15 Databases for Pediatric Cardiac Transplantation: The United Network for Organ Sharing/ Scientific Registry of Transplant Recipients (UNOS/SRTR) and the Pediatric Heart Transplant Study (PHTS)

Ryan R. Davies

Abstract

Collection, analysis, and dissemination of data have been part of the transplantation since its earliest days. The two largest databases containing information on pediatric cardiac transplant patients are the United Network for Organ Sharing/Scientific Registry of Transplant Recipients (UNOS/SRTR) database and the Pediatric Heart Transplant Study (PHTS). These data have enabled examination of patients undergoing transplantation, including modeling of outcomes, analysis of allocation decisions, and the examination of criteria for listing. Extensive literature exists utilizing this data, but must be read critically, recognizing the limitations presented by missing variables (whether uncollected or collected but left blank), reproducibility, and small sample sizes among pediatric patients. However, despite these limitations, these datasets provide an important resource in the ongoing examination of cardiac transplantation in children.

Keywords

Transplantation • Cardiac failure • Pediatric cardiac transplantation • Pediatric cardiac failure • Pediatric cardiac disease • Congenital cardiac disease • United Network for Organ Sharing/Scientific Registry of Transplant Recipients (UNOS/SRTR) database • Pediatric Heart Transplant Study (PHTS)

Introduction

This chapter is based in part on a presentation at The Seventh Annual Meeting of The Multi-Societal Database Committee for Pediatric and Congenital Heart Disease: "Meeting Theme: The relationship between Outcomes Analysis,

R.R. Davies, MD
Nemours Cardiac Center, A.I. duPont Hospital for Children and Department of Surgery, Thomas Jefferson University,
1600 Rockland Road, Wilmington, DE 19806, USA
e-mail: rdavies@nemours.org

P.R. Barach, J.P. Jacobs, S.E. Lipshultz, P.C. Laussen (eds.),
Pediatric and Congenital Cardiac Care: Volume 1: Outcomes Analysis,
DOI 10.1007/978-1-4471-6587-3_15,

Quality Improvement, and Patient Safety", Tuesday, September 20, 2011 and Wednesday, September 21, 2011, Selwyn College, University of Cambridge, Cambridge, United Kingdom, and, subsequently published in the World Journal of Pediatric and Congenital Heart Surgery [1].

Even the busiest pediatric cardiac transplant centers have averaged fewer than 21 transplants per year over the past 25 years [2]. Thus, in common with other areas of pediatric heart surgery, outcomes analysis is hampered by the limited sample size available at any individual institution. In this setting, multi-institutional data collection is necessary in order to develop statistically-sound, comprehensive analyses and conclusions.

There are multiple databases, including both voluntary multi-institutional collaborations and federally mandated submissions, containing clinical outcomes data on patients undergoing cardiac transplantation. Each of these databases has advantages and disadvantages. A thorough understanding of the historical background, data collection and distribution, and techniques of analysis each dataset is important in critically evaluating published outcomes data.

The UNOS/SRTR Database

Historical Background

There is an alphabet soup of acronyms for organizations involved in administering transplantation with the United States of America. The dataset that is commonly referred to as the United Network for Organ Sharing (UNOS) Database consists of information collected by UNOS and maintained and analyzed by the Scientific Registry of Transplant Recipients (SRTR). UNOS is the public corporation which administers the Organ Procurement and Transplant Network (OPTN), under contract with the federal government. In addition to administering the OPTN, UNOS performs other functions including education and awareness of issues surrounding organ donation and transplantation. In the literature, the UNOS Database may be referred to by any of the following acronyms: SRTR database, UNOS database, OPTN database (or combinations thereof). The acronym used is often an indicator of the administrative source of data analyzed. However, in all cases the majority of the underlying data is collected by UNOS as part of the process of listing, donation, transplantation, and follow-up. SRTR combines this information with data from other sources including the Social Security Death Master File. Throughout this chapter we have referred to this database as the **UNOS/SRTR database**.

From the first successful renal transplant (in 1954) and the first organ retrieval from a cadaveric donor (in 1962) through the 1970s, transplantation was coordinated by local and regional groups of hospitals and transplant physicians [3, 4]. This resulted in variability in the provision of transplant care, including definitions of donor brain death and the allocation of donor organs. In response to this variability (as well as a concern about monetary remuneration of donors), the United States Congress passed the National Organ Transplantation Act (NOTA) in 1984. Among its effects was the creation of a single Organ Procurement and Transplantation Network (OPTN) and nationalization of the transplant lists. The United Network for Organ Sharing (UNOS) (a successor to one of the regional groups: Southeastern Organ Procurement Organization), has had the contract to administer the OPTN since its inception.

As part of developing equitable organ allocation schemes, NOTA stated explicitly that one of the roles of the OPTN was to "collect, analyze, and publish data concerning organ donations and transplants." It also established what would become the Scientific Registry of Transplant Recipients (SRTR):

> The Secretary [of Health and Human Services] shall, by grant or contract, develop and maintain a scientific registry of the recipients of organ transplants. The registry shall include such information respecting patients and transplant procedures as the Secretary deems necessary to an ongoing evaluation of the scientific and clinical status of organ transplantation [5].

The SRTR is currently administered by the Minneapolis Medical Research Foundation (MMRF) and supports ongoing evaluation of solid

organ transplantation. By providing a rigorous data and analytic component, it has an essential role in providing data to support the development of evidence-based policies of allocation through collaboration with the transplant community and OPTN. Therefore, NOTA enshrined ongoing data collection and analysis as an integral part of OPTN and organ transplantation.

In addition to the contracted analytic functions of the SRTR, the OPTN Final Rule committed to the importance of public access to scientific data:

> **Respond to reasonable requests from the public for data needed for bona fide research or analysis purposes**, to the extent that the OPTN's or Scientific Registry's resources permit, or as directed by the Secretary. The OPTN or the Scientific Registry may impose reasonable charges for the separable costs of responding to such requests. Patient-identified data may be made available to bona fide researchers upon a showing that the research design requires such data for matching or other purposes, and that appropriate confidentiality protections, including destruction of patient identifiers upon completion of matching, will be followed. All requests shall be processed expeditiously, with data normally made available within 30 days from the date of request (emphasis added) [6].

This OPTN Final Rule has resulted in a situation in which UNOS members (transplant centers, organ provider organizations (OPOs), histocompatibility laboratories) can obtain free access to the entire OPTN dataset. Fee-based access is available to interested researchers who are not UNOS members through the SRTR, and the SRTR can also provide additional programming. The UNOS/SRTR data is thereby both easily accessible to a wide-range of researchers and analyzed in a rigorous and consistent manner by the SRTR to provide comprehensive and reliable data to UNOS and the public.

Data Collection

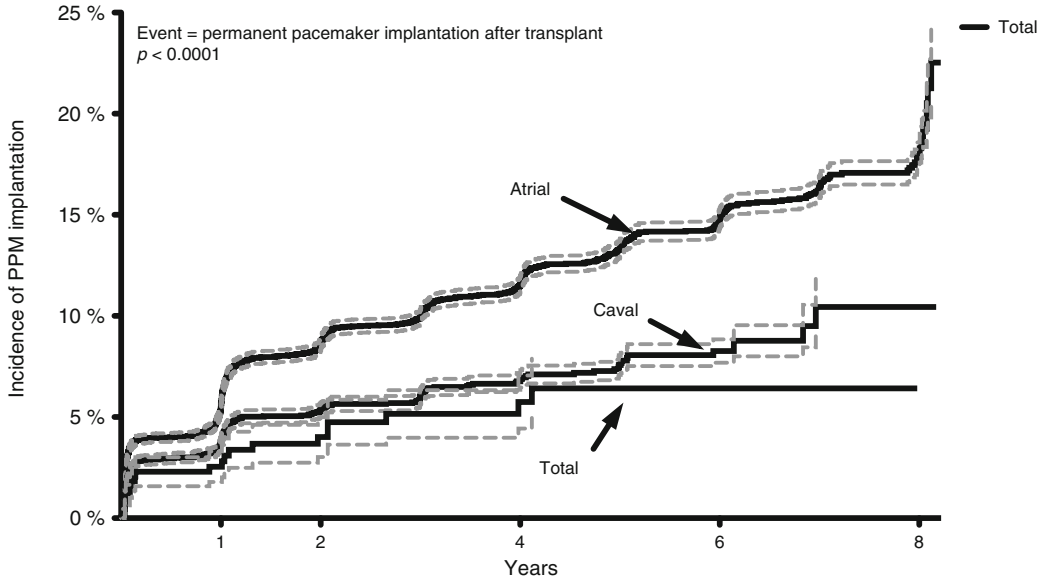
The UNOS/SRTR Database consists of all transplants performed in the United States from 1988 to the present. It consists of data collected at listing, at transplantation (both regarding the recipient and the donor), and in yearly follow-up. Data submission is a mandatory aspect of membership in UNOS and allocation of organs from the OPTN [7]. However, data submission may not necessarily be complete and missing data are a persistent problem in analyzing UNOS/SRTR data (see below) [7].

With respect to pediatric heart transplants, the primary weakness of the UNOS/SRTR dataset is the lack of data collection specifically directed at issues in pediatric and congenital patients, including exact congenital diagnosis, previous procedures, and physiologic status when listed. To date, studies evaluating congenital heart disease as a risk factor have had to use the broad and non-specific designation lumping all patients with congenital heart disease (CHD) together [8–10]. In addition, potential risk factors that may be important among pediatric patients may not be adequately captured in the adult-centric UNOS/SRTR dataset; such potential risk factors include [11–16]:

- technical aspects such as the need for pulmonary artery reconstruction,
- timing following failure of attempted surgical palliation,
- preoperative functional status, and
- the presence of non-cardiac congenital anomalies or genetic syndromes.

As the challenges with missing data make clear, another important drawback of the UNOS/SRTR dataset is the lack of an audit mechanism. While UNOS audits transplant centers and other transplant organizations on a routine basis, it is interested primarily in factors which might influence equitable allocation and quality assurance programs to prevent important errors such as misidentification of ABO type resulting in hyper-acute graft rejection. Factors which may be important to outcomes analysis, including levels of panel reactive antibodies, the numbers of previous sternotomies, are unlikely to be audited and compared to the medical record for accuracy. Therefore, the accuracy of the data (especially secondary outcomes such as lengths-of-stay, time to rejection episodes, and the incidence of non-compliance) has not been independently verified.

In addition to the potential for data inaccuracies, follow-up data within the dataset is submitted



Subjects at risk

Atrial	9,175	6,771	4,842	3,012	840
Caval	4,855	3,061	1,498	397	26
Total	438	280	159	43	2

Fig. 15.1 Kaplan-Meier estimates of the cumulative hazard of permanent pacemaker insertion after transplantation. Eight-year estimates are illustrated as a function of the type of transplant anastomosis: *CAVAL* Bicaval anastomosis, *ATRIAL* biatrial anastomosis, *TOTAL* total heterotopic transplant anastomo- sis. Numbers of subjects at risk at each time point are given across the *bottom*, and standard errors are shown by the *dashed lines*. P<0.0001 (caval vs atrial) (Reprinted from Davies et al. [72], with permission from Elsevier)

yearly by the transplant center, rather than event-driven submissions. This strategy of collection of data leads to follow-up data with steps reflecting yearly submission of follow-up data forms, rather than gradual slopes indicating the actual date of occurrence of the event (Fig. 15.1). Therefore, other than endpoints such as graft failure or death, the analysis of long-term outcomes is constrained.

Data Access and Analysis

As noted above, the legislative history of NOTA and the OPTN Final Rule has resulted in a database that is easily accessible to a wide-range of investigators. The result is that a wide-range of investigators with differing interests and differing expertise have the potential to perform complex statistical analyses of the data and provide relatively frequent updates to previous analyses. This contrasts with other multi-institutional databases within cardiac surgery, such as the Society of Thoracic Surgeons-Congenital Heart Surgery Database, the New York State Cardiac Surgery Reporting System, and the Pediatric Heart Transplant Study. In these cases, access to the raw data is limited and controlled. Also, statistical analyses are often performed by a single entity, and funding may be required to reimburse for statistical analysis (similar to the SRTR analyses of UNOS/SRTR data).

The more open nature of the UNOS/SRTR database has resulted in a wide-range of publications. Often, multiple authors may investigate the same question using different methods – as with the comparison between bicaval and biatrial anastomoses [17, 18], the impact of ventricular assist devices on post-transplant outcomes [19, 20], or outcomes following transplantation among adults with congenital heart disease [8, 9]. While this approach may result in duplicative effort, it often results in a broader understanding of the issue, and consistency of results across analytic methods reinforces the reliability of the findings.

However, the lack of standardization evident in these various analyses also illustrates an important pitfall of open access to raw data. Readers of manuscripts based on UNOS/SRTR data must be diligent in assessing the statistical methods. Different research teams may handle missing variables in importantly different ways [17, 18], or may convert raw data (especially the often informative but labor-intensive text fields) into variables using different techniques. Therefore [19, 20], the open-access nature of the UNOS/SRTR data places a higher burden on the clinician to evaluate the methods used within each individual manuscript.

Pediatric Heart Transplant Study

Historical Background

In the late 1980s, data from both the International Society for Heart and Lung Transplantation Registry (see below) and UNOS/SRTR suggested that there were significant differences in survival and risk factors for death between adult and pediatric heart transplant recipients [21]. In 1991, to address the lack of pediatric specific date, a group of pediatric heart transplant clinicians along with investigators within the Department of Surgery at the University of Alabama-Birmingham formed a voluntary, multi-institutional, collaborative effort to "advance the science and treatment of children while waiting for cardiac transplantation [21]." This collaborative effort, called the Pediatric Heart Transplant Study (PHTS), began collecting data in 1993. In 2000, the PHTS adopted a more formal structure including a governing board and standing committees to supervise various aspects of the effort. Members of the PHTS support research efforts through annual fees. Current membership consists of 44 member institutions from the United States, Canada, and the United Kingdom [22].

Data Collection

In contrast to the mandatory, publicly accessible UNOS/SRTR database, the PHTS is a voluntary association of transplant centers. Membership and data submission is voluntary. PHTS currently includes approximately 66 % of the pediatric transplants performed in the United States [4]. There are several advantages to both the data fields collected and the data collection methods as compared to the UNOS/SRTR data collection.

First, because the PHTS is a pediatric-specific database, data collection is geared toward variables of particular interest to pediatric transplantation, including congenital diagnoses and previous surgeries [23]. This advantage is somewhat mitigated by changes over time in the diagnostic and procedural categories through iterations of data collection, reinforcing the importance of standardized diagnostic and procedural coding, as described elsewhere in this book (in the chapter by Franklin and colleagues titled: ***Nomenclature for Congenital and Pediatric Cardiac Disease: Historical Perspectives and the International Pediatric and Congenital Cardiac Code***).

Second, in contrast to UNOS/SRTR, data collection is event-driven. Following entry into the database at listing, information is gathered annually but also at any of the following events [22]:

- transplantation,
- death,
- rejection,
- infection,
- malignancy,
- allograft vasculopathy, and
- retransplantation.

Time-to-event analysis is, therefore, more robust than within the UNOS/SRTR data set. In addition, the information collected at each event is much more detailed because data submission includes event-specific forms.

Data Access and Analysis

The data is not publicly accessible, nor is it directly accessible to member institutions. Instead, data is collected and centralized at the PHTS within the University of Alabama – Birmingham (UAB). Proposals for research are submitted to a Scientific Committee which meets twice a year to approve projects. Statistical analysis is performed by PHTS/UAB staff [22]. While advantages exist in

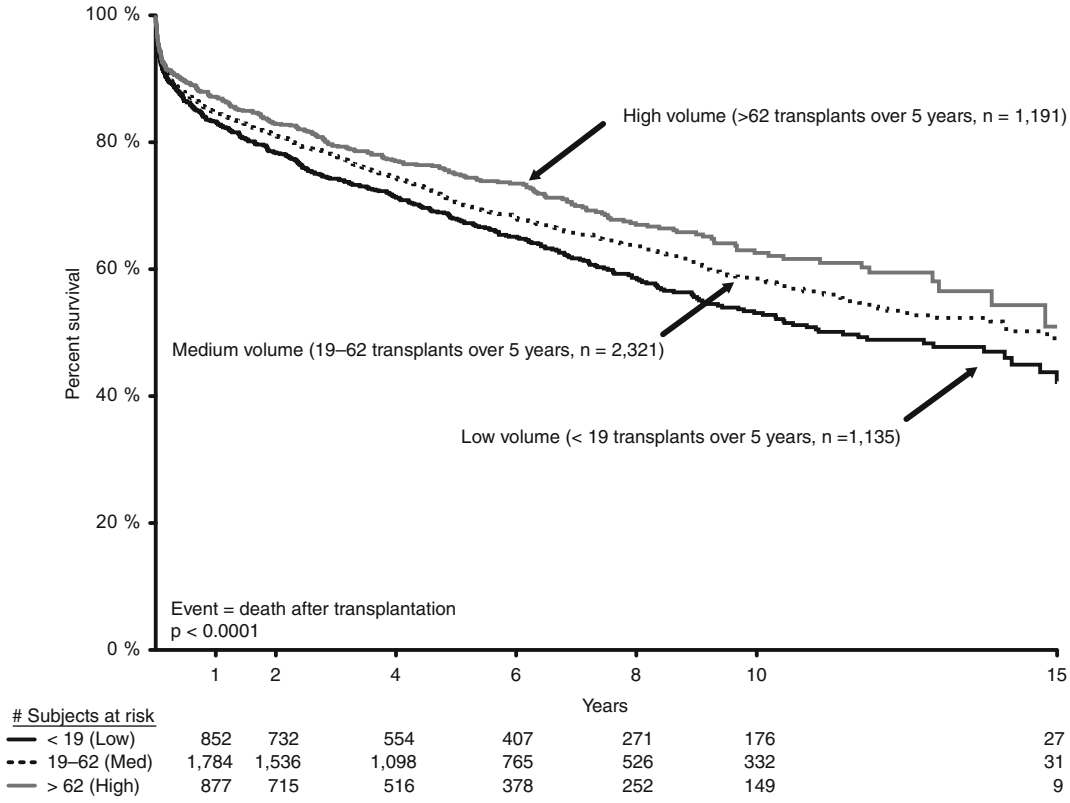


Fig. 15.2 Fifteen-year Kaplan-Meier survival estimates as a function of transplant center volume ($P<0.0001$), unadjusted for risk. The number of patients at risk is given at the *bottom* of the graph (Reprinted from Davies et al. [24])

terms of consistency and reliability, this strategy does result in a more limited number of publications derived from the data source. In addition, it is important to recognize that the PHTS transplant centers primarily higher volume, children's hospitals. The extent to which the experience within the PHTS centers is representative of the experience across the broad spectrum of transplant centers performing pediatric cardiac transplantation is not clear, especially when lower volume centers have higher mortality – especially in high risk patients (Figs. 15.2 and 15.3) [24].

Other Databases Including Pediatric Transplant Data

While the majority of multi-institutional publications regarding pediatric cardiac transplantation are based on either UNOS/SRTR or PHTS data, other databases have important applications in analyzing outcomes of children undergoing cardiac transplantation. These additional databases that capture information related to patients undergoing transplantation for pediatric and congenital cardiac disease include:

- The International Society for Heart and Lung Transplantation (ISHLT) Registry,
- INTERMACS/PEDIMACS, and
- The Society of Thoracic Surgeons-Congenital Heart Surgery Database (STS-CHSD).

International Society for Heart and Lung Transplantation (ISHLT) Registry

The ISHLT created its transplant registry to provide an ongoing assessment of the status of thoracic organ transplantation worldwide.

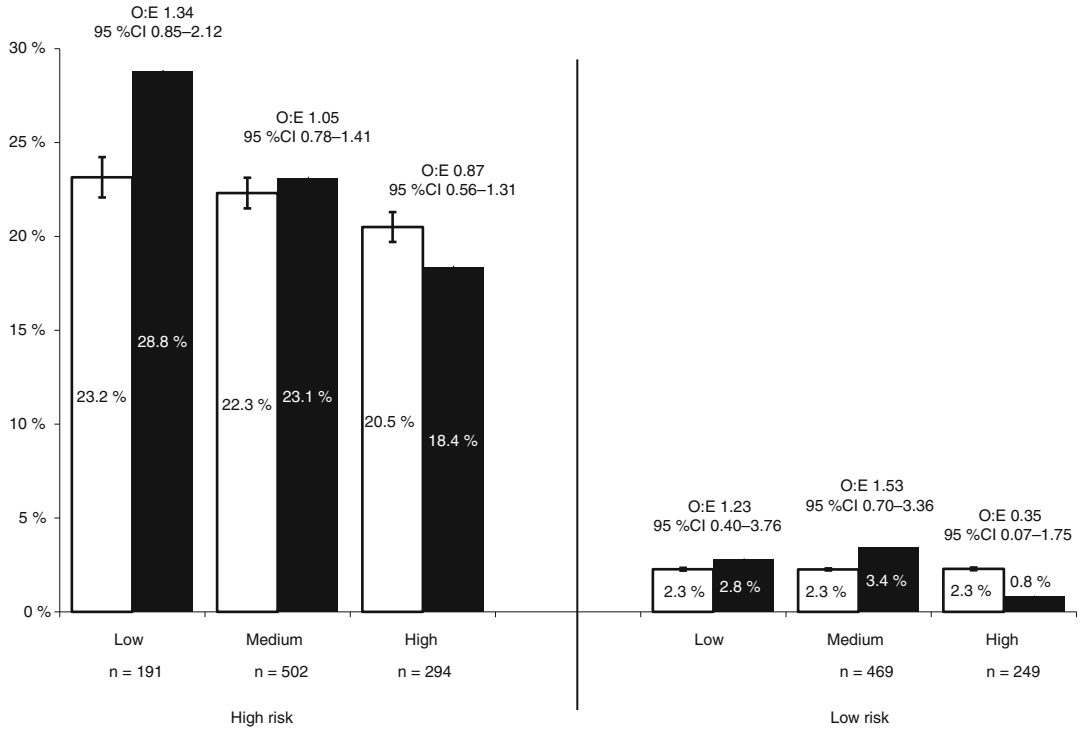


Fig. 15.3 Predicted (*white* column) versus observed (*black* column) postoperative mortality rates by volume of transplants performed in the previous 5 years by the transplant center. Results are stratified by patient risk: high-risk patients (>75th percentile for postoperative mortality) are shown at the *left*, low-risk patients (<25th percentile for postoperative mortality) are shown on the *right* (Reprinted from Davies et al. [24])

It currently aggregates data from nearly 400 transplant centers, including both individual institutions and through data interfaces with government agencies including UNOS/SRTR [25]. As such, the data has the same weaknesses as UNOS/SRTR data, magnified across the diversity of submitting institutions. The primary advantage of the ISHLT registry is that it allows for international comparisons of transplant outcomes. Otherwise, the data is essentially a subset of the data collected by UNOS/SRTR.

INTERMACS/PEDIMACS

The INTERMACS database is a voluntary database funded by a contract from the National Heart Lung and Blood Institute and currently run by staff also at the University of Alabama. Although voluntary, reimbursement for destination ventricular assist device therapy from the Centers for Medicare and Medicaid Services is contingent on submission of data to a national, audited database, and most high-volume ventricular assist device centers participate [26]. To date, submission of pediatric data is limited, but as mechanical circulatory support becomes more common in children, it will provide an important adjunct to the two previous databases in exploring the outcomes of patients with end-stage heart failure [27].

Society of Thoracic Surgeons Congenital Heart Surgery Database (STS-CHSD)

Other chapters in this text provide a more extensive description of the STS-CHSD. Currently, the STS-CHSD has not been used in analyzing pediatric transplant data, largely because it does not contain variables of critical importance to

transplant outcomes, including donor and match variables, as well as long-term graft follow-up. However, it contains substantially more data regarding congenital diagnoses, historical procedures, and technical details of the transplant operation than any of the previously described data sources. Linkage of the STS-CHSD to UNOS/SRTR or PHTS data has the potential to leverage the strengths of the different databases and mitigate the weaknesses.

Outcomes Analysis in Pediatric Cardiac Transplantation Using Large Datasets

Analysis of outcomes in transplantation is needed for several distinct but related areas: (1) prediction of individual risk of transplantation and identification of appropriate transplant candidates, (2) evaluation of individual transplant programs, including quality assessment and improvement as well as public reporting of results, and (3) evaluation of the impact of global policy decisions – especially regarding organ allocation – in order to optimize the utility of each available donor allograft.

Each of these areas of analysis has unique challenges, but they have in common the limited outcomes measures available. Whether using the UNOS/SRTR dataset or data from the PHTS, patient and graft survival are the primary outcomes available within the datasets. These data provide only a limited picture. Other outcomes that may be even more pertinent include indicators of quality of life and of functional status. With the increasing use of implantable ventricular assist devices (especially in older, near-adult, pediatric patients), quality of life rather than absolute survival will become more important as the survival following transplantation and VAD implantation becomes equivalent [28].

Currently, however, the ease of collection and analysis of a binary and easily assessed outcome, such as patient survival, graft survival, or the occurrence of drug-treated infection, make these the de facto standard for assessments of outcomes in pediatric cardiac transplantation. We will focus on these binary outcomes here.

Prediction of Individual Risk

Estimation of the risk of mortality or graft failure for an individual patient following cardiac transplantation is crucial to all aspects of outcomes analysis. Obviously counseling of individual patients and their families regarding the patient's likelihood of post-transplant survival is necessary for informed decisions regarding candidacy. In addition, without being able to risk-adjust outcomes at individual center, it becomes impossible to compare centers with each other or to assess changes outcomes at an individual center over time. Furthermore, estimates of the survival with and without an allograft are critical to optimizing allocation schema.

Models of Risk on the Waitlist

Models of waitlist outcomes have been published in both adults and children, but – in addition to the predominance of adult research – they have several drawbacks [8, 29–33]:

- First, within the pediatric population, in order to identify as many risk factors as possible, longer periods of time are used to increase the sample size [24, 34]. As the field advances and clinical care evolves, use of these longer periods of time may result in a heterogeneous population being analyzed together. Especially where mortality has decreased over time [35], much of the mortality will have occurred in the least contemporary population and the risk factors important in this earlier era will be overweighted in any combined analysis.
- Second, to date these models have been constructed to examine specific risk factors as opposed to attempting to identify the most accurate model [31, 32, 36].
- Third, reporting of waitlist mortality models often fails to include enough information (including intercepts and model parameter estimates) to reconstruct the model for use in individual risk prediction [33, 35, 37].
- Fourth, the heterogeneity of the pediatric heart failure population (including dilated cardiomyopathy [DCM] patients, patients with

CHD, and those with restrictive cardiomyopathy, among others) suggests that risk factors may vary between diagnoses. Factors important to patients with CHD may differ significantly from those important in patients with DCM [11, 31, 38].

- Finally – and most importantly – to date no waitlist model has been constructed and validated in a separate population in order to identify its independent accuracy for use outside of the derivation population.

Despite these limitations, data from both the PHTS and UNOS/SRTR has been consistent in identifying certain risk factors as predictive of waitlist mortality, including: the need for ECMO, mechanical ventilation, and a diagnosis of congenital cardiac disease [31–37, 39]. Other factors, including race, socioeconomic status, and age have varied across models. If we are to move to a model for allocation of hearts similar to the system for allocation of lungs currently in use (see below), more accurate prediction of mortality on the waitlist is required in order to allocate available allografts to those patients least likely to survive without transplantation. Not all of the limitations can be addressed, but further analysis of the UNOS/SRTR database and the PHTS database, as well as potential linkages to other datasets, should enable improvements in the accuracy of predicting mortality on the waitlist.

Models of Risk of Mortality After Transplantation

Several researchers have published risk prediction models using both UNOS/SRTR and PHTS data [10, 24, 40, 41]. These models may be helpful in estimating risk for an individual patient. However, a critical assessment of model accuracy is essential prior to using the model in a particular population of patients.

The c-statistic is valuable as a rough (though not perfect) [42] estimate of model accuracy. For example, Weiss et al. have recently published a score to be used in predicting outcomes among adults following cardiac transplantation [43]. The c-statistic for the final model was only 0.65, suggesting that it lacks significant discriminatory ability. In contrast, models used in identifying the importance of volume in outcomes following pediatric heart transplant have a c-statistic of 0.75 [24], suggesting that better discrimination is possible. However, a c-statistic of 0.75 suggests that much of the variation in outcomes results from variables not in the model. It is likely that other variables, poorly contained within the UNOS/SRTR dataset, may be particularly important including functional status, nutritional status, and the presence of cachexia. Validation of the model in a population distinct from that in which it was derived is an important step in assessing the accuracy of any model.

Table 15.1 Risk factors to derive simplified score predictive of mortality after cardiac transplantation in children

Risk factor	Weighted score
ECMO	4
Number of high risk criteria >3*	3
Reoperation	2
Stroke	2
Renal insufficiency (creatinine clearance <40 cc/min)	2
Congenital heart disease	1
Mechanical ventilation	1
Admitted to ICU	1

*High risk criteria include: PVRI >6 woods units, creatinine clearance >40 cc/min, hepatitis C positivity, donor: recipient weight ratio <0.7, panel reactive antibody >40 %, retransplantation, age ≤1 year

Given these limitations, are there models which may be useful? Prediction of risk is often a balance between accuracy and simplicity. For example, the group from Columbia has looked at estimates of mortality among high-risk transplant recipients using a simplified risk score (Table 15.1) (Fig. 15.4) [10]. While the model provides a rough estimate of outcomes and may be useful in broadly assessing the risk of any individual patient, this comes at the expense of accuracy (importantly, measures of accuracy of the model are not reported in the manuscript). The data from that study also illustrates one problem with many of these risk prediction models, which is the small number of patients at the highest risk levels. This problem often results in

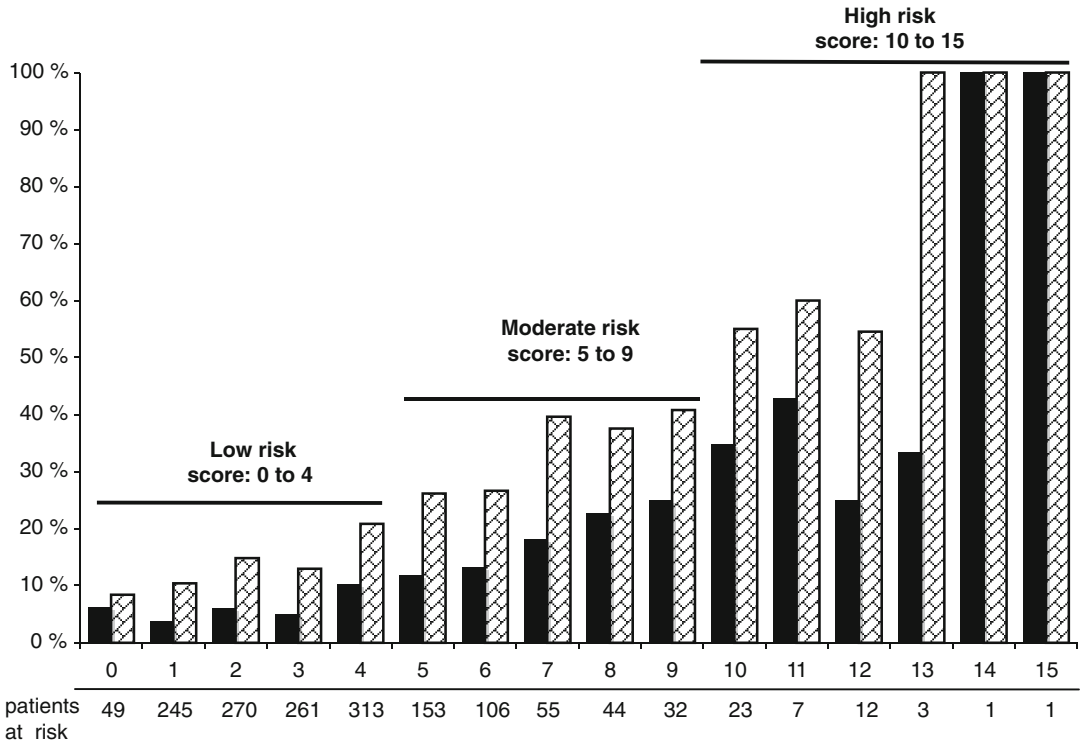


Fig. 15.4 Observed 30-day (*black*) and 1-year (*slanted brick pattern*) mortality for each risk score in patients with at least one high risk criteria ($P < 0.0001$) (Reprinted from Davies et al. [24])

models overestimating risk among the highest risk patients [44].

The PHTS dataset has the potential to provide more accurate estimates of post-transplant outcomes because it is more comprehensive with regard to variables of specific interest in pediatric cardiac transplantation [31]. A predictive model based on that data would be particularly interesting. While a predictive model based on PHTS data was presented in 2008, it has not yet been published in a form which would enable prediction of individual risk of post-transplant mortality [40]. Similarly, an attempt to investigate high-risk criteria for pediatric transplant has not moved from the abstract to completed manuscript phase [39].

As with waitlist models, there is broad agreement on several risk factors for poor outcomes after pediatric cardiac transplantation, including congenital heart disease, the need for extracorporeal membrane oxygenation or mechanical ventilation, and renal failure [10, 24, 45]. Other factors, including measurements of cardiac dimensions and the etiology of cardiomyopathies, may be important in specific subsets of pediatric patients [31]. Current data have identified risk factors for poor outcomes, and currently available modeling enables broad stratification of patients into risk categories [10]; however, accurate prediction of individual risk may require comprehensive modeling within patients subsets, likely categorized by etiology. UNOS/SRTR data may not be sufficient and linkage to other datasets may be required.

Summary

In summary, while there exist several published models of both pre-transplant mortality and post-transplant mortality among children requiring cardiac transplantation, none have been externally validated. Even the most accurate models suggest that additional variables not currently captured

within the datasets explain important amounts of variation in outcome. Ongoing research, including the potential linkage of UNOS/SRTR or PHTS data to other datasets such as the STS-CHSD may be required to provide modeling with the accuracy to predict individual outcomes in these children.

Assessment of Individual Transplant Centers

Estimates of outcomes at individual transplant centers are publicly available based on SRTR analysis of the UNOS/SRTR dataset (see SRTR website: [http://www.srtr.org/csr/current/Centers/Default.aspx]) on a semi-annual basis. The SRTR uses risk-adjustment models that are available on the website to evaluate and compare programs. Unfortunately, the SRTR models have several limitations in assessing inter-institutional variation. First, the models do not account for several factors known to influence outcomes, including

- preoperative kidney function [24, 46],
- etiology of heart failure [24, 46–50], and
- reoperative sternotomy [24, 47, 49].

Furthermore, as noted in the introduction to this chapter, pediatric cardiac transplantation at even the busiest programs is a relatively low-volume procedure.

Throughout pediatric and congenital heart surgery, low center volume for individual procedures makes statistically-valid comparison of outcomes across centers challenging [51]. Of the 51 programs performing pediatric heart transplants, the SRTR was only able to identify a single program (with a 25 % 1-year survival rate among four patients) as having a statistically significant lower than predicted survival [52]. Thus, there are important limitations to the use of the results published in the SRTR data or program-specific reports as a measure of outcomes across centers.

Improvements in predictive mortality models will not address this fundamental challenge: low volumes of patients undergoing pediatric cardiac transplantation at individual centers makes it difficult to identify significant deviations from predicted outcomes. However, accurate estimates of risk adjusted mortality may enable identification of centers with excellent outcomes and opportunities for improvement at lower performing centers even in the absence of statistically significant variation.

Evaluation of National Policies and Rules of Allocation

The UNOS/SRTR database is particularly useful in evaluating national policies and rules of allocation because it includes all of the transplants performed in the United States of America. In contrast, analysis of the more limited (by number of centers) and broader (by country) PHTS database, may not lead to conclusions valid across the entire spectrum of centers of transplantation in the United States of America. Single center studies have even more potential for findings which cannot be generalized across the entire spectrum of transplant centers.

Criteria for listing and transplant candidacy are based on a combination of anecdotal experience, individual or consensus expert opinion, published single center results, and previous research utilizing large multi-institutional datasets. In all cases, the open nature of the UNOS dataset enables clinicians and researchers with a countervailing opinion to analyze or re – analyze the data and identify areas where current criteria are not consistent with current national experience. This availability of data provides the opportunity for evidence-based refinement.

Among the important challenges to conventional listing criteria are suggestions that a body mass index (BMI) greater than 30 kg per meter squared might be a contraindication to transplant [53], and a bias against allocation across ABO blood types in infants in UNOS heart allocation rules. Evaluation of BMI has, rather than confirming the bias against patients with BMI greater than 30 kg per meter squared, suggested that (as in other areas of cardiac surgery) the association between BMI and mortality is U-shaped. Patients at both the lowest and highest BMI are at high risk

for early mortality and those with BMI between 30 and 34.9 had mortality equivalent to those with "normal" BMI [54]. Similarly, in the context of ABO-incompatible cardiac transplantation, recent research using the UNOS database (as well as outcomes from individual centers) suggests that early outcomes are equivalent among infants with ABO-compatible allografts and ABO-incompatible allografts [55, 56]. These data have contributed to recent proposals to change UNOS rules to eliminate allocation preference given to ABO compatible allograft offers for infants awaiting cardiac transplantation [30, 57].

The broad-based nature of the UNOS/SRTR dataset may also provide a more "realistic" picture of true transplant outcomes than single-center experience. While high-volume centers have demonstrated that transplantation to patients with elevated pulmonary vascular resistance index (PVRI) as high as 9 woods units is not associated with increased mortality [58], PHTS data corroborates these findings [59]. In contrast, UNOS data suggests that among patients over 1 year of age, higher PVRI is associated with poor outcomes [60]. How to reconcile these findings? Perhaps, high volume transplant centers can lessen the risk of "high-risk" transplants, so that the findings from the high-volume centers and PHTS are real, but caution should be exercised as lower volume centers embark on "high-risk" transplants. Thus the UNOS/SRTR data provides an important counter-weight to the reporting of outcomes from only high-volume institutions. In the context of transplantation where volume and outcomes are linked (especially in high-risk patients) [24], evaluation of the broader experience is critical to defining broad criteria and truly estimating risk.

Accurate estimation of both post-transplant and waiting list risk of mortality in a national sample may also be critical in refining allocation of cardiac allografts. Currently allocation of pediatric donor hearts is predicated on reducing waitlist mortality. Factors indicating more severe cardiac failure are used as the primary criteria for listing status (Table 15.2). But when donor allografts are assigned to patients at high-risk for post-transplant mortality, this strategy may result in an overall loss of efficiency and wasting of donor organs. As stated in the OPTN Final Rule: "allocation policies ….[s]hall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement [7]" (Table 15.1). In contrast to the situation with cardiac transplantation, current strategies of allocation of lungs demonstrate the potential for UNOS/SRTR data to provide support for optimizing the allocation of organs using a combination of predicted survival on the waitlist and predicted survival after transplantation in each patient.

Table 15.2 Listing status criteria (Source: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_9.pdf)

Status 1A
Requires assistance with a ventilator
Requires assistance with a mechanical assist device (e.g. ECMO)
Requires assistance with a balloon pump
A candidate less than 6 months old with congenital or acquired heart disease and reactive pulmonary hypertension at greater than 50 % of systemic level
Requires infusion of high dose (e.g. dobutamine>/=7.5 mcg/kg/min or milrinone>/=0.50 mcg/kg/min) or multiple inotropes
A candidate who does not meet the above criteria but has a life expectancy of less than 14 days without cardiac transplantation
Status 1B
Requires infusion of low dose single inotrope
Less than 6 months old but does not meet status 1A criteria
Growth failure (i.e. 5th percentile for weight and/or height or loss of 1.5 standard deviations of expected growth (height or weight) based on the National Center for Health Statistics for pediatric growth curves)
Status 2
All other candidates

A complete description and analysis of the development of the lung allocation score (LAS) and its advantages and disadvantages is beyond the scope of this review. In brief, the LAS combines a model predicting mortality on the waitlist with one predicting survival after transplantation in order to accomplish three goals consistent with the OPTN Final Rule [29]:

1. reduction of mortality on the lung waiting list;
2. prioritization of candidates based on urgency while avoiding futile transplants; and
3. de- emphasizing the role of waiting time and geography in lung allocation within the limits of ischemic time.

Using a similar scheme for allocation of cardiac allografts would require publication and validation of accurate models of both waitlist and post-transplant survival. Early results suggest that the current allocation scheme does result in a less than optimal allocation of organs at the highest stratum of risk [61]. More accurate models, validated in an external group, are required prior to use of modeling in allocation of hearts, but eventual use of a cardiac allocation score has the potential to increase the overall survival among children with cardiac failure.

Interpreting Data Analysis in UNOS/SRTR and PHTS Studies

Handling of Missing Data

Large datasets inevitably involve missing data. Decisions regarding the handling of missing data while analyzing these datasets have important effects on the results. While a full discussion of missing data is well beyond the scope of this chapter, it is an important topic in the context of critically evaluating literature based on the UNOS/SRTR and PHTS datasets in particular (although these issues also apply more broadly to other large dataset analyses).

Several methods of handling missing data are available. The most commonly used methods in the context of medical literature are complete case analysis and overall mean imputation. Both of these methods are easy to implement and easy to understand. They are often used without explicit description. Unfortunately, they both result in a loss in sample size, and a loss in power. More importantly, they both have the potential to result in severely biased estimates of statistical significance [62, 63].

When handling of missing values is not reported in the context of multivariable logistic regression, it implies that complete case analysis has been performed. This eliminates any records where complete data for all variables in the analysis is not available. In doing so, the sample size is severely curtailed.

Imputation as a general method is simply the replacement of a missing value with an estimate of the likely value. Mean imputation involves the replacement of missing variables with the mean result across the entire population; while simple, it relies on the assumption that the variables are missing completely at random, that is the probability of a variable being missing is unrelated to the outcome of interest or to any other variable in the dataset. This assumption is rarely true, and in the unlikely event that the assumption is met, mean imputation may still result in biased estimates [62].

Rather than estimating missing values using the mean value across the population, the missing value can be estimated using regression analysis. The main drawback of this method is that in subsequent analyses the estimated value is treated as a measured value, resulting in overestimation of the precision of subsequent analyses. Multiple imputation creates multiple datasets with estimations of the missing values and then performs the analysis in each dataset, resulting in estimates of both the statistical association and the precision of that association that more accurately reflect the error introduced by substituting estimated values for missing values [18, 62, 64].

The topic of handling of missing data is not merely a topic of esoteric statistical interest, because differences in the handling of missing data may result in significant differences in the results of any analysis. For example, two separate analyses of the UNOS database examining the impact of bicaval versus biatrial anastomosis have been performed [17, 18]. Despite using nearly identical datasets, the results were different, with the study using multiple imputations [18] able to include nearly twice as many patients in the analysis as the study using complete case analysis [17]. Similarly, research in adults looking at the impact of ventricular assist devices on post-transplant outcomes resulted in significant differences based on the effort with

which missing data was augmented by examination of free-text fields (including the potential for misspellings and typographical errors) [19]. Thus, it is important in reviewing the results of studies using large datasets to critically examine the methods used to handle missing data and the completeness with which issues of missing data are reported in the manuscript.

Accuracy of Logistic Regression Models

As noted above, evaluation of published models derived from analyses of large datasets should include a critical appraisal of the accuracy. Although a complete discussion of the evaluation of statistical models of outcomes is beyond this review, some general guidelines should be enumerated. Among the criteria that should be used to evaluate a model are:

1. estimates of global model fit such as the Bayes Information Criteria,
2. indices of discrimination (how well a model discriminates between outcomes, most commonly c-statistic), and
3. indices of calibration (how well it functions across different subgroups, most commonly the Hosmer-Lemeshow test) should be evaluated [42].

Ideally, models should be derived in one population and validated in another before becoming part of clinical practice or programmatic evaluation.

Future Directions

As data continues to be collected, multiple opportunities exist for improving the usefulness of the UNOS/SRTR and PHTS datasets, including

- improving the feedback to individual transplant centers,
- developing links between the UNOS dataset and other large datasets with complementary information, and
- tailoring certain fields of data collection to pediatric and congenital cardiac surgery.

Currently, the time delay between submission of data and analysis of data by the SRTR limits the utility of the UNOS/SRTR dataset as an ongoing tool for the assessment of quality. Improvements in modeling and in the turn-around of analytics might enable application of techniques such as cumulative sum failure analysis (CUSUM) in order to provide real-time assessment of quality of transplantation. CUSUM, which is borrowed from monitoring quality on a production line, has been used both in congenital cardiac surgery [65] and in other transplantation procedures [66], as well as in a broad swath of other medical domains [67, 68]. These techniques enable ongoing monitoring of outcomes without running into problems caused by repeatedly analyzing the same data [69]. These techniques could be implemented using the ongoing submission of data to large datasets such as UNOS and provide early feedback and warning of potential problems to transplant centers. By collecting data of specific relevance to pediatric and congenital transplantation, and developing models predicting mortality [40], the PHTS might be particularly well-suited to develop an ongoing role in the assessment of quality using these types of techniques. The possibility of such techniques being used increases with contemporary rapid increases in the power of computers and the ability to collect and analyze data.

The UNOS/SRTR database – like many large datasets – is limited by the fields of data collected. No single database can be all-inclusive, and adding fields of data eventually makes the collection of data too onerous and causes the rate of missing data to increase. Linking databases with complementary information enhances opportunities for investigation without necessitating redesigning data collection or duplicating information between multiple data submissions to different entities. For example, linkage of the STS-CHSD to other databases has already been performed [70, 71]. With regard to transplant databases, linkages between the STS-CHSD and the UNOS dataset may address weaknesses in each. Specific congenital diagnosis are missing from the UNOS/SRTR database [8], while the STS-CHSD includes diagnostic information

consistent with current standards of nomenclature. In contrast, the STS-CHSD does not contain long-term follow-up data and has no provision for follow-up of specific outcomes of transplantation (graft outcomes such as rejection and allograft vasculopathy). Linking these datasets would facilitate analyses of data not available in each dataset individually.

In addition to linking currently available datasets, some alterations to the data collected by UNOS/SRTR would improve the ability to model outcomes in pediatric and congenital patients. While PHTS already has some of these data (including previous operations and congenital diagnoses), it has been collected using differing categorization schemes over time and is inconsistent with current standardized international nomenclature in pediatric and congenital cardiac disease. Improved collection of these data would enable more powerful research into issues of specific interest to pediatric and congenital patients.

Conclusion

The historical context of the UNOS/SRTR and PHTS datasets play important roles in the analysis of outcomes following pediatric cardiac transplantation. The UNOS/SRTR Database and the PHTS Database are complementary data sources, with differing strengths and weaknesses. An understanding of the limitations of each database, as well as the limitations of various analytic techniques, is essential to a critical reading of the literature based on these sources of data. Outcomes models developed using these datasets may

- enable risk-adjusted evaluation of individual transplant centers (both for internal quality improvement and external review by the public), as well as
- facilitate optimization of rules regarding allocation of organs, guidelines for transplant candidacy, and benchmarks for high quality programs.

Future directions should include

- ongoing improvements in the outcome models,
- inclusion of currently unavailable data (either through linking of databases or enhanced collection of data), as well as
- more timely feedback to enable ongoing assessment of quality in real-time.

References

1. Davies RR, Pizarro C. Using the UNOS/SRTR and PHTS databases to improve quality in pediatric cardiac transplantation. World J Pediatr Congenit Heart Surg. 2012;3(4):421–32. doi:10.1177/2150135112443971.
2. Organ Procurement and Transplantation Network (OPTN) Data, based on OPTN data as of May 17 2013. optntransplanthrsagov. Available at: http://optn.transplant.hrsa.gov/latestData/advancedData.asp. Accessed 23 May 2013.
3. Murray JE, Merrill JP, Harrison JH, Wilson RE, Dammin GJ. Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. N Engl J Med. 1963;268:1315–23. doi:10.1056/NEJM196306132682401.
4. Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. J Am Med Assoc. 1956;160(4):277–82.
5. National Organ Transplant Act. 42 U.S.C. 273 et seq; 1984.
6. OPTN Final Rule. 42 C.F.R. Part 121.
7. OPTN Final Rule. 42 C.F.R. Part 121.11 (b) (2).
8. Davies RR, Russo MJ, Yang J, Quaegebeur JM, Mosca RS, Chen JM. Listing and transplanting adults with congenital heart disease. Circulation. 2011;123(7):759–67. doi:10.1161/CIRCULATIONAHA.110.960260.
9. Karamlou T, Hirsch J, Welke K, et al. A United Network for Organ Sharing analysis of heart transplantation in adults with congenital heart disease: outcomes and factors associated with mortality and retransplantation. J Thorac Cardiovasc Surg. 2010;140(1):161–8. doi:10.1016/j.jtcvs.2010.03.036.
10. Davies RR, Russo MJ, Mital S, et al. Predicting survival among high-risk pediatric cardiac transplant recipients: an analysis of the United Network for Organ Sharing database. J Thorac Cardiovasc Surg. 2008;135(1):147–55, 155.e1–2. doi:10.1016/j.jtcvs.2007.09.019.
11. Chen JM, Davies RR, Mital SR, et al. Trends and outcomes in transplantation for complex congenital heart disease: 1984 to 2004. Ann Thorac Surg. 2004;78(4):1352–61. doi:10.1016/j.athoracsur.2004.04.012; discussion 1352–61.
12. Lytrivi ID, Blume ED, Rhodes J, Dillis S, Gauvreau K, Singh TP. Prognostic value of exercise testing during heart transplant evaluation in children. Circ Heart Fail. 2013;6(4):792–9. doi:10.1161/CIRCHEARTFAILURE.112.000103.

13. Kanter KR, Mahle WT, Vincent RN, Berg AM, Kogon BE, Kirshbom PM. Heart transplantation in children with a Fontan procedure. Ann Thorac Surg. 2011;91(3):823–9. doi:10.1016/j.athoracsur.2010.11.031; discussion 829–30.
14. Bernstein D, Naftel DC, Chin C, et al. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. Circulation. 2006;114(4):273–80.
15. Khairy P, Fernandes SM, Mayer JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation. 2008;117(1):85–92. doi:10.1161/CIRCULATIONAHA.107.738559.
16. Davies RR, Sorabella RA, Yang J, Mosca RS, Chen JM, Quaegebeur JM. Outcomes after transplantation for "failed" Fontan: a single-institution experience. J Thorac Cardiovasc Surg. 2012;143(5):1183–92.e4. doi:10.1016/j.jtcvs.2011.12.039.
17. Weiss ES, Nwakanma LU, Russell SB, Conte JV, Shah AS. Outcomes in bicaval versus biatrial techniques in heart transplantation: an analysis of the UNOS database. J Heart Lung Transplant. 2008;27(2):178–83. doi:10.1016/j.healun.2007.11.003.
18. Davies RR, Russo MJ, Morgan JA, Sorabella RA, Naka Y, Chen JM. Standard versus bicaval techniques for orthotopic heart transplantation: an analysis of the United Network for Organ Sharing database. J Thorac Cardiovasc Surg. 2010;140(3):700–8, 708.e1–2. doi:10.1016/j.jtcvs.2010.04.029.
19. Russo MJ, Hong KN, Davies RR, et al. Posttransplant survival is not diminished in heart transplant recipients bridged with implantable left ventricular assist devices. J Thorac Cardiovasc Surg. 2009;138(6):1425–32.e1–3. doi:10.1016/j.jtcvs.2009.07.034.
20. Bull DA, Reid BB, Selzman CH, et al. The impact of bridge-to-transplant ventricular assist device support on survival after cardiac transplantation. J Thorac Cardiovasc Surg. 2010;140(1):169–73. doi:10.1016/j.jtcvs.2010.03.026.
21. Hsu DT, Naftel DC, Webber SA, et al. Lessons learned from the pediatric heart transplant study. Congenit Heart Dis. 2006;1(3):54–62. doi:10.1111/j.1747-0803.2006.00011.x.
22. Pediatric Heart Transplant Study. University of Alabama – Birmingham. Available at: http://www.uab.edu/ctsresearch/phts/archivedforms.html. Accessed Dec 2011.
23. Pediatric Heart Transplant Study (PHTS) – forms. University of Alabama (UAB). Available at: http://www.uab.edu/ctsreaserch/phts/forms.html. Accessed 1 Sept 2011.
24. Davies RR, Russo MJ, Hong KN, et al. Increased short- and long-term mortality at low-volume pediatric heart transplant centers: should minimum standards be set? Retrospective data analysis. Ann Surg. 2011;253(2):393–401. doi:10.1097/SLA.0b013e31820700cc.
25. International Society for Heart and Lung Transplantation. ISHLT registries – heart/lung registries. ishltorg. Available at: http://www.ishlt.org/registries/heartLungRegistry.asp. Accessed 24 May 2013.
26. CMS Centers for Medicare and Medicaid Services. National coverage determination. 5th ed. 2010. Available at: http://www.cmms.hhs.gov/medicare-coverage-database.
27. Blume ED, Naftel DC, Bastardi HJ, et al. Outcomes of children bridged to heart transplantation with ventricular assist devices: a multi-institutional study. Circulation. 2006;113(19):2313–9.
28. Williams ML, Trivedi JR, McCants KC, et al. Heart transplant vs left ventricular assist device in heart transplant-eligible patients. Ann Thorac Surg. 2011;91(5):1330–3. doi:10.1016/j.athoracsur.2011.01.062; discussion 1333–4.
29. Egan TM, Murray S, Bustami RT, et al. Development of the new lung allocation system in the United States. Am J Transplant. 2006;6(5 Pt 2):1212–27. doi:10.1111/j.1600-6143.2006.01276.x.
30. Everitt MD, Donaldson AE, Casper TC, et al. Effect of ABO-incompatible listing on infant heart transplant waitlist outcomes: analysis of the United Network for Organ Sharing (UNOS) database. J Heart Lung Transplant. 2009;28(12):1254–60. doi:10.1016/j.healun.2009.06.024.
31. Pietra BA, Kantor PF, Bartlett HL, et al. Early predictors of survival to and after heart transplantation in children with dilated cardiomyopathy. Circulation. 2012. doi:10.1161/CIRCULATIONAHA.110.011999.
32. Singh TP, Almond CS, Piercey G, Gauvreau K. Trends in wait-list mortality in children listed for heart transplantation in the United States: era effect across racial/ethnic groups. Am J Transplant. 2011;11(12):2692–9. doi:10.1111/j.1600-6143.2011.03723.x.
33. Almond CSD, Thiagarajan RR, Piercey GE, et al. Waiting list mortality among children listed for heart transplantation in the United States. Circulation. 2009;119(5):717–27. doi:10.1161/CIRCULATIONAHA.108.815712.
34. Davies RR, Russo MJ, Reinhartz O, et al. 483 Lower socioeconomic status predicts poor waitlist and post-heart transplant survival in children. J Heart Lung Transplant. 2011;30(4S):S164.
35. Singh TP, Almond CS, Taylor DO, Graham DA. Decline in heart transplant wait list mortality in the United States following broader regional sharing of donor hearts. Circ Heart Fail. 2012;5(2):249–58. doi:10.1161/CIRCHEARTFAILURE.111.964247.
36. Davies RR, Russo MJ, Hong KN, et al. The use of mechanical circulatory support as a bridge to transplantation in pediatric patients: an analysis of the United Network for Organ Sharing database. J Thorac Cardiovasc Surg. 2008;135(2):421–7, 427.e1. doi:10.1016/j.jtcvs.2007.09.048.
37. Singh TP, Gauvreau K, Thiagarajan R, Blume ED, Piercey G, Almond CS. Racial and ethnic differences in mortality in children awaiting heart transplant in the United States. Am J Transplant. 2009;9(12):2808–15. doi:10.1111/j.1600-6143.2009.02852.x.

38. Kirk R, Naftel D, Hoffman TM, et al. Outcome of pediatric patients with dilated cardiomyopathy listed for transplant: a multi-institutional study. J Heart Lung Transplant. 2009;28(12):1322–8. doi:10.1016/j.healun.2009.05.027.
39. Davies RR. Multiple high risk criteria predict poor survival among pediatric heart transplant recipients. J Heart Lung Transplant. 2008;27(2):255–6.
40. Naftel DC. Fourteen years of improving results illustrated by patient specific predictions. J Heart Lung Transplant. 2008;27(2):253–4.
41. Auerbach SR, Richmond ME, Chen JM, et al. Multiple risk factors before pediatric cardiac transplantation are associated with increased graft loss. Pediatr Cardiol. 2011;32(5):615–20. doi:10.1007/s00246-011-0077-7.
42. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. Circulation. 2007;115(7):928–35. doi:10.1161/CIRCULATIONAHA.106.672402.
43. Weiss ES, Allen JG, Arnaoutakis GJ, et al. Creation of a quantitative recipient risk index for mortality prediction after cardiac transplantation (IMPACT). Ann Thorac Surg. 2011;92(3):914–21. doi:10.1016/j.athoracsur.2011.04.030; discussion 921–2.
44. Wendt D, Osswald BR, Kayser K, et al. Society of Thoracic Surgeons score is superior to the EuroSCORE determining mortality in high risk patients undergoing isolated aortic valve replacement. Ann Thorac Surg. 2009;88(2):468–74. doi:10.1016/j.athoracsur.2009.04.059; discussion 474–5.
45. Murtuza B, Fenton M, Burch M, et al. Pediatric heart transplantation for congenital and restrictive cardiomyopathy. Ann Thorac Surg. 2013. doi:10.1016/j.athoracsur.2013.01.014.
46. Rajagopal SK, Yarlagadda VV, Thiagarajan RR, Singh TP, Givertz MM, Almond CSD. Pediatric heart failure and worsening renal function: association with outcomes after heart transplantation. J Heart Lung Transplant. 2011. doi:10.1016/j.healun.2011.08.018.
47. Joffe AR, Quiñonez LG, Robertson CMT, et al. Outcomes after heart transplantation in children under six years of age. Ann Thorac Surg. 2011;92(1):174–82. doi:10.1016/j.athoracsur.2011.02.038.
48. Dipchand A, Cecere R, Delgado DH, et al. Canadian Consensus on cardiac transplantation in pediatric and adult congenital heart disease patients 2004: executive summary. Can J Cardiol. 2005;21(13):1145–7.
49. Kirk RC, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: eleventh official pediatric heart transplantation report–2008. J Heart Lung Transplant. 2008;27(9):970–7. doi:10.1016/j.healun.2008.06.016.
50. Singh TP, Edwards LB, Kirk R, Boucek MM. Era effect on post-transplant survival adjusted for baseline risk factors in pediatric heart transplant recipients. J Heart Lung Transplant. 2009;28(12):1285–91. doi:10.1016/j.healun.2009.05.003.
51. Jacobs JP, O'Brien SM, Pasquali SK, et al. Variation in outcomes for benchmark operations: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. Ann Thorac Surg. 2011;92(6):2184–91. doi:10.1016/j.athoracsur.2011.06.008; discussion 2191–2.
52. Scientific Registry of Transplant Recipients. Available at: http://www.srtr.org/csr/current/Centers/TransplantCenters_New201106x.aspx?organcode=HR. Accessed 7 Sept 2011.
53. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates–2006. J Heart Lung Transplant. 2006;25(9):1024–42. doi:10.1016/j.healun.2006.06.008.
54. Russo MJ, Hong KN, Davies RR, et al. The effect of body mass index on survival following heart transplantation: do outcomes support consensus guidelines? Ann Surg. 2010;251(1):144–52. doi:10.1097/SLA.0b013e3181b5db3c.
55. Dipchand AI, Pollock BarZiv SM, Manlhiot C, West LJ, VanderVliet M, McCrindle BW. Equivalent outcomes for pediatric heart transplantation recipients: ABO-blood group incompatible versus ABO-compatible. Am J Transplant. 2010;10(2):389–97. doi:10.1111/j.1600-6143.2009.02934.x.
56. Patel ND, Weiss ES, Scheel J, Cameron DE, Vricella LA. ABO-incompatible heart transplantation in infants: analysis of the united network for organ sharing database. J Heart Lung Transplant. 2008;27(10):1085–9. doi:10.1016/j.healun.2008.07.001.
57. Almond CS, Almond CS, Gauvreau K, et al. Impact of ABO-incompatible listing on wait-list outcomes among infants listed for heart transplantation in the United States: a propensity analysis. Circulation. 2010;121(17):1926–33. doi:10.1161/CIRCULATIONAHA.109.885756.
58. Chiu P, Russo MJ, Davies RR, Addonizio LJ, Richmond ME, Chen JM. What is high risk? Redefining elevated pulmonary vascular resistance index in pediatric heart transplantation. J Heart Lung Transplant. 2012;31(1):61–6. doi:10.1016/j.healun.2011.08.021.
59. Richmond ME, Law YM, Das B, Everitt MD. Elevated pre-transplant pulmonary vascular resistance is not associated with mortality in children without congenital heart disease: a multi-center study. J Heart Lung Transplant. 2013;31(4 Suppl):S35.
60. Buddhe S, Du W, L'ecuyer T. Impact of pulmonary hypertension on transplant outcomes in pediatric cardiomyopathy patients. Pediatr Transplant. 2012;16(4):367–72. doi:10.1111/j.1399-3046.2012.01678.x.
61. Singh TP, Almond CS, Piercey G, Gauvreau K. Risk stratification and transplant benefit in children listed for heart transplant in the United States. Circ Heart Fail. 2013;6(4):800–8. doi:10.1161/CIRCHEARTFAILURE.112.000280.
62. Donders ART, van der Heijden GJMG, Stijnen T, Moons KGM. Review: a gentle introduction to imputation of missing values. J Clin

Epidemiol. 2006;59(10):1087–91. doi:10.1016/j.jclinepi.2006.01.014.
63. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol. 1995;142(12):1255–64.
64. Rubin D. Multiple imputation for non-response in surveys. New York: Wiley; 1987.
65. de Leval MR, Francois K, Bull C, Brawn W, Spiegelhalter D. Analysis of a cluster of surgical failures. Application to a series of neonatal arterial switch operations. J Thorac Cardiovasc Surg. 1994;107(3):914–23; discussion 923–4.
66. Axelrod DA, Guidinger MK, Metzger RA, Wiesner RH, Webb RL, Merion RM. Transplant center quality assessment using a continuously updatable, risk-adjusted technique (CUSUM). Am J Transplant. 2006;6(2):313–23. doi:10.1111/j.1600-6143.2005.01191.x.
67. Holzhey DM, Jacobs S, Walther T, Mochalski M, Mohr FW, Falk V. Cumulative sum failure analysis for eight surgeons performing minimally invasive direct coronary artery bypass. J Thorac Cardiovasc Surg. 2007;134(3):663–9. doi:10.1016/j.jtcvs.2007.03.029.
68. Bolsin S, Colson M. The use of the Cusum technique in the assessment of trainee competence in new procedures. Int J Qual Health Care. 2000;12(5):433–8.
69. McPherson K. Statistics: the problem of examining accumulating data more than once. N Engl J Med. 1974;290(9):501–2. doi:10.1056/NEJM197402282900907.
70. Jacobs JP, Haan CK, Edwards FH, et al. The rationale for incorporation of HIPAA compliant unique patient, surgeon, and hospital identifier fields in the STS database. Ann Thorac Surg. 2008;86(3):695–8. doi:10.1016/j.athoracsur.2008.04.075.
71. Pasquali SK, Jacobs JP, Shook GJ, et al. Linking clinical registry data with administrative data using indirect identifiers: implementation and validation in the congenital heart surgery population. Am Heart J. 2010;160(6):1099–104. doi:10.1016/j.ahj.2010.08.010.