated by increasing experience; however, patients with more complexity will require longer convalescent times.

In conjunction with prior reports, we believe that our results from 1351 operations provide useful data in the surgical management of ACHD. Adult congenital heart surgery is a growing discipline with increasing clinical relevance; therefore, benchmark data for early outcomes after surgery are needed. The current estimated growth rate of the ACHD population is 5% per year with roughly 27,000 adults per year added to the ACHD population.[52] One should note that expansion of the ACHD population is a lagging indicator (by roughly 2 decades) of improvements made at the pediatric level of care. Current growth in ACHD prevalence is a manifestation of advances in care made during 1980s and early

1990s. As a result of continued refinements in neonatal and pediatric cardiac care, the ACHD population is likely to grow in number and evolve in complexity well beyond 2020. As the ACHD population burgeons, the number of adults requiring congenital heart surgery will continue to grow. It is probable that an increasing number of institutions will initiate adult congenital heart surgery programs. Benchmark data from dedicated ACHD centers such as Toronto are necessary to give general guidelines for approximate estimated early outcomes. Our data suggest that surgical repair of congenital heart disease in adults can be accomplished in a dedicated center having adequate experience and volume with similar risk-adjusted results to those observed in surgical repair of acquired heart disease.

The association between surgical volume and early outcomes is an important one. Our analysis found that increasing annual volume is associated with decreased hospital mortality rate and modest reduction in length-of-stay. We believe that adult congenital heart surgery is a highly specialized discipline requiring a multidisciplinary approach for optimal outcomes.[53] Birkmeyer and colleagues have reported extensively on the impact of institutional and surgeon volume on surgical outcomes in highly specialized, high-risk operations such as coronary bypass, aortic aneurysm repair, or pancreaticoduodenectomy.[54-56] They have repeatedly shown that higher volume is associated with improved measures of early outcome including hospital mortality and length-of-stay.

Another important aspect of our study is the analytic methodology utilized. Because hospital death and discharge are mutually exclusive time-related events, a

competing risks analysis was used to generate a single model quantifying the prevalence of each end-point and their respective risk factors over time after surgery. The traditional approach to these early outcomes would include separate analyses for mortality and length-of-stay. For hospital mortality, logistic regression or Cox proportional hazards analysis would be used for risk factor determination. For length-of-stay, patients dying prior to discharge would be removed from the dataset and a linear regression model utilized. Our analysis indicates that a single multivariable competing risks model can be solved for patient characteristics to generate predicted levels of risk imposed by single or combinations of risk factors.

Our multivariable competing risks analysis can be contrasted to two recent approaches to risk-adjustment in congenital heart surgery. In an approach dubbed Risk Adjusted Congenital Heart Surgery (RACHS), Jenkins and colleagues defined categories of congenital heart operations associated with increasing levels of mortality risk.[57] Their analysis compared outcomes among stratified groups of patients across institutions. Although an improvement over simple comparison of overall crude mortality rates, their analysis did not adjust for baseline characteristics of patients. Lacour-Gayet and associates devised a scoring system called the Aristotle score aimed at adjusting surgical mortality rates based on patient complexity.[58] In their approach, factors believed to increase mortality risk and the weight, or magnitude, of each factor was subjectively scored by a group of experts in congenital cardiac care. In contrast to our study, their system was not derived from data. Our study determined risk factors for each end-point, and the weight assigned to each variable was determined from the multivariable analysis of data.

We believe that adjusting outcomes for significant baseline factors is most accurate and objective when based on data from the underlying population.

It is important to note several limitations of our analysis. The study period spanned nearly three decades. Although all models were adjusted for era effect, there may exist a degree of colinearity between time and annual volume that cannot be fully accounted for using the current data and analysis. In addition, there is an inherent selection bias in this series that may affect generalization of our results. Compared with other ACHD reports, there are a larger proportion of patients with hypertrophic obstructive cardiomyopathy (HOCM). There are also smaller proportions of patients with congenital aortic valve disease and simple shunt lesions such as ASDs in our series because some of these patients are operated on by surgeons at our institution outside of the TCCCA or undergo catheter based therapy by interventional cardiologists.

In closing, many ACHD patients are at risk for poor outcomes due to natural progression of uncorrected defects and/or progression of hemodynamically important residual lesions. Once identified, surgical intervention in these patients can decrease the risk for, or delay, unfavorable outcomes. Further definition of the modified natural history of repaired congenital heart disease, operative indications, and long-term outcomes after operation in adulthood must occur if care for ACHD is to be optimized. Because this unique population is rapidly growing in the present era, ongoing requirements in health care delivery for ACHD such as resource allocation and development of specialized centers of care need to be met.

Conclusions

In conclusion, competing risks methodology is useful in analyzing time-related end-points when a cohort is at simultaneous risk of experiencing one of multiple independent outcome events. As with other high-risk conditions such as cancer, competing risks are often encountered in patients undergoing congenital heart surgery. When competing end-points are identified, actuarial methods of estimating the probability of outcome events are inaccurate as a result of censoring competing end-states. However, competing risks methodology is appropriate for estimating the cumulative incidence of simultaneously occurring end-states within a cohort. When competing risks is analyzed in the parametric hazard function domain, clinically relevant multivariable models which demonstrate the impact of important risk factors on outcomes can be generated. These models can be used for predicting the distribution of outcomes among individuals with specific baseline characteristics.

Future Directions. As the population living with congenital heart disease grows in number and complexity, there will be a need to follow outcomes beyond the time of reaching a first end-point. Therefore, an extension of competing risks methods known as Markov modeling may be useful in following large cohorts of patients experiencing multiple levels of competing risks. Although competing risks is limited to analyzing time to a first end-state, Markov modeling accounts for the subsequent competing risks encountered over time among those reaching a common first end-point. Practical application of Markov modeling for clinical outcomes is not yet widely available.

References

1. David HA, Moeschberger ML. The theory of competing risks. In New York: Macmillian; 1978:45-56.

2. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley; 1980.

3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-481.

4. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chronic Dis 1958; 8:699-712.

5. Cox DR. Regression models and life tables. J Royal Stat Soc B 1972; 34:187-220.

6. Cox DR, Oakes D. Analysis of Survival Data. London: Chapman & Hall; 1984.

7. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representatives of old estimators. Statist Med 1999; 18:695-706.

8. Grunkemeier GL, Jameison WRE, Miller DC. Actuarial versus actual risk of porcine structural valve deterioration. J Thorac Cardiovasc Surg 1994; 108:709-718.

9. Schwarzer G, Schumacker M, Maurer TB, Ochsner PE. Statistical analysis of failure times in total joint replacement. J Clin Epidemiol 2001; 54:997-1003.

10. Grunkemeier GL, Wu Y. Interpretation of nonfatal events after cardiac surgery: actual versus actuarial reporting. J Thorac Cardiovasc Surg 2001; 122:216-219.

11. Shen Y, Thall PF. Parametric likelihoods for multiple non-fatal competing risks and death. Statist Med 1998; 17:999-1015.

12. Lipkowitz E. The physicians' dilemna in the 18th-century French smallpox debate. J Am Med Assoc 2003; 290:2329-2331.

13. Bernoulli D. De la mortalite causee par la petite verole, et des avantages de l'inoculation pour la prevenir. In Memoires de l'Academie Royale des Sciences - Histoire Annee 1760. Paris, France: Imprimerie Royale; 1766:29.

14. Sweat SD, Bergstrahl EJ, Slezak J, Blute ML, Zincke H. Competing risk analysis after radical prostatectomy for clinically nonmetastatic prostate adenocarcinoma according to clinical Gleason score and patient age. J Urol 2002; 168:525-529.

15. Tai BC, Machin D, White I, Gebski V. Competing risks analysis of patients with osteosarcoma: a comparison of four different approaches. Statist Med 2001; 20:661-684.

16. Gaynor JJ, Feuer EJ, Tan CC, Wu DH, Little CR, Straus DJ, Clarkson BD, Brennan MF. On the use of cause-specific failure and conditional failure probabilities: examples from clinical oncology data. J Am Stat Assoc 1993; 88:400-409.

17. McGiffin DC, Galbraith AJ, O'Brien MF, McLachlan GJ, Naftel DC, Adams P, Reddy S, Early L. An analysis of valve re-replacement following aortic valve replacement with biologic devices. J Thorac Cardiovasc Surg 1997; 113:311-318.

18. Blackstone EH, Lytle BW. Competing risks afte coronary bypass surgery: the influence of death on reintervention. J Thorac Cardiovasc Surg 2000; 119:1221-1232.

19. Ashburn DA, McCrindle BW, Tchervenkov CI, Jacobs ML, Lofland GK, Bove EL, Spray TL, Williams WG, Blackstone EH, member of Congenital Heart Surgeons Society. Outcomes after the Norwood operation in neonates with critical aortic stenosis or aortic valve atresia. J Thorac Cardiovasc Surg 2003; 125:1070-1082.

20. Jacobs ML, Blackstone EH, Bailey LL. Intermediate survival in neonates with aortic atresia: a multi-institutional study. J Thorac Cardiovasc Surg 1998; 116:417-431.

21. McGiffin DC, Naftel DC, Kirklin JK, Morrow WF, Towbin J, Shaddy R, Alejos J, Rossi A, and Pediatric Heart Transplant Study Group. Predicting outcome after listing for heart transplantation in children: comparison of Kaplan-Meier and parametric competing risk analysis. J Heart Lung Transplant 1997; 16:713-722.

22. Ashburn DA, Blackstone EH, Wells WJ, Jonas RA, Pigula FA, Manning PB, Lofland GK, Williams WG, McCrindle BW, members of Congenital Heart Surgeons Society. Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. J Thorac Cardiovasc Surg 2004; 127:1000-1008.

23. Ashburn DA, Webb GD, VanArsdell GS, Heggie JE, Williams MG, Williams WG. Cardiac surgery in adults with congenital heart disease. Scientific Sessions of the American Heart Association 2002; Chicago, IL.:November 2002.

24. Zuberbuhler JR, Anderson RH. Morphological variations in pulmonary atresia with intact ventricular septum. Br Heart J 1979; 41:281-288.

25. Calder AL, Co EE, Sage MD. Coronary arterial abnormalities in pulmonary atresia with intact ventricular septum. Am J Cardiol 1987; 59:436-442.

26. Hanley FL, Sade RM, Blackstone EH, Kirklin JW, Freedom RM, Nanda NC, and Congenital Heart Surgeons Society. Outcomes in neonatal pulmonary atresia with intact ventricular septum. A multiinstitutional study. J Thorac Cardiovasc Surg 1993; 105:406-427.

27. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. J Am Stat Assoc 1986; 81:615-624.

28. Breiman L. Bagging predictors. Machine Learning 1996; 26:123-140.

29. Blackstone EH. Breaking down barriers: helpful breakthrough statistical methods you need to understand better. J Thorac Cardiovasc Surg 2001; 122:430-439.

30. Blackstone EH, Rice TW. Clinical-pathologic conference: choice and use of statistical methods for the clinical study "Superficial adenocarcinoma of the esophagus". J Thorac Cardiovasc Surg 2001; 122:1063-1076.

31. Joshi SV, Brawn WJ, Mee RB. Pulmonary atresia with intact ventricular septum. J Thorac Cardiovasc Surg 1986; 91:192-199.

32. Foker JE, Braunlin EA, St.Cyar JAS, et al. Management of pulmonary atresia with intact ventricular septum. J Thorac Cardiovasc Surg 1986; 92:706-715.

33. Hawkins JA, Thorne JK, Boucek MM, et al. Early and late results in pulmonary atresia and intact ventricular septum. J Thorac Cardiovasc Surg 1990; 100:492-497.

34. Mainwaring Rd, Lamberti JJ. Pulmonary atresia with intact ventricular septum. Surgical approach based on ventricular size and coronary anatomy. J Thorac Cardiovasc Surg 1993; 106:733-738.

35. Najm HK, Williams WG, Coles JG, Rebeyka IM, Freedom RM. Pulmonary atresia with intact ventricular septum: results of the Fontan procedure. Ann Thorac Surg 1997; 63:669-675.

36. Rychik J, Levy H, Gaynor JW, et al. Outcome after operations for pulmonary atresia with intact ventricular septum. J Thorac Cardiovasc Surg 1998; 116:924-931.

37. Jahangiri M, Zurakowski D, Bichell D, Mayer J, del Nido PJ, Jonas RA. Improved results with selective management in pulmonary atresia with intact ventricular septum. J Thorac Cardiovasc Surg 1999; 118:1046-1052.

38. Bull C, Kostelka M, Sorensen K, de Leval M. Outcome measures for the neonatal management of pulmonary atresia with intact ventricular septum. J Thorac Cardiovasc Surg 1994; 107:359-366.

39. Joelsson E, Hanseus SJ, Jonzon BH, Jogi A, Lundell B. The outcome of children born with pulmonary atresia and intact ventricular septum in Sweden from 1980 to 1999. Scand Cardiovasc J 2001; 35:192-198.

40. Mair DD, Julsrud PR, Puga FJ, Danielson GK. The Fontan procedure for pulmonary atresia with intact ventricular septum: operative and late results. J Am Coll Cardiol 1997; 29:1359-1364.

41. Diez Roux AV. Multilevel analysis in public health research. Annu Rev Public Health 2000; 21:171-192.

42. Duncan C, Jones K, Moon G. Context, composition, and heterogeneity: using multilevel models in health research. Soc Sci Med 1998; 46:97-117.

43. DiPrete TA, Forristal JD. Multilevel models: methods and substance. Annu Rev Sociol 1994; 20:331-357.

44. Choi YH, Seo JW, Choi JY, Yun YS, Kim SH, Lee HJ. Morphology of tricuspid valve in pulmonary atresia with intact ventricular septum. Pediatr Cardiol 1998; 19:381-390.

45. Moodie DS. Diagnosis and management of congenital heart disease in the adult. Cardiol Rev 2001; 9:276-281.

46. Webb GD, Williams RG. 32nd Bethesda Conference. Care of the adult with congenital heart disease: Introduction. J Am Coll Cardiol 2001; 37:1166-1169.

47. Garson A, Allen HD, Gersony WM, Gilette PC, Hohn AR, Pinsky WW, Mikhail O. The cost of congenital heart disease in children and adults: a model for multicenter assessment of price and practice variation. Arch Ped Adol Med 1994; 148:1039-1045.

48. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task Force 1: The changing profile of congenital heart disease in adult life. J Am Coll Cardiol 2001; 37:1170-1175.

49. Dore A, Glancy DL, Stone S, Menashe VD, Somerville J. Cardiac surgery for grown-up congenital heart patients: survey of 307 consecutive operations from 1991-1994. Am J Cardiol 1997; 80:906-913.

50. Mott AR, Fraser CD, McKenzie ED, Bezold LI, Andropolous DB, Reul GJ, Miranda CH, Bedford SL, Feltes TF. Perioperative care of the adult with congenital heart disease in a free-standing tertiary pediatric facility. Pediatr Cardiol 2002; 23:624-630.

51. M.Gail Williams. Cardiovascular Surgery Database. Hospital for Sick Chidlren gwillms@istar ca 2004.

52. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. N Engl J Med 2000; 342:256-263.

53. Landzberg MJ, Murphy DJ, Davidson WR, Jarcho JA, Krumholz HM, Mayer JE, Mee RB, Sahn DJ, Van Hare GF, Webb GD, Williams RG. Task Force 4: Organization of delivery systems for adults with congenital heart disease. J Am Coll Cardiol 2001; 37:1187-1193.

54. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. N Engl J Med 2002; 346:1128-1137.

55. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003; 349:2117-2127.

56. Goodney PP, Stukel TA, Lucas FL, Finlayson EV, Birkmeyer JD. Hospital volume, length of stay, and readmission rates in high-risk surgery. Ann Surg 2003; 238:161-167.

57. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg 2002; 123:110-118.

58. Lacour-Gayet F, Clarke D, Jacobs J, Comas J, Aristotle Committee. The Aristotle score: a complexity-adjusted method to evaluate surgical results. Eur J Cardiothorac Surg 2004; 25:911-924.

Table 1. Morphologic characteristics in 334 neonates for whom an RV size score was assigned.

RV Size	n	% of 334	Tricuspid Valve Z score			RV-CA Fistula(e)	RV-dependent Coronary circ
			Median	*Range**	*25th Percentile*		
-5 (severe hypoplasia)	62	19%	-2.3	-5.4 to 4.8	-3.3	35 (56%)	5 (8%)
-4	100	30%	-2.3	-5.3 to 0.6	-3.1	55 (55%)	10 (10%)
-3	79	24%	-1.1	-5.2 to 5.0	-1.9	28 (35%)	4 (14%)
-2	40	12%	-0.3	-3.1 to 3.2	-1.0	5 (13%)	0
-1	22	7%	0.4	-2.9 to 2.9	-1.2	3 (14%)	0
0 (normal for age)	16	5%	1.5	-1.6 to 5.0	0.6	0	0
≥1 (enlarged)	15	4%	2.4	-1.0 to 6.0	0.4	0	0

*High upper limits of TV Z score in neonates with a diminutive RV are attributable to associated Ebstein malformation.

Key: *RV*, right ventricle; *CA*, coronary artery; *circ*, circulation.

Table 2. Incremental factors associated with reaching each of 5 defined end-states in 408 neonates with pulmonary atresia with intact ventricular septum.

Factor	Parameter Estimate ± SE	*P*	Reliability(%)
2-ventricle repair			
Early phase			
RV size* closer to normal	0.32 ± 0.08	<.001	99
TV Z score closer to normal (per 1 std dev)	0.27 ± 0.12	.026	54
Higher LV pulse pressure (per 5 mmHg)	0.26 ± 0.11	.020	55
Institution E	1.28 ± 0.64	.044	56
Late phase			
Lesser degree of RV-CA fistula(e)†	0.62 ± 0.18	<.001	95
TV Z score‡ closer to normal (per 1 std dev)	2.79 ± 0.94	.003	75
RV size* closer to normal	0.25 ± 0.10	.014	72
Higher birth weight (per 1 kg)	0.51 ± 0.25	.042	56
Institution M	1.74 ± 0.63	.007	78
Institution B	0.91 ± 0.44	.040	54

Institution L	1.79 ± 0.54	<.001	70
Institution E	0.84 ± 0.41	.042	52

*Grade of RV size entered after square transformation.

†Graded spectrum ranging from no fistulae to fistulae with severe RV-dependent coronary circulation.

‡Entered after exponential transformation.

1.5-ventricle repair

Early phase

Higher RV systolic pressure (per 10 mmHg)	0.31 ± 0.11	.007	60
TV Z score closer to normal (per 1 std dev)	0.32 ± 0.12	.010	73
Institution G	2.62 ± 0.61	<.001	86
Institution A	2.10 ± 0.72	.004	84

1-ventricle repair

Early phase

Lower TV Z score*	4.00 ± 0.92	<.001	91
Institution T	1.94 ± 0.36	<.001	97
Institution E	2.38 ± 0.51	<.001	90

Institution M	1.47 ± 0.53	.006	83

*Entered after exponential transformation.

Heart transplantation

Early phase

Later date of admission (per 1 year)	0.42 ± 0.13	.002	93
Institution R	2.61 ± 0.80	.002	72

Death prior to attaining definitive repair

Early phase

Lower birth weight*	4.32 ± 1.18	<.001	84
Severe TV incompetence	1.47 ± 0.28	<.001	90
Lower (and higher) TV Z score	0.28 ± 0.08	<.001	75
Enlarged RV	1.31 ± 0.32	<.001	75
Institution Y	1.26 ± 0.33	<.001	91
Institution D	1.23 ± 0.46	.008	66
Institution H	1.44 ± 0.40	<.001	86
Institution S	0.90 ± 0.29	.003	83

Late phase			
Lower RV:LV systolic pressure ratio†	0.87 ± 0.35	.014	81
Prior balloon atrial septostomy	1.41 ± 0.52	.007	50
Earlier date of admission‡ (per 1 year)	1.00 ± 0.27	.001	63
Institution C	2.06 ± 0.65	.002	71
Institution P	2.01 ± 0.78	.010	58

*Entered after inverse transformation.

†Entered after square transformation.

‡Measured as time since Oct 1, 1987. Entered after logarithmic transformation.

Key: *TV*, tricuspid valve; *RV*, right ventricle; *SE*, standard error; *LV*, left ventricle; *CA*, coronary artery.

Table 3. 5-year prevalence of endstates for each "risk-factor" institution. Percent value represents the predicted prevalence of each end-state averaged across the spectrum of Z scores from –5 to 0. RV size was adjusted commensurate with TV Z score with all other predictors set at median value and held constant for all institutions.

			Mean ± SD Predicted 5-Year Prevalence				
Institution	**n**	**High-Prevalence states**	*2-V Repair*	*Fontan*	*1.5-V Repair*	*Death Before Repair*	*Alive without Repair*
Inst E	20	2-V, Fontan	36 ± 28%	48 ± 26%	3 ± 1%	13 ± 7%	-
Inst M	9	2-V, Fontan	56 ± 29%	39 ± 31%	-	3 ± 1%	1 ± 1%
Inst T	19	Fontan	8 ± 8%	73 ± 10%	1 ± 1%	16 ± 4%	2 ± 4%
Inst L	14	2-V	47 ± 27%	23 ± 17%	-	25 ± 11%	2 ± 2%
Inst B	13	2-V	35 ± 23%	17 ± 9%	4 ± 1%	37 ± 10%	7 ± 5%
Inst Y	27	Death	17 ± 15%	9 ± 2%	-	59 ± 13%	15 ± 3%
Inst H	17	Death	25 ± 24%	14 ± 2%	-	54 ± 21%	-
Inst D	11	Death	28 ± 25%	18 ± 9%	-	41 ± 17%	10 ± 4%
Inst S	41	Death	18 ± 17%	19 ± 6%	1 ± 0%	47 ± 12%	13 ± 2%
Inst P	10	Death	19 ± 15%	-	-	24 ± 6%	57 ± 10%

Key: *2-V*, completed 2-ventricle repair; *SD*, standard deviation; *1.5-V*, 1.5-ventricle repair.

Table 4. Patient and procedural characteristics of 1351 adults undergoing operation for congenital heart disease.

Variable	Value or Frequency
Mean ± SD age in years	38 ± 14
Mean ± SD weight in kilograms	69 ± 16
Diagnostic class	
Primary obstructive or valvular lesions	438 (32.4%)
Repair of late residual lesions	337 (24.9%)
Primary repair of L-R shunt lesions	304 (22.5%)
Late definitive repair of non-simple lesions	141 (10.4%)
Palliative surgery	109 (8.1%)
Miscellaneous	22 (1.6%)
Presence of systemic right ventricle	71 (5.3%)
Operative sequence	
Primary operation	857 (63.4%)
First reoperation	451 (33.4%)
Second or greater reoperation	43 (3.2%)
Cardiopulmonary bypass used	1270 (94%)
Number of procedures performed at operation	
1	666 (49.3%)
2	335 (24.8%)
3	225 (16.7%)
4	100 (7.4%)
5	18 (1.3%)
≥6	7 (0.5%)
mean ± SD	1.9 ± 1.1
Secondary valvular procedure	191 (14.1%)
Valve replacement other than pulmonary valve	122 (9.0%)
Conduit surgery	229 (17.0%)
Initial insertion	160 (11.9%)
Replacement	69 (5.1%)
Concomitant coronary artery bypass grafting	51 (3.8%)

Concomitant ascending aortic surgery	48 (3.6%)
Repair	25 (1.9%)
Replacement	23 (1.7%)
Arrhythmia procedure	132 (9.8%)
Pacemaker insertion or replacement	51 (3.8%)
Reoperation during same admission	72 (5.3%)

Key: *SD*, standard deviation; *L*-*R*, left to right.

Table 5. Incremental risk factors for surgical mortality after operation for congenital heart disease in adult patients.

Variable	Parameter estimate ± SE*	P
Palliative surgery	1.67 ± 0.34	<0.001
Lower annual volume (per 10 cases/year)†	1.13 ± 0.43	0.009
Late definitive repair	1.19 ± 0.36	0.001
Valve replacement other than PV	0.97 ± 0.38	0.010
Reoperation during same admission	0.68 ± 0.32	0.033
Primary repair of left-to-right shunt lesion‡	-1.59 ± 0.84	0.058

*****For a single constant hazard phase. Model adjusted for variations in surgical mortality across the time span of the study by entering a time variable (in years since September 19, 1973) for all operations.

†Entered after logarithmic transformation

‡Associated with reduced mortality risk as indicated by negative parameter estimate

Key: *SE*, standard error; *PV*, pulmonary valve.

Table 6. Risk-adjusted impact of various risk factors on surgical mortality in adults with congenital heart disease. Values indicate predicted mortality (with 90% confidence interval) based on the presence or absence of the risk factor obtained by solution of the multivariable model with all other predictor variables set to their median value. Predictions were generated for three years (1980, 1990, and 2001) to show changes in outcome over the study period.

	% Surgical Mortality (90% C. I.)		
Variable	***1980***	***1990***	***2001***
Primary repair of L-R shunt			
Yes	0.7 (0.2-3.2)	0.5 (0.1-1.9)	0.4 (0.1-1.4)
No	4.5 (2.6-7.8)	2.7 (1.9-4.1)	1.9 (0.9-3.9)
Late definitive repair			
Yes	8.2 (3.5-18.2)	5.2 (2.5-10.5)	3.8 (1.4-9.8)
No	2.7 (1.4-5.1)	1.6 (1.0-2.6)	1.2 (0.6-2.3)
Palliative surgery			
Yes	17.0 (6.5-37.7)	10.5 (4.9-21.1)	7.0 (2.5-18.2)
No	2.6 (1.4-4.8)	1.6 (1.0-2.5)	1.1 (0.6-2.3)
Reoperation during same admission			
Yes	10.2 (4.4-21.9)	5.9 (3.0-11.4)	3.5 (1.5-8.3)
No	2.8 (1.5-5.3)	1.7 (1.1-2.7)	1.3 (0.6-2.5)
Valve replacement other than PV			
Yes	11.3 (4.8-24.6)	6.6 (3.2-13.1)	4.1 (1.6-10.0)
No	2.7 (1.4-5.0)	1.6 (1.0-2.6)	1.2 (0.6-2.4)

Key: *CI,* confidence interval; *L-R,* left to right; *PV,* pulmonary valve.

Table 7. Incremental factors associated with time to hospital discharge for adults undergoing surgery for congenital heart disease.

Variable	Parameter estimate ± SE*	P
Early phase		
Older age (per 10 yrs)	0.10 ± 0.02	<0.001
Increasing number of concomitant procedures (per 1 procedure)	0.16 ± 0.03	<0.001
Increasing sequence of operations (per 1 reoperation)†	0.09 ± 0.02	<0.001
Reoperation during same admission	0.64 ± 0.14	<0.001
Valve replacement other than PV	0.54 ± 0.10	<0.001
Palliative surgery	0.37 ± 0.13	0.004
Placement or replacement of pacemaker	0.33 ± 0.15	0.026
Late repair of residual lesions‡	-0.30 ± 0.10	0.003
Primary repair of left-to-right shunt lesions‡	-0.27 ± 0.08	<0.001
Constant phase		
Older age (per 10 yrs)	0.46 ± 0.21	0.027
Increasing number of concomitant procedures (per procedure)	2.52 ± 1.03	0.015
Increasing annual volume (per 10 cases/yr)‡	-1.00 ± 0.20	<0.001
Primary repair of L-R shunt lesions‡	-1.08 ± 0.53	0.026

*For an early and constant hazard phase. Adjusted for variations in LOS across the time span of the study by entering time (in years) since September 19, 1973 for all operations.

†Entered after square transformation.

‡Associated with reduced LOS as indicated by negative parameter estimate.

Key: *SE*, standard error; *PV*, pulmonary valve; *L*-*R*, left to right.

Table 8. Risk-adjusted impact of risk factors on median LOS after surgery in adults with congenital heart disease. Values indicate the predicted median LOS (with 90% confidence interval) based on the presence or absence of the risk factor obtained by solution of the multivariable model with all other variables set to their median value. Predictions were generated for three years (1980, 1990, and 2001) to show changes in outcome occurring across the study period.

	Median LOS in days (90% C. I.)		
Variable	***1980***	***1990***	***2001***
Age at operation			
25	10.8 (10.3-11.2)	9.0 (8.8-9.3)	7.7 (7.5-7.9)
40	11.4 (11.0-11.9)	9.2 (9.4-9.0)	8.1 (7.8-8.3)
55	12.1 (11.5-12.8)	10.0 (9.7-10.3)	8.4 (8.2-8.7)
70	12.7 (11.8-13.8)	10.3 (9.8-10.9)	8.9 (8.5-9.3)
Primary repair of L-R shunt			
Yes	10.0 (9.5-10.6)	8.8 (8.5-9.0)	7.5 (7.3-7.8)
No	11.6 (11.1-12.1)	9.6 (9.4-9.8)	8.2 (8.0-8.4)
Palliative operation			
Yes	12.5 (11.1-14.2)	10.5 (9.7-11.6)	8.9 (8.2-9.6)
No	11.2 (10.9-11.7)	9.3 (9.2-9.5)	8.0 (7.8-8.2)
Repair of late residual lesions			
Yes	10.4 (9.7-11.1)	8.7 (8.3-9.1)	7.5 (7.2-7.7)
No	11.7 (11.2-12.1)	9.7 (9.5-9.9)	8.2 (8.0-8.4)
Number of concomitant procedures			
0	9.5 (8.5-10.8)	8.2 (7.5-8.9)	7.2 (6.7-7.6)
1	10.7 (10.3-11.1)	9.0 (8.8-9.2)	7.7 (7.5-7.9)
2	11.4 (11.2-11.6)	9.5 (9.4-9.6)	8.1 (8.0-8.3)
3	12.2 (11.9-12.6)	10.1 (9.9-10.2)	8.5 (8.3-8.6)
4	13.0 (12.4-13.6)	10.8 (10.4-11.1)	9.0 (8.8-9.2)
Number of prior cardiac operations			
0	10.3 (9.9-10.7)	9.1 (8.9-9.3)	7.8 (7.6-8.0)
1	12.2 (11.6-12.9)	10.1 (9.8-10.5)	8.5 (8.2-8.8)
2	14.4 (13.1)	12.1 (11.3-13.2)	10.1 (9.5-10.8)
3	17.5 (13.9-23.6)	15.3 (12.6-19.3)	13.0(11.0-15.9)

Reoperation during same admission				
	Yes	13.9 (12.3-16.2)	11.8 (10.6-13.2)	9.8 (9.0-10.7)
	No	11.2 (10.8-11.6)	9.3 (9.1-9.5)	7.9 (7.8-8.1)
Valve replacement other than PV				
	Yes	13.4 (12.2-14.8)	11.3 (10.5-12.2)	9.4 (8.8-10.1)
	No	11.1 (10.8-11.6)	9.3 (9.1-9.4)	7.9 (7.7-8.1)
Need for pacemaker insertion				
	Yes	12.8 (11.3-14.8)	10.7 (9.7-11.9)	8.9 (8.2-9.7)
	No	11.3 (10.9-11.7)	9.4 (9.2-9.5)	8.0 (7.8-8.2)

Key: *LOS,* length of stay; *CI,* confidence interval; *L-R,* left to right; *PV,* pulmonary valve.

Figure 1. Schematic of a Single Time-Related Outcome Event. The figure depicts a model of death occurring after surgical repair among a cohort of children with a complex congenital heart defect. After a common starting point (surgical repair, time=0), children remain in the default state (alive) until experiencing the single defined end-state (death). Actuarial analysis estimates the prevalence of a single end-state across time by mathematically "censoring" children remaining in the default state at the time of their last follow-up.

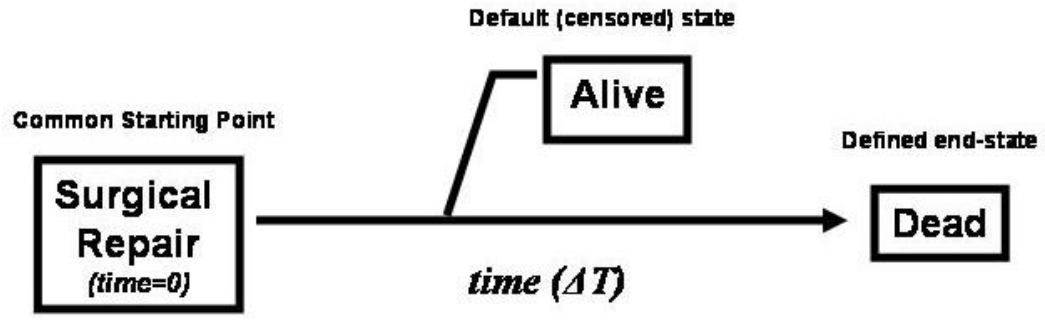


Figure 2. Schematic of Multiple Competing Time-Related Outcome Events. The figure depicts potential models of reoperation occurring after surgical repair among a cohort of children with a complex congenital heart defect. **A.** In addition to the censored state (alive without reoperation) and the end-state of interest (reoperation), there is an "other" state composed of patients who die after repair but prior to reoperation. Because actuarial techniques only account for one censored state and one end-state, an attempt to analyze this situation using actuarial methods requires that the "other" state be grouped into one of the other states. **B.** Patients who die prior to reoperation may be grouped into the default state and censored at the time of their death, artificially increasing the prevalence of reoperation because the at-risk denominator is decreased by censoring. **C.** Alternatively, patients who die prior to reoperation may be grouped into the defined end-state with reoperated patients. Combining end-states leads to oversimplified, less precise results that are difficult to interpret. Creating a combined end-state also interferes with accurate risk factor selection as each component event may have its own unique risk factors. **D.** Reoperation and death occurring prior to a reoperation are different outcome events potentially driven by different factors. They should be considered as two mutually exclusive end-states in a competing risks manner. After the common starting point (surgical repair, time=0), patients remain in the default state (alive after surgical repair) until migrating into one of the two defined end-states – reoperation or death occurring before reoperation. Competing risks allows censoring of the default state while simultaneously accounting for *each* of multiple outcome events.

Figure 2

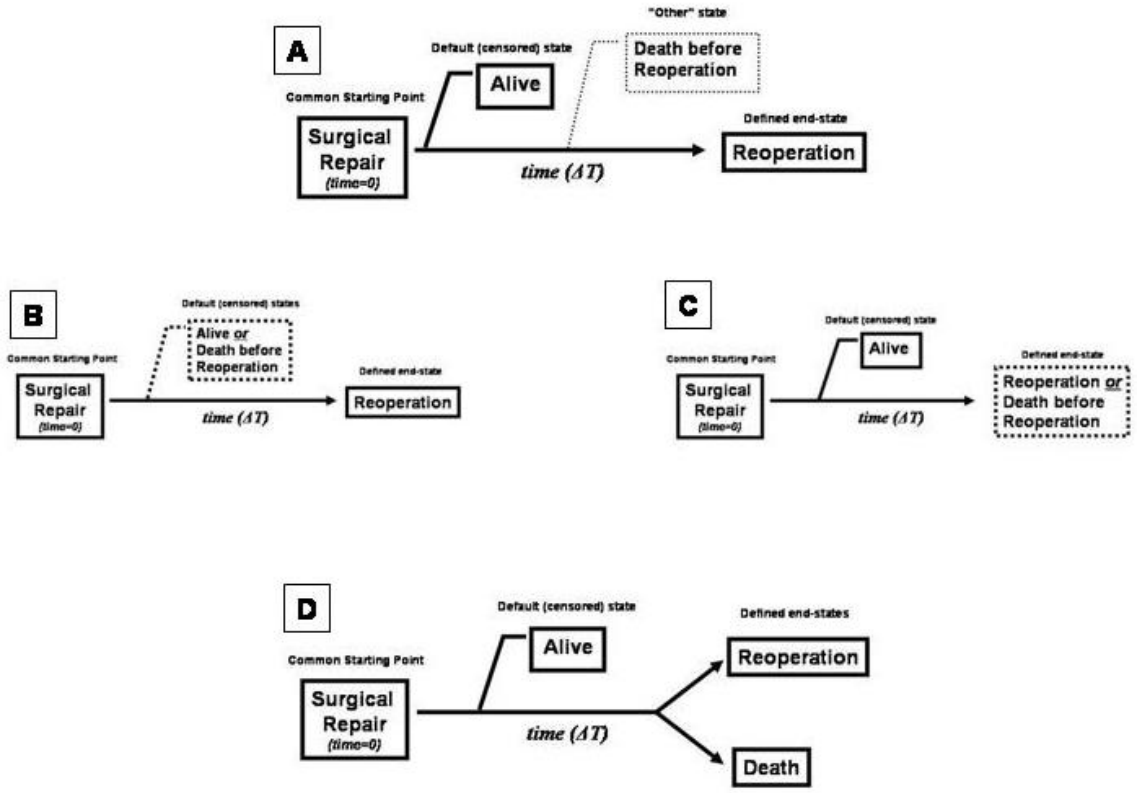

A
"Other" state
Default (censored) state
Death before Reoperation
Alive
Common Starting Point
Surgical Repair (time=0)
Defined end-state
Reoperation
time (ΔT)
B
Default (censored) states
Alive or Death before Reoperation
Common Starting Point
Surgical Repair (time=0)
Defined end-state
Reoperation
time (ΔT)
C
Default (censored) state
Alive
Common Starting Point
Surgical Repair (time=0)
Defined end-state
Reoperation or Death before Reoperation
time (ΔT)
D
Default (censored) state
Alive
Defined end-states
Reoperation
Common Starting Point
Surgical Repair (time=0)
time (ΔT)
Death

Figure 3. Schematic of Enzyme Kinetics. A. In an enzymatic reaction, an enzyme converts substrate into a given product. **B.** The enzymatic reaction proceeds from time=0 at a defined rate. The reaction rate may vary over time as defined by the rate law – a mathematical equation quantifying the speed at which substrate is converted into products. The reaction rate increases or decreases in response to modulating factors such as heat, light, solution pH, or concentration. **C.** If three non-interacting enzymes are added to the solution, each enzyme *competes* with the other enzymes to convert substrate into products. Although occurring in the same solution, each of the three independent enzymatic reactions has a unique rate law and unique modulating factors. Depending on the modulating factors present, changes in the reaction rate of one enzyme impacts availability of substrate and reaction rate of the other enzymes. The proportions of Products A, B, and C over time are dependent upon the combination of various modulating factors present.

Figure 3A

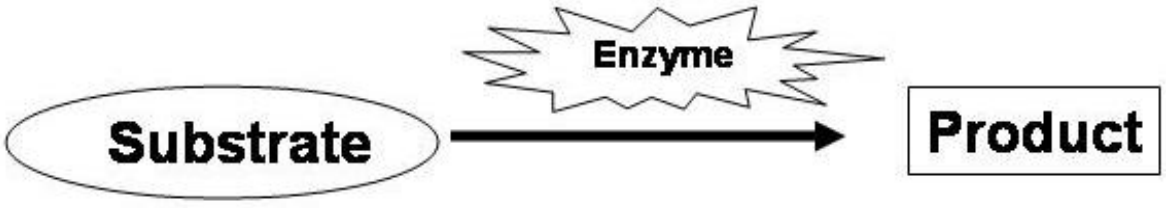


Figure 3B

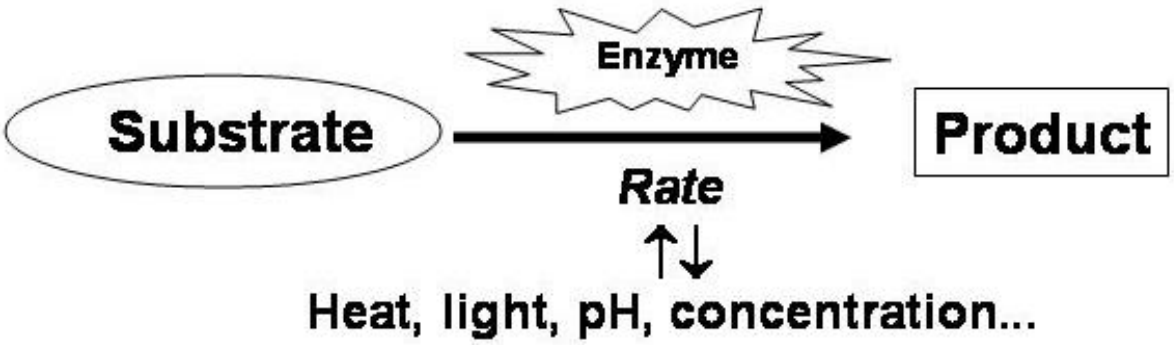


Figure 3C

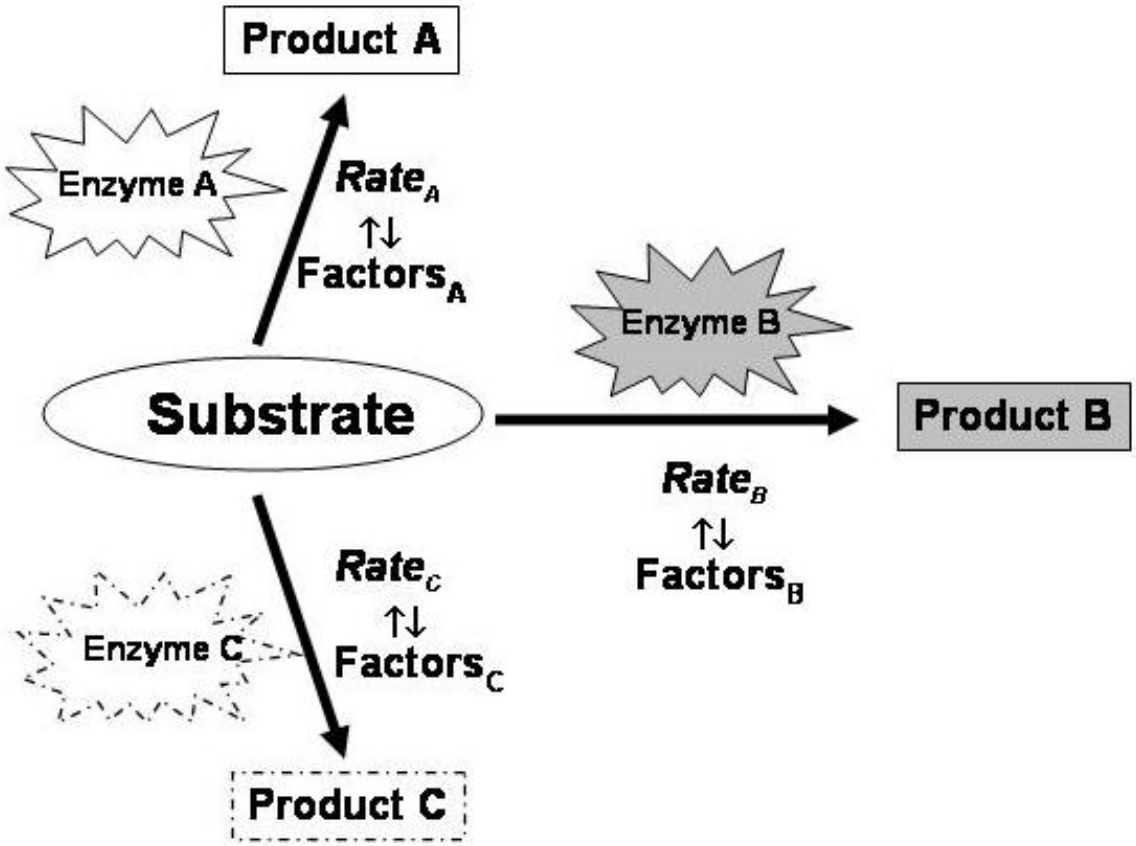


Figure 4. Schematic of Competing End-States in Neonates with Pulmonary Atresia with Intact Ventricular Septum (PAIVS). Analogous to enzyme kinetics (see Figure 3), neonates born with PAIVS (substrate) may migrate into one of several competing end-states (products) after initial hospital admission. At time=0, all neonates are alive at the time of initial hospital admission. Thereafter, they may migrate over time into one defined end-state: 2-ventricle repair, 1.5-ventricle repair, 1-ventricle repair, heart transplant, or death before reaching a definitive repair. The instantaneous rate, or *hazard*, of migration into each end-state may vary over time and may be quantified by a mathematical equation known as the *hazard function*. The hazard function for migration into each end-state is independent of the other end-states and increases or decreases in response to a unique set of modulating factors. The proportions of neonates in each definitive end-state across time are upon the combination of various modulating factors present.

Figure 4

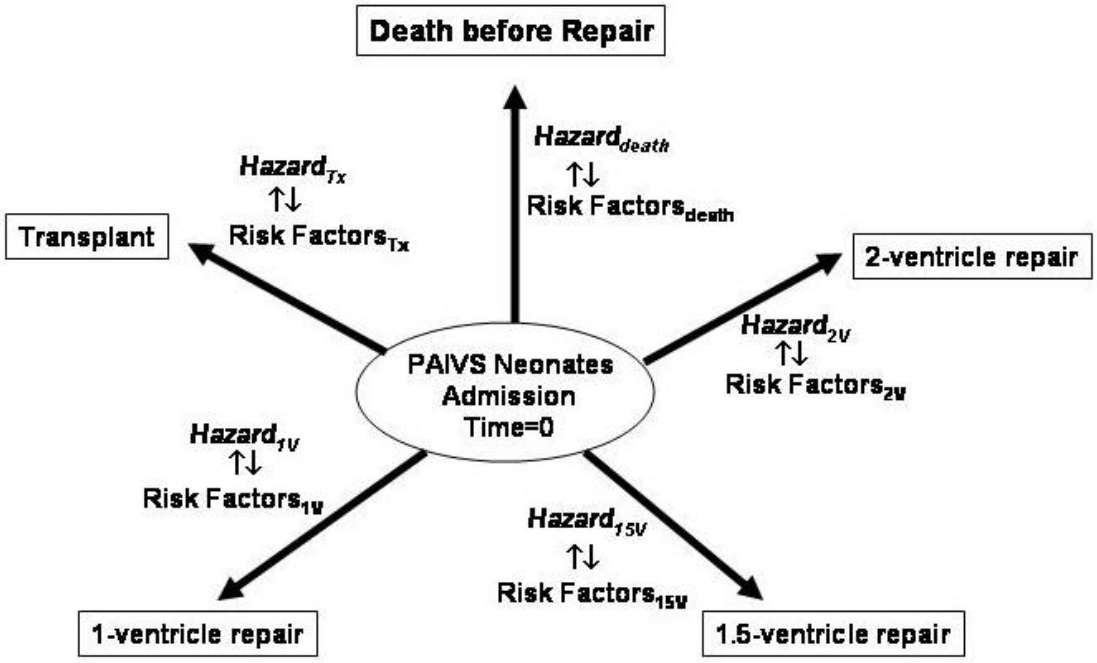

Death before Repair
Hazard death
↑↓
Risk Factors death
Hazard Tx
↑↓
Risk Factors Tx
Transplant
2-ventricle repair
Hazard 2V
↑↓
Risk Factors 2V
PAIVS Neonates
Admission
Time=0
Hazard 1V
↑↓
Risk Factors 1V
Hazard 1.5V
↑↓
Risk Factors 1.5V
1-ventricle repair
1.5-ventricle repair

Figure 5. Overestimation of Prevalence of Competing End-States by Actuarial Analysis in Neonates with PAIVS. The cumulative incidence of each end-state is individually calculated using actuarial techniques. For each curve, children are censored at the time of reaching other end-states. The resulting curves are overlayed on the graph to illustrate the impact of censoring competing end-states on prevalence estimates. At 15 years after initial admission, the sum of prevalences of end-state is 230% (2V repair – 82%; Death before definitive repair – 61%; Fontan repair – 60%; 1.5V repair – 23%; and heart transplant – 4%). Because each child may attain only one end-state, the sum of "actual" cumulative incidences of end-states should not exceed 100%. Therefore, actuarial techniques do not accurately quantify the actual prevalence of multiple competing outcomes.

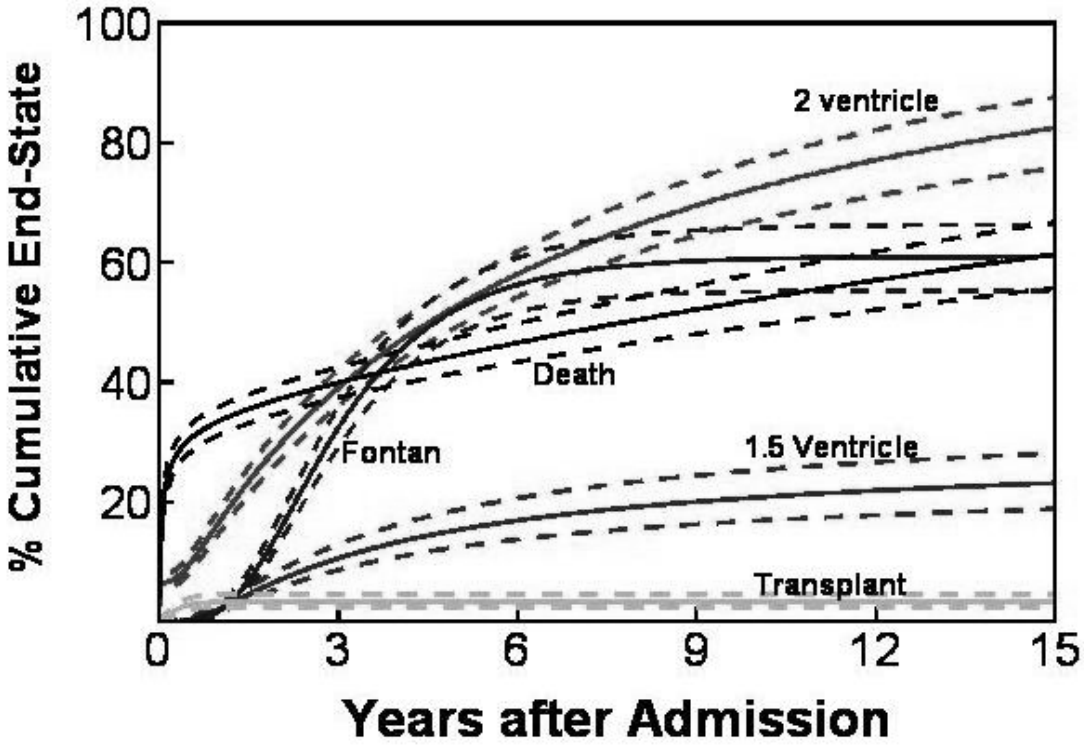


Figure 6. Non-Risk-Adjusted Competing Risks Depiction of End-States in 408 Neonates with PAIVS. **A.** Proportion of children reaching each of five end-states over time after initial hospital admission. All patients begin in the default state - alive at the time of initial admission (time = 0), and, thereafter, migrate to an end-state at a time-dependent rate defined by competing hazard functions. At any time point, the sum of proportion of children in each state is 100%. For example, at 5 years the estimated prevalences of end-states are 2-ventricle repair, 28%; Fontan operation, 19%; 1.5-ventricle repair, 5%; cardiac transplantation, 2%; death before reaching a repair state, 36%; and alive without end-state, 11%. *Solid lines* represent parametric estimates (surrounded by their 70% confidence interval in *dashed lines*) of the accumulative effect of each hazard function applicable to patients remaining alive without a definitive repair at each point in time. **B.** Parametric hazard functions (*solid curves*) with 70% confidence intervals (*dashed curves*) represent the instantaneous risk of attaining each of 5 end-states at any given time up to 15 years after initial admission. For clarity, the inset expands the 2-ventricle hazard function.

Figure 6A

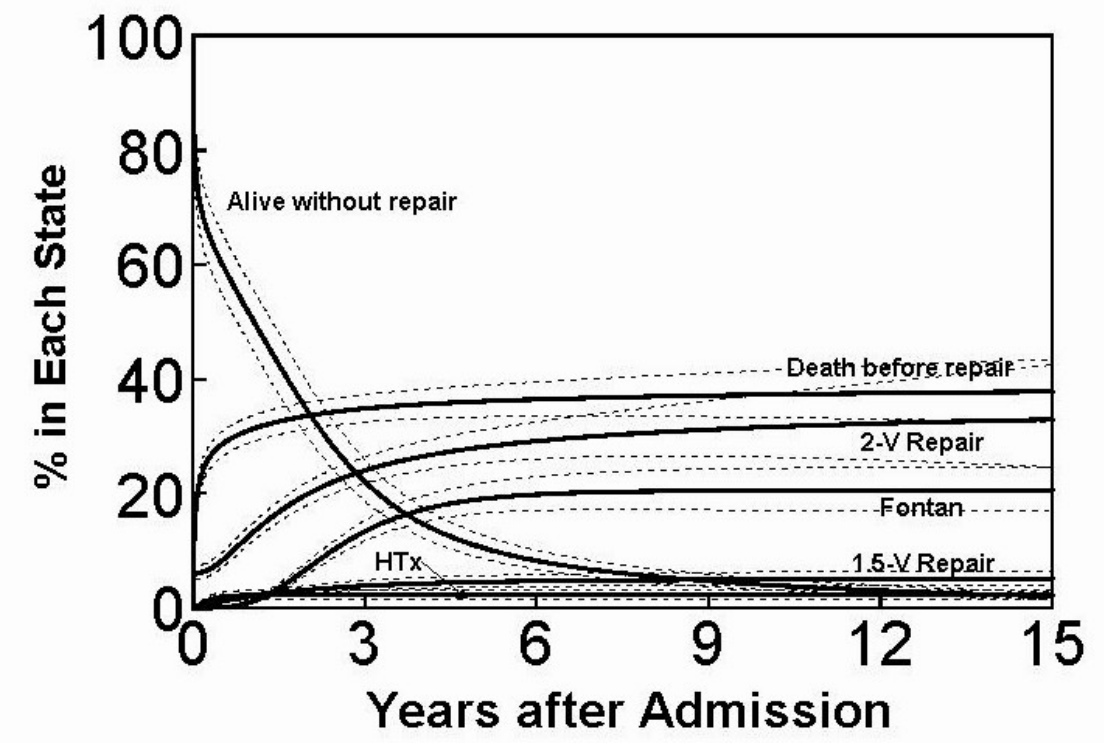


Figure 6B

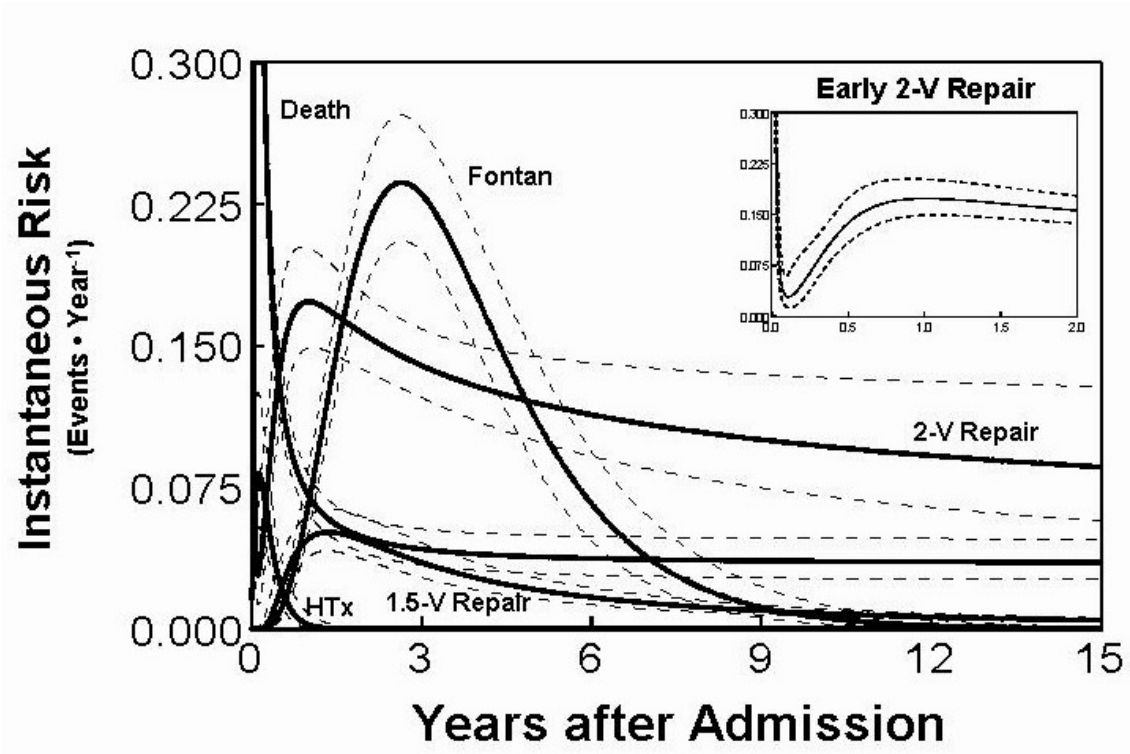


Figure 7. Risk-Adjusted Competing Risks Nomograms for Individual Institutions Based on Morphologic Spectrum of PAIVS. The predicted 5-year prevalences of end-states (vertical axis) are plotted against tricuspid valve Z-score with commensurate adjustment of RV size. To isolate the impact of morphology and institution, all other predictors are set to their median value. **A.** Institution L favored 2-ventricle repair. For favorable morphology (ie larger right heart), a high proportion of 2-ventricle repairs is achieved. For unfavorable morphology, the rate of Fontan operation is comparably low, mortality is high, and a small proportion of patients remain alive without definitive repair. **B.** Institution T favored Fontan operation for most morphology. In exchange for a small proportion of neonates with favorable morphology receiving a 2-ventricle repair, the institution achieved a low rate of mortality, particularly for severe morphology. **C.** Institution Y was a high risk institution for death. The large proportion remaining alive at 5 years without definitive repair indicates that it favored neither a 2-ventricle nor Fontan pathway. **D.** Institution E favored both 2-ventricle and Fontan pathways. For severe morphology, a large proportion of neonates achieved Fontan operation. For favorable morphology, a large proportion achieve 2-ventricle repair. Across the morphologic spectrum, the mortality rate is comparably low, and essentially all children had a definitive repair by 4 years.

Figure 7A

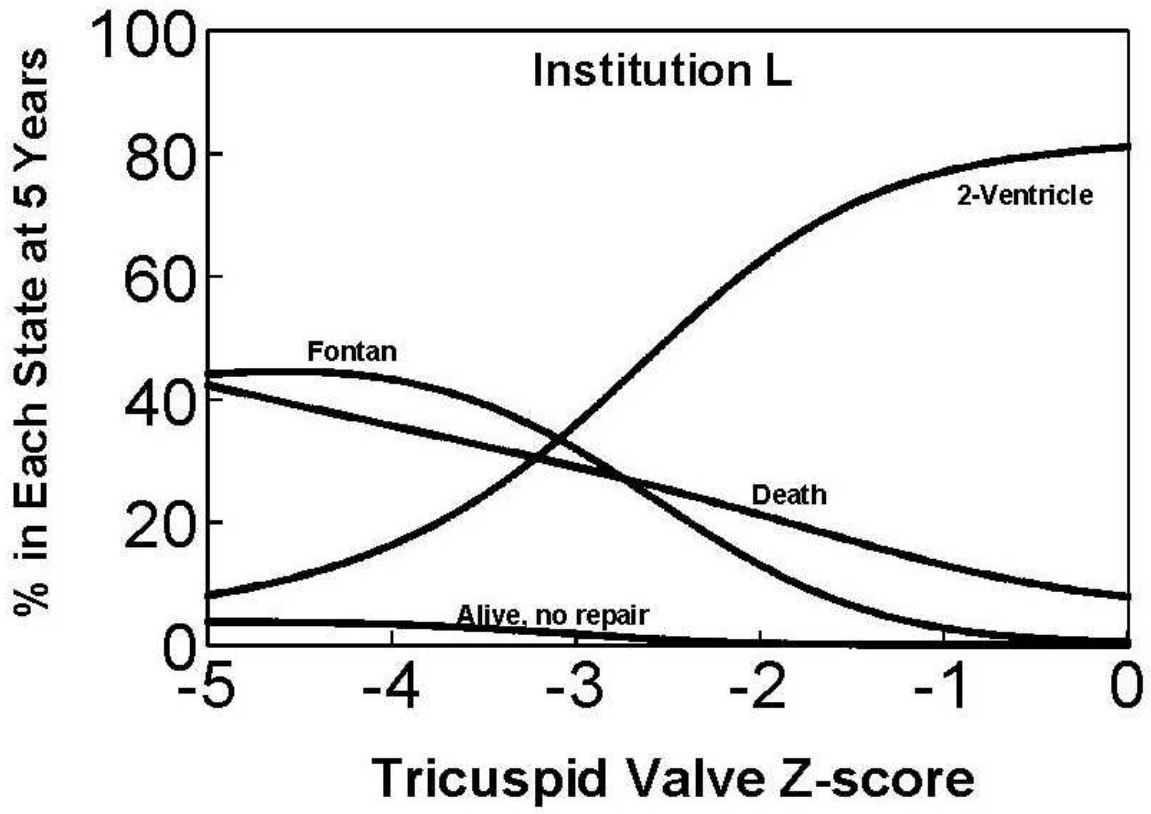

Institution L
% in Each State at 5 Years
100
80
60
40
20
0
-5
-4
-3
-2
-1
0
Tricuspid Valve Z-score
2-Ventricle
Fontan
Death
Alive, no repair

Figure7B

.

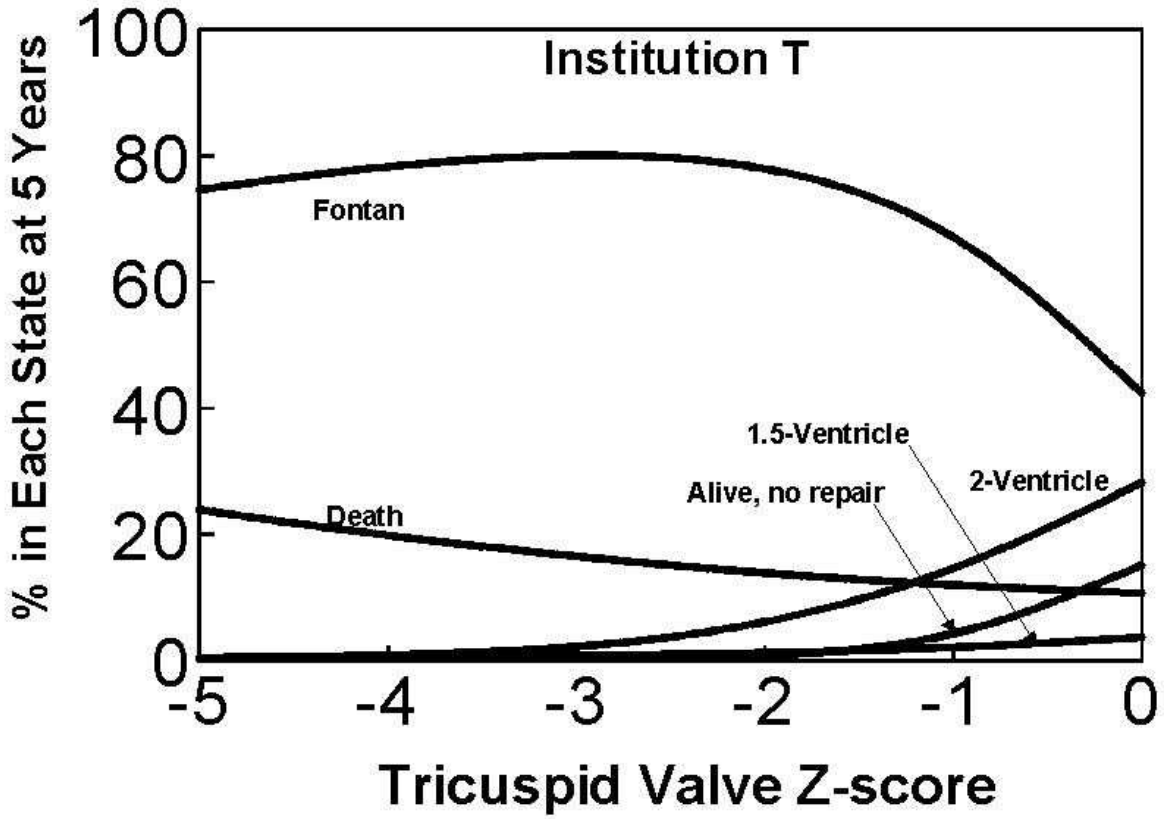

Institution T
% in Each State at 5 Years
100
80
60
40
20
0
-5
-4
-3
-2
-1
0
Tricuspid Valve Z-score
Fontan
Death
Alive, no repair
1.5-Ventricle
2-Ventricle

Figure 7C

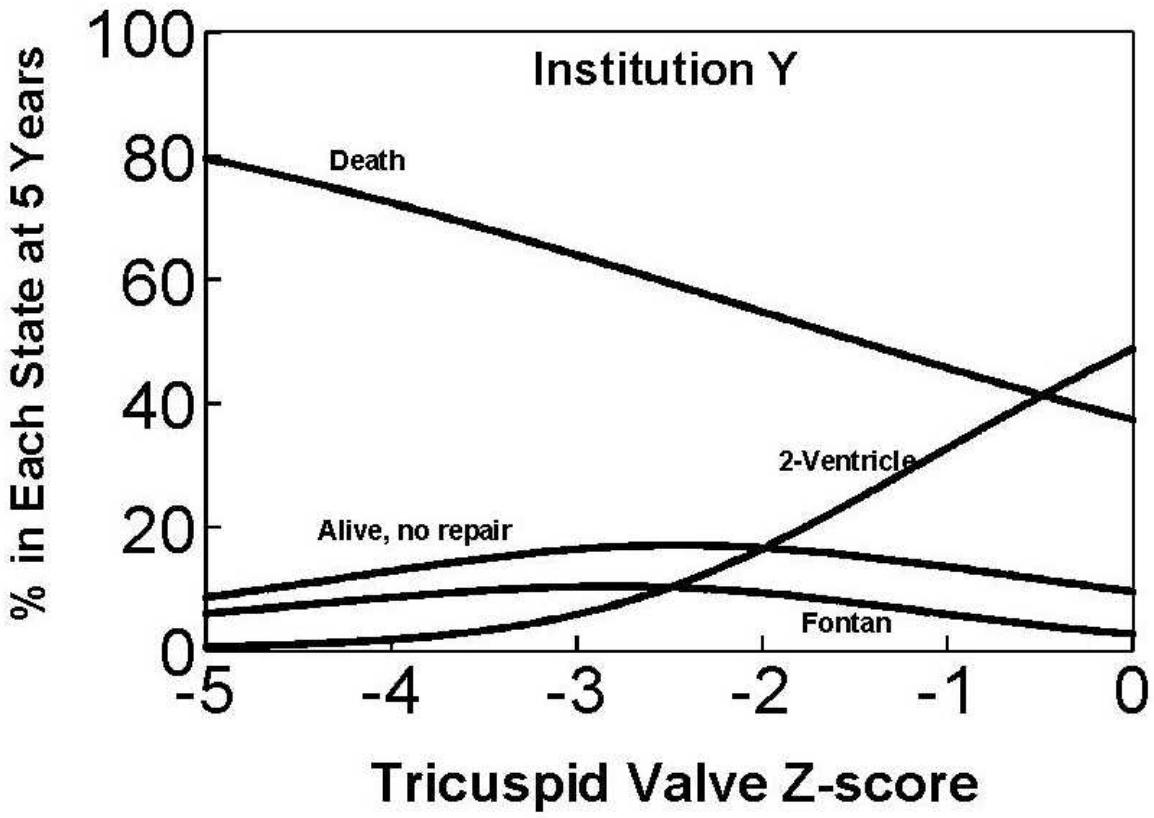

Institution Y
Death
2-Ventricle
Alive, no repair
Fontan
% in Each State at 5 Years
100
80
60
40
20
0
-5
-4
-3
-2
-1
0
Tricuspid Valve Z-score

Figure 7D

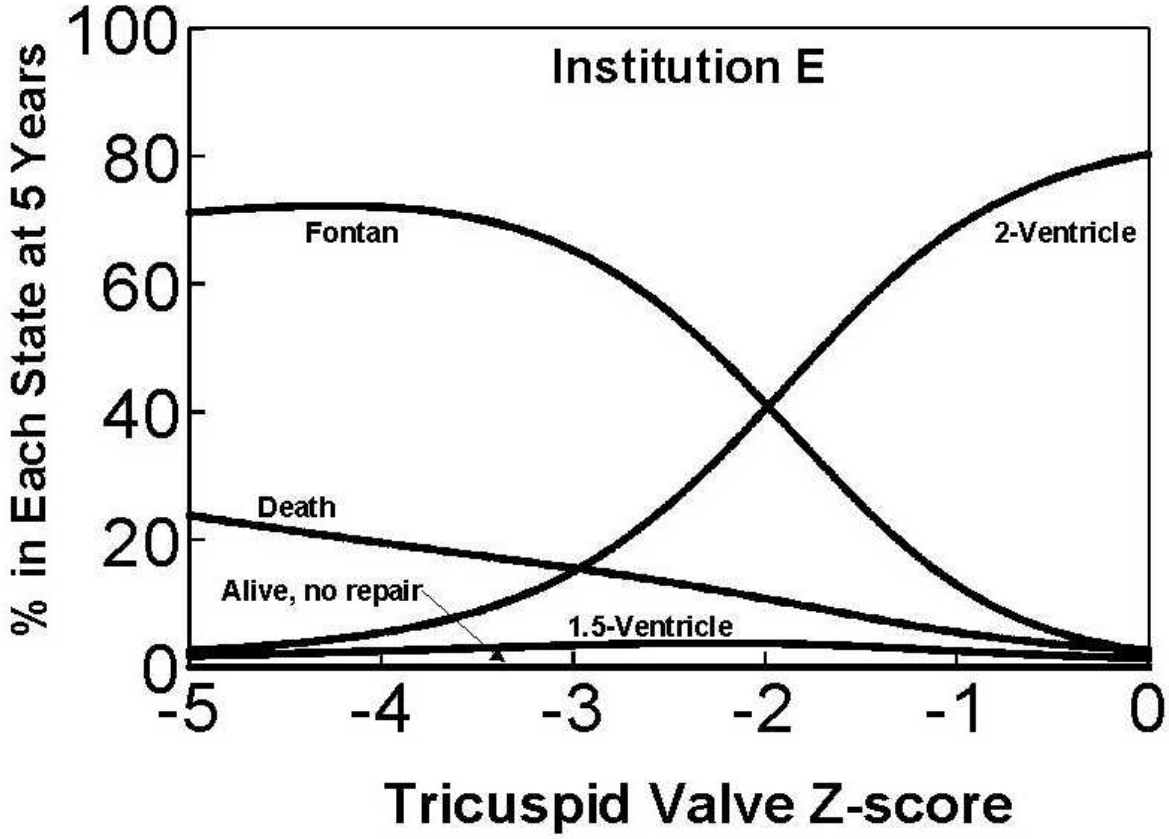

Institution E
% in Each State at 5 Years
100
80
60
40
20
0
-5
-4
-3
-2
-1
0
Tricuspid Valve Z-score
Fontan
2-Ventricle
Death
Alive, no repair
1.5-Ventricle

Figure 8. Schematic of Competing Hospital Hazards and Outcomes – Mortality and Discharge – in Adults Having Congenital Heart Surgery. Adults may migrate into one of two end-states. At time=0, all patients are alive in the operating room. Thereafter, they migrate over time into one of either end-states – hospital discharge or death before discharge. Each end-state has a unique hazard function that may increase or decrease in response to unique modulating factors. Both the prevalence and timing of death and discharge after surgery depend upon the communication of various modulating factors present.

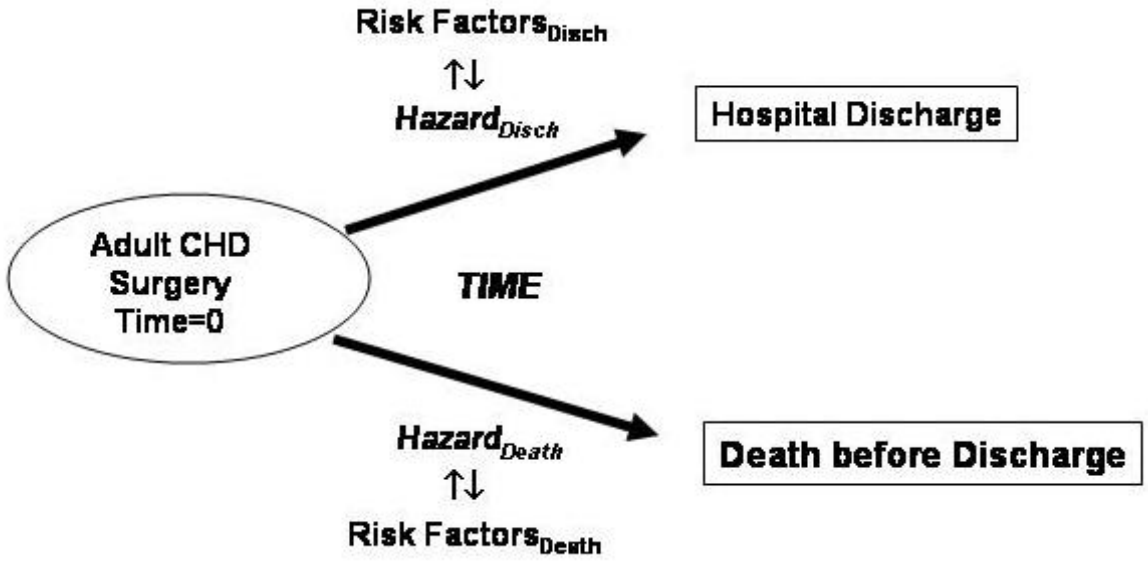


Figure 9. Actuarial Analysis of Competing Risks, Death and Discharge, After Adult Congenital Heart Surgery. The cumulative incidence of competing risks after surgery - death and discharge - are individually estimated actuarially with censoring of other end-state. The resulting curves are overlayed on the same graph to illustrate the impact of censoring competing end-states on prevalence estimates. At 60 days after surgery, the sum of prevalences of each end-state is 127% (discharge 98%, death 29%). Because each adult may attain only one of these end-states, the sum of "actual" cumulative incidences should not exceed 100%. Thus, actuarial techniques do not accurately quantify actual prevalence of competing outcomes.

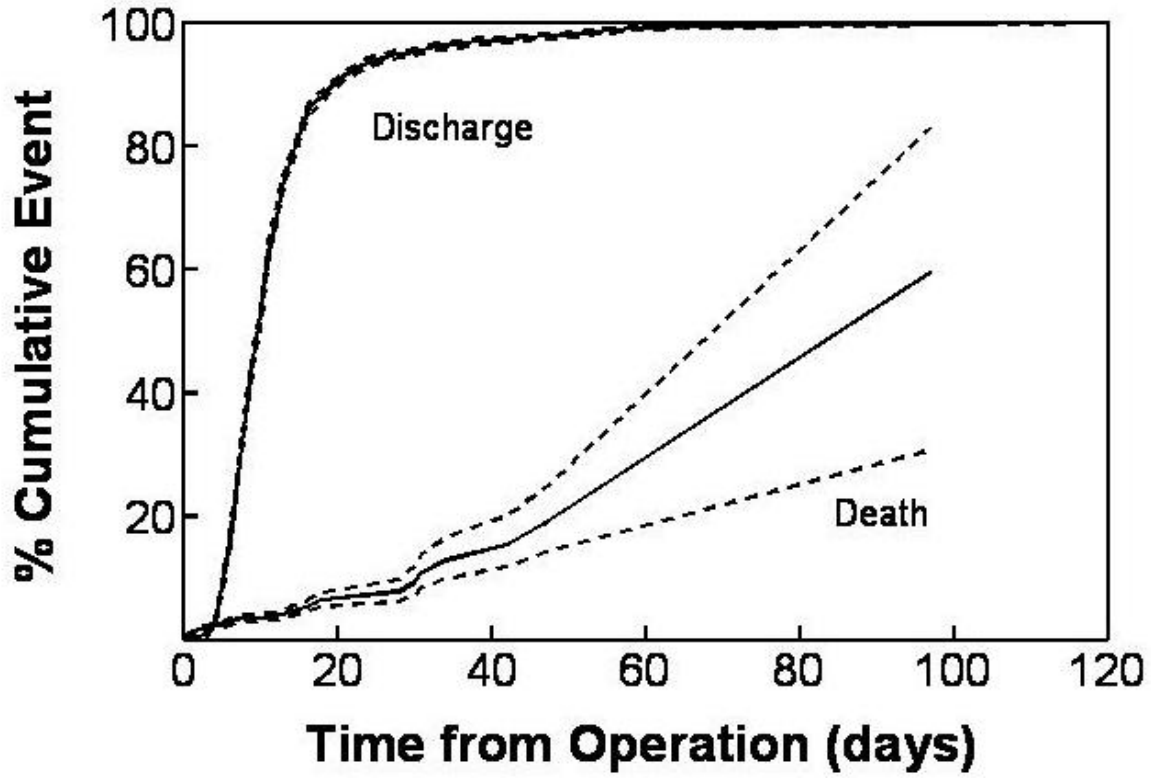


Figure 10. Impact of Individual Risk Factor on Competing Risks Model. The multivariable parametric competing risks model was solved twice to demonstrate the impact of non-pulmonary valve replacement – a risk factor for hospital mortality and longer length-of-stay. All other covariates were set to their median value to isolate the impact of valve replacement (risk-adjustment). The time variable was set to 2001. The curve for the default state, alive in hospital after surgery, has been removed for clarity. The model quantitates the impact of valve replacement: 1) hospital mortality rises (4.1% vs. 1.2%), 2) the proportion discharged from hospital necessarily decreases (95.9% vs. 98.8%), and 3) median length of stay increases (9.4 days vs. 7.9 days).

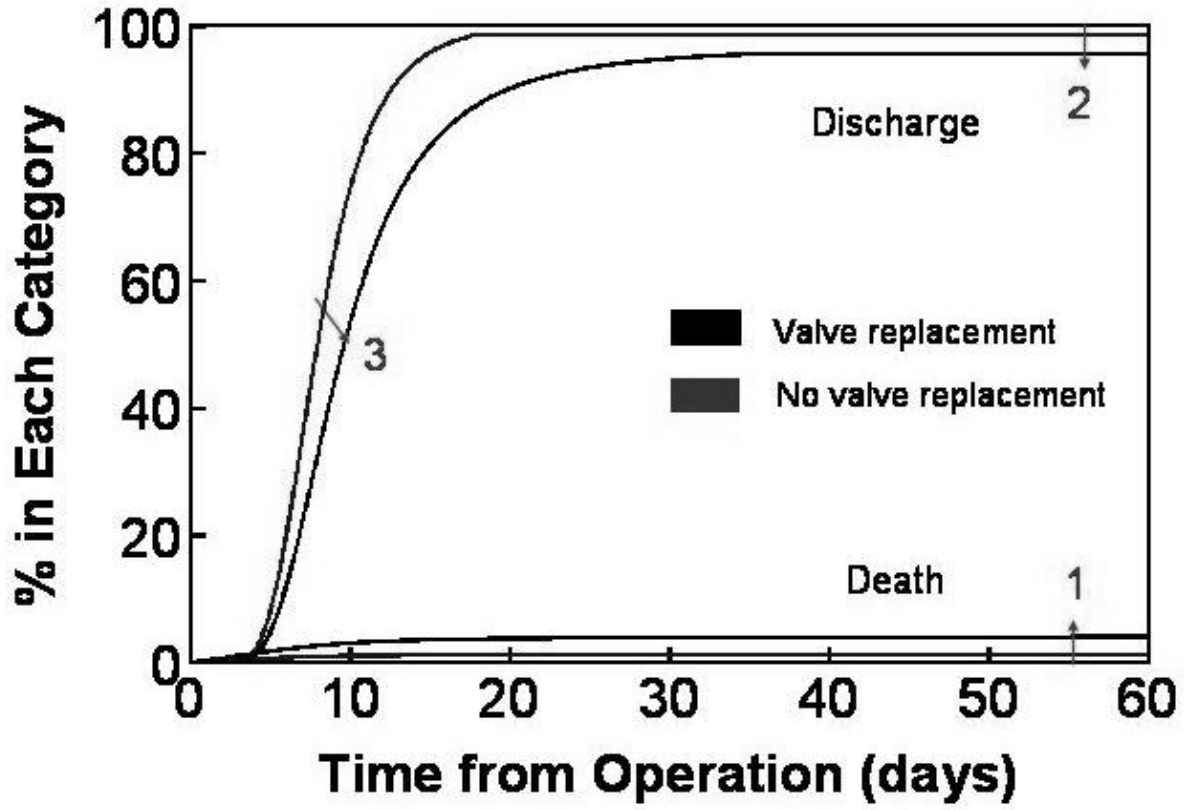


Figure 11. Trends in Surgical Volume in Adults with Congenital Heart Disease Based on Type of Operation. The largest increase in volume occurred in patients with obstructive or valvular lesions and those with residual lesions returning for late reoperation.

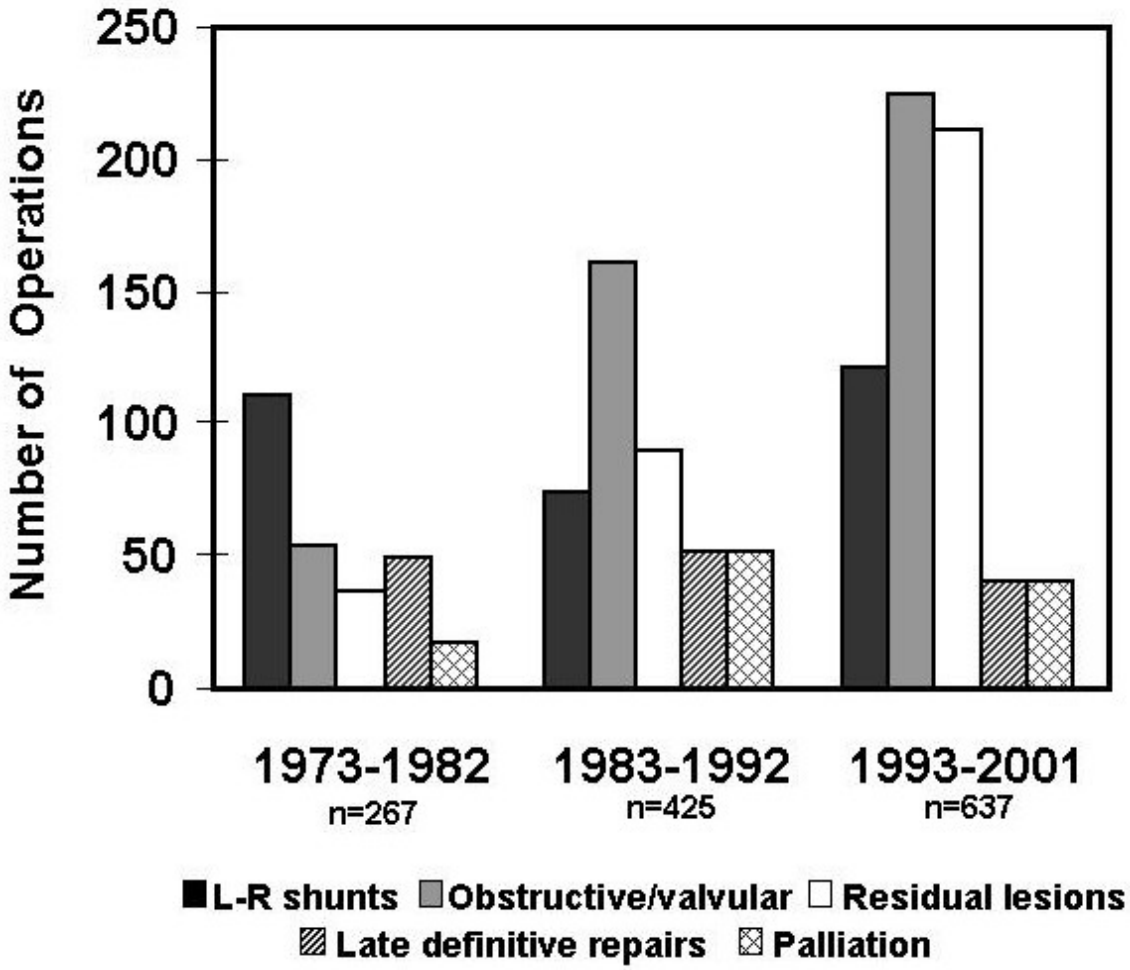


Figure 12. Non-Risk-Adjusted Competing Risks Analysis for Hospital Mortality and Discharge After 1351 Operations in Adults with Congenital Heart Disease. Early after congenital heart surgery in adults, discharge from the hospital and death occurring prior to discharge are competing time-related events. **A.** Hazard (*solid curves*), or instantaneous risk, surrounded by its 95% confidence interval (*dashed curves*) is plotted across time for hospital mortality and discharge. Based on the distribution of times to death, there is a low, but constant, risk of death throughout post-operative hospitalization. For discharge, there is a rapidly rising early phase that begins at 4 days and peaks at 11 days. **B.** The proportion of patients experiencing each of three outcomes (death, discharge, and alive awaiting discharge) across time during the post-operative period is depicted. All patients begin alive at the time of surgery (time=0), and, thereafter, migrate to death or discharge at a time-dependent rate defined by the hazard functions. At any time point, the sum of proportion of patients in all categories is 100%. The *solid lines* represent parametric estimates (surrounded by their 95% confidence interval in *dashed lines*) of the accumulative effect of each hazard function operating on the original group of patients. *Circles* represent non-parametric estimates obtained by Greenwood multiple decrement analysis.

Figure 12A

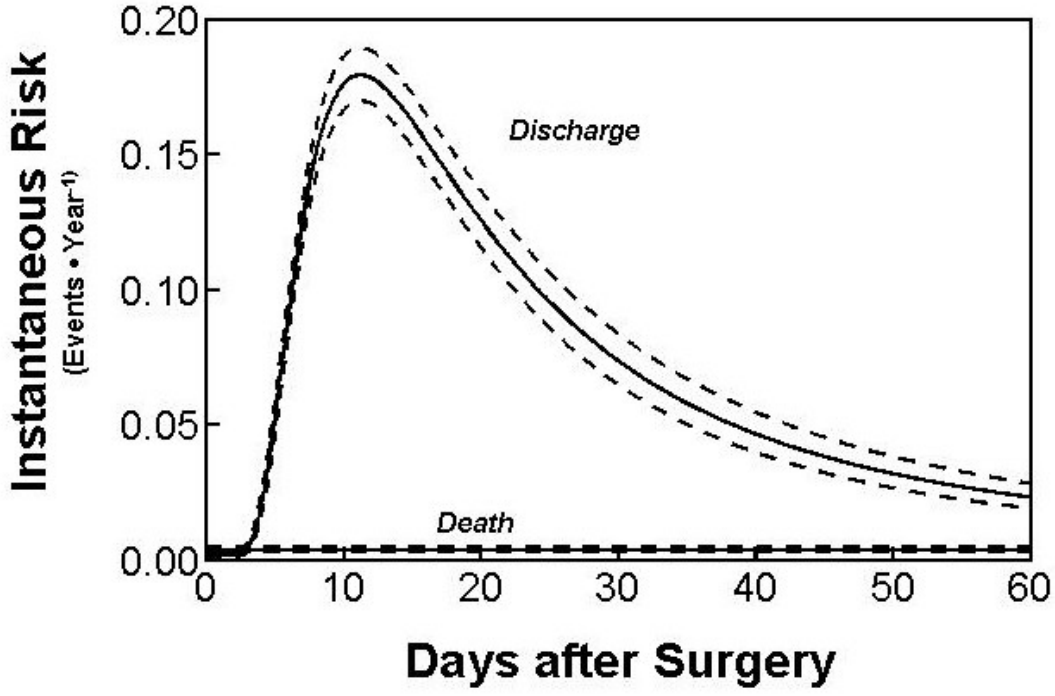


Figure 12B

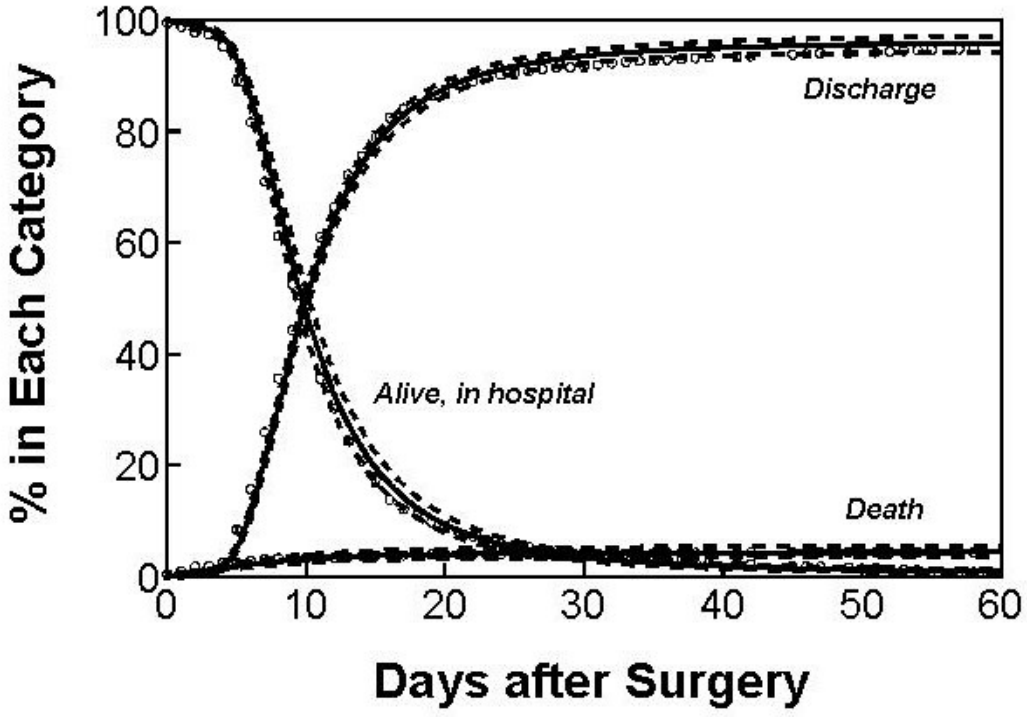
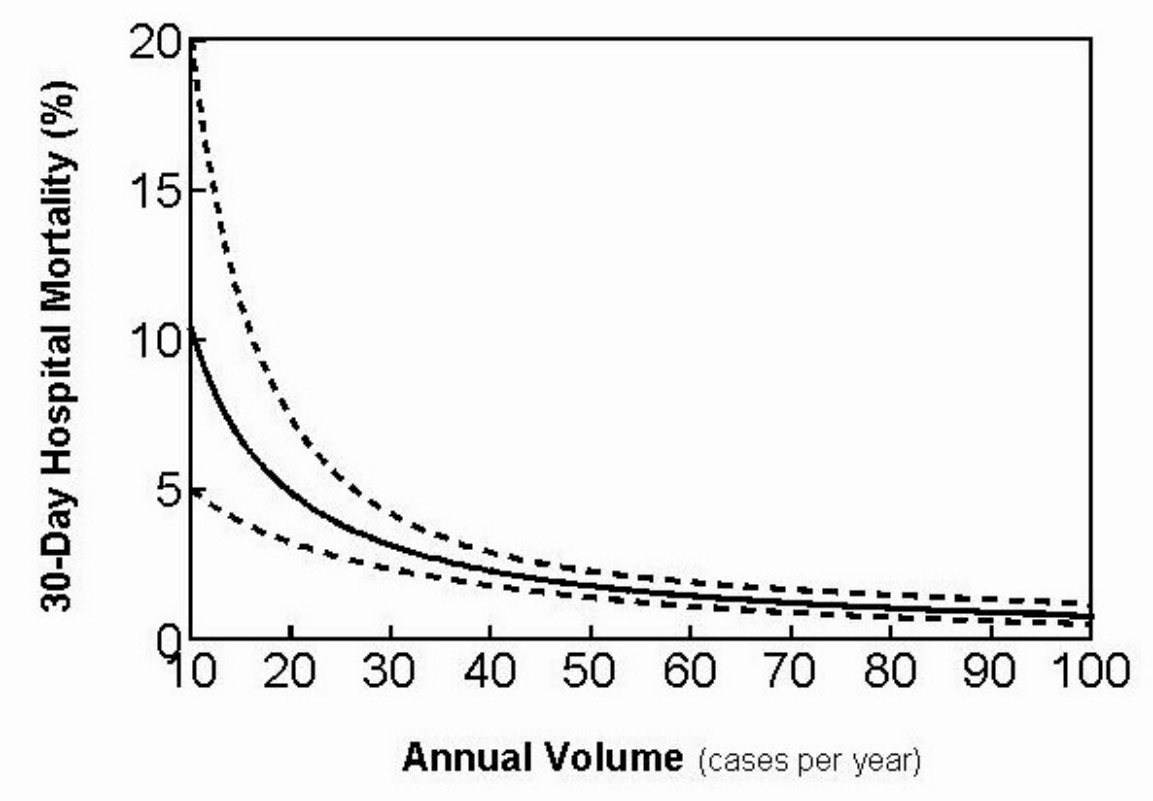


Figure 13. Nomogram of Risk-Adjusted Impact of Annual Surgical Volume on Hospital Mortality for Adults Undergoing Congenital Heart Surgery. The graph is generated by solution of the multivariable equation in the competing risks domain. The risk variable, annual surgical volume, is scaled along the x-axis. Corresponding risk-adjusted predicted 30 day hospital mortality is portrayed on the y-axis. All other predictor variables were entered as their median. *Solid li*ne represents continuous parametric point estimates, and *dashed lines* enclose 95% confidence limits.



Appendix 1. Primary Procedure Performed in 1351 Operations in Adults with Congenital Heart Disease.

	N (%)
Primary repair of L-R shunt lesions	**304 (23%)**
Atrial septal defect closure	239 (79%)
Secundum	132
Sinus venosus/PAPVD	59
Primum	47
Coronary sinus defect	1
Ventricular septal defect closure	48 (16%)
Perimembranous	40
Subarterial	4
Muscular	3
Patent ductus arteriosus closure	13 (4%)
Other	4 (1%)
Primary repair of obstructive/valvular lesions	**438 (32%)**
Subaortic resection	317 (72%)
Muscular	291
Fibromuscular	26
Tricuspid valve	41 (9%)
Replacement	22
Repair	19
Aortic valve	27 (6%)
Replacement	15
Repair	2
Sinus of Valsalva aneurysm repair	10
Pulmonary valvotomy/RVOT repair	24 (6%)
Coarctation of the aorta	17 (4%)
Mitral valve replacement	8 (2%)

Cor triatriatum repair	4 (1%)
Reoperation for late residual (post-repair) lesions	**337 (25%)**
Pulmonary valve/RVOT reconstruction	154 (45%)
Conduit operation	142
Non-conduit operation	12
Septal defects	39 (11%)
Atrial	14
Ventricular	25
Aortic lesions	34 (10%)
Coarctation	15
Ascending aortic replacement	11
Arch repair	8
Subaortic resection	26 (8%)
Muscular	15
Fibromuscular	11
Tricuspid valve	23 (7%)
Replacement	19
Repair	4
Mitral valve	22 (7%)
Replacement	21
Repair	1
Aortic valve replacement	13 (4%)
Arrhythmia	6 (2%)
Other	20 (6%)
Late definitive repair of non-simple defects	**141 (10%)**
Tetralogy of Fallot	51 (36%)
Ventricular septal defect + pulmonary stenosis	38 (27%)
Corrected transposition	22 (15%)

Complete transposition	13 (9%)
Rastelli operation	9
Atrerial switch operation	3
Mustard operation	1
Double outlet right ventricle	8 (6%)
Pulmonary atresia + ventricular septal defect	4 (3%)
Other	5 (4%)
Palliative surgery	**109 (8%)**
Fontan surgery	77 (70%)
Initial	52
RA-RV Conduit replacement	15
Conversion	10
Systemic-pulmonary shunt surgery	9 (8%)
Pulmonary artery banding	5 (5%)
Other	18 (17%)
Miscellaneous	**22 (2%)**
Vascular ring division	8 (36%)
Arrhythmia investigation/ablation	5 (22%)
Coronary artery bypass	3 (14%)
Other	6 (28%)