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Post-Surgical Transplant-Free Survival Among Children with Turner Syndrome and Congenital Heart Disease

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Post-Surgical Transplant-Free Survival Among Children with Turner Syndrome and Congenital Heart Disease

By

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An abstract of
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Abstract

Post-Surgical Transplant-Free Survival Among Children with Turner Syndrome and Congenital Heart Disease

By Michael Mortillo

Background: Turner syndrome (TS) is a neurogenetic disorder affecting approximately 1 in 2,000 live-born females, characterized by partial or complete monosomy-X. A high rate of morbidity exists among the TS population, primarily due to congenital heart disease (CHD) conditions acquired at birth. People with CHD often undergo various corrective surgical procedures, and depending on the efficacy of the surgery, a subsequent transplant may be required. Though there is much knowledge regarding TS in concert with CHD, little is known about how TS affects post-surgical transplant-free survival (TFS) in people with CHD.

Objective: Assess post-surgical TFS among children with TS and CHD (cases) compared to children with just CHD (controls), to determine if TS increases risk of transplant/mortality.

Methods: This matched cohort study enrolled 704 patients (< 21 years of age) from the Pediatric Cardiac Care Consortium (PCCC), a multi-institutional registry of interventions for CHD from 1982-2011 in 47 US centers. Controls were matched to cases 3:1 by age, primary CHD diagnosis, and year of first surgery. Survival analysis was used to compare TFS between cases and all controls, cases and male controls, and cases and female controls.

Results: Cases had a slightly higher risk of death/transplant during follow-up compared to all controls (HR: 1.27; 95% CI: 0.65 – 2.50; p-value: 0.4872), male controls (HR: 1.40; 95% CI: 0.68 – 2.91; p-value: 0.3610), and female controls (HR: 1.03; 95% CI: 0.45 – 2.39; p-value: 0.9365). Interaction assessment between TS and CHD found no evidence of interaction (X^2: 0.6583; p-value: 0.4172).

Conclusions: TS does not appear to increase risk of transplant/mortality in children with CHD, as no significant differences in survival were seen between cases and controls. We recommend further studies to better confirm the association between TS and CHD in TFS.

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Background

Turner syndrome (TS) is a neurogenetic disorder characterized by partial or complete monosomy-X, usually the result of a sporadic chromosomal nondisjunction. It is one of the most common sex chromosome abnormalities and is the most common genetic disorder in females, affecting approximately 1 in 2,000 live-born females. While males have an XY sex-chromosome arrangement, females have an XX arrangement. TS is displayed when females lack the second X chromosome (either partially or entirely), thereby having an XO arrangement.[7] The majority (approximately 50%) of females with TS have a 45,X karyotype (one less than the usual 46 chromosomes). Several karyotype variations exist including short or long arm deletion, ring X, fusion of chromosome arms, and mosaicism. Physical phenotypes associated with TS include short stature, ovarian failure, webbed neck, cardiac abnormalities, impaired glucose tolerance, thyroid disease and hearing loss, and estrogen deficiency. There is considerable heterogeneity of phenotypic features, with short stature and gonadal dysgenesis being the most consistent. Therefore, a majority of females with TS are treated with growth hormone and estrogen replacement therapies (ERT).[2]

Cardiac abnormalities are considered the most serious medical problems associated with TS. A high rate of morbidity exists among the TS population, due to congenital heart disease (CHD) conditions acquired at birth. It is estimated that nearly 50% of people with TS have some form of CHD, and it is the most common cause of mortality among patients with TS.[5] There are multiple outcomes that can be assessed when looking at CHD in concert with TS; a 2017 prospective cohort study assessed coronary artery calcification among a cohort of 128 females (62 of whom had TS). The results showed that adults with TS are 63% more likely to have coronary artery

calcification than controls, with an age cutoff of 51.7 years for a probability of >50% for the presence of coronary calcifications.[14] In contrast, a 2018 retrospective cohort study instead looked at aortic stiffness in adolescent Turner and Marfan syndrome (MFS) patients. Results showed that patients with TS and MFS had reduced distensibility in the ascending aortic arch when compared with controls.[13]

Most people with CHD and TS have a left heart abnormality, either a two-ventricle abnormality (commonly referred to as left heart obstructive lesion, or LHOL), or a single-ventricle abnormality (referred to as hypoplastic left heart syndrome, HLHS). A 2016 retrospective cohort study on 542 patients, 11 of whom had TS, studied long-term survival and causes of death in patients with TS and HLHS (HLHS/TS+), compared to patients with HLHS and no TS (HLHS/TS-). Neonatal mortality was 36% in HLHS/TS+ compared to 27% in HLHS/TS-. 10 of the 11 TS+ patients died during the study period, for a cumulative mortality of 91% vs. 50%.[9] Another study, conducted in 2017, assessed the effect that chromosomal abnormalities have on surgical outcomes in infants with HLHS. Results showed that the three most common chromosomal abnormalities associated with HLHS among the patients were Turner (25%), DiGeorge (22%), and Downs (12.7%).[15] There are many LHOL associated with TS, but the most commonly seen ones include bicuspid aortic valve (BAV), partial anomalous pulmonary venous return (PAPVR), elongation of the transverse aortic arch, coarctation of the aorta (COA), and ascending aortic dilatation.[4] In addition to left heart obstructive defects, there are a variety of other metabolic conditions associated with TS, including early-onset hypertension, ischemic heart disease, and stroke. All of these work in concert to reduce the life span of those with TS.[15]

Due to the wide array of cardiac abnormalities in people with TS, it is quite common for these people to receive heart transplants after the initial corrective surgery. Assessing whether or not a transplant occurs after the corrective surgery is crucial to understanding the post-surgical status of the patient. A 2018 retrospective cohort study looked at 14 female heart transplantation (HTx) recipients, all of whom had TS. Results showed that the median length of follow-up after primary HTx was 2.6 years, and median TFS was 4.1 years. For patients that survived past 1 year, follow-up ranged from 4.1 to 10.9 years, during which no deaths were observed; however, two patients underwent re-transplant at 4.1 and 10.5 years. Following initial HTx, 6 patients died, all in the first year following HTx, with five occurring within the first months. 3 of these patients had HLHS and TS. For the patients who underwent re-transplantation, one died 20 days post-HTx from multi-organ failure in the setting of sepsis and one was alive at last follow-up of 3.9 years.[3]

In this study, we aim to understand the effect, if any, that TS has on TFS in children with CHD, in order to determine if TS is a risk factor for transplant/mortality in children with CHD. We also hope to see if interaction exists between CHD and TS.

Methods

Study Design

In this study, we performed a matched cohort study by comparing TFS among two cohorts; one comprised of children with TS and some type of CHD, either LHOL or HLHS, (regarded as cases), and one comprised of children with only LHOL or HLHS (regarded as controls). We

compared those with TS to matched females and males separately because, although those with TS are female, they lack the protective effect of having two X chromosomes.

Patients were recruited from the Pediatric Cardiac Care Consortium (PCCC), which is a large multi-center cohort of children treated for CHD between 1982 and 2003. The PCCC contains a registry of cardiac catheterizations, surgical operations, and autopsies performed for infants, children, and adults with congenital heart disease. It also contains about 600 children with some form of CHD and TS.[1]

Collection of Cases

Using PCCC, we obtained an initial cohort of 293 patients with CHD and TS. Figure 1 shows the exclusion criteria implemented to identify cases. Our two preliminary criteria that we used were whether or not the patient had any CHD surgical repair at any point, and whether or not they received a CHD surgical repair prior to enrolling in PCCC. We are only interested in looking at those who had a repair (so that we can assess TFS post-surgery), and more specifically only looking at those that had a repair *after* enrolling in PCCC. We found that 55 patients out of the original 293 (19%) had no CHD surgical repair at any point, and thus were excluded from the study. We also found that 24 out of 293 (8%) had a CHD surgical repair prior to enrolling in PCCC, and likewise were excluded from the study. These reductions yielded an eligible cohort of 214 patients. Of these 214 patients, 1 was omitted because they were 21 or older at the time of the first surgery (since this is a pediatric study, we are only looking for patients younger than 21 at the time of the first surgery). We also excluded 6 patients due to their records being submitted to the National Death Index (NDI) with no first name. These exclusions bought our cohort down to 207 patients, all of whom were submitted to NDI with adequate identifiers for linkage.

We then excluded 31 (15%) patients that did not have a left heart abnormality. These included 8 patients (25.8%) with an atrial septal defect (ASD), 5 patients (16.1%) with an atrioventricular canal (AVC) defect, 1 patient (3.2%) with aortic insufficiency (AI), 3 patients (9.6%) with a single ventricle dominant left ventricle (SV dominant LV), 1 patient with ventricular septal defect plus (VSD plus – defined as VSD with either ASD, RVOTO, subaortic stenosis (subAS), or AI), 1 patient (3.2%) with truncus arteriosus (TA), 1 patient (3.2%) with dextro-transposition of the great arteries with arterial switch operation (dtGA w/ Aaso), 3 patients (9.6%) with Tetralogy of Fallot (TOF), 2 patients (6.4%) with right ventricular outflow tract obstruction (RVOTO), and 6 patients (19.4%) with partial anomalous pulmonary venous connection (PAPVC). As a result, we were left with a final cohort of 176 patients, all of whom had adequate identifiers for NDI and had some type of left heart abnormality. This included 20 patients (11.4%) with single ventricle dominant right ventricle (SV dominant RV), 1 patient (0.57%) with interrupted aortic arch (IAA), 28 patients (15.9%) with coarctation of aorta plus (COA plus – defined as COA with either ASD, VSD, or AS), 115 patients (65.3%) with COA, and 12 patients (6.8%) with left ventricular outflow tract obstruction (LVOTO).

Collection of Controls

Figure 2 details the exclusion criteria implemented to identify controls. Using PCCC, we obtained an initial cohort of 16,910 patients with CHD and no TS. We excluded 2,362 patients (14%) who received no CHD surgical repair at any point. We also excluded 2,543 patients (15%) who received a CHD surgical repair prior to enrolling in PCCC. This left us with an eligible cohort of 12,005 patients. We removed 274 patients (2.3%) who were 21 or older at the time of their first surgery, as well as 160 patients (1.3%) who were submitted to NDI with no first name.

We then excluded 3,328 patients with no left heart abnormality. This included 936 patients (28.9%) with PAPVC, 1,956 (60.4%) with VSD plus, 245 patients (7.6%) with AI, and 101 patients (3.1%) with mitral stenosis (MS). This left us with a final cohort of 8,333 patients, all of whom had adequate identifiers for linkage and some type of left heart abnormality. Among these were 1,724 patients (20.7%) with SV dominant RV, 321 patients (3.9%) with IAA, 1,110 patients (28.5%) with COA plus, 3,556 patients (91.5%) with COA, and 1,622 patients (41.7%) with LVOTO. Among both cases and controls, those with COA, COA Plus, IAA, and LVOTO were classified as having LHOL, while those with SV dominant RV were classified as HLHS.

Statistical Analysis

All statistical analysis, including matching, was completed through Statistical Analysis Software (SAS). Controls were matched to cases on a 3:1 ratio. Cases and controls were matched on primary CHD diagnosis, age, and year of first surgery. We allowed SAS to tolerate a maximum 1-year difference in age and year of first surgery (ie: a 12-year old case who had their first surgery in 1994 could be matched to a control with an age of either 11, 12, or 13, who had their first surgery in either 1993, 1994, or 1995). Primary CHD diagnoses had to be an exact match. In preparing results, we reported median and interquartile range (IQR) for continuous variables (due to a non-normal distribution in continuous variables among cases and controls). For categorical variables, we reported count and percentages of sample. Categorical variables, such as age group, year of first surgery, and primary CHD diagnosis were trichotomized.

The main form of statistical analysis we employed was survival analysis. We felt this was the most appropriate type of statistical analysis because our outcome variable is the time until transplant or mortality occurs after the first surgery. As a result, we felt survival analysis would

best help us approximate differences in TFS between cases and controls. Through survival analysis, Kaplan Meier (KM) survival curves were obtained to draw comparisons between the cohorts. We also obtained log-rank test statistics to test the null hypothesis of no difference in survival between the two cohorts. Hazard ratios (HR) were also obtained, along with 95% confidence intervals (CIs).

To help us perform our survival analysis, we calculated follow-up time in days, months, and years for each patient. This was done by creating an NDI end date variable. If a patient had a transplant or death date listed in the dataset, then this date was set as the NDI end date. These people were coded as having gotten the outcome. If no transplant or death date was listed, then the NDI end date was set as December 31, 2014, which is the last date that PCCC holds information for. These people were coded as having not gotten the outcome. We also accounted for in-hospital deaths, by setting those with an exit type of death to have their NDI end date equal their exit date. Follow-up days were then calculated by subtracting a patient's exit date from their NDI end date, and then conversions were implemented to obtain follow-up months and years.

This study was supported by the NIH/NHLBI Award: R01 HL122392 and received Emory IRB approval.

Results

Table 1 displays demographic characteristics of our cohort before matching was implemented, and shows comparisons between cases and the comparison group, which was split between males

and females (since this is the method in which we ran the analysis). Though we included those with other, non-left heart abnormalities in the table, we did not include these patients when running our analysis (since we are only interested in patients with a left-heart defect). Results show statistically significant differences in median age, age groups, and primary CHD diagnosis ($p < 0.0001$) across the three groups. Year of first surgery (trichotomized into decades), was not statistically significantly different across the groups ($p = 0.1560$). Age group was also trichotomized, with newborns being classified as age < 4 weeks, infants as age 4 weeks – 1 year, and children as age > 1 year. We see that in the male and female comparison groups, children comprised the majority of the sample (47.01% and 43.93%, respectively). However, the cases cohort is comprised primarily of newborns (42.03%). More than half of the patients in the cases and male and female comparison groups had their first surgery between 1990-1999 (56.04%, 56.24%, and 55.88%, respectively). LHOL was the most prevalent diagnosis across cases as well as male and female groups (75.36%, 59.52%, and 52.95%). This was expected, as the majority of patients had either COA or COA plus, which is considered LHOL.

Table 2, created after matching was conducted, displays median follow-up years among the three comparison groups, stratified by our three matching covariates: primary CHD diagnosis (excluding those with non-left heart abnormalities), age (trichotomized into age groups), and year of first surgery (trichotomized into decades). We see that overall follow-up years across the three groups are all within one year of each other. As for follow-up time related to age group, newborns have the shortest follow-up time in the cases and male and female control groups (14.70, 14.80, and 13.61 years, respectively). Infants have the next shortest follow-up time, followed by children, who have the longest follow-up time of the three age groups (21.06, 21.71, and 20.98 years across cases, male and female controls). Patients who had their first surgical

admission between 1980-1989 appear to have the longest follow-up time among the cases, male and female controls (26.12, 26.30, and 26.43 years, respectively). Patients with a surgical admission between 1990-1999 have the next longest follow-up time, followed by patients with a surgical admission between 2000-2011 having the shortest follow-up time (12.43, 12.75, and 12.17 years across cases, male and female controls). We also see a large differentiation in follow-up years between patients with LHOL and HLHS, though this is likely due to the small number of patients with HLHS compared to LHOL. We also see across all three matched covariates, follow-up years are statistically significantly different among cases and the control groups ($p < 0.0001$). However, overall median follow-up years were not significantly different among the cohorts ($p = 0.3120$).

Figure 3 shows KM survival curves among cases and all controls, not including in-hospital deaths (IHD), along with a survival table detailing the number of at-risk patients every 5 years of follow-up. Table 3 shows survival estimates along with 95% CIs for every 5 years of follow-up. At the beginning of follow-up, there were 157 cases and 463 controls at risk, with 19 cases and 65 controls being excluded due to IHD. During the 25 years of follow-up recorded, there were 12 deaths or transplants among the cases, and 28 deaths or transplants among the controls. A higher hazard of death/transplant during follow-up was observed among the cases (HR: 1.27; 95% CI: 0.65 – 2.50). Survival curves also show patients who were censored due to their follow-up time ending, along with a log-rank p-value of 0.4872. Cases had an 88.9% estimate of surviving to year 25 of follow-up (95% CI: 82.2 – 96.1), while controls had a 93.1% estimate (95% CI: 90.5 – 95.9) (Table 3).

Figure 4 shows KM survival curves among cases and male controls. Similar to Figure 3, 157 cases were at risk at the start of follow-up, with 19 excluded due to IHD. 327 male controls were at risk, with 34 excluded through IHD. Throughout follow-up, 12 deaths or transplants among cases and 18 among controls occurred. Cases saw an increased hazard of death or transplant during follow-up when compared to male controls (HR: 1.40; 95% CI: 0.68 - 2.91; p = 0.2883). Cases had the same 25-year survival estimate as they did in the overall comparison (88.9%; 95% CI: 82.2 – 96.1), while controls had an estimate of 93.7% (95% CI: 90.5 – 96.9) (Table 3).

Figure 5 shows KM survival curves among cases and female controls. At the beginning of follow-up there were 157 cases and 136 female controls at risk, with 19 cases and 31 controls excluded due to IHD. Throughout follow-up, 12 deaths or transplants in cases and 10 deaths or transplants in controls occurred. Cases saw an increased hazard of death or transplant during follow-up compared to female controls (HR: 1.03; 95% CI: 0.45 – 2.39; p = 0.9365). Cases had the same 25-year survival estimate as they did in the overall comparison (87.9%; 95% CI: 81.2 – 95.2), while controls had an estimate of 91.9% (95% CI: 87.2 – 96.9) (Table 3).

One aspect of our original research question was we wanted to determine is if interaction existed between CHD and TS in TFS. After running an interaction assessment, we found there to be no evidence of interaction between CHD and TS ($X^2 = 0.6583$; p = 0.4172).

Discussion

The lower TFS in cases compared to controls is consistent with results obtained in recent studies involving CHD and procedural outcomes among patients with TS. A recent retrospective cohort

study showed that among those with TS and CHD, there was an increased risk of post-operative mortality compared to those with just CHD.[10] In Figures 3 – 5, we see slightly lower TFS among cases compared to all controls and cases to male controls. Female controls appear to have lower survival than cases. This is likely due to a smaller sample size of female controls compared to male controls (about half as many female controls). The larger number of male controls is consistent with gender-specific associations with many of the left-heart abnormalities included in our study; studies have shown that males tend to be disproportionally affected with LHOL such as COA, VSD, and LVOTO.

There are several reasons as to why TS may further complicate any pre-existing CHD conditions and potentially contribute to lower TFS. Aside from TS increasing the risk of developing LHOL, TS can also increase the risk of other severe metabolic conditions. A recent study in children with TS and CHD showed that TS can increase the risk of aortic dissection at a young age, as well as increase the risk of hypertension, ischemic heart disease, and stroke.[6] Secondly, from a more genetic viewpoint, recent evidence has shown that there are at least 12 genes needed in two copies – one in each of the two sex chromosomes present in XX or XY cells – to function properly. It is likely that TS patients, lacking a second sex chromosome, manifest disease because of the haploinsufficiency of these 12 genes.[9] These additional diseases and abnormalities exacerbated by TS could help explain why children with CHD and TS were seen to have a lower TFS than those with just CHD.

In Table 3, we can see that among cases vs. all controls and cases vs. male controls comparisons, cases have a slightly lower survival estimate in every time period increment (5 years, 10 years, etc.). However, among cases vs. female controls, we see that female controls actually have lower

survival estimates in many of the time periods, before cases finishing off with a lower 25-year survival. This is likely due to the smaller number of female controls who did not have an IHD compared to cases without an IHD. We see that cases have a higher hazard of death or transplant during follow-up among all three comparisons, with cases having a 27% higher hazard of death or transplant when compared to all controls, a 40% higher hazard when compared to male controls, and a 3% higher hazard when compared to female controls (Table 3). The Log-Rank p-values obtained for all three comparison groups were insignificant, which we attribute to small sample sizes among the three groups, particularly among cases. The 95% CIs associated with HRs among the three comparisons are also very wide and cross the null, further explaining the insignificant p-values. However, the obvious differences in TFS, illustrated by KM survival curves, show a meaningful effect. The 95% CIs also overlap significantly in all three survival curves, which is expected with insignificant results. These results show that TS likely presents a greater burden of transplant/mortality in children with CHD.

Our follow-up time results were also consistent with results obtained in previous studies. A 2014 retrospective cohort study looked at long-term clinical follow-up among children with CHD, and found an average follow-up time of 18.6 years.[12] Table 2 shows an overall median follow-up time of 17.65 years for cases, 17.67 years for male controls, and 17.00 years for female controls. We also see that newborns had the shortest follow-up time among all three groups, due to an increased number of deaths or transplants during follow-up, likely attributed to a lesser-developed heart than those of infants or children. The lack of interaction between CHD and TS further supports the insignificant p-values among the three groups.

There are several limitations to this study. Our initial dataset contained a large number of patients with unknown or missing races and ethnicities. This made matching on this covariate difficult. Matching cases to controls based on race or ethnicity may have been appropriate to eliminate confounding and provide more efficiency to the study. A 2018 population-based cohort study assessed racial and ethnic disparities in CHD outcomes. Results shows that Hispanic ethnicity was associated with a poor outcome (OR: 1.72, 95% CI: 1.37 – 2.17). Researchers hypothesized that the poor outcomes observed in Hispanic patients appear to be in large part due to lower education status and public insurance status as compared with non-Hispanic white patients.[11] It is possible that Hispanic patients in our study may have had lesser insurance coverage under their parent's plan compared to insurance coverage among patients of white or African American parents. This could have resulted in less treatment options for their LHOL, thereby leading to a higher proportion of mortality or transplants among these patients. Additionally, the large number of unique treatment centers in our initial dataset made it challenging to match on this covariate. Some treatment centers may have had better treatment or surgery options and overall care than others, thereby leading to a higher proportion of mortality or transplants among patients being cared for at treatment centers with less effective forms of treatment. Matching proved to be difficult because there may have been cases who received their first surgery at a treatment center that no controls had received their first surgery at.

Our small sample size among the cases also made it difficult to obtain sufficient study power to extrapolate the results to the overall population. The small sample of cases increased the likelihood of a Type II error occurring; confirming the H_0 (that there is no difference in TFS between cases and controls) when in fact the H_A is true (there is a difference in TFS between cases and controls). This would explain why our TFS comparisons and interaction assessment

yielded insignificant p-values. Due to our small sample size among cases, we are forced to settle with less conclusive results, and further studies into this topic should include more cases.

The uneven distribution of patients who received their first surgery in different years may have biased our results away from the null. Among cases and both control groups, there was a large number of patients who received their first surgery between 1980 - 1989, and, due to the less-developed technology at the time, may have presented a higher risk of death/transplant. This would cause our results to show that more deaths/transplants occurred not from TS, but rather from less efficacy in surgical treatments at the time. Additionally, these patients will have a longer follow-up time than patients who received a first surgery later, and therefore have a greater chance of death or transplant during a longer time period. However, our decision to match on year of first surgery may have helped minimize these effects.

Additionally, it is difficult to ascertain an exact cause for the differences in TFS between cases and controls. We know that males and females have different survival statistics due to inherent gender differences, so we are unsure if the differences in TFS are attributed to TS or the fact that everyone in our TS cohort is female. Matching on gender would help adjust for this, however it was not possible to match on gender due to our TS cohort all being female.

In conclusion, this study shows that TS does not appear to increase risk of transplant/mortality among children with CHD, as no significant differences in survival were seen between cases and controls. We recommend further studies to better confirm the association between TS and CHD in TFS.

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Tables

Table 1 - Demographic Characteristics of Pre-Matching Cohort	**Cases**	**Comparison Cohort**		
	Turner Syndrome + CHD (N = 207)	CHD - Males (N = 7,345)	CHD - Females (N = 4,225)	p-value*
Median age at first surgery (IQR) (months)	1.77 (38.30)	8.47 (68.57)	6.80 (52.27)	<0.0001**
Age range (years)	0 - 18	0 - 20	0 - 20	
Age group (n, %)				<0.0001
Newborns[a]	87 (42.03)	2,345 (31.93)	1,372 (32.47)	
Infants[b]	45 (21.74)	1,547 (21.06)	997 (23.60)	
Children[c]	75 (36.23)	3,453 (47.01)	1,856 (43.93)	
Year of first surgery (n, %)				0.1560
1980-1989	51 (24.64)	1,372 (18.68)	809 (19.15)	
1990-1999	116 (56.04)	4,131 (56.24)	2,361 (55.88)	
2000-2011	40 (19.32)	1,842 (25.08)	1,055 (24.97)	
Primary Diagnosis (n, %)				<0.0001
LHOL[d]	156 (75.36)	4,372 (59.52)	2,237 (52.95)	
HLHS[e]	20 (9,66)	1,102 (15.00)	622 (14.72)	
Other[f]	31 (14.98)	1,871 (25.47)	1,366 (32.33)	

*chi-square
**one-way non-parametric anova
[a]age < 4 weeks
[b]age 4 weeks - 1 year
[c]age > 1 year
[d]includes COA, COA Plus, LVOTO, IAA
[e]includes SV Dominant RV
[f]includes AI, ASD, AVC Other, dtGA w/ Aaso, MS, PAPVC, RVOTO, SV Dominant LV, SV Other, TA, TOF, VSD Plus

Table 2 - Follow-Up Years of Matched Covariates Among Cases and Controls				
	Cases (N = 176)	**Controls - Males (N = 361)**	**Controls - Females (N = 167)**	**p-value***
	Median Follow-up Years (IQR)	Median Follow-up Years (IQR)	Median Follow-up Years (IQR)	
Overall	17.65 (9.58)	17.67 (9.39)	17.00 (10.69)	0.3120**
Primary Diagnosis				<0.0001
LHOL	18.35 (8.09)	18.69 (9.06)	18.56 (8.14)	
HLHS	0.00 (0.01)	0.03 (11.73)	0.00 (0)	
Age Group				<0.0001
Newborns	14.70 (19.44)	14.80 (15.39)	13.61 (18.95)	
Infants	18.19 (8.08)	17.70 (7.11)	17.19 (7.74)	
Children	21.06 (10.05)	21.71 (9.82)	20.98 (8.68)	
Year of first surgery				<0.0001
1980-1989	26.12 (6.03)	26.30 (4.27)	26.43 (15.18)	
1990-1999	18.00 (5.59)	18.09 (5.56)	17.52 (7.99)	
2000-2011	12.43 (13.21)	12.75 (2.87)	12.17 (14.03)	

*****two-way non-parametric anova
**one-way non-parametric anova

Table 3 - Survival Summary Statistics for Cases and Controls, with No IHD Included						
	Overall		**Males Only**		**Females Only**	
	Cases	Controls	Cases	Controls	Cases	Controls
Deaths or Transplants/Total at-Risk	12/157[a]	28/463[b]	12/157[a]	18/327[c]	12/157[a]	10/136[d]
Hazard Ratio (95% CI)[Cox]	1.27 (0.65 – 2.50)	Ref.	1.40 (0.68 - 2.91)	Ref.	1.03 (0.45 – 2.39)	Ref.
Survival Estimates (95% CI)[KM]						
5 years	94.9 (91.5 - 98.4)	95.9 (94.1 -97.7)	94.9 (91.5 - 98.4)	96.3 (94.3 - 98.4)	94.9 (91.5 - 98.4)	94.9 (91.2 – 98.6)
10 years	94.2 (90.7 – 98.0)	95.9 (94.1 - 97.7)	94.2 (90.7 – 98.0)	96.1 (94.3 - 98.4)	94.2 (90.7 – 98.0)	94.9 (91.2 - 98.6)
15 years	94.2 (90.7 – 98.0)	94.9 (92.9 – 97.0)	94.2 (90.7 – 98.0)	94.4 (93.0 - 97.06	94.2 (90.7 – 98.0)	94.0 (90.0 - 98.1)
20 years	92.9 (88.6 – 97.5)	93.8 (91.5 - 96.2)	92.9 (88.6 – 97.5)	94.6 (92.0 - 97.3)	92.9 (88.6 – 97.5)	91.9 (87.2 - 96.9)
25 years	88.9 (82.2 - 96.1)	93.1 (90.5 - 95.9)	88.9 (82.2 - 96.1)	93.7 (90.5 - 96.9)	88.9 (82.2 - 96.1)	91.9 (87.2 - 96.9)
P-Value*	0.4872	-	0.3610	-	0.9365	-

*Log-Rank Test
[Cox]Cox Model
[KM]Kaplan-Meier method
[a]19 IHD Excluded
[b]65 IHD Excluded
[c]34 IHD Excluded
[d]31 IHD excluded

Figures

Figure 1. Exclusion Criteria for Cases

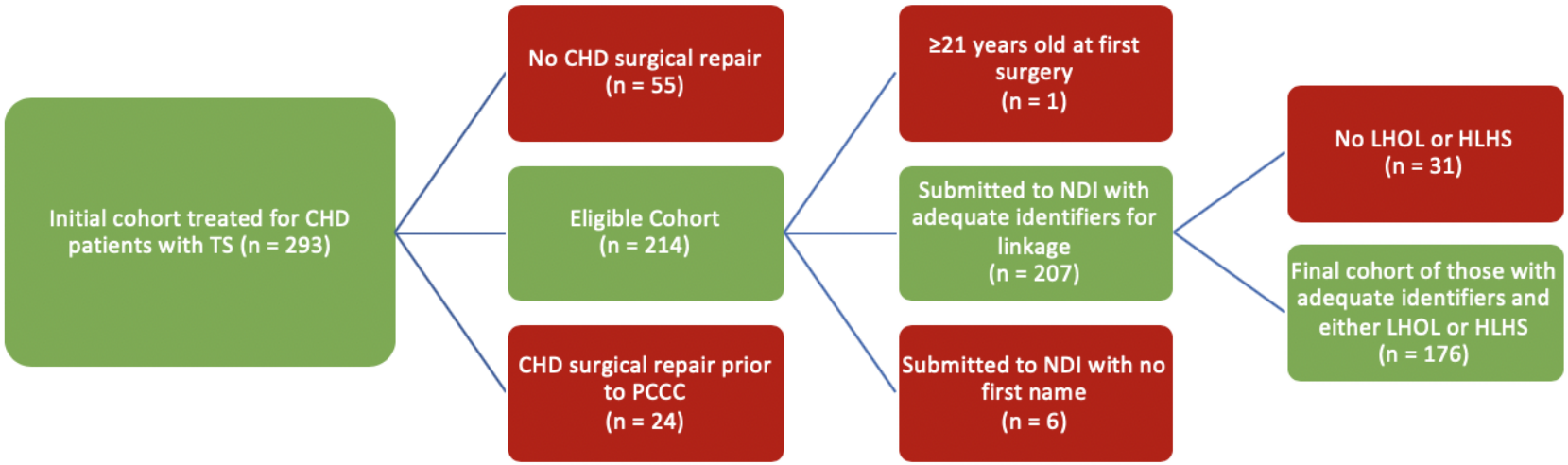

Figure 2. Exclusion Criteria for Controls

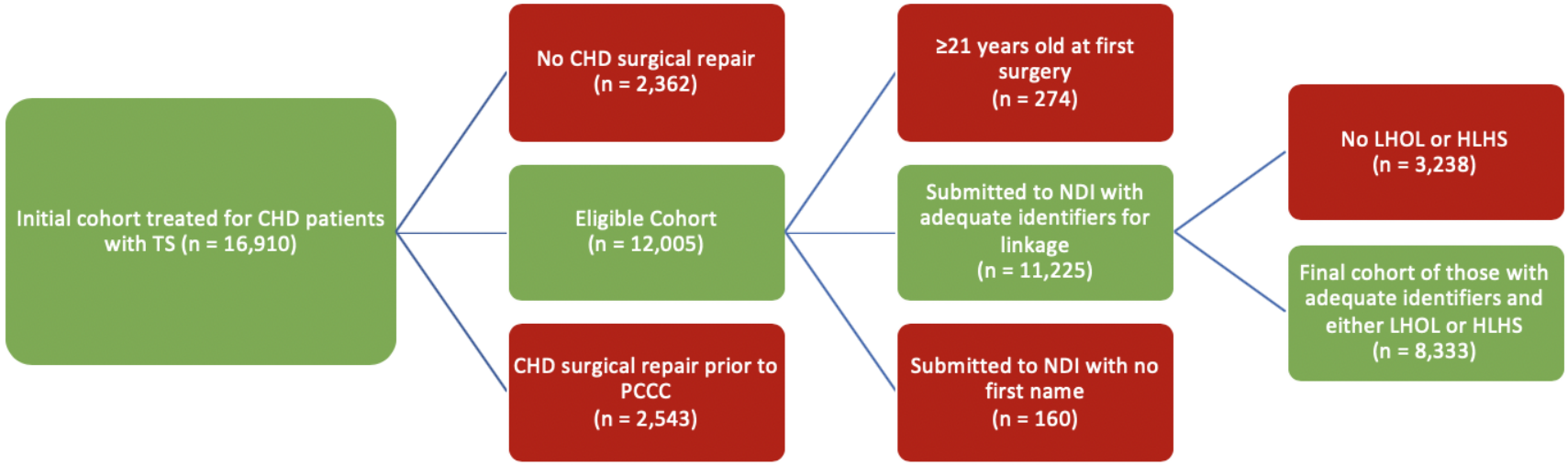

Figure 3. Kaplan-Meier Survival Curves for Cases and All Controls, no IHD

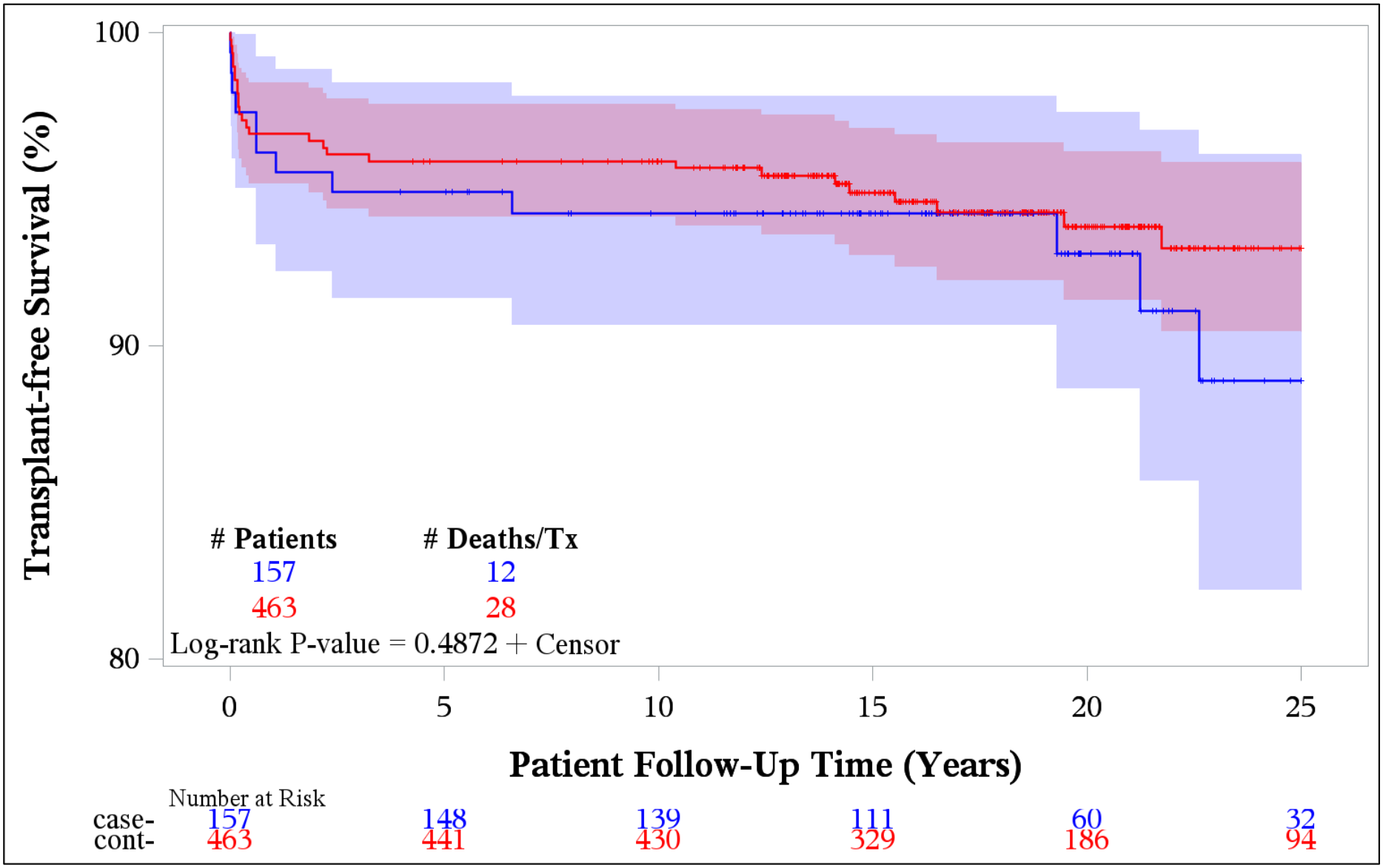

Figure 4. Kaplan-Meier Survival Curves for Cases and Male Controls, no IHD

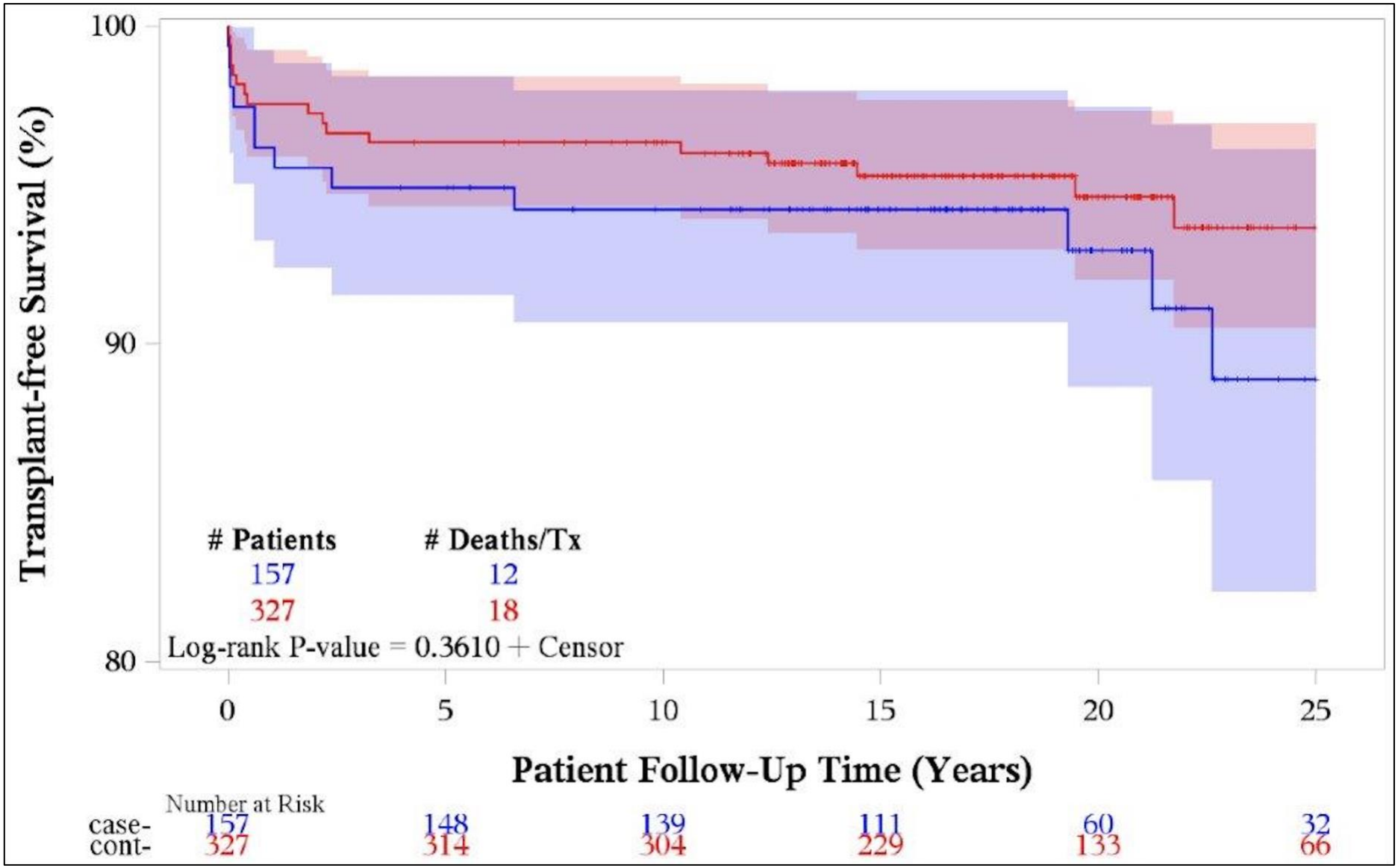

Figure 5. Kaplan-Meier Survival Curves for Cases and Female Controls, no IHD