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Long-Term Survival and Causes of Death in Children with Trisomy 21 After Congenital Heart Surgery

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Abstract

Objective: To evaluate long-term transplant-free survival and causes of death in the Trisomy 21 (T21) population after surgery for congenital heart disease (CHD) in comparison with euploidic patients.

Study design: This is a retrospective cohort study from the Pediatric Cardiac Care Consortium, enriched with prospectively collected data from the National Death Index and the Organ Procurement and Transplantation Network for patients with sufficient direct identifiers. Kaplan-Meier survival plots were generated and multivariable Cox proportional hazards models were used to examine risk factors for mortality between T21 and 1:1 matched euploidic patients with a comparable CHD.

Results: Long-term survival analysis was completed for 3,376 patients with T21 (75,155 person-years) who met inclusion criteria. Thirty-year survival for patients with T21 ranged from 92.1%

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for ventricular septal defect to 65.3% for complex common atrioventricular canal. Of these, 2,185 patients with T21 were successfully matched to a euploidic patient. After a median follow-up of 22.86 years (IQR 19.45–27.14 years), 213 deaths occurred in the T21 group (9.7%), compared with 123 (5.6%) in the euploidic comparators. After adjustment for age, sex, era, congenital heart disease complexity and initial palliation, the hazard ratio of CHD-related mortality was 1.34 times higher in patients with T21 (95% CI 0.92–1.97, $P = .127$).

Conclusion: CHD-related mortality for patients with T21 following cardiac surgical intervention is comparable with euploidic comparators. Children with T21 require lifelong surveillance for co-occurring conditions associated with their chromosomal abnormality.

Keywords

congenital heart surgery; genetics; outcomes; statistics (survival analysis)

Congenital heart disease (CHD) is present in 40–50% of children born with Trisomy 21 (T21)[1] with several epidemiologic studies highlighting the impact CHD has on their survival.[1–7] Despite the additional co-occurring conditions associated with T21, early operative mortality for some types of two-ventricle CHD has been reported to be similar in patients with T21 versus those without.[8–12] However, long-term outcomes of children with T21 who survive CHD interventions are not well understood.[13]

The purpose of this retrospective cohort study was to describe in-hospital and long-term transplant-free survival, causes of death, and predictors of long-term mortality in children with T21 following surgical intervention for CHD with two-ventricle physiology. Additionally, we aimed to directly compare the long-term survival between children with T21 and euploidic children with equivalent CHD diagnoses and related surgeries.

METHODS

This study was approved by the Institutional Review Board at MemorialCare Health Services, the University of Minnesota, and Emory University with a waiver of consent.

Data were obtained from the Pediatric Cardiac Care Consortium (PCCC), a large US-based registry formed in 1982, encompassing over 140,000 patient outcomes of CHD interventions through 2011.[14] Patients with T21 who were enrolled in the PCCC and underwent their first CHD surgery in a US PCCC center before the age of 21 years and April 15, 2003 (implementation date of stricter Health Insurance Portability and Accountability Act [HIPAA] privacy rules) were eligible for inclusion. We included only patients who underwent their initial CHD surgery at a PCCC center to avoid introducing immortal person-time bias. A STROBE diagram is detailed in Figure 1 (available at www.jpeds.com). We excluded patients who underwent initial cardiac transplant, isolated patent ductus arteriosus ligation, a diagnosis of heterotaxy syndrome or its features (such as interrupted inferior vena cava, asplenia or polysplenia, situs ambiguous, or intestinal malrotation), single ventricle CHD, and patients who underwent a superior cavo-pulmonary anastomosis as part of a “one and a half” ventricle repair strategy. Long-term survival of children with T21 following single ventricle palliation was previously reported from our group.[15]

Data collection included age and weight at operation, year of operation, cardiac diagnoses, cardiac surgical interventions, and discharge outcome. The primary cardiac diagnosis was categorized as mild, moderate, or severe using a modified complexity classification proposed by the Canadian Consensus Conference on Adult Congenital Heart Disease in 1996.[16–18] Based on this categorization, we identified the eight most common intracardiac diagnoses that could be matched with euploidic PCCC comparators from the same time period. These diagnostic categories included: 1) atrial septal defect (ASD), including ostium primum, secundum and sinus venosus type of defects; 2) incomplete atrioventricular canal, including partial or transitional atrioventricular canal (iAVC); 3) simple ventricular septal defect (VSD), including isolated perimembranous, supracristal or muscular defects; 4) complex VSD, with associated aortic valve stenosis, coarctation of the aorta (CoA), right ventricular outflow tract obstruction, or double outlet right ventricle (DORV with VSD physiology); 5) common atrioventricular canal (CAVC); 6) CAVC associated with tetralogy of Fallot (TOF) or DORV with TOF physiology with or without pulmonary atresia (CAVC-TOF); 7) CAVC with aortic arch obstruction including coarctation of the aorta (CoA) or interrupted aortic arch; and 8) Tetralogy of Fallot (all forms of TOF with and without pulmonary atresia). Other forms of CHD were excluded from the comparison analysis.

We collected data on subsequent procedures and reoperations performed within PCCC through 2011. Long-term survival of these patients with T21 was compared with PCCC euploidic comparators, matched 1:1 by cardiac diagnosis category. We categorized the treatment era as early (1982–1992), middle (1993–1997) and late (1998–2003) based on approximate tertiles of the date of first PCCC operation. Age groups were defined as neonatal (<28 days), infant (28 days to 364 days), child (1 to 5 years), and older child (6 to 20 years).

Death and transplant that occurred beyond the initial surgical hospitalization were obtained by subsequent PCCC records, linkage to the National Death Index (NDI) and the Organ Procurement and Transplantation Network (OPTN) respectively.[19] Data registry forms were reviewed to obtain additional clinical details as needed. Linkage through December 31, 2019 was possible for the subset of patients who had direct identifiers available. The NDI is the “gold standard” of mortality and cause of death information in the United States (US).[20] Sensitivity of the overall PCCC-NDI linkage reached 88.1% for death events among patients with adequate identifiers, and specificity exceeded 99%.[19] Available PCCC identifiers were submitted to OPTN to determine transplant status from January 1988 (earliest available data from OPTN registry) through December 31, 2019. The OPTN data system includes data on all donor, wait-listed candidates and transplant recipients in the US, submitted by its members. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN contractor. Transplant status was defined as transplant listing or organ transplant identified through PCCC report or OPTN data. The sensitivity of the PCCC-OPTN linkage reached 89.7% and specificity exceeded 99%.[19]

Long-term mortality was assessed by death events reported in the NDI following discharge after the first PCCC cardiac surgery. Underlying and contributing causes of death were categorized using ICD-9/10 codes as reported by the NDI-PLUS, a supplementary NDI

service collecting causes of death from death certificates. Underlying and contributing modes of death included CHD-related, cardiovascular disease (CVD)-related, and non-CHD, non-CVD-related deaths.

Demographic and clinical characteristics were summarized overall and by the comparator group using means and standard deviations, medians and ranges or counts and percentages, as appropriate. Group comparisons utilized Chi-square or Fisher exact test for categorical variables and independent sample t-test or Wilcoxon rank sum test for continuous variables. Kaplan-Meier survival estimates and log-rank tests were used to describe long-term transplant-free survival. Follow-up duration was determined from the date of first PCCC surgical hospital discharge through date of death, transplant or December 31, 2019 (date of latest NDI and OPTN update), whichever occurred first.

Risk factors associated with long-term survival were examined using univariable and multivariable Cox proportional hazard regression modeling and are presented as hazard ratios (HRs) with associated 95% confidence intervals. Univariable predictors with a significance < 0.20 were included in the multivariable model. The multivariable model for long-term survival included sex, age group, surgical era, initial palliation status, and CHD complexity. A similar multivariable model was fitted for patients with simple CAVC because this is the most common type of CHD in patients with T21. The Cox proportional hazard assumption was assessed graphically and statistically, and when violated, a Heaviside function was employed to address time-varying effects. Meaningful cut points for each time-varying variable were determined by graphical significance. Competing risk regression was used to compare CHD-related mortality between patients with T21 and euploidic controls, using non-CHD-related mortality or transplant as the competing risks. A two-sided p value < 0.05 was considered statistically significant. Statistical analysis was completed using STATA version 16.1 (StataCorp LLC, College Station, TX). The T21 cohort of eight most common diagnoses was matched 1:1 to PCCC patients without genetic conditions and with the same diagnosis category using simple random sampling.

RESULTS

A total of 4,560 patients with T21 underwent their first surgery for a two-ventricle CHD in the PCCC between 1982 and April 15, 2003 (Figure 1). The eight most common primary cardiac diagnoses were identified (n = 4,458), and the remaining 102 patients were excluded from further analysis. After exclusion of patients with insufficient identifiers or incorrect information, a total of 3,571 (80.1%) patients with T21 remained eligible for PCCC-NDI linkage (Figure 1). This accounts for 9.5% of the whole PCCC cohort meeting the same eligibility criteria and 69% of the patients with a chromosomal anomaly within this cohort.[17] Within the T21 cohort, there were 247 deaths reported by PCCC records; of these, 230 had a matching NDI record of death, yielding a PCCC-NDI linkage sensitivity of 93.1% (95% CI 89.2–95.9%) for T21 in-hospital mortality. Characteristics of the T21 PCCC cohort by outcome are presented in Table I (available at www.jpeds.com). The most common CHD among patients with T21 was CAVC (44.0%) and therefore most fell under the moderate complexity category (59.5%). Patients with confirmed death following the first surgical hospitalization were more likely to have had initial surgery in the earliest surgical era, initial

palliation, and more complex CHD than those not confirmed dead. Table 2 (available at www.jpeds.com) summarizes the initial and subsequent congenital heart surgeries during the same or subsequent hospitalization performed in the T21 cohort. Repair of CAVC (n = 1,445, 40.4%) and VSD closure (n = 948, 26.6%) were the most common initial operations, and the most common subsequent procedures were left atrioventricular valve repair/replacement (n = 188, 22.1%) or permanent pacemaker procedure (n = 167, 19.6%). In-hospital mortality for the first surgical procedure was 5.46% (195/3,571), and improved significantly from the earliest to the latest treatment era (from 8.1% to 3.8%, $p < 0.001$).

A total of 386 deaths (11.4%) occurred in the T21 long-term survival analysis group (n = 3,376) following discharge after the first cardiac surgery. Median follow-up duration was 22.6 years (IQR 19.0–27.0). Overall, transplant-free survival was 92.3% at 10 years, 89.8% at 20 years and 86.5% at 30 years (Figure 2, A). Survival varied significantly by the complexity of the underlying CHD (Figure 2, B) (all log-rank $p < 0.001$) and by individual lesion type (Figure 2, C–F). At the 30-year landmark, survival ranged from a high of 92.1% for simple VSD to low of 65.3% for CAVC with aortic arch obstruction; however, survival did not differ significantly between ASD, iAVC, simple VSD or complex VSD. Survival at 30 years was 85.6% for CAVC, the most common lesion among patients with T21.

T21 and euploidic comparators matched 1:1 by cardiac diagnosis and who survived their first CHD surgery (T21 n = 2,185, euploidic comparators n = 2,185) formed the cohort for comparative survival analysis. Clinical characteristic comparison between them is presented in Table 3 (available at www.jpeds.com). There were no differences between the groups with regards to sex, surgical era, complexity, or need for initial palliative procedure. However, the T21 group was significantly younger than euploidic comparators at the time of both the initial and corrective cardiac surgeries ($p < 0.001$). Beyond the first cardiac surgical procedure, 30-year survival of patients with T21 was 88% (95% CI 86.0–89.7%) compared with 93.1% in comparators (95% CI 91.5–94.3%, log-rank $p < 0.001$) although the age at death was similar.

Univariable predictors of late all-cause mortality (following discharge from the first cardiac surgery) with a significance less than 0.2 between patients with T21 and euploidic comparators included sex, age group at first surgery, surgical era, need for initial palliation, and CHD complexity. These variables were included in the Cox hazards model with application of a Heaviside function for predictors that violated the proportional hazards assumption. In the multivariable model, T21 was associated with a late all-cause mortality hazard ratio of 1.83 (95% CI 1.46–2.28, $p < 0.001$), compared with euploidic comparators. Earlier surgical era, need for initial palliation, and more complex CHD were also associated with increased hazard of late mortality, as was neonatal or infant age at first surgery in the first 2 years of follow-up (Table 4). Analysis of late all-cause mortality predictors specific among patients with CAVC identified T21 (HR 2.23, 95% CI: 1.39–3.60, $p = 0.001$), earlier surgical era, and need for initial palliation as statistically significant predictors of mortality (Table 4). In the comparative survival cohort T21 was not associated with increased risk of CHD-related mortality in competing risk regression (SHR 1.34, 95% CI 0.92–1.97, p = 0.127) (Table 5).

The distribution and comparison of underlying and contributing causes of death (COD) between patients with T21 and euploidic comparators are presented in Table 6. Euploidic patients were more likely to have CHD identified as the underlying COD (40.7% vs 27.2%, $p = 0.016$), but less likely to have other cardiovascular disease (CVD) identified as the underlying COD (13.0% vs 22.9%, $p = 0.016$). Among those with CVD-related underlying COD, patients with T21 were more likely to die from pulmonary hypertension (6.1% vs 0.8%, $p = 0.021$) or cerebrovascular disease (4.2% vs 0, $p = 0.029$). They were also more likely to die from leukemia and other cancers (8.9% vs 2.4%, $p = 0.038$), and less likely to die from external causes such as accidents or medical complications (5.6% vs 12.2%, $p = 0.038$).

Pulmonary hypertension was also more commonly identified as a CVD-related contributing COD in patients with T21 (17.1% vs 2.9%, $p < 0.001$). Overall, patients with T21 had higher number of contributing CODs per death event than euploidic comparators (3.31 vs 2.82, p = 0.005) (Table 3). Patients with T21 were more likely to have contributing COD such as cardiac arrest, pneumonia, other respiratory causes, and leukemia or other cancer and the comparators were more likely to have arrhythmia. Trisomy 21 was identified as the underlying COD in 13.6% of deaths and a contributing COD in 37.6% of deaths in the T21 group.

DISCUSSION

Long-term outcome studies from the PCCC and other sources reported the increased risk for premature mortality among patients with operated CHD, compared with the general population.[17,21,22] Additional risk for premature death was observed in the subgroup with chromosomal abnormalities compared with those without.[17] However, limited data exist on the specific effect of T21 on long-term survival after congenital heart surgery.

Our study identified T21 as a significant predictor of 30-year all-cause mortality across each one of the diagnostic subgroups. However, our study did not identify T21 as a significant predictor of CHD-related mortality. This dichotomous finding is related to the serious life-threatening co-occurring conditions such as pulmonary hypertension, respiratory illnesses, higher incidence of leukemia and other cancers in patients with T21, which increase the risk of long-term mortality independently of their CHD.

Previous studies that examined the effect of T21 on short- or mid-term outcomes across the spectrum of congenital heart surgery did not find differences in mortality between patients with or without T21.[8,9,23–28] In a longer-term study, Reller et al reported that survival up to 20 years following repair of CAVC was significantly shorter for children with T21, although there were no differences in long-term survival in other types of CHD. In the T21 group with CAVC, pulmonary hypertension was judged to have contributed to 55% of late deaths.[11] Several other smaller studies failed to identify differences between T21 and euploidic patients.[10,28–33]

There may be several explanations for the discrepancies between our results and previous studies, such as smaller sample sizes, single center or single subset of CHD, which all can

affect the generalizability of results.[10,28–33] In addition, the potential inadvertent inclusion of patients with heterotaxy in comparison studies may have adversely affected both short- and long-term survival.[34] Some previous studies that compared in-hospital or long-term outcomes between patients with or without T21 did not specifically report if patients with heterotaxy were excluded.[9,26,32,35]

The COD analysis in our cohort confirms the report by Reller et al that pulmonary hypertension is an important underlying and contributing COD in patients with T21.[11] This finding underscores the need for ongoing assessment and treatment of pulmonary hypertension with phosphodiesterase-type 5 inhibitors or endothelin receptor antagonists as indicated.[36–40] Indirect causes of pulmonary hypertension such as obstructive sleep apnea and sleep-disordered breathing are also common in patients with T21.[41–43] Pneumonia and the increased incidence of respiratory infections in children with T21 throughout their life is well known, and likely due to a combination of immunological vulnerability, anatomical abnormalities, obstructive sleep apnea, gastroesophageal reflux and oropharyngeal aspiration.[44] Pneumonia in patients with T21 is also associated with increased severity of the illness, leading to increased risk of hospitalization and need for mechanical ventilation.[45] Health supervision guidelines for children with T21 have previously been established [46], and similar evidence-based guidelines for adults with T21 are now available.[47] The role of the adult congenital cardiology clinic is important to provide ongoing monitoring and follow-up of sequelae of T21 with CHD.[48] In addition, primary care provider and specialist coordination, as well as family education is imperative to mitigate the long-term health consequences in patients with T21. As seen in this study, co-occurring conditions related to T21 may be more influential in long-term mortality than repaired CHD, so a true medical home and coordinated primary and specialty care are crucial for ongoing health maintenance in children and adults with T21.

Trisomy 21 remains a significant risk factor for shortened long-term survival following congenital heart surgery, but not a predictor of CHD-related mortality. Co-occurring conditions of T21 such as pulmonary hypertension, pneumonia, and sleep-disordered breathing as well as hematological malignancies are important factors in long-term mortality. Patients with T21 would benefit from a multidisciplinary and cooperative approach in managing their lifelong co-occurring conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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authors and in no way should be seen as an official policy of or interpretation by the OPTN or the U.S. Government. The authors declare no conflicts of interest.

Abbreviations

CHD	Congenital heart disease
T21	Trisomy 21
PCCC	Pediatric Cardiac Care Consortium
HIPAA	Health Insurance Privacy and Portability Act
ASD	Atrial septal defect
iAVC	Incomplete atrioventricular canal (transitional and partial)
VSD	Ventricular septal defect
DORV	Double outlet right ventricle
CAVC	Common atrioventricular canal
TOF	Tetralogy of Fallot
NDI	National Death Index
OPTN	Organ Procurement and Transplantation Network
US	United States
CVD	Cardiovascular disease

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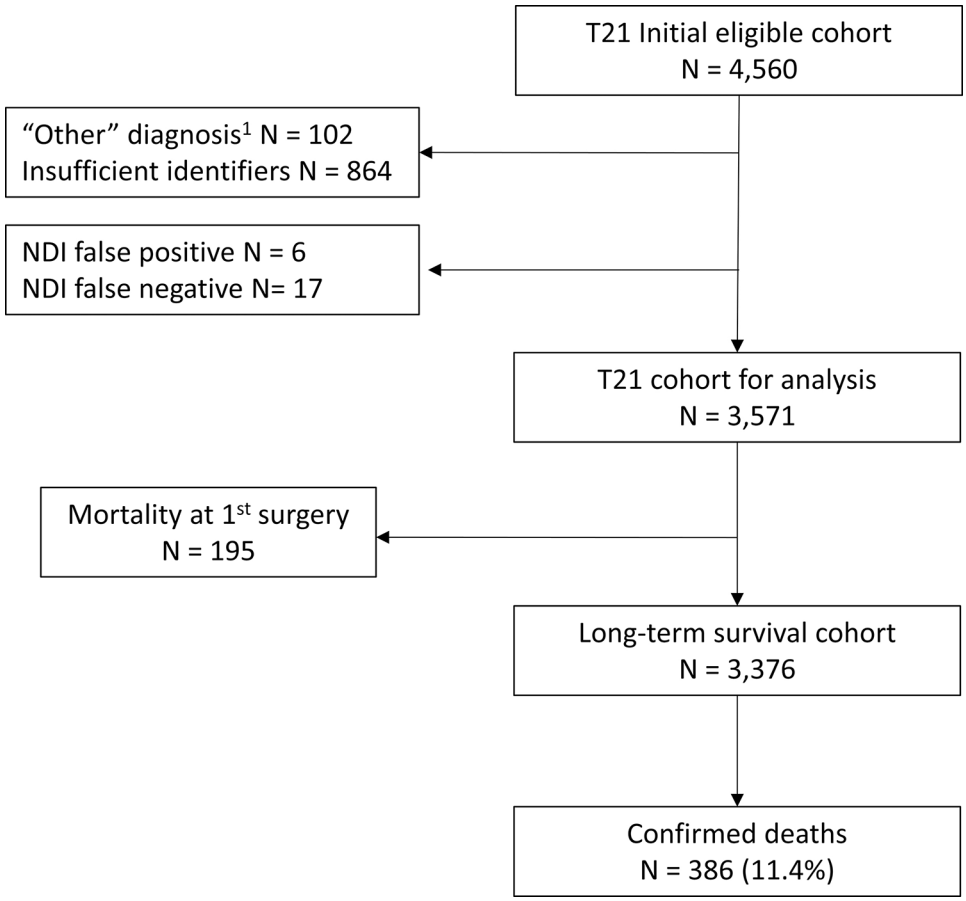

Figure 1,
online only. STROBE diagram of Trisomy 21 two-ventricle congenital heart surgery patients.

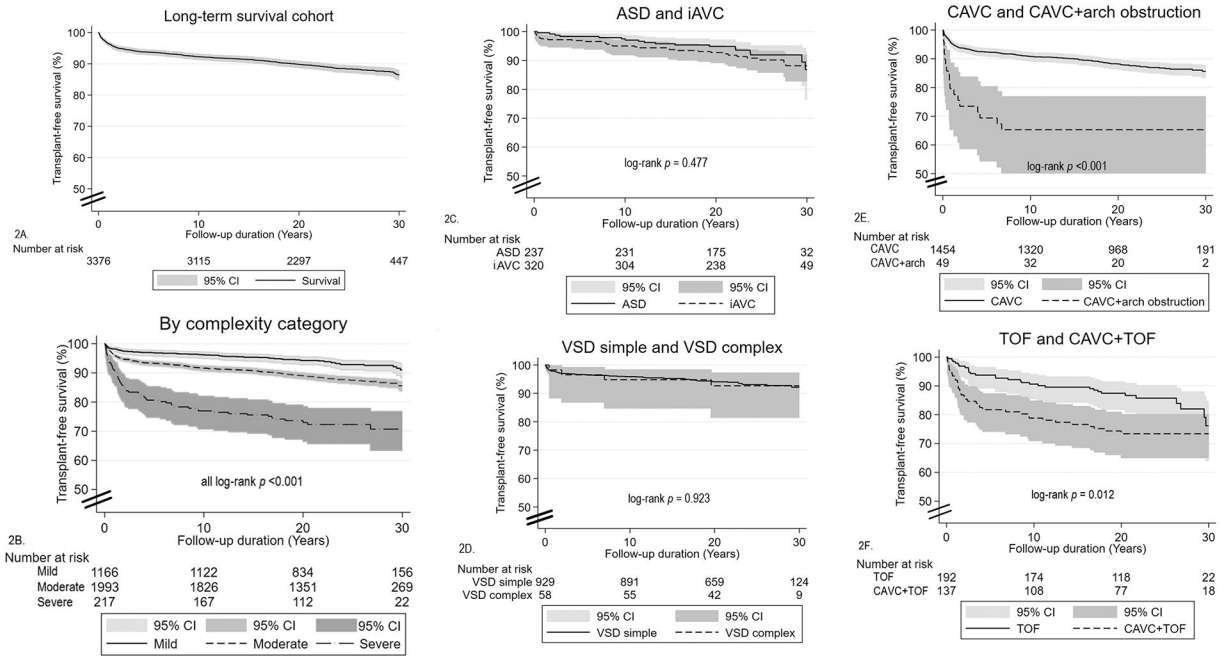

Figure 2.

Kaplan-Meier transplant-free survival plots for patients with T21, conditioned on being discharged alive following first congenital heart surgery, by diagnosis group.

Table 1, online only.

Characteristics of PCCC T21 cohort

	Total (n = 3,571)	Death at 1st surg. hosp (n = 195)	Long-term survival (n = 2,990)	Confirmed death (n = 386)	P value
Age 1st surg N (%)					<0.001
< 28 days	134 (3.8)	28 (14.4)	79 (2.6)	27 (7.0)	
28–364 days	2,587 (72.4)	145 (74.4)	2,173 (72.7)	269 (69.7)	
1–5 yr	685 (19.2)	17 (8.7)	596 (19.9)	72 (18.6)	
6–20 yr	165 (4.6)	5 (2.6)	142 (4.7)	18 (4.7)	
Age 1st surgery (yrs) median, (IQR)	0.51 (0.33–0.94)	0.40 (0.20–0.65)	0.52 (0.34–0.98)	0.51 (0.28–0.90)	<0.001
Sex N (%)					0.326
Male	1,725 (48.3)	91 (46.7)	1,434 (48.0)	200 (51.8)	
Female	1,846 (51.7)	104 (53.3)	1,556 (52.0)	186 (48.2)	
Era 1st surg N (%)					<0.001
Early: 1982–1992	1,092 (30.6)	89 (45.6)	837 (28.0)	166 (43.0)	
Middle: 1993–1997	1,103 (30.9)	54 (27.7)	937 (31.3)	112 (29.0)	
Late: 1999–2003	1,376 (38.5)	52 (26.7)	1,216 (40.7)	108 (28.0)	
Palliation N (%)	313 (8.8)	35 (17.9)	182 (6.1)	96 (24.9)	<0.001
Complexity N (%)					<0.001
Mild	1,191 (33.4)	25 (12.8)	1,085 (36.3)	81 (21.0)	
Moderate	2,124 (59.5)	131 (67.2)	1,749 (58.5)	244 (63.2)	
Severe	256 (7.2)	39 (20.0)	156 (5.2)	61 (15.8)	
ECLS at 1st surgical hospitalization N (%)	15 (0.4)	10 (5.1)	5 (0.2)	0	<0.001
PPM at 1st surgical hospitalization N (%)	75 (2.1)	3 (1.5)	57 (1.9)	15 (3.9)	0.050
Cardiac Dx N (%)					<0.001
ASD	239 (6.7)	2 (1.0)	219 (7.3)	18 (4.7)	
Incomplete AVC	324 (9.1)	4 (2.0)	289 (9.7)	31 (8.0)	
VSD simple	952 (26.7)	23 (11.8)	866 (29.0)	63 (16.3)	
VSD complex	60 (1.7)	2 (1.0)	54 (1.8)	4 (1.0)	
CAVC	1,570 (44.0)	116 (59.5)	1,268 (42.1)	186 (48.2)	
CAVC+ arch obstr	62 (1.7)	13 (6.7)	32 (1.1)	17 (4.4)	
TOF	205 (5.7)	13 (6.7)	162 (5.4)	30 (7.8)	
CAVC + TOF	159 (4.5)	22 (11.3)	100 (3.3)	37 (9.6)	

Given are number (N) and percent (%) by column for categorical variables, median and interquartile range (IQR) for continuous variable. P values represent differences between death at first surgical hospitalization, alive at follow-up, and confirmed death groups using Chi-square or Fisher's exact test as appropriate for categorical variables, Kruskal-Wallis test for continuous variables. Surg.hosp = surgical hospitalization; ECLS = extracorporeal life support; PPM = permanent pacemaker; Dx = diagnosis; ASD = atrial septal defect; Incomplete AVC = partial or transitional atrioventricular canal; VSD = ventricular septal defect; CAVC = common atrioventricular canal; arch obstr = aortic arch obstruction including coarctation or interrupted aortic arch; TOF = tetralogy of Fallot.

Table 2, online only.

Initial and subsequent surgical procedures in patients with Trisomy 21[a]

Procedure Name N (%)	Initial procedure (n = 3,571)	Procedure Name N (%)	Subsequent procedure (n =852)
CAVC repair	1,445 (40.4)	LAVV repair or replacement	188 (22.1)
VSD closure	948 (26.6)	Permanent pacemaker	
		initial	115 (13.5)
		replacement	52 (6.1)
Incomplete AVC repair	319 (8.9)	CAVC repair	126 (14.8)
ASD repair	238 (6.7)	VSD closure	74 (8.7)
TOF repair	152 (4.3)	Subaortic resection	58 (6.8)
PA band	135 (3.8)	TOF repair	54 (6.3)
AP shunt	132 (3.7)	TOF + CAVC repair	39 (4.6)
TOF + CAVC repair	75 (2.1)	AP shunt	26 (3.0)
CoA/IAA repair	54 (1.6)	RVOT procedure	17 (2.0)
PDA ligation	43 (1.2)	Supravalvar aortic stenosis repair	14 (1.6)
Other[1]	30 (1.0)	Other[2]	89 (10.5)

Given are frequency (n) and percent (%).

[a]Note that diagnoses and procedures do not match completely; some patients underwent palliative procedures or reoperations.

CAVC = common atrioventricular canal; VSD = ventricular septal defect; Incomplete AVC = incomplete atrioventricular canal (partial and transitional); ASD = atrial septal defect; TOF = tetralogy of Fallot; PA = pulmonary artery; AP = aortopulmonary; CoA = coarctation of the aorta; IAA = interrupted aortic arch; PDA = patent ductus arteriosus; LAVV = left atrioventricular valve; RVOT = right ventricular outflow tract.

[1]Other includes left ventricle to aorta tunnel (n= 13), CAVC + CoA (n = 8), RVOT procedure (n = 7), left atrioventricular (mitral) valve repair/ replacement (n = 2).

Other[2] includes right atrioventricular valve repair/replacement (n = 13), pulmonary valve replacement n= 12, ASD repair (n = 11), PA band (n = 10), pulmonary arterioplasty (n = 10), PDA ligation (n= 8), incomplete AVC repair (n= 7), CoA/IAA repair (n = 5), extracorporeal life support (n = 4), subpulmonary stenosis repair (n = 4), left ventricle to aorta tunnel (n = 2), atrial mass resection (n= 2) CAVC + CoA repair (n = 1).

Table 3, online only.

Characteristics of T21 patients and matched euploidic comparators

	Euploidic comparators	T21	p-value
	N = 2,185	**N = 2,185**	
Males N (%)	1,055 (48.3)	1,064 (48.7)	0.809
Surgical era N (%)			0.674
Early 1982–1992	629 (28.8)	632 (28.9)	
Mid 1993–1997	720 (32.9)	694 (31.8)	
Late 1998–2003	836 (38.3)	859 (39.3)	
Diagnosis category N (%)			NC
ASD	237 (10.9)	237 (10.9)	
Incomplete AVC	320 (14.6)	320 (14.6)	
VSD simple	929 (42.5)	929 (42.5)	
VSD complex	58 (2.6)	58 (2.6)	
CAVC	391 (17.9)	391 (17.9)	
CAVC+ aortic arch obstruction	37 (1.7)	37 (1.7)	
TOF	192 (8.8)	192 (8.8)	
CAVC + TOF	21 (1.0)	21 (1.0)	
CHD complexity N (%)			0.457
Mild	1,166 (53.4)	1,157 (52.9)	
Moderate	921 (42.1)	945 (43.2)	
Severe	98 (4.5)	83 (3.8)	
Staged repair N (%)	164 (7.5)	137 (6.3)	0.120
Age at 1st surgery (Yrs) median (IQR)	0.96 (0.39–3.51)	0.61 (0.37–1.38)	<0.001
Age at corrective surgery (Yrs) median (IQR)	1.13 (0.46–3.71)	0.67 (0.40–1.56)	< 0.001
ECLS at surgery N (%)	4 (0.2)	1 (<0.1)	0.375
First permanent pacemaker N (%)	61 (2.8)	66 (3.0)	0.719
Postop < 6 months SND or heart block	53 (86.9)	50 (75.8)	0.115
Other indication[1]	8 (13.1)	16 (24.2)	
Heart or Lung Transplant N (%)	4 (0.2)	1 (< 0.1)	0.375
Any LAVV reop after iAVC N (%)	24 (7.5)	17 (5.3)	0.333
Any LAVV reop after CAVC N (%)	61 (14.2)	32 (7.4)	0.001
Any reoperation N (%)	304 (13.9)	316 (14.5)	0.633
30-year survival % (95% CI)	93.1 (91.5–94.3)	88.0 (86.0–89.7)	<0.001
Age at death (Yrs) median (IQR)	7.07 (0.93–21.57)	6.76 (1.27–18.53)	0.876
Follow-up duration (Yrs) median (IQR)	23.14 (19.7–27.29)	22.70 (19.17–27.00)	0.020
Cause of death N (%)			0.013
CHD-related	50 (40.7)	58 (27.2)	
Other cardiac-related	16 (13.1)	51 (23.9)	
Not cardiac-related	57 (46.3)	104 (48.8)	
# Contributing COD/death event			

	Euploidic comparators	T21	p-value
	N = 2,185	**N = 2,185**	
Mean (SD)	2.82 (1.52)	3.31 (1.54)	0.005

Given are frequency (N) and percent (%) for categorical variables, median and interquartile range (IQR) or mean and standard deviation (SD) for continuous variables. 30-year survival is Kaplan-Meier survival estimate. P values represent Fisher's exact test for categorical variables, log-rank test, t-test or Wilcoxon rank-sum test for continuous variables.

[1] Other indication included late (>6 months postoperative) sinus node dysfunction or heart block in 14 T21 patients and 5 euploidic comparators, preoperative sinus node dysfunction or heart block in 4, biventricular pacing in 1.

NC= not calculated, two groups were matched 1:1 on diagnosis category; ASD = atrial septal defect; iAVC = incomplete atrioventricular canal (partial and transitional; VSD = ventricular septal defect; CAVC = common atrioventricular canal; TOF = tetralogy of Fallot; ECLS = extracorporeal life support; LAVV = left atrioventricular valve; reop = reoperation including repair or replacement; SND = sinus node dysfunction; CHD = congenital heart disease; COD = cause of death

Table 4.

Univariable and multivariable predictors of all-cause mortality following first cardiac surgery for T21 cohort and euploidic comparators

	Univariable		Multivariable	
Risk Factor	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
T21	1.74 (1.39–2.17)	<0.001	1.83 (1.46–2.28)	<0.001
Euploidic	Ref		Ref	
Sex				
Male	1.16 (0.94–1.44)	0.159	1.15 (0.93–1.43)	0.196
Female	Ref		Ref	
Age at first surgery				
< 28 days *				
≤ 2 yrs follow-up	7.31 (4.86–11.00)	<0.001	4.64 (2.26–9.53)	<0.001
>2 yrs follow-up	1.99 (1.08–3.66)	0.044	0.57 (0.26–1.23)	0.153
28–364 days *				
≤ 2 yrs follow-up	1.41 (1.00–1.99)	0.048	2.69 (1.50–4.85)	0.001
> 2 yrs follow-up	0.77 (0.58–1.02)	0.071	0.74 (0.47–1.16)	0.192
1–5 yrs	0.78 (0.61–0.99)	0.038	1.06 (0.68–1.65)	0.786
6–20 yrs	Ref		Ref	
Surgical Era				
Early 1982–1992	Ref		Ref	
Middle 1993–1997	0.78 (0.63–0.98)	0.031	0.66 (0.50–0.84)	0.001
Late 1998–2003	0.76 (0.56–0.1.02)	0.062	0.53 (0.37–0.76)	0.001
Initial palliation	4.87 (3.80–6.24)	<0.001	3.09 (2.24–4.27)	<0.001
Complexity Category				
Simple	Ref		Ref	
Moderate	1.41 (1.14–1.75)	0.001	1.72 (1.36–2.18)	<0.001
Severe	4.69 (3.46–6.35)	<0.001	2.96 (1.96–4.47)	<0.001
For CAVC	**Univariable**		**Multivariable**	
Risk Factor	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
T21	1.89 (1.19–3.00)	0.006	2.23 (1.39–3.60)	0.001
Euploidic	Ref		Ref	
Sex				
Male	1.21 (0.78–1.89)	0.386	1.21 (0.77–1.90)	0.412
Female	Ref		Ref	
Age at first surgery				
< 28 days	3.65 (1.59–8.41)	0.010	0.68 (0.15–3.05)	0.620
28–264 days	0.69 (0.42–1.14)	0.574	0.57 (0.17–1.86)	0.352
1–5 yrs	1.03 (0.56–1.90)	0.926	0.78 (0.22–2.79)	0.706
6–20 yrs	Ref		Ref	

Surgical Era				
Early 1982–1992	Ref		Ref	
Middle 1993–1997	0.72 (0.46–1.12)	0.147	0.44 (0.29–0.75)	0.002
Late 1998–2003	0.46 (0.24–0.90)	0.013	0.35 (0.16–0.76)	0.008
Initial palliation	6.84 (4.23–11.07)	<0.001	7.07 (4.03–12.42)	<0.001

Reported are hazard ratio (HR) and 95% confidence intervals for multivariable Cox regression.

* Proportional hazards assumption was violated and follow-up duration cut points were created based on survival curve.

Ref = reference category; T21 = Trisomy 21; CAVC = common atrioventricular canal; PPM = permanent pacemaker; LAVV = left atrioventricular valve

Table 5.

Competing risk univariable and multivariable regression for CHD-related mortality following discharge after initial cardiac surgery

	Univariable		Multivariable	
Risk Factor	**SHR (95% CI)**	**P value**	**SHR (95% CI)**	**P value**
Trisomy 21	1.16 (0.80–1.70)	0.425	1.34 (0.92–1.97)	0.127
Euploidic	Ref		Ref	
Sex				
Male	1.28 (0.87–1.87)	0.204	1.21 (0.81–1.79)	0.346
Female	Ref		Ref	
Age at first surgery				
< 28 days	9.08 (5.84–14.13)	<0.001	2.74 (0.78–9.60)	0.114
28–364 days	0.77 (0.52–1.12)	0.172	1.77 (0.61–5.09)	0.291
1–5 yrs	0.68 (0.44–1.06)	0.093	1.77 (0.63–5.03)	0.280
6–20 yrs	Ref		Ref	
Surgical Era				
Era 1982–1992	Ref		Ref	
Middle 1993–1997	0.65 (0.44–0.94)	0.025	0.48 (0.31–0.74)	0.001
Late 1998–2003	0.58 (0.33–1.00)	0.051	0.34 (0.18–0.65)	0.001
Initial palliation	12.47 (8.55–18.20)	<0.001	6.16 (3.48–10.92)	<0.001
Complexity Category				
Simple	Ref		Ref	
Moderate	1.55 (1.06–2.27)	0.023	2.64 (1.60–4.37)	<0.001
Severe	8.80 (5.74–13.50)	<0.001	4.16 (1.99–8.68)	<0.001

Reported are subdistribution hazard ratio (SHR) and 95% confidence intervals. Competing risk was non-CHD related death or transplant. Ref = reference category

Table 6.

Comparison of underlying and contributing causes of death between T21 and euploidic comparators following congenital heart surgery

Underlying Cause of Death				Contributing Causes of Death			
Cause	**Euploidic N = 123**	**T 21 N = 213**	**P-value**	**Cause**	**Euploidic N = 123**	**T 21 N = 213**	**P-value**
CHD N (%)	50 (40.7)	58 (27.2)	0.016	**CHD**	62 (50.4)	98 (46.0)	0.496
CVD N (%)	16 (13.0)	51 (22.9)	0.016	**CVD**[a]	68 (55.3)	127 (59.6)	0.491
Pulmonary HTN	1 (0.8)	13 (6.1)	0.021	Heart failure	23 (18.7)	42 (19.7)	0.886
Other CVD	7 (5.7)	6 (2.8)	0.241	Cardiac arrest	9 (7.3)	43 (20.2)	0.002
Cerebrovascular disease	0 (0)	9 (4.2)	0.029	Other CVD	25 (20.3)	32 (15.0)	0.229
Endocarditis	4 (3.3)	7 (3.3)	0.986	Pulmonary HTN	3 (2.4)	36 (16.9)	< 0.001
Heart failure	2 (1.6)	8 (3.8)	0.336	Arrhythmia	22 (17.9)	15 (7.0)	0.003
Ischemic heart disease	1 (0.8)	6 (2.8)	0.430	Cerebrovascular disease	4 (3.3)	7 (3.3)	0.986
Cardiac arrest	0 (0)	2 (0.9)	0.534	Ischemic heart disease	1 (0.8)	5 (2.3)	0.421
Arrhythmia	1 (0.8)	0 (0)	0.366	Endocarditis	4 (3.3)	4 (1.9)	0.471
Non-CVD, non-CVD	57 (46.3)	104 (48.8)	0.734	**Non-CHD, non CVD**[a]	88 (71.5)	181 (85.0)	0.004
Trisomy 21	0 (0)	29 (13.6)	< 0.001	Other respiratory	20 (16.3)	62 (29.1)	0.008
External causes: Accidents, injuries, complications	15 (12.2)	12 (5.6)	0.038	Trisomy 21	0 (0)	80 (37.6)	< 0.001
Other respiratory	8 (6.5)	14 (6.6)	0.980	Unknown or other	28 (22.8)	35 (16.4)	0.191
Leukemia, other malignancy or hematologic	3 (2.4)	19 (8.9)	0.022	External causes: Accidents, injuries, complications	23 (18.7)	33 (15.5)	0.451
Unknown or other	9 (7.3)	11 (5.2)	0.476	Infection/sepsis	13 (10.6)	23 (10.8)	0.948
Gastrointestinal	6 (4.9)	7 (3.3)	0.560	Pneumonia/ARDS	5 (4.1)	28 (13.1)	0.007
Pneumonia/ARDS	2 (1.6)	12 (5.6)	0.093	Neurologic	14 (11.4)	18 (8.5)	0.441
Infection/sepsis	9 (7.3)	0 (0)	<0.001	Leukemia, other malignancy or hematologic	6 (4.9)	24 (11.3)	0.049
Neurologic	5 (4.1)	0 (0)	0.006	Gastrointestinal	7 (5.7)	17 (8.0)	0.514

Given are frequency and (percent) for categorical variables. P value from Fisher's exact test. CHD = congenital heart disease; CVD = cardiovascular disease; HTN = hypertension; ARDS = adult respiratory distress syndrome.

[a]Percentages do not equal 100% because most patients had more than one contributing cause of death.