Long-Term Transplant-Free Survival After Repair of Total Anomalous Pulmonary Venous Connection

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Background. **Long-term survival, risk of transplantation, and causes of death after repair of total anomalous pulmonary venous connection (TAPVC) remain unknown. By linking the Pediatric Cardiac Care Consortium with the National Death Index and the United Network for Organ Sharing, we evaluated long-term transplant-free survival in children undergoing repair of TAPVC.**

Methods. **We identified 777 infants within the Pediatric Cardiac Care Consortium who underwent TAPVC repair (median 21 days; interquartile range, 5 to 80) and had sufficient personal identifiers for linkage with the National Death Index and United Network for Organ Sharing. Sixty-six deaths, ten cardiac transplantations, and one bilateral lung transplantation had occurred by the end of 2014. Data collected included age and weight at time of procedure, TAPVC type, associated cardiac lesions, and postoperative length of stay. The study cohort was divided into simple and complex TAPVC based on the presence of an associated cardiac lesion. Parametric survival plots were constructed, and risk factor analyses were performed to identify demographic and clinical characteristics associated with long-term outcomes.**

Results. **Mortality or need for transplantation was 9.7% with a median follow-up of 18.4 years and a median age of death or transplant of 0.74 years. The risk of mortality and transplant after TAPVC repair was highest during the first 18 months after hospital discharge. Cardiac causes accounted for the majority of deaths. Multivariate regression models for transplant-free survival demonstrated that complex TAPVC, mixed TAPVC, and postoperative length of stay were associated with increased risk of death/transplant.**

Conclusions. **Transplant-free survival after TAPVC repair is excellent, with most deaths or transplant events occurring early. Factors associated with the worst long-term outcomes included complex TAPVC, mixed TAPVC, and prolonged postoperative length of stay.**

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Perioperative mortality after correction of complex congenital heart defects (CHD) has decreased to less than 5% over the last several decades [1, 2]. Long-term survival, causes of death and risk of organ transplantation remain largely undefined. Most contemporary reports addressing these issues are from small, individual centers [3, 4] or national registries from countries with state-directed health care systems [5, 6]. The use of linkage strategies with current government-sponsored registries to ascertain outcomes of specific patient groups has prompted increases in financial support to address critical clinical gaps in the understanding of their long-term outcomes [7, 8].

The purpose of this analysis is to evaluate the long-term transplant-free survival of infants who underwent repair of total anomalous pulmonary venous connection (TAPVC) using linked data from the Pediatric Cardiac Care Consortium (PCCC), the National Death Index (NDI), and the United Network for Organ Sharing (UNOS).

Patients and Methods

We first queried the PCCC database for patients with TAPVC who had undergone surgical repair in a US center at less than 1 year of age between January 1, 1982 (start of PCCC registry), and April 15, 2003 (date of stricter HIPAA

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Abbreviations and Acronyms

CHD = congenital heart defect
CI = confidence interval
HR = hazard ratio
IQR = interquartile range
NDI = National Death Index
PCCC = Pediatric Cardiac Care Consortium
TAPVC = total anomalous pulmonary venous connection
UNOS = United Network for Organ Sharing

implementation). Death or transplantation was identified from subsequent encounters in PCCC and by linkage to both NDI and UNOS. Patient identifiers used for linkage included first name, last name, date and year of birth, sex, and state of birth. Data used in this analysis were covered by the Data Use Agreement provided from individual member institutions. The study was approved by the Institutional Review Boards of Emory University and Children's Mercy Hospital.

Variables reviewed included demographic information, weight at birth, age and weight at operation, date of surgical repair, timing of operative correction, pulmonary venous obstruction, anatomic type of TAPVC, associated CHD, noncardiac malformations, discharge date, and mortality status. Inhospital mortality was defined as death at any time during the admission for repair of TAPVC. Emergent operation was defined as surgery performed (1) when patient was less than 2 days old; (2) on a weekend day; or (3) on a major US holiday. Patients were classified by the type of anatomic connection, pulmonary venous obstruction (as coded by the admitting center), and the coexisting type of associated CHD. Simple TAPVC was defined as any type of TAPVC without the coexistence of other CHD (excluding patent ductus arteriosus and atrial septal defect), whereas complex was defined as TAPVC associated with any other CHD (excluding patent ductus arteriosus and atrial septal defect).

Postdischarge mortality or need for transplantation was obtained from subsequent PCCC encounters and linkage to NDI and UNOS. As we reported, the sensitivity and specificity of linkage to detect death (NDI) and transplant events (UNOS) for patients with appropriate direct identifiers were 89% and more than 99%, respectively [7]. For every NDI match, NDI-Plus (enhanced service of the NDI) provided the date and state of death as well as causes of death reported on the death certificate. Follow-up was defined as time from the date of surgery until date of death or until December 31, 2014.

Statistical Analysis

Statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Statistical significance was assessed at the 0.05 level. Descriptive statistics were calculated for variables of interest and included mean with standard deviation for continuous variables, median with interquartile range (IQR) for parametric variables with skewed distribution, or count and percentages for categorical variables. Predictors of inhospital survival after TAPVC repair were assessed by univariate analysis with χ^2 tests for categoric data or Wilcoxon rank sum tests for continuous data. For some categoric comparisons with small expected counts, Fisher's exact test was used. The variables examined in univariate analysis were sex, birth and surgical weight, weight less than 2.5 kg at time of surgery as proxy for prematurity or significant growth retardation, age at repair, anatomic type of TAPVC, coexisting CHD, preoperative pulmonary venous obstruction, emergent operation, and surgical era (broken down by decade) [9, 10].

Survival without transplant after hospital discharge for repair of TAPVC was treated as a time-dependent outcome and modeled parametrically. Parametric probability estimates for this used models based on multiple overlapping phases of risk using PROC HAZARD (SAS Institute). Maximum likelihood estimates were iteratively calculated using nonlinear optimization-based algorithms. Smoothed survival curves were generated using the HAZPRED procedure in SAS. The PROC HAZPRED computes predictions for the survivorship and hazard functions along with their confidence limits. To identify risk factors associated with death/transplant after TAPVC repair, parametric survival models were constructed using one risk factor at a time. Multivariate models were created using forward entry of variables significant at the 0.2 level in univariate analysis. Effects of covariates on the probability of outcomes in survival models are given as hazard ratio (HR) with 95% confidence interval (CI).

Results

A total of 1,334 patients underwent TAPVC repair before 1 year of age in a US center between January 1, 1982, and April 21, 2003. After excluding patients with inadequate NDI and UNOS identifiers and those not having a primary operation, 1,057 patients were available for analysis, as outlined in Figure 1. Among them were 280 inhospital deaths, with 235 of these (84%) having a matching record in the NDI. That resulted in a similar sensitivity as described for the entire PCCC cohort [7]. The remaining 777 patients were discharged alive and form the study cohort.

Comparison of the survivor cohort with the cohort that did not survive to hospital discharge after TAPVC repair is presented in Table 1. Older age, surgical weight above 2.5 kg, nonemergent operation, lack of pulmonary venous obstruction, cardiac or supracardiac type of TAPVC, and absence of coexisting CHD were each associated with increased chance of survival to discharge ($p < 0.001$). For infants who survived to hospital discharge (n = 777), the median postoperative length of stay was 11 days (IQR: 7 to 18). The greatest risk of death or need for transplantation occurred within the first 18 months after hospital discharge.

Characteristics of the cohort (n = 777) who survived to hospital discharge are presented in Table 2. Additional