The Academic Database: Lessons Learned from the Congenital Heart Surgeons' Society Data Center

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Christopher A. Caldarone, Jeffrey A. Poynter, and William G. Williams

Abstract

During its more than 40 year history, The Congenital Heart Surgeons Society (CHSS) has evolved from an informal club to a mature organization. In 1985, Drs. John W. Kirklin and Eugene H. Blackstone founded the CHSS Data Center. Its purpose was to develop disease-specific inception cohorts of congenital heart disease (CHD) patients and extract knowledge from the combined clinical experience of centers across North America. The mission has evolved to training of research fellows, prospective testing of patients in our lifelong cohorts, organization of a tissue bank registry, and provision of quality improvement tools for members. The hub of this activity is in the CHSS Data Center, housed within the Hospital for Sick Children in Toronto. Our review will highlight lessons learned during the course of this evolution.

Keywords

Statistics • Database structure • Clinical trials • Outcomes research • Survival analysis • Registry • Quality improvement

C.A. Caldarone, MD (✉)
Division of Cardiovascular Surgery,
The Hospital for Sick Children,
University of Toronto, 555 University Avenue,
Toronto, ON M5G 1X8, Canada
e-mail: chris.caldarone@sickkids.ca

J.A. Poynter, MD, MSc
Department of Surgery,
Indiana University School of Medicine,
545 Barnhill Dr., Emerson Hall, Room 202,
Indianapolis, IN 46231, USA
e-mail: poynterj@iupui.edu

W.G. Williams, MD, FRCSC
Division of Cardiovascular Surgery,
Department of Cardiac Surgery, The Hospital for Sick Children, University of Toronto, Congenital Heart Surgeons' Society Data Center,
555 University Avenue, #4437,
Toronto, ON M5G 1X8, Canada
e-mail: bill.williams@sickkids.ca

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Background

The rationale for establishing the Congenital Heart Surgeons Society (CHSS) Data Center was the recognition among congenital heart surgeons that pooling clinical information in an organized fashion to facilitate data analysis would help improve patient outcomes. The rarity of congenital heart disease (CHD), the wide spectrum of anatomic and physiologic variations in presentation and the extensive array of available medical and surgical management strategies contribute to the difficulties faced by any one surgeon (or institution) in determining the optimal management for a given lesion. Acknowledging these fundamental difficulties, the CHSS embarked upon a collaborative venture in 1985 to share experiences and analyze aggregate data to improve the CHD management.

The first cohort assembled by the CHSS between 1985 and 1989 enrolled patients with transposition of the great arteries. During the first 4 years of enrollment, 985 neonates admitted to a CHSS institution within the first 2 weeks of life were enrolled. There were few concerns with institutional review boards and obtaining patient/family consent in this era. The robust enrollment of patients in this cohort was fueled by an urgent desire to rapidly develop a knowledge base on which to compare more traditional atrial switch strategies with the newer arterial switch strategy. Thus, the CHSS rapidly established itself as an organization that could address contemporary clinical problems in direct response to the academic needs of the membership.

The success of this cohort was followed by the conception of 11 other cohorts with over 5,400 patients enrolled for long-term follow-up. The 12 CHSS Study Cohorts are displayed in Table 13.1. Seven of these studies are no longer actively enrolling patients, and five of these studies are still actively enrolling patients. These cohorts have provided the data for numerous analyses and publications on behalf of the CHSS. A list of CHSS publications is available on our website at www.CHSSdc.org.

Table 13.1 Twelve CHSS diagnostic cohorts

Diagnostic cohort	Enrollment	Number of patients enrolled
Transposition of the Great Arteries (TGA) study	1985–1989	891
Interrupted Aortic Arch (IAA) study	1987–1997	470
Coarctation study	1990–1993	883
Pulmonary Atresia Intact Ventricular Septum (PAIVS) study	1987–1997	444
Pulmonary Stenosis with Intact Ventricular Septum (PSIVS) study	1987–1997	187
Critical aortic stenosis study	1987–1997	422
Aortic valve atresia study	1987–1997	563
Tricuspid Atresia (TA) study	1999–2013	307
Pulmonary Conduit (PC) study	2002–2013	591
Critical Left Ventricular Outflow Tract (LVOTO) study	2005–2013	674
Anomalous Aortic Origin of a Coronary Artery (AAOCA) study	1998–2013	284
Unbalanced atrioventricular septal defect (uAVSD) study	2012–2013	84

CHSS Data Center Structure

Personnel

The CHSS Data Center employs a Research Program Manager, a Database Programmer with statistical expertise, two Clinical Research Project Assistants, and two data abstraction nurses who have extensive clinical experience with CHD. In 2001, a Research Fellowship was created (the Kirklin/Ashburn Fellowship, discussed below). The Data Center is housed within the Hospital for Sick Children in Toronto with two suites including 1,200 sq. ft. of office space with all required computers and information technology resources, as well as secure storage for all electronic and hard copy data. The active interchange of information and ideas among the Data Center staff (i.e., teamwork) is

essential for continuous improvement in data management practice.

Legal/Ethical Issues

The Data Center seeks Research Ethics Board (REB) approval on an annual basis to insure that general operations of Data Center comply with the Health Insurance Portability and Accountability Act of 1996 of the United States of America (HIPAA), and other laws and regulations regarding patient confidentiality and data security. In addition, each participating CHSS institution requires their institutional REB approval for every cohort being followed. Direct patient consent for yearly follow up by Data Center staff is also obtained. Direct patient consent facilitates communication with patients who relocated to new caregivers and hospitals. Sharing of patient data also requires a Data Use Agreement between the Data Center and each CHSS institution.

Communication

The Data Center provides bi-monthly Newsletters to the CHSS members and their data managers. We also maintain a Website (www.CHSSdc.org) to provide members, our patients and the general public with current activities, publication access, lay summaries of publications, a patient blog, and links to relevant Websites. Extensive use is made of emails to members and a web-based dropbox for secure data transfer. The Data Center website also posts inclusion/exclusion criteria for each cohort and templates of REB applications for each institution to use in their institutional REB application. The availability of templates avoids duplication of effort and facilitates institutional enrollment in CHSS studies

Work Weekends

The Data Center organizes a semi-annual 3-day weekend for interested members to work in the Data Center. The members 'brain-storm' to develop new cohorts, direct statistical analyses, construct abstracts and manuscripts, and refine presentations.

Finances

Each CHSS institution is required to support the Data Center with an annual contribution. Support is mandatory. Additional funds are sought from peer reviewed grant applications, industry partners and philanthropic individuals and institutions.

Voluntary Contribution of Data

An important lesson learned in the CHSS Data Center is that our reliance upon voluntary enrollment of data creates the potential for failure to include all eligible patients in a cohort and introduction of selection bias into our cohorts. Parameters that influence enrollment are not well-studied but are likely to include the clinical 'urgency' associated with the research question that was the rationale for inception of the cohort. For example, as noted above, the cohort of patients with transposition of the great arteries acquired patients with extreme velocity. (985 neonates were enrolled from 100 % of all CHSS institutions (24 at that time) within 4 years). In contrast, a recent inception cohort of patients with critical left ventricular outflow tract obstruction (LVOTO) has enrolled relatively slowly (718 patients from 16 institutions over 4 years). The LVOTO enrollment can be compared to the contemporaneous National Institutes of Health (NIH) funded Pediatric Health Network Single Ventricle Reconstruction (SVR) Trial, which had a more narrow diagnostic range of entry criteria and fewer participating institutions but enrolled at a far greater rate than the LVOTO cohort. It is likely that the presence of paid coordinators 'on the ground' in each institution with scrutinized enrollment rates, and potential for financial penalties for failure to enroll contributed to the far more complete enrollment in the funded SVR trial when compared to the voluntary CHSS cohort.

Centralized Abstraction of Data

The CHSS relies upon centralized data abstraction. This lesson was learned after an unsuccessful

attempt to develop a web-based data entry system for patients enrolled in our pulmonary conduit cohort. Our expectation was that surgeons or their delegates would enter the data and this would improve overall efficiency of the data collection process. In fact, the absence of training in data entry led to a high proportion of records with incomplete data entry, a high frequency of errors, and a lack of means to redress these deficiencies. Furthermore, addition of new data fields to the research data set was difficult because there was no easy mechanism to recall the person entering data at the first setting and induce them to find an old record, abstract the required new data points, and enter the data in the web-based system. To redress these problems, the Data Center currently uses centralized data abstraction where paper and electronic medical records for each patient are collected and stored within the Data Center. Data are abstracted by specially trained personnel who are conversant with the data entry forms and have a vested interest in the accuracy of entered data.

Because hard copies of the patient records are available for review, a 'follow-on' unplanned analysis can be undertaken whenever needed. For example, a detailed analysis of the aortic valve stenosis/aortic valve atresia cohort enabled a complex analysis of the role of the Ross-Konno and Yasui procedures many years after inception of the cohort [1]. For this subset of patients, unique data fields were required and the analysis would have been impossible if the raw data were not available in the Data Center.

The Kirklin/Ashburn Fellowship

The John W. Kirklin/David A. Ashburn Fellowship is a central component of the CHSS research model and represents an important 'lesson learned' in the CHSS. Employing a dedicated Fellow to undertake complex statistical analyses transformed the research activity in the CHSS Data Center from an intermittent effort predicated on part time efforts of CHSS members to a continuous effort led by the Kirklin/Ashburn Fellow – with a fundamental transformation in the productivity of the Data Center.

In exchange for the high level of productive work performed, the Kirklin/Ashburn Fellow enjoys many academic benefits. The Kirklin/Ashburn Fellows typically have studied in the Data Center for 2 years and have enrolled in concurrent Masters or PhD programs at the University of Toronto. Their tenure in the Data Center has been supported by intensive tutelage from Drs. Eugene Blackstone and Brian McCrindle, and Sally Cai. Using this support network, the Fellows have forged new analyses of CHSS cohorts using state of the art statistical techniques. The Fellows have led the analysis through collaboration with participating members from the inception of addressable questions, 'cleaning' of the data, development of an analysis plan, correspondence with working groups, creation of presentations, and writing of manuscripts. All these activities have been supported by the Data Center staff in Toronto to provide the Fellows with mentorship, and help to focus their analyses and fine-tune interpretation of results. The Fellowship is highly visible amongst congenital heart surgeons and has allowed the intellectual firepower of future congenital heart surgeons to shine among the membership where prospects for future employment are bright. Building a training program into the structure of the Data Center has promoted academic output and helped to keep the CHSS Data Center as a hub of activity within the CHSS.

Research Strategies in the CHSS Data Center

The Research Question

Clinical research should be driven by a research question or questions. The question(s) define the dataset; therefore, any proposed analysis begins with the identification of one or more specific research questions. This process typically requires several hours of thoughtful discussion. One must collect the data points that will address the proposed research question(s), including the specific information on outcomes to be determined. A common error in the early years of the

Data Center was to try to collect too much information including information which did not contribute to the central research questions.

Focus on Diagnosis-Based Inception Cohorts

During the years from 1985 to 2003, the CHSS focused on diagnosis-based cohorts over procedure-based cohorts. The rationale was to capture the wide variety of potential operative and non-operative management strategies utilized across institutions. This approach allowed evaluation of important patient subsets that are typically excluded from procedure-based surgical reports. For example, inclusion of non-operated patients who die prior to operation is an important tool to compare management strategies across institutions. Using the all-comers approach, the CHSS endeavors to avoid the filtering of patients that is often a foundation of published procedure-based reports. One institution may exclude certain patient subsets from consideration for surgical therapy whereas another institution may choose to provide therapy – making comparison of published reports from different institutions problematic. An example of the importance of inclusion of all patients is demonstrated in an analysis of the CHSS pulmonary atresia cohort [2]. In Fig. 13.1, the transition from entry in the study (diagnosis) to a definitive single-, 1.5-, or two-ventricle repair is shown. Note that a large proportion of the patients never achieved one of these 'endstates'. Consequently, a procedure-based surgical report might have neglected to account for the substantial proportion of patients who died without undergoing a 'definitive' procedure. The inclusion of non-operative patients also allows comparison between institutions by using statistical methods to control for differences in patient selection.

Data Entry

The Data Center constructs a database to record all data required to address the research question.

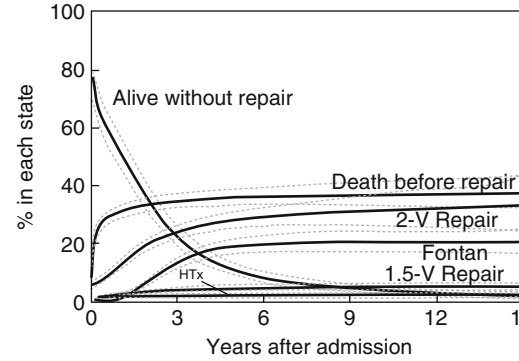


Fig. 13.1 Non–risk-adjusted competing-risks depiction of end states in 408 neonates with PAIVS illustrating the proportion of children reaching each end state over time after initial hospital admission. All patients begin alive at the time of initial admission (time = 0) and migrate to an end state at a time-dependent rate defined by the hazard functions. At 5 years, the estimated prevalences of end states are as follows: 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 % (Reprinted with permission from Ashburn et al. [2])

In the past we have collected hard copies of specified parts of the patient's hospital chart, such as admission sheet, admission history and physical, all diagnostic reports, operative reports and follow-up investigation and reports. These data are extracted by highly knowledgeable and experienced professionals. We are making a transition to collect these data via Internet e-based records using secure file transfer. Annual cross-sectional follow-up data is conducted within specific months of each year and the information, including interval procedures and/or investigations added to the dataset.

Data Integrity (The Essential Underappreciated Integral Step)

Prior to beginning any data analysis it is essential to check the dataset for errors, omissions, outliers, unknown data points, and any possible misinterpretation of data extraction. Even the most committed and compulsive professional cannot be perfect extracting data. More commonly the information from clinical records will contain

typographic errors, omissions, and outliers. We cannot overstress the essential nature of this very labor intensive requiring considerable time, effort and ingenuity to make the dataset as accurate and complete as possible.

Diagnostic Images

Institutional reports of diagnostic images vary in consistency. We have found that obtaining copies of the actual echo, computed tomography (CT) or magnetic resonance imaging (MRI) studies is relatively easy. And it has been amazing to us to see the enthusiasm of expert reviewers in undertaking detailed review of each image. The quality and detail of the diagnostic data is enormously enhanced by expert review. To do the reviews, the reviewers needed to work in the Data Center for many days at their own expense. As a further step to facilitate this expert review process we have setup a CHSS Core Lab to upload de-identified images to our central server so that the experts can review each image from the convenience of their home institution. In addition, the data from each expert review is entered into an Internet-based database (RedCap) [3] housed within the Data Center file server. The merged data is then available for analysis.

Evaluation of Uncommon Lesions

The CHSS Data Center is well suited to examine uncommon lesions because of the large number of participating institutions. For example, the CHSS assembled a large cohort of patients with interrupted aortic arch representing a relatively rare congenital heart lesion. Interestingly, among the 472 patients with interrupted aortic arch, concomitant aortopulmonary window was identified in 20 patients. Because of the large number of centers enrolling patients, the analysis spawned an important sub-analysis of patients with an extremely rare combination of interrupted aortic arch and aortopulmonary window – a feat that could not be accomplished in a single center cohort (Fig. 13.2).

The CHSS Data Center has leveraged its multi-institutional resources to develop a prospective inception cohort of patients with anomalous aortic origin of a coronary artery (AAOCA). AAOCA is diagnosed when one or both coronary arteries arise from outside their appropriate sinus of Valsalva (Fig. 13.3). Although relatively rare, the diagnosis of AAOCA provokes intense anxiety among patients (and clinicians) because there are no clearly defined management algorithms and the potential for sudden death is not well understood. Currently (as of August 2013),

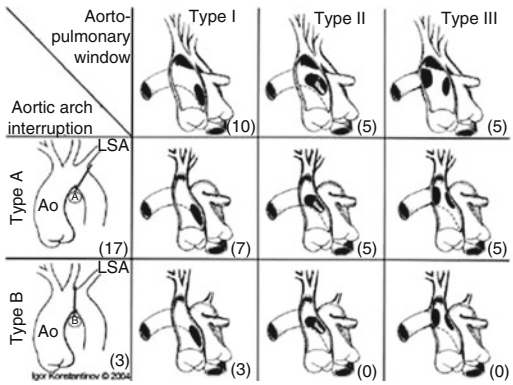
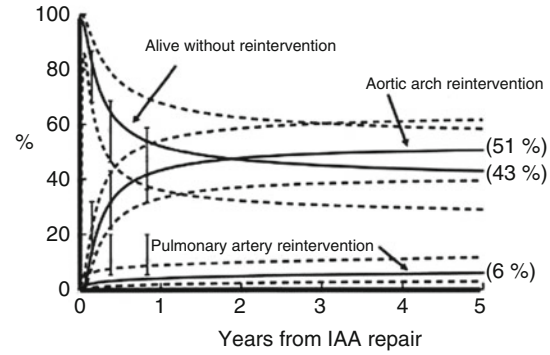


Fig. 13.2 Rare combinations of lesions can be examined within larger CHSS cohort. Konstantinov et al. examined outcomes in patients with interrupted aortic arch and concomitant aortopulmonary window and were able to make important inferences to assist in clinical decision making.



This would be difficult or impossible for any single institution to perform due to the rare prevalence of this combination of lesions (Reprinted with permission from Konstantinov et al. [9])

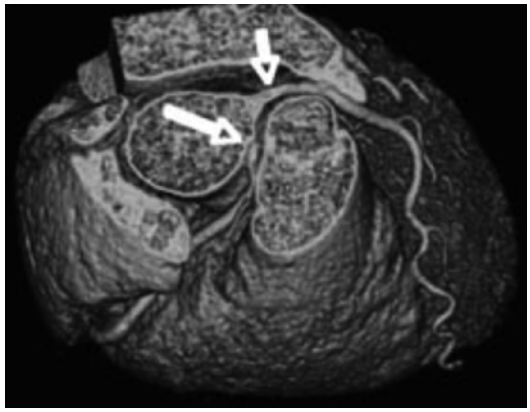


Fig. 13.3 Anomalous aortic origin of the right coronary artery (*large arrow*) from the left coronary sinus (*small arrow* identifies left main coronary artery) [10]

the Data Center has enrolled 249 patients and continues to enroll. This rapid accrual of a large cohort of patients with a relatively rare lesion will allow unprecedented analysis of the relationships between symptomatology, preoperative diagnostic data, surgical findings, operative and non-operative treatment strategies, and long term outcomes.

Data Analysis

Complex Cohorts Require Complex Statistical Techniques

An important lesson learned in the CHSS Data Center has resulted from the use of complex statistical techniques to evaluate the complex management strategies utilized in our multi-institutional patient cohort. This strategic focus distinguishes the CHSS from more traditional large-scale research ventures that tend to focus on straightforward comparisons using prospective randomized trial designs. Although randomized trials can facilitate direct evaluation of very specific hypotheses, randomized designs are less appropriate when a wide range of management options exist and/or the condition to be studied is rare. Under such circumstances, it is frequently not feasible to incorporate multiple management options into a randomized controlled trial design.

Evolution of Statistical Techniques

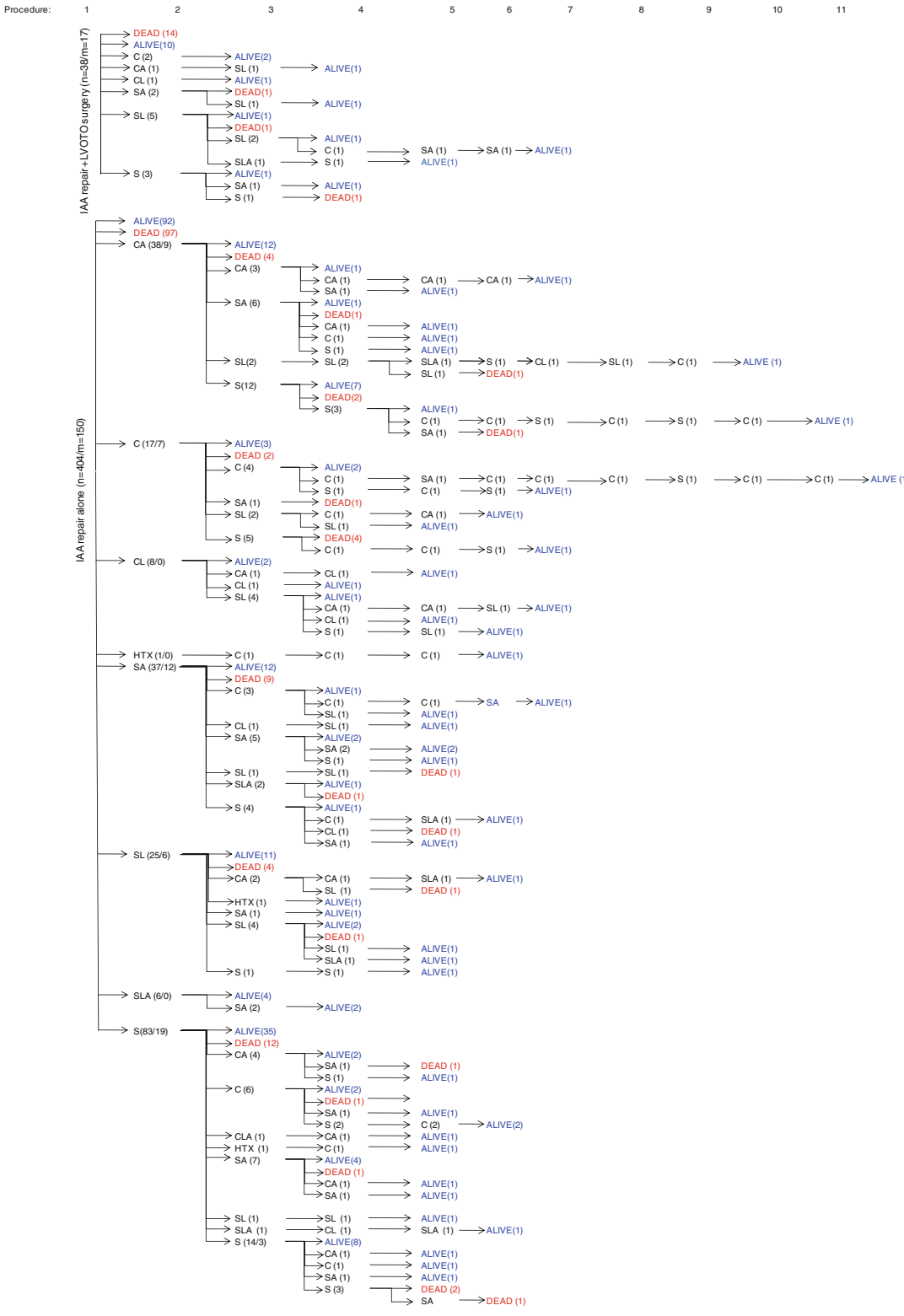
The data abstracted in the Data Center is derived from highly complex cohorts and the complexity in our cohorts is a direct result of the interaction between a wide array of management options in common clinical practice, the high degree of variability in the timing of these interventions between institutions, and the relatively high probability of multiple reinterventions and diagnostic procedures. An example of a complex cohort is demonstrated in Fig. 13.4. In order to deal with this complexity, the Data Center has evolved to utilize a wide array of advanced statistical techniques to facilitate analysis of extremely complex cohorts. The statistical evolution of the CHSS Data Center has been led by Drs. Eugene Blackstone and Brian McCrindle, Sally Cai, and the Kirklin/Ashburn Fellows.

Statistical Techniques in Use at the CHSS Data Center

Parametric Hazard Phase Decomposition

CHSS studies incorporating parametric hazard analysis nearly always incorporate a method pioneered by Eugene Blackstone and colleagues to decompose the overall time-related hazard (Fig. 13.5a) into as many as three 'phases' [4] (Fig. 13.5b). This method is well-suited to model the hazard of various outcomes surgical patients because it can account for transient but high 'early phase' of postoperative risk, a period of attrition at a constant rate (the 'constant phase'), and a 'late phase' of increasing risk. This method permits the identification of risk factors unique to each phase. Risk factors which modify one phase may not always be incorporated into the model describing another phase. For example, factors which are associated with early postoperative risk of death may quite different than factors associated with death in the late postoperative period.

The decomposition of hazard into phases is a fundamental strategy and serves as the statistical method of choice for almost all of our analyses. Adoption of this method has permitted accurate


Procedure: 1 2 3 4 5 6 7 8 9 10 11
IAA repair+LVOTO surgery (n=38/m=17)
DEAD (14)
ALIVE(10)
C (2) → ALIVE(2)
CA (1) → SL (1) → ALIVE(1)
CL (1) → ALIVE(1)
SA (2) → DEAD(1)
SL (1) → ALIVE(1)
SL (5) → ALIVE(1)
DEAD(1)
SL (2) → ALIVE(1)
C (1) → SA (1) → SA (1) → ALIVE(1)
SLA (1) → S (1) → ALIVE(1)
S (3) → ALIVE(1)
SA (1) → ALIVE(1)
S (1) → DEAD(1)
IAA repair alone (n=404/m=150)
ALIVE(92)
DEAD (97)
CA (38/9) → ALIVE(12)
DEAD (4)
CA (3) → ALIVE(1)
CA (1) → CA (1) → ALIVE(1)
SA (1) → ALIVE(1)
SA (6) → ALIVE(1)
DEAD(1)
CA (1) → ALIVE(1)
C (1) → ALIVE(1)
S (1) → ALIVE(1)
SL(2) → SL (2) → SLA (1) → S (1) → CL (1) → SL (1) → C (1) → ALIVE (1)
SL (1) → DEAD(1)
S(12) → ALIVE(7)
DEAD(2)
S(3) → ALIVE(1)
C (1) → C (1) → S (1) → C (1) → S (1) → C (1) → ALIVE (1)
SA (1) → DEAD(1)
C (17/7) → ALIVE(3)
DEAD (2)
C (4) → ALIVE(2)
C (1) → SA (1) → C (1) → C (1) → C (1) → S (1) → C (1) → C (1) → ALIVE (1)
S (1) → C (1) → S (1) → ALIVE(1)
SA (1) → DEAD(1)
SL (2) → C (1) → CA (1) → ALIVE(1)
SL (1) → ALIVE(1)
S (5) → DEAD(4)
C (1) → C (1) → S (1) → ALIVE(1)
CL (8/0) → ALIVE(2)
CA (1) → CL (1) → ALIVE(1)
CL (1) → ALIVE(1)
SL (4) → ALIVE(1)
CA (1) → CA (1) → SL (1) → ALIVE(1)
CL (1) → ALIVE(1)
S (1) → SL (1) → ALIVE(1)
HTX (1/0) → C (1) → C (1) → C (1) → ALIVE(1)
SA (37/12) → ALIVE(12)
DEAD (9)
C (3) → ALIVE(1)
C (1) → C (1) → SA → ALIVE(1)
SL (1) → ALIVE(1)
CL (1) → SL (1) → ALIVE(1)
SA (5) → ALIVE(2)
SA (2) → ALIVE(2)
S (1) → ALIVE(1)
SL (1) → SL (1) → DEAD (1)
SLA (2) → ALIVE(1)
DEAD (1)
S (4) → ALIVE(1)
C (1) → SLA (1) → ALIVE(1)
CL (1) → DEAD (1)
SA (1) → ALIVE(1)
SL (25/6) → ALIVE(11)
DEAD (4)
CA (2) → CA (1) → SLA (1) → ALIVE(1)
SL (1) → DEAD (1)
HTX (1) → ALIVE(1)
SA (1) → ALIVE(1)
SL (4) → ALIVE(2)
DEAD (1)
SL (1) → ALIVE(1)
SLA (1) → ALIVE(1)
S (1) → S (1) → ALIVE(1)
SLA (6/0) → ALIVE(4)
SA (2) → ALIVE(2)
S(83/19) → ALIVE(35)
DEAD (12)
CA (4) → ALIVE(2)
SA (1) → DEAD (1)
S (1) → ALIVE(1)
C (6) → ALIVE(2)
DEAD (1)
SA (1) → ALIVE(1)
S (2) → C (2) → ALIVE(2)
CLA (1) → CA (1) → ALIVE(1)
HTX (1) → C (1) → ALIVE(1)
SA (7) → ALIVE(4)
DEAD (1)
CA (1) → ALIVE(1)
SA (1) → ALIVE(1)
SL (1) → SL (1) → ALIVE(1)
SLA (1) → CL (1) → SLA (1) → ALIVE(1)
S (14/3) → ALIVE(8)
CA (1) → ALIVE(1)
C (1) → ALIVE(1)
SA (1) → ALIVE(1)
S (3) → DEAD (2)
SA → DEAD (1)

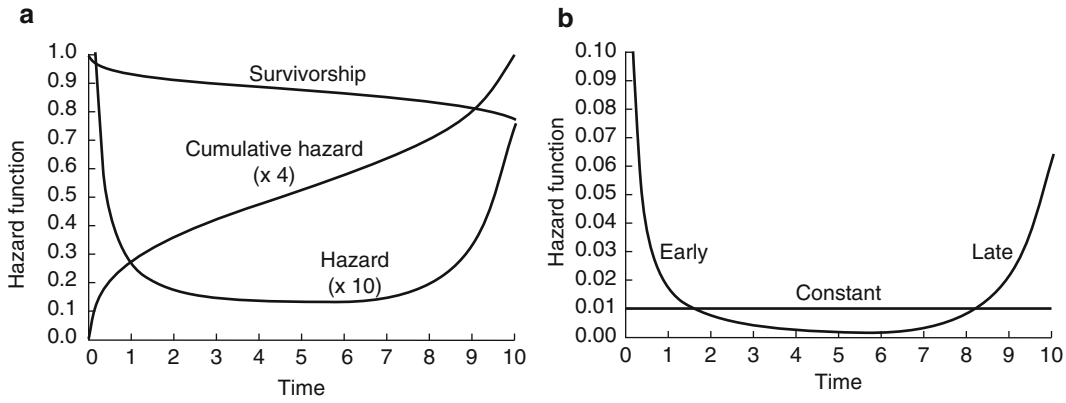


Fig. 13.5 Functions used to describe time-related events. (**a**) The cumulative hazard function accelerates rapidly before reaching a constant slope. Later, it begins to rise rapidly again. This cumulative hazard function corresponds to a survivorship function which decreases rapidly, then stabilizes before accelerating again. The hazard function is infinite at time zero, decreases to a constant rate and then increases late in follow-up. (**b**) The hazard function, decomposed into early, constant and late phases. Each phase quantifies the hazard according to time. The sum of these three phases of hazard is equivalent to the overall hazard function from the upper panel (Reprinted from Blackstone et al. [4])

modeling of every 'shape' of hazard curve yet observed, permitted the identification of risk factors unique to each phase, and facilitated the use of parametric analyses.

Time Zero

Nearly every Data Center study uses survival analysis methods which require that one define a "time zero" as the starting time for the analysis. We define time zero as the time at which the patients becomes at risk of the defined outcome. For example, a study of surgical techniques which evaluate survival after tetralogy of Fallot repair would specify time zero as the initiation of the surgical repair. In contrast, a diagnosis-based study of tetralogy of Fallot would specify time zero as the moment the diagnosis was made – irrespective of a surgical procedure. The latter example would include patients who are not expected to undergo surgery or die prior to planned surgery.

Practical aspects of data abstraction present certain challenges. For example, the date of diagnosis may actually precede birth when the diagnosis is made in utero. Similarly, if the diagnosis is made outside the CHSS member institution, the precise date may be unavailable if the Data Center does not have access to records of that initial diagnostic study (which is often the case). When formulating the precise research question it is best to specify time zero with careful consideration of these practical issues, in order to ensure that all patients in the study can be proven to have become at risk at a precise date (and not the date of their transfer to the CHSS member institution).

Advantages of Parametric Hazard Analysis

A major benefit of parametric hazard analysis over more traditional non-parametric and semi-parametric methods (e.g., Cox regression) is the generation of prediction plots by solving the

Fig. 13.4 A wide variety of management strategies were utilized in the care of patients with Interrupted Aortic Arch. This figure illustrates the complex of management strategies. There is significant crossover amongst treatment pathways, and a large number of unplanned intervening procedures between planned stages of repair. An analysis of outcomes amongst this difficult group of patients necessitates that the statistical methods account for the complexity of management (Reproduced with permission from the Congenital Heart Surgeons' Society Data Center)

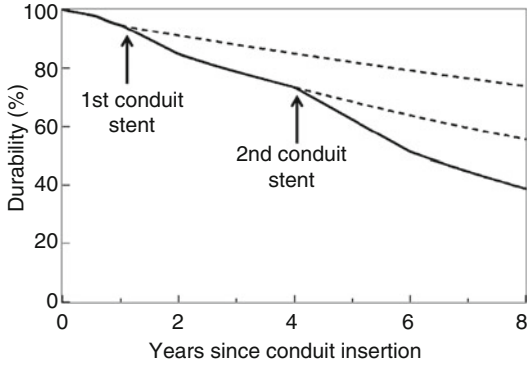


Fig. 13.6 Solution of the parametric equation illustrating the durability of a non-decellularized aortic allograft with z-score +2 inserted in a child with no other risk factors, who underwent two successive conduit stentings at 1 and 4 years after insertion. The *solid line* depicts predicted durability over years since conduit insertion on the x-axis. *Dotted lines* denote predicted durability in a child who did not undergo the first or second conduit stenting procedures. Each stenting is associated with an approximate 18 % reduction in 8-year durability (From Poynter et al. [5], copyright 2013, with permission from Elsevier)

parametric equation to reflect changing values of one or more risk factors included in the model. While Cox regression can support basic plots in which a single covariates may change, the results of Cox regression are generally presented in tables due to the poor compatibility of this method with graphical display of results. Cox regression does not support the creation of prediction plots based upon multiple changing values of covariables. Parametric hazard analysis, on the other hand, can easily support the creation of prediction plots reflecting any clinically feasible combination of values amongst the covariables (so long as they do not exceed the bounds of the original data). As a result, the reader can readily differentiate between a statistically significant result of low (and clinically unimportant) magnitude, and a statistically significant covariable that is associated with clinically important changes in outcome when modulated. The ability to directly compare time-related prediction estimates between multiple significant covariables which are simultaneously changing permits the graphical presentation of as many prediction curves as desired, with any combination of changes amongst any or all of the covariables included in the model. Feedback from our studies incorporating these prediction plots has been very positive because they facilitate visual representation of the impact of alterations in a risk factor. An example is shown in Fig. 13.6. This plot shows the predicted durability of a hypothetical aortic allograft inserted into a child with no other known risk factors for allograft failure and undergoes (or does not undergo) conduit stenting at 1 and 4 years after insertion. The dotted lines indicate the predicted time-related allograft durability if the conduit were not stented at the 1 or 4 year mark. The table within this manuscript [5] listed a parameter estimate of 0.33 and a p value <0.01. These numerical data are not nearly as informative as a plot of time-dependent durability according to whether the conduit was stented 0, 1 or 2 times.

Competing Risks

More traditional mortality studies can often be addressed by consideration of a simple binary outcome – e.g., survival versus death. Children with congenital heart disease, however, are often subject to multiple mutually exclusive 'competing risks' that often include death but may also include cardiac transplantation, re-operation or the achievement of one or more types of 'definitive' repair. Competing risks can be separated to form multiple estimates of time-related hazard of each competing risk [2]. At any point in time the survival estimate of the sum of the various competing risks always equals 100 %. Thus, a survival curve can be generated for each competing endstate and then decomposed into hazard phases to identify risk factors specific to each hazard phase for the respective end-state. Opting not to use competing risks methods requires that the researcher either ignore certain end-states, or combine the competing risks of different end-states into a binary outcome. If this is done, the patients at risk can be inappropriately censored, falsely reducing the denominator. Thus the estimate of risk for the binary outcome may be overestimated if the Kaplan-Meier method is used when there are more than two mutually exclusive possible outcomes [6]. Figure 13.7, from a seminal paper by McGiffin and colleagues, demonstrates the differences in estimates of cardiac transplantation depending on whether death is considered as a separate outcome from transplant (i.e., competing risks) or is not (i.e., the Kaplan-Meier method).

The Data Center began using the competing risks method over a decade ago to evaluate our

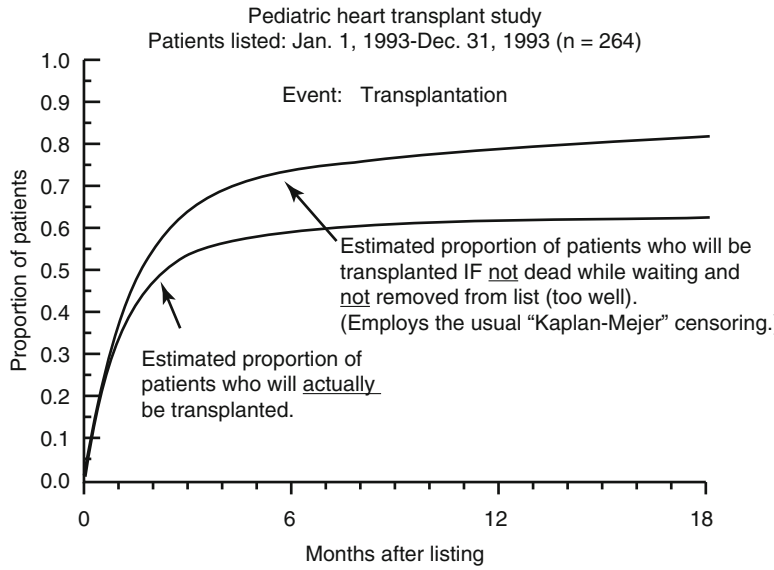


Fig. 13.7 Comparison of the Kaplan-Meier method versus competing risks methodology in analyzing outcomes of patients awaiting heart transplantation. The parametric estimate of proportion of patients who are transplanted by use of Kaplan-Meier right-censoring to remove patients from the denominator at risk and dying while waiting (*upper curve*), and parametric estimate of proportion of patients who will actually undergo transplantation (*lower curve*) are shown. The upper curve overestimates the transplantation probability by removing patients who have died while awaiting transplant. The lower curve is a more accurate estimate of the proportion of patients who will actually be transplanted, because it has considered the competing risk of death separately (From McGiffin et al. [6])

pulmonary atresia with intact ventricular septum cohort [2]. The analysis utilized the mutually exclusive end-points of: survival without repair, death, transplantation, univentricular repair, biventricular repair or 1.5-ventricle repair (Fig. 13.1). Factors associated with each of these unique end-states were identified. Had we performed a more traditional, separate sub-analysis of each of these important groups, important information about those who did not experience each outcome of interest would have been unaccounted for. The lesson here is that utilizing a competing risks analysis is essential when study subjects are at risk of multiple mutually exclusive outcomes (Fig. 13.8).

Segmentation of Longitudinal Records to Facilitate Analysis

A further extension of parametric hazard analysis can also include the incorporation of time-dependent covariables into the record. Using this method, each patient's longitudinal record may be divided into multiple intervals punctuated by interval events (e.g., multiple catheter interventions between surgical procedures) that are expressed as separate observations within the dataset. Each evaluated time interval contains time-independent variables (constant values such as gender) and time-dependent variables (such as the number of cumulative catheter interventions on the repair). Along with those variables, the dataset structure includes a mechanism to 'stitch together' each segment to replicate the longitudinal record as certain values change over time (Fig. 13.9). This technique was used most recently by the Data Center in an analysis by Poynter and colleagues to analyze the durability of right ventricle to pulmonary artery conduits [5].

Propensity Score Matching

The Data Center performs observational inception cohort studies rather than randomized controlled trials. Although observational studies are well suited to the study of congenital heart disease, on occasion we have had a need to balance groups for comparison. We have used balancing scores in order to provide more meaningful comparisons of groups. One type of balancing score called a propensity score has proven to be of

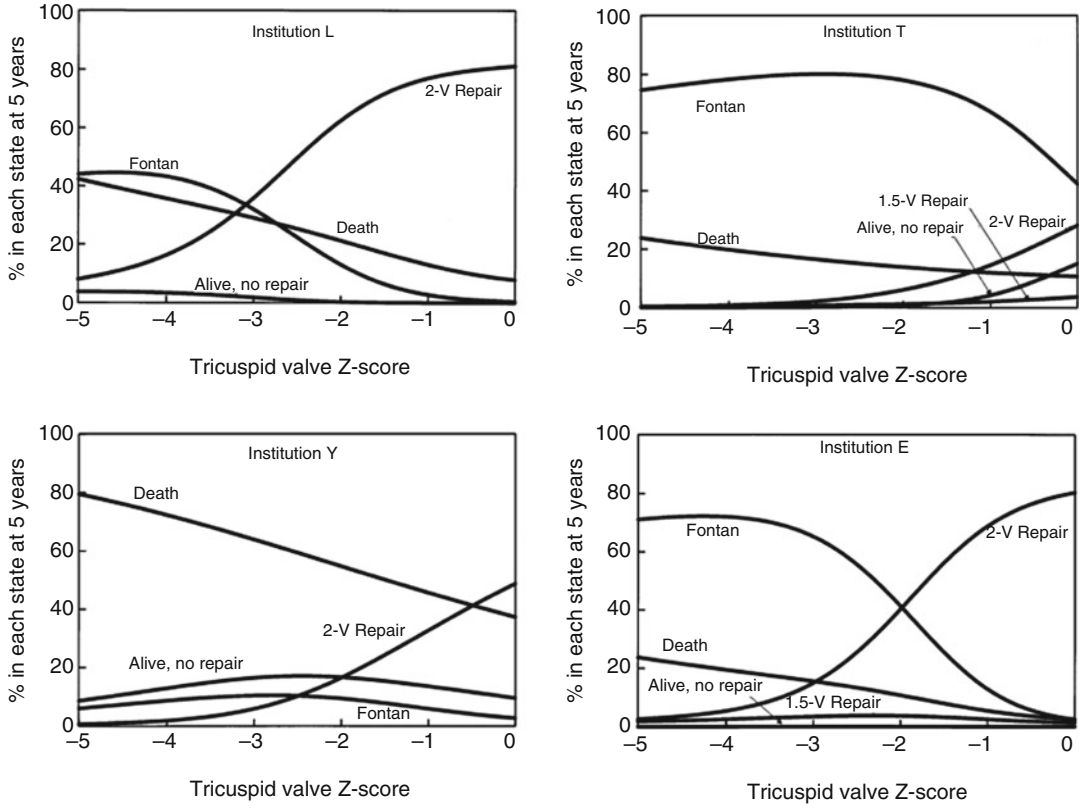
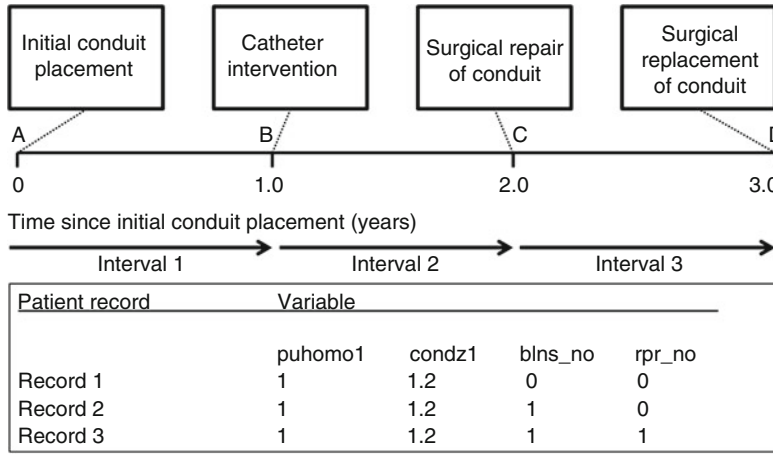


Fig. 13.8 A competing risks analysis is used to examine the relationship between tricuspid valve z-score, inter-institutional management patterns, and a group of mutually exclusive endstates. The z-score was previously found to be a useful surrogate for the size and adequacy of right heart structures in pulmonary atresia with intact ventricular septum. Using this analysis, it is apparent that there are differences in the relationship between tricuspid valve z-score and death between institutions. Importantly, it is also apparent that some institutions (e.g. Institution T) use a Fontan strategy across a wide spectrum of tricuspid valve z-scores with a low death rate, but at the expense of failing to offer two-ventricle palliation to patients with relatively large tricuspid valves (e.g. z-scores between 0 and −2). In contrast, Institution L chose more frequent two-ventricle repairs (and less frequent Fontan strategies) in patients with small tricuspid valves with a relative increase in the death rate in the patients with the smallest tricuspid valves. Finally, Institution E had a balanced strategy with two-ventricle repairs in patients with larger tricuspid valves and Fontan strategies in patients with smaller tricuspid valves – and a corresponding low death rate across the spectrum of tricuspid valve z-scores (Reprinted with permission from Ashburn et al. [2]

particular value. These scores reflect the probability of a given patient to have fallen in one group or the other, based upon various demographic and morphologic characteristics. The scores are included in the parametric hazard analysis to adjust for differences in baseline characteristics among the groups for comparison. This well-established statistical method has proven to be an essential tool to minimize (but not eliminate) an important limitation of our observational studies – i.e., that patients are not randomized into treatment groups.

Modulated Renewal

Management of patients with congenital heart disease often requires post-operative reintervention. Thus the repair is 'renewed,' just as if an old pair of shoes was re-soled. Using the re-soled shoe analogy, we hypothesize that the new sole may be 'better than new', 'as good as new', or 'worse than new'- depending on the durability of the new sole. Similarly, a surgical repair may have any of the same three potential trajectories depending on the durability of the re-intervention. The statistical technique is called



Patient record	Variable			
	puhomo1	condz1	blns_no	rpr_no
Record 1	1	1.2	0	0
Record 2	1	1.2	1	0
Record 3	1	1.2	1	1

Fig. 13.9 Example of "chopping" of a hypothetical child's longitudinal record into multiple discrete segments. Time zero is set to the date of initial pulmonary allograft insertion, which was followed by conduit balloon dilatation with stenting, surgical conduit repair, and finally conduit replacement, at 1-year intervals. Thus, the four events are used to punctuate three segments that are used to model the occurrence of these events. Records 1, 2 and 3 refer to segments AB, BC and CD along the timeline. Record 1 has a left censoring time of A and a right-censoring time of B, record 2 is left censored by B and right censored by C, and so on. The variables puhomo1 and condz1 are constant because they refer to the initial type and z-score of the conduit, respectively. However, the variables blns_no (cumulative number of conduit dilatations with stenting) and rpr_no (cumulative number of surgical conduit repairs) are time-varying; each variable turns from 0 to 1 when the corresponding interval arises. These two variables track the cumulative exposure to these interval treatment events, thus the values are ordinal and do not decrease with time. A proposed method to incorporate many longitudinal echocardiographic measurements of conduit dysfunction – a heretofore unmet challenge in parametric hazard analysis of this type – would involve the expansion of the "events" bracketing each interval by including various echocardiographic measurements from dozens of diagnostic studies performed across the entirety of the patient record (Reproduced from Poynter [11])

modulated renewal. Jegatheeswaran and colleagues used modulated renewal methodology to characterize the risk of re-interventions among children with repaired interrupted aortic arch [7] and the analysis provides insight into the degree to which interrupted aortic arch is a chronic condition that frequently requires multiple subsequent reinterventions.

Scoring Systems Based on Common Dataset Integrated Parametric Models

Another important lesson learned through experience concerns the creation of clinical calculators. Hickey and colleagues developed a parametric equation to facilitate decision making in neonates with critical aortic stenosis in whom one- and two- ventricle repairs were being considered [8]. The authors used a parametric equation to estimate 5-year survival if the same (theoretical patient) had a one-ventricle repair compared to a two-ventricle repair. Surgeons using the calculator could input specific patient variables to generate an estimate the relative advantage (or disadvantage) of a one-ventricle over a two-ventricle repair. The calculator translates a complex statistical model into a practical tool to facilitate clinical decisions at the bedside.

Conclusion

The CHSS Datacenter is a unique research organization that has evolved and learned since 1985. The focus on rare lesions and complex management strategies has played to the strengths of the Data Center: superb statistical leadership, a dedicated Data Center staff collecting data from institutions across North America, and lifetime follow up of our cohorts. The institution of the Kirklin/Ashburn Fellowship has been a critical ingredient in our ongoing academic

success. All this, however, would never have been possible without the steadfast financial support and academic contributions of the membership of the Congenital Heart Surgeons Society.

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