Long-Term Outcomes of Children With Trisomy 13 and 18 After Congenital Heart Disease Interventions

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Background. **The purpose of this study is to report short- and long-term outcomes after congenital heart defect (CHD) interventions in patients with trisomy 13 or 18.**

Methods. **A retrospective review of the Pediatric Cardiac Care Consortium (PCCC) identified children with trisomy 13 or 18 with interventions for CHD between 1982 and 2008. Long-term survival and cause of death were obtained through linkage with the National Death Index.**

Results. **A total of 50 patients with trisomy 13 and 121 patients with trisomy 18 were enrolled in PCCC between 1982 and 2008; among them 29 patients with trisomy 13 and 69 patients with trisomy 18 underwent intervention for CHD. In-hospital mortality rates for patients with trisomy 13 or trisomy 18 were 27.6% and 13%, respectively. Causes of in-hospital death were primarily cardiac (64.7%) or multiple organ system failure (17.6%). National Death Index linkage confirmed 23 deaths after discharge. Median survival (conditioned to hospital discharge) was 14.8 years (95% confidence interval [CI]: 12.3 to 25.6 years) for patients with trisomy 13 and 16.2 years (95% CI: 12 to 20.4 years) for patients with trisomy 18. Causes of late death included cardiac (43.5%), respiratory (26.1%), and pulmonary hypertension (13%).**

Conclusions. **In-hospital mortality rate for all surgical risk categories was higher in patients with trisomy 13 or 18 than that reported for the general population. However, patients with trisomy 13 or 18, who were selected as acceptable candidates for cardiac intervention and who survived CHD intervention, demonstrated longer survival than previously reported. These findings can be used to counsel families and make program-level decisions on offering intervention to carefully selected patients.**

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Trisomy 13 (T13) and 18 (T18) are frequently (up to 80%) associated with multiple anomalies, including congenital heart defects (CHDs) such as atrial or ventricular septal defect (VSD), patent ductus arteriosus, atrioventricular septal defect, tetralogy of Fallot (TOF), and others [1]. These lesions can be successfully repaired or palliated in the general population; a previous study from the Pediatric Cardiac Care Consortium (PCCC) reported 91% hospital discharge survival in patients with T13 or T18 [2]. Historically, the presence of T13 or T18 has been considered to be incompatible with long-term survival, with death occurring frequently within 1 year and mostly attributed to causes other than the associated CHD [3–5]. A recent large study of children with T13 or T18 reported a 5-year survival of 9.7% for children with T13 and 12.3% for children with T18, although clinical treatment data were not available [6]. Because of this short expected life span and the low functional status of these patients, aggressive treatment of associated CHDs has been controversial.

Studies published in the past decade suggest that survival in children with T13 and T18 may be longer after intervention for CHD [7–10]. A Japanese study of 34

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Abbreviations and Acronyms

CHD	=	congenital heart defect
CI	=	confidence interval
HIPAA	=	Health Insurance Portability and Accountability Act
IQR	=	interquartile range
NDI	=	National Death Index
PCCC	=	Pediatric Cardiac Care Consortium
RACHS-1	=	Risk Adjustment in Congenital Heart Surgery, version 1
STAT	=	The Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery Mortality
T13	=	trisomy 13
T18	=	trisomy 18
TOF	=	tetralogy of Fallot
VSD	=	ventricular septal defect

patients with T18 reported 22% 2-year survival after corrective or palliative cardiac operation, compared with 9% survival with only medical therapy [7]. Similarly, improved survival with surgical management has been reported by other small studies [8, 9]. However, these small series with relatively short postoperative follow-up are not sufficient to guide health care providers and families about long-term survival after CHD interventions in patients with T13 or T18. At the same time, there is increased need for this information because families have become increasingly knowledgeable through social media, support groups, and the Internet and are considering interventions for their children [11].

We report long-term survival and causes of death in a subgroup of patients with T13 and T18 from the PCCC cohort with long-term follow-up data available through linkage with the National Death Index (NDI).

Patients and Methods

This study was approved by the institutional review boards at the University of Minnesota, Emory University, and MemorialCare Health Services, with a waiver of consent and Health Insurance Portability and Accountability Act (HIPAA) authorization. A Data Use Agreement was in place between the investigators and the respective institutions.

Data Collection

The PCCC was established in 1982 as a multicenter registry for the purpose of quality improvement [12]. Between 1982 and 2008, the PCCC collected data on more than 137,000 patients, 118,000 operations, and 123,000 cardiac catheterizations [13]. This retrospective review included patients from the United States and Canada who were enrolled in the PCCC from 1982 to 2008 with a diagnosis code for T13 or T18 (including mosaic forms) and CHD. Short-term mortality was defined as in-hospital death after CHD intervention. Patients were assigned to one of three treatment pathways: (1) corrective, which included complete CHD repair, with or without initial palliation; (2) palliative, which included patent ductus arteriosus ligation with coexisting major intracardiac CHD, pulmonary artery banding, or aortopulmonary shunt; and (3) single ventricle palliation, which included bidirectional Glenn anastomosis or Fontan procedure. Treatment era was separated into three groups: 1982 to 1989, 1990 to 1999, and 2000 to 2008. Age groups were defined as neonates (<30 days), infants (31 days to 1 year), and children (>1 year and <18 years). Primary surgical procedure was defined as the first surgical procedure that addressed the main anatomic abnormality of each patient. Surgical procedure complexity was scored using The Society of Thoracic Surgeons/European Association for Cardiothoracic Surgery Congenital Heart Surgery Mortality (STAT) risk categories [14]. For patients with multiple procedures in the same admission, the primary procedure was considered the one with the highest STAT risk score. For comparison purposes with same-era procedures from within the PCCC, we also assigned Risk Adjustment in Congenital Heart Surgery, version 1 (RACHS-1) complexity categories [15, 16]. Procedural indications were abstracted as reported in the catheterization and operative notes. Complications included those reported by the participating centers or identified by registry staff during the coding process.

Long-term mortality was defined as death after hospital discharge and was available for the US subcohort with sufficient direct identifiers, enrolled in PCCC before April 15, 2003 (date that stricter HIPAA privacy rule took effect). This subgroup was submitted to the NDI to obtain survival status and cause of death up to December 31, 2014 [17]. NDI data is considered to be the gold standard of national death registries for obtaining death information in the United States [18]; the sensitivity of the PCCC-NDI linkage reaches 88.1% (95% confidence interval [CI]: 87.1% to 89.0%) with a specificity exceeding 99%, when a patient's first and last names are available [17].

Statistical Analysis

Descriptive statistics were used to describe the study cohort by genetic diagnosis. Comparisons between groups were analyzed with χ^2 or Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables. Kaplan-Meier survival analysis and log-rank tests were used to describe long-term survival and to compare groups, respectively, in the subset of patients who were submitted to the NDI with first and last names available. Follow-up duration was determined from the date of first cardiac intervention. Statistical analysis was completed with Statistical Package for the Social Science version 23 (IBM, Armonk, NY).

Results

Fifty patients with T13 and 121 patients with T18 were identified, including instances of mosaic or partial trisomy genotypes (20 for T13 and 16 for T18). Seventy-three patients (21 with T13, 52 with T18) were excluded from further analysis because they did not undergo CHD intervention. Characteristics of patients with and without interventions are described in Table 1. Compared with patients offered