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Risk of heart failure-related death and transplant after congenital heart surgery in childhood

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Risk of heart failure-related death and transplant after congenital heart surgery in childhood

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An abstract of
A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in clinical research
2020

Abstract

Risk of heart failure-related death and transplant after congenital heart surgery in childhood
By Lydia Wright

Background
Congenital heart disease (CHD) is a major cause of heart failure (HF) in children and young adults, but the longitudinal risk of HF-related death or transplantation after congenital heart surgery (CHS) is unknown. We aimed to describe this risk and how it varies across the spectrum of CHD.

Methods and Results
We performed a retrospective cohort study of all patients in the Pediatric Cardiac Care Consortium, a US-based multi-center registry of pediatric cardiac surgery, who were discharged transplant-free after their first CHS between 1983 and 2003. Outcomes were obtained by linkage to national death and transplant databases; primary outcome was time from CHS discharge to HF death, transplantation, or ventricular assist device placement. Non-HF death was accounted for as a competing risk. Primary outcome rates were compared to the general population. Among 35,611 patients who survived their first CHS, there were 715 HF-related events over 33 years of follow-up (median 18; IQR 14-22). The cumulative incidence of HF events at 20 years of follow-up was 2.1% (95% CI: 1.9%-2.2%). After risk factor adjustment, hazard ratio (HR) for HF events compared to mild CHD was 30 (95% CI 20-44) for single ventricle (1V), 10 (95% CI 7-14) for severe two-ventricle (2V), and 3.2 (95% CI 2.2-4.6) for moderate CHD. In addition, the presence of a systemic right ventricle was associated with a higher risk of HF-related events in those with severe disease (2V and 1V). All groups had higher rates of HF-related death than the general population.

Conclusions:
In this large US cohort, risk of HF-related events after CHS is high across the (entire) spectrum of CHD. While those with single or systemic right ventricles are at highest risk, even those with mild disease are at greater risk than the general population.

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INTRODUCTION

The changing medical management and development of advanced surgical techniques for congenital heart disease (CHD) over the last 40 years has significantly improved the expected lifespan of patients born with these defects. (1-5) Despite these advances, and in some situations because of the improved survival of patients with complex anatomy, many patients remain at risk for developing end-stage heart failure (HF) over the course of their lives. Many factors likely play a role in the development of HF in this population, including underlying myocardial abnormalities, residual valve regurgitation and outflow obstructions, myocardial injury at surgery or related to coronary abnormalities, as well as the effects of arrhythmias and pacing. This risk undoubtedly varies across the spectrum of CHD, but the true risk and timing of advanced HF leading to death or transplantation remains unknown, as does the relative importance of leading risk factors.

Current knowledge on advanced HF leading to death or transplant in patients with operated CHD is largely derived from single center or lesion-specific studies, or conversely from transplant registries tracking only those patients listed for or receiving cardiac transplant.(6-8) Currently, patients with CHD make up approximately 50% of pediatric and 10% of young adult heart transplant recipients, but those patients with HF who did not survive to transplant are less well described.(9, 10)

In this study, we used the linked dataset of the Pediatric Cardiac Care Consortium (PCCC), a US-based multi-center registry of congenital cardiac surgeries, with national death and transplant databases to examine the long-term incidence of advanced HF leading to death, cardiac transplant, or ventricular assist device (VAD) placement in patients with operated CHD. (11, 12) We aimed to determine how underlying anatomy and type of surgical repair affect this risk throughout childhood and into early adulthood.

BACKGROUND

Congenital heart disease (CHD) is the most common congenital anomaly, with an estimated prevalence of nearly one in 100 live births (13). Lesions can range from simple, surgically correctable defects such as atrial septal defects, to complex lesions leading to single ventricle physiology and requiring multiple palliative surgeries. Survival has improved significantly across the spectrum of severity of congenital heart disease, and in the current era more than 90% of children born with CHD are expected to live to adulthood (14). With this improved survival, particularly amongst those with complex lesions, more patients are at risk of developing long term complications of their disease as they age.

Heart failure (HF) is one of these complications and can play a major role in both mortality and morbidity in individuals with CHD. Given the heterogeneity of both the anatomy and physiology of CHD, as well as changes in symptomatology with age, HF can have many different presentations; defining HF in this population can be challenging. The American Heart Association in their 2016 Scientific Statement on "Chronic Heart Failure in Congenital Heart Disease" defines HF as "a syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction"(15). This definition, or a similar one, has been used in most literature on HF in CHD. HF can progress, with or without therapy, to death. Ultimate therapy for end-stage HF, in all populations including the CHD population, is cardiac transplantation.

There are many contributing factors to the development of severe heart failure in the CHD population, though most are not completely understood across the lifespan. There can be inherent abnormalities in the myocardium in patients with CHD, such as disarray of ventricular myocardial fibers (16), which can place patients at higher risk of developing both systolic and

diastolic dysfunction. Certain cardiomyopathies, such as left ventricular non-compaction (LVNC) are more prevalent in individuals with CHD than in the general population (17). Residual volume and pressure overload lesions, as well as the cumulative effect of these lesions prior to repair, can contribute to the development of HF. Cardiopulmonary bypass and surgical techniques such as ventriculotomies during congenital heart surgery (CHS) can also lead to both immediate and long-term stress on the myocardium. These factors can lead to the development of HF, both in the immediate post-operative period and later in childhood and into adulthood, when the cumulative burden of these effects may be felt. The timing of the development of heart failure in the CHD population as a whole have not been well studied, as well as the importance of various risk factors have not been well studied. There remain important questions, particularly on the variation in incidence and timing of heart failure across the spectrum of severity of CHD, as well as the importance of the type of systemic ventricle in this process.

Previous work on the risk of HF, and the need for end-stage therapies such as transplantation, in varying types of CHD has primarily been limited to either studies focused on single lesions, or on select populations of survivors – such as adult CHD patients, or patients listed for transplantation (6, 7, 18). From this work, it is clear that HF is most prevalent in those patients with the most severe form of CHD, single ventricle anatomy. HF death and transplant are common in this population, both in childhood and adulthood. In one of the few prospective trials following a population of neonates with hypoplastic left heart syndrome (HLHS), heart failure developed in 15% by 6 years of age (7), and patients with HLHS make up a significant proportion of children listed for heart transplant(8). The risk of transplantation after the Fontan procedure has been estimated between 2 and 10% in two longitudinal studies, though the rates varied significantly across locations (19, 20). Risk of heart failure in patients with milder forms

of disease have been less well-described, particularly the risk of transplant in this population. Several population based studies from Europe have demonstrated that heart failure death continues to account for a significant percentage of deaths in patients with mild and moderate forms of CHD, though less than that seen in those with single ventricles (21).

The impact on the underlying morphology of the systemic ventricle on the development of end-stage heart failure in the CHD population is also somewhat poorly understood. The shape, cellular make-up, and structure of the right and left ventricle as well as the associated AV valves are thought to be suited to the expected pressures and workloads of the pulmonary and systemic circulations respectively (22). However, in many forms of congenital heart disease the morphologic right ventricle may have to perform the functions of a systemic ventricle. This can occur in forms of CHD with single ventricle physiology (e.g. hypoplastic left heart syndrome (HLHS)) as well as two-ventricle physiology (e.g. L-transposition of the great arteries). Early failure of the systemic right ventricle has been seen in patients with l-TGA as well as those with d-TGA after atrial switch (23). Similarly, patients with single right ventricle physiology have been shown to have worse ventricular function after Fontan palliation (24) and worse overall growth than their counterparts with a single left ventricle (25). The specific relationship between underlying ventricular morphology and the timing of heart failure and need for transplant has not been previously evaluated and could provide important insight into expected outcomes for these patients.

METHODS

Aims of project:

1. Describe the long-term risk of heart failure leading to death or transplant after surgery for congenital heart disease
2. Evaluate effect of ventricular morphology, CHD anatomy and physiology, surgical era, and demographic characteristics on risk
3. Estimate cause-specific standardized mortality ratios for individuals with operated CHD compared to general age- and sex-matched US population

Hypothesis:

All children who have undergone surgery for congenital heart disease are at higher risk of heart failure death and transplantation throughout their lives than the general population. This risk is highest in those patients with more complex anatomy and with systemic right ventricles and changes over time.

Study population:

We performed a retrospective cohort study of patients who underwent congenital heart surgery (CHS) before age 21 in one of the member centers of the Pediatric Cardiac Care Consortium (PCCC) between 1982 and 2003 and had adequate identifiers for linkage with the National Death Index (NDI) and Organ Procurement and Transplantation Network (OPTN) databases. Previous work has demonstrated sensitivity of greater than 88% and specificity of greater than 99% in identifying deaths and transplants in this linkage.(12) The PCCC includes

detailed information on cardiac surgeries and catheterizations performed at 47 centers in North America.(2) Participating centers perform between 15-30% of all congenital cardiac surgeries in the United States (depending on year), with similar case distribution as those seen nationally.(11, 26) Only those patients who underwent first surgery in the PCCC were included. Patients who died or underwent cardiac transplantation during initial surgery hospitalization were excluded, as were those patients with inadequate identifiers for linkage with NDI and OPTN. Study was approved by the Institutional Review Board of Emory University, the NDI, and OPTN.

Clinical variables:

Demographic data collected at first CHS included sex, age at surgery, presence of known chromosomal abnormality or other non-chromosomal genetic syndromes, race, and ethnicity. Race and ethnicity data were supplemented by birth record data when available. Each patient's first CHS was designated as index procedure and length of stay for index hospitalization was calculated for each patient. Three surgical eras were defined based on roughly equivalent patient volumes as early (1982-1992), middle (1993-1997), and late (1998-2003); surgical era was assigned for each patient based on year of index procedure. Details of subsequent cardiac surgeries and catheterizations were available for all surgeries performed within the PCCC.

Primary cardiac diagnosis was recorded for each patient at the time of initial CHS. Severity of CHD and underlying physiology were assigned utilizing the classification scheme developed at the Canadian Conference on the care of adults with CHD in 1996, which has been used in other reports on long-term outcomes in this population.(27),(12) Severity categories included mild two 2V, moderate 2V, severe 2V, and 1V, as described before.(4) Lesions not fitting into any of these groups were designated non-classifiable. Additional subgroupings were used for lesions sharing

common anatomo-pathophysiologic characteristics whenever possible as described before (4). Systemic ventricle was determined for all patients based on underlying diagnosis and surgical history. In diagnoses or surgical strategies in which systemic ventricle could not be broadly determined, such as a single ventricle physiology due to an unbalanced atrioventricular canal or d-transposition of the great arteries palliated with an aortopulmonary shunt without further definitive repair, systemic ventricle was designated as indeterminate.

Outcome data:

Outcome data were obtained for all patients from available PCCC forms and by linkage to the NDI and OPTN up to the last update in December 2014. Date and cause of death were ascertained from the NDI for all patients who died. Each patient had one designated underlying cause of death as well as multiple (up to 18) contributing causes of death. Transplant listing date, transplantation date, and indication for transplant were obtained for all patients listed for cardiac transplant. Our primary outcome was a composite outcome of HF death, cardiac transplant, or ventricular assist device (VAD) placement. HF deaths were identified as any death 1) with HF listed as an underlying or contributing cause on NDI (428.0, 428.1, 428.9, I50.0, I50.1, I50.9 or P29.0) 2) with HF listed as diagnosis on autopsy performed in PCCC or, 3) that occurred while a patient was actively listed for heart transplant. VAD placement was identified in any patient who underwent VAD placement in a PCCC center, or who had VAD placement during or before listing for transplant, with available VAD data in OPTN. Primary outcome was time to the composite outcome of HF-related event as defined above, with time zero being discharge date from index CHS hospitalization. Death without known HF as defined above was termed a "non-HF death" and was treated as a competing risk.

Statistical analysis:

Descriptive statistics were calculated and are presented as mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile ranges (IQR) for non-normally distributed continuous variables, and frequencies and percent for all categorical variables. Competing risk methods were utilized to estimate the cumulative incidence of HF-related events in the setting of the non-independent competing risk of death without HF.(28) Cumulative incidence curves were generated to determine risk of HF-related events based on surgical era, severity of CHD, systemic ventricular morphology, and presence or absence of known chromosomal abnormality. Gray's test of equality was used to compare differences in incidence curves. Multivariable models were developed using the Fine and Gray method of modeling the sub-distribution hazard to evaluate the overall risk of HF-related events for 1) the entire cohort and 2) those alive without transplant at 5 years after discharge from initial CHS.(29) In order to assess the effect of era on outcome, follow-up time was limited to 15 years from the index surgery for the primary model (longest possible follow-up for those in the most recent era). Proportional hazards assumption was assessed using time-dependent interaction terms and was met for all variables included in the final model, except for systemic ventricle. Heaviside functions were used to determine the change in hazards over time for systemic ventricle categories. Subgroup analyses by race and ethnicity were performed on only those patients with known race and ethnicity to evaluate possible effects of these factors on the primary outcome. Cause-specific standardized mortality ratios (SMR) were generated by comparing the study population to the age- and sex-matched U.S. population using data from the National Vital Statistics' Multiple Cause of Death Database (deaths 1982-1998) and the Center for Disease Control's WONDER database (deaths

1999-2014). Transplant status was not considered in either our cohort or general population in this analysis, as population-level data on transplants for the age groups represented in our population were not available.

In subgroup analysis of patients who experienced primary outcome, patients were categorized as either listed for heart transplant (waitlist death or successful heart transplant) or died without transplant listing (heart failure death without transplant listing). Multivariable logistic regression was used to evaluate predictors of being listed for transplant in this subgroup.

Statistical significance was assessed at the 0.05 level. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary NC).

RESULTS

A total of 47,033 patients underwent CHS during the study period. Of the 38,481 with adequate identifiers for linkage with the NDI, 35,611 survived their index surgery without transplant and were included in the final cohort (Figure 1). Demographic and clinical characteristics of the cohort are described in Table 1. There was a slight male predominance, and 13% of patients had a known chromosomal abnormality. Of the 35% with race and ethnicity data available, the vast majority were white non-Hispanic. The most common diagnoses were atrial septal defect in 13.5% and ventricular septal defect in 12.6% (Table 2). A systemic right ventricle (RV) was present in 3.4 % of patients, including those categorized as severe 2V defects [d-transposition of the great arteries (d-TGA) with atrial switch], miscellaneous 2V defects [l-transposition of the great arteries (l-TGA) with an anatomic repair], and single ventricle defects [hypoplastic left heart syndrome and variants]. Median follow-up time was 18.0 years (IQR 14.4 – 22.1), with a median age at end of follow-up of 20.7 years (IQR 16.0 – 26.0).

Over 642,387 person-years of follow-up, 715 patients experienced the primary outcome of HF-related death, cardiac transplant, or VAD placement at a median of 1.6 years (IQR 0.3 – 8.5) after discharge from index hospitalization. This included 481 HF deaths without transplant listing or VAD placement, 67 transplant waiting list deaths, 161 cardiac transplants, and six VAD placements. Death due to HF without listing predominated in the early years, with increasing transplants and waitlist deaths over time (Figure 2). Later year of outcome, older age at outcome, systemic RV, and lack of chromosomal abnormality were predictive of transplant listing instead of death without listing (Table 3). Of the six VAD placements, three (all before 2000) were performed without concomitant transplant listing and resulted in patient death, and three (all after 2008) were pursued as a bridge to transplantation. There were 2,236 additional non-HF deaths

occurring at a median of 1.5 years (IQR 0.3 – 9.5) after discharge from index hospitalization (Figure 1). One-year risk of HF event for transplant-free survivors was highest early after hospitalization discharge at an estimated 0.5% per year (95% CI 0.49%-0.52), decreased steadily until approximately 5 years after discharge, and remained relatively stable for transplant-free survivors at around 0.05% per year for the subsequent 20 years (Figure 3).

There were significant differences in the cumulative incidence of HF death, transplant, or VAD based on patient characteristics (Table 4). Males had a higher incidence of HF-related events with 1.7% and 2.6% 10- and 20-year incidence compared with 1.4% and 1.8% respectively in females (Gray's test p-value <0.001). Higher incidence of the primary outcome was also seen in those who underwent CHS in an earlier surgical era (p<0.001). Incidence increased along with the severity of CHD with 20-year incidence of 0.3% in mild 2V (95% CI 0.2%-0.5%), 1.1% in moderate 2V (95% CI 1.0% - 1.3%), 3.9% in severe 2V (95% CI 3.3% - 4.6%) , and 13.3% in 1V (95% 11.9% - 14.9%) (Table 1). There was a significantly higher incidence of HF-related events at 20 years in patients with a systemic RV compared to patients with systemic LV and similar defect severity, though the pattern of incidence varied between severity categories (p-value <0.001 for all categories; Figure 4). Patients with severe 2V defects and a systemic RV (primarily d-TGA with atrial switch) had lower rates of HF death early post-operatively than other severe 2V patients, but incidence steadily increased throughout childhood with higher rates in adolescence. Single right ventricle patients had consistently higher incidence of HF than those with single left or indeterminate ventricles, and this difference also widened over time. The incidence of HF death, transplant, or VAD for individual lesions within each category are shown in Table 2. Amongst moderate 2V lesions, complete AV canal (20-year incidence of 3.1%) and Ebstein's anomaly (20-year incidence of 5.3%) carried significantly higher rates of HF-related events than other lesions.

Patients with l-TGA (all but four of whom had physiologic as opposed to anatomic repairs with a resultant systemic RV) had quite high incidence of HF, both early and late (3.6% at one year, 11.8% at 20 years), similar to the HF incidence seen in patients with a single non-RV.

In multivariable analysis of the full cohort, severity of CHD was the most important factor in predicting HF events (Table 5). Hazard ratio for single ventricle patients was 29.9 (95% CI 20.4-43.8) compared with mild 2V lesions. Type of systemic ventricle has different effects early post-operatively (<2 years) compared to late. In the early period, right ventricle (HR 1.41; 95%CI 1.05-1.91), but not indeterminate systemic ventricle (HR 1.032, 95%CI 0.69-1.51), was associated with higher rates of the primary outcome compared to those with systemic left ventricle. This effect was stronger at ≥ 2 years after surgery, with a HR of 2.60 (95% CI 1.87-3.63) for systemic RV and a HR of 1.71 (95% CI 1.11-2.64) for indeterminate systemic ventricle compared to systemic LV. Earlier era (1982-1992 and 1993-1997 as compared with 1998-2003), presence of chromosomal abnormality, pacemaker placement during initial hospitalization, and length of stay >30 days (the 95% for length of stay for the cohort) were also associated with the primary outcome. After adjusting for other variables, there was no significant difference based on sex [HR for males 0.96 (95% CI 0.82-1.12)]. In subgroup analysis of those patients with race data available, there was no significant difference in the development of HF events between white vs. black when controlling for sex, presence of chromosomal abnormality, CHD severity, systemic ventricle, and era (Table 6).

In a multivariable model conditioning on surviving without transplant >5 years after discharge from index hospitalization (after the majority of patients would be expected to have completed planned palliation, if applicable) (Table 7), systemic right ventricle and single ventricle CHD remained strongly associated with the primary outcome (HR 33.8 and 2.39, respectively).

Presence of pacemaker at 5 years post-discharge (including those placed during initial hospitalization as well as those placed between discharge and 5 years after discharge) was also associated with the primary outcome when controlling for other factors, with a HR of 2.99 (95% CI 1.51-5.93). Length of stay at index surgery and surgery during the middle surgical era (1993-1997) were not significantly associated with the primary outcome in this subpopulation of five-year survivors.

HF-specific mortality was higher in all groups compared to the age- and sex-matched general population, with an overall HF-specific standardized mortality ratio (SMR) of 63.6 (95% CI 57.5-69.7). HF-specific SMR increased across severity categories, from 16 (95% 2.7-24.6) for those with mild CHD to 256 (95% CI 212-299) in the 1V group (Figure 3). In those patients alive without transplant at 5 years, HF-specific SMR was slightly lower at 33 (95% CI 27-39). All groups continued to have significantly higher rates of heart failure-specific death than the general population (Figure 5).

DISCUSSION

This study is the largest to date to evaluate the occurrence of HF-related death, VAD, or cardiac transplant in patients who have undergone surgery for CHD. We found a significant burden of HF events through adolescence and young adulthood in this population. Several risk factors predicted those patients at higher risk in the cohort, though even the lowest risk patients in our cohort were at higher risk than the general age-matched population.

Severity of underlying CHD was by far the most important predictor of HF events. Risk increased steadily as severity of CHD increased, with single ventricle disease having an adjusted risk of nearly 30 times that for those with mild two-ventricle disease. This finding is consistent with previous literature examining both symptomatic non-terminal HF and transplantation in children and adults with CHD.(30, 31) Several studies have demonstrated high rates of HF in the single ventricle population, particularly those with hypoplastic left heart syndrome (HLHS).(7, 32, 33) A 2006 German study evaluating the risk of HF in adults with CHD, as defined by elevation of N-terminal-pro-brain natriuretic peptide (NT-pro-BNP), found single ventricle patients to have an OR of 7.21 as compared to simple left-to-right shunt lesions.(31) This study also found high rates of HF (OR 4.67, probability at age 20 of approximately 35%) in patients with repaired Tetralogy of Fallot, a relatively low-risk group for HF-related events in our cohort. This discrepancy is likely due to the difference in outcome measures. More specifically, BNP, a marker of intracardiac wall tension, may be sensitive in detecting increased cardiac load related to pressure or volume loaded right ventricular lesions such as Tetralogy of Fallot, but not very specific in the same context for identifying patients at risk for imminent death or transplant, which was the outcome measured in our cohort.(34)

Timing of HF events appeared relatively uniform across the different severity categories, with a strong initial increase immediately after discharge from index surgery followed by a slow rise throughout childhood and into adulthood. This is reflected in our median time to event of approximately 2 years; as most events were in those who underwent surgery as neonates or infants, median age of HF event was similar. A similar pattern was seen in a population-based study evaluating causes of death in patients with CHD in Finland, where the median time to HF death after cardiac surgery was 2.1 years. (35) Similarly, among patients with HLHS enrolled in the Single Ventricle Reconstruction (SVR) trial, the median age of HF event following Norwood procedure was 1.3 years.(7)

Patients with systemic right ventricles had more than two times higher rates of HF-related events than those with comparable lesions with left or indeterminate ventricles, and this disadvantage worsened as they entered adolescence and adulthood. At 20 years of follow up, patients with d-TGA undergoing arterial switch operation had only a 1.3% incidence of HF events, while those treated with atrial switch had a 6.1% incidence a HF event within comparable period of time. Patients with l-TGA had an even higher rate of 11.9%. Many studies have demonstrated this poor performance of a systemic right ventricle through adulthood in these two-ventricle lesions,(18, 31, 36) prompting transition towards anatomic surgical correction to ensure a systemic left ventricle. In the time period studied, the "double switch" procedure, or physiologic repair of l-TGA, had just been introduced; as a result, only four patients in our cohort underwent this procedure. None of them developed a HF event within the study period, but the number is too small for a meaningful interpretation. Our results confirm previous reports demonstrating that those patients with single RV have the highest rates of HF events of all patients with CHD.(32) The near 20% incidence of HF death, transplant, or VAD in our cohort at 20 years was comparable

to that seen in other studies on this population.(33) Close monitoring of this population for early development of HF is clearly warranted.

An additional high-risk group appears to be those patients who require pacemaker placement. Both patients who underwent pacemakers during initial hospitalizations and between discharge and five years had nearly three times the risk of heart failure death, transplant, and VAD than those who did not have known pacemaker placements. This is consistent with intermediate outcomes from smaller studies using elevated BNP levels and low peak oxygen consumption (VO_2max) as proxy variables for identification of HF in young adults with various forms of CHD who had undergone pacemaker implantation compared to those who had not.(37) Chronic subpulmonary LV pacing was also found to be associated with worsening New York Heart Association class and RV function in a cohort of individuals with L-TGA.(38) Finally, need for pacemaker has also been identified as a risk factor for transplantation or death in individuals with single ventricle physiology who have undergone Fontan palliation.(39, 40) Several authors have advocated the use of biventricular pacing when possible to avoid or decrease degree of ventricular dyssynchrony aiming to mitigate the risk of ventricular dysfunction, particularly in those with systemic RVs.(41) We did not examine different pacing modalities in our cohort; however our data does highlight the heightened risk for severe heart failure in individuals with pacemakers, and the need to develop strategies to mitigate this risk.

Improvement in survival after CHS over the past decades has been well documented.(4, 21) It appears that these general improvements have also translated to a lower burden of HF events after CHS. The adverse effect of the earliest era (1982-1992) was most pronounced when included patients with both early and late HF events but the risk persisted in patients who survived >5 years after CHS. The middle era of 1993-1998 was also associated with overall higher rate of HF events

compared to the more recent era, but this risk was attenuated among five-year survivors. A similar trend of decreasing HF deaths in those patients undergoing surgery after 1990, was noted also in the study from .(21) While this group did not include transplantation and therefore the change could reflect an increased use of that modality to prevent deaths, their data taken together with ours makes the case that improved surgical and medical care at the time of initial repair does have an effect on overall rate of HF events in this population.

Our data also point to the changing management of patients with CHD and end-stage HF. Whereas in the earlier years covered, HF deaths without accompanying transplant listing were more common, in later years more patients were either transplanted or died on the transplant waiting list. Some of this change is accounted for by the reduction in early deaths due to improvements as discussed above. However, there has also been a growing understanding of the role of VAD and transplantation in this population.(42) Prior reports have seen increases in transplants for operated CHD over this time period, at the same time as primary transplantation (particularly for HLHS) became less common.(43) Given improved survival early in life and a larger, more complex adult CHD population, as well as the contemporary engineering advances in VADs, it is not surprising that both transplants and VAD use has increased in this population, particularly the adults among them.(44, 45) Older age was associated with successful transplant or waitlist death compared to death without listing in our cohort. While VAD use was rare in our cohort, all VADs in the most recent era were used as a bridge to transplant, reflecting change in practice.

Study Strengths and limitations

Through the unique linkage of a large clinical database with national death and transplant databases, we were able to gain a comprehensive view into the HF related events in this population that might be missed by evaluating HF death and transplantation separately. The detailed surgical and anatomic information available in the PCCC, which is often unavailable in large registries allowed for categorization of patients into meaningful categories based on diagnosis and systemic ventricle, which have strong effects on the development of HF.

There are several limitations in this study related to the use of cause of death data from death certificates leading to underreporting chronic conditions such as HF as a cause of death. We attempted to ameliorate this in our cohort by including autopsy-designated or transplant waitlist deaths as HF deaths, but we may still have missed some patients who died outside the PCCC without being listed for transplant. Additionally, we were unable to capture the outcome of VAD placement if it occurred outside the PCCC and some patients who underwent VAD placement without being listed for transplant were likely not identified. These misclassifications, if present, would likely lead to underestimation of the overall risk of HF events in this population at high risk for progressive deterioration of heart function. Additionally, as OPTN data was available only after 1988, early transplants outside of the PCCC may have been missed. Lastly, with this dataset we were not able to address the occurrence of significant symptomatic heart failure that does not necessitate heart transplant listing or result in death.

CONCLUSIONS

Individuals with CHD remain at risk for end-stage heart failure leading to death, transplantation, or VAD placement at rates higher than the general population through early adulthood. Risk is highest among those with single or systemic right ventricles but can occur even in those with mild disease. Further follow-up is necessary as these patients age, to determine the changing burden of disease as childhood risk factors related to underlying CHD begin to interact with known adult risk factors for acquired heart disease.

TABLES AND FIGURES

Table 1: Baseline characteristics of all patients discharged from initial CHD surgery

	Total Patients N = 35,611 N (%) or median (IQR)
Sex	
Female	17,096 (48)
Male	18,515 (52)
Known chromosomal abnormality	
Yes	4,779 (13)
No	30, 832 (87
Race	
White	10,023 (28)
Black	2,002 (6)
Other	328 (1)
Missing	23,258 (65)
Ethnicity	
Hispanic	994 (3)
Non-Hispanic	11,015 (32)
Missing	23,602 (66)
Era of first surgery	
Early (1982-1992)	10,192 (29)
Middle (1993-1997)	11,782 (33)
Late (1998-2003)	13,637 (38)
CHD severity	
Mild	12,476 (35)
Moderate	13,442 (38)
Severe two ventricle	
Systemic LV	4,247 (12)
Systemic RV	252 (1)
Indeterminate	75 (1)
Single ventricle	
Systemic LV	1,008 (3)
Systemic RV	763 (2)
Indeterminate	565 (1)
Non-classifiable two ventricle	
Systemic LV	2,595 (7)
Systemic RV	188 (1)
Critical CHD	13,324 (37)
Underlying physiology	
Left to right shunt	16,582 (47)
Impaired systemic flow	5,626 (16)
Impaired pulmonary flow	4,781 (13)
Transposition physiology	1,530 (4)
Complex lesions	1,995 (6)
Complete mixing	257 (1)
Anomalous pulmonary venous return	682 (2)
Other two ventricle	1,822 (5)
Single ventricle	2,336 (7)
Pacemaker	
Before discharge from index hospitalization	97 (0.3)
In first 5 years following discharge	286 (0.8)
Post-operative length of stay after first CHS (days)	6 (4 – 10)
Age at first surgery (years)	0.8 (0.2 - 3.8)
Age at last follow-up (years)	20.6 (16.0 – 26.0)

IQR = interquartile range, LV = left ventricle, RV = right ventricle

Table 2: Cumulative Incidence of Heart Failure Death, Transplant, or VAD by Underlying Diagnosis

Diagnosis	Total Patients	Total Events	Cumulative incidence of HF event					p-value
			1 year	5 years	10 years	15 years	20 years	
Mild 2V								
ASD	4,997	7	0.0%	0.0%	0.1%	0.1%	0.1%	ref
PDA	2,975	9	0.1%	0.2%	0.2%	0.3%	0.3%	0.135
VSD	4,504	25	0.4%	0.4%	0.5%	0.5%	0.6%	<0.001
Moderate 2V								
Coarctation of the aorta	3,006	17	0.3%	0.4%	0.4%	0.5%	0.5%	ref
ToF	2,963	36	0.4%	0.7%	0.9%	1.1%	1.2%	0.007
Complete AV canal	2,145	63	1.6%	2.2%	2.4%	2.7%	3.1%	<0.001
VSD + ASD, PS or AS	1,715	10	0.3%	0.4%	0.5%	0.6%	0.6%	0.918
Partial AV canal	1,187	9	0.3%	0.3%	0.4%	0.5%	0.8%	0.476
Aortic disease	788	3	0.3%	0.4%	0.5%	0.6%	0.6%	0.554
PAPVC	774	2	0.1%	0.1%	0.1%	0.1%	0.4%	0.319
Pulmonary stenosis	721	4	0.1%	0.1%	0.4%	0.4%	0.4%	0.939
Ebstein's anomaly	136	7	2.2%	4.4%	4.4%	5.3%	5.3%	<0.001
Severe 2V								
d-TGA s/p arterial switch	1,237	15	0.8%	1.0%	1.0%	1.2%	1.3%	ref
Coarctation + ASD, VSD or AS	886	31	2.6%	2.9%	2.9%	3.3%	3.7%	<0.001
TAPVC	682	8	1.0%	1.0%	1.2%	1.2%	1.2%	0.918
ToF w/ pulmonary atresia	633	43	2.4%	5.2%	5.5%	5.9%	7.1%	<0.001
Interrupted aortic arch	311	13	1.9%	3.2%	3.5%	4.3%	4.3%	<0.001
d-TGA s/p atrial switch	252	18	0.8%	1.6%	2.0%	3.2%	6.1%	<0.001
Truncus arteriosus	257	11	3.5%	3.5%	3.9%	4.3%	4.3%	<0.001
d-TGA s/p Rastelli	137	8	1.5%	5.1%	5.1%	5.8%	5.8%	<0.001
Single Ventricle								
Systemic left ventricle	1,008	103	4.2%	7.1%	8.3%	9.6%	10.9%	ref
Systemic right ventricle	763	129	6.0%	11.9%	13.9%	15.3%	18.0%	<0.001
Unclassifiable ventricle	565	62	3.5%	6.9%	8.9%	10.4%	11.7%	0.609
Miscellaneous 2V								
Aortic stenosis	1,277	12	0.2%	0.4%	0.4%	0.6%	0.4%	ref
Mitral regurgitation	212	4	1.9%	1.9%	1.9%	1.9%	1.9%	0.229
Coronary abnormalities	240	2	0.4%	0.4%	0.8%	0.8%	0.8%	0.819
PA/IVS (2V)	197	5	2.5%	2.5%	2.5%	2.5%	2.5%	0.020
Aortic insufficiency	193	3	1.0%	1.0%	1.0%	1.6%	1.0%	0.493
L-TGA	192	21	3.6%	7.3%	7.8%	10.1%	11.9%	<0.001
ToF w/ absent pulmonary valve	109	3	0.9%	0.9%	1.8%	2.8%	1.8%	0.094
Cor triatriatum	77	2	1.3%	1.3%	1.3%	2.7%	1.3%	0.208
Mitral stenosis	70	4	2.9%	2.9%	2.9%	4.4%	2.9%	<0.001

ASD = atrial septal defect, PDA = patent ductus arteriosus, VSD = ventricular septal defect, ToF = tetralogy of Fallot, TGA= transposition of the great arteries, PAPVC = partial anomalous pulmonary venous connection, TAPVC = total anomalous pulmonary venous connection, AV canal = atrioventricular canal, PA/IVS = pulmonary atresia with intact ventricular septum, 2V = two ventricle, PS = pulmonary stenosis, AS = aortic stenosis

Table 3: Cumulative incidence of HF event after discharge by patient characteristics

				Cumulative incidence of HF event					
	Total Patients	HF Events	Non-HF Deaths	1 year	5 years	10 years	15 years	20 years	p-value
Sex									
Female	17096	298	941	0.8%	1.2%	1.4%	1.6%	1.8%	ref
Male	18515	417	1295	0.9%	1.5%	1.7%	2.0%	2.6%	<0.001
Chromosomal abnormality									
Yes	4779	100	481	1.0%	1.5%	1.7%	1.9%	2.2%	0.589
No	30832	615	1755	0.8%	1.4%	1.6%	1.8%	2.1%	ref
Era of first surgery									
Early (1982-1992)	10192	281	903	1.0%	1.7%	2.0%	2.2%	2.6%	<0.001
Middle (1993-1997)	11782	225	656	0.9%	1.4%	1.5%	1.8%	1.9%	0.236
Late (1998-2003)	13637	209	677	0.7%	1.1%	1.3%	1.6%	N/A.	ref
CHD severity									
Mild 2V	12476	41	373	0.2%	0.2%	0.2%	0.3%	0.3%	ref
Moderate	13442	151	674	0.5%	0.8%	0.9%	1.0%	1.1%	<0.001
Severe two ventricle									
Systemic LV	4155	143	402	1.8%	2.7%	2.8%	3.1%	3.5%	<0.001
Systemic RV	248	18	25	0.8%	1.6%	2.0%	3.2%	6.2%	<0.001
Non-classifiable two ventricle									
Systemic LV	2595	38	173	0.7%	0.8%	0.9%	1.2%	1.6%	<0.001
Systemic RV	188	21	22	3.7%	7.5%	8.0%	10.3%	12.1%	<0.001
Single ventricle									
Systemic LV	1008	103	173	4.2%	7.1%	8.3%	9.6%	10.9%	<0.001
Systemic RV	763	129	233	6.0%	11.9%	13.9%	15.3%	18.0%	<0.001
Indeterminate	565	62	135	3.5%	6.9%	8.9%	10.4%	11.7%	<0.001
Underlying physiology									
Left to right shunt	16582	115	638	0.4%	0.5%	0.5%	0.6%	0.7%	ref
Impaired systemic flow	5626	80	289	0.8%	1.0%	1.0%	1.3%	1.5%	<0.001
Impaired pulmonary flow	4781	100	384	0.8%	1.4%	1.7%	1.9%	2.1%	<0.001
Single ventricle	2336	294	540	4.6%	8.7%	10.3%	11.7%	13.3%	<0.001
Transposition physiology	1530	36	59	0.8%	1.3%	1.4%	1.8%	2.6%	<0.001
Complex lesions	1995	37	137	0.9%	1.4%	1.5%	1.7%	1.9%	<0.001
Complete mixing	257	11	37	3.5%	3.5%	3.9%	4.3%	4.3%	<0.001
Anomalous PV return	682	8	41	1.0%	1.0%	1.2%	1.2%	1.2%	0.145
Other	1822	34	111	0.7%	1.3%	1.5%	1.8%	2.0%	<0.001
Pacemaker									
Yes	97	10	14	1.0%	7.2%	7.2%	8.3%	12.2%	<0.001
No	35514	705	2222	0.9%	1.4%	1.8%	2.1%	2.4%	ref

HF = heart failure, PV = pulmonary venous, LV = left ventricle, RV = right ventricle

Table 4 : Multivariable model of patient characteristics associated with listing for transplant among those with primary outcome (N=715)

	Adjusted OR (95% CI)*	p-value
Male sex	0.98 (0.68 – 1.44)	0.942
Chromosomal abnormality	0.12 (0.04 – 0.26)	<0.001
CHD severity		
Mild 2V	ref	-
Moderate 2V	0.56 (0.22 – 1.43)	0.234
Severe 2V	0.64 (0.22 – 1.43)	0.336
Miscellaneous 2V	0.94 (0.22 – 2.59)	0.675
Single ventricle	0.82 (0.33 – 2.05)	0.902
Systemic ventricle		
Left	ref	-
Right	1.85 (1.16 – 2.95)	0.013
Unclassifiable	0.95 (0.50 – 1.80)	0.725
Era of first surgery		
Early (1982-1992)	ref	-
Middle (1993-1997)	0.95 (0.56 – 1.63)	0.860
Late (1998-2003)	1.27 (0.72 – 2.23)	0.420
Decade of death/transplant		
1982-1992	ref	-
1993-2003	2.85 (1.40 – 5.80)	0.004
2004-2014	6.27 (2.53 – 15.5)	<0.001
Age at death/transplant (years)		
Infant (<1 year)	ref	-
Child (1-12 years)	2.67 (1.78 – 4.24)	<0.001
Adolescent (13-17 years)	6.52 (3.17 – 13.4)	<0.001
Adult (>18 years)	1.25 (0.50 – 3.14)	0.638

*All listed variables included in adjusted model; 2V = two ventricle, CHD =congenital heart disease

Table 5: Competing risk regression model for HF events

	Period at risk	Unadjusted			Adjusted*		
		HR	95% CI	p-value	HR	95% CI	p-value
Severity							
Mild 2V	Overall	ref	-		ref	-	-
Moderate 2V		3.40	2.35 – 4.87	<0.001	3.18	2.22 – 4.56	<0.001
Severe 2V		11.2	7.82 – 16.1	<0.001	9.91	6.92 – 14.2	<0.001
Non-classifiable 2V		5.36	4.17 – 9.70	<0.001	6.31	4.16 – 9.57	<0.001
Single ventricle		41.2	29.2 – 58.1	<0.001	29.9	20.4 – 43.8	<0.001
Systemic ventricle							
Left	<2 years	ref	-	-	ref	-	-
Right		7.59	5.89 – 9.79	<0.001	1.41	1.05 – 1.91	0.023
Indeterminate		6.91	4.91 – 9.73	<0.001	1.02	0.69 – 1.51	0.924
Left	≥2 years	ref	-	-	ref	-	-
Right		13.7	10.4 – 18.5	<0.001	2.60	1.87 – 3.63	<0.001
Indeterminate		11.7	7.97 – 17.3	<0.001	1.71	1.12 – 2.64	0.014
Chromosomal abnormality							
No	Overall	ref	-	-	ref	-	-
Yes		1.07	0.86 – 1.34	0.550	1.76	1.39 – 2.23	<0.001
Sex							
Female	Overall	ref	-	-	ref	-	-
Male		1.25	1.07 – 1.46	0.006	0.96	0.82 – 1.12	0.596
Surgical era							
Early (1982-1992)	Overall	1.45	1.20 – 1.75	<0.001	1.72	1.42 – 2.08	<0.001
Middle (1993-1997)		1.14	0.94 – 1.38	0.197	1.33	1.09 – 1.61	0.004
Late (1998-2003)		ref	-	-	ref	-	-
LOS at initial surgery							
≤ 30 days	Overall	ref	-	-	ref	-	-
>30 days		4.91	4.10 – 5.87	<0.001	1.95	1.58 – 2.40	<0.001
Pacemaker present							
No	≥2 years	ref	-		ref	-	-
Yes		4.74	2.38 – 9.43	<0.001	2.72	1.32 – 5.58	0.007

* all variables listed included in adjusted model; 2V = two ventricle, LOS = length of stay

Table 6: Competing risk regression model on the effect of race on time to primary outcome among those patients with race data available

	Unadjusted		Adjusted*		
	HR	**95% CI**	**HR**	**95% CI**	**p-value**
Race					
Black	1.21	0.93 – 1.56	1.30	0.99 – 1.70	0.06
Other	0.84	0.42 – 1.70	0.84	0.41 – 1.73	0.64
White	ref	-	ref	-	

*Adjusted for sex, presence of chromosomal abnormality, CHD severity, systemic ventricle, and era

Table 7: Competing risk regression model for HF-event for event-free survivors 5 years after first CHS (n=33,664)

	Unadjusted		p-value	Adjusted*		p-value
	HR	95% CI		HR	95% CI	
Sex						
Male	1.18	0.85 – 1.64	0.316	0.91	0.65 – 1.26	0.908
Female	ref	-		ref	-	-
Chromosomal abnormality						
Yes	1.12	0.70 – 1.77	0.639	2.13	1.28 – 3.54	0.004
No	ref	-		ref	-	-
Surgical era						
Early (1982-1992)	1.38	0.94 – 2.02	0.098	1.84	1.24 – 2.75	0.003
Middle (1993-1997)	0.82	0.54 – 1.25	0.358	1.00	0.66 – 1.52	0.993
Late (1998-2003)	ref	-		ref	-	-
Severity						
Mild 2V	ref	-	-	ref	-	-
Moderate 2V	2.98	1.46 – 6.07	0.003	2.77	1.34 – 5.72	0.006
Severe 2V	6.99	3.33 – 14.7	<0.001	6.19	2.93 – 13.1	<0.001
Non-classifiable 2V	7.50	3.41 – 16.5	<0.001	7.38	3.34 -16.3	<0.001
Single ventricle	51.4	26.5 – 99.8	<0.001	33.8	15.7 – 72.8	<0.001
Systemic ventricle						
Right	13.6	9.15 – 20.2	<0.001	2.39	1.44 – 3.98	<0.001
Indeterminate	15.4	9.51 – 25.0	<0.001	1.82	0.99 – 3.36	0.054
Left	ref	-				
LOS at index surgery						
>30 days	4.91	4.10 – 5.87	<0.001	1.50	0.93 – 2.42	0.094
≤ 30 days	ref	-	-	ref	-	-
Pacemaker present						
Yes	4.47	2.94 – 6.79	<0.001	2.99	1.51 – 5.93	0.002
No			-	ref	-	-

* all variables listed included in adjusted model; 2V = two ventricle, LOS = length of stay

Figure 1: CONSORT flowchart with included subjects

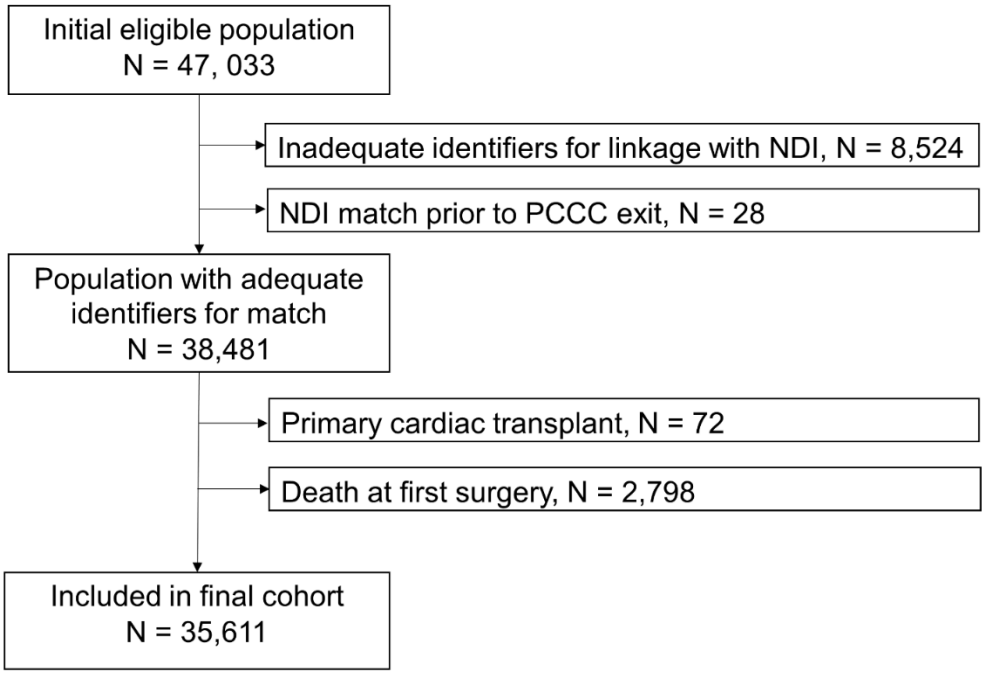


Figure 2: Distribution of type of primary outcome by event year in subgroup analysis of those who experienced heart failure death, transplant, or VAD

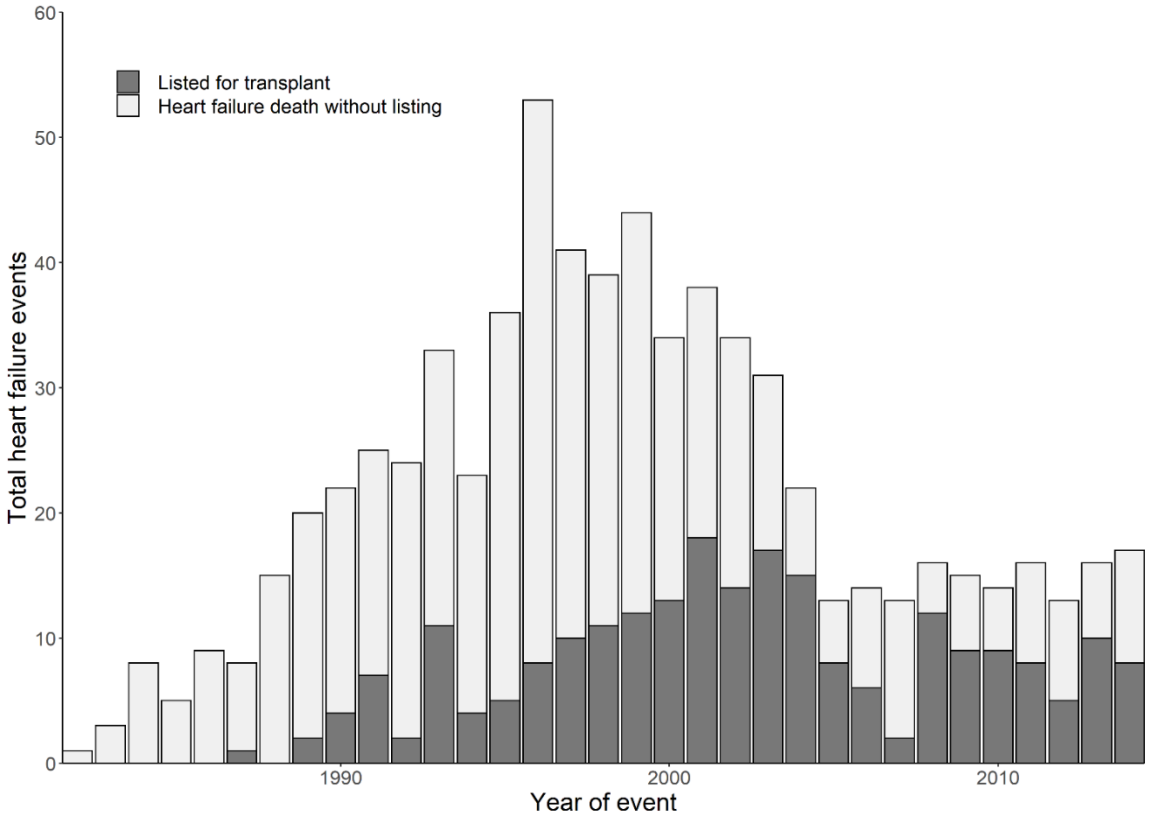


Figure 3: Cumulative incidence of competing risks in all patients discharged alive from first CHS

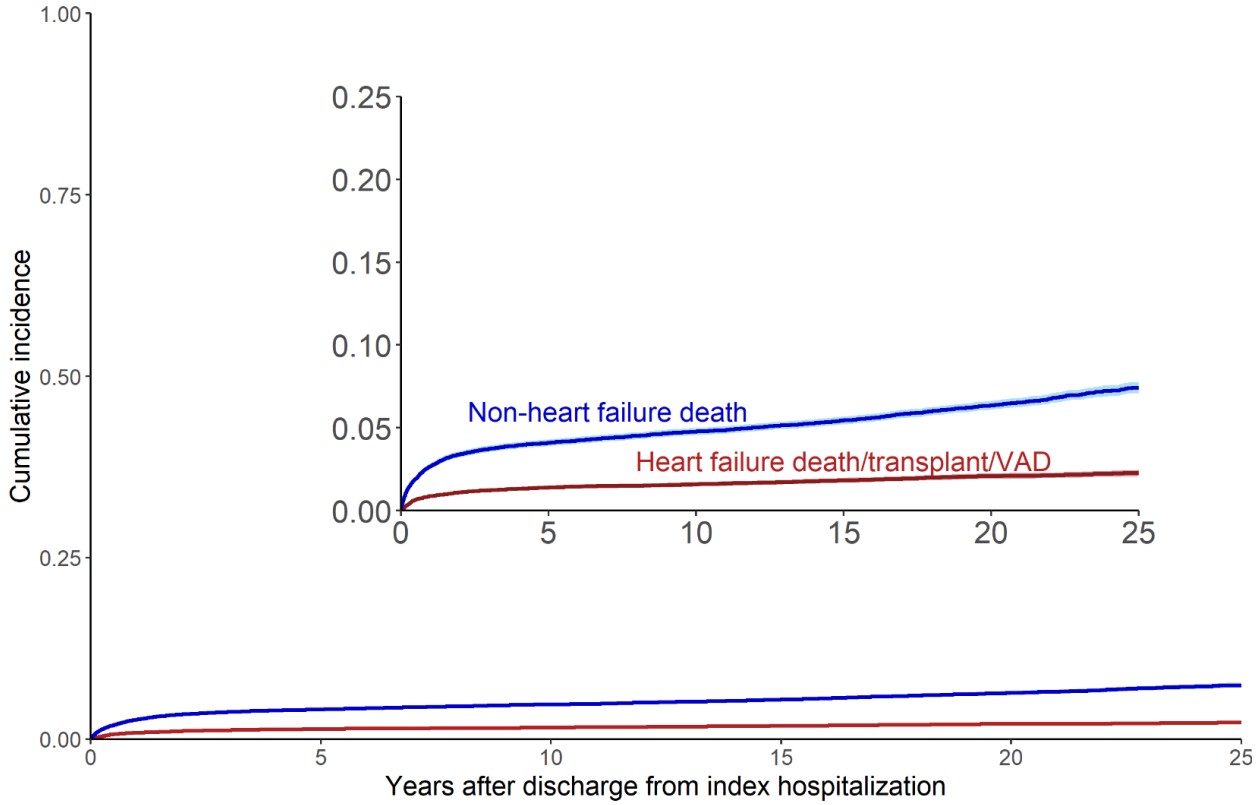


Figure 4: Cumulative incidence of HF event stratified by severity of congenital heart disease and type of systemic ventricle

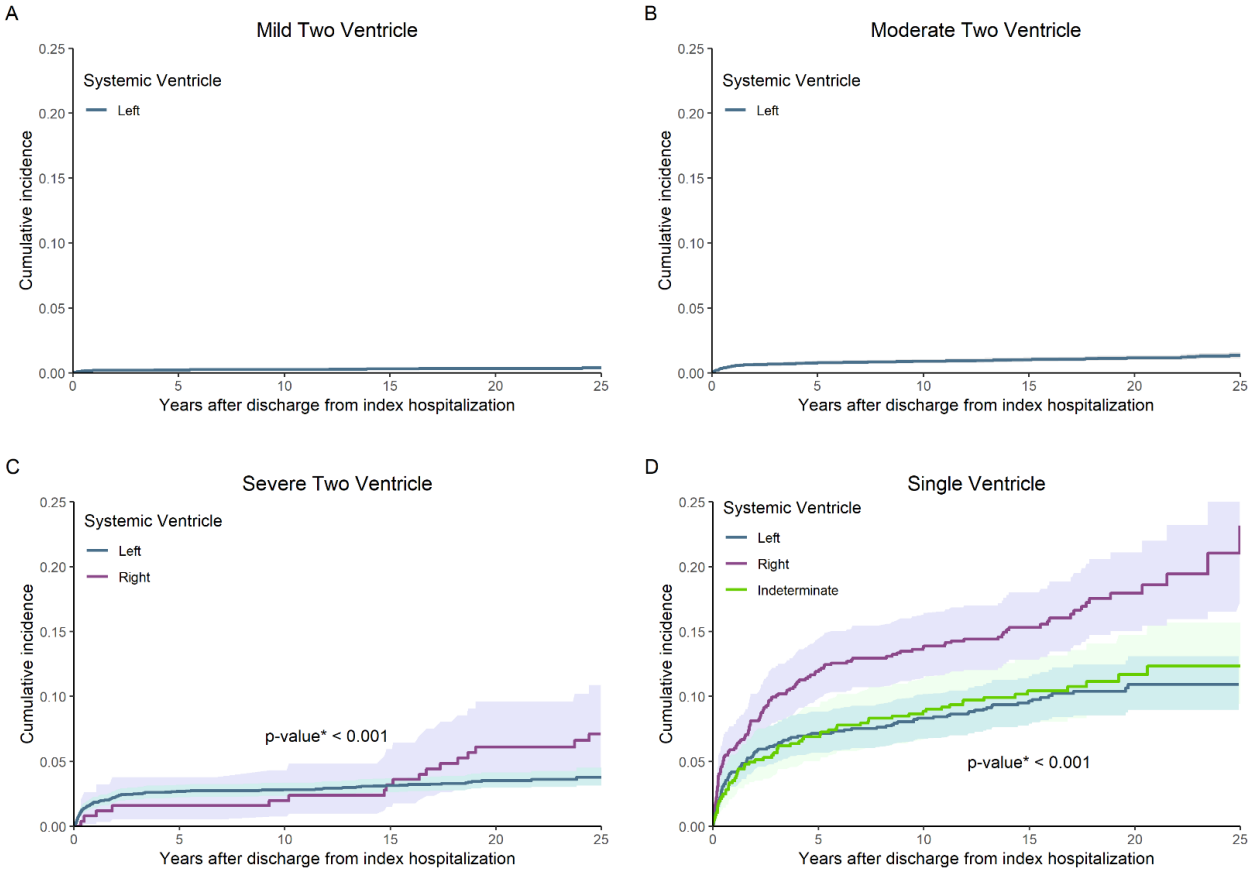
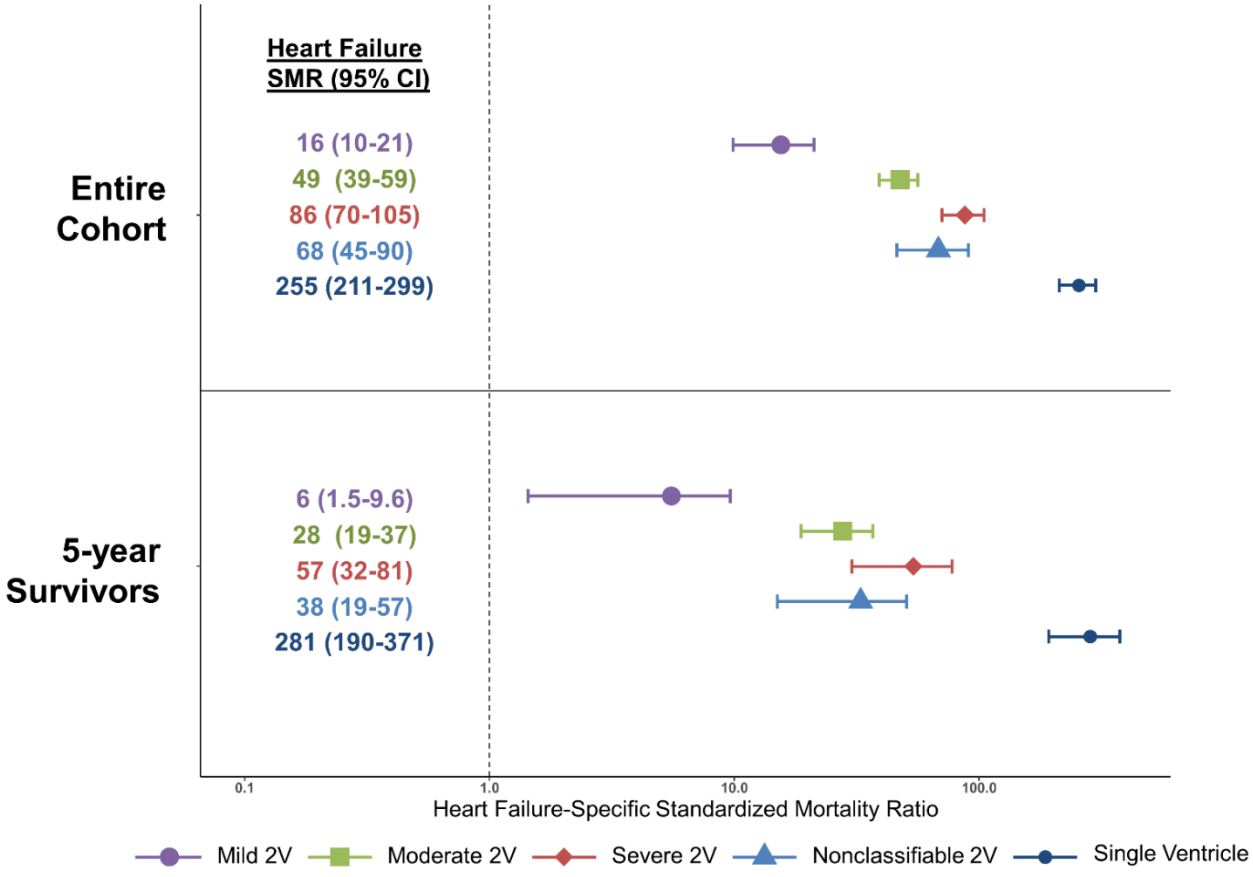


Figure 5: Heart-failure specific standardized mortality stratified by severity of CHD for entire cohort and 5-year survivors



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