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14. ABSTRACT
Advances in the surgical management of congenital heart diseases (CHD) have led to a growing population of CHD survivors whose health must be monitored over time to understand the impact of early treatment decisions on subsequent events. This study will address knowledge gaps identified by clinical experts and public health officials related to the subject of long-term outcomes of CHD.

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Introduction

Congenital heart disease (CHD) is the most common type of structural birth defect, affecting approximately 1% of all births in the United States.[1, 2] Advances in the surgical management of CHD have led to a growing population of CHD survivors whose health must be monitored.[3, 4] Based on rough estimates by applying data from Canada to the US population, there are over 2.4 million persons with CHD in the United States (US), more than half of whom are adults.[1, 5-7] Among them, there is a large number of patients with a surgically repaired or palliated CHD with unique exposures to risk factors that medicine has not faced ever before. Therefore, the health status of this cohort needs to be monitored over time to understand the impact of early treatment decisions on subsequent events. With age, these patients are continuously exposed to additional cardiovascular and non-cardiovascular morbidities similar to the general population that may further affect their prognosis.[8-11] Understanding the long-term outcomes of this cohort is important for identifying opportunities for intervention and planning for health services for CHD patients with high resource utilization and would be highly valuable to healthcare providers, families and patients. Lack of knowledge concerning their CHD and appropriate medical follow-up are modifiable issues, which if addressed could improve outcomes in this at-risk population.[12] Unfortunately, neither the long-term trajectory of these patients nor their actual number by each group of CHD is known for the US. This study supported by the Department of Defense (DoD) will address knowledge gaps identified by clinical experts and public health officials related to the subject of CHD[13-16].

Body

The protocol objective aims to capture end-stage organ failure and mortality patterns in a large cohort of patients after interventions for CHD by linking the Pediatric Cardiac Care Consortium (PCCC), a long-standing US-based registry of outcomes for pediatric cardiac interventions, with the National Death Index (NDI) and the Organ Procurement and Transplantation Network (OPTN). The PCCC-NDI-OPTN data will then be used to calculated national survival estimates utilizing data from the Agency for Health Care Research and Quality (AHRQ) Kids' Inpatient Database (KID).

The specific aims of this project are:

Specific Aim 1: To describe transplant-free survival for patients with CHD after discharge from their first palliative or corrective intervention. Separate survival curves will be generated by subgroups of severity, pathophysiology and individual lesions as far as the numbers allow.

Specific Aim 2: Conditional survival probabilities will be estimated at specific time points (e.g., 6 months, 1 year, 10 years) or milestones (stages of repair or definite repair) following CHD surgery. Conditional survival probabilities will be estimated using conditional Kaplan-Meier estimates. Relative conditional survival will be used to compare conditional survival in the CHD cohort to the general population stratified by calendar year, age and sex. All survival estimates will be accompanied by associated 95% CI. To characterize the change in risk for death/transplant following CHD surgery, we propose a nonparametric approach to estimate the hazard rate function for the time-dependent outcome death/transplant following initial palliation or repair for CHD. Hazard rate functions will be calculated for procedure and lesion specific subgroups and will be estimated utilizing kernel or spline estimators using local bandwidths to better characterize the variation in risk over time. In addition, we propose to examine the time-varying effect of patient and procedure specific characteristics on transplant-free survival. These may include risk factors such as age at repair, sex, presence of genetic condition, prematurity and others. Both the varying-coefficient Cox model [13] and the natural generalization Cox model with temporal covariate effects [14] will be adopted. The former approach models evolving effects on the hazard, whereas the latter on the survival function.

Specific Aim 3: For each defect group, post-discharge survival and transplant-free survival for surgeries performed in 2000, and 2003 will be estimated separately using the Kaplan-Meier method in the PCCC-NDI-OPTN linked dataset. Survival will be stratified by sex, age at surgery, and race/ethnicity as described above. The national weights corresponding to each stratum estimated from KID will then be applied to the stratum-specific survival estimates from PCCC. A weighted average of the overall defect grouping Kaplan-Meier survival curve will then be calculated using the method of Cupples [15], where PCCC post-discharge survival estimates are adjusted to the US population (direct standardization). Similar analyses adjusting post-discharge survival curves to the US population will be performed for individual congenital heart conditions (e.g., isolated VSD) where sample size permits.

Key Research Accomplishments

During the first year of this award we accomplished the following tasks:

1) IRB approval was obtained for this study. Additionally, the DoD Human Research Protection Office (HRPO) has also approved the study protocol and granted permission for project activities to begin.

2) The application to the National Death Index (NDI) was submitted and approved to obtain updated data on mortality and causes of death of the PCCC cohort up to December 31, 2019. The PCCC cohort was restricted to patients with an intervention for CHD between January 1st, 1982 up to April 23,2003 who had sufficient direct identifiers available for linkage, regardless of vital status at the discharge. The updated results were received on June 15, 2020 and analysis of data was started once results became available. Our methodology to link NDI results through a custom multistep matching process has previously been described for CHD patients in the PCCC [16]. However, the NDI has recently restricted the use of alias information in data submission causing lower probabilistic match scores of subjects who were previously submitted with any alias information. Subsequently, we needed to revise our matching algorithm to optimize the performance of the matching process and recalculate its sensitivity and specificity based on the updated results. This process also resulted in identifying false-positive matches (n=61), which were removed from the final dataset.

   To estimate the sensitivity and specificity of the updated matching algorithm, known deaths reported in the PCCC (i.e. patients not surviving to hospital discharge) were used as the gold standard as before. Sensitivity was calculated as the number of known deaths who matched in the NDI divided by the total number of known deaths in PCCC submitted for linkage (sensitivity = 88.1%). Overall, 3,990 of 4,771 deaths had a matching record in the NDI (sensitivity of 83.6%); however, the sensitivity for the 3,985 patients with sufficient direct identifiers with 4,524 deaths among them was higher and reached 88.1%, which is comparable with the one reported at the first phase of this project [16].

   Specificity will be estimated by using as denominator the number of individuals with multiple hospital admissions in the PCCC, for whom a period of transplant-free survival can be inferred between the date the PCCC stopped collecting new data on 12/31/2011 and from the beginning of the PCCC on 1/1/1982 for the NDI [or from 11/1/1987 for the Organ Procurement Transplant Network (OPTN) because OPTN did not begin tracking transplants until that time]. The calculations for the specificity are still in process.

3) The same cohort submitted to the NDI was also submitted to the OPTN and was approved to obtain updated transplant status information. Results from OPTN underwent a similar matching process and were obtained July 21, 2020. Final matches were included in the dataset and are now available for analysis as well (see Table 1). The sensitivity of the OPTN matching for transplant events was 92.6%.

Table 1. PCCC patients with history of intervention for CHD who received heart (or heart-lung) transplant between 11/1/1987 and 12/31/2019

Number of patients with transplant in PCCC	421
Number of patients with transplant in PCCC confirmed by OPTN	390
Number of patients with transplant outside the PCCC confirmed by OPTN	364
Total number of patients with transplant (PCCC/OPTN)	785

4) In regards to specific Aim 3, we have created a preliminary dataset containing aggregate data of PCCC patients with codes consistent with specific interventions for CHD at PCCC centers participating in the KID database in the years 2000 and 2003 (see Table 2). Additional work is underway to add diagnostic codes to procedures that can be applied to more than one CHD, so we can calculate lesion-specific national weights based on the KID database. In parallel, our collaborators at Boston Children's Hospital, have compiled the list of patients operated at their center for submission to the NDI to get updated results from a cohort that is believed to provide an upper boundary for lesion-specific long-term outcomes.

Table 2. Benchmark procedures at PCCC centers participating in the KID database for years 2000 and 2003

		Year 2000		Year 2003	
	Procedure	**KID**	**PCCC**	**KID**	**PCCC**
1	Annuloplasty [unspecified valve]	2	16	2	9
2	Aortic stenosis, Subvalvar, Repair	7	45	11	36
3	AP window repair	0	1	2	3
4	Arterial switch operation (ASO)	26	47	40	60
5	Arterial switch operation (ASO) and VSD repair	7	10	14	13
6	ASD creation/enlargement [Atrial septectomy]	2	8	1	6
7	ASD primum repair	7	24	23	51
8	ASD repair	101	169	111	127
9	Atrial switch operation	6	4	8	1
10	Atrial switch operation and VSD repair	1	0	0	0
11	AVC (AVSD) repair, Complete or transitional	27	40	70	70
12	Coarctation repair	78	138	93	150
13	Coarctation repair + VSD repair	7	2	12	14
14	Conduit placement, RV to PA	11	0	23	0
15	L-TGA repair, Atrial switch and ASO (double switch)	0	1	1	1
16	Cor triatriatum repair	1	2	3	4
17	Ebstein's repair	1	2	1	1
18	Fontan	25	51	59	84
19	Glenn shunt	16	54	33	74
20	Interrupted aortic arch repair	15	3	40	3
21	Interrupted aortic arch repair + VSD repair	4	8	5	11
22	Konno procedure	0	0	0	1
23	PA banding (PAB)	2	17	13	30
24	PAPVC repair	9	34	15	36
25	PDA closure, Surgical, age > 30 days	39	80	51	72
26	Pulmonary atresia - VSD (including TOF, PA) repair	2	34	5	46
27	Rastelli procedure	1	2	2	1

28	Ross procedure	11	23	14	23
29	RVOT procedure [Right ventricular infundibulectomy]	6	13	5	25
30	Shunt, Systemic to pulmonary artery	57	84	72	73
31	Stage 1 repair	23	42	51	65
32	TAPVC repair	16	24	21	34
33	TOF repair	63	90	99	123
34	TOF repair, RV-PA conduit	4	0	7	0
35	Truncus arteriosus repair	9	8	11	16
36	Truncus arteriosus repair + Interrupted aortic arch repair	0	0	2	2
37	Valve replacement, Aortic (AVR)	8	10	16	17
38	Valve replacement, Mitral (MVR)	5	7	6	12
39	Valve replacement, Pulmonic (PVR)	7	9	30	38
40	Valve replacement, Tricuspid (TVR)	1	0	2	2
41	Valvuloplasty/valvotomy, Aortic	28	6	28	16
42	Valvuloplasty/valvotomy, Mitral	15	16	33	21
43	Valvuloplasty/valvotomy, Pulmonic	7	12	17	7
44	Valvuloplasty/valvotomy, Tricuspid	3	1	9	5
45	VSD repair	44	70	49	63
46	VSD repair + ASD repair	44	90	101	142
47	VSD repair + Pulmonary valvotomy or Infundibular resection	8	19	10	4
	Total	**756**	**1316**	**1221**	**1592**

Reportable Outcomes

No reportable outcomes are available at this point, as the study is still in the phase of data acquisition.

Conclusion

We have accomplished significant milestones in the data acquisition phase for this study and satisfactory progress was made towards achieving the project's objectives. There was an unanticipated delay in achieving the goals of the project between March-June 2020 due to the impact of the COVID-19 pandemic on the workflow of the research team and delays in the process of data through the National Death Index.

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Appendices