Mortality and Cause of Death Following Pediatric Cardiac Surgery for Congenital Heart Defects

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Abstract

Congenital heart defects (CHD) affect almost 1% of births. The primary method for managing these defects is surgery. These analyses used data from the Pediatric Cardiac Care Consortium (PCCC), a large, US-based registry of pediatric interventions for CHDs. The PCCC was previously linked to the National Death Index and was linked to the American Medical Association Physician Masterfile as part of this dissertation. The first two analyses examined the associations between surgeon and center characteristics and post-surgical mortality using multilevel modeling. These analyses examined procedure-specific volume at the surgeon and center levels as well as training center status at the center level and years since graduation from medical school at the surgeon level. In the third analysis, multiple cause of death data were examined to determine the burden of contributing causes of death. Standardized mortality ratios and competing risk Cox regression compared these results with those calculated using underlying cause of death. The first analysis found that after adjusting for known patient-level risk factors, center factors including procedure-specific volume were not associated with early post-discharge mortality. The second analysis of short and medium term mortality demonstrated a consistent center-level association between procedure-specific volume and mortality among several complex repairs. No association was observed among patients with relatively simple ventricular septal defect repairs. Finally, we found that standardized mortality ratios based on underlying cause of death underestimated the burden of death associated with injury as well as perinatal, infectious, endocrine, genitourinary, and circulatory diseases. These differences varied by age and defect severity. Perinatal and endocrine disease were highest among those with severe defects. Differences in mortality due to infection showed a bimodal association with age at the time of death. The combination of multi-level modeling and multiple cause of death methods leveraged in these analyses advances the understanding of the roles of healthcare systems and multiple causes of death.

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LIST OF ABBREVIATIONS

ABC	Aristotle Basic Complexity
ACGME	Accreditation Council of Graduate Medical Education
AMA	American Medical Association
ASO	Arterial switch operation
ASD	Atrial septal defect(s)
AVSD	Atrio-ventricular septal defect(s)
CCHD	Critical congenital heart defect(s)
CHD	Congenital heart defect(s)
CHS	Congenital heart surgery
COA	Coarctation of the aorta
EACTS	European Association for Cardio-Thoracic Surgery
HLHS	Hypoplastic left heart syndrome
ICD	International Statistical Classification of Diseases and Related Health Problems
LOS	Length of stay
PCCC	Pediatric Cardiac Care Consortium
RACHS-1	Risk Adjustment for Congenital Heart Surgery
SES	Socioeconomic status
STS	Society of Thoracic Surgeons
TA	Truncus arteriosus
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect(s)

CHAPTER 1: DIAGNOSIS AND TREATMENT OF CONGENITAL HEART DEFECTS

Overview

Congenital heart defects (CHDs) are the leading cause of birth defect-related death in infants.[1] In the United States, 8 out of 1,000 births are determined to have a CHD within the first year.[2,3] Approximately 40,000 children are born with a CHD in the US annually [4], a quarter of whom will require surgery.[1] Despite improvements in surgical technique and training over the last 30 years,[5] the life expectancy for individuals who had pediatric cardiac surgery continues to trail behind the general population.[6] Mortality following pediatric congenital heart surgery are between 3.6 and 35.0 times higher for individuals with mild lesions and those with single-ventricle disease, respectively.[6]

We are currently in a period of increased focus on CHD research. The importance of understanding post-surgical outcomes for CHD has been highlighted in academic and lay publications. In 2016, the National Heart Lung and Blood Institute (NHLBI)/Adult Congenital Heart Association Working Group published emerging research directions, which identified a lack of US-based, long-term outcomes of pediatric cardiac surgery.[7] These findings were echoed by the Centers for Disease Control and Prevention (CDC) which also noted gaps in health service delivery for the management of CHD.[7,8] Additionally, a recent investigative report by the New York Times highlighted the critical role of surgeons and surgical centers in patient outcomes[9] emphasizing the critical need to identify center and surgeon-level factors associated with mortality.

The purpose of this dissertation was to identify factors associated with and contributing causes of death following pediatric cardiac surgery. The first two aims

examined characteristics of centers and surgeons associated with mortality. The first aim was to describe the relationship between center characteristics and short-term mortality following pediatric cardiac surgery. The second aim was to determine the association between surgeons and surgical centers on survival following pediatric cardiac surgery. Together these aims help characterize the relationship between centers and surgeons and mortality within a complex pediatric patient population. In the third aim, we examined contributing causes of death following successful intervention for CHD in comparison to the general population to identify elevated disease burden associated with CHD with the goal of identifying targets for monitoring and intervention.

For this dissertation, we used data from the Pediatric Cardiac Care Consortium (PCCC), a large, retrospective longitudinal cohort of children and young adults who had surgery for CHD starting in 1982.[10,11] The PCCC offered an opportunity to efficiently assess factors associated with mortality as well as contributing causes of death in a diverse, national population at multiple critical time points including in-hospital, immediately post-discharge, and long-term. Additionally, the abstraction of surgeon names allowed the use of hierarchical modeling to examine center and surgeon level variables simultaneously. Previous linkage to the National Death Index (NDI) provides highly accurate information about the time and cause of death. The large sample size of the PCCC provided sufficient statistical power to assess the associations between characteristics of pediatric cardiac surgery care and mortality for individual surgical procedures. These data were augmented with data from the American Medical Association (AMA) Physician Masterfile.[12,13] Additionally, we used data from the

National Bureau of Economic Research to tabulate contributing causes of death from national vital statistics records.[14]

Natural History of Congenital Heart Defects

Although severe defects are often diagnosed before birth, mild defects may not be identified until adulthood. Severe defects can be identified using fetal cardiac ultrasound and echocardiography during prenatal screening or pulse oximetry and echocardiography shortly after birth.[15,16]

Congenital heart defects are a diverse collection of structural birth defects of the heart and great vessels.[3] Recent changes in nomenclature from congenital heart defects to congenital cardiovascular defects reflect the inclusion of the vascular lesions.[3] Ultimately, these defects impede or prevent the heart from efficiently circulating blood through the body.

These defects can range from mild to severe and may be present in isolation or in combination with other CHD.[17] Mild lesions may include ventricular septal defects (VSD) whereas severe lesions include most cyanotic heart diseases.[18] Severity may vary within a given CHD.[18] For example, most VSDs resolve without intervention over the first year of life and are considered mild lesions; however, 10-25% of VSDs are hemodynamically significant and may result in congestive heart failure or death if untreated.[18]

Categorization of Risk

A number of systems have been developed to characterize defect severity and surgical complexity. The most commonly utilized are the Aristotle Basic Complexity

(ABC) and Risk Adjustment for Congenital Heart Surgery (RACHS-1) scores.[19–21] Expert panels developed both scores.[19–23] The ABC score was designed to characterize procedure complexity while the RACHS-1 was developed to assess risk of mortality.[19] More recently, a modeling-based approach was used to develop Congenital Heart Surgery Mortality Score and Mortality Categories using the Society of Thoracic Surgeons (STS) and European Association for Cardiothoracic Surgery (EACTS) Congenital Heart Surgery Databases.[21]

The RACHS-1 score was developed in part using data from the Pediatric Cardiac Care Consortium (PCCC).[22,23] Compared to the ABC score, the RACHS-1 has higher discrimination for post-surgical mortality.[21] It has also been shown to be highly predictive of length of stay and 30-day readmission.[22,24] In a single center analysis, RACHS-1 alone had inconsistent predictive ability of increased in-hospital morbidity and mortality at an individual level.[25] RACHS-1 scores for various procedures are shown in Table A1.

Age at Detection

In the United States, 15% of all CHDs are detected before birth.[15] Prenatal diagnosis of CHD is achieved using ultrasound and echocardiography.[26,27] Fetal echocardiography started in 1964 and has been used to screen for CHD since the mid-1980s.[28] Techniques have been refined throughout the use of fetal echocardiography for CHD. Prenatal diagnosis of complex CHD increased from 63.1% in 2000 to 83.3% in 2017.[27] Currently, if an obstetric ultrasound suggests a CHD, a fetal cardiac evaluation and echocardiogram are recommended [26]. Fetal echocardiography may also be recommended if the mother has pre-gestational or gestational diabetes mellitus,

phenylketonuria, Lupus or Sjogrens, infection or certain medication exposures, or when relevant family history or fetal factors are present.[26] Prenatal diagnosis of CHD is more common in fetuses with severe defect.[15,28,29]

Symptoms of CHDs and the time they emerge in children vary by structural characteristics of the defect. Conceptually, they may fall into one of three categories based on the time symptoms emerge and their presentation.[30] The first group presents with severe cyanosis one to two hours after birth most frequently due to HLHS or TGA. In the second group, mild cyanosis develops six hours to several days after birth with symptoms worsening following the closure of the patent ductus arteriosus (PDA).[30] These defects are the results of PDA dependent pulmonary or systemic circulation including PS, TOF with PS, Ebstein's anomaly, COA, or AS.[30] Finally, the third group presents with mild cyanosis, congestive heart failure, and reduced pulmonary vascular resistance several days to months after birth due to TOF, TA, or TPVR.[30]

Since 2011, screening for critical congenital heart defects (CCHD) has been part of the Recommended Uniform Screening Panel for Newborns.[29,31] Widespread but not universal adoption of pulse oximetry screening has reduced late detection of CCHD, defined as more than three days after birth, which is associated with worse outcomes.[31,32] Congenital heart defects including CCHDs may also be identified based on symptoms observed including cyanosis, acidosis, respiratory distress, heart failure, and failure to thrive.[29,30] Despite improvements in diagnosis, between 14% and 30% of CCHD are not diagnosed before discharge home.[30,33] Delayed diagnosis of CCHDs are associated with greater morbidity and mortality.[31–33]

Benchmark Procedures

In order to better study surgical outcomes, researchers have identified a number of procedures with consistent surgical repairs, or benchmark procedures.[34,35] These procedures represent a wide range of abnormal anatomy and surgical difficulty.[35] The first list of benchmark procedures included coarctation of the aorta (COA), ventricular septal defect (VSD), Tetralogy of Fallot (TOF), atrioventricular septal defect (AVSD), and truncus arteriosus (TA) repairs as well as arterial switch operations (ASOs) for the repair of transposition of the great arteries (TGA).[35] Researchers using the Society of Thoracic Surgeons (STS) database identified a similar list of eight procedures, which excluded COA, added Norwood and Fontan procedures, and included arterial switch with VSD repair as a unique procedure.[34] Further revisions to this list include the addition of Glenn/Hemi-Fontan procedures and off-bypass COA repair.[36]

Similarly, the World Society for Pediatric and Congenital Heart Surgery (WSPCHS) identified a list of tier 1 procedures, on which to focus data collection efforts.[37] Tier 1 procedures consist of VSD, AVSD, COA, partial anomalous pulmonary venous connection (PAPVC), total anomalous pulmonary venous return (TAPVR), TOF, TA, and Ebstein's anomaly repairs as well as Norwood, Glenn/Hemi-Fontan, and Fontan procedures and HLHS biventricular repairs for the management of HLHS and ASOs.[37]

For this dissertation the following benchmark procedures were considered: COA, VSD, TOF, AVSD and TA repairs as well as Norwood, Glenn, and Fontan procedures and ASOs (Table 1.1). Brief descriptions of these defects, their corresponding repairs, and technical difficulty follow.

Table 1.1: Benchmark congenital heart defect surgeries

Defect	Severity	Procedure
Hypoplastic left heart syndrome (HLHS)	6	Norwood (stage I)
Truncus arteriosus (TA)	4	TA repair
Transposition of the great arteries (TGA)	4	Arterial switch operation
HLHS	3	Fontan (stage 3)
Atrioventricular septal defect (AVSD)	3	AVSD repair
HLHS	2	Glenn (stage 2)
Tetralogy of Fallot (TOF)	2	TOF repair
VSD	2	VSD repair
Coarctation of the aorta (COA)	1-2	COA repair

Severity based on RACHS-1 score, COA repair has a RACHS-1 score of 1 after 30 days and 2 on or before 30 days

Coarctation of the Aorta

Coarctation, or constriction, of the aorta (COA) can vary significantly.[38] Severity of the obstruction of blood flow can vary significantly. Severe obstruction, present at or shortly after birth is deemed 'critical'.[38] Although generally considered a simple surgical procedure, COA repairs performed less than 30 days after birth are scored higher than repairs after 30 days according to the RACHS-1 scoring system.[39] Additionally, COA may occur in combination with more complex defects.[38]

Ventricular Septal Defects

Ventricular septal defects are the most common congenital cardiac defect that requires intervention. Excluding bicuspid aortic valves, they make up 40% of CHDs.[40] Broadly, VSDs are caused by a hole in or adjacent to the muscle separating the right and left ventricles of the heart.[38,40] These defects can vary by size and location and occur in isolation or in combination with other defects.[40,41]

Defects occurring in the membranous portion of the septum adjacent to the tricuspid valve are described as perimembranous VSDs.[38] These defects may close spontaneously.[38] Subaortic or conoventricular VSDs are large muscular defects adjacent

to the interventricular septa.[38] This subtype of VSD is often associated with TOF, which is discussed in the next section.[38] Inlet VSDs occur between the tricuspid valve and adjacent muscular tissue.[38] Subpulmonary VSDs occur below the pulmonary and aortic valves.[38] Proximity to the aortic valve may lead to prolapse and regurgitation of the valve.[38] Finally, muscular VSDs are defects occurring throughout the muscular portion of the septum.[38]

Ventricular septal defects may close on their own or may be repaired through surgery, transcatheter, or hybrid approaches.[40] Surgical repair of VSDs began in the 1950s with advances continuing through the early 2000s.[38]

Tetralogy of Fallot

Tetralogy of Fallot is characterized by four coexisting defects: VSD, dextroposition or overriding of the aorta, right ventricular hypertrophy, and pulmonary stenosis or atresia.[38] This defect arises from a poorly developed septum in the right ventricle, which results in the defect in the septum and the incorrect position of the aorta.[38]

The method of repair may vary based on pulmonary valve involvement.[38] Patients with pulmonary stenosis may undergo a single or two-staged surgical repair.[38] Patients with pulmonary atresia typically undergo a two-staged repair.[38] Due to being considered a moderately complex defect to repair, TOF outcomes are often used as benchmarks of surgical performance by centers.[38]

Atrioventricular Septal Defect

Atrioventricular septal defects (AVSD), previously known as atrioventricular canal or endocardial cushion defects are a group of CHDs characterized by common junction between the atria and ventricles of the heart.[42] These defects were previously categorized into three subtypes depending on their anatomy; partial, intermediate, or complete.[38,42] These categories have been expanded to reflect the presence or absence of atrial or septal defects.[42]

Complete AVSD is the most severe manifestation in which there are defects in the atrial and ventricular septums as well as a single atrioventricular valve in place of the mitral and tricuspid valves.[38,42] These defects require intervention within the first year of life and may be performed as early as two to three months following birth.[38] Modern repairs involve the use of one or two patches to close the defects in the septum.[38] Sutures are used to divide the single atrioventricular valve into two valves.[38] The specific techniques vary by AVSD subtype and surgical training or preference.[38] Atrioventricular septal defects including complete AVSD are commonly associated with Down's syndrome.[38,42]

Truncus Arteriosus

Truncus arteriosus (TA) is characterized by a multi-leaflet crescent-shaped valve in place of separate aortic and pulmonary valves.[38] It is typically accompanied by a VSD.[38] Surgery to repair TA is ideally performed within a week of birth.[38] If not repaired, a child will become severely symptomatic within one or two months.[38] During surgical repair, the truncus is divided and the truncal valve is refashioned to replace the

aortic valve and human donor tissue is used to connect the pulmonary artery to the right ventricle.[38] If present, the VSD is repaired with a patch.[38]

Transposition of the Great Arteries

Transposition of the great arteries (TGA) occurs when the aorta and pulmonary artery are switched.[38] As a result, blood cycles between the lungs and body in two separate, closed loops.[38] Following birth and the closure of the ductus arteriosus this results in deoxygenated blood recirculating through the body causing cyanosis.[38] Two forms of the defect may occur; the dextro-transposition (or d-transposition) or the much less common levo-transposition (or l-transposition).[38] For the purposes of this dissertation, we ignored l-TGA, which is not a cyanotic CHD.

Destro-transposition of the great arteries requires early intervention. If the infant does not have a septal defect, a balloon atrial septostomy, a transcatheter procedure where a balloon is used to open the foramen ovale, is performed to allow oxygenated and deoxygenated blood to mix in the atria heart.[38] Once an infant is stable, an ASO can be performed which will transpose the aorta and pulmonary artery as well as move the coronary arteries.[38] Previously, an atrial switch or Senning procedure may have been performed creating a baffle or channel between the left and right atria redirecting blood flow.[38]

Hypoplastic Left Heart Syndrome

Univentricular defects are a group of defects that result in a single ventricular chamber.[38] Defects can generally be described by whether the right or left ventricle is affected.[38] The most common of these defects is hypoplastic left heart syndrome

(HLHS).[38] This defect is the result of the left side of the heart, importantly the ventricle, being underformed.[38] Hypoplastic left heart syndrome occurs with stenosis or atresia of the aortic and mitral valves.[38]

This complex defect is typically repaired in three stages.[38] In the first stage, the Norwood procedure, the pulmonary artery is divided. The distal pulmonary artery is connected via a Sano shunt to the right ventricle and the proximal pulmonary artery is connected to the ascending aorta.[38] In the Glenn procedure, the superior vena cava is connected to the pulmonary artery.[38] The Fontan procedure connects the inferior vena cava to the pulmonary arteries separating the circulation of oxygenated and deoxygenated blood.[38] In recent years, hybrid approaches combining surgical and transcatheter techniques have been utilized for some univentricular defects.[38]

Surgical Management of Congenital Heart Defects

Early Surgical Management

The earliest attempts to repair CHDs occurred over 80 years ago. The first successful PDA ligation performed at Boston Children's Hospital by Robert Gross and John Hubbard in 1938 and subsequently published in the Journal of the American Medical Association the following year.[43] In 1944 the first successful repair of COA and use of an arterial shunt were performed at Karolinska Hospital and Johns Hopkins, respectively.[43,44] Pulmonary artery banding was introduced in 1952.[43]

At this point, the time to perform any more complicated surgical repairs exceeded the length of time the heart could be stopped without causing death or disability.[43] This led to the development of a number of medical devices which are still used today. The

use of hypothermia by surgeons at the University of Minnesota and other institutions extended operating time from three to 10 minutes.[43] The first successful ASD repair followed in 1952.[43] More complex repairs required the development of cardiopulmonary bypass, which was first attempted successfully in 1953 at Massachusetts General Hospital by Dr. John Gibson[43,44] All 17 additional repairs attempted with early heart-lung machines between 1952 and 1954 resulted in death.[43]

Dr. Gibson's early screen oxygenator was improved by Drs. Kirklin and Jones leading to its successful use in the repair of a VSD in 1955 at Mayo Clinic.[43] Simultaneously, Richard DeWall developed the bubble oxygenator at the University of Minnesota which would become widely adopted in the US and around the world.[43] In the late 1960s surgeons in Japan and New Zealand began repairing defects in infancy, with promising results.[43]

Adoption of surgical techniques and devices was rapidly adopted in the middle of the 20th century. Prior to 1960, individuals with hemodynamically significant VSD, now considered a relatively simple surgical repair with excellent outcomes, were unlikely to survive.[18] Regular surgical intervention for TOF began in the 1960s, but effective surgical treatment was not widely available until 1980.[18] In the 1980s, ASO for the repair of transposition of the great arteries and three stage repairs of hypoplastic left heart syndrome were performed and perfected.[43] Similar patterns are seen for the management of many types of CHD.[18] A brief summary of the adoption of surgical repairs for these defects is presented in Table 1.2.[38,45–47] Surgical techniques continue to be refined, particularly for more complex lesions.

Table 1.2: Introduction of surgical repairs of congenital heart defects

Defect	Repair technique	Year
Coarctation of the aorta	First successful repair	1944
	Subclavian flap aortoplasty	1966
	Balloon angioplasty	1982
	Extended end to end anastomosis for associated hypoplastic arch	1987
	First pulmonary artery band	1952
Ventricular septal defects	VSD closure using cross-circulation	1954
	VSD closure using Mayo-Gibbon pump oxygenator	1955
	Transatrial closure	1958
	Early primary VSD closure	1969
Tetralogy of Fallot	First successful subclavian artery to pulmonary artery anastomosis (Blalock and Taussig shunt)	1945
	Descending aorta to left pulmonary artery anastomosis	1946
	First open repair	1954
	Ascending aorta to right pulmonary artery anastomosis	1962
	Prosthetic subclavian artery and pulmonary artery conduit	1962
	Early TOF repair	1972
Atrioventricular septal defect	AVSD repair using cross-circulation	1954
	Successful partial AVC repair	1955
	Early AVSD repair	1975
Transposition of the great arteries	Atrial septectomy	1950
	Senning procedure	1959
	Mustard procedure	1964
	Arterial switch operation (Jatene)	1975
Hypoplastic left heart syndrome	First pulmonary artery band	1952
	Routine pulmonary artery band placement	1970
	Norwood procedure	1979
	First successful Fontan procedure	1983
	Modified Norwood (right ventricle to pulmonary artery conduit, Sano shunt)	1998

Modern Surgical Management

Improvements in surgical techniques, particularly for more complex lesions, has resulted in improved short and long-term mortality following pediatric surgery for CHDs. Significant declines in discharge mortality overall and within the most severe categories of CHD have been observed beginning in the 1980s.[48,49] Similar results were observed in

the Nationwide Inpatient Sample (NIS) between 1988 and 2005 and Kids' Inpatient Database (KID) in 2003.[49]

Like short-term mortality, long-term mortality following pediatric cardiac surgery for CHDs has also decreased in the US.[6,50,51] Between 1982 and 2003 the 15-year standardized mortality ratio for individuals with pediatric cardiac surgery decreased from 12.7 to 10.0.[6] Improved long-term survival has been observed in England, Finland, and Norway over the same time.[50,52,53] However, despite improvements in surgical management, the life expectancy for adults who had pediatric cardiac surgery continues to trail behind the general population.[6]

Pediatric Cardiothoracic Surgical Training

Following the relatively rapid development of surgical techniques, there have been significant efforts to improve and standardize training for pediatric cardiac surgeons.[54] In 2007 the Accreditation Council of Graduate Medical Education (ACGME) formally recognized the congenital cardiac surgery fellowship.[55] For a program to receive accreditation it must demonstrate sufficient faculty and caseload to provide the necessary clinical experience to fellows.[55] The fellowship outlines core competencies and minimum surgical experience for total CHD surgeries and specific procedures.[55]

As of 2015, the 13 ACGME accredited programs have trained 44 fellows.[55] Despite progress made standardizing the fellowship curriculum, not all fellows meet the minimum surgical requirements for specific procedures, and analyses suggested the failure to meet minimum requirements was not related to center volume.[55] The lack of exposure to complex cases is a known challenge facing programs and trainees

worldwide.[56] Additional concerns include the current age of fellows upon graduation is 40 years old.[57]

CHAPTER 2: EPIDEMIOLOGY AND PUBLIC HEALTH RELEVANCE OF CONGENITAL HEART DEFECTS

Incidence and Prevalence of Congenital Heart Defects

As previously stated, 8 out of 1,000 births in the United States are determined to have congenital heart defects (CHDs) within the first year.[18] The most frequent defects, as observed by the National Birth Defects Prevention Network and Metropolitan Atlanta Congenital Defects Program, are: ventricular septal defects (VSD, 4.2 per 1000 births), atrial septal defects (ASD, 1.3 per 1000 births), pulmonary valve stenosis (PS, 0.6 per 1000 births), tetralogy of Fallot (TOF, 0.4-0.5 per 1000 births), atrioventricular septal defects (AVSD, 0.4-0.5 per 1000 births), coarctation of the aorta (COA, 0.4 per 1000 births), transposition of the great arteries (TGA, 0.2-0.3 per 1000 births), hypoplastic left heart syndrome (HLHS, 0.23 per 1000 births), and truncus arteriosus (TA, 0.07 per 1000 births).[3,4,16,58,59]

Birth prevalence is anticipated to increase as more CHDs are diagnosed before or shortly after birth due to improvements in diagnostic technique.[60,61] Additionally, the difficulty diagnosing some defects early in life is likely responsible for some of the variation observed in domestic estimates of birth prevalence.[62]

In 2010, approximately 2.4 million adults and children were living with CHD in the U.S.[3] Among adults, 1 in 150 is living with a CHD [3]. The most common defect among children and adults is VSD.[3]

Among high income countries, between 1990 and 2017 congenital heart defects fell from the second to the fourth leading cause of death among children under the age of one.[63] In 2017, birth prevalence was 1255.5 per 100,000.[63] Age standardized prevalence 196.4 per 100,000.[63] Globally, CHDs fell from the seventh to sixth leading cause of death.[63] Global birth and age standardized prevalences were 1,787.6 and 170.6 per 100,000 in 2017, respectively.[63]

Health Inequities

Multiple researchers have demonstrated health inequities among patients who had pediatric surgery for CHDs. In addition to racial and ethnic disparities, evidence of the impact of institutional racism on surgical outcomes can be observed in the associations between mortality and lower maternal education and enrollment in Medicaid.[3,64,65]

Inequities have been observed at multiple points throughout the continuum of care. Black infants with CHD were more likely to be born underweight or premature than white or Hispanic infants.[66] Although non-white children are not referred to a pediatric cardiologist or diagnosed later than white children with CHD,[24,31] Black and Hispanic children have higher mortality following surgery for CHD than white children.[3] Black infants had 45% higher risk of dying than white children.[67] Black adolescents continued to be at greater risk of mortality at almost all age categories.[67] These disparities have persisted despite improved surgical outcomes for CHDs.[51,68] There is limited evidence these associations may be strongest among patients with less complex CHD.[3,69,70]

Among patients under the age of 19, Hispanic patients were more likely than white patients to be readmitted after surgery.[24,71] Additionally, non-white infants were more likely to experience a lapse in care and experienced lapses earlier than their white

counterparts,[72] Routine follow up is important for the early identification of arrhythmia or heart failure, which are significant causes of mortality following surgery for CHD,[72] Black and Hispanic infants were also more likely to be born to younger mothers with less education, who likely had access to fewer resources to assist caring for an infant with CHD.[66] Therefore these lapses in care may have significant impacts on outcomes for Black and Hispanic patients following pediatric surgery for CHD.

Children born in rural areas may also be at increased risk of mortality. Previously, researchers found that urban teaching hospitals had lower mortality following Norwood procedure.[73] More recently, researchers found that maternal proximity to a top pediatric cardiac center was associated with lower mortality among children with CHDs after adjusting for the mother's race/ethnicity, education, and education.[65] In this analysis, all of the top 50 pediatric cardiac centers were located in metropolitan areas.[65] The association between health inequities, specifically racism and the rural-urban divide, and mortality is explored further in chapter three.

Economic Burden

Pediatric CHD hospitalization costs represent 23% of all pediatric hospitalization costs.[3] In 2012, hospitalization costs due to CHD for patients less than 21 years old totaled $6.6 billion.[3] The median cost for children who required surgery was $51,302.[3] The highest costs were associated with younger age at the time of surgery and critical CHD.[3]

In addition to the significant cost to treat CHD, families of children with CHD experience significant financial burden. One report found that 35.0% of families had financial problems and 42.8% of families reduced or stopped working.[74] After

adjustments, this corresponded to a 70-80% higher economic burden compared to families who did not have a child with CHD.[74] Overall 89.1% of families reported at least one indicator of financial burden over the last year.[74] A qualitative analysis of financial burden on families of children with CHD found their experience as characterized by lifestyle changes and uncertainty as a result of the economic impact of medical care and associated costs.[75]

CHAPTER 3: FACTORS ASSOCIATED WITH MORTALITY FOLLOWING CONGENITAL HEART DEFECT REPAIR

For the purposes of this dissertation, we identified factors associated with post-surgical mortality within three levels of the care system (summarized in Table 3.1). The first is patient-level. These characteristics are largely non-modifiable and not the primary focus of these analyses. However, they are important factors and require consideration in all three analyses. Surgeon-level factors include measures of training and experience. These variables will be explored in chapter five. Finally, center-level characteristics focus on dimensions of the center structure including surgical volume. Center-level characteristics are assessed in chapters five and six.

Table 3.1: Patient, surgeon and center-level characteristics

Patient	Surgeon	Center
Defect severity (RACHS-1)	Surgical experience	Surgery volume
Age at surgery, days or years	Medical training	Training center status
Weight at surgery, kg		Region/urbanicity
Sex		
Chromosomal defects		
Race/ethnicity		
Surgical era		

Patient-Level

Mortality following pediatric cardiac surgery is closely related to the complexity of the defect.[3,6,51] In addition to defect severity, previous analyses have identified sex, age at the time of surgery, year of birth and proxies of socioeconomic status (SES) as important factors associated with mortality.[3,6,51,76–79]

Defect Severity

The most significant risk factor for mortality with or without surgery is defect severity. Long-term mortality rates following congenital heart surgery range from 3.6 times greater for mild lesions to 35.0 for those with single-ventricle disease.[6] Recent assessment of all-cause mortality in Norway found the mortality rate ranged from 3.0% to 17.4% for children with mild to severe defects, respectively.[3] Multiple ranking systems have been developed to characterize congenital heart defect (CHD) severity and risk of mortality for comparing outcomes between surgical centers.[19–23,39]

Age

Age at the time of surgery reflects both the need to intervene earlier on more severe lesions as well as increased technical difficulty of surgical repair at younger ages. Discharge mortality rates from the STS Congenital Heart Surgery Database (CHSD) range from 8.6% for neonates to 1.0% for children between the ages of one and 18 years old.[3] In addition to time since birth, preterm birth is also associated with CHD outcomes. Overall, mortality is inversely associated with gestational age at birth from 34 to 40 weeks.[3,80] This association is particularly strong among children with severe CHD.[81,82]

Weight

The association between low birth weight, defined as weighing less than 2.5 kg, and congenital heart defects has been recognized for decades.[83] Recent assessments showed that low birth weight was twice as frequent in infants with CHDs.[84] Additionally, infants with CHD may experience growth restriction. One center reported that between 18 and 23% of children aged between zero and three years were growth restricted prior to surgical repair [85]. Multiple studies have demonstrated that very low birth weight[3,86] and growth restricted [87] infants have higher mortality following surgical repair of CHDs.

Biological Sex

Biological sex has been shown in multiple studies to be associated with CHD birth prevalence, complications, prognoses and outcomes.[3,88] Males are more likely to be diagnosed with aortic stenosis (AS), coarctation of the aorta (COA), transposition of great arteries (TGA), tetralogy of Fallot (TOF), and double outlet right ventricle (DORV).[88] Girls are more likely to have an atrial septal defect (ASD) or atrio-ventricular septal defect (AVSD).[88,89] These differences are likely driven by genetic factors.[89] The presence of a second X chromosome in females is thought to protect against defects of the aorta or aortopathy, which is observed with greater frequency in males.[89]

The different distributions of CHDs between males and females have resulted in different trends in surgical outcomes. Overall, males have higher mortality rates following surgery.[3] Higher mortality observed in males has multiple contributing factors. Males typically have more severe defects and are more likely to have multiple coexisting defects requiring repair compared to females.[3] As a result, males require higher risk

surgical repairs and more surgical repairs in infancy.[3] However, female children with high-risk CHD have 39% higher adjusted mortality compared to males.[3,69]

Chromosomal and Genetic Defects

A variety of chromosomal and genetic defects are associated with CHD. Aneuploidy, which is the presence of an abnormal number of chromosomes, is associated with 9% to 18% of births with CHD.[90,91] Defects are also associated with the addition or deletion of partial chromosomes.[90] Copy number variations and point mutations may also be associated with CHD.[90]

Down syndrome, Edwards syndrome, and Patau syndrome, which are the result of the presence of a third copy of the 21, 18, or 13 chromosome, respectively, are associated with increased risk of CHD.[3] Between 35-50% of children born with Down syndrome have a CHD.[90–92] The most common CHD in children with Down's syndrome is AVSD; however, VSD, ASD or patent ductus arteriosus (PDA) may also be present.[90,92] Children born with Edwards or Patau syndromes have an even higher prevalence of CHD with between 60-80% children having at least one CHD.[90]

Turner syndrome, which is caused by the partial or complete absence of a X chromosome, is also associated with increased risk of CHD.[88,90] A third of individuals with Turner will have a CHD with COA, bicuspid aortic valve and aortic stenosis being the most common.[90,91] Interestingly, females with Turner syndrome have elevated risk of aortopathy, which is typically seen in males.[88] This supports the hypothesis that the absence of a second X chromosome is associated with defects of the aorta.

In addition to chromosomal defects, copy number variants (CNV) and point mutations have also been associated with CHD.[3,90,93] DiGeorge and Williams syndromes,

CNVs associated with del22q11 and del17q11 respectively, are associated with CHDs.[3,91] Point mutations associated with CHD may be either inherited or random.[94] Approximately 2% of CHD are caused by inherited mutations and 10% of CHD are caused by random or *de novo* mutations.[90] These mutations can help inform genes responsible for CHD. However, the genes responsible for most defects remain unknown.[3]

Researchers have consistently shown that children with a trisomy have higher mortality following CHD surgery than their peers without chromosomal defects.[92,94] In addition to increasing the risk of CHD, Down syndrome, Edwards syndrome, and Patau syndrome are also associated with significant intellectual disabilities.[95] With improved screening, fetuses with these conditions are increasingly likely to be terminated before birth.[95,96] Children born with a trisomy may also be treated less aggressively than cognitively normal children. Historically, the management of children with these conditions focused on palliative care.[92,94] Due to worse outcomes and less aggressive management associated with chromosomal defects, children with known chromosomal defects are frequently excluded from analyses; however, due to the growing importance of outcomes in this population, children with chromosomal defects are included in these analyses.

Comorbidities

Children with CHDs may have a number of comorbidities including neurodevelopmental disability, respiratory disease, renal dysfunction, arrhythmia, heart failure, pulmonary hypertension, and malignancies.[90] These comorbidities can complicate medical management of CHD and are associated with higher morbidity and mortality.[90]

Neurodevelopmental disability is a relatively common comorbidity of CHD present in 50% of individuals with severe CHD and 10% of all CHD.[90] Neurodevelopmental disability may be present prior to CHD surgery, but it is also associated with reduced cerebral perfusion or oxygenation prior to surgery or length of circulatory arrest during surgery.[90]

Among children with hypoplastic left heart syndrome (HLHS), pre-operative length of stay and shock, extended use of ventilatory or circulatory support, as well as the development of arrhythmia or complete atrioventricular block are associated with elevated mortality following a Norwood procedure.[97]

Race and Ethnicity

Multiple researchers have identified racial and ethnic health disparities in morbidity and mortality following surgical repair of CHDs.[3,64,67,69,78] White children had lower short-term mortality following surgery.[66,69] Elevated mortality among Black and Hispanic individuals extends into adulthood[67,68] Recent trends in CHD outcomes show declines in mortality rates among Black and Hispanic children; however, these rates remain higher than in white children.[51,68,79]

There is limited evidence indicating mortality varies by defect severity among racial and ethnic groups. One study found that after stratifying by defect severity, there was no association between race and mortality among children with complex defects.[69]

Researchers have also identified a number of sociodemographic factors associated with mortality. Medicaid or government sponsored insurance are associated with higher in-hospital mortality[1] and 30-day readmissions.[24] Government insurance is also associated with increased length of stay following surgery.[79] Hispanic ethnicity is

associated with increased odds of 30-day readmission, which is itself a risk factor for mortality.[24] Maternal race/ethnicity, education, and marital status have also been associated with higher post-surgical infant mortality.[70] An analysis of the Kids Inpatient Database (KID) found that racial and ethnic differences were not significantly associated with mortality after thoroughly adjusting for healthcare disparities.[79]

Surgical Advances

As previously discussed in chapter one, the surgical management of CHD has greatly improved since the 1980s.[38,43,44] This has resulted in improved survival for children with CHDs.[1,6,48] From the periods between 1982 to 1992 and 1998 to 2003, survival one year after surgery increased from 94.6% to 96.6% overall and 66.3% to 76.0% for children born with single ventricles.[6] Due to these trends, longitudinal analyses, such as this dissertation, necessitate adjustment by year of birth or surgical era.

Surgeon-Level

To date, researchers studying the association between surgeons and mortality following pediatric cardiac surgery for CHD have largely focused on volume.[98] Researchers have also considered alternative measurements of surgical experience and surgical training as factors related to mortality following repair of CHDs.

Surgical Experience

Generally, higher pediatric CHD surgical volume is associated with improved mortality rates for surgeons.[99,100] Surgeons who performed more than 75 CHD surgeries annually had lower in-hospital mortality.[99] Experience was also examined as years of

experience performing pediatric CHD surgeries. In recent analyses of the STS CHSD, researchers found similar mortality outcomes for early, mid and late career surgeons; however, surgeons with more than 35 years of experience have higher odds of major morbidity or mortality in-hospital or 30 days after surgery.[101]

Analyses of the association between surgeon volume and mortality among children with severe CHD, including HLHS, are less conclusive. The adjusted odds of in-hospital mortality for low volume surgeons compared to high volume was 1.60 (95% CI = 1.13-2.27) in an analysis of the STS CHSD.[102] An analysis of the Pediatric Heart Network Single Ventricle Reconstruction found surgeon volume was independently associated with morbidity, but not 30-day mortality following Norwood procedure, which is the first stage of repair for HLHS.[103] One analysis of Norwood repairs found an inverse but not statistically significant association between surgeon volume and 28-day mortality among a population of neonates.[104] Finally, an analysis of data from the Congenital Heart Surgeons Society found patient-level factors were more influential than either surgeon or center volume among neonates with severe CHD including HLHS.[105] A summary of the previous research related to surgeon volume is in Tables A2 and A3.[99,101–105]

Medical Training

Finally, given the efforts to improve CHD surgical training for fellows, it is pertinent to examine the association between medical training and CHD surgery outcomes. Medical training has not been well studied in CHD outcome research; however, previous analyses of surgical residencies found that surgeons trained in university-based programs had better patient outcomes than those trained in non-university-based programs.[106] Modest but statistically significant differences were

observed between surgeons trained in the top tertile of residency programs compared to those in the lowest had lower rate of complications (9.68% vs 10.79%) but slightly higher rate of death (0.483% vs 0.476%).[107]

Center-Level

Similar to the study of the association between surgeons and CHD surgical outcomes, the study of the association with centers has also focused on volume.[98] Generally, previous analyses have focused on either surgeon or center-level associations and did not assess the complex relationship between centers and surgeons.

Surgery Volume

To date, research on the associations between center and surgeon on mortality following pediatric cardiac surgery for CHD has largely focused on volume,[98] and yielded inconsistent results. Several studies suggest centers that perform more than 100 surgeries annually have lower in-hospital mortality,[76,98,99] Another study suggests a volume of 200 surgeries is associated with reduced in-hospital mortality.[49] However, the association between center volume and mortality is not consistent and is usually stronger for complex procedures.[49,97,98]

Similar trends have been observed in analyses of data from Europe. Analysis of data from the European Association for Cardio-Thoracic Surgery (EACTS) Congenital Database has observed an inverse association between surgical volume and mortality and both overall and major postoperative complications.[108] Importantly, mortality in high volume centers following post-operative complications was also reduced.[108] In these analyses, low and high volume centers were defined as those with less than 150 or more

than 350 cases annually.[108] The authors later examined the association between center volume and mortality among neonates in the EACTS database and found that centers performing fewer than 60 surgeries on neonates annually had higher mortality.[109]

A systematic review of the association between center volume and mortality comparing results in the United States and Canada, which has a single payer health care system, showed several differences.[110] Although the trend persisted, the association between surgical volume and mortality was stronger in US studies compared to Canadian studies [110]. Authors theorized that smaller study sample sizes in Canada or differences in health delivery may drive these differences.[110]

Several analyses have also examined the association between procedure-specific center volume and mortality. The Norwood procedure is the first step in the repair of HLHS and carries a RACHS-1 score of six indicating the highest risk category.[23] Data from the STS CHSD from 2000 to 2009 demonstrated that centers performed a median of 7.5 Norwood procedures annually (IQR 5.3–11.3).[97] Researchers found that center volume was inversely associated with mortality.[97] Authors also noted that center volume, although statistically significant, did not explain the majority of the variation observed in mortality.[97] An analysis of 29 centers in the Pediatric Health Information System found a similar association.[104] They found center volume was associated with improved 28-day survival in neonates.[104] Interestingly, previous research has shown that above average outcomes in one surgical procedure is not associated with above average outcomes in another procedure.[111]

Previous analyses of the PCCC found procedure-specific center volume was associated with length of stay following CHD surgery for VSD and ASO repairs in crude

analyses.[112] After adjusting for patient- and center-level factors, the association between center volume and length of stay in VSD repair, which is a less technically complex procedure, was attenuated and no longer significant.[112] Crude analyses found center volume and mortality were associated for VSD and ASO.[112] Results of previous research examining center volume as well as surgeon volume are summarized in Tables A2 and A3.[49,73,76,77,97,99,101–105,105,112–125]

Training Center Status

Norwood procedures, due to their complexity, are often used as a benchmark of CHD surgery outcomes. Several studies have examined the association between hospital type and mortality following Norwood repair. Analysis of the Kids Inpatient Database (KID) found that non-teaching hospitals had significantly higher in-hospital mortality (OR 2.6, 95% CI 1.3-5.3) compared to teaching hospitals after adjustment.[100,113] A later analysis of KID found that teaching hospitals in urban settings had the lowest mortality for Norwood procedures.[73,100]

Length of Stay

Post-procedure length of stay is a crucial measure for understanding surgical outcomes for CHD as both an outcome and risk factor. Length of stay is a major contributor to inpatient medical costs.[126] Analyses of adult CHD surgical outcomes stratified by CHD anatomy found that bacterial infection, acute renal disease, surgeries performed without compensation, pulmonary heart disease, heart failure, complications, and anemia were associated with an increased length of stay of approximately 2 or more days.[126] These associations were similar for stratified and non-stratified analyses.[126]

When examining cost as an outcome, these results remained similar, however readmission and CHD anatomy, which was not examined as covariates in the later analysis, were the most significant factors driving cost.[127]

Region and Urbanicity

As previously mentioned in chapter two, some researchers have found that children from rural areas are at higher risk of post-surgical mortality, which may be driven in part by proximity to a top pediatric cardiac center.[65,73] Additionally, children from low-income neighborhoods also had higher rates of mortality, length of stay, and resource utilization than peers from high-income neighborhoods.[128] In New York state, distance to a pediatric cardiac center was identified as a barrier to maintaining care in adolescence, which may negatively impact health outcomes.[129]

Case Mix

ABC, RACHS-1, and STS–EACTS scores and categories were developed to adjust for CHD case mix to compare surgical centers with varying distributions of CHDs and surgical procedures.[21] Case mix describes the relative number of surgical cases by difficulty performed by a surgeon or within a surgical center. Appropriate adjustments for case mix is necessary to accurately compare mortality outcomes between centers.[19,130,131]

Summary

Assessing CHD outcomes in pediatric populations is a complicated endeavor; however, improving our understanding of factors associated with and contributing causes of death following pediatric cardiac surgery for CHD is crucial to improve short and long

term outcomes. In this dissertation, we applied hierarchical methods to better understand factors and comorbidities associated with mortality following pediatric cardiac surgery. As a result of the relatively recent improvements in CHD management, adolescents and adults who had pediatric cardiac surgery represent a new and growing population. For individuals with CHD, the health effects are a lifelong consideration.

CHAPTER 4: STUDY DESIGN OF THE PEDIATRIC CARDIAC CARE CONSORTIUM

This dissertation utilized data from the Pediatric Cardiac Care Consortium (PCCC), which had several valuable advantages over other pediatric congenital heart defect (CHD) data sources available in the US. The PCCC included pre-discharge as well as short and long-term post-discharge outcomes including mortality rather than being limited to short-term follow-up.[132] It had been successfully linked to the National Death Index (NDI) for accurate information on the time and cause of death.[132]

Study Design and Population

The PCCC was initiated in 1982 in an effort to compare pediatric post-procedure CHD outcomes between US institutions. Participating institutions submitted information on procedures including catheterizations, operations and autopsies as well as post-procedure medical records to the PCCC. The data was maintained by the University of Minnesota and supervised by a Board of Directors.[10,11,133] The data are currently maintained by Emory University.

The PCCC started with five original centers and expanded to include 48 centers from 27 states.[11] Between the start of the PCCC registry in 1982 and the last enrollment in 2011, more than 137,654 patients were enrolled.[11,133] These patients underwent

117,756 operations, which depending on the year represent 15-30% of the estimated national total.[11,133] The PCCC contains information on patient demographics, cardiac and non-cardiac diagnoses, and genetic syndromes as well as diagnostic and interventional procedures including surgeries and their discharge status and date.[11] Identifying information on patients allows assessment of staged repairs within the cohort.[134]

The National Heart Lung and Blood Institute (NHLBI) supported efforts to link the PCCC to the NDI and the Organ Procurement and Transplantation Network (OPTN).[135] Linkages to the NDI were updated through December 31st 2019. In total, 59,324 patients with sufficient identifying information who had surgery before the implementation of HIPAA were submitted to NDI and OPTN.[135] Following implementation of HIPAA in 2003, only a minimal dataset without names was available making these records unsuitable for linkage studies.[135] The Institutional Review Board (IRB) of Emory University, the NDI, and the United Network for Organ Sharing which manages the OPTN database approved the use of a subset of the PCCC dataset, from January 1, 1982 until April 15, 2003 for research purposes with waived informed consent.

Data Linkage

National Death Index

The PCCC team successfully linked records from patients who underwent their first congenital heart surgery in the PCCC with death and transplant events through December 31, 2014, and later December 31, 2019.[135] Patients were matched to the NDI using their first name, middle initial (when available), last name, date of birth, sex, state

of last known residence, and state of birth.[135] Patients missing identifying information could not be linked to the NDI.[135]

The NDI provides highly accurate information on the date and cause of death. The sensitivity of the PCCC-NDI matching was 88.1% (95% CI, 87.1-89) for patients with in-hospital deaths and full set of identifiers, and specificity exceeded 99.5%.[135] Successful data linkage was not associated with CHD diagnosis or intervention.[135] Therefore, it is unlikely linkage success impacted the internal validity of these findings.

American Medical Association Physician Masterfile

The American Medical Association (AMA) Physician Masterfile is a database of all physicians who practiced or are practicing in the United States.[13,136] Key variables include physician name, date of birth, medical and residency location and graduation, board certifications, and practice specialty.[13] The AMA Physician Masterfile is highly accurate. A statewide review found 99.8% of licensed, practicing physicians were represented in the database.[136] We linked data from the AMA Physician Masterfile to the PCCC-NDI-OPTN dataset to provide information on the training of the surgeons necessary for the second aim.

Human Subjects

This secondary data analysis posed minimal risk to PCCC patients. These analyses utilized existing data from the PCCC and patients were not contacted. The most salient risk was the inadvertent breach of patient confidentiality. Strong safeguards, described below, were put into place to prevent such a breach. The chance of harm from this potential risk was very low. The linked dataset utilized for these analyses included

35,998 patients. The sample was 47% female and 81% of those with reported race were white. Additionally, the PCCC ensured the protection of the identities of surgeons and prohibited the publication of data on individual surgeons or their names.

The linked dataset received a waiver of informed consent from all organizations involved in the creation of the dataset. The PCCC has maintained high standards of ethics with regard to patient confidentiality and data protection since its inception. The University of Minnesota IRB reviewed the analyses described in this proposal and determined they were exempt from IRB review (STUDY00006464).

Inadvertent release of confidential information was minimized through careful adherence to best practices for data management. All patient data was identified using unique identification numbers not related to any personal identification information. A file containing the link between the study ID and individually identifying information is maintained by research staff at Emory University on a username and password protected file-server. The master PCCC database is behind and protected by a layered firewall system. Access to, edits to, and additions to the master database was the responsibility of only a few authorized individuals. The proposed analyses were performed on data exported from the master database. Data is only reported in aggregate and no identifying characteristics of patients or surgeons will be published or presented.

There is no direct benefit to PCCC patients as a result of the proposed data analyses. However, the benefit lies in the knowledge to be gained as a result of the proposed research, which is to identify characteristics of surgeons and centers associated with short and long-term mortality following pediatric cardiac surgery for CHD. Results from this secondary data analysis will help to further our understanding of key

characteristics of surgical training and surgical center structure associated with better post-surgical outcomes and identify potential avenues for improving surgical center structure.

Strengths and Limitations

The PCCC is an exceptionally high quality dataset, which is approximately 99.95% complete and consistent.[10] It was the only US cohort with both short and long-term outcomes following surgery for CHD and has a median follow-up time of 22.5 years (810,925 person-years).[6] Additionally, the PCCC included identifying information of patients, which has provided highly accurate death information through linkage to the NDI.[6]

Although the PCCC data had many advantages, several limitations existed. The PCCC was not inclusive of all centers performing pediatric surgery for CHD in the US.[11] Therefore, these findings may not be generalizable to the entire United States. Additionally, it may result in underestimating surgeon volume since surgeries performed by surgeons at non-PCCC centers between 1982 and 2003 were not captured. Additionally, movement of surgeons to and from non-PCCC centers was not captured in the data.

Like other hospital-based cohorts, the PCCC had limited information on race and socioeconomic status (SES), which were known patient-level predictors of mortality following pediatric cardiac surgery.[51,64,78,137] Information on race is available for only 34% of PCCC subjects; this information was obtained when race/ethnicity was included in the original PCCC enrollment records by happenstance or through linkage to public

birth records (which were available for the states of Arkansas, Minnesota, Missouri, Ohio and South Carolina).

CHAPTER 5: CHARACTERISTICS OF SURGICAL CENTERS ASSOCIATED WITH EARLY POST-DISCHARGE MORTALITY

Introduction

Previously, researchers have found center volume to be associated with survival following pediatric congenital heart surgery (CHS) in the United States. In-hospital mortality was found to be lower in high volume centers, defined as those performing 100 to 200 procedures annually, depending on the analysis.[49,76,98,99] The association between center volume and mortality is not consistent and is usually stronger for complex procedures.[49,97,98]

Researchers have also examined this association among Norwood procedures, the first step in the repair of hypoplastic left heart syndrome.[23] As with total center volume, researchers have found that center volume was inversely associated with mortality at or before 30 day following surgery.[97,104] Interestingly, previous research has shown that above average outcomes in one surgical procedure is not associated with above average outcomes in another procedure.[111]

Previous analyses of the Pediatric Cardiac Care Consortium (PCCC) found procedure-specific center volume was associated with length of stay following CHS for ventricular septal defect (VSD) closure and arterial switch operation (ASO) in crude analyses.[112] After adjusting for patient- and center-level factors, the association between

center volume and length of stay in VSD repair, which is a less technically complex procedure, was attenuated and no longer significant.[112] Crude analyses found center volume and mortality were associated for VSD and ASO.[112]

In this analysis, we investigated center-level characteristics to determine if, after adjusting for patient and surgery characteristics, it is associated with post-surgical mortality. Based on previous research, which found that center success in one procedure may not confer success in other CHS,[111] we conducted procedure-stratified analyses. We utilized hierarchical modeling to model these associations.

Methods

We conducted a retrospective cohort study using data from the PCCC, a large, US-based registry of children and young adults who had surgery for CHD between 1982 and 2011. The PCCC includes 48 centers from 27 states. Patients in the PCCC have an average of 22.5 years of follow up, including data from the time of surgery through one year post-procedure.[10,11,133] The PCCC was previously linked to the National Death Index (NDI) to obtain information on patient mortality.[135] Linkage to the NDI was updated through December 31, 2019.

We identified patients who had a benchmark procedure at a PCCC center before 21 years of age. Benchmark procedures, in the study of CHS, are defects with consistent surgical repairs representing a variety of surgical complexity.[34,35] Benchmark procedures included in this analysis were coarctation of the aorta (COA), atrioventricular septal defect (AVSD), tetralogy of Fallot (TOF), and truncus arteriosus (TA) repairs as well as VSD closures, ASO for treatment of transposition of the great arteries, and Norwood, Glenn and Fontan procedures for the treatment of hypoplastic left heart syndrome.

Patients were excluded from analysis if they were enrolled after the implementation of HIPAA (April, 15, 2003), were not US residents, or died prior to discharge. Patients missing sufficient identifying information to be linked to the National Death Index were also excluded.

We considered the following center-level variables: total volume, procedure-specific surgery volume, teaching hospital status (Y/N), and hospital setting (metropolitan/non-metropolitan). Center volume was calculated annually. We ascertained teaching hospital status at the time the center entered the PCCC using publicly available records. Urbanicity was defined using United States Department of Agriculture (USDA) Rural-Urban Continuum Codes by County in 1983 and 1993,[138] which correspond to the year after the PCCC was started and approximately halfway through enrollment in the cohort. Geographical regions were characterized using the United States Census Bureau defined regions and divisions.[139] We also adjusted for case mix using the Risk Adjusted Classification for Congenital Heart Surgery system, version 1 (RACHS-1) where appropriate. RACHS-1 classifies the congenital cardiac operations into six categories based on expected early mortality rates, where risk category 1 surgeries have the lowest risk of death and risk category 6 the highest.[23,39] We defined complex procedures as those with a RACHS-1 score of 4 or higher.

We considered the following established patient-level risk factors: age and weight at the time of surgery, biological sex, presence of a chromosomal defect, race, and surgical era. Race was categorized as white, Black/African American, other or multiple races, and unknown. We dichotomized age based on current literature and the distribution of age for each procedure. The outcome was mortality, which was obtained from the

linkage to the NDI. Survival time was calculated from the date of surgery to death or December 31st, 2019.

Statistical Analysis

We examined characteristics of centers and patients overall and by procedure using means and standard deviations for continuous variables and counts and percent for categorical variables. We used medians and IQRs for skewed variables. We used box plots to examine center volume for each procedure.

We used Cox regression models to examine survival overall and for each benchmark procedure and adjusted for center-level volume and teaching hospital status. We examined total, complex and procedure-specific annual center volume. We assessed the proportional hazards assumption and if it was not met we included an interaction between the natural log of time and the risk factor.

We used mixed effect Cox regression models, also known as frailty models, to assess center-level characteristics while adjusting for the following patient-level variables: age (days or years) and weight (kg) at the time of birth, sex, presence of a chromosomal defect, race, and surgical era. We estimated hazard ratios (HRs) 90 days and 1, and 3 years after surgery.

A two-sided p-value of 0.05 was used throughout the analyses. Data management and analysis were conducted in SAS 9.4.

Results

The 44 PCCC centers analyzed were located in the Midwest, South, and West regions of the United States. The centers were predominantly teaching hospitals (53%)

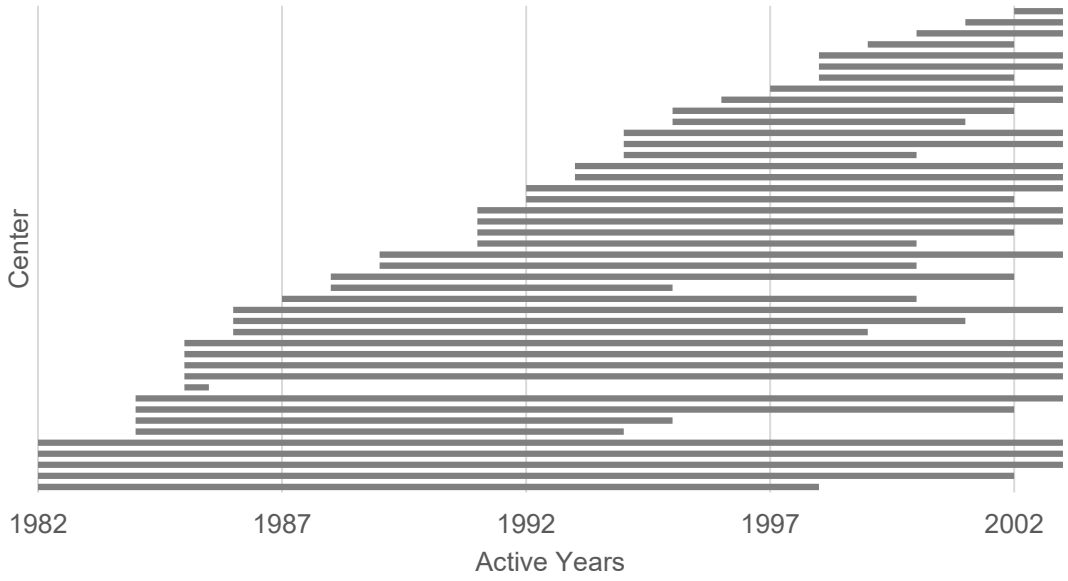
Table 5.1: PCCC center characteristics

Variables		Overall	ASO	AVSD	COA	Fontan	Glenn	Norwood	TOF	TA	VSD
N		44	38	40	43	41	41	38	44	34	43
Annual surgery volume, M (IQR)		28.5 (12.4 - 2.1)	2.9 (1.7 - 3.7)	3.3 (2.2 - 4.5)	3.1 (1.9 - 5)	3 (2 – 5.6)	3 (2 – 6.8)	1.8 (1.2 – 3)	5.3 (2.7 – 7.8)	1 (1 – 1.5)	12.2 (4.5 – 20.4)
Teaching Hospital, N (%)		30 (65.2%)	26 (68.4%)	27 (67.5%)	28 (65.1%)	27 (65.9%)	28 (68.3%)	27 (71.1%)	29 (65.9%)	26 (76.5%)	28 (65.1%)
Region, N (%)	Midwest	19 (41.3%)	14 (36.8%)	15 (37.5%)	16 (37.2%)	15 (36.6%)	15 (36.6%)	14 (36.8%)	17 (38.6%)	12 (35.3%)	16 (37.2%)
Division, N (%)	East North Central	5 (10.9%)	3 (7.9%)	3 (7.5%)	3 (7%)	3 (7.3%)	3 (7.3%)	3 (7.9%)	4 (9.1%)	2 (5.9%)	3 (7%)
	West North Central	14 (30.4%)	11 (29%)	12 (30%)	13 (30.2%)	12 (29.3%)	12 (29.3%)	11 (29%)	13 (29.6%)	10 (29.4%)	13 (30.2%)
Region, N (%)	South	21 (45.7%)	20 (52.6%)	21 (52.5%)	21 (48.8%)	21 (51.2%)	21 (51.2%)	20 (52.6%)	21 (47.7%)	17 (50%)	21 (48.8%)
Division, N (%)	South Atlantic	12 (26.1%)	12 (31.6%)	12 (30%)	12 (27.9%)	12 (29.3%)	12 (29.3%)	12 (31.6%)	12 (27.3%)	10 (29.4%)	12 (27.9%)
	East South Central	4 (8.7%)	3 (7.9%)	4 (10%)	4 (9.3%)	4 (9.8%)	4 (9.8%)	4 (10.5%)	4 (9.1%)	4 (11.8%)	4 (9.3%)
	West South Central	5 (10.9%)	5 (13.2%)	5 (12.5%)	5 (11.6%)	5 (12.2%)	5 (12.2%)	4 (10.5%)	5 (11.4%)	3 (8.8%)	5 (11.6%)
Region, N (%)	West	6 (13%)	4 (10.5%)	4 (10%)	6 (14%)	5 (12.2%)	5 (12.2%)	4 (10.5%)	6 (13.6%)	5 (14.7%)	6 (14%)
Division, N (%)	Mountain	2 (4.4%)	1 (2.6%)	1 (2.5%)	2 (4.7%)	1 (2.4%)	1 (2.4%)	1 (2.6%)	2 (4.6%)	1 (2.9%)	2 (4.7%)
	Pacific	4 (8.7%)	3 (7.9%)	3 (7.5%)	4 (9.3%)	4 (9.8%)	4 (9.8%)	3 (7.9%)	4 (9.1%)	4 (11.8%)	4 (9.3%)
Metropolitan, N (%)		27 (87.1%)	22 (88%)	23 (88.5%)	25 (86.2%)	23 (85.2%)	23 (85.2%)	21 (84%)	25 (86.2%)	18 (81.8%)	25 (86.2%)
Metropolitan, N (%)		23 (88.5%)	17 (85%)	18 (85.7%)	21 (87.5%)	19 (86.4%)	19 (86.4%)	17 (85%)	21 (87.5%)	15 (83.3%)	21 (87.5%)

ASO = arterial switch operation, AVSD = atrioventricular septal defect, COA = coarctation of the aorta, TOF = tetralogy of Fallot, TA = truncus arteriosus, VSD = ventricular septal defect; M (IQR) = median (interquartile range)

and were located in metropolitan areas (87%). Centers performed an average of 34 benchmark procedures annually. Annually, centers reported an average of 13 VSD repairs and less than one TA repair. Centers reported less than five of each benchmark procedure annually with the exception of VSD and TOF repairs. Not all centers performed all procedures. The fewest centers performed TA repairs (Table 5.1). Centers contributed between one and 21 years of surgical data (Figure 5.1).

Figure 5.1: PCCC center years contributed



This analysis included 19,123 patients who averaged 205 days old at the time of surgery. Age at the time of surgery varied based on procedure with the mean age for an ASO being 6 days while Fontan procedures were performed at the age of 3 years (1,150 days). Overall, 56% of patients were male. Sex varied by procedure with 46% of AVSD repairs and 70% of ASOs performed in males. The race of 63% of patients was unknown, 30% were white, and 6% were African American/Black. Approximately 1% of patients were Asian, Pacific Islander, Indian, other, or more than one race. 15% of patients had a

Table 5.2 PCCC baseline patient demographics

Variables		Overall	ASO	AVSD	COA	Fontan	Glenn	Norwood	TOF	TA	VSD
N		19123	1104	1596	1779	1529	1735	758	3239	214	7169
Age at surgery, days, M (IQR)		205 (80-564)	6 (4-10)	154.5 (109-202.5)	22 (9-81)	1150 (859-1609)	230 (175-339)	7 (4-11)	323 (171-671)	36 (9-86)	262 (126-801)
Age at surgery, years, M (IQR)		0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)	3 (2-4)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-2)
Weight at surgery, kg, M (IQR)		6.1 (4.1-9.8)	3.5 (3.1-3.9)	4.76 (3.9-5.6)	3.7 (3.1-4.7)	13.5 (11.7-15.8)	6.8 (5.8-8)	3.37 (3-3.7)	8 (6.1-10.8)	3.37 (2.8-4.1)	6.6 (4.6-11.4)
Length of stay, days, M (IQR)		7 (5-13)	11 (8-17)	9 (6-15)	6 (5-10)	11 (8-19)	7 (5-11)	22 (14-34)	7 (5-10)	15 (10-26)	6 (4-10)
Male, N (%)		10788 (56.4%)	772 (69.9%)	727 (45.6%)	1105 (62.1%)	945 (61.8%)	1047 (60.4%)	515 (67.9%)	1825 (56.3%)	118 (55.1%)	3734 (52.1%)
Race, N (%)	White	5702 (29.8%)	350 (31.7%)	504 (31.6%)	570 (32%)	512 (33.5%)	551 (31.8%)	294 (38.8%)	859 (26.5%)	78 (36.5%)	1984 (27.7%)
	Black	1189 (6.2%)	28 (2.5%)	113 (7.1%)	56 (3.2%)	92 (6%)	126 (7.3%)	53 (7%)	231 (7.1%)	13 (6.1%)	477 (6.7%)
	Other	202 (1.1%)	6 (0.5%)	10 (0.6%)	10 (0.6%)	16 (1.1%)	18 (1%)	4 (0.5%)	42 (1.3%)	(0%)	96 (1.3%)
	Unknown	12030 (62.9%)	720 (65.2%)	969 (60.7%)	1143 (64.3%)	909 (59.5%)	1040 (59.9%)	407 (53.7%)	2107 (65.1%)	123 (57.5%)	4612 (64.3%)
Ethnicity, N (%)	Hispanic	659 (3.5%)	44 (4%)	41 (2.6%)	47 (2.6%)	78 (5.1%)	94 (5.4%)	36 (4.8%)	65 (2%)	10 (4.7%)	244 (3.4%)
	Non-Hispanic	6306 (33%)	330 (29.9%)	555 (34.8%)	599 (33.7%)	493 (32.2%)	577 (33.3%)	309 (40.8%)	1030 (31.8%)	78 (36.5%)	2335 (32.6%)
	Unknown	12158 (63.6%)	730 (66.1%)	1000 (62.7%)	1133 (63.7%)	958 (62.7%)	1064 (61.3%)	413 (54.5%)	2144 (66.2%)	126 (58.9%)	4590 (64%)
Chromosomal defect, N (%)		2889 (15.1%)	3 (0.3%)	1293 (81%)	86 (4.8%)	29 (1.9%)	58 (3.3%)	17 (2.2%)	231 (7.1%)	11 (5.1%)	1161 (16.2%)
Era, N (%)	Early	4423 (23.1%)	134 (12.1%)	339 (21.2%)	461 (25.9%)	267 (17.5%)	150 (8.7%)	108 (14.3%)	928 (28.7%)	51 (23.8%)	1985 (27.7%)
	Middle	6310 (33%)	425 (38.5%)	537 (33.7%)	535 (30.1%)	518 (33.9%)	621 (35.8%)	230 (30.3%)	1065 (32.9%)	60 (28%)	2319 (32.4%)
	Late	8390 (43.9%)	545 (49.4%)	720 (45.1%)	783 (44%)	744 (48.7%)	964 (55.6%)	420 (55.4%)	1246 (38.5%)	103 (48.1%)	2865 (40%)

ASO = arterial switch operation, AVSD = atrioventricular septal defect, COA = coarctation of the aorta, TOF = tetralogy of Fallot, TA = truncus arteriosus, VSD = ventricular septal defect; eras defined as early (1982-1992), middle (1993-1997), and late (1998-2003); M (IQR) = median (interquartile range)

chromosomal defect ranging from less than 1% having ASO and 81% having an AVSD repair (Table 5.2).

One year after surgery, we found that procedure-specific center volume was inversely associated with mortality for Glenn procedures (HR = 0.95, p-value = 0.0381; 95% CI = 0.91, 1.00 for 1 additional procedure). After adjusting for patient level risk factors the association was attenuated and no longer statistically significant. There was no association between teaching hospital status and mortality (Table 5.3).

Table 5.3 Hazard ratios at 1 year

		Model 1		Model 2	
Procedure	**Variables**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
ASO	Volume	0.96 (0.84, 1.1)	0.5598	0.99 (0.85, 1.15)	0.8651
	Teaching hospital	0.77 (0.23, 2.52)	0.6635	0.49 (0.13, 1.83)	0.286
AVSD	Volume	0.94 (0.89, 1)	0.0634	0.96 (0.9, 1.02)	0.1967
	Teaching hospital	1.07 (0.58, 1.96)	0.8349	0.88 (0.46, 1.68)	0.6962
COA	Volume	0.95 (0.88, 1.04)	0.2455	0.98 (0.89, 1.07)	0.6017
	Teaching hospital	0.94 (0.43, 2.06)	0.8852	0.6 (0.25, 1.42)	0.243
Fontan	Volume	0.95 (0.88, 1.03)	0.2245	1.01 (0.92, 1.11)	0.8127
	Teaching hospital	1.55 (0.59, 4.05)	0.3753	0.94 (0.31, 2.92)	0.9186
Glenn	Volume	0.95 (0.91, 1)	0.0381	0.97 (0.92, 1.01)	0.1447
	Teaching hospital	1.28 (0.66, 2.51)	0.4668	0.98 (0.54, 1.8)	0.9567
Norwood	Volume	0.98 (0.93, 1.02)	0.2926	1 (0.95, 1.05)	0.9352
	Teaching hospital	1.01 (0.58, 1.73)	0.9842	0.93 (0.56, 1.56)	0.7842
TOF	Volume	1.01 (0.96, 1.06)	0.694	0.99 (0.94, 1.04)	0.64
	Teaching hospital	0.92 (0.44, 1.96)	0.8382	0.91 (0.4, 2.09)	0.8228
TA	Volume	0.59 (0.35, 1.01)	0.0541	0.56 (0.29, 1.07)	0.081
	Teaching hospital	1.49 (0.41, 5.46)	0.5483	0.99 (0.21, 4.58)	0.9868
VSD	Volume	1 (0.98, 1.01)	0.7761	0.99 (0.97, 1)	0.1523
	Teaching hospital	1.1 (0.65, 1.86)	0.7305	1.01 (0.56, 1.84)	0.9625

ASO = arterial switch operation, AVSD = atrioventricular septal defect, COA = coarctation of the aorta, TOF = tetralogy of Fallot, TA = truncus arteriosus, VSD = ventricular septal defect; adjusted for age and weight at surgery, sex, race, chromosomal abnormalities, and surgical era

Results were similar at 90 days and 3 years after surgery. At these time points, the association between procedure-specific volume and mortality was statistically significant (HR = 0.88, p-value = 0.0238, 95% CI = 0.78, 0.98 and HR = 0.96, p-value = 0.0108, 95% CI = 0.94, 0.99). Three years after surgery, procedure-specific volume was also

inversely associated with mortality for AVSD and TA repairs in center only models. The association was no longer significant after adjustment for patient-level factors (Tables 5.4 and 5.5).

Table 5.4 Hazard ratios at 90 days

		Model 1		Model 2	
Procedure	**Variables**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
ASO	Volume	0.96 (0.8, 1.14)	0.6265	0.92 (0.75, 1.13)	0.4073
	Teaching hospital	0.78 (0.16, 3.87)	0.7601	0.65 (0.1, 4.16)	0.6505
CoA	Volume	0.95 (0.85, 1.07)	0.3918	0.98 (0.86, 1.12)	0.7937
	Teaching hospital	1.34 (0.44, 4.05)	0.6039	0.72 (0.22, 2.32)	0.5821
AVSD	Volume	0.96 (0.89, 1.04)	0.3115	0.97 (0.9, 1.06)	0.5396
	Teaching hospital	1.75 (0.67, 4.57)	0.2569	1.25 (0.46, 3.37)	0.6661
Fontan	Volume	0.91 (0.76, 1.07)	0.2513	0.91 (0.75, 1.1)	0.3197
	Teaching hospital	2.22 (0.27, 18.09)	0.4551	1.58 (0.18, 13.85)	0.6786
Glenn	Volume	0.88 (0.8, 0.98)	0.0167	0.88 (0.78, 0.98)	0.0238
	Teaching hospital	2.67 (0.6, 11.9)	0.1991	1.39 (0.28, 7.03)	0.6879
Norwood	Volume	1.01 (0.95, 1.07)	0.8673	1.01 (0.95, 1.08)	0.6967
	Teaching hospital	0.8 (0.43, 1.48)	0.4809	0.87 (0.47, 1.61)	0.6541
TOF	Volume	1.01 (0.95, 1.08)	0.6579	1 (0.93, 1.06)	0.8801
	Teaching hospital	0.75 (0.31, 1.84)	0.5326	0.79 (0.31, 1.99)	0.6135
TA	Volume	0.78 (0.47, 1.31)	0.35	0.67 (0.35, 1.3)	0.2347
	Teaching hospital	2.48 (0.29, 21.22)	0.4069	1.65 (0.16, 16.94)	0.6718
VSD	Volume	1 (0.98, 1.02)	0.963	0.99 (0.97, 1.01)	0.3157
	Teaching hospital	1.03 (0.52, 2.02)	0.9411	0.96 (0.46, 2.01)	0.9213

ASO = arterial switch operation, AVSD = atrioventricular septal defect, COA = coarctation of the aorta, TOF = tetralogy of Fallot, TA = truncus arteriosus, VSD = ventricular septal defect; adjusted for age and weight at surgery, sex, race, chromosomal abnormalities, and surgical era

Table 5.5 Hazard ratios at 3 years

		Model 1		Model 2	
Procedure	**Variables**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
ASO	Volume	0.96 (0.84, 1.1)	0.5598	0.99 (0.85, 1.15)	0.8651
	Teaching hospital	0.77 (0.23, 2.52)	0.6635	0.49 (0.13, 1.83)	0.286
CoA	Volume	0.95 (0.88, 1.03)	0.2134	0.98 (0.9, 1.07)	0.5883
	Teaching hospital	0.88 (0.43, 1.81)	0.7295	0.59 (0.27, 1.31)	0.1958
AVSD	Volume	0.94 (0.89, 0.99)	0.026	0.96 (0.9, 1.01)	0.1318
	Teaching hospital	1.17 (0.69, 1.98)	0.5728	0.98 (0.54, 1.76)	0.9352
Fontan	Volume	0.96 (0.9, 1.02)	0.2117	1.01 (0.94, 1.09)	0.7298
	Teaching hospital	1.25 (0.6, 2.61)	0.5473	0.76 (0.33, 1.72)	0.5048
Glenn	Volume	0.97 (0.95, 1)	0.0386	0.96 (0.94, 0.99)	0.0108
	Teaching hospital	1.07 (0.71, 1.61)	0.7467	0.87 (0.61, 1.26)	0.4739
Norwood	Volume	0.97 (0.93, 1.01)	0.0875	0.98 (0.94, 1.03)	0.4358
	Teaching hospital	1.09 (0.72, 1.66)	0.6859	0.96 (0.64, 1.42)	0.819

TOF	Volume	1.01 (0.97, 1.05)	0.6452	0.99 (0.95, 1.03)	0.666
	Teaching hospital	0.94 (0.52, 1.7)	0.8393	0.99 (0.5, 1.95)	0.9753
TA	Volume	0.62 (0.39, 0.99)	0.047	0.62 (0.35, 1.09)	0.0973
	Teaching hospital	1.77 (0.48, 6.62)	0.3944	0.98 (0.21, 4.56)	0.9796
VSD	Volume	0.99 (0.98, 1.01)	0.4066	1.11 (0.66, 1.89)	0.6928
	Teaching hospital	1.14 (0.7, 1.86)	0.6094	0.55 (0.38, 0.79)	0.0014

ASO = arterial switch operation, AVSD = atrioventricular septal defect, COA = coarctation of the aorta, TOF = tetralogy of Fallot, TA = truncus arteriosus, VSD = ventricular septal defect; adjusted for age and weight at surgery, sex, race, chromosomal abnormalities, and surgical era

Discussion

In an examination of center characteristics associated with post discharge mortality, we found procedure-specific volume was inversely associated with higher risk of mortality following second stage HLHS (Glenn) procedure one year after surgery. After adjusting for patient level factors, this association remained significant at 90 days and 3 years after surgery. We observed no association between teaching hospital status and risk of mortality for any procedure.

Researchers have previously examined the possible association between procedure-specific volume and mortality, often using the Norwood procedure as a standard for complex CHD repair. An analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database from 2000 to 2009 found that center volume was inversely associated with mortality.[97] In this analysis, centers performed a median of 7.5 Norwood procedures (IQR 5.3–11.3).[97] which is notably higher than the annual volume of Norwood procedures observed in the PCCC. An analysis of 29 centers in the Pediatric Health Information System found a similar association.[104] Researchers found center volume was associated with improved 28-day survival in neonates.[104] Interestingly, previous research has shown that above average outcomes in one surgical procedure is not associated with above average outcomes in another procedure.[111]

In the context of previous findings, the absence of a statistically significant association between procedure-specific volume and mortality in our analyses may be the result of lower center volume. Within the PCCC, we observed an average of less than 3 procedures annually for ASO, Norwood procedure, and TA repair. These repairs represent the most complex benchmark procedures. Previous analyses have suggested that the association between volume and mortality might be strongest for complex procedures.[49,98]

Expanding short-term post-surgical outcomes beyond 30 days may have significant implications for follow-up care and inform future research on what may be causing differences in mortality rates beyond 30-days.

Strengths and Limitations

Despite the advantages of the PCCC, a number of limitations exist to the current analysis. Although the PCCC is a relatively large cohort, stratifying the analyses by procedure reduced statistical power and our ability to identify significant factors associated with post-discharge mortality. In order to work around this limitation, we focused this analysis on benchmark procedures, which, in addition to consisting of standardized surgical repairs, are relatively common CHDs. We recognize however that trends observed in common defects may not be generalizable to those with rare defects. Additionally, many patients with CHD have multiple lesions. In these instances we categorized patients based on their most complex repair, which fails to capture the possible influence of coexisting lesions on mortality. This approach has been used previously in analyses of the PCCC.[6]

In addition, procedure-specific volume was based on surgeries reported to the PCCC. Therefore it may be an underestimate of the number of procedures performed annually. Training hospital status was assessed at the time the center entered the PCCC. Most PCCC centers were training sites for pediatric residents and offered rotations to pediatric surgery, however, few were training places for pediatric cardiothoracic surgery. This distinction should be considered in future analyses. Finally, the PCCC has limited information on patient race and ethnicity, which have been identified as risk factors for mortality in previous analyses. Therefore it is difficult to adjust for and assess the impact of these factors in these analyses.

Despite these limitations, the PCCC has numerous advantages over other cohorts of CHD patients. The PCCC is sufficiently large to examine multiple benchmark procedures. Detailed information on procedure allowed identification of multiple benchmark cohorts. Additionally, the cohort includes identifying information on patients allowing linkage to the NDI and thus information on mortality more than 30 days after surgery.

Summary

We found no association between center characteristics and post-discharge mortality. Our focus on post-discharge mortality reduced the number of deaths observed, particularly for complex repairs thus reducing statistical power. However, as Pasquali et al. recognized, center characteristics do not explain the majority of variation observed in mortality following congenital heart surgery.[97] Thus, although center volume may be associated with reduced post-surgical mortality, demographic and clinical characteristics

of children undergoing congenital heart surgery remain the most informative factors for predicting mortality.

CHAPTER 6: ASSOCIATION BETWEEN SURGEON AND CENTER FACTORS AND MORTALITY FOLLOWING PEDIATRIC CARDIAC SURGERY

Introduction

The relationship between surgeon and center performance on outcomes has been previously explored within a number of surgical specialties. In 2017, the Annals of Surgery dedicated an issue of the journal to the discussion of the association between surgical volume and outcomes in a variety of specialties.[140] This issue highlighted that the study of pediatric cardiac surgery poses unique difficulties due to the low volume of procedures performed annually.[140]

Most analyses found a positive association between center and surgeon volume and survival following pediatric cardiac surgery [99,100]. Similarly, surgical experience operationalized as years since training completion, is also associated with improved survival.[101] However, surgeons with more than 35 years of experience had a 24% higher odds of major morbidity or mortality in-hospital and 30 days after surgery [101].

Assessments of the association between center and surgeon volume and mortality among children with severe CHD, including hypoplastic left heart syndrome (HLHS), are less conclusive. An analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database found higher odds of in-hospital mortality among low volume surgeons.[102] Another analysis of Norwood repairs in the Pediatric Health Information System database found an inverse but not statistically significant association between

surgeon volume and 28-day mortality among a population of neonates.[104] Results from the Pediatric Heart Network Single Ventricle Reconstruction found surgeon volume was associated with morbidity, but not 30-day mortality following Norwood procedure.[103] Finally, an analysis of data from the Congenital Heart Surgeons Society found patient-level factors were more influential than either surgeon or center volume among neonates with severe CHD including HLHS.[105]

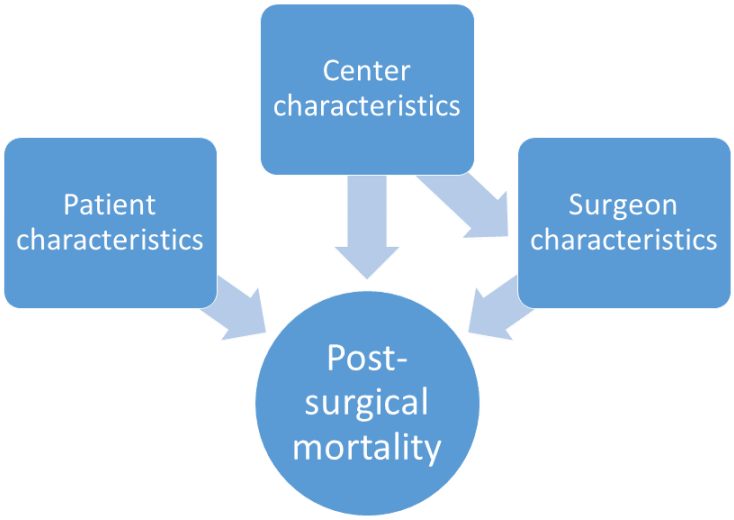
The preponderance of evidence suggests that center and surgeon characteristics may be associated with surgical outcomes for CHD (Hannan et al., 1998; Pieper et al., 2014; Preston et al., 2015); however, previous analyses have significant methodological limitations. Importantly, in an extensive review of the literature, only one analysis examined center and surgeon characteristics simultaneously while adjusting for clustering (Appendix 3 and 4). However, this analysis is only adjusted for clustering among patients.[102] Additionally, most analyses are limited to in hospital or 30 day mortality. Based on these limitations, the following analysis adds to existing literature by leveraging hierarchical models to examine center and surgeon level characteristics simultaneously over short (90 day) and medium-term (5 year) follow-up.

Methods

I assessed the relationship between surgeon and center characteristics and in-hospital, short-, and long-term survival among children who had surgery for CHD. We hypothesized that i.) mid- and late-career surgeons with the most experience characterized by procedure-specific surgical volume and years since graduation will have the lowest mortality, and ii.) surgery at high volume or training centers may attenuate differences due to surgeon-level characteristics. These findings build on the previous

chapter, which examined key center-level characteristics (Figure 6.1). Together these chapters help characterize the relationship between centers and surgeons and mortality within a complex pediatric patient population.

Figure 6.1: Relationship between surgeon and center characteristics and post-surgical mortality



The Pediatric Cardiac Care Consortium (PCCC) offered an opportunity to efficiently assess the relationship between centers and surgeons and mortality in a diverse, national population at multiple key postoperative time points. The PCCC includes medical records, including operative reports. As a result, it was possible to link patients with the surgeons who performed their surgeries. Additionally, the use of hierarchical modeling allowed us to examine center and surgeon level characteristics simultaneously.

For this analysis, we included all PCCC patients enrolled between 1982 and the implementation of HIPAA (April, 15, 2003) who were US residents, and had a benchmark repair for a CHD within the first year of life. Patients missing identifying

information were excluded from the analysis. Of 6,992 participants identified in the cohort, 1252, had an arterial switch operation (ASO), 1,662 had a atrioventricular septal defect (AVSD) repair, 1312 had a Norwood procedure, 239 had truncus arteriosus (TA) repair, and 2,527 had ventricular septal defect (VSD) repair. The ASO cohort included those with and without VSD closure. The VSD cohort included muscular and non-muscular defects. Procedures without a corresponding surgeon name were subsequently excluded from the analysis.

Data

We calculated total, and procedure-specific annual and cumulative procedure-specific volumes for all surgeons. Procedure-specific volumes were calculated using the number of surgeries observed in the PCCC. The time since graduation from medical school was calculated in years. We obtained the year of medical school graduation and medical school name from the American Medical Association (AMA) Physician Masterfile. Training information for surgeons who could not be matched to the AMA was obtained through publicly available records with the assistance of a surgeon researcher (JDS).

Center characteristics were previously described in chapter five. For each center, we calculated annual total and procedure-specific volume. Total and complex center volume were previously calculated.[123] we identified teaching hospital status (Y/N) using publicly available records at the time the center entered the PCCC.

Patient-level variables were previously abstracted from the PCCC.[137] we examined age in days or years and weight in kilograms at the time of surgery, sex, race, presence of a chromosomal defect, and surgical era. Race was categorized as

Black/African American, white, or other/unknown. Eras were defined as early (1982 to 1992), middle (1993-1997), and late (1998 to 2003) based on the distribution of surgeries by year.[137] Definitions for center and patient-level variables are consistent with the previous chapter.

Data Abstraction and Linkage

A team of three researchers (RZ, ZW, JF) abstracted the first, middle and last names of the primary and secondary surgeons listed on the identified cases. Information on the surgical report was also recorded including whether the primary surgeon was clearly identified, the names were handwritten, and when applicable, the reason a name was not available. The PCCC dataset and linked surgical reports are hosted by a HIPAA-compliant data hosting company (VM Racks, Etica Inc., CA) and are accessible remotely using a password protected secure portal. Study data were abstracted and managed using REDCap electronic data capture tools hosted at Emory University.[141,142] REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Surgeon names were cleaned and spelling errors were corrected by hard coding the names. Cleaned names were linked to the AMA Physician Masterfile using CDC LinkPlus Version 2.0.[143] After conducting the initial linkage, records with a match probability < 80% were reviewed manually. Following linkage, we searched publicly

available records of surgeons who were not successfully linked to the AMA to identify training information where possible. Prior to statistical analysis surgeon names were replaced with unique identifiers.

Statistical Analysis

We examined characteristics of centers, surgeons and patients overall and by survival status using means and standard deviations for continuous variables and counts and percent for categorical variables. Medians and IQRs were used for skewed variables.

We used hierarchical generalized linear models to examine survival at discharge, 90 days, and 1, 3, and 5 years post-surgery. Three-level models were constructed in six stages as previously described by Bell et al.[144] Relative risks were estimated using a Poisson distribution with a log link.[145,146]

Models were adjusted for the following patient-level risk factors: age at surgery (days or years), weight at surgery (kg), presence of a chromosomal defect, defect severity, and surgical era. A two-sided p-value of 0.05 was used throughout the analysis. Adjustments were not made for multiple comparisons. Descriptive and statistical analyses will be completed in SAS 9.4.

Results

A total of 152 surgeons and 42 centers were included in this analysis. Surgeons contributed a median of 3.5 benchmark procedures per year and 3.5 years to the PCCC. Centers contributed a median of 11.3 years and 13.1 benchmark procedures annually. 67% of centers were training hospitals (Table 6.1).

Table 6.1: Surgeon and center characteristics of critical benchmark cohort

Variables		Surgeons		Centers	
N		152		42	
Ivy league, N (%)		20	(13.2%)		
Career stage	Early, N (%)	76	(50%)		
	Middle, N (%)	53	(34.9%)		
	Senior, N (%)	17	(11.2%)		
	Very senior, N (%)	6	(4%)		
Years since medical school, M (IQR)		15	(11 - 21)		
Teaching hospital, N (%)				28	(66.7%)
Years contributed, M (IQR)		3.5	(1 - 8)	11.3	(7 - 14)
Annual volume	Total, M (IQR)	3.5	(1.5 - 8.6)	13.1	(3.7 - 19.7)
	ASO, M (IQR)	1	(0 - 2.5)	3	(1.5 - 4.2)
	AVSD, M (IQR)	1	(0 - 2.4)	3.6	(2.2 - 4.3)
	Norwood, M (IQR)	1	(0 - 2.3)	3.2	(1.5 - 4.7)
	TA, M (IQR)	0	(0 - 1)	1.2	(1 - 1.5)
	VSD, M (IQR)	2	(1 - 3.5)	5.2	(2 - 6.6)
Total volume	Total, M (IQR)	13.5	(2 - 64)	166.5	(50 - 233)
	ASO, M (IQR)	1	(0 - 11)	29.8	(6 - 47)
	AVSD, M (IQR)	2	(0 - 14)	39.6	(12 - 59)
	Norwood, M (IQR)	2	(0 - 10)	31.2	(5 - 49)
	TA, M (IQR)	0	(0 - 2)	5.7	(1 - 8)
	VSD, M (IQR)	6	(1 - 22)	60.2	(14 - 73)

ASO = arterial switch operation, AVSD = atrioventricular septal defect, TA = truncus arteriosus, VSD = ventricular septal defect, M (IQR) = median (interquartile range)

Of 6,992 patients included in the analysis, 1,150 (16.4%) died during follow-up. On average, patients who died following surgical repair were younger and weighed less at the time of surgery. They were less likely to have a chromosomal abnormality. More than half of patients who died had a Norwood procedure for the management of HLHS. Patients who had surgery between 1998 and 2003 were less likely to die than their earlier counterparts (Table 6.2).

Table 6.2: Patient demographics of critical benchmark cohort by survival status

Variables	Overall	Alive	Deceased
N	6992	5842	1150
Age at surgery, days, M (SD)	97 (8-177)	114 (14-186)	9 (5-43)
Weight at surgery, kg, M (SD)	4.2 (3.4-5.32)	4.415 (3.55-5.5)	3.4 (2.92-4)
Male, N (%)	3817 (54.59%)	3139 (53.73%)	678 (58.96%)

Race	Black/African American, N (%)	452 (6.46%)	343 (5.87%)	109 (9.48%)
	Asian, N (%)	25 (0.36%)	23 (0.39%)	2 (0.17%)
	Indian, N (%)	12 (0.17%)	7 (0.12%)	5 (0.43%)
	Pacific Islander, N (%)	18 (0.26%)	18 (0.31%)	(%)
	White, N (%)	2422 (34.64%)	1765 (30.21%)	657 (57.13%)
	More than one race, N (%)	1 (0.01%)	1 (0.02%)	(%)
	Other, N (%)	8 (0.11%)	6 (0.1%)	2 (0.17%)
	Unknown, N (%)	4054 (57.98%)	3679 (62.98%)	375 (32.61%)
Ethnicity	Hispanic, N (%)	261 (3.73%)	229 (3.92%)	32 (2.78%)
	Non-Hispanic, N (%)	2472 (35.35%)	1964 (33.62%)	508 (44.17%)
	Unknown, N (%)	4259 (60.91%)	3649 (62.46%)	610 (53.04%)
Chromosomal defect		2110 (30.18%)	1931 (33.05%)	179 (15.57%)
Procedure	ASO, N (%)	1252 (17.91%)	1096 (18.76%)	156 (13.57%)
	AVSD, N (%)	1662 (23.77%)	1514 (25.92%)	148 (12.87%)
	Norwood, N (%)	1312 (18.76%)	580 (9.93%)	732 (63.65%)
	TA, N (%)	239 (3.42%)	205 (3.51%)	34 (2.96%)
	VSD, N (%)	2527 (36.14%)	2447 (41.89%)	80 (6.96%)
Era	Early, N (%)	1436 (20.54%)	1123 (19.22%)	313 (27.22%)
	Middle, N (%)	2436 (34.84%)	2015 (34.49%)	421 (36.61%)
	Late, N (%)	3120 (44.62%)	2704 (46.29%)	416 (36.17%)

Eras defined as early (1982-1992), middle (1993-1997), and late (1998-2003); ASO = arterial switch operation, AVSD = atrioventricular septal defect, TA = truncus arteriosus, VSD = ventricular septal defect

First we examined associations with surgeon volume. Three years after surgery, every additional ASO and AVSD repair performed annually by a surgeon was associated with a 9 and 8% lower risk of mortality, respectively (RR = 0.91, 95% CI = 0.84-0.98; RR = 0.92, 95% CI = 0.85-0.98) Among TA repairs, we observed a 26% lower risk of mortality. However, due to the small sample size, the confidence interval was wide and not significant (95% CI = 0.41 - 1.32). No association was observed between surgeon volume and mortality among VSD repairs (Table 6.3).

Next, we examined the association between center characteristics and mortality. For those who had a Norwood procedure, every five additional surgeries performed by a center resulted in a 29% lower risk of mortality (RR= 0.71, 95% CI = 0.55-0.93). No association was observed for patients who had an ASO or AVSD, TA or VSD repairs at 3

Table 6.3: Mixed-effect generalized linear regression results at 1, 3, and 5 years for annual surgical volume

			5 Years			3 Years			1 Year		
Defect	**N**	**Variable**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
ASO	1252	Surgeon volume, 1	0.91	0.84 - 0.98	0.0153	0.91	0.84 - 0.98	0.0155	0.91	0.84 - 0.98	0.0182
		Center volume, 5	0.73	0.42 - 1.27	0.2561	0.76	0.44 - 1.31	0.3064	0.73	0.42 - 1.26	0.2491
		Teaching hospital	0.95	0.58 - 1.57	0.8491	0.92	0.57 - 1.50	0.7425	0.96	0.59 - 1.57	0.8628
AVSD	1662	Surgeon volume, 1	0.90	0.84 - 0.96	0.0022	0.92	0.85 - 0.98	0.0159	0.94	0.87 - 1.01	0.1030
		Center volume, 5	0.82	0.58 - 1.14	0.2324	0.76	0.53 - 1.09	0.1262	0.72	0.48 - 1.07	0.1015
		Teaching hospital	0.99	0.65 - 1.50	0.9536	1.12	0.70 - 1.77	0.6312	1.07	0.66 - 1.74	0.7710
Norwood	1312	Surgeon volume, 1	1.00	0.98 - 1.02	0.8561	1.00	0.98 - 1.02	0.9464	1.00	0.97 - 1.02	0.7992
		Center volume, 5	0.72	0.56 - 0.93	0.0137	0.71	0.55 - 0.93	0.0129	0.72	0.54 - 0.95	0.0214
		Teaching hospital	1.02	0.84 - 1.25	0.8246	1.03	0.84 - 1.26	0.7766	1.04	0.84 - 1.30	0.6976
TA	239	Surgeon volume, 1	0.75	0.43 - 1.31	0.3045	0.74	0.41 - 1.32	0.3032	0.69	0.36 - 1.33	0.2688
		Center volume, 5	0.47	0.04 - 5.06	0.5203	0.42	0.03 - 5.46	0.4968	0.47	0.03 - 7.36	0.5811
		Teaching hospital	1.15	0.40 - 3.28	0.7929	1.06	0.37 - 3.06	0.9093	0.96	0.32 - 2.85	0.9415
VSD	2527	Surgeon volume, 1	1.00	0.95 - 1.06	0.9351	1.00	0.95 - 1.06	0.9490	1.00	0.94 - 1.07	0.9700
		Center volume, 5	0.86	0.74 - 1.00	0.0439	0.88	0.75 - 1.02	0.0862	0.91	0.76 - 1.07	0.2479
		Teaching hospital	1.46	0.78 - 2.71	0.2249	1.28	0.68 - 2.39	0.4366	1.18	0.59 - 2.36	0.6343

ASO = arterial switch operation, AVSD = atrioventricular septal defect, TA = truncus arteriosus, VSD = ventricular septal defect; surgeon and center volume scaled to 1 and 5 procedure change, respectively; all models adjusted for age and weight at surgery, chromosomal defect, and surgical era

Table 6.4: Mixed-effect generalized linear regression results at 1, 3, and 5 years for cumulative surgical volume

			5 Years			3 Years			1 Year	
Defect	**N**	**Variable**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
ASO	1252	Surgeon volume, 1	1.00	0.98 - 1.01	0.6685	1.00	0.98 - 1.01	0.7181	1.00	0.98 - 1.01	0.6333
		Center volume, 5	0.58	0.34 - 1.01	0.0530	0.6	0.35 - 1.03	0.0631	0.59	0.34 - 1.01	0.0555
		Teaching hospital	1.00	0.61 - 1.65	0.9999	0.97	0.60 - 1.58	0.8990	1.00	0.61 - 1.65	0.9879
AVSD	1662	Surgeon volume, 1	0.99	0.98 – 1.00	0.1275	0.99	0.98 – 1.00	0.2122	0.99	0.98 – 1.00	0.1995
		Center volume, 5	0.72	0.51 - 1.02	0.0618	0.68	0.47 - 0.98	0.0391	0.68	0.46 - 1.01	0.0530
		Teaching hospital	1.00	0.65 - 1.54	0.9885	1.13	0.71 - 1.80	0.5967	1.09	0.67 - 1.77	0.7332
Norwood	1312	Surgeon volume, 1	1.00	1.00 - 1.01	0.7448	1.00	1.00 – 1.00	0.9805	1.00	1.00 - 1.01	0.7707
		Center volume, 5	0.72	0.56 - 0.92	0.0105	0.71	0.55 - 0.92	0.0113	0.70	0.53 - 0.92	0.0115
		Teaching hospital	1.02	0.84 - 1.25	0.8070	1.03	0.84 - 1.27	0.7772	1.05	0.84 - 1.30	0.6753
Truncus	239	Surgeon volume, 1	1.05	0.93 - 1.20	0.4331	1.04	0.91 - 1.19	0.5619	1.08	0.93 - 1.24	0.3098
		Center volume, 5	0.21	0.02 - 2.78	0.2254	0.21	0.01 - 3.51	0.2674	0.15	0.01 - 3.08	0.2106
		Teaching hospital	1.07	0.38 - 3.04	0.8958	0.99	0.34 - 2.85	0.9799	0.89	0.30 - 2.62	0.8318
VSD	2527	Surgeon volume, 1	0.99	0.98 – 1.00	0.1453	0.99	0.98 – 1.00	0.1084	0.99	0.97 – 1.00	0.1114
		Center volume, 5	0.89	0.78 - 1.02	0.0996	0.91	0.79 - 1.05	0.1978	0.95	0.81 - 1.11	0.4936
		Teaching hospital	1.50	0.81 - 2.79	0.1888	1.32	0.71 - 2.47	0.3694	1.22	0.60 - 2.45	0.5750

ASO = arterial switch operation, AVSD = atrioventricular septal defect, TA = truncus arteriosus, VSD = ventricular septal defect; all models adjusted for age and weight at surgery, chromosomal defect, and surgical era; all models adjusted for age and weight at surgery, chromosomal defect, and surgical era

Table 6.5: Mixed-effect generalized linear regression results at 1, 3, and 5 years for years since graduation

			5 Years			3 Years			1 Year	
Defect	**N**	**Variable**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
ASO	1252	Years since graduation, 5	1.18	1.07 - 1.29	0.0005	1.17	1.07 - 1.28	0.0008	1.17	1.06 - 1.28	0.0011
		Center volume, 5	0.53	0.33 - 0.84	0.0089	0.55	0.35 - 0.87	0.0116	0.54	0.34 - 0.85	0.0097
		Teaching hospital	1.21	0.77 - 1.9	0.4029	1.16	0.75 - 1.82	0.4911	1.20	0.76 - 1.89	0.4220
AVSD	1662	Years since graduation, 5	0.97	0.87 - 1.08	0.5797	0.96	0.85 - 1.07	0.4565	0.96	0.85 - 1.09	0.5613
		Center volume, 5	0.67	0.48 - 0.95	0.0248	0.64	0.45 - 0.92	0.0182	0.64	0.43 - 0.94	0.0236
		Teaching hospital	0.97	0.62 - 1.51	0.8882	1.07	0.66 - 1.74	0.7690	1.03	0.62 - 1.71	0.9003
Norwood	1312	Years since graduation, 5	1.02	0.97 - 1.07	0.4668	1.02	0.97 - 1.07	0.4658	1.01	0.96 - 1.07	0.6461
		Center volume, 5	0.72	0.56 - 0.91	0.0085	0.70	0.55 - 0.90	0.0071	0.70	0.54 - 0.91	0.0104
		Teaching hospital	1.03	0.84 - 1.27	0.7716	1.04	0.84 - 1.28	0.7309	1.05	0.83 - 1.31	0.6901
Truncus	239	Years since graduation, 5	0.86	0.67 - 1.09	0.2039	0.81	0.63 - 1.05	0.1081	0.85	0.65 - 1.10	0.2083
		Center volume, 5	0.47	0.04 - 5.30	0.5308	0.51	0.04 - 7.37	0.6126	0.46	0.03 - 7.64	0.5782
		Teaching hospital	0.87	0.29 - 2.66	0.8023	0.73	0.23 - 2.29	0.5786	0.72	0.22 - 2.30	0.5661
VSD	2527	Years since graduation, 5	0.91	0.78 - 1.06	0.2441	0.92	0.78 - 1.07	0.2775	0.84	0.70 - 1.01	0.0623
		Center volume, 5	0.86	0.75 - 0.98	0.0255	0.88	0.77 – 1.00	0.0576	0.91	0.78 - 1.06	0.2004
		Teaching hospital	1.44	0.77 - 2.67	0.2415	1.26	0.67 - 2.35	0.4670	1.13	0.56 - 2.28	0.7208

ASO = arterial switch operation, AVSD = atrioventricular septal defect, TA = truncus arteriosus, VSD = ventricular septal defect; all models adjusted for age and weight at surgery, chromosomal defect, and surgical era; all models adjusted for age and weight at surgery, chromosomal defect, and surgical era

years. Results 1 and 5 years after surgery were similar for both surgeons and center characteristics (Table 6.3).

Finally, we examined models which replaced annual surgeon volume with cumulative surgeon volume and years since graduation. In models with cumulative surgeon volume there was no association between surgeon volume and mortality at 1, 3 or 5 years after surgery. Examining center characteristics, five additional Norwood procedures and AVSD repairs were associated with 29% and 32% lower mortality 3 years after surgery, respectively (RR = 0.71, 95% CI = 0.55-0.92; RR = 0.68, 95% CI = 0.47 - 0.98). Results were similar at 1 and 5 years however associations within the AVSD cohort were no longer statistically significant (Table 6.4)

Examining models with years since graduation we observed a 17% higher risk of mortality for every five additional years since graduation (95% CI = 1.07-1.28) 3 years after surgery. We also observe associations between center volume and mortality. We observed 45%, 36% and 30% reductions in mortality among the ASO, ASVD and Norwood cohorts for every 5 additional procedures performed at a center annually (RR = 0.55, 95% CI = 0.35-0.87; RR = 0.64, 95% CI 0.45-0.92; RR = 0.70, 95% CI = 0.55-0.90). No significant associations were among the TA and VSD cohorts 3 years after surgery. Results were similar for all cohorts 1 and 5 years after surgery (Table 6.5).

Discussion

We observed significant associations between surgeon and center volume and mortality with center volume more consistently associated with mortality in this population. Previous research examining the association between surgeon and center volume and post-surgical mortality showed volume was generally inversely related to mortality,

particularly for complex surgical repairs.[49,97,98] The results of this analysis were consistent with these findings. Notably, statistically significant inverse associations were observed between surgeon volume and mortality for ASO and AVSD repairs, which are moderately complex repairs with RACHS-1 scores between 3 and 4.[39] There was no statistically significant association between surgeon volume and mortality for Norwood procedures; however a significant association between center volume and reduced mortality was observed. Norwood procedures have a RACHS-1 score of 6, the highest score, and are commonly used as a benchmark standard for assessing congenital heart surgery outcomes.[34,39]

One possible explanation for the trend observed for Norwood procedures lies in the postoperative period for these patients. Norwood procedures are the most costly congenital heart surgery performed with a median cost of $165,168 in 2010.[147] This cost is driven by the longest postoperative length of stay, averaging between 17.5 and 67.5 days,[120] and complex care needs of these patients.[148] One analysis of Norwood procedures, found that 35% of total hospital costs were attributed to the cardiac ICU compared to only 7% of costs attributed to the operating room.[148] Further, extracorporeal membrane oxygenation (ECMO) accounted for a further 6.9% of total hospital costs.[148] Mechanical circulatory support, such as ECMO, is used postoperatively in 2.4% of all pediatric congenital heart surgeries but 17% of Norwood procedures.[148,149] Based on these previous findings, the association between center volume observed for Norwood procedures may highlight the role of clinicians and staff beyond surgical staff in the care of these infants.

Strengths and Limitations

The PCCC provides a unique opportunity to assess center and surgeon characteristics simultaneously and for greater than 30 days; however, this analysis has several limitations. Most importantly, the center and surgeon volumes were based on center-reported procedures. Therefore these values may be underestimations of the true volume. Additionally, procedures performed by surgeons outside of the PCCC were not captured in this analysis. Therefore surgeons may appear less experienced than they were when considering volume. Less than 2% of surgical reports did not include the name of the surgeon who performed the procedure. However, there was no association between missing surgeon names and mortality so missing data appears to be random.

In addition, procedure-specific cohorts are heterogeneous. This is particularly notable among VSD closures which include at least three subtypes of defects. The TA cohort was noticeably smaller than the other cohorts. The smaller than expected sample size limited the ability to observe statistically significant trends in this cohort. Finally, although many significant changes in pediatric cardiac surgical technique occurred between 1960 and 1990, surgical technique continues to be refined, thus this sample did not reflect surgical advances since 2003. However, we believe that the driving forces behind successful centers and surgeons have remained consistent.

Summary

An investigative report by the New York Times highlighted the critical role of surgeons and surgical centers in patient outcomes.[9] The investigative reporters found unacceptably poor outcomes in surgeons with good surgical training and experience.[9] They also illustrated the need for active involvement of hospital administration.[9] This

analysis emphasizes the importance of both surgeon and center experience in improving mortality following pediatric cardiac surgery.

CHAPTER 7: MULTIPLE CONTRIBUTING CAUSES OF DEATH FOLLOWING SURGERY

Introduction

Researchers have long known that reliance on the underlying cause of death when characterizing mortality may greatly underestimate the burden of key causes of death.[150,151] Previously, researchers found that the inclusion of multiple causes of death data resulted in a 10 fold increase in the number of deaths attributed to some causes of death.[151] Despite these findings, most analyses rely solely on the underlying cause of death.

The medical portion of modern death certificates consists of two parts; the first part includes the causal chain of diseases or complications that lead to death and the second part includes additional significant causes of death[152]. Part I of the medical certification of death begins with the immediate cause of death and ends with the underlying cause of death.[152] The medical certification of death may include up to 20 causes of death. Data from death certificates are processed by NDI Plus, an automated system which assigns the underlying cause of death.[153] Underlying and multiple causes of death are then transformed into ICD codes, which are reported by the National Death Index (NDI).[153]

Based on this evidence, we proposed reexamining a previous analysis to determine if including data on contributing causes of death significantly altered results in the context of congenital heart defects (CHDs), which are rare but severe structural

defects of the heart.[3] Earlier analysis of the Pediatric Cardiac Care Consortium (PCCC) using underlying cause of death data from the NDI Plus found that patients with history of congenital heart surgery in childhood were at increased risk of death due to cardiovascular disease, including CHD, other congenital malformations, respiratory disease, infections, and neoplasms compared to the general population.[137] These findings were similar to those observed in a contemporary cohort of patients in North Carolina.[154] Previous findings provide valuable insight into the health of individuals following surgery for CHD; however, they were limited by the use of the underlying cause of death which fails to capture conditions that are on the causal pathway of death or contribute to death. In this analysis, we examined the impact of using multiple cause of death data to assess the risk of death following pediatric cardiac surgery for CHD. We utilized standardized mortality ratios to compare the risk of death in patients following pediatric surgical repair of a CHD due to major disease classes to the general U.S. population. By comparing these results with those using the underlying cause of death we obtained a more granular understanding of mortality in this population and the influence of multiple causes of death data.

Methods

The PCCC is a US-based registry established in 1982 to track outcomes after interventions for pediatric heart diseases. Between 1982 and 2011, the PCCC enrolled patients from 48 centers in 27 states. Participating institutions submitted information on patient demographics, cardiac and non-cardiac diagnoses, and genetic syndromes as well as diagnostic and interventional procedures including surgeries and their discharge status and date to the PCCC. Details about the PCCC have been published elsewhere.[10,133]

Previously, patients enrolled in a US PCCC center between 1982 and the implementation of HIPAA (April, 15, 2003), with sufficient identifying information were submitted to the National Death Index (NDI) for linkage through December 31, 2014.[135] Linkage with the NDI was recently updated through December 31, 2019.

In addition to having sufficient identifying information for linkage to the NDI, we further restricted the sample to US residents who had their first surgery at a PCCC center. Patients who did not survive until discharge and premature infants (<37 weeks) with patent ductus arteriosus ligation as their only CHD surgery were excluded. For patients who had multiple pediatric cardiac surgeries, their first surgery was used as the index surgery.

To obtain a national comparison for causes of death from 1982 to 2016, we used data from the National Vital Statistics System of the National Center for Health Statistics. These data are maintained online by the National Bureau of Economic Research (available at http://www.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html).[14] Finally, national population data were obtained from CDC Wonder (available at https://wonder.cdc.gov/).[155] National data were similarly restricted to US residents.

Statistical Analysis

From an analytic sample of 35,998, a total of 3,531 patients died before January 1, 2020. We examined characteristics of PCCC patients overall and by survival status using means and standard deviations for continuous variables and counts and percent for categorical variables. Medians and IQRs were used for skewed variables.

We tabulated the number of deceased individuals both in the PCCC and national data with any mention of death attributed to each International Classification of Diseases (ICD) chapter annually from 1982 through 2016. We also tabulated deaths due to select ICD subchapters chosen *a priori* based on previous findings. ICD-9 and ICD-10 codes used to define causes of death are shown in Table A4. Deaths are presented by age group.

We characterized contributing cause of death status as underlying (no contributing causes of death), underlying (with contributing causes of death), lone contributor, one of two contributors, or one of at least three contributors. The percentage of each contributing cause of death status was graphed by ICD chapter.

We calculated standardized mortality ratios (SMRs) for each cause of death overall as well as by age group (<1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-34 years), sex, defect severity (mild, moderate, severe two-ventricle, severe one-ventricle), and era (early, 1982-1992; mid, 1993-1997; late, 1998-2003) to assess differences in mortality between the post-surgical repair cohort and the general US population. Defect severity was previously defined in the PCCC (Table A5).[6] Standardized mortality ratios were adjusted for age group, sex, and year unless otherwise specified. We compared these results with SMRs calculated using the underlying cause of death, and illustrated the magnitudes of the differences between the results using a heatmap.

Next, we used Cox regression to examine the relationship between pediatric cardiac surgery for CHD and mortality due to major causes of death at 90 days, 1, 5, 10, and 15 years overall and for each strata of CHD severity and sex. Extended Cox regression was used if the proportional hazards assumption was not met. Next, we utilized Fine and Grey extended Cox regression, which is a sub-distribution hazard

regression, to examine the impact of competing risk of death on the hazard ratios.[156,157] Sub-distribution hazard regression allows the estimation of effect size of covariates in a model while adjusting for the competing risk of death due to other causes.[156,157] We adjusted for the following patient-level variables: sex, age, year of first surgery, year of surgery, presence of a chromosomal defect, and race (where available; categorized as black, white or other).

National multiple causes of death data were tabulated in Python 3.7 with the support of the Minnesota Supercomputing Institute. Data management, descriptive statistics, and analyses were completed in SAS 9.4. A two-sided p-value of 0.05 was used throughout the analysis.

Results

We analyzed a cohort of 35,998 patients in the PCCC that met inclusion criteria. Overall, 48.0% were female. 37.7% of patients had mild defects, 41% of patients had moderate defects, 14% had severe two-ventricle defects, and 7.4% had severe one-ventricular defects. 13.5% of these individuals had a known chromosomal defect. The median age at the time of surgery was 0.8 years with a midspread of 0.19 to 3.8 years (Table 7.1).

Table 7.1 Characteristics of PCCC patients by survival status

Characteristic		Overall	Alive	Deceased
N		35998	32467	3531
Age at surgery, years (IQR)		0.8 (0.19, 3.8)	0.91 (0.23, 3.98)	0.28 (0.03, 1.26)
Male		18713 (52%)	16648 (51.3%)	2065 (58.5%)
Chromosomal defect		4866 (13.5%)	4152 (12.8%)	714 (20.2%)
Defect severity	Mild	12497 (37.7%)	11964 (39.9%)	533 (16.7%)
	Moderate	13590 (41%)	12538 (41.8%)	1052 (32.9%)
	Severe 2V	4658 (14%)	3917 (13.1%)	741 (23.2%)
	Severe 1V	2445 (7.4%)	1574 (5.3%)	871 (27.2%)
Era	Early	10345 (28.7%)	8912 (27.5%)	1433 (40.6%)
	Mid	11933 (33.2%)	10842 (33.4%)	1091 (30.9%)
	Late	13720 (38.1%)	12713 (39.2%)	1007 (28.5%)

Eras defined as early (1982-1992), middle (1993-1997), and late (1998-2003)

Within our sample, 3,531 patients passed away during follow up. Compared to those who died during follow up, surviving patients had surgery later (0.91 years vs. 0.28 years) as well as were more likely to be female (48.7% vs. 41.5%) (Table 7.1). Additional characterization of this cohort can be found in previous publications.[6,137]

We examined the prevalence of contributing causes of death by age group. Overall, congenital malformation was the most prevalent cause of death present on 69% of death certificates followed by circulatory diseases (53%) and injury (21%), which includes surgical complications. Among the subchapters examined, congenital heart disease (66%), arrhythmia (17%), and sudden cardiac death (17%) were the most common. Congenital malformations were listed as a contributing cause of death on 83% of birth certificates when the death occurred before the age of 10 dropping to 55% and 36% for those who died between the ages of 10 and 19 and over the age of 19 (Table 7.2).

Figure 7.1: Frequency of ICD chapter mentions by contributing status

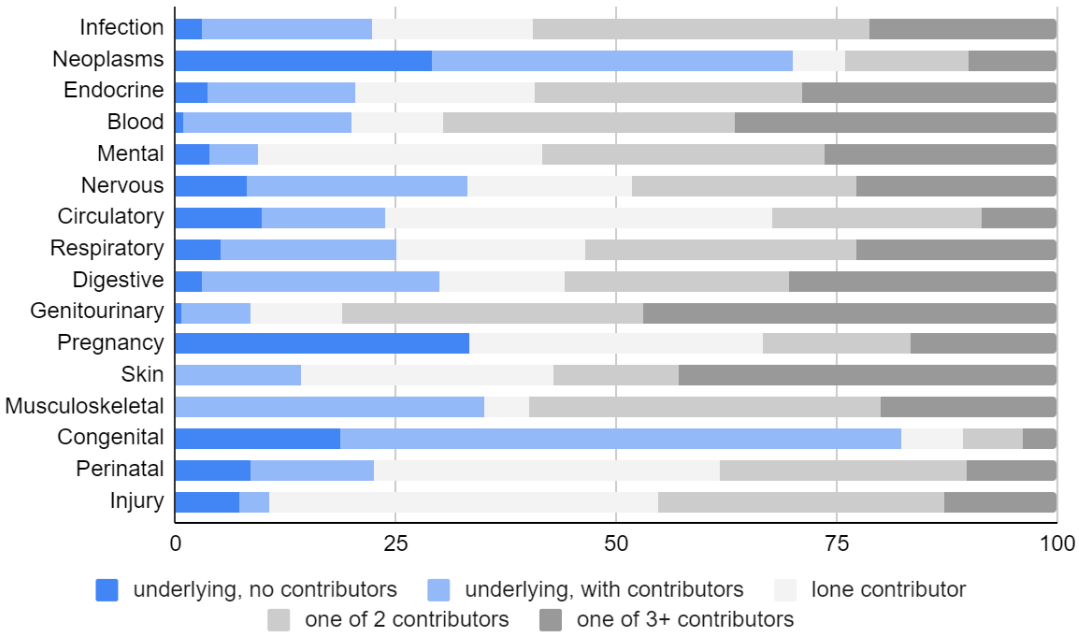


Table 7.2: Prevalence of contributing causes of death by age category

International Classification of Diseases Chapter	Overall	Age Group < 10 years	10 – 19 years	> 19 years
Infectious and Parasitic Diseases	373 (10.6%)	239 (10.6%)	63 (11%)	71 (10%)
Neoplasms	115 (3.3%)	38 (1.7%)	36 (6.3%)	41 (5.8%)
Endocrine, nutritional and metabolic disease of immunity disorders	180 (5.1%)	101 (4.5%)	27 (4.7%)	52 (7.3%)
Diseases of blood and blood-forming organs	121 (3.4%)	66 (2.9%)	29 (5.1%)	26 (3.7%)
Mental Disorders	68 (1.9%)	3 (0.1%)	9 (1.6%)	56 (7.9%)
Diseases of the nervous system and sense organs	235 (6.7%)	117 (5.2%)	62 (10.8%)	56 (7.9%)
Diseases of the circulatory system	1858 (52.6%)	1156 (51.4%)	328 (57.2%)	374 (52.8%)
Diseases of the respiratory system	518 (14.7%)	281 (12.5%)	105 (18.3%)	132 (18.6%)
Diseases of the digestive system	211 (6%)	125 (5.6%)	36 (6.3%)	50 (7.1%)
Diseases of the genitourinary system	165 (4.7%)	72 (3.2%)	40 (7%)	53 (7.5%)
Complications of pregnancy, childbirth and puerperium	8 (0.2%)	(0%)	1 (0.2%)	7 (1%)
Diseases of the skin and subcutaneous tissue	9 (0.3%)	2 (0.1%)	2 (0.4%)	5 (0.7%)
Disease of the musculoskeletal system and connective tissue	24 (0.7%)	4 (0.2%)	5 (0.9%)	15 (2.1%)
Congenital malformation, deformations, and chromosomal abnormalities	2436 (69%)	1865 (82.9%)	316 (55.2%)	255 (36%)
Certain conditions originating in the perinatal period	107 (3%)	100 (4.5%)	6 (1.1%)	1 (0.1%)
External causes of injury and poisoning	745 (21.1%)	414 (18.4%)	129 (22.5%)	202 (28.5%)

We examined where on the death certificate causes of death were mentioned and found that neoplasms (70%) and congenital malformations (82.3%) were overwhelmingly listed as the underlying cause of death when present on a death certificate. Diseases of the circulatory, respiratory, genitourinary, and digestive systems as well as infection were most frequently listed as contributing causes of death (Figure 7.1).

Finally, we compared SMRs calculated using multiple causes of death with previous results calculated using underlying cause of death. We found causes of death fell into three primary categories: SMR with multiple causes of death was higher, SMRs were similar, and SMR with underlying cause of death was higher (Table 7.3, Figure 7.2).

Figure 7.2: Ratio between SMRs with and without Multiple Causes of Death

	Injury	Perinatal	Infection	Endocrine	Genitourinary	Circulatory	Blood	Digestive	Neoplasms	Musculoskeletal	Respiratory	Congenital	Skin	Pregnancy	Nervous	Mental
Overall	9.7*	2.9*	2.0*	1.7*	1.7	1.6*	1.5	1.4	1.1	1.1	1.0	1.0	0.9	0.8	0.7*	0.6
<1 year	11.0*	3.0*	3.5*	2.2*	2.0	2.1*	1.4	1.5	3.0	-	1.5	1.0	-	NA	0.5	-
1–4 years	7.6*	1.2	2.4*	1.5	5.7*	1.6*	1.4	1.3	1.3	-	1.1	0.9	-	NA	0.8	0.4
5–9 years	3.5*	1.0	2.9	3.4	2.1	0.9	3.9	0.9	1.1	0.7	1.1	0.9	-	NA	0.8	-
10–14 years	6.6*	-	0.8	2.0	1.3	1.0	1.8	0.8	0.9	0.8	1.2	1.0	-	0.6	1.1	0.6
15–19 years	10.3*	-	1.0	1.9	1.7	1.1	1.6	1.4	1.5	0.9	1.4	1.0	-	-	0.6	-
20–24 years	18.7*	-	1.2	1.3	0.8	1.1	1.0	1.0	0.9	1.1	0.8	1.0	0.2	0.6	0.8	0.9
25–34 years	-	-	3.3	0.8	1.1	0.9	1.0	2.1	0.8	-	0.7	1.0	0.5	1.3	1.3	0.5
Females	9.9*	2.4*	1.8*	1.6	1.6	1.5*	1.4	1.3	1.2	0.7	1.1	1.0	0.6	NA	0.7	-
Males	9.7*	3.4*	2.1*	1.9*	2.0	1.6*	1.6	1.4	1.1	1.5	1.0	1.0	-	NA	0.7	0.4
Mild	5.8*	1.6	1.4	1.3	4.5	1.1	1.1	1.1	0.9	1.5	0.9	1.1	-	0.6	0.7	0.3
Moderate	9.8*	2.2	1.3	0.8	0.9	0.9	1.0	0.8	0.8	0.5	0.7	1.0	0.5	-	0.7	0.4
Severe 2V	10.9*	7.8*	2.4*	2.4	4.1	1.7*	1.4	1.4	1.2	0.7	1.0	1.0	0.2	-	0.5	0.3
Severe 1V	22.9*	4.2*	2.5*	10.4*	1.8	1.8*	-	1.3	1.8	-	2.0*	0.9	-	1.2	0.6	-
Early	4.3*	3.3*	2.6*	2.1	0.7	1.3*	1.6	1.1	1.2	1.7	0.8	0.9	-	0.0	0.8	0.8
Mid	8.1*	2.3	2.4*	1.2	1.5	1.2	0.8	0.9	0.9	0.4	1.2	0.9	-	-	0.5*	-
Late	-	3.0*	1.3	1.0	2.8	1.0	1.6	1.1	0.8	0.7	1.1	1.0	-	0.5	0.6	0.5

Ratio calculated as SMR_{MCOD}/SMR_{UCOD}; values > 1 in blue, values < 1 in grey; * denotes statistically significant difference between SMRs; SMRs calculated for women only for pregnancy; NA = not applicable; - indicates insufficient information to calculate ratio; eras defined as early (1982-1992),middle (1993-1997), and late (1998-2003)

We observed higher SMRs calculated with the underlying cause of death for injury and infection as well as several disease chapters. The inclusion of multiple causes of death resulted in the greatest magnitude of change for injury, which includes surgical complication, where we observed a 9.72 fold increase in mentions of injury (SMR 3.11, 95% CI: 2.87, 3.34 vs. SMR 0.32, 95% CI: 0.24, 0.39). We observed a two fold increase in mortality attributed to infection (SMR 15.03, 95% CI: 13.42, 16.64 vs SMR 7.51, 95% CI: 5.81, 9.21). We observed fold increases between 1.50 and 1.73 for diseases of the blood, circulatory, genitourinary, and endocrine diseases (Table 7.3, Figure 7.2).

We found that the inclusion of multiple causes of death data resulted in 0.98 to 1.13 fold change indicating little impact on SMRs for neoplasms (SMR 3.25, 95% CI: 2.58, 3.91 vs. SMR 2.88, 95% CI: 2.23, 3.53), congenital defects (SMR 60.81, 95% CI: 58.34, 63.28 vs. SMR 62.13, 95% CI: 59.36, 64.9), and respiratory disease (SMR 12.13, 95% CI: 11.02, 13.24 vs. SMR 11.57, 95% CI: 9.63, 13.51) (Table 7.3, Figure 7.2).

The inclusion of multiple causes of death resulted in 0.29 fold lower SMR for diseases of the nervous system (SMR 7.1, 95% CI: 6.14, 8.05 vs. SMR 10.02, 95% CI: 8.34, 11.71). Modest reductions were also observed in diseases of the skin (SMR 7.46, 95% CI: 1.93, 12.98 vs. SMR 8.15, 95% CI: 0, 19.45) and associated with pregnancy (SMR 1.65, 95% CI: 0.03, 3.26 vs. SMR 2.14, 95% CI: 0, 4.55); however, there were few observed events in the cohort and no statistical significant difference was observed between the cohort and the national population for these outcomes (Table 7.3, Figure 7.2).

Table 7.3: Standardized mortality ratios calculated with underlying and multiple cause of death data by ICD chapter

Cause of Death		Underlying Cause			Multiple Causes		
Infections		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		7.51	(5.81, 9.21)	<.0001	15.03	(13.42, 16.64)	<.0001
Age group	<1 year	7.93	(4.27, 11.59)	0.0002	27.37	(22.37, 32.37)	<.0001
	1–4 years	12.43	(7.24, 17.63)	<.0001	30.2	(24.39, 36)	<.0001
	5–9 years	3.52	(0, 7.51)	0.2149	10.1	(5.67, 14.52)	<.0001
	10–14 years	16.03	(6.56, 25.5)	0.0019	12.8	(7.78, 17.81)	<.0001
	15–19 years	13.33	(5.45, 21.2)	0.0022	13.12	(8.65, 17.6)	<.0001
	20–24 years	6.63	(2.04, 11.23)	0.0163	7.99	(4.86, 11.12)	<.0001
	25–34 years	0.84	(0, 2.01)	0.7882	2.73	(1.3, 4.16)	0.0178
Sex	Females	8.15	(5.41, 10.89)	<.0001	14.98	(12.54, 17.43)	<.0001
	Males	7.05	(4.89, 9.2)	<.0001	15.07	(12.94, 17.2)	<.0001
Defect severity	Mild	4.55	(2.25, 6.85)	0.0025	6.18	(4.41, 7.95)	<.0001
	Moderate	7.52	(4.74, 10.31)	<.0001	9.48	(7.67, 11.3)	<.0001
	Severe 2V	8.43	(3.66, 13.2)	0.0023	19.94	(15.23, 24.64)	<.0001
	Severe 1V	24.83	(12.27, 37.4)	0.0002	60.93	(48.05, 73.8)	<.0001
Era	Early	5.82	(2.87, 8.76)	0.0013	15.27	(11.84, 18.71)	<.0001
	Mid	7.17	(3.76, 10.58)	0.0004	16.97	(13.46, 20.47)	<.0001
	Late	15.62	(10.29, 20.95)	<.0001	19.53	(15.96, 23.11)	<.0001
Neoplasms		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		2.88	(2.23, 3.53)	<.0001	3.25	(2.58, 3.91)	<.0001
Age group	<1 year	2.12	(0, 6.27)	0.5976	6.35	(0.13, 12.57)	0.092
	1–4 years	3.31	(1.26, 5.35)	0.0274	4.34	(2.07, 6.62)	0.004
	5–9 years	4.16	(2.18, 6.14)	0.0017	4.67	(2.63, 6.72)	0.0004
	10–14 years	2.81	(1.15, 4.46)	0.0328	2.66	(1.09, 4.24)	0.0383
	15–19 years	2.89	(1.32, 4.47)	0.0183	4.24	(2.38, 6.1)	0.0006
	20–24 years	2.43	(0.92, 3.94)	0.0626	2.3	(0.87, 3.72)	0.0743
	25–34 years	2.24	(1.07, 3.41)	0.0384	1.79	(0.78, 2.81)	0.1257
Sex	Females	2.82	(1.86, 3.78)	0.0002	3.4	(2.37, 4.42)	<.0001
	Males	2.93	(2.06, 3.81)	<.0001	3.13	(2.25, 4)	<.0001
Defect severity	Mild	2.41	(1.45, 3.37)	0.0042	2.18	(1.29, 3.07)	0.0095
	Moderate	3.1	(2.01, 4.19)	0.0002	2.41	(1.65, 3.18)	0.0003
	Severe 2V	3.81	(1.56, 6.06)	0.0144	4.42	(2.32, 6.53)	0.0014
	Severe 1V	2.65	(0, 5.65)	0.2806	4.88	(1.26, 8.49)	0.0354
Era	Early	2.98	(1.47, 4.49)	0.0101	3.55	(1.99, 5.11)	0.0013
	Mid	3.61	(1.99, 5.23)	0.0016	3.22	(1.81, 4.63)	0.002

	Late	4.03	(2.39, 5.68)	0.0003	3.15	(1.86, 4.44)	0.0011
Blood		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		9.42	(5.73, 13.11)	<.0001	14.12	(11.48, 16.76)	<.0001
Age group	<1 year	20.67	(4.13, 37.21)	0.0198	28.13	(18.53, 37.73)	<.0001
	1–4 years	13.5	(2.7, 24.29)	0.0233	19.24	(11.2, 27.28)	<.0001
	5–9 years	3.37	(0, 9.99)	0.4817	13.26	(5.43, 21.1)	0.0022
	10–14 years	6.45	(0, 15.38)	0.2321	11.55	(4.39, 18.7)	0.0039
	15–19 years	9.53	(0.19, 18.88)	0.0734	15.06	(7.9, 22.22)	0.0001
	20–24 years	9.68	(0.19, 19.17)	0.0729	9.6	(3.93, 15.28)	0.003
	25–34 years	4.17	(0, 9.94)	0.2825	3.99	(0.8, 7.18)	0.0664
Sex	Females	11.12	(5.07, 17.16)	0.001	15.88	(11.65, 20.12)	<.0001
	Males	8.08	(3.51, 12.65)	0.0024	12.75	(9.41, 16.09)	<.0001
Defect severity	Mild	7.47	(1.94, 13)	0.0219	8.5	(5.02, 11.97)	<.0001
	Moderate	8.95	(3.1, 14.79)	0.0077	8.95	(5.85, 12.05)	<.0001
	Severe 2V	20.33	(5.27, 35.39)	0.0119	28.97	(19.09, 38.86)	<.0001
	Severe 1V	0	(0, 0)	0	34.23	(17.46, 51)	0.0001
Era	Early	5.83	(0, 12.42)	0.1514	9.34	(4.61, 14.07)	0.0005
	Mid	14.29	(4.39, 24.19)	0.0085	10.89	(5.99, 15.79)	<.0001
	Late	14.98	(5.7, 24.27)	0.0032	23.8	(17.2, 30.4)	<.0001
Endocrine		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		4.75	(3.28, 6.23)	<.0001	8.24	(6.92, 9.56)	<.0001
Age group	<1 year	9.74	(3.7, 15.78)	0.0045	21.28	(15.99, 26.58)	<.0001
	1–4 years	11.91	(4.87, 18.94)	0.0024	17.7	(11.66, 23.73)	<.0001
	5–9 years	1.48	(0, 4.39)	0.7445	5.05	(1.01, 9.09)	0.0495
	10–14 years	3.54	(0, 7.55)	0.2138	7.05	(2.68, 11.42)	0.0067
	15–19 years	3.43	(0.07, 6.79)	0.1566	6.6	(3.14, 10.05)	0.0015
	20–24 years	2.01	(0, 4.27)	0.3853	2.67	(0.82, 4.51)	0.0772
	25–34 years	3.51	(1.08, 5.93)	0.0432	2.87	(1.46, 4.28)	0.0092
Sex	Females	5.68	(3.25, 8.1)	0.0002	9	(6.89, 11.1)	<.0001
	Males	4.03	(2.22, 5.84)	0.0011	7.67	(5.98, 9.36)	<.0001
Defect severity	Mild	2.97	(1.03, 4.91)	0.0467	3.9	(2.37, 5.43)	0.0002
	Moderate	5.7	(3.07, 8.33)	0.0005	4.36	(3.07, 5.65)	<.0001
	Severe 2V	4.83	(0.6, 9.07)	0.0761	11.64	(7.67, 15.62)	<.0001
	Severe 1V	2.37	(0, 7.01)	0.5635	24.6	(15.32, 33.88)	<.0001
Era	Early	7.9	(3.23, 12.57)	0.0038	16.96	(12.35, 21.58)	<.0001
	Mid	9.55	(4.72, 14.38)	0.0005	11.17	(7.75, 14.59)	<.0001
	Late	5.99	(2.45, 9.53)	0.0057	6.08	(3.83, 8.33)	<.0001
Mental		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**

Overall		2.65	(0.69, 4.61)	0.0996	1.56	(1.07, 2.06)	0.0266
Age group	<1 year	0	(0, 0)	0	0	(0, 0)	0
	1–4 years	12.99	(0, 38.44)	0.356	5.75	(0, 13.71)	0.2427
	5–9 years	0	(0, 0)	0	2.45	(0, 7.25)	0.5539
	10–14 years	7.9	(0, 23.38)	0.3824	4.78	(0, 10.19)	0.1707
	15–19 years	0	(0, 0)	0	1.46	(0.18, 2.74)	0.4801
	20–24 years	1.37	(0, 4.06)	0.7868	1.17	(0.41, 1.93)	0.6625
	25–34 years	3.21	(0.06, 6.36)	0.1683	1.54	(0.83, 2.25)	0.1366
Sex	Females	0	(0, 0)	0	1.59	(0.65, 2.53)	0.2189
	Males	4.16	(1.08, 7.25)	0.0444	1.55	(0.97, 2.14)	0.0651
Defect severity	Mild	2.9	(0, 6.17)	0.2568	0.86	(0.26, 1.45)	0.6434
	Moderate	3.03	(0, 6.46)	0.246	1.27	(0.65, 1.89)	0.3934
	Severe 2V	4.48	(0, 13.25)	0.4374	1.12	(0, 2.4)	0.8482
	Severe 1V	0	(0, 0)	0	1.16	(0, 3.43)	0.8914
Era	Early	3.18	(0, 9.41)	0.493	2.7	(0.33, 5.08)	0.1587
	Mid	0	(0, 0)	0	0.78	(0, 1.87)	0.696
	Late	3.31	(0, 9.8)	0.4852	1.62	(0.32, 2.92)	0.3481
Nervous		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		10.02	(8.34, 11.71)	<.0001	7.1	(6.14, 8.05)	<.0001
Age group	<1 year	18.72	(12.02, 25.41)	<.0001	10.12	(6.61, 13.63)	<.0001
	1–4 years	15.45	(10.4, 20.49)	<.0001	11.76	(8.81, 14.72)	<.0001
	5–9 years	7.96	(3.79, 12.13)	0.0011	6.44	(3.86, 9.01)	<.0001
	10–14 years	5.46	(2.23, 8.68)	0.0067	6.14	(3.73, 8.54)	<.0001
	15–19 years	11.04	(6.95, 15.13)	<.0001	6.54	(4.31, 8.78)	<.0001
	20–24 years	6.54	(3.11, 9.97)	0.0015	5.3	(3.14, 7.47)	<.0001
	25–34 years	2.53	(0, 5.4)	0.2946	3.35	(1.65, 5.04)	0.0066
Sex	Females	9.29	(6.72, 11.87)	<.0001	6.91	(5.42, 8.41)	<.0001
	Males	10.5	(8.28, 12.72)	<.0001	7.22	(5.98, 8.45)	<.0001
Defect severity	Mild	6.07	(3.82, 8.32)	<.0001	4.43	(3.15, 5.71)	<.0001
	Moderate	7.84	(4.83, 10.85)	<.0001	5.58	(4.28, 6.87)	<.0001
	Severe 2V	16.76	(9.41, 24.1)	<.0001	8.33	(5.57, 11.09)	<.0001
	Severe 1V	40.03	(22.03, 58.04)	<.0001	22.94	(15.74, 30.14)	<.0001
Era	Early	9.49	(6.04, 12.95)	<.0001	7.67	(5.57, 9.78)	<.0001
	Mid	14.63	(10.04, 19.22)	<.0001	7.72	(5.64, 9.8)	<.0001
	Late	12.92	(8.37, 17.46)	<.0001	7.49	(5.53, 9.46)	<.0001
Circulatory		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		18.89	(17.02, 20.76)	<.0001	29.42	(28.02, 30.82)	<.0001
Age group	<1 year	26.52	(20.52, 32.53)	<.0001	54.99	(50.54, 59.43)	<.0001

	1–4 years	42.66	(32.94, 52.38)	<.0001	66.62	(60.45, 72.79)	<.0001
	5–9 years	30.48	(20.24, 40.73)	<.0001	28.65	(23.55, 33.76)	<.0001
	10–14 years	24.88	(16.97, 32.79)	<.0001	25.95	(21.42, 30.48)	<.0001
	15–19 years	21.36	(16, 26.72)	<.0001	22.72	(19.35, 26.1)	<.0001
	20–24 years	12.96	(9.25, 16.66)	<.0001	13.65	(11.21, 16.09)	<.0001
	25–34 years	8.93	(6.72, 11.13)	<.0001	8.35	(6.88, 9.82)	<.0001
Sex	Females	21.41	(18.18, 24.65)	<.0001	32.7	(30.33, 35.06)	<.0001
	Males	17.36	(15.09, 19.64)	<.0001	27.34	(25.61, 29.06)	<.0001
Defect severity	Mild	8.29	(6.21, 10.36)	<.0001	9.09	(7.76, 10.43)	<.0001
	Moderate	18.22	(15.22, 21.21)	<.0001	16.88	(15.45, 18.31)	<.0001
	Severe 2V	23.88	(17.79, 29.97)	<.0001	40.79	(36.68, 44.89)	<.0001
	Severe 1V	63.99	(48.19, 79.79)	<.0001	116.8	(105.7, 127.9)	<.0001
Era	Early	33.72	(27.55, 39.88)	<.0001	45.22	(41.43, 49.01)	<.0001
	Mid	27.66	(22.32, 33)	<.0001	34.5	(31.24, 37.76)	<.0001
	Late	29.79	(24.29, 35.28)	<.0001	31.24	(28.39, 34.1)	<.0001
Respiratory		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		11.57	(9.63, 13.51)	<.0001	12.13	(11.02, 13.24)	<.0001
Age group	<1 year	11.67	(7.75, 15.59)	<.0001	17.56	(14.36, 20.75)	<.0001
	1–4 years	19.9	(13.73, 26.07)	<.0001	21.36	(17.47, 25.25)	<.0001
	5–9 years	12.79	(6.09, 19.49)	0.0006	13.55	(9.76, 17.35)	<.0001
	10–14 years	8.47	(3.46, 13.48)	0.0034	10.46	(7.33, 13.58)	<.0001
	15–19 years	6.73	(2.33, 11.12)	0.0107	9.7	(7.07, 12.34)	<.0001
	20–24 years	10.53	(5.2, 15.86)	0.0005	7.98	(5.67, 10.29)	<.0001
	25–34 years	7.96	(3.79, 12.12)	0.0011	5.48	(3.76, 7.21)	<.0001
Sex	Females	12.1	(9.01, 15.18)	<.0001	13.31	(11.51, 15.11)	<.0001
	Males	11.2	(8.72, 13.69)	<.0001	11.29	(9.9, 12.69)	<.0001
Defect severity	Mild	8.7	(5.73, 11.67)	<.0001	8.24	(6.67, 9.81)	<.0001
	Moderate	11.22	(8.11, 14.33)	<.0001	8.08	(6.75, 9.41)	<.0001
	Severe 2V	16.73	(10.84, 22.62)	<.0001	16.23	(12.95, 19.51)	<.0001
	Severe 1V	17.55	(8.36, 26.74)	0.0004	35.65	(28.07, 43.23)	<.0001
Era	Early	14.91	(10.34, 19.47)	<.0001	12.16	(9.65, 14.67)	<.0001
	Mid	10.98	(7.11, 14.84)	<.0001	12.96	(10.53, 15.39)	<.0001
	Late	14.28	(10.06, 18.51)	<.0001	15.36	(12.99, 17.72)	<.0001
Digestive		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		9.76	(7.33, 12.19)	<.0001	13.2	(11.33, 15.08)	<.0001
Age group	<1 year	11.49	(5.86, 17.11)	0.0003	17.33	(12.95, 21.72)	<.0001
	1–4 years	20.92	(10.98, 30.87)	<.0001	26.93	(19.54, 34.32)	<.0001
	5–9 years	15.02	(3, 27.04)	0.0222	13.97	(6.65, 21.29)	0.0005

	10–14 years	16.32	(4.23, 28.41)	0.013	13.37	(6.37, 20.37)	0.0005
	15–19 years	9.33	(1.15, 17.51)	0.0459	13.38	(7.37, 19.4)	<.0001
	20–24 years	9.5	(2.46, 16.53)	0.0179	9.17	(4.68, 13.67)	0.0004
	25–34 years	1.95	(0.04, 3.87)	0.329	4.19	(2.14, 6.24)	0.0023
Sex	Females	11.41	(7.26, 15.56)	<.0001	14.44	(11.37, 17.51)	<.0001
	Males	8.66	(5.7, 11.61)	<.0001	12.35	(9.99, 14.71)	<.0001
Defect severity	Mild	6.57	(3.13, 10.02)	0.0015	7.37	(4.93, 9.82)	<.0001
	Moderate	8.82	(5.05, 12.59)	<.0001	7.04	(5.26, 8.82)	<.0001
	Severe 2V	9.02	(2.77, 15.27)	0.0119	12.48	(8.16, 16.8)	<.0001
	Severe 1V	39.56	(19.54, 59.58)	0.0002	51.18	(37.4, 64.96)	<.0001
Era	Early	17.2	(9.26, 25.15)	<.0001	18.16	(13.17, 23.14)	<.0001
	Mid	12.79	(6.32, 19.26)	0.0004	11.33	(7.73, 14.93)	<.0001
	Late	12.46	(7, 17.92)	<.0001	13.81	(10.31, 17.3)	<.0001
Skin		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		8.15	(0, 19.45)	0.2147	7.46	(1.93, 12.98)	0.022
Age group	<1 year	0	(0, 0)	0	17.74	(0, 52.52)	0.3454
	1–4 years	0	(0, 0)	0	0	(0, 0)	0
	5–9 years	0	(0, 0)	0	22.62	(0, 66.95)	0.3392
	10–14 years	0	(0, 0)	0	12.91	(0, 38.22)	0.3562
	15–19 years	0	(0, 0)	0	8.39	(0, 24.85)	0.3784
	20–24 years	19.84	(0, 58.72)	0.3423	4.92	(0, 14.55)	0.4257
	25–34 years	11.5	(0, 34.02)	0.3612	5.33	(0, 12.71)	0.2506
Sex	Females	15.12	(0, 36.09)	0.1866	8.67	(0.17, 17.17)	0.0768
	Males	0	(0, 0)	0	6.28	(0, 13.39)	0.1453
Defect severity	Mild	0	(0, 0)	0	5.43	(0, 12.97)	0.2485
	Moderate	11.11	(0, 32.89)	0.3628	5.75	(0, 12.27)	0.1524
	Severe 2V	40.08	(0, 118.6)	0.3295	8.35	(0, 24.71)	0.3787
	Severe 1V	0	(0, 0)	0	23.11	(0, 68.41)	0.3387
Era	Early	0	(0, 0)	0	0	(0, 0)	0
	Mid	0	(0, 0)	0	18.7	(0, 39.87)	0.1011
	Late	0	(0, 0)	0	4.9	(0, 14.5)	0.4261
Musculoskeletal		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		4.85	(1.26, 8.43)	0.0358	5.55	(2.91, 8.19)	0.0007
Age group	<1 year	0	(0, 0)	0	0	(0, 0)	0
	1–4 years	0	(0, 0)	0	15.67	(0, 37.39)	0.1855
	5–9 years	15.38	(0, 45.53)	0.3498	11.17	(0, 26.66)	0.1979
	10–14 years	5.51	(0, 16.32)	0.413	4.53	(0, 10.81)	0.2705
	15–19 years	3.43	(0, 10.15)	0.4787	3.2	(0, 7.64)	0.3308

	20–24 years	10.5	(0.21, 20.78)	0.0704	11.58	(3.55, 19.6)	0.0098
	25–34 years	0	(0, 0)	0	1.19	(0, 3.53)	0.871
Sex	Females	4.26	(0.09, 8.43)	0.126	4.26	(0.09, 8.43)	0.126
	Males	5.94	(0, 12.66)	0.1497	5.94	(0, 12.66)	0.1497
Defect severity	Mild	1.62	(0, 4.79)	0.702	2.43	(0, 5.18)	0.3081
	Moderate	3.85	(0, 9.18)	0.2952	2.11	(0, 4.5)	0.3623
	Severe 2V	15.5	(0, 36.99)	0.1858	11.29	(0.23, 22.35)	0.0683
	Severe 1V	0	(0, 0)	0	14.89	(0, 35.54)	0.1871
Era	Early	5.04	(0, 14.91)	0.4229	8.54	(0.17, 16.91)	0.0774
	Mid	4.4	(0, 13.01)	0.4398	1.76	(0, 5.21)	0.6659
	Late	12.55	(0, 26.75)	0.1109	9.35	(1.87, 16.83)	0.0287
Genitourinary		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		7.44	(3.68, 11.21)	0.0008	12.75	(10.63, 14.87)	<.0001
Age group	<1 year	4.71	(0, 10.04)	0.1725	9.34	(6.05, 12.62)	<.0001
	1–4 years	6.81	(0, 20.17)	0.3935	38.67	(24.59, 52.74)	<.0001
	5–9 years	10.33	(0, 30.58)	0.3664	21.25	(9.23, 33.27)	0.001
	10–14 years	16.83	(0, 40.17)	0.1835	21.33	(10.54, 32.13)	0.0002
	15–19 years	11.32	(0, 27.02)	0.1973	19.24	(11.01, 27.48)	<.0001
	20–24 years	9.74	(0, 20.77)	0.1201	8.03	(3.49, 12.57)	0.0024
	25–34 years	5.64	(0, 12.02)	0.1542	6.37	(3.51, 9.24)	0.0002
Sex	Females	9.68	(3.36, 16)	0.0071	15.2	(11.69, 18.71)	<.0001
	Males	5.53	(1.1, 9.95)	0.0448	10.86	(8.26, 13.46)	<.0001
Defect severity	Mild	1.5	(0, 4.44)	0.7385	6.71	(4.02, 9.39)	<.0001
	Moderate	8.12	(1.62, 14.62)	0.0317	7.16	(5.02, 9.3)	<.0001
	Severe 2V	3.3	(0, 9.78)	0.4856	13.4	(8.25, 18.55)	<.0001
	Severe 1V	22.75	(0, 48.5)	0.0977	40.14	(26.23, 54.05)	<.0001
Era	Early	13.05	(1.61, 24.5)	0.0389	9.44	(5.3, 13.58)	<.0001
	Mid	7.37	(0, 15.72)	0.1344	11.08	(6.9, 15.26)	<.0001
	Late	6.16	(0, 13.13)	0.1468	17.02	(12.39, 21.64)	<.0001
Pregnancy		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		2.14	(0, 4.55)	0.3571	1.65	(0.03, 3.26)	0.4329
Age group	<1 year	0	(0, 0)	0	0	(0, 0)	0
	1–4 years	0	(0, 0)	0	0	(0, 0)	0
	5–9 years	0	(0, 0)	0	0	(0, 0)	0
	10–14 years	110	(0, 325.5)	0.3217	61	(0, 180.5)	0.3253
	15–19 years	0	(0, 0)	0	0	(0, 0)	0
	20–24 years	1.87	(0, 5.52)	0.6425	1.03	(0, 3.05)	0.9757
	25–34 years	1.59	(0, 4.72)	0.7094	2.11	(0, 5.03)	0.4576

Sex	Females	2.14	(0, 4.55)	0.3571	1.65	(0.03, 3.26)	0.4329
	Males	0	(0, 0)	0	0	(0, 0)	0
Defect severity	Mild	2.8	(0, 6.68)	0.3632	1.63	(0, 3.9)	0.5835
	Moderate	0	(0, 0)	0	0	(0, 0)	0
	Severe 2V	0	(0, 0)	0	0	(0, 0)	0
	Severe 1V	31.47	(0, 93.15)	0.3329	37.08	(0, 88.47)	0.1688
Era	Early	13.5	(0, 39.97)	0.3545	0	(0, 0)	0
	Mid	0	(0, 0)	0	0	(0, 0)	0
	Late	7.54	(0, 22.32)	0.3857	4.07	(0, 12.04)	0.4507
Perinatal		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		0.57	(0.36, 0.78)	<.0001	1.63	(1.32, 1.94)	<.0001
Age group	<1 year	0.43	(0.25, 0.62)	<.0001	1.31	(1.03, 1.59)	0.0317
	1–4 years	11.53	(2.3, 20.75)	0.0253	13.97	(6.9, 21.05)	0.0003
	5–9 years	7.56	(0, 22.39)	0.3855	7.25	(0, 17.29)	0.2228
	10–14 years	0	(0, 0)	0	15.01	(0, 32)	0.1059
	15–19 years	0	(0, 0)	0	20.79	(0, 44.32)	0.0992
	20–24 years	0	(0, 0)	0	0	(0, 0)	0
	25–34 years	0	(0, 0)	0	0	(0, 0)	0
Sex	Females	0.79	(0.39, 1.19)	0.3101	1.87	(1.33, 2.4)	0.0014
	Males	0.43	(0.2, 0.66)	<.0001	1.47	(1.1, 1.85)	0.0135
Defect severity	Mild	0.94	(0.29, 1.6)	0.8637	1.5	(0.79, 2.21)	0.1699
	Moderate	0.56	(0.21, 0.91)	0.0142	1.24	(0.79, 1.69)	0.3028
	Severe 2V	0.22	(0, 0.47)	<.0001	1.72	(1.11, 2.33)	0.0198
	Severe 1V	0.6	(0.01, 1.19)	0.1887	2.53	(1.47, 3.59)	0.0046
Era	Early	0.58	(0.18, 0.98)	0.041	1.91	(1.27, 2.54)	0.0049
	Mid	0.74	(0.3, 1.18)	0.2502	1.7	(1.13, 2.28)	0.016
	Late	0.43	(0.15, 0.72)	<.0001	1.31	(0.88, 1.74)	0.1627
Congenital Malformations		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		62.13	(59.36, 64.9)	<.0001	60.81	(58.34, 63.28)	<.0001
Age group	<1 year	43.49	(40.69, 46.28)	<.0001	41.79	(39.25, 44.33)	<.0001
	1–4 years	148.4	(136.2, 160.5)	<.0001	138.6	(128.2, 149)	<.0001
	5–9 years	75.59	(61.78, 89.41)	<.0001	68.26	(56.95, 79.57)	<.0001
	10–14 years	75.34	(60.79, 89.89)	<.0001	71.61	(59.62, 83.61)	<.0001
	15–19 years	78.83	(63.89, 93.76)	<.0001	78.45	(66.02, 90.88)	<.0001
	20–24 years	67.41	(50.35, 84.46)	<.0001	69.52	(55.47, 83.58)	<.0001
	25–34 years	64.82	(45.88, 83.76)	<.0001	67.47	(52.4, 82.54)	<.0001
Sex	Females	63.27	(58.97, 67.56)	<.0001	62.9	(59.03, 66.77)	<.0001

	Males	61.3	(57.67, 64.92)	<.0001	59.28	(56.07, 62.49)	<.0001
Defect severity	Mild	20.4	(17.08, 23.72)	<.0001	22.38	(19.3, 25.47)	<.0001
	Moderate	45.15	(41.25, 49.04)	<.0001	46.94	(43.37, 50.51)	<.0001
	Severe 2V	67.4	(61.42, 73.38)	<.0001	65.06	(59.69, 70.42)	<.0001
	Severe 1V	192.7	(177.9, 207.5)	<.0001	182.4	(169.2, 195.5)	<.0001
Era	Early	82.73	(76.73, 88.73)	<.0001	73.45	(68.28, 78.62)	<.0001
	Mid	60.2	(55.25, 65.15)	<.0001	56.78	(52.4, 61.17)	<.0001
	Late	50.79	(46.55, 55.02)	<.0001	51.03	(47.21, 54.85)	<.0001
Injury		**SMR**	**95% CI**	**P-value**	**SMR**	**95% CI**	**P-value**
Overall		0.32	(0.24, 0.39)	<.0001	3.11	(2.87, 3.34)	<.0001
Age group	<1 year	3.07	(1.4, 4.74)	0.0151	33.73	(29.02, 38.44)	<.0001
	1–4 years	1.18	(0.64, 1.73)	0.5103	8.95	(7.51, 10.39)	<.0001
	5–9 years	1.7	(0.91, 2.48)	0.0816	5.97	(4.55, 7.39)	<.0001
	10–14 years	0.51	(0.13, 0.89)	0.0121	3.36	(2.41, 4.31)	<.0001
	15–19 years	0.12	(0.03, 0.21)	<.0001	1.24	(0.96, 1.53)	0.0969
	20–24 years	0.06	(0, 0.13)	<.0001	1.12	(0.86, 1.39)	0.357
	25–34 years	0	(0, 0)	0	1.39	(1.06, 1.73)	0.0208
Sex	Females	0.43	(0.25, 0.6)	<.0001	4.24	(3.71, 4.78)	<.0001
	Males	0.28	(0.2, 0.36)	<.0001	2.71	(2.45, 2.96)	<.0001
Defect severity	Mild	0.29	(0.17, 0.41)	<.0001	1.69	(1.4, 1.98)	<.0001
	Moderate	0.25	(0.14, 0.35)	<.0001	2.45	(2.11, 2.78)	<.0001
	Severe 2V	0.49	(0.2, 0.79)	0.0007	5.33	(4.39, 6.28)	<.0001
	Severe 1V	0.74	(0.15, 1.34)	0.4001	16.92	(14.14, 19.71)	<.0001
Era	Early	1.47	(1.06, 1.89)	0.0261	6.37	(5.52, 7.21)	<.0001
	Mid	0.59	(0.33, 0.86)	0.0026	4.8	(4.06, 5.54)	<.0001
	Late	0	(0, 0)	0	4.18	(3.5, 4.85)	<.0001

All values adjusted for age, sex, and year; pregnancy associated mortality calculated among women and girls only; eras defined as early (1982-1992),middle (1993-1997), and late (1998-2003)

Several patterns emerged across age groups and defect severity. Multiple cause of death data saw higher fold differences at younger ages. For deaths attributed to infection, neoplasms, circulatory disease, and respiratory disease the greatest difference was seen between SMRs calculated with underlying and multiple causes of death among infants (< 1 year old). Differences in deaths with genitourinary disease was highest among 1-4 years

olds while differences peaked between 5-9 years old for endocrine and blood diseases. Examining differences by defect severity we observed that generally, differences were smallest among children with moderately severe defects and largest for severe defects, particularly single ventricle defects.

Finally we assessed mortality with and without considering the competing risk of death from other causes. Overall adjusted Cox results showed that males and those with chromosomal defects were at elevated risk of death (HR = 1.14, p-value = 0.0008, HR = 1.58, p-value < 0.0001, respectively). We observed a positive association between mortality and RACH Score (HR = 1.59, p-value < 0.0001) and an inverse association between mortality and age (HR = 0.954, p-value < 0.0001) and year of surgery (HR = 0.946, p-value < 0.0001). Adjusting for competing risk slightly attenuated associations between risk factors and mortality. Although year of surgery was generally inversely associated with mortality, year was positively associated with mortality due to blood diseases (HR = 1.06, p-value =0.0287) and pregnancy 1.17, p-value < 0.0001). Similarly, positive associations were observed between age and mental disorders (HR = 1.12, p-value = 0.0009) and musculoskeletal diseases (HR = 1.12, p-value = 0.0143). Chromosomal defects were associated with higher risk of death across all causes of death except pregnancy where no pregnancies were observed among members of the PCCC with a chromosomal defect (Table 7.4).

Table 7.4: Traditional and competing risk cox regression results

		Traditional		Competing Risk	
Cause of Death	**Variable**	**HR**	**p-value**	**HR**	**p-value**
Overall	Age, years	0.954	<.0001		NA
	Year of surgery	0.946	<.0001		NA
	Male	1.139	0.0008		NA
	RACHS-1	1.59	<.0001		NA

	Chromosomal defect	1.582	<.0001	NA	
Infection	Age, years	0.92	0.0007	0.924	0.0128
	Year of surgery	0.98	0.1084	0.981	0.1119
	Male	1.088	0.4759	1.094	0.454
	RACHS-1	1.638	<.0001	1.567	<.0001
	Chromosomal defect	2.218	<.0001	2.184	<.0001
Neoplasm	Age, years	1.033	0.2129	1.036	0.174
	Year of surgery	0.991	0.735	0.99	0.721
	Male	0.99	0.9658	0.988	0.9584
	RACHS-1	1.204	0.0745	1.145	0.1663
	Chromosomal defect	2.045	0.0095	1.986	0.0137
Cardiovascular	Age, years	0.971	0.0004	0.973	0.0079
	Year of surgery	0.939	<.0001	0.94	<.0001
	Male	1.056	0.3005	1.057	0.2962
	RACHS-1	1.638	<.0001	1.597	<.0001
	Chromosomal defect	1.6	<.0001	1.584	<.0001
Congenital	Age, years	0.88	<.0001	0.881	<.0001
	Year of surgery	0.934	<.0001	0.934	<.0001
	Male	1.035	0.4373	1.035	0.4478
	RACHS-1	1.696	<.0001	1.694	<.0001
	Chromosomal defect	1.588	<.0001	1.584	<.0001

Discussion

Our analyses suggest that the inclusion of multiple causes of death data illuminate the underestimation of mortality due to specific causes among patients following pediatric surgical repair of a CHD. Despite improvements in the surgical management of CHDs, researchers in the United States have identified elevated risk of mortality among patients following pediatric cardiac surgery for CHDs.[6,48] Previously, researchers identified elevated risk of cardiovascular disease including heart failure,[158] arrhythmias ,[159] pulmonary hypertension,[160] and endocarditis[161] among patients following surgery for CHD. This risk is particularly high for patients with severe CHD.[3,137] More recently, elevated risk of cancer among patients following surgical repair of a CHD has been

noted.[162,163] Previous analyses of data from the PCCC found elevated risk of death from congenital malformations, respiratory disease, infections and neoplasms.[137] Raissadati *et al*. also noted elevated risk of death due to neurological disease.[164] The inclusion of multiple causes of death data suggest that deaths attributed to injury, infection, as well as blood, circulatory, genitourinary, and endocrine diseases are higher than previous analyses of this population have suggested.

We found that death due to injury, infection and due to conditions originating in the perinatal period were most underestimated by reliance on the underlying cause of death. These findings make sense within the context of a population that had pediatric surgery given that injury including surgical complication[24] as well as infection[165] are known risks of surgery. More importantly, we found that death due to blood, circulatory, genitourinary, and endocrine diseases were also underestimated. These causes of death were listed as the underlying cause of death on less than 25% of death certificates. Conversely, neoplasms and congenital malformations were overwhelmingly listed as the underlying cause of death on death certificates and the burden of these diseases was not underestimated. These findings suggest that the inclusion of multiple causes of death data provides valuable context for understanding mortality among patients who had pediatric cardiac surgery for a CHD.

Despite widespread use in epidemiological research, researchers have long known that the underlying cause of death has questionable accuracy. One early assessment of death certificates from 1980 found a sensitivity for underlying cause of death of 72% based on clinical data compared to autopsy.[166] When the underlying cause of death was circulatory disease, the sensitivity ranged from 69% to 82%.[166,167] For congenital

anomalies including congenital heart defects (CHDs), the sensitivity of underlying cause of death is slightly higher at 76% to 88%.[166,167] Within a more contemporary sample obtained from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, the sensitivity of cardiovascular mortality was 73% when comparing underlying cause of death from the National Death Index and the study expert adjudicators.[153] Additionally, the analysis of REGARDS showed discordance between NDI and adjudicated underlying cause of death by age, race-sex groups, and the presence of common chronic diseases including diabetes mellitus and hypertension.[153] These findings highlight the need for the consideration of multiple causes of death to reduce chances of ignoring the true underlying cause of death and provide a more complete picture of disease states present at the time of death. Despite these benefits, multiple cause of death data is computationally and analytically more difficult than underlying causes of death; however, there are well established methods for analyzing these data.[156,157]

Strengths and Limitations

The PCCC is an exceptionally high quality dataset, which is approximately 99.95% complete and consistent.[10] It is the only US cohort with both short and long-term outcomes following surgery for CHD and has a median follow-up time of 22.5 years (810,925 person-years). The distribution of defect severity within PCCC centers is representative of the national administrative and clinical datasets.[132] Deaths were ascertained through linkage to the NDI, the most accurate source of these data in the United States.[168]

This analysis is not without limitations. Almost a fifth of PCCC patients had insufficient identifying information available to link to the NDI. Previous analyses have shown that these patients had more severe defects and were younger at the time of surgery[6]. Despite the sample size, more data are needed to better assess the impact of MCOD on mortality due to mental disorders, diseases of the skin and musculoskeletal system, and associated with pregnancy. The PCCC has limited information available on the socioeconomic status, including race, of patients. This hindered our ability to examine these undoubtedly important factors in relation to causes of death.

Finally, the medical certification of death is completed by physicians, often medical residents, who often receive minimal training on how to complete a death certificate.[152,169] A recent examination of death certificates found that 53% contained errors and when a blinded medical examiner completed a mock certificate 60% had a change to the UCOD.[169] These errors may introduce misclassification bias into the analysis. However, deaths related to cardiothoracic surgery and pediatrics had some of the highest rates of autopsy request,[170] which is associated with improved death certificate accuracy.[171]

Summary

Despite these limitations, our analysis highlights advantages of using multiple cause of death data in certain circumstances. Multiple causes of death data provide a more complete picture of a patient's conditions at the time of death. This includes intermediate and contributing conditions not reflected in the underlying cause of death. For clinicians, these conditions may be better targets for intervention or indicators of the condition of a patient than underlying cause of death. Providers caring for patients with

CHDs should be aware of the underestimation of death due to blood, circulatory, genitourinary, and endocrine diseases. Additionally, researchers conducting cause of death analyses should consider including multiple causes of death in their future analyses despite the additional methodological considerations these data require.

CHAPTER 8: CONCLUSION

Congenital heart defects (CHDs) pose a significant health burden to the individuals affected. They occur in almost 1% births, and are the leading cause of birth defect related deaths in infants.[3,8] A quarter of individuals with CHDs will require intervention within the first year of life with others requiring repair as children or young adults.[8] Surgery remains the primary method of treating these defects.[8] Despite significant improvements in surgical techniques for repairing CHDs in children over the last 30 years,[5] the life expectancy for adults who had pediatric cardiac surgery continues to trail behind the general population.[6]

Previous analyses found that following congenital heart surgery individuals have higher short and long-term mortality.[6] The majority of studies addressing mortality following surgery for CHD have focused on patient-level characteristics including sex, race, year of birth, age at surgery, non-cardiac comorbidities and chromosomal defects.[3,6,51] However, some evidence suggests that surgeon and center volume may be associated with improved short-term survival, particularly for complex surgeries.[97–100]

Researchers have also shown that after congenital heart surgery individuals are at higher risk of CHD or cardiovascular disease, other congenital malformations, respiratory disease, infection, and neoplasms compared to the general population.[137] However, these findings do not address multiple causes of death or competing risk of death, which

provide valuable insight into the precipitating events leading to death following congenital heart surgery.

For this dissertation, we examined center and surgeon characteristics associated with post-surgical mortality as well as the role of contributing causes of death among these deaths. This research builds upon previous analyses of the Pediatric Cardiac Care Consortium (PCCC), a retrospective cohort of approximately 35,000 children who had congenital heart surgery, linked to the National Death Index. We augmented these data by linking the PCCC to the American Medical Association Physician Masterfile, which provides information on the surgeon training. National mortality data provided a comparison to assess differences between individuals with repaired CHDs and the general population.

In the first analysis, we examined center characteristics associated with post-discharge mortality. In multilevel Cox regression models, there was no association between either center volume or training hospital status and mortality after adjusting for established patient-level risk factors.

The second analysis extended these findings by assessing both center and surgeon characteristics associated with short and medium term post-surgical mortality. This analysis captured the accumulation of experience by surgeons within PCCC centers. Surgeon experience was operationalized as annual procedure-specific volume, cumulative procedure-specific volume, and years since graduation. In analyses combining center and surgeon characteristics, we found that center volume was generally more strongly associated with mortality than surgeon volume. This was particularly true for the most complex benchmark surgical repair, the Norwood procedure.

Finally, we characterized the contributions of multiple cause of death data among patients following congenital heart surgery. Although competing risk Cox regression models did not provide additional insights, a comparison of standardized mortality ratios calculated with multiple and underlying causes of death provided valuable insight. The burden of diseases that were frequently recorded as underlying causes of death, such as congenital disease and neoplasms, did not change significantly with the inclusion of multiple causes of death. However, the contribution of perinatal, endocrine, and genitourinary diseases as well as infection was underestimated in standardized mortality ratios calculated using underlying cause of death only. This knowledge can be used to develop a better understanding of disease processes that contribute to death following pediatric cardiac surgery.

These findings provide targets within pediatric hospitals that may be modified to improve mortality outcomes of congenital heart surgery. The results address limits of existing US-based long-term outcomes of pediatric cardiac surgery, which was identified by the National Heart, Lung, and Blood Institute/Adult Congenital Heart Association Working Group as well as gaps in long-term outcomes and health service delivery identified by the Centers for Disease Control and Prevention.[8,163] The first two analyses inform programmatic volume for surgical centers while the last emphasizes the need for long-term multidisciplinary care following surgical repair of CHDs.

This dissertation has a number of strengths. Most importantly, the Pediatric Cardiac Care Consortium (PCCC) is a high quality registry with personal identifying information unavailable in most multicenter studies. This has permitted linkage to the National Death Index, which provides gold-standard mortality information from the time

of hospital discharge to an average of 22 years following surgery. The inclusion of original surgical reports allowed the abstraction of the names of surgeons who performed the repairs and the subsequent linkage to information on their medical training. Finally, we utilized mixed effect modeling to best approximate the hospital systems consisting of centers, surgeons, and patients, which has not been utilized in many previous analyses.

These findings inform several future directions of research. In subsequent analyses we will extend the second analysis to include additional procedures to increase the number of procedures observed by each surgeon and reflect less difficult surgical procedures. Additionally, we will assess the association between center program stability and mortality. We will also use machine learning techniques to describe clustering in causes of death which occur together in an effort to identify the chain of events which lead to death. These analyses will continue to improve our understanding of factors associated with mortality following pediatric cardiac surgery.

REFERENCES

1. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131(5):e1502-8. doi:10.1542/peds.2012-3435
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890-1900.
3. Virani Salim S., Alonso Alvaro, Aparicio Hugo J., et al. Heart Disease and Stroke Statistics—2021 Update. *Circulation*. 2021;143(8):e254-e743. doi:10.1161/CIR.0000000000000950
4. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. *J Pediatr*. 2008;153(6):807-813. doi:10.1016/j.jpeds.2008.05.059
5. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol*. 2010;56(14):1149-1157. doi:10.1016/j.jacc.2010.03.085
6. Spector LG, Menk JS, Knight JH, et al. Trends in Long-Term Mortality After Congenital Heart Surgery. *J Am Coll Cardiol*. 2018;71(21):2434-2446. doi:10.1016/j.jacc.2018.03.491
7. Gurvitz M, Burns KM, Brindis R, et al. Emerging Research Directions in Adult Congenital Heart Disease: A Report From an NHLBI/ACHA Working Group. *J Am Coll Cardiol*. 2016;67(16):1956-1964. doi:10.1016/j.jacc.2016.01.062
8. Oster ME, Riehle-Colarusso T, Simeone RM, et al. Public health science agenda for congenital heart defects: report from a Centers for Disease Control and Prevention experts meeting. In: *J Am Heart Assoc*. Vol 2. ; 2013:e000256. doi:10.1161/jaha.113.000256
9. Gabler E. Doctors Were Alarmed: 'Would I Have My Children Have Surgery Here?' *The New York Times*. May 31, 2019.
10. Moller JH, Borbas C. The Pediatric Cardiac Care Consortium: a physician-managed clinical review program. *QRB Qual Rev Bull*. 1990;16(9):310-316.
11. Moller JH, Hills CB, Pyles LA. A multi-center cardiac registry. A method to assess outcome of catheterization intervention or surgery. *Prog Pediatr Cardiol*. 2005;20(1):7-12. doi:10.1016/j.ppedcard.2004.12.009
12. Grumbach K, Becker SH, Osborn EH, Bindman AB. The challenge of defining and counting generalist physicians: an analysis of Physician Masterfile data. *Am J Public Health*. 1995;85(10):1402-1407.
13. Shea JA, Kletke PR, Wozniak GD, Polsky D, Escarce JJ. Self-reported physician specialties and the primary care content of medical practice: a study of the AMA physician masterfile. American Medical Association. *Med Care*. 1999;37(4):333-338. doi:10.1097/00005650-199904000-00003
14. National Center for Health Statistics. Vital Statistics NCHS Multiple Cause of Death Data, 1959-2017. Published 2016 1982. Accessed May 10, 2019. http://data.nber.org/data/vital-statistics-mortality-data-multiple-cause-of-death.html
15. Ailes EC, Gilboa SM, Riehle-Colarusso T, et al. Prenatal diagnosis of nonsyndromic congenital heart defects. *Prenat Diagn*. 2014;34(3):214-222. doi:10.1002/pd.4282

16. Mai CT, Riehle-Colarusso T, O'Halloran A, et al. Selected birth defects data from population-based birth defects surveillance programs in the United States, 2005-2009: Featuring critical congenital heart defects targeted for pulse oximetry screening. *Birth Defects Res Clin Mol Teratol*. 2012;94(12):970-983.
17. Miller A, Riehle-Colarusso T, Alverson CJ, Frias JL, Correa A. Congenital heart defects and major structural noncardiac anomalies, Atlanta, Georgia, 1968 to 2005. *J Pediatr*. 2011;159(1):70-78.e2. doi:10.1016/j.jpeds.2010.12.051
18. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J*. 2004;147(3):425-439. doi:10.1016/j.ahj.2003.05.003
19. Jacobs JP, Jacobs ML, Lacour-Gayet FG, et al. Stratification of complexity improves the utility and accuracy of outcomes analysis in a Multi-Institutional Congenital Heart Surgery Database: Application of the Risk Adjustment in Congenital Heart Surgery (RACHS-1) and Aristotle Systems in the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. *Pediatr Cardiol*. 2009;30(8):1117-1130. doi:10.1007/s00246-009-9496-0
20. Jacobs JP, Mavroudis C, Jacobs ML, et al. Nomenclature and databases - the past, the present, and the future : a primer for the congenital heart surgeon. *Pediatr Cardiol*. 2007;28(2):105-115. doi:10.1007/s00246-006-1447-4
21. O'Brien SM, Clarke DR, Jacobs JP, et al. An empirically based tool for analyzing mortality associated with congenital heart surgery. *J Thorac Cardiovasc Surg*. 2009;138(5):1139-1153. doi:10.1016/j.jtcvs.2009.03.071
22. Boethig D, Jenkins KJ, Hecker H, Thies WR, Breymann T. The RACHS-1 risk categories reflect mortality and length of hospital stay in a large German pediatric cardiac surgery population. *Eur J Cardiothorac Surg*. 2004;26(1):12-17. doi:10.1016/j.ejcts.2004.03.039
23. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. 2002;123(1):110-118.
24. Benavidez OJ, He W, Lahoud-Rahme M. Readmissions Following Congenital Heart Surgery in Infants and Children. *Pediatr Cardiol*. 2019;40(5):994-1000. doi:10.1007/s00246-019-02104-4
25. Simsic JM, Cuadrado A, Kirshbom PM, Kanter KR. Risk adjustment for congenital heart surgery (RACHS): is it useful in a single-center series of newborns as a predictor of outcome in a high-risk population? *Congenit Heart Dis*. 2006;1(4):148-151. doi:10.1111/j.1747-0803.2006.00026.x
26. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2014;129(21):2183-2242. doi:10.1161/01.cir.0000437597.44550.5d
27. Gorla SR, Chakraborty A, Garg A, Gugol RA, Kardon RE, Swaminathan S. Emerging trends in the prenatal diagnosis of complex CHD and its influence on infant mortality in this cohort. *Cardiol Young*. Published online December 26, 2018:1-7. doi:10.1017/s1047951118002147
28. Friedman AH, Kleinman CS, Copel JA. Diagnosis of cardiac defects: where we've been, where we are and where we're going. *Prenat Diagn*. 2002;22(4):280-284. doi:10.1002/pd.305
29. Olney RS, Ailes EC, Sontag MK. Detection of critical congenital heart defects:

Review of contributions from prenatal and newborn screening. *Semin Perinatol*. 2015;39(3):230-237. doi:10.1053/j.semperi.2015.03.007
30. Desai K, Rabinowitz EJ, Epstein S. Physiologic diagnosis of congenital heart disease in cyanotic neonates. *Curr Opin Pediatr*. 2019;31(2):274-283. doi:10.1097/MOP.0000000000000742
31. Peterson C, Ailes E, Riehle-Colarusso T, et al. Late detection of critical congenital heart disease among US infants: estimation of the potential impact of proposed universal screening using pulse oximetry. *JAMA Pediatr*. 2014;168(4):361-370. doi:10.1001/jamapediatrics.2013.4779
32. Kuehl KS, Loffredo CA, Ferencz C. Failure to diagnose congenital heart disease in infancy. *Pediatrics*. 1999;103(4 Pt 1):743-747. doi:10.1542/peds.103.4.743
33. Liberman RF, Getz KD, Lin AE, et al. Delayed diagnosis of critical congenital heart defects: trends and associated factors. *Pediatrics*. 2014;134(2):e373-381. doi:10.1542/peds.2013-3949
34. Jacobs JP, O'Brien SM, Pasquali SK, et al. Variation in outcomes for benchmark operations: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. *Ann Thorac Surg*. 2011;92(6):2184-2191; discussion 2191-2. doi:10.1016/j.athoracsur.2011.06.008
35. Stark JF, Gallivan S, Davis K, et al. Assessment of mortality rates for congenital heart defects and surgeons' performance. *Ann Thorac Surg*. 2001;72(1):169-174; discussion 174-175. doi:10.1016/s0003-4975(01)02689-3
36. Jacobs JP, Mayer JE, Pasquali SK, et al. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2019 Update on Outcomes and Quality. *Ann Thorac Surg*. 2019;107(3):691-704. doi:10.1016/j.athoracsur.2018.12.016
37. St Louis JD, Kurosawa H, Jonas RA, et al. The World Database for Pediatric and Congenital Heart Surgery: The Dawn of a New Era of Global Communication and Quality Improvement in Congenital Heart Disease. *World J Pediatr Congenit Heart Surg*. 2017;8(5):597-599. doi:10.1177/2150135117725458
38. Jonas R. *Comprehensive Surgical Management of Congenital Heart Disease*. 2nd ed. CRC Press; 2014.
39. Jenkins KJ. Risk adjustment for congenital heart surgery: the RACHS-1 method. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2004;7:180-184.
40. Penny DJ, Vick GW 3rd. Ventricular septal defect. *Lancet*. 2011;377(9771):1103-1112. doi:10.1016/s0140-6736(10)61339-6
41. Chen LT, Yang TB, Wang TT, et al. [Association of single nucleotide polymorphisms of transcription factors with congenital heart diseases in the Chinese population: a Meta analysis]. *Zhongguo Dang Dai Er Ke Za Zhi*. 2018;20(6):490-496.
42. Rigby M. Atrioventricular Septal Defect: What Is in a Name? *J Cardiovasc Dev Dis*. 2021;8(2). doi:10.3390/jcdd8020019
43. Castaneda A. Congenital heart disease: a surgical-historical perspective. *Ann Thorac Surg*. 2005;79(6):S2217-20. doi:10.1016/j.athoracsur.2005.03.031
44. Kiess M. History and evolution of the treatment of adult congenital heart disease | British Columbia Medical Journal. *BCMJ*. 2016;58(7):368-372.
45. Jenkins NP, Ward C. Coarctation of the aorta: natural history and outcome after surgical treatment. *QJM Int J Med*. 1999;92(7):365-371.

doi:10.1093/qjmed/92.7.365
46. van Doorn C. The unnatural history of tetralogy of Fallot: surgical repair is not as definitive as previously thought. *Heart*. 2002;88(5):447-448.
47. Yabrodi M, Mastropietro CW. Hypoplastic left heart syndrome: from comfort care to long-term survival. *Pediatr Res*. 2017;81(1):142-149. doi:10.1038/pr.2016.194
48. Jacobs JP, He X, Mayer JE Jr, et al. Mortality Trends in Pediatric and Congenital Heart Surgery: An Analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database. *Ann Thorac Surg*. 2016;102(4):1345-1352. doi:10.1016/j.athoracsur.2016.01.071
49. Welke KF, O'Brien SM, Peterson ED, Ungerleider RM, Jacobs ML, Jacobs JP. The complex relationship between pediatric cardiac surgical case volumes and mortality rates in a national clinical database. *J Thorac Cardiovasc Surg*. 2009;137(5):1133-1140. doi:10.1016/j.jtcvs.2008.12.012
50. Kempny A, Dimopoulos K, Uebing A, et al. Outcome of cardiac surgery in patients with congenital heart disease in England between 1997 and 2015. *PLoS One*. 2017;12(6):e0178963. doi:10.1371/journal.pone.0178963
51. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. *Circulation*. 2010;122(22):2254-2263. doi:10.1161/circulationaha.110.947002
52. Erikssen G, Liestol K, Seem E, et al. Achievements in congenital heart defect surgery: a prospective, 40-year study of 7038 patients. *Circulation*. 2015;131(4):337-346; discussion 346. doi:10.1161/circulationaha.114.012033
53. Jousilahti P, Laatikainen T, Salomaa V, Pietila A, Vartiainen E, Puska P. 40-Year CHD Mortality Trends and the Role of Risk Factors in Mortality Decline: The North Karelia Project Experience. *Glob Heart*. 2016;11(2):207-212. doi:10.1016/j.gheart.2016.04.004
54. Kogon BE. The training of congenital heart surgeons. *J Thorac Cardiovasc Surg*. 2006;132(6):1280-1284. doi:10.1016/j.jtcvs.2006.08.045
55. Kogon B, Karamlou T, Baumgartner W, Merrill W, Backer C. Congenital cardiac surgery fellowship training: A status update. *J Thorac Cardiovasc Surg*. 2016;151(6):1488-1495. doi:10.1016/j.jtcvs.2016.02.039
56. Beasley SW. The challenges facing training in pediatric surgery worldwide. *Front Pediatr*. 2013;1:24. doi:10.3389/fped.2013.00024
57. Fraser CD. Becoming a congenital heart surgeon in the current era: Realistic expectations. *J Thorac Cardiovasc Surg*. 2016;151(6):1496-1497. doi:10.1016/j.jtcvs.2016.02.054
58. Canfield MA, Mai CT, Wang Y, et al. The association between race/ethnicity and major birth defects in the United States, 1999-2007. *Am J Public Health*. 2014;104(9):e14-23. doi:10.2105/ajph.2014.302098
59. Parker SE, Mai CT, Canfield MA, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res Clin Mol Teratol*. 2010;88(12):1008-1016. doi:10.1002/bdra.20735
60. Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. *Pediatrics*. 2001;107(3):E32. doi:10.1542/peds.107.3.e32
61. Koppel RI, Druschel CM, Carter T, et al. Effectiveness of pulse oximetry

screening for congenital heart disease in asymptomatic newborns. *Pediatrics*. 2003;111(3):451-455. doi:10.1542/peds.111.3.451
62. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139(10):e56-e528. doi:10.1161/cir.0000000000000659
63. Zimmerman MS, Smith AGC, Sable CA, et al. Global, regional, and national burden of congenital heart disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Child Adolesc Health*. 2020;4(3):185-200. doi:10.1016/S2352-4642(19)30402-X
64. Chan T, Pinto NM, Bratton SL. Racial and insurance disparities in hospital mortality for children undergoing congenital heart surgery. *Pediatr Cardiol*. 2012;33(7):1026-1039. doi:10.1007/s00246-012-0221-z
65. Kaltman JR, Burns KM, Pearson GD, Goff DC, Evans F. Disparities in Congenital Heart Disease Mortality Based on Proximity to a Specialized Pediatric Cardiac Center. *Circulation*. 2020;141(12):1034-1036. doi:10.1161/CIRCULATIONAHA.119.043392
66. Nembhard WN, Salemi JL, Ethen MK, Fixler DE, Dimaggio A, Canfield MA. Racial/Ethnic disparities in risk of early childhood mortality among children with congenital heart defects. *Pediatrics*. 2011;127(5):e1128-1138. doi:10.1542/peds.2010-2702
67. Nembhard WN, Pathak EB, Schocken DD. Racial/ethnic disparities in mortality related to congenital heart defects among children and adults in the United States. *Ethn Dis*. 2008;18(4):442-449.
68. Lopez Keila N., Morris Shaine A., Sexson Tejtel S. Kristen, Espaillat Andre, Salemi Jason L. US Mortality Attributable to Congenital Heart Disease Across the Lifespan From 1999 Through 2017 Exposes Persistent Racial/Ethnic Disparities. *Circulation*. 2020;142(12):1132-1147. doi:10.1161/CIRCULATIONAHA.120.046822
69. Lasa JJ, Cohen MS, Wernovsky G, Pinto NM. Is race associated with morbidity and mortality after hospital discharge among neonates undergoing heart surgery? *Pediatr Cardiol*. 2013;34(2):415-423. doi:10.1007/s00246-012-0475-5
70. Pace ND, Oster ME, Forestieri NE, Enright D, Knight J, Meyer RE. Sociodemographic Factors and Survival of Infants With Congenital Heart Defects. *Pediatrics*. 2018;142(3). doi:10.1542/peds.2018-0302
71. Kogon B, Jain A, Oster M, Woodall K, Kanter K, Kirshbom P. Risk factors associated with readmission after pediatric cardiothoracic surgery. *Ann Thorac Surg*. 2012;94(3):865-873. doi:10.1016/j.athoracsur.2012.04.025
72. Jackson JL, Morack J, Harris M, DeSalvo J, Daniels CJ, Chisolm DJ. Racial disparities in clinic follow-up early in life among survivors of congenital heart disease. *Congenit Heart Dis*. 2019;14(2):305-310. doi:10.1111/chd.12732
73. Hirsch JC, Gurney JG, Donohue JE, Gebremariam A, Bove EL, Ohye RG. Hospital mortality for Norwood and arterial switch operations as a function of institutional volume. *Pediatr Cardiol*. 2008;29(4):713-717. doi:10.1007/s00246-007-9171-2
74. McClung N, Glidewell J, Farr SL. Financial burdens and mental health needs in families of children with congenital heart disease. *Congenit Heart Dis*.

2018;13(4):554-562. doi:10.1111/chd.12605
75. Connor JA, Kline NE, Mott S, Harris SK, Jenkins KJ. The meaning of cost for families of children with congenital heart disease. *J Pediatr Health Care*. 2010;24(5):318-325. doi:10.1016/j.pedhc.2009.09.002
76. Bazzani LG, Marcin JP. Case volume and mortality in pediatric cardiac surgery patients in California, 1998-2003. *Circulation*. 2007;115(20):2652-2659. doi:10.1161/circulationaha.106.678904
77. Chan T, Kim J, Minich LL, Pinto NM, Waitzman NJ. Surgical volume, hospital quality, and hospitalization cost in congenital heart surgery in the United States. *Pediatr Cardiol*. 2015;36(1):205-213. doi:10.1007/s00246-014-0987-2
78. Oster ME, Strickland MJ, Mahle WT. Racial and ethnic disparities in post-operative mortality following congenital heart surgery. *J Pediatr*. 2011;159(2):222-226. doi:10.1016/j.jpeds.2011.01.060
79. Peterson JK, Chen Y, Nguyen DV, Setty SP. Current trends in racial, ethnic, and healthcare disparities associated with pediatric cardiac surgery outcomes. *Congenit Heart Dis*. 2017;12(4):520-532. doi:10.1111/chd.12475
80. Cnota JF, Gupta R, Michelfelder EC, Ittenbach RF. Congenital heart disease infant death rates decrease as gestational age advances from 34 to 40 weeks. *J Pediatr*. 2011;159(5):761-765. doi:10.1016/j.jpeds.2011.04.020
81. Best KE, Tennant PWG, Rankin J. Survival, by Birth Weight and Gestational Age, in Individuals With Congenital Heart Disease: A Population-Based Study. *J Am Heart Assoc*. 2017;6(7). doi:10.1161/jaha.116.005213
82. Swenson AW, Dechert RE, Schumacher RE, Attar MA. The effect of late preterm birth on mortality of infants with major congenital heart defects. *J Perinatol*. 2012;32(1):51-54. doi:10.1038/jp.2011.50
83. Levin DL, Stanger P, Kitterman JA, Heymann MA. Congenital heart disease in low birth weight infants. *Circulation*. 1975;52(3):500-503. doi:10.1161/01.cir.52.3.500
84. Malik S, Cleves MA, Zhao W, Correa A, Hobbs CA, National Birth Defects Prevention Study. Association between congenital heart defects and small for gestational age. *Pediatrics*. 2007;119(4):e976-982. doi:10.1542/peds.2006-2742
85. Costello CL, Gellatly M, Daniel J, Justo RN, Weir K. Growth Restriction in Infants and Young Children with Congenital Heart Disease. *Congenit Heart Dis*. 2015;10(5):447-456. doi:10.1111/chd.12231
86. Anderson AW, Smith PB, Corey KM, et al. Clinical outcomes in very low birth weight infants with major congenital heart defects. *Early Hum Dev*. 2014;90(12):791-795. doi:10.1016/j.earlhumdev.2014.09.006
87. Eskedal LT, Hagemo PS, Seem E, et al. Impaired weight gain predicts risk of late death after surgery for congenital heart defects. *Arch Dis Child*. 2008;93(6):495-501. doi:10.1136/adc.2007.126219
88. Yoo BW. Epidemiology of Congenital Heart Disease with Emphasis on Sex-Related Aspects. *Adv Exp Med Biol*. 2018;1065:49-59. doi:10.1007/978-3-319-77932-4_3
89. Corbitt H, Gutierrez J, Silberbach M, Maslen CL. The genetic basis of Turner syndrome aortopathy. *Am J Med Genet C Semin Med Genet*. 2019;181(1):117-125. doi:10.1002/ajmg.c.31686

90. Simmons MA, Brueckner M. The genetics of congenital heart disease... understanding and improving long-term outcomes in congenital heart disease: a review for the general cardiologist and primary care physician. *Curr Opin Pediatr*. 2017;29(5):520-528. doi:10.1097/mop.0000000000000538
91. Zaidi S, Brueckner M. Genetics and Genomics of Congenital Heart Disease. *Circ Res*. 2017;120(6):923-940. doi:10.1161/circresaha.116.309140
92. Morales-Demori R. Congenital heart disease and cardiac procedural outcomes in patients with trisomy 21 and Turner syndrome. *Congenit Heart Dis*. 2017;12(6):820-827. doi:10.1111/chd.12521
93. Soemedi R, Wilson IJ, Bentham J, et al. Contribution of global rare copy-number variants to the risk of sporadic congenital heart disease. *Am J Hum Genet*. 2012;91(3):489-501. doi:10.1016/j.ajhg.2012.08.003
94. Ma MH, He W, Benavidez OJ. Congenital Heart Surgical Admissions in Patients with Trisomy 13 and 18: Frequency, Morbidity, and Mortality. *Pediatr Cardiol*. 2019;40(3):595-601. doi:10.1007/s00246-018-2032-3
95. de Graaf G, Buckley F, Skotko BG. Estimates of the live births, natural losses, and elective terminations with Down syndrome in the United States. *Am J Med Genet A*. 2015;167a(4):756-767. doi:10.1002/ajmg.a.37001
96. Norton ME, Kuppermann M. Women should decide which conditions matter. *Am J Obstet Gynecol*. 2016;215(5):583-587.e1. doi:10.1016/j.ajog.2016.06.045
97. Pasquali SK, Jacobs JP, He X, et al. The complex relationship between center volume and outcome in patients undergoing the Norwood operation. *Ann Thorac Surg*. 2012;93(5):1556-1562. doi:10.1016/j.athoracsur.2011.07.081
98. Preston L, Turner J, Booth A, et al. Is there a relationship between surgical case volume and mortality in congenital heart disease services? A rapid evidence review. *BMJ Open*. 2015;5(12):e009252. doi:10.1136/bmjopen-2015-009252
99. Hannan EL, Racz M, Kavey RE, Quaegebeur JM, Williams R. Pediatric cardiac surgery: the effect of hospital and surgeon volume on in-hospital mortality. *Pediatrics*. 1998;101(6):963-969.
100. Pieper D, Mathes T, Asfour B. A systematic review of the impact of volume of surgery and specialization in Norwood procedure. *BMC Pediatr*. 2014;14:198. doi:10.1186/1471-2431-14-198
101. Anderson BR, Wallace AS, Hill KD, et al. Association of Surgeon Age and Experience With Congenital Heart Surgery Outcomes. *Circ Cardiovasc Qual Outcomes*. 2017;10(7). doi:10.1161/circoutcomes.117.003533
102. Hornik CP, He X, Jacobs JP, et al. Relative impact of surgeon and center volume on early mortality after the Norwood operation. *Ann Thorac Surg*. 2012;93(6):1992-1997. doi:10.1016/j.athoracsur.2012.01.107
103. Tabbutt S, Ghanayem N, Ravishankar C, et al. Risk factors for hospital morbidity and mortality after the Norwood procedure: A report from the Pediatric Heart Network Single Ventricle Reconstruction trial. *J Thorac Cardiovasc Surg*. 2012;144(4):882-895. doi:10.1016/j.jtcvs.2012.05.019
104. Checchia PA, McCollegan J, Daher N, Kolovos N, Levy F, Markovitz B. The effect of surgical case volume on outcome after the Norwood procedure. *J Thorac Cardiovasc Surg*. 2005;129(4):754-759. doi:10.1016/j.jtcvs.2004.07.056
105. Karamlou T, McCrindle BW, Blackstone EH, et al. Lesion-specific outcomes in

neonates undergoing congenital heart surgery are related predominantly to patient and management factors rather than institution or surgeon experience: A Congenital Heart Surgeons Society Study. *J Thorac Cardiovasc Surg*. 2010;139(3):569-577.e1. doi:10.1016/j.jtcvs.2008.11.073
106. Sellers MM, Keele LJ, Sharoky CE, Wirtalla C, Bailey EA, Kelz RR. Association of Surgical Practice Patterns and Clinical Outcomes With Surgeon Training in University- or Nonuniversity-Based Residency Program. *JAMA Surg*. 2018;153(5):418-425. doi:10.1001/jamasurg.2017.5449
107. Bansal N, Simmons KD, Epstein AJ, Morris JB, Kelz RR. Using Patient Outcomes to Evaluate General Surgery Residency Program Performance. *JAMA Surg*. 2016;151(2):111-119. doi:10.1001/jamasurg.2015.3637
108. Kansy A, Ebels T, Schreiber C, Tobota Z, Maruszewski B. Association of center volume with outcomes: analysis of verified data of European Association for Cardio-Thoracic Surgery Congenital Database. *Ann Thorac Surg*. 2014;98(6):2159-2164. doi:10.1016/j.athoracsur.2014.07.065
109. Kansy A, Zu Eulenburg C, Sarris G, et al. Higher Programmatic Volume in Neonatal Heart Surgery Is Associated With Lower Early Mortality. *Ann Thorac Surg*. 2018;105(5):1436-1440. doi:10.1016/j.athoracsur.2017.11.028
110. Urbach DR, Croxford R, MacCallum NL, Stukel TA. How are volume-outcome associations related to models of health care funding and delivery? A comparison of the United States and Canada. *World J Surg*. 2005;29(10):1230-1233. doi:10.1007/s00268-005-7994-7
111. Brown EG, Anderson JE, Burgess D, Bold RJ. Examining the "Halo Effect" of Surgical Care Within Health Systems. *JAMA Surg*. 2016;151(10):983-984. doi:10.1001/jamasurg.2016.1000
112. Scott WA, Fixler DE. Effect of center volume on outcome of ventricular septal defect closure and arterial switch operation. *Am J Cardiol*. 2001;88(11):1259-1263. doi:10.1016/s0002-9149(01)02087-2
113. Berry JG, Cowley CG, Hoff CJ, Srivastava R. In-hospital mortality for children with hypoplastic left heart syndrome after stage I surgical palliation: teaching versus nonteaching hospitals. *Pediatrics*. 2006;117(4):1307-1313. doi:10.1542/peds.2005-1544
114. Gutgesell HP, Gibson J. Management of hypoplastic left heart syndrome in the 1990s. *Am J Cardiol*. 2002;89(7):842-846. doi:10.1016/s0002-9149(02)02196-3
115. Berry JG, Lieu TA, Forbes PW, Goldmann DA. Hospital Volumes for Common Pediatric Specialty Operations. *Arch Pediatr Adolesc Med*. 2007;161(1):38. doi:10.1001/archpedi.161.1.38
116. Hickey P, Gauvreau K, Connor J, Sporing E, Jenkins K. The relationship of nurse staffing, skill mix, and Magnet recognition to institutional volume and mortality for congenital heart surgery. *J Nurs Adm*. 2010;40(5):226-232. doi:10.1097/NNA.0b013e3181da3f71
117. Jenkins KJ, Newburger JW, Lock JE, Davis RB, Coffman GA, Iezzoni LI. In-hospital mortality for surgical repair of congenital heart defects: preliminary observations of variation by hospital caseload. *Pediatrics*. 1995;95(3):323-330.
118. McHugh KE, Hillman DG, Gurka MJ, Gutgesell HP. Three-stage palliation of hypoplastic left heart syndrome in the University HealthSystem Consortium.

Congenit Heart Dis. 2010;5(1):8-15. doi:10.1111/j.1747-0803.2009.00367.x
119. Oster ME, Strickland MJ, Mahle WT. Impact of prior hospital mortality versus surgical volume on mortality following surgery for congenital heart disease. *J Thorac Cardiovasc Surg*. 2011;142(4):882-886. doi:10.1016/j.jtcvs.2011.04.011
120. Pasquali SK, Gaies MG, Jacobs JP, William Gaynor J, Jacobs ML. Centre variation in cost and outcomes for congenital heart surgery. *Cardiol Young*. 2012;22(6):796-799. doi:10.1017/s104795111200159x
121. Sakai-Bizmark R, Mena LA, Kumamaru H, et al. Impact of pediatric cardiac surgery regionalization on health care utilization and mortality. *Health Serv Res*. 2019;54(4):890-901. doi:10.1111/1475-6773.13137
122. Seifert HA, Howard DL, Silber JH, Jobes DR. Female gender increases the risk of death during hospitalization for pediatric cardiac surgery. *J Thorac Cardiovasc Surg*. 2007;133(3):668-675. doi:10.1016/j.jtcvs.2006.11.014
123. Vinocur JM, Menk JS, Connett J, Moller JH, Kochilas LK. Surgical volume and center effects on early mortality after pediatric cardiac surgery: 25-year North American experience from a multi-institutional registry. *Pediatr Cardiol*. 2013;34(5):1226-1236. doi:10.1007/s00246-013-0633-4
124. Welke KF, Diggs BS, Karamlou T, Ungerleider RM. The relationship between hospital surgical case volumes and mortality rates in pediatric cardiac surgery: a national sample, 1988-2005. *Ann Thorac Surg*. 2008;86(3):889-896; discussion 889-96. doi:10.1016/j.athoracsur.2008.04.077
125. Welke KF, Shen I, Ungerleider RM. Current Assessment of Mortality Rates in Congenital Cardiac Surgery. *Ann Thorac Surg*. 2006;82(1):164-171. doi:10.1016/j.athoracsur.2006.03.004
126. Cedars A, Benjamin L, Burns SV, Novak E, Amin A. Clinical predictors of length of stay in adults with congenital heart disease. *Heart*. 2017;103(16):1258-1263. doi:10.1136/heartjnl-2016-310841
127. Cedars AM, Burns S, Novak EL, Amin AP. Lesion-Specific Factors Contributing to Inhospital Costs in Adults With Congenital Heart Disease. *Am J Cardiol*. 2016;117(11):1821-1825. doi:10.1016/j.amjcard.2016.03.016
128. Anderson BR, Fieldston ES, Newburger JW, Bacha EA, Glied SA. Disparities in Outcomes and Resource Use After Hospitalization for Cardiac Surgery by Neighborhood Income. *Pediatrics*. 2018;141(3). doi:10.1542/peds.2017-2432
129. Sommerhalter KM, Insaf TZ, Akkaya-Hocagil T, et al. Proximity to Pediatric Cardiac Surgical Care among Adolescents with Congenital Heart Defects in 11 New York Counties. *Birth Defects Res*. 2017;109(18):1494-1503. doi:10.1002/bdr2.1129
130. Maas MB, Jaff MR, Rordorf GA. Risk adjustment for case mix and the effect of surgeon volume on morbidity. *JAMA Surg*. 2013;148(6):532-536. doi:10.1001/jamasurg.2013.1509
131. Mavroudis C, Jacobs JP. Congenital heart disease outcome analysis: methodology and rationale. In: *J Thorac Cardiovasc Surg*. Vol 123. ; 2002:6-7.
132. Vinocur JM, Moller JH, Kochilas LK. Putting the Pediatric Cardiac Care Consortium in context: evaluation of scope and case mix compared with other reported surgical datasets. *Circ Cardiovasc Qual Outcomes*. 2012;5(4):577-579. doi:10.1161/circoutcomes.111.964841

133. Moller JH. Using Data to Improve Quality: the Pediatric Cardiac Care Consortium. *Congenit Heart Dis*. 2016;11(1):19-25. doi:10.1111/chd.12297
134. Pyles LA, Hills CM, Larson VE, Moller JH. Pediatric Cardiac Care Consortium: an instrument for evidence-based clinical decision support. *J Cardiovasc Transl Res*. 2009;2(2):219-224. doi:10.1007/s12265-009-9091-z
135. Spector LG, Menk JS, Vinocur JM, et al. In-Hospital Vital Status and Heart Transplants After Intervention for Congenital Heart Disease in the Pediatric Cardiac Care Consortium: Completeness of Ascertainment Using the National Death Index and United Network for Organ Sharing Datasets. *J Am Heart Assoc*. 2016;5(8). doi:10.1161/jaha.116.003783
136. Cherkin D, Lawrence D. An evaluation of the American Medical Association's Physician masterfile as a data source--one state's experience. *Med Care*. 1977;15(9):767-769. doi:10.1097/00005650-197709000-00004
137. McCracken C, Spector LG, Menk JS, et al. Mortality Following Pediatric Congenital Heart Surgery: An Analysis of the Causes of Death Derived From the National Death Index. *J Am Heart Assoc*. 2018;7(22):e010624. doi:10.1161/jaha.118.010624
138. 1983 and 1993 Rural-Urban Continuum Codes. Published online May 20, 2004. Accessed December 1, 2020. https://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx
139. 2010 Census Regions and Divisions of the United States. Published online August 20, 2018. Accessed December 1, 2020. https://www.census.gov/geographies/reference-maps/2010/geo/2010-census-regions-and-divisions-of-the-united-states.html
140. Lillemoe KD. Surgical Volume/Outcome Debate. *Ann Surg*. 2017;265(2):270. doi:10.1097/sla.0000000000002110
141. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208
142. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010
143. *LinkPlus*. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 2020. Accessed March 4, 2021. https://www.cdc.gov/cancer/npcr/tools/registryplus/lp.htm
144. Bell B, Ene M, Smiley W, Schoeneberger J. A Multilevel Model Primer Using SAS PROC MIXED. *SAS Glob Forum 2013*. Published online 2013.
145. Dai J, Li Z, Rocke D. Hierarchical Logistic Regression Modeling with SAS GLIMMIX. *SAS Conf Proc West Users SAS Softw 2006 Irvine CA*. https://www.lexjansen.com/wuss/2006/analytics/ANL-Dai.pdf
146. Zhao K. Proper Estimation of Relative Risk Using PROC GENMOD in Population Studies.
147. Pasquali SK, Jacobs ML, He X, et al. Variation in congenital heart surgery costs across hospitals. *Pediatrics*. 2014;133(3):e553-560. doi:10.1542/peds.2013-2870

148. Kogon BE, Kanter K, Alsoufi B, Maher K, Oster ME. Outcomes and hospital costs associated with the Norwood operation: beyond morbidity and mortality. *Cardiol Young*. 2015;25(5):853-859. doi:10.1017/S1047951114002224
149. Mascio CE, Austin EH, Jacobs JP, et al. Perioperative mechanical circulatory support in children: an analysis of the Society of Thoracic Surgeons Congenital Heart Surgery Database. *J Thorac Cardiovasc Surg*. 2014;147(2):658-664: discussion 664-665. doi:10.1016/j.jtcvs.2013.09.075
150. Wrigley JM, Nam CB. Underlying versus Multiple Causes of Death: Effects on Interpreting Cancer Mortality Differentials by Age, Sex, and Race. *Popul Res Policy Rev*. 1987;6(2):149-160.
151. Redelings MD, Sorvillo F, Simon P. A Comparison of Underlying Cause and Multiple Causes of Death: US Vital Statistics, 2000–2001. *Epidemiology*. 2006;17(1):100–103. doi:10.1097/01.ede.0000187177.96138.c6
152. Brooks EG, Reed KD. Principles and Pitfalls: a Guide to Death Certification. *Clin Med Res*. 2015;13(2):74-82; quiz 83-84. doi:10.3121/cmr.2015.1276
153. Olubowale OT, Safford MM, Brown TM, et al. Comparison of Expert Adjudicated Coronary Heart Disease and Cardiovascular Disease Mortality With the National Death Index: Results From the REasons for Geographic And Racial Differences in Stroke (REGARDS) Study. *J Am Heart Assoc*. 2017;6(5). doi:10.1161/JAHA.116.004966
154. Goldstein Sarah A., D'Ottavio Alfred, Spears Tracy, et al. Causes of Death and Cardiovascular Comorbidities in Adults With Congenital Heart Disease. *J Am Heart Assoc*. 2020;9(14):e016400. doi:10.1161/JAHA.119.016400
155. Centers for Disease Control and Prevention. CDC Wonder. Published 2016. Accessed May 11, 2020. https://wonder.cdc.gov/
156. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med*. 2017;36(27):4391-4400. doi:10.1002/sim.7501
157. Haller B, Schmidt G, Ulm K. Applying competing risks regression models: an overview. *Lifetime Data Anal*. 2013;19(1):33-58. doi:10.1007/s10985-012-9230-8
158. Norozi K, Wessel A, Alpers V, et al. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. *Am J Cardiol*. 2006;97(8):1238-1243. doi:10.1016/j.amjcard.2005.10.065
159. Triedman JK. Arrhythmias in adults with congenital heart disease. *Heart*. 2002;87(4):383-389.
160. Lowe BS, Therrien J, Ionescu-Ittu R, Pilote L, Martucci G, Marelli AJ. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. *J Am Coll Cardiol*. 2011;58(5):538-546. doi:10.1016/j.jacc.2011.03.033
161. Verheugt CL, Uiterwaal CSPM, van der Velde ET, et al. Turning 18 with congenital heart disease: prediction of infective endocarditis based on a large population. *Eur Heart J*. 2011;32(15):1926-1934. doi:10.1093/eurheartj/ehq485
162. Mandalenakis Z, Karazisi C, Skoglund K, et al. Risk of Cancer Among Children and Young Adults With Congenital Heart Disease Compared With Healthy Controls. *JAMA Netw Open*. 2019;2(7):e196762-e196762. doi:10.1001/jamanetworkopen.2019.6762

163. Gurvitz M. Increasing Evidence for and a Word of Caution About an Association Between Cancer and Congenital Heart Disease. *JAMA Netw Open*. 2019;2(7):e196756-e196756. doi:10.1001/jamanetworkopen.2019.6756
164. Raissadati A, Nieminen H, Haukka J, Sairanen H, Jokinen E. Late Causes of Death After Pediatric Cardiac Surgery: A 60-Year Population-Based Study. *J Am Coll Cardiol*. 2016;68(5):487-498. doi:10.1016/j.jacc.2016.05.038
165. Sen AC, Morrow DF, Balachandran R, et al. Postoperative Infection in Developing World Congenital Heart Surgery Programs: Data From the International Quality Improvement Collaborative. *Circ Cardiovasc Qual Outcomes*. 2017;10(4). doi:10.1161/CIRCOUTCOMES.116.002935
166. Engel LW, Strauchen JA, Chiazze L, Heid M. Accuracy of death certification in an autopsied population with specific attention to malignant neoplasms and vascular diseases. *Am J Epidemiol*. 1980;111(1):99-112. doi:10.1093/oxfordjournals.aje.a112879
167. Kircher T, Nelson J, Burdo H. The autopsy as a measure of accuracy of the death certificate. *N Engl J Med*. 1985;313(20):1263-1269. doi:10.1056/NEJM198511143132005
168. Cowper DC, Kubal JD, Maynard C, Hynes DM. A primer and comparative review of major US mortality databases. *Ann Epidemiol*. 2002;12(7):462-468. doi:10.1016/s1047-2797(01)00285-x
169. McGivern L, Shulman L, Carney JK, Shapiro S, Bundock E. Death Certification Errors and the Effect on Mortality Statistics. *Public Health Rep*. 2017;132(6):669-675. doi:10.1177/0033354917736514
170. Sinard JH. Factors affecting autopsy rates, autopsy request rates, and autopsy findings at a large academic medical center. *Exp Mol Pathol*. 2001;70(3):333-343. doi:10.1006/exmp.2001.2371
171. Schottenfeld D, Eaton M, Sommers SC, Alonso DR, Wilkinson C. The autopsy as a measure of accuracy of the death certificate. *Bull N Y Acad Med*. 1982;58(9):778-794.

APPENDIX

Table A1: RACHS-1 risk categories and associated defects

Category	Procedures
1	Atrial septal defect surgery (including atrial septal defect secundum, sinus venosus atrial septal defect, patent foramen ovale closure)
	Aortopexy
	Patent ductus arteriosus surgery at age >30 d
	Coarctation repair at age >30 d
	Partially anomalous pulmonary venous connection surgery
2	Aortic valvotomy or valvuloplasty at age >30 d
	Subaortic stenosis resection
	Pulmonary valvotomy or valvuloplasty
	Pulmonary valve replacement
	Right ventricular infundibulectomy
	Pulmonary outflow tract augmentation
	Repair of coronary artery fistula
	Atrial septal defect and ventricular septal defect repair
	Atrial septal defect primum repair
	Ventricular septal defect repair
	Ventricular septal defect closure and pulmonary valvotomy or infundibular resection
	Ventricular septal defect closure and pulmonary artery band removal
	Repair of unspecified septal defect
	Total repair of tetralogy of Fallot
	Repair of total anomalous pulmonary veins at age >30 d
	Glenn shunt
	Vascular ring surgery
	Repair of aorta-pulmonary window
	Coarctation repair at age ≤30 d
	Repair of pulmonary artery stenosis
	Transection of pulmonary artery
	Common atrium closure
	Left ventricular to right atrial shunt repair
3	Aortic valve replacement
	Ross procedure
	Left ventricular outflow tract patch
	Ventriculomyotomy
	Aortoplasty
	Mitral valvotomy or valvuloplasty
	Mitral valve replacement
	Valvectomy of tricuspid valve
	Tricuspid valvotomy or valvuloplasty
	Tricuspid valve replacement
	Tricuspid valve repositioning for Ebstein anomaly at age >30 d
	Repair of anomalous coronary artery without intrapulmonary tunnel

	Repair of anomalous coronary artery with intrapulmonary tunnel (Takeuchi)
	Closure of semilunar valve, aortic or pulmonary
	Right ventricular to pulmonary artery conduit
	Left ventricular to pulmonary artery conduit
	Repair of double-outlet right ventricle with or without repair of right ventricular obstruction
	Fontan procedure
	Repair of transitional or complete atrioventricular canal with or without valve replacement
	Pulmonary artery banding
	Repair of tetralogy of Fallot with pulmonary atresia
	Repair of cor triatriatum
	Systemic to pulmonary artery shunt
	Atrial switch operation
	Arterial switch operation
	Reimplantation of anomalous pulmonary artery
	Annuloplasty
	Repair of coarctation and ventricular septal defect closure
	Excision of intracardiac tumor
4	Aortic valvotomy or valvuloplasty at age ≤30 d
	Konno procedure
	Repair of complex anomaly (single ventricle) by ventricular septal defect enlargement
	Repair of total anomalous pulmonary veins at age ≤30 d
	Atrial septectomy
	Repair of transposition, ventricular septal defect, and subpulmonary stenosis (Rastelli)
	Atrial switch operation with ventricular septal defect closure
	Atrial switch operation with repair of subpulmonary stenosis
	Arterial switch operation with pulmonary artery band removal
	Arterial switch operation with ventricular septal defect closure
	Arterial switch operation with repair of subpulmonary stenosis
	Repair of truncus arteriosus
	Repair of hypoplastic or interrupted arch without ventricular septal defect closure
	Repair of hypoplastic or interrupted aortic arch with ventricular septal defect closure
	Transverse arch graft
	Unifocalization for tetralogy of Fallot and pulmonary atresia
	Double switch
5	Tricuspid valve repositioning for neonatal
	Ebstein anomaly at age ≤30 d
	Repair of truncus arteriosus and interrupted arch
6	Stage 1 repair of hypoplastic left heart syndrome (Norwood operation)
	Stage 1 repair of nonhypoplastic left heart syndrome conditions

Damus-Kaye-Stansel procedure

Adapted from Jenkins *et al.*, 2002

Table A2: Authorship, year of publication, and data source for articles assessing center and surgeon volume

Authors	Year	Data	Size	Procedures
Anderson, BR et al.	2017	Society of Thoracic Surgeons-Congenital Heart Surgery Database	91 centers, 206 surgeons, 62,851 procedures	Any
Bazzani LG et al.	2007	Patient Discharge Database from California	52 centers, 12,801 procedures	Any
Berry JG et al.	2006	Kids' Inpatient Database	1,634 procedures	Norwood
Berry JG et al.	2007	Kids' Inpatient Database	113 centers, 2,301 procedures	VSD
Chan T et al.	2015	Kids' Inpatient Database	333 centers, 24,992 procedures	Any
Chang RR et al.	2002	Nationwide Inpatient Sample	47 centers, 346 procedures	Norwood
Checchia PA et al.	2005	Pediatric Health Information System	29 centers, 87 surgeons, 801 procedures	Norwood
Gutgesell et al.	2002	University Hospital Consortium	1,203 procedures	Norwood
Hannan EL et al.	1998	New York's Cardiac Surgery Reporting System	7,169 procedures	Any
Hickey P et al.	2010	Pediatric Health Information System Database	38 centers, 19,736 procedures	Any
Hirsch JC et al.	2008	Kids' Inpatient Database	ASO: 74 centers, 547 procedures; Norwood: 60 centers, 624 procedures	Norwood, ASO
Hornik CP et al.	2012	Society of Thoracic Surgeons Congenital Heart Surgery Database	53 centers, 111 surgeons, 2,555 procedures	Norwood
Jenkins KJ et al.	1995	California and Massachusetts hospital discharge data	37 centers, 2833 procedures	Any
Karamlou T et al.	2010	Congenital Heart Surgeons Society	33 centers, 2,421 procedures	IIA, Norwood, PAIVS, TGA
McHugh et al.	2010	University HealthSystem Consortium	118 centers, 5,416 procedures	Norwood
Oster et al.	2011	Pediatric Health Information Systems database	38 centers, 24,112 patients	Any
Pasquali SK et al.	2012	Society of Thoracic Surgeons Congenital Heart Surgery Database	53 centers, 2,557 procedures	Norwood
Pasquali SK et al.	2012	Society of Thoracic Surgeons Congenital Heart Surgery Database	68 centers, 35,776 procedures	Any
Sakai-Bizmark R et al.	2019	Arizona, California, Florida, Massachusetts, Maryland, Michigan, North Carolina, New Jersey, New York, Pennsylvania, and Washington State Inpatient Databases (SID)	718 centers, 33,288 procedures	Any
Scott WA et al.	2001	Pediatric Cardiac Care Consortium	24 centers, 16,795 procedures	VSD, ASO
Seifert et al.	2007	Kids' Inpatient Database	10,282 procedures	Any
Tabbutt S et al.	2012	Pediatric Heart Network	15 centers, 549 procedures	Norwood

Vinocur JM et al.	2013	Pediatric Cardiac Care Consortium	49 centers, 85,023 procedures	Any
Welke KF et al.	2006	Congenital Heart Surgeon's Society (CHSS) member institutions	11 centers, 16,805 procedures	Any

Table A3: Model specifications and results for the assessment of surgeon and center volume

Authors	Model	Exposure	Adjustments	Association
Anderson, BR et al.	Mixed-effect logistic regression	years since graduation	patient characteristics (age at surgery, prematurity, weight (among neonates and infants), sex, year of surgery, presence of non-cardiac anatomic abnormalities or syndromes/chromosomal abnormalities, previous cardiothoracic operation, and preoperative mechanical ventilation, circulatory support, persistent shock, renal failure, or the presence of any other preoperative risk factor, STAT Mortality Category), institutional/surgeon volumes, various measures of institutional surgeon team experience	$OR_{15–24\ years}$ = 0.88 (0.73, 1.08), $OR_{25–34\ years}$ = 0.93 (0.74, 1.16), $OR_{>35\ y}$ = 0.98 (0.76, 1.27)
Bazzani LG et al.	Logistic regression	center volume	age, surgical complexity categories 2, 3, and 4, non-elective admission status, cardiopulmonary bypass surgery, pulmonary hypertension present on admission, extracardiac anomalies, expected non–private payer status	$OR_{annual\ volume/100}$ = 0.86 (0.81–0.92)
Berry JG et al.	Logistic regression	center volume	prematurity/low birthweight, non-cardiac structural anomaly, teaching hospital status	OR_{High} = ref, OR_{Low} = 3.1 (1.1–8.3) .03, $OR_{Mid\text{-}low}$ = 2.0 (0.7–5.7) .18, $OR_{Mid\text{-}high}$ = 1.0 (0.5–1.8) .98
Berry JG et al.	Logistic regression	center volume	NA	$OR_{1\text{-}6}$ = ref, $OR_{7\text{-}18}$ = 1.98 0.22-17.5), $OR_{19\text{-}35}$ = 2.96 (0.37-23.63), $OR_{36\text{-}179}$ = 1.59 (0.20-12.71)
Chan T et al.	Mixed-effect logistic regression	center volume	surgical complexity, age category, insurance, race/ethnicity, prematurity, non-cardiac structural defects, hospital type, emergency admission, hospital urban status, teaching status	$OR_{>400}$ = ref, $OR_{<200}$ = 1.83 (1.20–2.79)
Chang RR et al.	Linear regression	center volume	NA	$r_{1988\text{-}1992}$ = -0.20, $r_{1993\text{-}1997}$ = -0.31, p < .01

Checchia PA et al.	Multiple regression	center and surgeon volume	NA	Center: $r^2 = 0.18$, p = 0.02;, surgeon: p = 0.312
Gutgesell et al.	no statistical test	center volume	NA	Mortality rate$_{< 50}$ = 50%, Mortality rate$_{> 50}$ = <40%
Hannan EL et al.	Logistic regression	center and surgeon volume	patient age, comorbidity, defect complexity	Mortality rate$_{average}$ = 6.75%, Mortality rate$_{center <100}$ = 8.26% (P < .05), Mortality rate $_{center \geq 100}$ = 5.95% (P < .05), Mortality rate $_{surgeon <75}$ = 8.77% (P < .05), Mortality rate $_{surgeon \geq 75}$ = 5.90% (P < .05), Mortality rate $_{center <100, surgeon <75}$ = 8.94%, Mortality rate $_{center \geq 100, surgeon \geq 75}$ = 5.45%
Hickey P et al.	Generalized estimating equation (GEE)	center volume	RACHS-1	OR $_{annual volume/100}$ = 0.93 (0.90-0.96)
Hirsch JC et al.	Logistic regression	center volume	gender, race/ethnicity, urban versus rural hospital, teaching versus nonteaching hospital, region of the country	Mortality rate$_{2 ASO/year}$ = 9.4%, Mortality rate$_{10 ASO/year}$ = 3.2%, Mortality rate$_{2 ASO/year}$ = 0.8%, Mortality rate$_{2 Norwood/year}$ = 34.8%, Mortality rate$_{10 Norwood/year}$ 25.7%, Mortality rate$_{20 Norwood/year}$ 16.7%
Hornik CP et al.	Logistic regression, GEE	center and surgeon volume	year of surgery, age, weight, sex, dominant ventricle, diagnosis of total anomalous pulmonary venous return, preoperative length of stay, the presence of any non-cardiac/genetic abnormality, pre-operative shock, mechanical ventilatory or circulatory support, arrhythmia, or neurologic deficit	$OR_{center >20}$ = ref, $OR_{center 0–10}$ = 1.56 (1.05–2.31), $OR_{center 11–20}$ = 1.28 (0.83–1.99), OR_{center} = 1.37 (0.92–2.05), OR_{center} = 1.20 (0.80–1.82) after adjusting for surgeon volume; OR $_{surgeon >10}$ = ref, OR $_{surgeon 0–5}$ = 1.60 (1.12–2.27), OR $_{surgeon 6–10}$ = 1.33 (0.94–1.87), OR $_{surgeon}$ = 1.47 (1.01–2.15), OR $_{surgeon}$ = 1.26 (0.88–1.78) after adjusting for center volume
Jenkins KJ et al.	GEE	center volume	sex, race, age, CPB, transfer from acute care hospital, complexity, state	$OR_{>300}$ = ref, $OR_{< 10}$ = 7.7 (1.6-37.8), OR_{10-100} = 2.9 (1.6-5.3), $OR_{101 - 300}$ = 3.0 1.8-4.9, Mortality rate$_{<10}$ = 18.5 (4.7-50.9),

Karamlou T et al.	Risk-adjusted parametric mortality models	center and surgeon volume	patient, demographic, and procedural factors	Mortality rate$_{10\text{-}100}$ = 7.9 (5.4-11.4), Mortality rate$_{101\text{-}300}$ = 8.2 (6.3-10.6), Mortality rate$_{>300}$ = 3.0 (2.1-4.3) Center: Mortality$_{\text{Norwood (per case)}}$ = -0.005 ± 0.01, p = .38, Mortality$_{\text{IAA (per case)}}$ = -0.03 ± 0.03, p = .37, Mortality$_{\text{PAIVS (per case)}}$ = 0.05 ± 0.04, p = .24, Mortality$_{\text{TGA (per case)}}$ = -0.07 ± 0.02 p <.001, Mortality$_{\text{Norwood}}$ -0.004 ± 0.007, p = .49, Mortality$_{\text{TGA}}$ -0.04 ± 0.01, p = .002
McHugh et al.	Logistic regression, GEE	center volume	sex, premature birth, chromosomal anomaly, endocardial cushion defect, double outlet right ventricle, era	OR$_{>64}$ = ref, OR$_{<20}$ = 2.49 (1.51–4.07) .0003, OR$_{20\text{-}64}$ = 1.75 (1.23–2.49) .0020,
Oster et al.	GEE Poisson regression models	center volume	age, race, sex, genetic syndrome, insurance type, surgery risk category (RACHS-1)	RACHS-1 1, 2, 3: Mortality risk$_{\text{annual volume/40}}$ -= 1.6% (-5.2, 2.2) .4122, RACHS-1 4, 5, 6: Mortality risk$_{\text{annual volume/40}}$ = -14.4% (-27.6, 1.2) .0678
Pasquali SK et al.	Logistic regression, GEE	center volume	year of surgery, age, weight, sex, dominant ventricle, diagnosis of total anomalous pulmonary venous return, pre-operative length of stay, the presence of any non-cardiac/genetic abnormality, pre-operative shock, mechanical ventilatory or circulatory support, arrhythmia, complete atrioventricular block, or neurologic deficit	OR$_{>20}$ = ref, OR$_{0\text{–}10}$ = 1.54 (1.02–2.32) 0.04, OR$_{11\text{–}20}$ = 1.27 (0.80–1.99) 0.31, OR$_{\text{continuous}}$ = 1.17 (1.01–1.35) 0.04
Pasquali SK et al.	Logistic regression	center volume	age, weight-for-age z score, any non-cardiac/genetic abnormality, any other preoperative risk factor (as defined above), preoperative length of stay, number of previous cardiothoracic surgeries, STS-EACTS surgical risk score	OR$_{>350}$ = ref, OR$_{<150}$ = 1.60 (1.23–2.08) .0004, OR$_{150\text{–}250}$ = 1.18 (0.92–1.52) .19, OR$_{250\text{–}350}$ = 1.25 (0.94–1.64) .12, OR$_{\text{continuous}}$ = 1.10 (1.04–1.17) .002
Sakai-Bizmark R et al.	Mixed-effect logistic regression	center volume	age, sex, race, insurance type, RACHS-1 category, year, state	OR$_{\leq 60}$ = ref, OR$_{61\text{-}144}$ = 0.84 (0.65, 1.08) 0.18, OR$_{>144}$ = 0.59 (0.46, 0.76) <0.01

Scott WA et al.	Logistic regression	center volume	risk, Trisomy 21, center, year, age, weight	RR_{VSD} = not significant, $RR_{ASO\ unadjusted}$ = 0.965, p <.05, $RR_{ASO\ adjusted}$ = not significant
Seifert et al.	Logistic regression	center volume	sex, time between admission and operation, age, race, insurance, month of admission, source of admission, type of admission, procedure, household income, state, comorbidities, weekend operation, procedures during hospitalization, pediatric hospital discharge percent, teaching hospital status	$OR_{Lowest\ tertile}$ = ref, OR_{Middle} = 0.68 0.46-1.00 .049, $OR_{Highest}$ = 0.50 0.35-0.71 .001
Tabbutt S et al.	Cox proportional hazard regression	center and surgeon volume	birth weight, gestational age, genetic abnormality, DHCA (deep hypothermic circulatory arrest) duration, total support time, ECMO (extracorporeal membrane oxygenation), open sternum	not significant
Vinocur JM et al.	Mixed-effect logistic regression	center volume	risk category, time period, age group, sex	$OR_{100\ cases/year}$ = 0.84 (0.78–0.90) p < 0.0001
Welke KF et al.	Logistic regression	center volume	NA	not reported, poor discrimination
Welke KF et al.	Logistic regression	center volume	patient-level risk factors, surgical case mix	All procedures $OR_{\geq 350}$ = ref, $OR_{250–349}$ = 1.05 (0.86–1.29) .63, $OR_{150–249}$ = 1.14 (0.84–1.55) .41, $OR_{<150}$ = 1.51 (1.19–1.90) .0005 Aristotle Basic Complexity ≤3: $OR_{\geq 350}$ = ref, $OR_{250–349}$ = 1.16 (0.87–1.53) .31, $OR_{150–249}$ = 1.08 (0.76–1.52) .68, $OR_{<150}$ = 1.21 (0.87–1.69) .26 Aristotle Basic Complexity >3: $OR_{\geq 350}$ = ref, $OR_{250–349}$ = 0.89 (0.69–1.15) .38, $OR_{150–249}$ = 1.22 (0.81–1.84) .35, $OR_{<150}$ = 2.41 (1.89–3.06) <.0001 Norwood procedures: $OR_{\geq 350}$ = ref, $OR_{250–349}$ = 1.43 (1.06–1.95) .020,

Welke KF et al.	Logistic regression	center volume	RACHS-1 category, age, year	$OR_{150–249}$ = 1.59 (1.09–2.32) .016, $OR_{<150}$ = 2.91 (1.98–4.28) <.0001 $OR_{>200}$ = ref, $OR_{\leq 20}$ = 0.99 (0.70–1.39) 0.94, $OR_{21–100}$ = 1.47 (1.25–1.73) <0.0001, $OR_{101–200}$ = 1.29 (1.10–1.52) 0.0023

Table A4: International classification of diseases codes for causes of death

Cause of Death	**ICD-9**	**ICD-10**
Infectious and parasitic diseases	001 – 139	A00 – B99
Neoplasms	140 – 239	C00 – D49
Endocrine, nutritional and metabolic disease of immunity disorders	240 – 279	E00 – E88
Type 2 Diabetes	250 – 250.9	E11
Diseases of blood and blood-forming organs	280 – 289	D50 – D89
Mental disorders	290 – 319	F01 – F99
Diseases of the nervous system and sense organs	320 – 389	G00 – G99, H00 – H95
Diseases of the circulatory system	390 – 459	I00 – I99
Hypertension	401 – 405.9	I10 – I16
Ischemic heart disease	410 – 414.9	I20 – I25
Conduction disorders	426 – 426.9	I44 – I45
Cardiac dysrhythmias	427 – 427.9	I47 – I49
Sudden cardiac death	427.5	I46.9
Heart failure	428 – 428.9	I50
Stroke	430 – 438.9	I60 – I69
Diseases of the respiratory system	460 – 519	J00 – J99
Diseases of the digestive system	520 – 579	K00 – K95
Diseases of the genitourinary system	580 – 629	N00 – N99
Complications of pregnancy, childbirth and puerperium	630 – 678	O00 – O99/9A
Diseases of the skin and subcutaneous tissue	680 – 709	L00 – L99
Disease of the musculoskeletal system and connective tissue	710 – 739	M00 – M99
Congenital malformation, deformations, and chromosomal abnormalities	740 – 759	Q00 – Q99
Congenital heart disease	745 – 747.4	Q20 – Q26
Non-CHD abnormalities	740 – 744, 747.5 – 759	Q00 – Q18, Q27 – Q99
Certain conditions originating in the perinatal period	760 – 779	P00 – P96
Symptoms, signs and ill-defined conditions	780 – 799	R00 – R99
External causes of injury and poisoning	800 – 999, E800 – E999	S00 – T88, V00 – Y89
Surgical and medical misadventures	E870 –E876.9	T80 – T89

Table A5: Categorization of defect severity

Defect severity	**Defects**
Mild	Patent ductus arteriosus, atrial septal defect (secundum), ventricular septal defect (isolated)
Moderate	atrial septal defect (primum), total anomalous pulmonary venous return and partial anomalous pulmonary venous return, common atrioventricular canal or partial atrioventricular canal, Ebstein's

	anomaly, pulmonary stenosis (moderate or severe), sub- or supra-aortic stenosis, ventricular septal defect (complex), coarctation of the aorta
Severe	Tricuspid atresia, mitral atresia, double-outlet ventricle, pulmonary atresia (all forms), d-TGA, TAC, L-TGA, single ventricle physiology, all other forms of cyanotic CHD not listed separately, other complex disease

Defect severity categories adapted from Spector *et al*. 2018