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Disparities in Survival and Mortality among Infants with Congenital Aortic, Pulmonary, and Tricuspid Valve Defects by Maternal Race/Ethnicity and Infant Sex

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Disparities in Survival and Mortality among Infants with Congenital Aortic, Pulmonary, and Tricuspid Valve Defects by Maternal Race/Ethnicity and Infant Sex

by

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ABSTRACT

Background: The etiology of congenital heart valve defects is not well understood; little is known about the risk factors that contribute to the survival and mortality outcomes of children with these defects.

Methods: Using data from the Texas Birth Defects Registry (TBDR) we conducted a retrospective cohort study of 2070 singleton infants with congenital aortic, pulmonary, or tricuspid valve atresia or stenosis born in Texas between January 1, 1996 and December 31, 2007 to Hispanic, Non-Hispanic (NH) black, and NH white women. TBDR data were death-to-birth matched by the Texas Vital Statistics Unit for deaths between January 1, 1996 and December 31, 2008. Using Kaplan-Meier survival estimates with log rank tests and Cox proportional hazards regression model hazard ratios (HR) with 95% confidence intervals (CI), we examined whether infant sex and maternal race/ethnicity affected early childhood survival or risk of mortality for children with congenital heart valve defects. Covariates included birth weight and gestational age, maternal age, maternal education, and number of co-occurring birth defects.

Results: In children with aortic valve atresia and aortic valve stenosis, we found males had higher early childhood survival than females (55.0% vs. 41.5%, P=0.0451 and 91.6% vs. 82.5%, P=0.0492, respectively). Early childhood survival for males (94.9%) with pulmonary valve stenosis was slightly lower than females (97.1%, P=0.0116), and was

also lower for NH black (94.1%) and Hispanic (95.3%) children than NH white children (97.8%, P=0.0340). After adjusting for covariates, early childhood mortality in children with pulmonary valve atresia with hypoplastic right ventricle was greater in NH black than NH white children (HR=2.93, CI 1.09-7.85, P=0.0329) and greater in NH black males than NH white males (HR=4.63, CI 1.12-19.19, P=0.0349). For children with tricuspid valve atresia, early childhood survival was lower in NH black males (35.7%) and Hispanic males (64.0%) than NH white males (81.0%, P=0.0269); after adjusting for covariates, risk for early childhood mortality was higher in NH black than NH white children (HR=3.39, CI 1.41-8.13, P=0.0062), and higher in NH black males than NH white males (HR=5.23, CI 133-20.58, P=0.0179).

Conclusions: Our findings demonstrate there are disparities in early childhood survival and risk of mortality by infant sex and maternal race/ethnicity for children with congenital heart valve defects. These findings provide a foundation for further investigation to better understand why these disparities exist and what can be done to improve the outcomes for children with these defects.

CHAPTER 1:

INTRODUCTION AND BACKGROUND

Birth defects are a primary cause of infant mortality in developed nations including the United States. Some of the most prevalent and fatal birth defects are congenital heart defects (Cleves, Ghaffar et al. 2003). The prevalence of congenital heart defects worldwide is approximately 8 per 1,000 live births (Samanek, Slavik et al. 1989; Marelli, Mackie et al. 2007; Amorim, Pires et al. 2008; Reller, Strickland et al. 2008; Bernier, Stefanescu et al. 2010; Wu, Chen et al. 2010). In the United States, hospitalization costs associated with birth defects were greater than $2 billion in 2004, and congenital heart defects represented more than 50% of these costs (Russo 2007).

Birth defect surveillance programs have been developed in many states, and data from these registries are useful for public health research in identifying causes for the development of prevention programs. Research has found differences in morbidity and mortality between males and females with congenital heart defects (Boneva, Botto et al. 2001; Lary and Paulozzi 2001; Seifert, Howard et al. 2007; Nembhard, Pathak et al. 2008; Engelfriet and Mulder 2009; Gilboa, Salemi et al. 2010). Studies have also shown racial disparity in prevalence, underlying cause of death, and survival for infants with congenital heart defects (Sadiq, Stumper et al. 1995; Boneva, Botto et al. 2001; Botto, Correa et al. 2001; Lary and Paulozzi 2001; Seifert, Howard et al. 2007; Nembhard,

Pathak et al. 2008; Almond, Thiagarajan et al. 2009; Fixler, Nembhard et al. 2010; Nembhard, Salemi et al. 2010; Nembhard, Wang et al. 2010; Nembhard 2011).

Congenital heart defect research has identified disparities, some of which are within a subset of congenital heart defects: congenital heart valve defects. However, little is known about mortality among infants with atresia and stenosis of the aortic, pulmonary, and tricuspid valves.

Understanding the race/ethnicity and sex differences in survival and mortality for infants with congenital heart valve defects can provide public health researchers and clinicians with information necessary to guide population health strategies and health care planning toward improving the lives of children and adults with these defects. Evaluations of potential disparity in survival probability and the risk of mortality in infants born with congenital heart valve defects are necessary to expand the current understanding of the role of race/ethnicity and sex in the complex etiology of these defects. Such knowledge will be useful in the development of prevention and treatment protocols for congenital heart valve defects. Our study evaluates race/ethnicity and sex as risk factors for congenital heart valve defect survival probability and risk of mortality.

ETIOLOGY OF CONGENITAL HEART DEFECTS

The etiology of congenital heart defects is unclear. There are numerous distinct congenital heart defects with various degrees of severity that contribute to the difficulty in clearly identifying the pathogenesis and etiology of the defects. Approximately 64% of congenital heart defects are isolated defects, most of the remaining cases are included with defects such as trisomies and syndromes (Botto, Lin et al. 2007). The cause for congenital heart defects can be categorized as follows: chromosomal abnormalities,

single gene defects, environmental factors, and family history (Thompson, McInnes et al. 1991). Other risk factors for congenital heart defects that have been identified include any of the following during pregnancy: maternal diabetes, maternal alcohol consumption, maternal exposure to prescription or non-prescription drugs or chemicals, and mothers who had rubella, rheumatic fever, or viral infection such as influenza during pregnancy (Sadler 2000). As such, the etiology of congenital heart defects is best understood as a complex interaction of environmental and genetic causes.

EMBRYOGENESIS OF THE HEART

Most congenital heart defects originate during the formation of the structure of the heart – during the first six weeks of gestation. By the 15th day post conception, mesoderm and ectoderm cells exist that will develop into the heart. Endocardial tubes are formed from these cells by the 19th day, and these tubes fuse and form heart cells (myocytes) by the 21st day. The heart starts beating on day 22 and blood is circulating by day 24. During the 23rd to 28th days the heart tube folds and twists to form atria and ventricles. Within the next two weeks the chambers of the heart form (Sadler 2000).

FETAL AND NEONATAL HEART DEVELOPMENT

Before birth, oxygen in the fetus' blood is provided by the mother. There is an opening between the right and left atrium, called the foramen ovale, through which blood flows from the right to left atrium. Blood bypasses the fetus' lungs through a blood vessel that connects the aorta and pulmonary arteries (ductus arteriosus). After birth the lungs fill with air, thereby reducing pulmonary resistance and increasing the blood flow from the right atrium to the right ventricle and into the pulmonary arteries. This reduces the flow of blood through the foramen ovale from the right atrium to the left atrium. These

changes result in the closing of the foramen ovale, and separation of the circulatory system into left and right halves. Once the baby is breathing on its own, the ductus arteriosus is no longer necessary and normally closes within days after birth (Moller and Neal 1990).

CONGENITAL HEART DEFECTS

Congenital heart defects are structural heart abnormalities of the arteries and veins near the heart, or the valves or walls within the heart, and are present at birth. Congenital heart defects disrupt the normal flow of blood through the heart, causing blood flow to slow down, flow in the wrong direction or to the wrong place, or be blocked completely (Moss and Allen 2008). There are many types of congenital heart defects with varied degrees of severity.

CONGENITAL HEART VALVE DEFECTS

In a normally functioning heart the flow of blood from the body through the heart and back out to the body is properly regulated by the opening and closing of heart valves with each heartbeat, as shown in Figure 1. Defective heart valves do not fully open or allow blood to leak back into heart chambers. Congenital heart valve defects include, but are not limited to: aortic valve atresia, aortic valve stenosis, pulmonary valve atresia, pulmonary valve stenosis, tricuspid valve atresia, and tricuspid valve stenosis. Congenital heart valve atresia is a defect that results when the valve fails to develop; stenosis is a defect resulting from narrowing or constriction of the valve, wherein the flaps of the valve do not fully open to allow enough blood to flow through (Moss and Allen 2008).

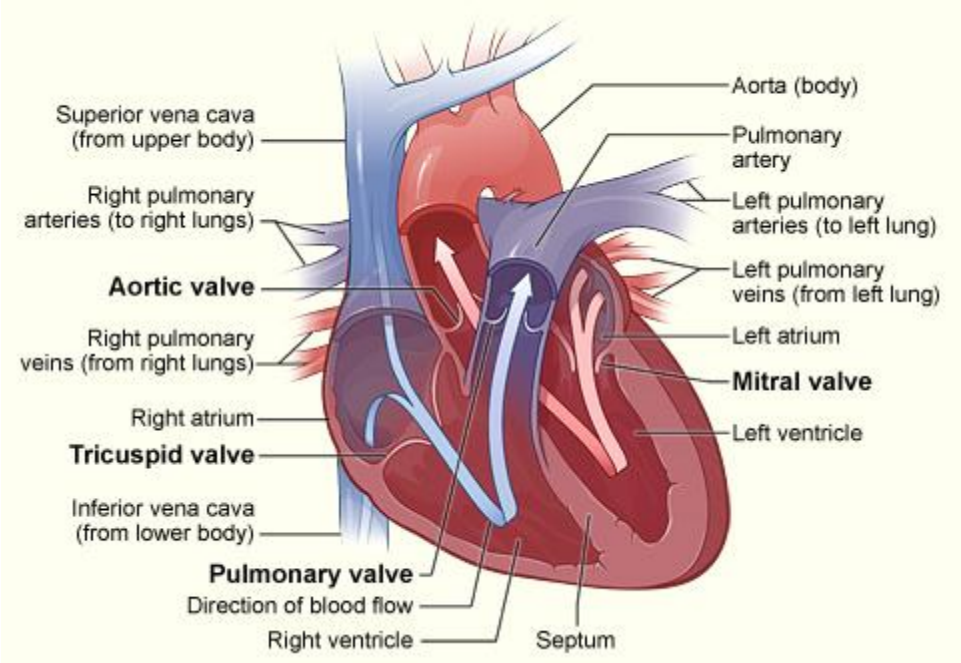

Figure 1. Cross section of a healthy heart. (U. S. Department of Health and Human Services).

NEED FOR THE STUDY

For nearly 20 years, researchers have reported disparities in risk factors for congenital heart defects and also among congenital heart valve defects. However, not all of the results of previous investigations agree. Limitations of previous studies include limited accuracy of congenital heart defect diagnosis documentation (Strickland, Riehle-Colarusso et al. 2008; Mangones, Manhas et al. 2009; Nembhard and Loscalzo 2009), and limitations of passive surveillance systems (Nembhard and Loscalzo 2009). In addition, previous studies did not evaluate all congenital heart valve defects individually; data for some defects were combined because of coding methods.

Perhaps the inconsistencies in results of previous investigations are due to reporting or diagnosis errors; a study using data with confirmed diagnoses might demonstrate stronger associations than have been observed in other studies. Verified data

are now available that clarify diagnoses for atresia and stenosis defect categories that have historically been combined. These data could also improve misdiagnosis limitations of previous studies.

Due to the variation in severity of heart valve defects, children with defects such as pulmonary or aortic valve stenosis might be expected to have better survival than children with pulmonary valve atresia (Samanek 1992; Samanek and Voriskova 1999). However, an evaluation of survival and mortality by sex or race/ethnicity for children with each specific congenital heart valve defect has not been reported. There is limited published information on survival probability and risk of mortality by sex or race/ethnicity for congenital heart valve defects. Our study determines survival and risk of mortality among children with congenital heart valve defects by infant sex and maternal race/ethnicity.

SPECIFIC AIMS AND HYPOTHESES

The purpose of this study was to evaluate risk factors associated with congenital heart valve defects in children. This study assesses whether the probability of survival or risk of mortality varies by infant sex or maternal race/ethnicity for each of six congenital heart valve defects. Two study aims with specific sub-aims and hypotheses are investigated. The study aims (1 and 2) intend to evaluate early childhood survival probability and risk of mortality for infants or children with congenital heart valve defects. Study sub-aims (a and b) further elucidate the evaluation of survival probability and risk of mortality to determine if differences exist within the study population based on infant sex or maternal race/ethnicity. The specific aims and hypotheses of this study are:

Aim 1

To determine if early childhood survival probabilities vary by infant sex or maternal race/ethnicity in children with congenital heart valve defects.

Sub-aim 1a

To determine if early childhood survival probability varies by infant sex for each of the congenital heart valve defects.

H_0: There is no difference in early childhood survival between males and females for each type of congenital heart valve defect.

Sub-aim 1b

To determine if early childhood survival probabilities vary by maternal race/ethnicity stratified by infant sex for each of the congenital heart valve defects.

H_0: There is no difference in early childhood survival between Hispanic or Non-Hispanic (NH) black infants compared to NH white infants for each type of congenital heart valve defect.

Aim 2

To determine if the risk of childhood mortality varies by infant sex or maternal race/ethnicity stratified by infant sex in children with congenital heart valve defects, after adjusting for potential confounders.

Sub-aim 2a

To determine if the risk of childhood mortality varies by infant sex for each of the congenital heart valve defects.

H_0: There is no difference in risk of childhood mortality between males and females for each type of congenital heart valve defect.

Sub-aim 2b

To determine if the risk of childhood mortality varies by maternal race/ethnicity, after stratifying by infant sex, for each of the congenital heart valve defects.

H_0: There is no difference in risk of childhood mortality between Hispanics or NH blacks compared to NH whites for each type of congenital heart valve defect.

FINDINGS OF THE STUDY

The results of this study are presented in three manuscripts: the first manuscript presents findings for maternal race/ethnicity and infant sex risk factors for early childhood survival probability and risk of mortality in infants born with aortic valve atresia and aortic valve stenosis. The second manuscript evaluates the hypotheses for pulmonary valve atresia and stenosis, and the third manuscript presents findings for tricuspid valve atresia. This research is significant because it advances knowledge from previous investigations to better understand the effects of race/ethnicity and sex on early childhood survival and mortality among infants born with these defects.

CHAPTER 2:

DISPARITIES IN SURVIVAL AND MORTALITY AMONG INFANTS WITH CONGENITAL AORTIC VALVE DEFECTS BY MATERNAL RACE/ETHNICITY AND INFANT SEX

ABSTRACT

Background: Little is known about racial/ethnic or infant sex differences contributing to the survival and mortality outcomes of children with aortic valve atresia or aortic valve stenosis.

Methods: Using data from the Texas Birth Defects Registry, we conducted a retrospective cohort study of 519 singleton infants born to Hispanic, Non-Hispanic (NH) white, and NH black women in Texas between January 1, 1996 and December 31, 2007 with congenital aortic valve atresia and stenosis. We used Kaplan-Meier survival estimates with log-rank tests and Cox proportional hazards regression ratios (HR) and 95% confidence intervals (CI) to determine, after adjusting for confounders, whether infant sex or maternal race/ethnicity affects early childhood survival or risk of mortality for these children.

Results: For children with aortic valve atresia and aortic valve stenosis, males had higher early childhood survival than females (55.0% vs. 41.5%, P=0.0451 and 91.6% vs. 82.5%, P=0.0492, respectively). After adjusting for covariates, there was no statistically significant differences in early childhood mortality between males and females with

aortic valve atresia (HR=0.89; CI 0.59-1.35; P=0.5840) or aortic valve stenosis (HR=0.80; CI 0.37-1.73; P=0.5748). There were no racial/ethnic differences in risk of early childhood mortality for children with either aortic valve atresia or aortic valve stenosis.

Conclusion: Our study found that early childhood survival in males with aortic valve atresia was better than survival in females with aortic valve atresia. Similarly, early childhood survival in males with aortic valve stenosis was better than survival in females with aortic valve stenosis. Our study did not identify race/ethnicity risk factors in the survival or risk of mortality for children with aortic valve defects.

INTRODUCTION

Birth defects are a primary cause of infant mortality and contribute more than half of the reported hospitalization costs associated with birth defects in the United States (Russo 2007). In order to improve the health and survival of infants and children, public health researchers need to better understand risk factors associated with congenital heart defects so that effective prevention and treatment programs can be developed and implemented (Botto, Correa et al. 2001; Nembhard, Waller et al. 2001; Cleves, Ghaffar et al. 2003; Nembhard, Salemi et al. 2007; Nembhard, Pathak et al. 2008; Nembhard, Salemi et al. 2009; Fixler, Nembhard et al. 2010; Nembhard, Salemi et al. 2010). We present our investigation of risk factors contributing to aortic valve atresia and aortic valve stenosis, toward that goal.

Aortic Valve Stenosis

Aortic valve stenosis is the narrowing of the valve located between the left ventricle and the aorta, resulting in restriction of oxygen-rich blood out of the heart to the body. Aortic valve stenosis is an obstruction defect and is included in the category of noncomplex left ventricular outflow tract obstruction malformations (i.e., aortic valve stenosis, coarctation of the aorta, and hypoplastic left heart syndrome). It can occur with patent ductus arteriosus, coarctation of the aorta, non-inlet ventricular septal defect, and atrial septal defect, and severity varies considerably. Mild cases can be undetected in early life; severe cases can cause heart failure in infants.

Table 1 provides a summary of literature findings for aortic valve defects. As shown in the table, some studies did not differentiate aortic valve stenosis from aortic valve atresia. The prevalence of aortic valve stenosis per 10,000 live births, ranges from

0.61 (95% CI 0.29-1.12) to 1.39 (95% CI 1.17-1.65) (Ferencz, Rubin et al. 1985; Pradat, Francannet et al. 2003). Racial/ethnic disparity in the prevalence of aortic valve stenosis has been reported. Correa-Villasenor (1991) reported an excess of aortic valve stenosis in whites compared to blacks (OR=3.6; 95% CI 1.7-7.6). Fixler, Pastor et al. (1993) found decreased risk of aortic valve stenosis in blacks than whites (blacks=0.07/1,000 live births; whites=0.4/1,000; $p<0.005$), as did Botto, Correa et al. (2001) (RR=0.38; 95% CI 0.22-0.64). Carmichael, Shaw et al. (2004) found lower risk of aortic valve stenosis in foreign-born Hispanics than NH whites (RR=0.7; 95% CI 0.6-0.8). Fixler, Pastor et al. (1993) also found decreased risk of aortic valve stenosis in Mexican-Americans than whites (0.20/1,000 vs. 0.4/1,000, respectively; $p<0.05$).

Aortic valve stenosis has consistently been found higher in males than females: male to female ratio=2.41 (95% CI 1.84-3.25) (Pradat, Francannet et al. 2003); RR=2.52 (95% CI 1.61-3.75) (Forrester and Merz 2004); PR=2.71 (95% CI 1.70-4.31) (McBride, Marengo et al. 2005); RR=1.51 (95% CI 1.11-2.07) (Lary and Paulozzi 2001); and boy to girl ratio=1.95:1 (Samanek 1994).

Other studies have reported disparities in aortic valve defects, but did not study aortic valve atresia and stenosis separately. Lubinsky (1997) reported more aortic valve anomalies in males (76%) than females (24%). One study of data for 9,352 singleton infants in Florida's passive surveillance birth defects registry found that aortic valve atresia/stenosis prevalence disparity was only statistically significant for male infants, (RR=0.34, 95% CI 0.13-0.94) for black males compared to white males; and (RR=0.32, 95% CI 0.12-0.89) for Hispanic males compared to white males (Nembhard, Wang et al. 2010). Another study using these data found NH black and Hispanic infants had lower

prevalence rates of aortic valve atresia/stenosis than NH white infants: (RR=0.46; 95% CI 0.24-0.89) for NH blacks, and (RR=0.53; 95% CI 0.28-0.97) for Hispanics (Nembhard, Salemi et al. 2010).

Survival during the first year of life of infants born with aortic valve stenosis is around 90% (Samanek 1992; Samanek and Voriskova 1999). There are no reported data for mortality or survival that differentiate by sex or race/ethnicity.

Aortic Valve Atresia

Aortic valve atresia is the absence of the aortic valve, prohibiting blood flow from the heart to the body. Babies with aortic valve atresia survive only when patent ductus arteriosus persists. Aortic valve atresia can be associated with hypoplastic left heart syndrome, a complex condition characterized by an undeveloped left side of the heart, including the aorta, left ventricle (a defect called hypoplastic left ventricle), and mitral valve (defects referred to as mitral valve atresia or mitral valve stenosis).

Although some studies have findings for aortic valve stenosis and aortic valve atresia/stenosis, there is a lack of information on disparity by sex or race/ethnicity (Table 1).

METHODS

Study Design and Data Source

We conducted a retrospective cohort study of 219 infants with congenital aortic valve atresia and 300 infants with aortic valve stenosis born in Texas between January 1, 1996 and December 31, 2007. Data was obtained from the Texas Birth Defects Registry (TBDR), which is maintained by the Birth Defects Epidemiology and Surveillance Branch of the Texas Department of State Health Services. In the TBDR population-based

active surveillance system TBDR personnel review medical records to identify infants diagnosed within the first year after birth with structural and chromosomal birth defects. The TBDR surveillance began in 1995, and since 1999 data have been collected for all births in the state of Texas. TBDR data are death-to-birth matched by the Texas Vital Statistics Unit using decedent name, date of death and date of birth, mother's first and maiden and/or current last names.

The TBDR utilizes six-digit birth defect coding that has evolved through British Pediatric Association (BPA) extension of the International Classification of Disease, ninth revision clinical modification diagnostic codes (ICD-9 codes). Our study used data coded according to the June 29, 2007 revision of TBDR's BPA coding system.

Study Population

The study population included all live-born singleton infants with aortic valve atresia or aortic valve stenosis (BPA Codes 746.480 and 746.300) born in Texas between January 1, 1996 and December 31, 2007 to NH white, NH black, or Hispanic women of any age. Aortic valve atresia and aortic valve stenosis cases with co-occurring heart defects (BPA Codes 745.000 through 747.490) were considered for inclusion in our study (Appendix A). However, cases associated with complex defects such as trisomies or syndromes (except for hypoplastic left heart syndrome) were excluded from our study. All cases were reviewed by a pediatric cardiologist, Dr. David E. Fixler, M.D., and aortic valve atresia cases were included only if at least one of the following heart defects was co-occurring: hypoplastic left heart syndrome (BPA Code 746.700), mitral valve stenosis (BPA Code 746.500), mitral valve atresia (BPA Code 746.505), or hypoplastic left

ventricle (BPA Code 746.881). Aortic valve stenosis cases were selected based on review of these cases and their co-occurring heart defects.

Covariates

We used infant and maternal covariate information obtained by the TBDR from birth certificate and medical records. We included infant sex, and maternal race/ethnicity based on maternal self-report. Gestational age categorized as term (≥37 completed weeks) or pre-term (<37 weeks) was included; gestational age was based on last menstrual period or clinical estimate of gestation from medical records was substituted when last menstrual period data were missing. Consistent with published literature, we included birth weight categorized as normal (≥2500 grams), low (1500-2499 grams), or very low (<1500 grams), as recorded on birth certificates (CDC 1990; Alexander, Kogan et al. 2003; Nembhard 2011). Also consistent with literature, gestational age and birth weight were included as a combination variable with six categories: <37 weeks and <1500 grams; <37 weeks and 1500-2499 grams; <37 weeks and ≥2500 grams; ≥37 weeks and <1500 grams; ≥37 weeks and 1500-2499 grams; and ≥37 weeks and ≥2500 grams (Bol, Collins et al. 2006; Nembhard 2011). Maternal age categorized as <20 years, 20-29 years, 30-39 years, and 40+ years and maternal education categorized as high school (12 years), <high school, or >high school were also included. Number of co-occurring birth defects was also included in the analyses as a continuous variable.

Data Analysis

Descriptive statistics were calculated for main study variables and covariates. We calculated survival time using date of birth and date of death for deceased infants. When

TBDR data did not have a date of death recorded, infants were censored at the end of the study period, December 31, 2008.

Early childhood survival was estimated for children with each defect using the Kaplan-Meier method. Kaplan-Meier survival curves were computed to compare survival estimates by infant sex, and maternal race/ethnicity, and tested the difference between the curves using the log-rank test.

Unadjusted and adjusted hazard ratios were calculated for mortality using Cox proportional hazard regression models. The adjusted hazard ratios were computed using a final regression model developed by backward selection method, removing variables with less than 10% effect on the hazard ratio. The models for infant sex and maternal race/ethnicity stratified by sex used females and NH whites as the reference groups. The proportional hazards assumption was tested to ensure the assumption was met; we inspected the proportionality by including time-dependent covariates in the model and testing for their significance. Variables included in the final model were: maternal age, maternal education, birth weight/gestational age, and number of defects. Although not all variables had a major effect on the adjusted hazard ratios (i.e., changing the hazard ratio by 10% or more), all of the variables included in the final model are biologically important based on published literature. Results were considered statistically significant if the 95% confidence interval excluded 1 or $P<0.05$. Calculations were performed using SAS 9.2 for Kaplan-Meier survival estimates and Cox proportional hazards regression models, and Stata Release 12 for Kaplan-Meier survival plots.

Protection of Human Subjects

The study was conducted with the approval of the University of South Florida Institutional Review Board (IRB), and the Texas Department of State Health Services.

Power and Sample Size

The formula used to estimate power for this study is an extension of Schoenfeld's sample-size formula for the proportional-hazards regression model, solved for power (1-β) (Hipwell, Strachan et al. 2000; Shechter, Sharir et al. 2000):

$$N = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{P\,(1-R^2)\,\sigma^2\,B^2}$$

Where N is the sample size; $z_{1-\alpha/2}$ and $z_{1-\beta}$ are standard normal deviates at a two-sided significance level α and power (1-β); P is the overall event rate or proportion of non-censored participants; R^2 is the effect size of covariates on the variable of interest; σ is the standard deviation of the variable of interest; and B is the effect size (log of the hazard ratio).

We calculated the power to detect hazard ratios of 1.5 and 3.0; the significance level, alpha, for our study was 0.05. Since our associations indicate risk or protective exposures, two sided hypotheses were tested. Standard deviation values of 0.5 and 0.7 were used to show a range of possibilities; the influence of covariates on the outcome, R^2 was estimated at 0.15. Based on the study data, estimates of study power were calculated based on three potential scenarios: 1) an event (death) rate of 5%, 2) an event rate of 10%, and 3) an event rate of 40%.

The results of these calculations are presented in Appendix B. Since our study size was fairly small for some of our stratified groups, our ability to observe statistically significant results may be limited.

RESULTS

Aortic Valve Atresia

Descriptive statistics for infants born with aortic valve atresia are provided in Table 2. The total number of aortic valve atresia cases in our study was 219 and included 89 NH white, 23 NH black, and 107 Hispanic children. Of these, 112 (51.1%) children were alive at the end of our study and 107 (48.9%) were deceased. More than half (52.2%) of the NH black children with aortic valve atresia died during the study period while fewer than half of the Hispanic (48.6%) or NH white (48.3%) children died. Approximately 80.4% of surviving children and 71.0% of deceased children were born full term (≥37 weeks) and at normal birth weight (≥2500 grams). There were considerably more males (62.6%) than females (37.4%) with aortic valve atresia.

Survival and Risk of Childhood Mortality by Infant Sex

Kaplan-Meier estimates, hazard ratios, and 95% confidence intervals are presented in Table 3. Early childhood survival for males (55.0%) with aortic valve atresia was significantly higher than for females (41.5%, P = 0.0451). After adjusting for covariates, there was no statistically significant difference in early childhood mortality between males and females with aortic valve atresia (HR 0.89; 95% CI 0.59-1.35; P=0.584).

Survival by Maternal Race/Ethnicity and Infant Sex

Kaplan-Meier estimates for children with aortic valve atresia are presented in Table 4, and survival curves are presented in Figure 2. The estimated survival for children was not significantly different for NH white (50.3%), NH black (47.4%), and Hispanic (50.2%) children (P=0.9956); NH black males (35.7%), NH white males (56.6%), and Hispanic (58.2%) males (P=0.3707); or NH black females (64.8%), NH white females (39.4%), and Hispanic (38.1%) females (P=0.3160).

Risk of Childhood Mortality by Maternal Race/Ethnicity and Infant Sex

Hazard ratios and CI for early childhood mortality in children with aortic valve atresia are presented in Table 5. After adjusting for covariates, NH black (HR 1.13; CI 0.58-2.22; P=0.7241) and Hispanic (HR 0.88; CI 0.57-1.38; P=0.5846) infants born with aortic valve atresia do not have significantly different early childhood mortality than NH white infants. Early childhood mortality was not statistically different in NH black females (HR 0.33; CI 0.09-1.18; P=0.0886) or Hispanic females (HR 0.95; CI 0.47-1.94; P=0.8886) compared to NH white females. NH black males (HR 1.95; CI 0.83-4.59; P=0.1283) or Hispanic males (HR 0.50; CI 0.50-1.73; P=0.8604), did not have statistically different early childhood mortality compared to NH white males.

Aortic Valve Stenosis

Descriptive statistics for infants born with aortic valve stenosis are provided in Table 6. The study included 300 aortic valve stenosis cases: 145 NH white, 14 NH black, and 141 Hispanic children. Of these, 268 (89.3%) were alive at the end of our study and 32 (10.7%) were deceased. Approximately 77.6% of surviving children and 56.3% of

deceased children were born full term (≥37 weeks) and at normal birth weight (≥2500 grams). There were considerably more males (68.7%) than females (31.3%) with aortic valve stenosis; however, of the deceased children approximately 46.9% were female.

Survival and Risk of Childhood Mortality by Infant Sex

Kaplan-Meier estimates, hazard ratios, and 95% confidence intervals are presented in Table 3. Early childhood survival for males (91.6%) with aortic valve stenosis was significantly higher than for females (82.5%, P=0.0492). After adjusting for covariates, there was no statistically significant difference in early childhood mortality between males and females with aortic valve stenosis (HR 0.80; 95% CI 0.37-1.73; P=0.5748).

Survival by Maternal Race/Ethnicity and Infant Sex

The Kaplan-Meier estimates for children with aortic valve stenosis are presented in Table 4, and Kaplan-Meier survival curves are presented in Figure 3. The estimated survival for children was not significantly different for NH white (89.4%), NH black (92.9%), and Hispanic (87.82%) children (P=0.8852); NH white males (91.9%) and Hispanic (90.5%) males (P=0.6236); or NH black females (83.3%), NH white females (83.3%), and Hispanic (81.6%) females (P=0.9625).

Risk of Childhood Mortality by Maternal Race/Ethnicity and Infant Sex

The Cox proportional hazards regression model results for children with aortic valve stenosis adjusted for covariates are presented in Table 5. NH black (HR 0.40; CI 0.05-3.23; P=0.386) and Hispanic (HR 0.51; CI 0.20-1.28; P=0.1493) infants born with

aortic valve stenosis do not have significantly lower risk for early childhood mortality than NH white infants.

Cox proportional hazards model results by maternal race/ethnicity stratified by infant sex and adjusted for covariates are presented in Table 5. Risk of early childhood mortality was not statistically different in NH black females (HR 0.94; CI 0.09-9.75; P=0.9608) or Hispanic females (HR 0.25; CI 0.06-1.14; P=0.0728) compared to NH white females, or NH black males (HR undefined) and Hispanic males (HR 0.91; CI 0.26-3.22; P=0.8843) compared to NH white males with aortic valve stenosis.

DISCUSSION

We investigated 219 cases of aortic valve atresia and 300 cases of aortic valve stenosis and for each defect we found males had higher early childhood survival than females. After adjusting for covariates, we did not observe statistically significant differences in early childhood mortality.

Aortic valve atresia has not previously been studied as a defect isolated from aortic valve stenosis. Aortic valve atresia inclusion criteria for our study considered cases only if at least one of the following defects was co-occurring: hypoplastic left heart syndrome, mitral valve stenosis, mitral valve atresia, or hypoplastic left ventricle. As such, we did not investigate aortic valve atresia as an isolated defect since clinically this defect does not occur unless it is part of other malformations of the heart. For this reason, our results for aortic valve atresia may not be directly comparable to findings of previous studies.

Previous investigations have reported 1-year survival probabilities of 91 % (CI 89-92) (Samanek 1992) and 90% (CI 87-93) (Samanek and Voriskova 1999) for aortic

valve stenosis; our Kaplan-Meier survival curves for males do not conflict with these findings, but females' survival in the first year are below 90%, particularly for NH black and NH white females in our study.

We found infant sex differences in the pattern of survival for our study period. However, when considering the confounding influence of covariates, we did not see differences in the risk of early childhood mortality. The variables with most influence on the final regression model were birth weight/gestational age and number of co-occurring defects.

Sex disparities in early childhood survival indicate genetics may influence survival outcomes. Our study did not evaluate paternal variables such as paternal race/ethnicity. We also did not investigate maternal or paternal environmental factors, family history of congenital heart valve defects, or severity of defects. The possibility exists that there are unidentified factors that explain the sex disparities in early childhood survival for children with congenital aortic valve defects.

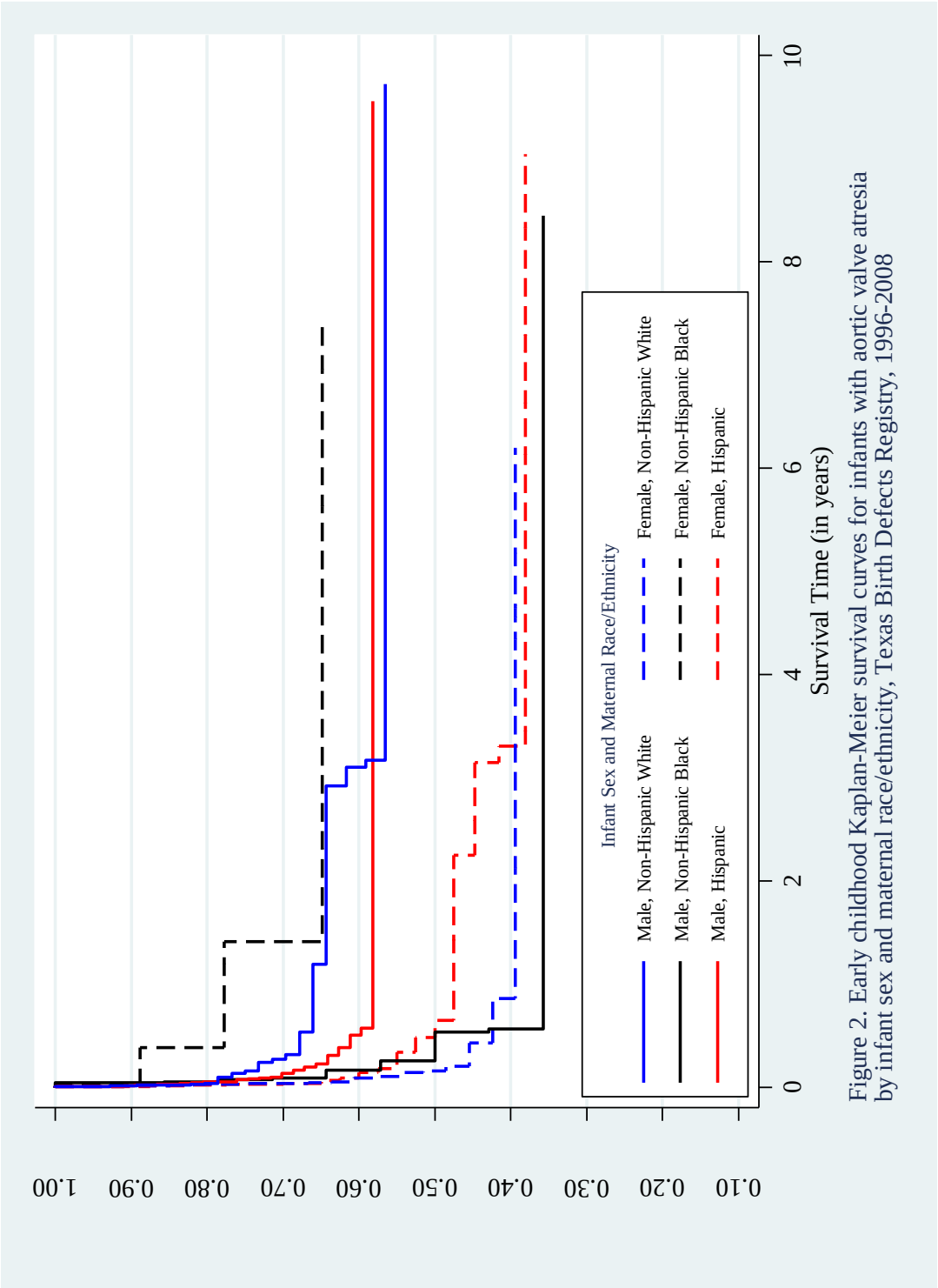

Figure 2. Early childhood Kaplan-Meier survival curves for infants with aortic valve atresia by infant sex and maternal race/ethnicity, Texas Birth Defects Registry, 1996-2008

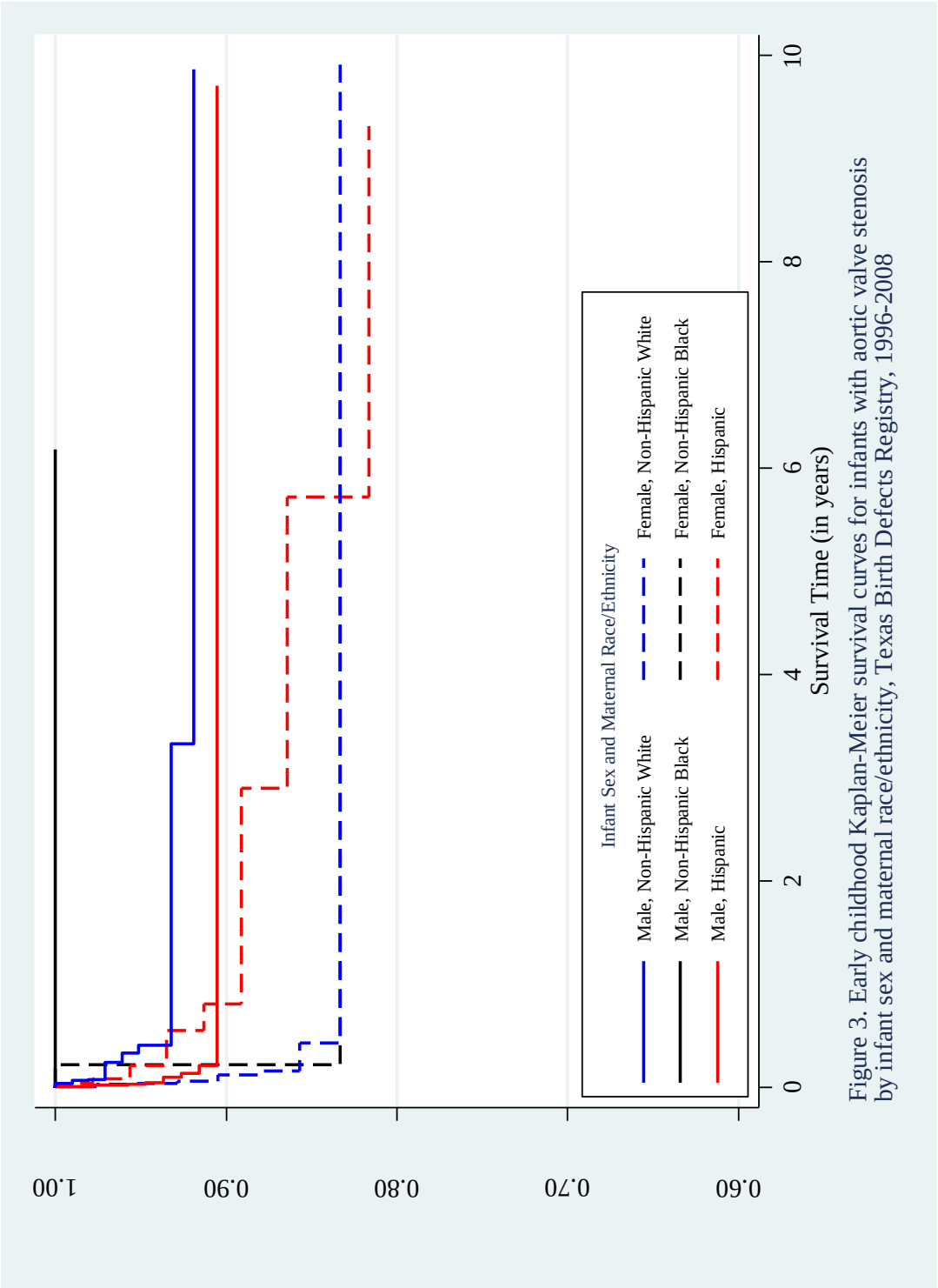

Figure 3. Early childhood Kaplan-Meier survival curves for infants with aortic valve stenosis by infant sex and maternal race/ethnicity, Texas Birth Defects Registry, 1996-2008

Table 1. Descriptive epidemiology of aortic valve defects from published studies, 1985-2010

Author	Study Population	Observation	Estimate (95% CI)
Prevalence Per 10,000 Births			
Ferencz et al. 1985	Baltimore-Washington Infant Study of 664 infants born in the study area between 1981 and 1982 and diagnosed with congenital heart disease.	AVS	0.81 (not reported)
Nembhard et al. 2010	Texas Birth Defects Registry data for 48,391 singleton infants born between January 1 and December 31, 1996 and diagnosed with major birth defects.	AVA/S in Hispanics	1.03 (0.72-1.51)
		AVA/S in Non-Hispanic Blacks	0.89 (0.59-1.36)
		AVA/S in Non-Hispanic Whites	1.95 (1.68-2.40)
Pradat et al. 2003	California, Sweden and France birth defect registry data for 12,932 infants born between 1981 and 1992 with congenital heart defects.	AVS in Asians	0.94 (0.55-1.51)
		AVS in Blacks	0.61 (0.29-1.12)
		AVS in Hispanics	0.81 (0.63-1.02)
		AVS in Whites	1.39 (1.17-1.65)
Prevalence Comparisons for Race/Ethnicity			
Nembhard, Wang et al. 2010	Florida Birth Defects Registry data for 16,788 singleton infants diagnosed with congenital heart defects, born between 1998 and 2003.	Lower AVA/S rates in non-Hispanic black males than non-Hispanic white males	RR=0.34 (0.13-0.94)
		Lower AVA/S rates in non-Hispanic black males than Hispanic males	RR=0.32 (0.12-0.89)
Nembhard et al. 2010	Texas Birth Defects Registry data for 48,391 singleton infants born between January 1 and December 31, 1996 and diagnosed with major birth defects.	Lower AVA/S rates in non-Hispanic blacks than non-Hispanic whites	RR=0.46 (0.24-0.89)
		Lower AVA/S in Hispanics than non-Hispanic whites	RR=0.53 (0.28-0.97)
Correa-Villasenor et al. 1991	Baltimore-Washington Infant Study of 2,087 infants with cardiovascular malformations between 1981 and 1987.	Higher odds of AVS in whites than blacks	OR=3.6 (1.7-7.6)
Botto et al. 2001	Metropolitan Atlanta Congenital Defects Program data for 5,813 infants with major congenital heart defects born between 1968 and 1997.	Lower AVS rate in blacks than whites	RR=0.38 (0.22-0.64)
Fixler et al. 1993	Dallas County, Texas data for 2,509 infants with congenital heart disease born between 1971 and 1984.	Lower AVS rate in blacks than whites	PR Blacks=0.07/1,000 PR Whites=0.4/1,000 ($p<0.005$)
		Lower prevalence of AVS in Mexican-Americans (M-A) than whites	PR M/A=0.20/1,000 PR Whites=0.4/1,000 ($p<0.05$)

Table 1. Descriptive epidemiology of aortic valve defects from published studies, 1985-2010

Author	Study Population	Observation	Estimate (95% CI)
Prevalence Comparisons for Race/Ethnicity, continued			
Carmichael et al. 2004	California Birth Defects Monitoring Program surveillance data for 2,234,846 infants and fetuses born between 1989 and 1997 with congenital malformations.	Lower risk for AVS in foreign-born Hispanics than US-born Hispanics, African-Americans or whites	ARR=0.7 (0.6-0.8)
Prevalence by Sex			
McBride et al. 2005	Texas Birth Defects Registry data for 499 infants with left ventricular outflow tract malformations (aortic valve stenosis, coarctation of the aorta, and hypoplastic left heart syndrome) born between 1999 and 2001.	Higher prevalence of AVS in males	PRR=2.71 (1.70-4.31)
Forrester and Merz 2004	Hawaii Birth Defects Program data for 5,010 infants with congenital heart defects born between 1986 and 1999.	Higher rate of AVS in males	RR=2.52 (1.61-3.75)
Pradat et al. 2003	California, Sweden and France birth defect registry data for 12,932 infants born between 1981 and 1992 with congenital heart defects.	Higher prevalence risk of AVS in males	Ratio of males to females= 2.41 (1.84-3.25)
Lary and Paulozzi 2001	Metropolitan Atlanta Congenital Defects Program data for 28,965 infants born between 1968 and 1995 with at least one major birth defect.	Higher risk of AVS in males	RR=1.51 (1.11-2.07)
Lubinsky 1997	Meta-analysis of sex biased congenital anomalies findings from studies published between 1967 and 1993.	Aortic valve anomalies diagnosed in males more frequently than in females	76% in males 24% in females (CI not reported)
Samanek 1994	4,409 children born in Bohemia between 1977 and 1984 with congenital heart malformations.	Higher ratio of AVS in boys	Boy to Girl Ratio=1.95:1
Survival Percent			
Samanek 1992	946 Bohemian children with congenital heart disease who died before they were 15 years of age; data were collected between 1952 and 1979.	AVS 1-year survival rate	91% (89-92)
Samanek and Voriskova 1999	5,030 children born in Bohemia between 1980 and 1990 with congenital heart disease. Children were followed until age 15, or until their death before reaching age 15.	AVS 1-year survival rate	90% (87-93)

OR – Odds Ratio ARR – Adjusted Relative Risk PRR – Prevalence Relative Risk AVS – Aortic Valve Stenosis
RR – Rate Ratio PR – Prevalence Rate AVA/AVS – Aortic Valve Atresia/Stenosis M-A – Mexican-American

Table 2. Descriptive statistics for characteristics of infants with aortic valve atresia and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=89)		Non-Hispanic Black (n=23)		Hispanic (n=107)		Total (n=219)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Infants	46	43	11	12	55	52	112	107
Sex								
Male	33 (71.7)	23 (53.5)	5 (45.5)	9 (75.0)	39 (70.9)	28 (53.8)	77 (68.8)	60 (56.1)
Female	13 (28.3)	20 (46.5)	6 (54.5)	3 (25.0)	16 (29.1)	24 (46.2)	35 (31.3)	47 (43.9)
Birth weight/gestational age								
< 37 wk < 1500 grams	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (9.6)	0 (0.0)	7 (6.5)
< 37 wk 1500-2499 grams	6 (13.0)	3 (7.0)	2 (18.2)	1 (8.3)	4 (7.3)	5 (9.6)	12 (10.7)	9 (8.4)
< 37 wk ≥ 2500 grams	2 (4.3)	3 (7.0)	0 (0.0)	0 (0.0)	7 (12.7)	6 (11.5)	9 (8.0)	9 (8.4)
≥ 37 wk < 1500 grams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 37 wk 1500-2499 grams	0 (0.0)	4 (9.3)	0 (0.0)	0 (0.0)	1 (1.8)	2 (3.8)	1 (0.9)	6 (5.6)
≥ 37 wk ≥ 2500 grams	38 (82.6)	31 (72.1)	9 (81.8)	11 (91.7)	43 (78.2)	34 (65.4)	90 (80.4)	76 (71.0)
Number of Defects - Males								
Isolated	0	0	0	0	0	0	0	0
≤ 5	12 (36.4)	3 (13.0)	1 (20.0)	1 (11.1)	7 (17.9)	9 (32.1)	20 (26.0)	13 (21.7)
> 5	21 (63.6)	20 (87.0)	4 (80.0)	8 (88.9)	32 (82.1)	19 (67.9)	57 (74.0)	47 (78.3)
Number of Defects - Females								
Isolated	0	0	0	0	0	0	0	0
≤ 5	4 (30.8)	4 (20.0)	3 (50.0)	0 (0.0)	3 (18.8)	5 (20.8)	10 (28.6)	9 (19.1)
> 5	9 (69.2)	16 (80.0)	3 (50.0)	3 (100.0)	13 (81.3)	19 (79.2)	25 (71.4)	38 (80.9)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 2. Descriptive statistics for characteristics of infants with aortic valve atresia and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=89)		Non-Hispanic Black (n=23)		Hispanic (n=107)		Total (n=219)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Mothers								
Maternal Age (years)								
< 20	1 (2.2)	1 (2.3)	4 (36.4)	3 (25.0)	11 (20.0)	7 (13.5)	16 (14.3)	11 (10.3)
20-29	26 (56.5)	27 (62.8)	6 (54.5)	6 (50.0)	33 (60.0)	32 (61.5)	65 (58.0)	65 (60.7)
30-39	18 (39.1)	13 (30.2)	1 (0.9)	3 (25.0)	10 (18.2)	9 (17.3)	29 (25.9)	25 (23.4)
> 40	1 (2.2)	2 (4.7)	0 (0.0)	0 (0.0)	1 (1.8)	4 (7.7)	2 (1.8)	6 (5.6)
Maternal Education								
< High School	3 (6.5)	3 (7.0)	1 (9.0)	2 (16.7)	13 (23.6)	19 (36.5)	17 (15.2)	24 (22.4)
High School	7 (15.2)	13 (30.2)	4 (36.4)	3 (25.0)	12 (21.8)	15 (28.8)	23 (20.5)	31 (29.0)
> High School	15 (32.6)	12 (27.9)	1 (9.0)	1 (8.3)	6 (10.9)	3 (5.8)	22 (19.6)	16 (15.0)
Missing	21 (45.7)	15 (34.9)	5 (45.5)	6 (50.0)	24 (43.6)	15 (28.8)	50 (44.6)	36 (33.6)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 3. Kaplan-Meier (KM) survival estimates with 95% confidence intervals (CIs) and Cox proportional hazard ratios (HRs) for children with congenital aortic valve defects using infant sex as a risk factor, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Female (Reference Group)			Male					
	Alive n	Deceased n	Estimate (95% CI)	Alive n	Deceased n	K-M Estimate (95% CI)	P value †	Adjusted HR (95% CI) *	P value †
Aortic Valve Atresia	35	47	41.5 (30.5-52.2)	77	60	55.0 (46.0-63.2)	**0.0451** †	0.89 (0.59-1.35)	0.5840
Aortic Valve Stenosis	79	15	82.5 (72.1-89.4)	189	17	91.6 (86.8-94.7)	**0.0492** †	0.80 (0.37-1.73)	0.5748

Study period 1996 to 2008; Kaplan-Meier estimate of study endpoint (December 31, 2008) survival probability.

CI - Confidence Interval

KM - Kaplan-Meier

HR - Hazard Ratio

† Statistically Significant at P<0.05

* Adjusted for maternal age, maternal education, birth weight/gestational age, infant sex, number of birth defects.

Table 4. Kaplan-Meier (KM) estimates with log-rank test and 95% confidence intervals (CIs) for survival in children with congenital aortic valve defects using maternal race/ethnicity stratified by infant sex as risk factors, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Non-Hispanic White			Non-Hispanic Black			Hispanic			P value †
	Alive n	Deceased n	Survival Estimate (95% CI)	Alive n	Deceased n	Survival Estimate (95% CI)	Alive n	Deceased n	Survival Estimate (95% CI)	
Aortic Valve Atresia	46	43	50.3 (39.2-60.5)	11	12	47.4 (26.3-65.9)	55	52	50.2 (40.0-59.5)	0.9956
Female	13	20	39.4 (23.1-55.4)	6	3	64.8 (25.3-87.2)	16	24	38.1 (22.7-53.2)	0.3160
Male	33	23	56.6 (41.8-68.9)	5	9	35.7 (13.0-59.4)	39	28	58.2 (45.5-68.9)	0.3707
Aortic Valve Stenosis	125	15	89.4 (83.0-93.5)	13	1	92.9 (59.1-99.0)	120	16	87.8 (80.6-92.4)	0.8852
Female	35	7	83.3 (68.2-91.7)	5	1	83.3 (27.3-97.5)	39	7	81.6 (63.6-91.3)	0.9625
Male	95	8	91.9 (84.4-95.9)	8	0	undefined	86	9	90.5 (82.6-95.0)	0.6236

Study period 1996 to 2008; Kaplan-Meier estimate of the study endpoint (December 31, 2008) survival probability.

CI - Confidence Interval

KM - Kaplan-Meier

† Statistically Significant at P<0.05

Table 5. Cox-proportional hazards regression model data for risk of mortality in children with congenital aortic valve defects using maternal race/ethnicity by infant sex as a risk factor, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Non-Hispanic White (Reference Group)	Non-Hispanic Black			Hispanic		
	n (%) [a]	n (%) [a]	Adjusted HR (95% CI) [**]	P value †	n (%) [a]	Adjusted HR (95% CI) [**]	P value †
Aortic Valve Atresia	89	23	1.13 (0.58-2.22) [*]	0.7241	107	0.88 (0.57-1.38) [*]	0.5846
Female	33 (37.1)	9 (39.1)	0.33 (0.09-1.18)	0.0886	40 (37.4)	0.95 (0.47-1.94)	0.8886
Male	56 (62.9)	14 (60.9)	1.95 (0.83-4.59)	0.1283	67 (62.6)	0.95 (0.50-1.73)	0.8604
Aortic Valve Stenosis	145	14	0.40 (0.05-3.23) [*]	0.3860	141	0.51 (0.20-1.28) [*]	0.1493
Female	42 (29.0)	6 (42.9)	0.94 (0.09-9.75)	0.9608	46 (32.6)	0.25 (0.06-1.14)	0.0728
Male	103 (71.0)	8 (57.1)	undefined	--	95 (67.4)	0.91 (0.26-3.22)	0.8843

Study period 1996 to 2008

HR - Hazard Ratio

CI - Confidence Interval

[a] Due to rounding effect, percentages may not total 100.0%.

† Statistically Significant at P<0.05

[*] Adjusted for maternal age, maternal education, birth weight/gestational age, infant sex, number of birth defects.

[**] Adjusted for maternal age, maternal education, birth weight/gestational age, number of birth defects; stratified by sex.

Table 6. Descriptive statistics for characteristics of infants with aortic valve stenosis and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=145)		Non-Hispanic Black (n=14)		Hispanic (n=141)		Total (n=300)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Infants	130	15	13	1	125	16	268	32
Sex								
Male	95 (73.1)	8 (53.3)	8 (61.5)	0 (0.0)	86 (68.8)	9 (56.3)	189 (70.5)	17 (53.1)
Female	35 (26.9)	7 (46.7)	5 (38.5)	1 (100.0)	39 (31.2)	7 (43.8)	79 (29.5)	15 (46.9)
Birth weight/gestational age								
< 37 wk < 1500 grams	4 (3.1)	2 (13.3)	0 (0.0)	0 (0.0)	5 (4.0)	1 (6.3)	9 (3.4)	3 (9.4)
< 37 wk 1500-2499 grams	5 (3.8)	2 (13.3)	3 (23.1)	0 (0.0)	10 (8.0)	5 (31.3)	18 (6.7)	7 (21.9)
< 37 wk ≥ 2500 grams	13 (10.0)	0 (0.0)	1 (7.7)	0 (0.0)	9 (7.2)	1 (6.3)	23 (8.6)	1 (3.1)
≥ 37 wk < 1500 grams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 37 wk 1500-2499 grams	2 (1.5)	2 (13.3)	1 (7.7)	0 (0.0)	7 (5.6)	1 (6.3)	10 (3.7)	3 (9.4)
≥ 37 wk ≥ 2500 grams	106 (81.5)	9 (60.0)	8 (61.5)	1 (100.0)	94 (75.2)	8 (50.0)	208 (77.6)	18 (56.3)
Number of Defects - Males								
Isolated	3	0	0	0	2	0	5	0
≤ 5	57 (60.0)	1 (12.5)	4 (50.0)	0 (0.0)	60 (69.8)	3 (33.3)	121 (64.0)	4 (23.5)
> 5	38 (40.0)	7 (87.5)	4 (50.0)	0 (0.0)	26 (30.2)	6 (66.7)	68 (36.0)	13 (76.5)
Number of Defects - Females								
Isolated	2	0	0	0	1	0	3	0
≤ 5	21 (60.0)	2 (28.6)	2 (40.0)	0 (0.0)	20 (51.3)	1 (14.3)	43 (54.4)	3 (20.0)
> 5	14 (40.0)	5 (71.4)	3 (60.0)	1 (100.0)	19 (48.7)	6 (85.7)	36 (45.6)	12 (80.0)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 6. Descriptive statistics for characteristics of infants with aortic valve stenosis and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=145)		Non-Hispanic Black (n=14)		Hispanic (n=141)		Total (n=300)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Mothers								
Maternal Age (years)								
< 20	10 (7.7)	2 (13.3)	2 (15.4)	0 (0.0)	22 (17.6)	2 (12.5)	34 (12.7)	4 (12.5)
20-29	72 (55.4)	8 (53.3)	5 (38.5)	1 (100.0)	63 (50.4)	7 (43.8)	140 (52.2)	16 (50.0)
30-39	47 (36.2)	5 (33.3)	5 (38.5)	0 (0.0)	36 (28.8)	6 (37.5)	88 (32.8)	11 (34.4)
> 40	1 (0.8)	0 (0.0)	1 (7.7)	0 (0.0)	4 (3.2)	1 (6.3)	6 (2.2)	1 (3.1)
Maternal Education								
< High School	7 (5.4)	3 (20.0)	0 (0.0)	0 (0.0)	40 (32.0)	7 (43.8)	47 (17.5)	10 (31.3)
High School	23 (17.7)	3 (20.0)	3 (23.1)	0 (0.0)	31 (24.8)	1 (6.3)	57 (21.3)	4 (12.5)
> High School	55 (42.3)	4 (26.7)	3 (23.1)	0 (0.0)	14 (11.2)	2 (12.5)	72 (26.9)	6 (18.8)
Missing	45 (34.6)	5 (33.3)	7 (53.8)	1 (100.0)	40 (32.0)	6 (37.5)	92 (34.3)	12 (37.5)

[a] Due to rounding effect, percentages may not total 100.0%.

CHAPTER 3:

DISPARITIES IN SURVIVAL AND MORTALITY AMONG INFANTS WITH CONGENITAL PULMONARY VALVE DEFECTS BY MATERNAL RACE/ETHNICITY AND INFANT SEX

ABSTRACT

Background: Little is known about racial/ethnic or infant sex differences contributing to the survival and mortality outcomes of children with pulmonary valve atresia or pulmonary valve stenosis.

Methods: We conducted a retrospective cohort study of 1561 singleton infants born to Hispanic, Non-Hispanic (NH) white, and NH black women in Texas between January 1, 1996 and December 31, 2007 with congenital pulmonary valve defects. Using data collected by the Texas Birth Defects Registry, we calculated Kaplan-Meier survival estimates, Cox-proportional hazards regression hazard ratios (HR) and 95% confidence intervals (CI) to determine, after adjusting for confounders, whether infant sex or maternal race/ethnicity affects early childhood survival or risk of mortality for these children.

Results: Early childhood mortality was greater in NH black than NH white children with pulmonary valve atresia and hypoplastic right ventricle (HRV) (HR=2.93; CI 1.09-7.85; P=0.0329); NH black males were at much greater risk of early childhood mortality than

NH white males (HR=4.63; CI 1.12-19.19; P=0.0349) with pulmonary valve atresia and HRV. Early childhood survival estimates for males (94.9%) with pulmonary valve stenosis were slightly lower (P=0.0116) than females (97.1%), and early childhood survival for NH black children (94.1%) and Hispanic (95.3%) children were lower than NH white (97.8%) children with pulmonary valve stenosis (P=0.0340).

Conclusion: We observed infant sex and racial/ethnic disparities in survival and early childhood mortality for infants born with pulmonary valve atresia with HRV and those without HRV.

INTRODUCTION

Birth defects are a primary cause of infant mortality and contribute more than half of the reported hospitalization costs associated with birth defects in the United States (Russo 2007). In order to improve the health and survival of infants and children, public health researchers need to better understand risk factors associated with congenital heart defects so that effective prevention and treatment programs can be developed and implemented (Botto, Correa et al. 2001; Nembhard, Waller et al. 2001; Cleves, Ghaffar et al. 2003; Nembhard, Salemi et al. 2007; Nembhard, Pathak et al. 2008; Nembhard, Salemi et al. 2009; Fixler, Nembhard et al. 2010; Nembhard, Salemi et al. 2010). We present our investigation of infant sex and maternal race/ethnicity risk factors contributing to early childhood survival and risk of mortality for infants born with pulmonary valve atresia or pulmonary valve stenosis.

Pulmonary Valve Stenosis

Pulmonary valve stenosis is a narrowing of the valve located between the right ventricle and the pulmonary artery, restricting blood flow from the heart to the lungs. It is an obstruction defect included in the broader category of right ventricular outflow tract obstruction (RVOTO). Pulmonary valve stenosis is relatively common, and accounts for approximately 10 percent of all children with congenital heart defects. Table 7 provides a summary of study findings for pulmonary valve defects. As shown in the table, some studies did not differentiate pulmonary valve stenosis from pulmonary valve atresia.

There are varied degrees of severity for pulmonary valve stenosis. In mild cases, pulmonary valve stenosis usually does not require treatment, but in severe cases, infants

are cyanotic at birth and eventually develop increasingly severe obstruction as he/she grows.

Pulmonary valve stenosis is a major component of another complex congenital heart defect – tetralogy of Fallot. There is a potential genetic contribution to risk of pulmonary valve stenosis since familial occurrence has been reported and the defect is associated with Algille syndrome and Noonan's syndrome (Moller and Neal 1990).

The reported prevalence of pulmonary valve stenosis per 10,000 live births ranges from 1.10 (95% CI 0.89-1.34) to 10.1 (95% CI 9.3-10.9) (Ferencz, Rubin et al. 1985; Pradat, Francannet et al. 2003; Dadvand, Rankin et al. 2009) (Table 7). Racial/ethnic disparity in pulmonary valve stenosis has been reported. Fewer cases of pulmonary valve stenosis have been reported for whites compared to blacks (Odds Ratio=0.6; 95% CI 0.4-0.8) (Correa-Villasenor, McCarter et al. 1991). Nembhard, Wang et al. (2010) found increased prevalence of pulmonary valve atresia/stenosis in NH black males, compared to NH white males (Rate Ratio (RR)=1.72; 95% CI 1.30-2.29) and in NH black females, compared to NH white females (RR=1.64; 95% CI 1.22-2.19). Another study found that NH black infants had a higher prevalence rate of pulmonary valve atresia/stenosis than NH white infants (RR=1.68; 95% CI 1.38-2.05) (Nembhard, Salemi et al. 2010). However, since data for pulmonary valve atresia and stenosis were combined in these studies.

Survival of infants born with pulmonary valve stenosis is high. It was reported as having the highest first year survival of congenital heart defects studied in Arkansas birth defects registry data for 1993 to 1998 (Cleves, Ghaffar et al. 2003). First-year survival for

infants born with pulmonary valve stenosis is about 96 to 97% (Samanek 1992; Samanek and Voriskova 1999).

A study using data from the Texas Birth Defects Registry (TBDR) found higher risk of early childhood mortality in NH black (HR 2.60; CI 1.32-5.12; P=0.0058) and Hispanic (HR 1.76; CI 1.06-2.91; P=0.0290) children compared to NH white children with pulmonary valve atresia without ventricular septal defect (Nembhard, Salemi et al. 2011). There are no reported significant disparities for the risk of mortality for infants with congenital pulmonary valve stenosis.

Pulmonary Valve Atresia

Pulmonary valve atresia is the absence of the pulmonary valve. Babies with pulmonary valve atresia can survive if the ductus arteriosus does not close, which is called patent ductus arteriosus. This defect sometimes occurs in conjunction with the underdevelopment of the right ventricle, a heart defect referred to as hypoplasia of the right ventricle. In other cases, hypoplasia of the right ventricle is absent. Pulmonary valve atresia is commonly present in conjunction with another congenital heart defect, ventricular septal defect, (an opening in the wall between the two heart ventricles). Pulmonary valve atresia with intact ventricular septum is uncommon; it can be diagnosed during the fetal stage (in utero) when pregnancy termination is an option. Pulmonary valve atresia is also associated with another congenital heart defect, Ebstein's anomaly. Pulmonary valve atresia is also associated with DiGeorge syndrome, a genetic mutation disease. Table 7 provides a summary of study findings for pulmonary valve defects. As shown in the table, some studies did not differentiate pulmonary valve stenosis from pulmonary valve atresia.

The prevalence of pulmonary valve atresia per 10,000 live births ranges from 0.73 (95% CI 0.55-0.91) to 5.8 (Ferencz, Rubin et al. 1985; Pradat, Francannet et al. 2003). Racial/ethnic disparity in pulmonary valve atresia has been reported. An excess of pulmonary valve atresia was found in whites compared to blacks (Odds Ratio=2.5; 95% CI 1.0-6.1) (Correa-Villasenor, McCarter et al. 1991). Also, as discussed for pulmonary valve stenosis, Nembhard, Wang et al. (2010) and Nembhard, Salemi et al. (2010) found racial/ethnic disparity in prevalence of pulmonary valve atresia/stenosis as a combined defect category.

Survival of infants born with pulmonary valve atresia is low; the 1-year survival for pulmonary valve atresia has been reported by Samanek and Voriskova (1999) as 19% (95% CI 8-30) and Samanek (1992) as 30% (95% CI 12-47). There are no reported data for survival by infant sex or maternal race/ethnicity or data on the risk of mortality for pulmonary valve atresia.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study of 238 infants with congenital pulmonary valve atresia and 1,323 infants with pulmonary valve stenosis born in Texas between January 1, 1996 and December 31, 2008. The source of data used in our study is the Texas Birth Defects Registry (TBDR), maintained by the Birth Defects Epidemiology and Surveillance Branch of the Texas Department of State Health Services. The TBDR includes population-based data obtained by active surveillance; TBDR personnel review medical records to identify infants diagnosed within the first year after birth with structural and chromosomal birth defects. The TBDR surveillance began in 1995, and

since 1999 data have been collected for all births in the state of Texas. TBDR data are death-to-birth matched by the Texas Vital Statistics Unit using decedent name, date of death and date of birth, mother's first and maiden and/or current last names.

The TBDR utilizes six-digit birth defect coding that has evolved through British Pediatric Association (BPA) extension of the International Classification of Disease, ninth revision clinical modification diagnostic codes (ICD-9 codes).

Study Population

The study population included all live-born singleton infants with pulmonary valve atresia or pulmonary valve stenosis (BPA Codes 746.000 and 746.010) born in Texas between January 1, 1996 and December 31, 2008 to NH white, NH black, or Hispanic women of any age. Pulmonary valve atresia and pulmonary valve stenosis cases with co-occurring heart defects (BPA Codes 745.000 through 747.490) were considered for inclusion in our study (Appendix A). However, cases associated with complex defects such as trisomies or syndromes were excluded. For example, pulmonary valve atresia associated with Ebstein's anomaly or DiGeorge syndrome and pulmonary valve stenosis associated tetralogy of Fallot, Algille syndrome, or Noonan's syndrome were not included in our study.

All cases were reviewed by a pediatric cardiologist (Dr. David Fixler, M.D.). Pulmonary valve atresia cases were included and evaluated as two separate conditions: if pulmonary valve atresia was co-occurring with hypoplastic right ventricle (HRV) (BPA Code 746.882) and if pulmonary valve atresia was not accompanied by HRV. We did not include or exclude cases of pulmonary valve atresia based on the presence or absence of

ventricular septal defect. Pulmonary valve stenosis cases were selected based on review of these cases and their co-occurring heart defects.

Covariates

We used infant and maternal covariate information obtained by the TBDR from birth certificate and medical records. We included infant sex and maternal race/ethnicity based on maternal self-report. Gestational age categorized as term (≥37 completed weeks) or pre-term (<37 weeks) was included; gestational age was based on last menstrual period or clinical estimate of gestation from medical records was substituted when last menstrual period data were missing. Consistent with published literature, we included birth weight categorized as normal (≥2500 grams), low (1500-2499 grams), or very low (<1500 grams), as recorded on birth certificates (CDC 1990; Alexander, Kogan et al. 2003; Nembhard 2011). Also consistent with literature, gestational age and birth weight were included as a combination variable with six categories: <37 weeks and <1500 grams; <37 weeks and 1500-2499 grams; <37 weeks and ≥2500 grams; ≥37 weeks and <1500 grams; ≥37 weeks and 1500-2499 grams; and ≥37 weeks and ≥2500 grams (Bol, Collins et al. 2006; Nembhard 2011). Maternal age categorized as <20 years, 20-29 years, 30-39 years, and 40+ years and maternal education categorized as high school (12 years), <high school, or >high school were also included. Number of co-occurring birth defects was also included in the analysis as a continuous variable.

Data Analysis

Descriptive statistics were calculated for main study variables and covariates. We calculated survival time using date of birth and date of death for deceased infants. When

TBDR data did not have a date of death recorded, infants were censored at the end of the study period, December 31, 2008.

Early childhood survival was estimated for children with each defect using the Kaplan-Meier method. Kaplan-Meier survival curves were computed to compare survival estimates by infant sex, and maternal race/ethnicity, and tested the difference between the curves using the log-rank test.

Unadjusted and adjusted hazard ratios were calculated for mortality using Cox proportional hazard regression models. The adjusted hazard ratios were computed using a final regression model developed by backward selection method, removing variables with less than 10% effect on the hazard ratio. The models for infant sex and maternal race/ethnicity stratified by sex used females and NH whites as the reference groups. The proportional hazards assumption was tested to ensure the assumption was met; we inspected the proportionality by including time-dependent covariates in the model and testing for their significance. Variables included in the final model were: maternal age, maternal education, birth weight/gestational age, and number of defects. Although not all variables had a major effect on the adjusted hazard ratios (i.e., changing the hazard ratio by 10% or more), all of the variables included in the final model are biologically important based on published literature. Results were considered statistically significant if the 95% confidence interval excluded 1 or $P<0.05$. Calculations were performed using the SAS 9.2 for Kaplan-Meier survival estimates and Cox proportional hazards regression models, and Stata Release 12 for Kaplan-Meier survival plots.

Protection of Human Subjects

The study was conducted with the approval of the University of South Florida Institutional Review Board (IRB) and the Texas Department of State Health Services.

Power and Sample Size

The formula used to estimate power for this study is an extension of Schoenfeld's sample-size formula for the proportional-hazards regression model, solved for power (1-β) (Hipwell, Strachan et al. 2000; Shechter, Sharir et al. 2000):

$$N = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{P\,(1-R^2)\,\sigma^2\,B^2}$$

Where N is the sample size; $z_{1-\alpha/2}$ and $z_{1-\beta}$ are standard normal deviates at a two-sided significance level α and power (1-β); P is the overall event rate or proportion of non-censored participants; R^2 is the effect size of covariates on the variable of interest; σ is the standard deviation of the variable of interest; and B is the effect size (log of the hazard ratio).

We calculated the power to detect hazard ratios of 1.5 and 3.0; the significance level, alpha, for our study was 0.05. Since our associations indicate risk or protective exposures, two sided hypotheses were tested. Standard deviation values of 0.5 and 0.7 were used to show a range of possibilities; the influence of covariates on the outcome, R^2 was estimated at 0.15. Based on the study data, estimates of study power were calculated based on three potential scenarios: 1) an event (death) rate of 5%, 2) an event rate of 10%, and 3) an event rate of 40%.

The results of these calculations are presented in Appendix B. Since our study size was fairly small for some of our stratified groups, our ability to observe statistically significant results may be limited.

RESULTS

Pulmonary Valve Atresia with HRV

Descriptive statistics for infants born with pulmonary valve atresia with HRV are provided in Table 8. The total number of cases in our study was 124 and included 40 NH white, 16 NH black, and 68 Hispanic children. Of these, 83 (66.9%) children were alive at the end of our study and 41 (33.1%) were deceased. Approximately 79.5% of surviving children and 56.1% of deceased children were born full term (≥37 weeks) and at normal birth weight (≥2500 grams). There were more males (55.6%) than females (44.4%) with pulmonary valve atresia and HRV.

Survival and Risk of Childhood Mortality by Infant Sex

Kaplan-Meier estimates, hazard ratios, and 95% CI are presented in Table 9. Early childhood survival for males (68.9%) with pulmonary valve atresia and HRV was not different from females (62.3%) (P = 0.4499), nor was there statistically significant difference in early childhood mortality between males and females with pulmonary valve atresia and HRV (HR 1.19; 95% CI 0.59-2.40; P=0.6333) after adjusting for potential confounders.

Survival by Maternal Race/Ethnicity and Infant Sex

Kaplan-Meier estimates for children with pulmonary valve atresia and HRV are presented in Table 10, and survival curves are presented in Figure 4. The estimated

survival for NH black children (43.8%) was not significantly lower than NH white (77.5%) and Hispanic (64.2%) children (P=0.1081). There were not statistically significant differences in estimated survival for NH black males (44.4%) compared to NH white males (75.0%) and Hispanic males (70.6%, P=0.2019), or for NH black females (42.9%) and Hispanic females (57.3%) compared to NH white females (81.3%, P=0.2547).

Risk of Childhood Mortality by Maternal Race/Ethnicity and Infant Sex

The Cox proportional hazards regression model results for risk of mortality in children with pulmonary valve atresia and HRV, comparing NH blacks to the reference group of NH whites adjusted for potential confounders and results for the model stratified by sex are presented in Table 11. Based on the results of our study, NH black children with pulmonary valve atresia and HRV have 193% higher risk of early childhood mortality than NH white children with the same defect (HR 2.93; CI 1.09-7.85; P=0.0329). Also shown in Table 11, this risk was due to the 363% higher risk of early childhood mortality in NH black male children compared to NH white males (HR 4.63; CI 1.12-19.18; P=0.0349), since NH black females with this defect do not have significantly higher risk of early childhood mortality than NH white children (HR 1.42; CI 0.27-7.57; P=0.6794).

The Cox proportional hazards model results by maternal race/ethnicity and by maternal race/ethnicity stratified by sex for children with pulmonary valve atresia and HRV, as presented in Table 11, do not show significant differences in risk of childhood mortality in Hispanic children (HR 1.04; CI 0.44-2.44; P=0.9258), Hispanic females (HR

0.88; CI 0.21-3.76; P=0.86), or Hispanic males (HR 1.17; CI 0.36-3.83; P=0.7974), compared to NH whites.

Pulmonary Valve Atresia without HRV

Descriptive statistics for characteristics of infants with pulmonary valve atresia without HRV and their birth mothers are provided in Table 12. The total number of cases in our study was 114 and included 41 NH white, 15 NH black, and 58 Hispanic children. Of these, 60 (52.6%) children were alive at the end of our study and 54 (47.4%) were deceased. Approximately 75% of surviving children and 63% of deceased children were born full term and at normal birth weight. There were approximately as many males (50.9%) as females (49.1%) that had pulmonary valve atresia without HRV.

Survival and Risk of Childhood Mortality by Infant Sex

Kaplan-Meier estimates, hazard ratios and 95% CI are presented in Table 9. Early childhood survival for males (60.3%) with pulmonary valve atresia without HRV was higher than females (44.3%), but not significantly (P = 0.1019). After adjusting for covariates, there was no statistically significant difference in early childhood mortality between males and females with pulmonary valve atresia without HRV (HR 0.77; 95% CI 0.41-1.46; P=0.4267).

Survival by Maternal Race/Ethnicity and Infant Sex

Kaplan-Meier estimates for children with pulmonary valve atresia without HRV are presented in Table 10, and survival curves are presented in Figure 5. The estimated survival was not significantly different for NH black children (40.0%) and Hispanic (48.3%) children compared to NH white children (62.4%, P=0.1767), NH black males

(28.6%) and Hispanic males (57.1%) compared to NH white males (73.9%, P=0.1052), or NH black females (50.0%) and Hispanic females (40.0%) compared to NH white females (49.4%, P=0.5851).

Risk of Childhood Mortality by Maternal Race/Ethnicity and Infant Sex

Hazard ratios and CI for early childhood mortality in children with pulmonary valve atresia without HRV are presented in Table 11. There was no statistical difference in early childhood mortality in NH black (HR 2.32; CI 0.93-5.83; P=0.0729) and Hispanic (HR 1.66; CI 0.80-3.45; P=0.1781) infants born with pulmonary valve atresia without HRV compared to NH white infants. Stratifying by sex and adjusting for covariates did not result in statistically different early childhood mortality in NH black females (HR 1.75; CI 0.42-7.27; P=0.4393) or Hispanic females (HR 1.45; CI 0.57-3.68; P=0.4385) compared to NH white females, or NH black males (HR 3.87; CI 0.96-15.57; P=0.057) and Hispanic males (HR 2.68; CI 0.72-10.01; P=0.1416) compared to NH white males.

Pulmonary Valve Stenosis

Descriptive statistics for infants born with pulmonary valve stenosis are provided in Table 13. The total number of cases in our study was 1323 and included 517 NH white, 169 NH black, and 637 Hispanic children. Of these, 1275 (96.4%) children were alive at the end of our study and 48 (3.6%) were deceased. Approximately 70% of surviving children and 39.6% of deceased children were born full term (≥37 weeks) and at normal birth weight (≥2500 grams); however, approximately 47.9% of deceased children were born pre-term (<37 weeks) and at low (1500-2499) or very low (<1500 grams) birth weight. There were fewer males (44.9%) than females (55.1%) that had

pulmonary valve stenosis; however, approximately 62.5% of the deceased cases were males.

Survival and Risk of Childhood Mortality by Infant Sex

Kaplan-Meier estimates, hazard ratios, and 95% confidence intervals are presented in Table 9. Early childhood survival for males (94.9%) with pulmonary valve stenosis was significantly lower (P=0.0116) than females (97.1%). After adjusting for covariates, there was no statistically significant difference in early childhood mortality between males and females with pulmonary valve stenosis (HR 1.74; 95% CI 0.94-3.21; P=0.0768).

Survival by Maternal Race/Ethnicity and Infant Sex

Kaplan-Meier estimates for children with pulmonary valve stenosis are presented in Table 10, and survival curves are presented in Figure 7. The estimated survival for NH black children (94.1%) and Hispanic (95.3%) children was statistically lower than NH white children (97.8%), (P=0.034). However, survival was not statistically different for NH black males (93.0%), Hispanic males (93.9%), and NH white males (97.2%, P=0.1661), or NH black females (94.9%), Hispanic females (96.70%), and NH white females (98.2%, P=0.1357).

Risk of Childhood Mortality by Maternal Race/Ethnicity and Infant Sex

Hazard ratios and CI for early childhood mortality in children with pulmonary valve stenosis are presented in Table 11. NH black children (HR 1.90; CI 0.78-4.62; P=0.1565) and Hispanic children (HR 0.89; CI 0.40-1.99; P=0.7806) born with pulmonary valve stenosis did not have significantly different risk of early childhood

mortality than NH white infants. After stratifying by infant sex and adjusting for covariates, early childhood mortality was higher but not statistically significant in NH black females (HR 2.34; CI 0.61-8.91; P=0.2138) and lower but not significant in Hispanic females (HR 0.66; CI 0.18-2.46; P=0.533) compared to NH white females. Differences in males were also not statistically significant: NH black males (HR 1.71; CI 0.50-5.90; P=0.3962), and Hispanic males (HR 1.19; CI 0.43-3.32; P=0.7424), when compared to NH white males.

DISCUSSION

We investigated 124 cases of pulmonary valve atresia with HRV, 114 cases of pulmonary valve atresia without HRV, and 1323 cases of pulmonary valve stenosis. We found that among children with pulmonary valve atresia with HRV, NH blacks had higher risk (193%) than NH whites and this risk was the result of NH black males having considerably higher risk (363%) of early childhood mortality than NH white males. We did not find differences by sex or race/ethnicity for children with pulmonary valve atresia without HRV indicating the risk factors for children with this defect differ from those affecting children with pulmonary valve atresia with HRV.

We found that males with pulmonary valve stenosis had lower early childhood survival than females with this defect. We also found that early childhood survival for children with aortic valve stenosis also varied by maternal race/ethnicity. NH white and Hispanic females had fewer deaths in the first year of life than their male counterparts but also had more deaths than males in subsequent years. After adjusting for confounders we did not find significant differences in early childhood mortality for children with pulmonary valve stenosis.

We found infant sex and maternal race/ethnicity differences in the pattern of survival for pulmonary valve stenosis during study period. However, when considering the confounding influence of covariates, we did not find differences in the risk of early childhood mortality for this defect. We found infant sex and maternal race/ethnicity differences in early childhood mortality for children with pulmonary valve atresia and HRV, but had no significant findings for children with pulmonary valve atresia without HRV. The variables with most influence on the final regression models for were birth weight/gestational age and number of co-occurring defects.

Sex disparities in early childhood survival indicate genetics may influence survival. Our study did not evaluate paternal variables such as paternal race/ethnicity. We also did not investigate maternal or paternal environmental factors, family history of congenital heart valve defects, or severity of defects. The possibility exists that there are unidentified factors that explain the sex disparities in early childhood survival for children with congenital pulmonary valve defects.

Pulmonary valve atresia inclusion criteria for our study were unique: we evaluated cases with HRV separately from cases without HRV. As discussed earlier and summarized in Table 7, findings of infant sex and maternal race/ethnicity disparities in the survival probability or risk of mortality in children with pulmonary valve defects have not been reported. However, pulmonary valve atresia has not previously been studied in the way we defined our defect, with or without HRV. Therefore, our results may not be directly comparable to findings of previous studies.

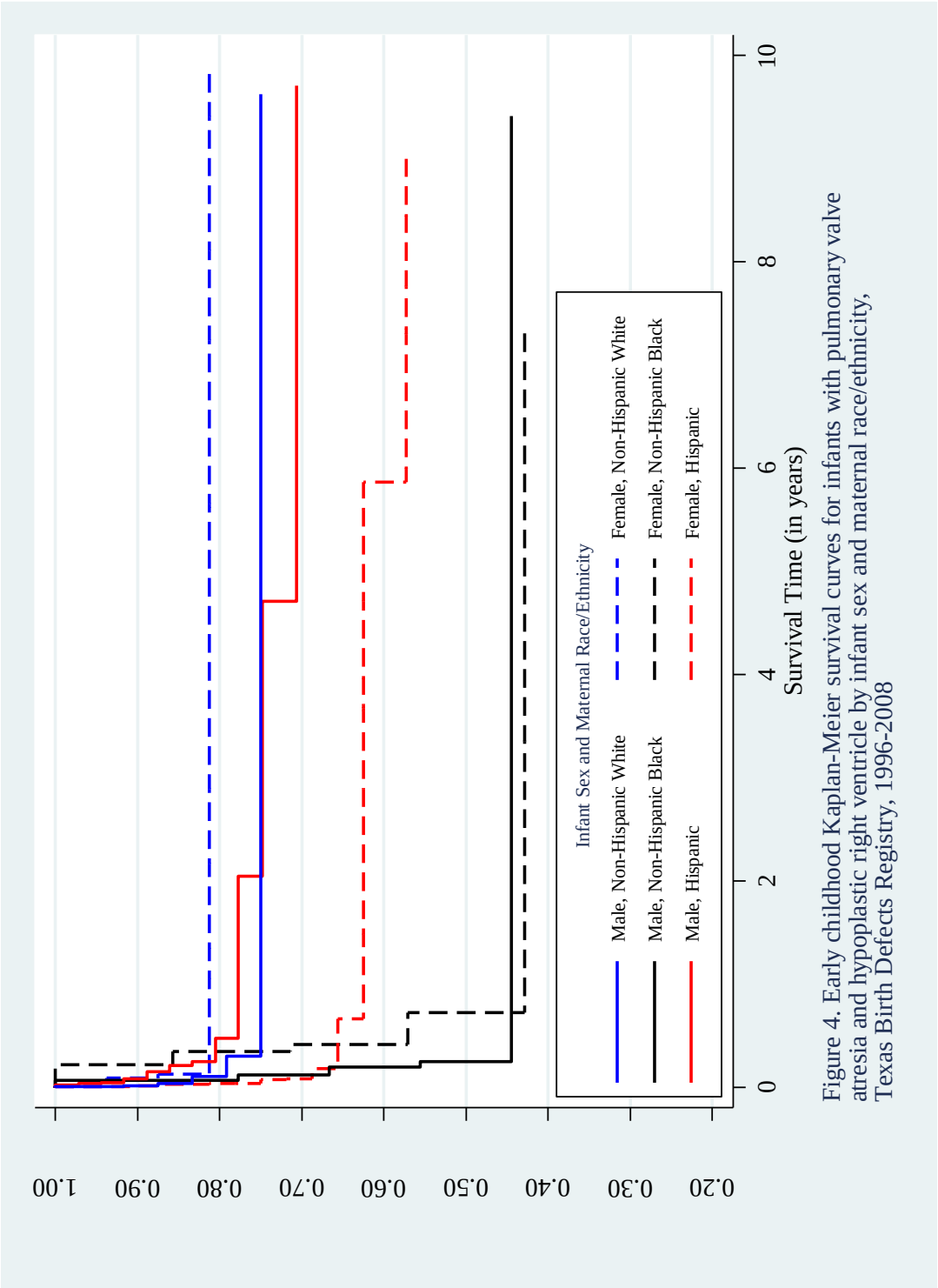

Figure 4. Early childhood Kaplan-Meier survival curves for infants with pulmonary valve atresia and hypoplastic right ventricle by infant sex and maternal race/ethnicity, Texas Birth Defects Registry, 1996-2008

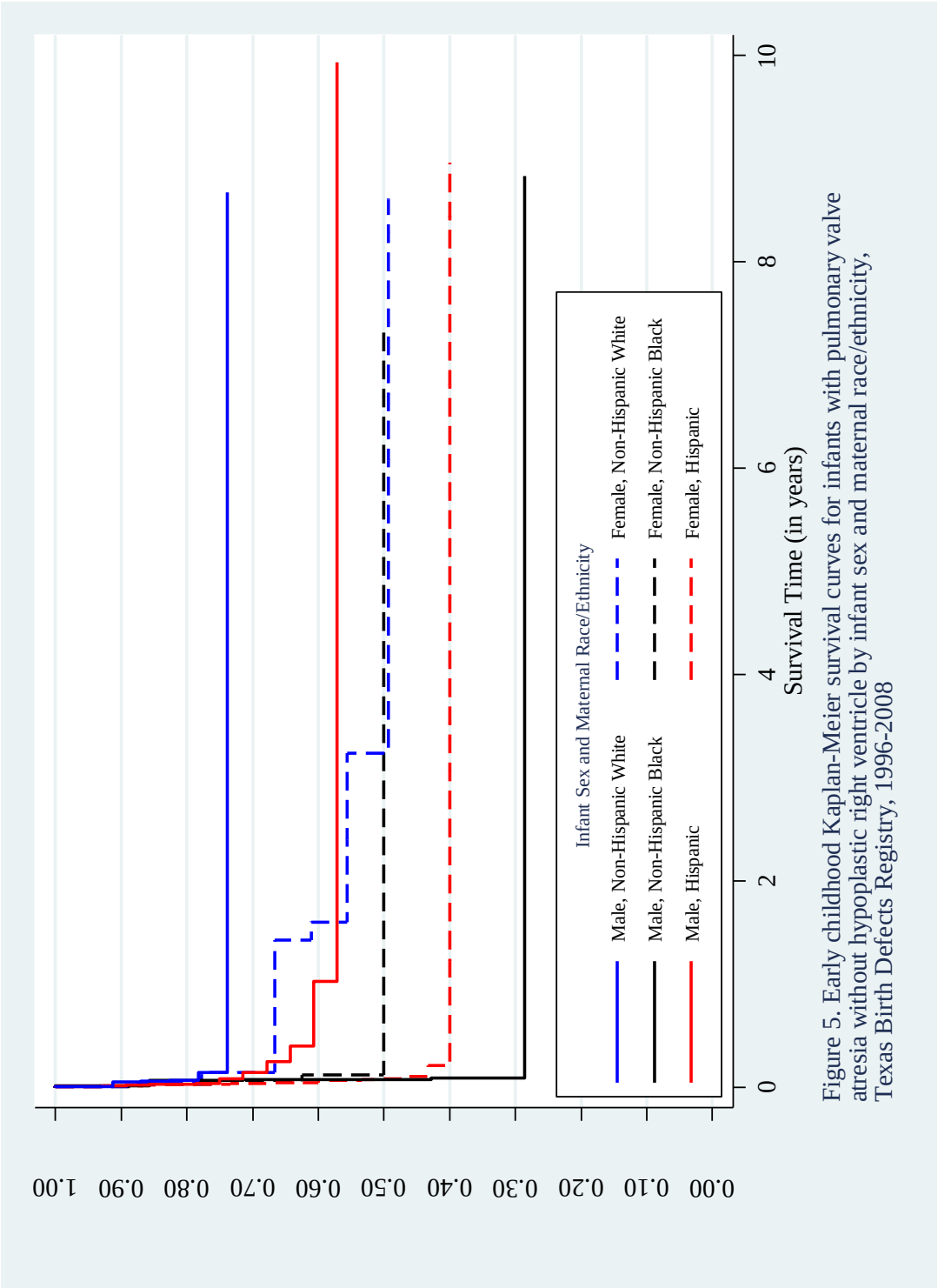

Figure 5. Early childhood Kaplan-Meier survival curves for infants with pulmonary valve atresia without hypoplastic right ventricle by infant sex and maternal race/ethnicity, Texas Birth Defects Registry, 1996-2008

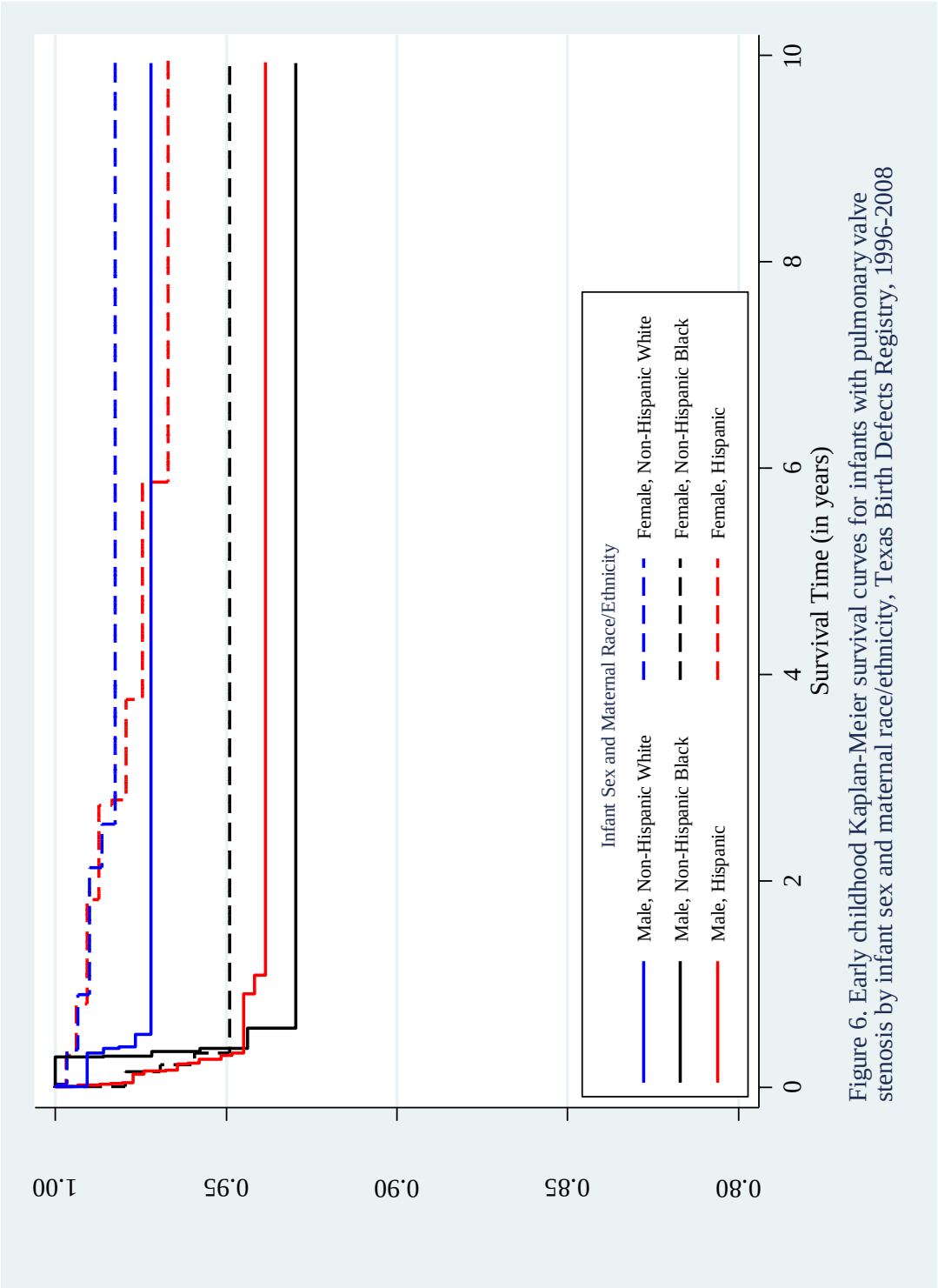

Figure 6. Early childhood Kaplan-Meier survival curves for infants with pulmonary valve stenosis by infant sex and maternal race/ethnicity, Texas Birth Defects Registry, 1996-2008

Table 7. Descriptive epidemiology of pulmonary valve defects from published studies, 1985-2011

Author	Study Population	Observation	Estimate (95% CI)
Prevalence Per 10,000 Births			
Nembhard et al. 2010	Texas Birth Defects Registry data for 48,391 singleton infants born between January 1 and December 31, 1996 and diagnosed with major birth defects.	PVA/S in Hispanics	8.91 (8.10-10.38)
		PVA/S in Non-Hispanic Blacks	14.73 (13.88-16.87)
		PVA/S in Non-Hispanic Whites	8.78 (8.40-9.90)
Dadvand et al. 2009	Northern region of England population-based register of 5,715 livebirths, stillbirths, and terminations of pregnancy for fetal anomaly, between 1985 and 2003.	PVS (North of England population)	10.1 (9.3, 10.9)
Ferencz et al. 1985	Baltimore-Washington Infant Study of 664 infants born in the study area between 1981 and 1982 and diagnosed with congenital heart disease.	PVA	5.8 (not reported)
		PVS	3.78 (not reported)
Pradat et al. 2003	California, Sweden and France birth defect registry data for 12,932 infants born between 1981 and 1992 with congenital heart defects.	PVA in Asians	0.94 (0.55-1.51)
		PVA in Blacks	0.79 (0.42-1.35)
		PVA in Hispanics	0.73 (0.55-0.91)
		PVA in Whites	0.76 (0.59-0.93)
		PVS in Asians	1.28 (0.81-1.92)
		PVS in Blacks	1.34 (0.84-2.02)
		PVS in Hispanics	1.10 (0.89-1.34)
		PVS in Whites	1.71 (1.46-1.98)
Prevalence Comparisons for Race/Ethnicity			
Nembhard, Wang et al. 2010	Florida Birth Defects Registry data for 16,788 singleton infants diagnosed with congenital heart defects, born between 1998 and 2003.	Higher PVA/S rates in non-Hispanic black males than non-Hispanic white males	RR=1.72 (1.30-2.29)
		Higher PVA/S rates in non-Hispanic black females than non-Hispanic white females	RR=1.64 (1.22-2.19)
Nembhard et al. 2010	Texas Birth Defects Registry data for 48,391 singleton infants born between January 1 and December 31, 1996 and diagnosed with major birth defects.	Higher PVA/S rates in non-Hispanic blacks than non-Hispanic whites	RR=1.68 (1.38-2.05)
Correa-Villasenor et al. 1991	Baltimore-Washington Infant Study of 2,087 live births with cardiovascular malformations between 1981 and 1987.	Lower odds for PVS in whites than blacks	OR=0.6 (0.4-0.8)
		Higher odds for PVA in whites than blacks	OR=2.5 (1.0-6.1)

Table 7. Descriptive epidemiology of pulmonary valve defects from published studies, 1985-2011

Author	Study Population	Observation	Estimate (95% CI)
Risk of Mortality			
Nembhard, Salemi et al. 2011	Texas Birth Defects Registry data for 19.530 singleton infants born between January 1, 1996 and December 31, 2003 and diagnosed with congenital heart defects.	Increased risk of early childhood mortality in Non-Hispanic Black children compared to Non-Hispanic White children.	HR=2.60 (1.32-5.12) P=0.0058
		Increased risk of early childhood mortality in Hispanic children compared to Non-Hispanic White children.	HR=1.76 (1.06-2.91) P=0.0290

HR – Hazard Ratio
OR – Odds Ratio
RR – Rate Ratio
PVA – Pulmonary Valve Atresia
PVS – Pulmonary Valve Stenosis
PVA/S – Pulmonary Valve Atresia/Stenosis

Table 8. Descriptive statistics for characteristics of infants with pulmonary valve atresia with hypoplastic right ventricle and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=40)		Non-Hispanic Black (n=16)		Hispanic (n=68)		Total (n=124)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Infants	31	9	7	9	45	23	83	41
Sex								
Male	18 (58.1)	6 (66.7)	4 (57.1)	5 (55.6)	26 (57.8)	10 (43.5)	48 (57.8)	21 (51.2)
Female	13 (41.9)	3 (33.3)	3 (42.9)	4 (44.4)	19 (42.2)	13 (56.5)	35 (42.2)	20 (48.8)
Birth weight/gestational age								
< 37 wk < 1500 grams	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (13.0)	0 (0.0)	4 (9.8)
< 37 wk 1500-2499 grams	3 (9.7)	1 (11.1)	0 (0.0)	0 (0.0)	4 (8.9)	4 (17.4)	7 (8.4)	5 (12.2)
< 37 wk ≥ 2500 grams	4 (12.9)	1 (11.1)	0 (0.0)	1 (11.1)	2 (4.4)	3 (13.0)	6 (7.2)	5 (12.2)
≥ 37 wk < 1500 grams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 37 wk 1500-2499 grams	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	4 (8.9)	2 (8.7)	4 (4.8)	4 (9.8)
≥ 37 wk ≥ 2500 grams	24 (77.4)	6 (66.7)	7 (100.0)	6 (66.7)	35 (77.8)	11 (47.8)	66 (79.5)	23 (56.1)
Number of Defects - Males								
Isolated	0	0	0	0	0	0	0	0
≤ 5	3 (16.7)	3 (50.0)	0 (0.0)	0 (0.0)	3 (11.5)	1 (10.0)	6 (12.5)	4 (19.0)
> 5	15 (83.3)	3 (50.0)	4 (100.0)	5 (100.0)	23 (88.5)	9 (90.0)	42 (87.5)	17 (81.0)
Number of Defects - Females								
Isolated	0	0	0	0	0	0	0	0
≤ 5	2 (15.4)	0 (0.0)	1 (33.3)	1 (33.3)	1 (5.3)	0 (0.0)	4 (11.4)	1 (5.0)
> 5	11 (84.6)	3 (100.0)	2 (66.7)	3 (66.7)	18 (94.7)	13 (100.0)	31 (88.6)	19 (95.0)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 8. Descriptive statistics for characteristics of infants with pulmonary valve atresia with hypoplastic right ventricle and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=40)		Non-Hispanic Black (n=16)		Hispanic (n=68)		Total (n=124)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Mothers								
Maternal Age (years)								
< 20	5 (16.1)	1 (11.1)	1 (14.3)	0 (0.0)	7 (15.6)	4 (17.4)	13 (15.7)	5 (12.2)
20-29	17 (54.8)	4 (44.4)	5 (71.4)	6 (66.7)	24 (53.3)	14 (60.9)	46 (55.4)	24 (58.5)
30-39	7 (22.6)	4 (44.4)	1 (14.3)	3 (33.3)	14 (31.1)	5 (21.7)	22 (26.5)	12 (29.3)
> 40	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	0 (0.0)
Maternal Education								
< High School	4 (12.9)	1 (11.1)	2 (28.6)	0 (0.0)	11 (24.4)	9 (39.1)	17 (20.5)	10 (24.4)
High School	8 (25.8)	3 (33.3)	0 (0.0)	2 (22.2)	11 (24.4)	6 (26.1)	19 (22.9)	11 (26.8)
> High School	12 (38.7)	3 (33.3)	3 (42.9)	4 (44.4)	7 (15.6)	1 (4.3)	22 (26.5)	8 (19.5)
Missing	7 (22.6)	2 (22.2)	2 (28.6)	3 (33.3)	16 (35.6)	7 (30.4)	25 (30.1)	12 (29.3)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 9. Kaplan-Meier (KM) survival estimates with 95% confidence intervals (CIs) and Cox proportional hazards ratios (HRs) for children with congenital pulmonary valve defects using infant sex as a risk factor, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Female (Reference Group)			Male					
	Alive n	Deceased n	Estimate (95% CI)	Alive n	Deceased n	K-M Estimate (95% CI)	P value †	Adjusted HR (95% CI) *	P value †
Pulmonary Valve Atresia w/ Hypoplastic Right Ventricle	35	20	62.3 (47.5-74.1)	48	21	68.9 (56.6-78.6)	0.4499	1.19 (0.59-2.40)	0.6333
Pulmonary Valve Atresia w/o Hypoplastic Right Ventricle	25	31	44.3 (31.0-56.8)	35	23	60.3 (46.6-71.6)	0.1019	0.77 (0.41-1.46)	0.4267
Pulmonary Valve Stenosis	711	18	97.1 (95.4-98.2)	564	30	94.9 (92.9-96.4)	**0.0116** †	1.74 (0.94-3.21)	0.0768

Study period 1996 to 2008; Kaplan-Meier estimate of study endpoint (December 31, 2008) survival probability.

CI - Confidence Interval

KM - Kaplan-Meier

HR - Hazard Ratio

† Statistically Significant at P<0.05

* Adjusted for maternal age, maternal education, birth weight/gestational age, infant sex, number of birth defects.

Table 10. Kaplan-Meier (KM) estimates with log-rank test and 95% confidence intervals (CIs) for survival in children with congenital pulmonary valve defects using maternal race/ethnicity stratified by infant sex as risk factors, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Non-Hispanic White			Non-Hispanic Black			Hispanic			P value [†]
	Alive n	Deceased n	Survival Estimate (95% CI)	Alive n	Deceased n	Survival Estimate (95% CI)	Alive n	Deceased n	Survival Estimate (95% CI)	
Pulmonary Valve Atresia w/ Hypoplastic Right Ventricle	31	9	77.5 (61.2-87.6)	7	9	43.8 (19.8-65.6)	45	23	64.2 (50.7-74.9)	0.1081
Female	13	3	81.3 (52.5-93.5)	3	4	42.9 (9.8-73.4)	19	13	57.3 (37.3-73.0)	0.2547
Male	18	6	75.0 (52.6-87.9)	4	5	44.4 (13.6-71.9)	26	10	70.6 (51.8-83.2)	0.2019
Pulmonary Valve Atresia w/o Hypoplastic Right Ventricle	26	15	62.4 (45.4-75.4)	6	9	40.0 (16.5-62.8)	28	30	48.3 (35.0-60.3)	0.1767
Female	9	9	49.4 (25.2-69.7)	4	4	50.0 (15.2-77.5)	12	18	40.0 (22.8-56.7)	0.5851
Male	17	6	73.9 (50.9-87.3)	2	5	28.6 (4.1-61.2)	16	12	57.1 (37.1-72.9)	0.1052
Pulmonary Valve Stenosis	493	11	97.8 (96.1-98.8)	154	10	94.1 (89.3-96.8)	591	27	95.3 (93.1-96.8)	**0.0340** [a]
Female	298	5	98.2 (95.8-99.3)	93	5	94.9 (88.2-97.8)	320	8	96.7 (93.2-98.4)	0.1357
Male	208	6	97.2 (93.9-98.7)	66	5	93.0 (83.9-97.0)	290	19	93.9 (90.5-96.0)	0.1661

Study period 1996 to 2008; Kaplan-Meier estimate of the study endpoint (December 31, 2008) survival probability.

CI - Confidence Interval

KM - Kaplan-Meier

[†] Statistically Significant at P<0.05

Table 11. Cox-proportional hazards regression model data for risk of mortality in children with congenital pulmonary valve defects using maternal race/ethnicity by infant sex as a risk factor, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Non-Hispanic White (Reference Group)	Non-Hispanic Black			Hispanic		
	n (%) [a]	n (%) [a]	Adjusted HR (95% CI) [**]	P value [†]	n (%) [a]	Adjusted HR (95% CI) [**]	P value [†]
Pulmonary Valve Atresia w/ Hypoplastic Right Ventricle	40	16	2.93 (1.09-7.85) [*]	**0.0329** [†]	68	1.04 (0.44-2.44) [*]	0.9258
Female	16 (40.0)	7 (43.8)	1.42 (0.27-7.57)	0.6794	32 (47.1)	0.88 (0.21-3.76)	0.8600
Male	24 (60.0)	9 (56.3)	4.63 (1.12-19.18)	**0.0349** [†]	36 (52.9)	1.17 (0.36-3.83)	0.7974
Pulmonary Valve Atresia w/o Hypoplastic Right Ventricle	41	15	2.32 (0.93-5.83) [*]	0.0729	58	1.66 (0.80-3.45) [*]	0.1781
Female	18 (43.9)	8 (53.3)	1.75 (0.42-7.27)	0.4393	30 (51.7)	1.45 (0.57-3.68)	0.4385
Male	23 (56.1)	7 (46.7)	3.87 (0.96-15.57)	0.0570	28 (48.3)	2.68 (0.72-10.01)	0.1416
Pulmonary Valve Stenosis	517	169	1.90 (0.78-4.62) [*]	0.1565	637	0.89 (0.40-1.99) [*]	0.7806
Female	303 (58.6)	98 (58.0)	2.34 (0.61-8.91)	0.2138	328 (51.5)	0.66 (0.18-2.46)	0.5330
Male	214 (41.4)	71 (42.0)	1.71 (0.50-5.90)	0.3962	309 (48.5)	1.19 (0.43-3.32)	0.7424

Study period 1996 to 2008

HR - Hazard Ratio

CI - Confidence Interval

[a] Due to rounding effect, percentages may not total 100.0%.

[†] Statistically Significant at P<0.05

[*] Adjusted for maternal age, maternal education, birth weight/gestational age, infant sex, number of birth defects.

[**] Adjusted for maternal age, maternal education, birth weight/gestational age, number of birth defects; stratified by sex.

Table 12. Descriptive statistics for characteristics of infants with pulmonary valve atresia without hypoplastic right ventricle and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=41)		Non-Hispanic Black (n=15)		Hispanic (n=58)		Total (n=114)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Infants	26	15	6	9	28	30	60	54
Sex								
Male	17 (65.4)	6 (40.0)	2 (33.3)	5 (55.5)	16 (57.1)	12 (40.0)	35 (58.3)	23 (42.6)
Female	9 (34.6)	9 (60.0)	4 (66.7)	4 (44.4)	12 (42.9)	18 (60.0)	25 (41.7)	31 (57.4)
Birth weight/gestational age								
< 37 wk < 1500 grams	1 (3.8)	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.6)	1 (3.3)	2 (3.3)	2 (3.7)
< 37 wk 1500-2499 grams	2 (7.7)	2 (13.3)	0 (0.0)	2 (22.2)	2 (7.1)	5 (16.7)	4 (6.7)	9 (16.7)
< 37 wk ≥ 2500 grams	3 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.7)	3 (10.0)	6 (10.0)	3 (5.6)
≥ 37 wk < 1500 grams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 37 wk 1500-2499 grams	1 (3.8)	2 (13.3)	1 (16.7)	1 (11.1)	1 (3.6)	3 (10.0)	3 (5.0)	6 (11.1)
≥ 37 wk ≥ 2500 grams	19 (73.1)	10 (66.7)	5 (83.3)	6 (66.7)	21 (75.0)	18 (60.0)	45 (75.0)	34 (63.0)
Number of Defects - Males								
Isolated	0	0	0	0	0	0	0	0
≤ 5	8 (47.1)	1 (16.7)	1 (50.0)	2 (40.0)	3 (18.8)	1 (8.3)	12 (48.0)	4 (17.4)
> 5	9 (52.9)	5 (83.3)	1 (50.0)	3 (60.0)	13 (81.3)	11 (91.7)	23 (52.0)	19 (82.6)
Number of Defects - Females								
Isolated	1	0	0	0	1	0	2	0
≤ 5	3 (33.3)	2 (22.2)	3 (75.0)	0 (0.0)	4 (33.3)	6 (33.3)	10 (40.0)	8 (25.8)
> 5	6 (66.7)	7 (77.8)	1 (25.0)	4 (100.0)	8 (66.7)	12 (66.7)	15 (60.0)	23 (74.2)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 12. Descriptive statistics for characteristics of infants with pulmonary valve atresia without hypoplastic right ventricle and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=41)		Non-Hispanic Black (n=15)		Hispanic (n=58)		Total (n=114)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Mothers								
Maternal Age (years)								
< 20	2 (7.7)	2 (13.3)	1 (16.7)	1 (11.1)	5 (17.9)	4 (13.3)	8 (13.3)	7 (13.0)
20-29	13 (50.0)	7 (46.7)	5 (83.3)	5 (55.5)	14 (50.0)	11 (36.7)	32 (53.3)	23 (42.6)
30-39	10 (38.5)	6 (40.0)	0 (0.0)	3 (33.3)	7 (25.0)	15 (50.0)	17 (28.3)	24 (44.4)
> 40	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)	0 (0.0)	3 (5.0)	0 (0.0)
Maternal Education								
< High School	1 (3.8)	1 (6.7)	1 (16.7)	2 (22.2)	10 (35.7)	9 (30.0)	12 (20.0)	12 (22.2)
High School	5 (19.2)	6 (40.0)	2 (33.3)	0 (0.0)	5 (17.9)	5 (16.7)	12 (20.0)	11 (20.3)
> High School	13 (50.0)	5 (33.3)	2 (33.3)	4 (44.4)	3 (10.7)	7 (23.3)	18 (30.0)	16 (29.6)
Missing	7 (26.9)	3 (20.0)	1 (16.7)	3 (33.3)	10 (35.7)	9 (30.0)	18 (30.0)	15 (27.8)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 13. Descriptive statistics for characteristics of infants with pulmonary valve stenosis and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=517)		Non-Hispanic Black (n=169)		Hispanic (n=637)		Total (n=1323)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Infants	506	11	159	10	610	27	1275	48
Sex								
Male	208 (41.1)	6 (54.5)	66 (41.5)	5 (50.0)	290 (47.5)	19 (70.4)	564 (44.2)	30 (62.5)
Female	298 (58.9)	5 (45.4)	93 (58.5)	5 (50.0)	320 (52.5)	8 (29.6)	711 (55.8)	18 (37.5)
Birth weight/gestational age								
< 37 wk < 1500 grams	35 (6.9)	2 (18.2)	33 (20.8)	7 (70.0)	62 (10.2)	7 (25.9)	130 (10.2)	16 (33.3)
< 37 wk 1500-2499 grams	41 (8.1)	1 (9.1)	21 (13.2)	3 (30.0)	62 (10.2)	3 (11.1)	124 (9.7)	7 (14.6)
< 37 wk ≥ 2500 grams	33 (6.5)	0 (0.0)	6 (3.8)	0 (0.0)	52 (8.5)	3 (11.1)	91 (7.1)	3 (6.3)
≥ 37 wk < 1500 grams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 37 wk 1500-2499 grams	14 (2.8)	0 (0.0)	8 (5.0)	0 (0.0)	16 (2.6)	3 (11.1)	38 (3.0)	3 (6.3)
≥ 37 wk ≥ 2500 grams	383 (75.7)	8 (72.7)	91 (57.2)	0 (0.0)	418 (68.5)	11 (40.7)	892 (70.0)	19 (39.6)
Number of Defects - Males								
Isolated	9	0	7	0	28	1	44	1
≤ 5	132 (7.7)	3 (27.3)	51 (17.6)	2 (20.0)	202 (16.6)	5 (14.8)	385 (13.2)	10 (18.8)
> 5	76 (51.4)	3 (54.5)	15 (52.8)	3 (40.0)	88 (54.1)	14 (66.7)	179 (52.9)	20 (58.3)
Number of Defects - Females								
Isolated	25	0	10	0	26	1	61	1
≤ 5	228 (37.9)	1 (18.2)	74 (27.7)	1 (30.0)	227 (26.1)	3 (14.8)	529 (31.0)	5 (18.8)
> 5	70 (7.3)	4 (18.2)	19 (8.2)	4 (10.0)	93 (33.1)	5 (33.3)	182 (19.7)	13 (25.0)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 13. Descriptive statistics for characteristics of infants with pulmonary valve stenosis and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=517)		Non-Hispanic Black (n=169)		Hispanic (n=637)		Total (n=1323)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Mothers								
Maternal Age (years)								
< 20	39 (7.7)	3 (27.3)	28 (17.6)	2 (20.0)	101 (16.6)	4 (14.8)	168 (13.2)	9 (18.8)
20-29	260 (51.4)	6 (54.5)	84 (52.8)	4 (40.0)	330 (54.1)	18 (66.7)	674 (52.9)	28 (58.3)
30-39	192 (37.9)	2 (18.2)	44 (27.7)	3 (30.0)	159 (26.1)	4 (14.8)	395 (31.0)	9 (18.8)
> 40	15 (3.0)	0 (0.0)	3 (18.9)	1 (10.0)	20 (3.1)	1 (3.7)	38 (3.0)	2 (4.2)
Maternal Education								
< High School	37 (7.3)	2 (18.2)	13 (8.2)	1 (10.0)	202 (33.1)	9 (33.3)	252 (19.7)	12 (25.0)
High School	93 (18.4)	3 (27.3)	41 (25.8)	4 (40.0)	96 (15.7)	4 (14.8)	230 (18.0)	11 (22.9)
> High School	191 (37.7)	4 (36.4)	35 (22.0)	2 (20.0)	62 (10.2)	0 (0.0)	288 (22.6)	6 (12.5)
Missing	185 (36.6)	2 (18.2)	70 (44.0)	3 (30.0)	250 (41.0)	14 (51.9)	505 (39.6)	19 (39.6)

[a] Due to rounding effect, percentages may not total 100.0%.

CHAPTER 4:

DISPARITIES IN SURVIVAL AND MORTALITY AMONG INFANTS WITH CONGENITAL TRICUSPID VALVE DEFECTS BY MATERNAL RACE/ETHNICITY AND INFANT SEX

ABSTRACT

Background: Tricuspid valve atresia is a serious congenital heart defect with poor survival outcomes for some infants with this defect. Risk factors that contribute to poor survival outcomes in children with tricuspid valve atresia are not well understood. The contribution of infant sex and maternal race/ethnicity as risk factors for poor survival has not been studied for this defect.

Methods: Using data collected by the Texas Birth Defects Registry, we conducted a retrospective cohort study of 149 singleton infants born to Hispanic, Non-Hispanic (NH) white, and NH black women in Texas between January 1, 1996 and December 31, 2007 with congenital tricuspid valve atresia. We used Kaplan-Meier survival estimates and Cox proportional hazards regression ratios (HR) and 95% confidence intervals (CI) to determine, after adjusting for confounders, whether infant sex or maternal race/ethnicity affects early childhood survival or risk of mortality for these children.

Results: We found that early childhood survival was considerably lower for NH black male children (35.7%) and Hispanic males (64.0%) than NH white males (81.0%) with tricuspid valve atresia (P=0.0269). After adjusting for covariates, we found that NH black

children with tricuspid valve atresia have 239% increased risk of early childhood mortality than NH white children (P=0.0062) and the difference in risk was because NH black males with tricuspid valve atresia have 423% increased risk of early childhood mortality than NH white males (CI 1.33-20.58; P=0.0179).

Conclusion: The results of our study demonstrate that male sex and NH black maternal race/ethnicity are risk factors for early childhood mortality in children born with tricuspid valve atresia. Tricuspid valve atresia is a serious congenital heart defect with poor survival outcomes for some children with this defect. Further investigation of the role of infant sex and race/ethnicity in prevention and treatment protocols is warranted to better understand why this disparity exists and what can be done to improve the outcome for NH black male children with this defect.

INTRODUCTION

Birth defects are a primary cause of infant mortality and contribute more than half of the reported hospitalization costs associated with birth defects in the United States (Russo 2007). In order to improve the health and survival of infants and children, public health researchers need to better understand risk factors associated with congenital heart defects so that effective prevention and treatment programs can be developed and implemented (Botto, Correa et al. 2001; Nembhard, Waller et al. 2001; Cleves, Ghaffar et al. 2003; Nembhard, Salemi et al. 2007; Nembhard, Pathak et al. 2008; Nembhard, Salemi et al. 2009; Fixler, Nembhard et al. 2010; Nembhard, Salemi et al. 2010). We present our investigation of infant sex and maternal race/ethnicity risk factors contributing to early childhood survival and risk of mortality for infants born with tricuspid valve atresia, in an effort to contribute to the effort to better understand outcome disparities.

Tricuspid Valve Stenosis

Tricuspid valve stenosis is a narrowing of the valve between the right atrium and right ventricle, restricting normal blood circulation. Tricuspid valve stenosis is uncommon and little data are available for isolated cases of this defect since tricuspid valve stenosis is usually associated with other anomalies, especially right ventricular outflow tract obstruction or atresia with secondary hypoplasia of the right ventricle. Also, tricuspid valve stenosis is often associated with Ebstein's anomaly. Since tricuspid valve stenosis is rare, our study did not evaluate stenosis of the tricuspid valve. We screened TBDR cases identified with BPA Code 746.100, anomalies of the tricuspid valve, as tricuspid valve atresia cases for inclusion in our study.

Tricuspid Valve Atresia

Tricuspid valve atresia is the absence of a valve between the right atrium and ventricle. Oxygen-depleted blood enters the right atrium but cannot flow to the right ventricle where blood would normally be pumped to the lungs. In order for blood to get to the lungs, at least one other heart defect must be present (i.e., patent ductus arteriosus; atrial septal defect, or ventricular septal defect). Tricuspid valve atresia commonly occurs in conjunction with the underdevelopment of the right ventricle, a heart defect referred to as hypoplasia of the right ventricle. Tricuspid valve atresia is a serious congenital heart defect that can be diagnosed in utero; pregnancy termination may be selected because of this diagnosis. Tricuspid valve atresia is also associated with Ebstein's anomaly.

Table 14 provides a summary of study findings for tricuspid valve defects. As shown in the table, some studies did not differentiate tricuspid valve atresia from tricuspid valve stenosis. The prevalence of tricuspid valve atresia per 10,000 live births ranges from 0.49 (95% CI 0.35-0.64) to 3.6 (Ferencz, Rubin et al. 1985; Pradat, Francannet et al. 2003). Tricuspid valve atresia has been found higher in boys than girls with a boy to girl ratio=1.45:1 (Samanek 1994). Racial/ethnic disparity has not been reported specifically for the prevalence of tricuspid valve atresia.

Survival of infants born with tricuspid valve atresia is low. As shown in Table 14, the 1-year survival for tricuspid valve atresia has been reported as 46 and 57 percent (Samanek 1992; Samanek and Voriskova 1999). There are no reported data for survival that differentiate by sex or race/ethnicity. In addition, there are no reported data on the risk of mortality for congenital tricuspid valve atresia.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study of 149 infants with congenital tricuspid valve atresia born in Texas between January 1, 1996 and December 31, 2008. Data was obtained from the Texas Birth Defects Registry (TBDR), which is maintained by the Birth Defects Epidemiology and Surveillance Branch of the Texas Department of State Health Services. In the TBDR population-based active surveillance system TBDR personnel review medical records to identify infants diagnosed within the first year after birth with structural and chromosomal birth defects. The TBDR surveillance began in 1995, and since 1999 data have been collected for all births in the state of Texas. TBDR data are death-to-birth matched by the Texas Vital Statistics Unit using decedent name, date of death and date of birth, mother's first and maiden and/or current last names.

The TBDR utilizes six-digit birth defect coding that has evolved through British Pediatric Association (BPA) extension of the International Classification of Disease, ninth revision clinical modification diagnostic codes (ICD-9 codes).

Study Population

The study population included all live-born singleton infants with tricuspid valve anomalies (BPA Code 746.100) born in Texas between January 1, 1996 and December 31, 2008 to NH white, NH black, or Hispanic women of any age. As previously stated, since tricuspid valve stenosis is rare, our study did not evaluate stenosis of the tricuspid valve. We screened TBDR cases identified with BPA Code 746.100, anomalies of the tricuspid valve, as tricuspid valve atresia cases for inclusion in our study. Tricuspid valve atresia cases with co-occurring heart defects (BPA Codes 745.000 through 747.490) were

considered for inclusion in our study (Appendix A). However, cases associated with complex defects such as trisomies or syndromes were excluded. For example, tricuspid valve atresia associated with Ebstein's anomaly was not included in our study. All cases were reviewed by a pediatric cardiologist (Dr. David E. Fixler, M.D.), and tricuspid valve atresia cases were included in our study only if hypoplastic right ventricle (HRV) (BPA Code 746.882) was a co-occurring defect.

Covariates

We used infant and maternal covariate information obtained by the TBDR from birth certificate and medical records. We included infant sex, and maternal race/ethnicity based on maternal self-report. Gestational age categorized as term (≥37 completed weeks) or pre-term (<37 weeks) was included; gestational age was based on last menstrual period or clinical estimate of gestation from medical records was substituted when last menstrual period data were missing. Consistent with published literature, we included birth weight categorized as normal (≥2500 grams), low (1500-2499 grams), or very low (<1500 grams), as recorded on birth certificates (CDC 1990; Alexander, Kogan et al. 2003; Nembhard 2011). Also consistent with literature, gestational age and birth weight were included as a combination variable with six categories: <37 weeks and <1500 grams; <37 weeks and 1500-2499 grams; <37 weeks and ≥2500 grams; ≥37 weeks and <1500 grams; ≥37 weeks and 1500-2499 grams; and ≥37 weeks and ≥2500 grams (Bol, Collins et al. 2006; Nembhard 2011). Maternal age categorized as <20 years, 20-29 years, 30-39 years, and 40+ years and maternal education categorized as high school (12 years), <high school, or >high school were also included. Our analysis also considered

number of recorded birth defects as reported in medical records as an additional covariate.

Data Analysis

Descriptive statistics were calculated for main study variables and covariates. We calculated survival time using date of birth and date of death for deceased infants. When TBDR data did not have a date of death recorded, infants were censored at the end of the study period, December 31, 2008.

Early childhood survival was estimated for children with each defect using the Kaplan-Meier method. Kaplan-Meier survival curves were computed to compare survival estimates by infant sex and maternal race/ethnicity, and tested the difference between the curves using the log-rank test.

Unadjusted and adjusted hazard ratios were calculated for mortality using Cox proportional hazard regression models. The adjusted hazard ratios were computed using a final regression model developed by backward selection method, removing variables with less than 10% effect on the hazard ratio. The created models for infant sex and maternal race/ethnicity stratified by sex used females and NH whites as the reference groups. The proportional hazards assumption was tested to ensure the assumption was met; we inspected the proportionality by including time-dependent covariates in the model and testing for their significance. Variables included in the final model were: maternal age, maternal education, birth weight/gestational age, and number of defects. Although not all variables had a major effect on the adjusted hazard ratios (i.e., changing the hazard ratio by 10% or more), all of the variables included in the final model are biologically important based on published literature. Results were considered statistically significant

if the 95% confidence interval excluded 1 or P<0.05. Calculations were performed using SAS 9.2 for Kaplan-Meier survival estimates and Cox proportional hazards regression models, and Stata Release 12 for Kaplan-Meier survival plots.

Protection of Human Subjects

The study was conducted with the approval of the University of South Florida Social and Behavioral Institutional Review Board (IRB) and the Texas Department of State Health Services.

Power and Sample Size

The formula used to estimate power for this study is an extension of Schoenfeld's sample-size formula for the proportional-hazards regression model, solved for power (1-β) (Hipwell, Strachan et al. 2000; Shechter, Sharir et al. 2000):

$$N = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{P\,(1-R^2)\,\sigma^2 B^2}$$

Where N is the sample size; $z_{1-\alpha/2}$ and $z_{1-\beta}$ are standard normal deviates at a two-sided significance level α and power (1-β); P is the overall event rate or proportion of non-censored participants; R^2 is the effect size of covariates on the variable of interest; σ is the standard deviation of the variable of interest; and B is the effect size (log of the hazard ratio).

We calculated the power to detect hazard ratios of 1.5 and 3.0; the significance level, alpha, for our study was 0.05. Since our associations indicate risk or protective exposures, two sided hypotheses were tested. Standard deviation values of 0.5 and 0.7

were used to show a range of possibilities; the influence of covariates on the outcome, R^2 was estimated at 0.15. Based on the study data, estimates of study power were calculated based on three potential scenarios: 1) an event (death) rate of 5%, 2) an event rate of 10%, and 3) an event rate of 40%.

The results of these calculations are presented in Appendix B. Since our study size was fairly small for some of our stratified groups, our ability to observe statistically significant results may be limited.

RESULTS

Tricuspid Valve Atresia

Descriptive statistics for infants born with tricuspid valve atresia are provided in Table 15. The total number of cases in our study was 149 and included 45 (30.2%) NH white, 28 (18.8%) NH black, and 76 (51%) Hispanic children. Of these, 96 (64.4%) children were alive at the end of our study and 53 (35.6%) were deceased. Approximately 79.2% of surviving children and 52.8% of deceased children were born full term (≥37 weeks) and at normal birth weight (≥2500 grams); however, of the approximately 28.3% of deceased children born pre-term (<37 weeks) and at low (1500-2499) or very low (<1500 grams) birth weight, most of these children were Hispanic (66.7%). There were approximately as many males (49.7%) as females (50.3%) that had tricuspid valve atresia.

Survival and Risk of Childhood Mortality by Infant Sex

Kaplan-Meier estimates, hazard ratios and 95% CI are presented in Table 16. Early childhood survival for males (63.5%) and females (63.1%) were not different (P=0.9023). Also, the risk of early childhood mortality was not different for males than

females with tricuspid valve atresia (HR 1.15; 95% CI 0.64-2.04; P=0.6449) after adjusting for covariates.

Survival by Maternal Race/Ethnicity and Infant Sex

Kaplan-Meier estimates for children with tricuspid valve atresia are presented in Table 17, and survival curves are presented in Figure 7. The estimated survival for NH black (50.0%) and Hispanic (60.5%) children was not statistically different than NH white children (76.9%), (P=0.0615), or for NH black females (64.3%), Hispanic females (56.5%), and NH white females (72.6%, P=0.454). However, survival was statistically different for NH black males (35.70%) and Hispanic males (64.0%) compared to NH white males (81.0%) with tricuspid valve atresia (P=0.0269).

Risk of Childhood Mortality by Maternal Race/Ethnicity and Infant Sex

Hazard ratios and CI for early childhood mortality in children with tricuspid valve atresia are presented in Table 18. As shown in the table, NH black children with tricuspid valve atresia have 239% increased risk of early childhood mortality than NH white children (HR 3.39; CI 1.41-8.13; P=0.0062), and this difference was because NH black males with tricuspid valve atresia have 423% increased risk of early childhood mortality than NH white males (HR 5.23; CI 1.33-20.58; P=0.0179).

Hispanic children born with pulmonary valve stenosis did not have significantly different risk of early childhood mortality than NH white children (HR 1.43; CI 0.66-3.10; P=0.3689) collectively, or when stratified by sex: Hispanic males (HR 1.33; CI 0.40-4.41; P=0.6412), Hispanic females (HR 0.67; CI 0.22-2.02; P=0.4753).

DISCUSSION

We investigated 149 cases of tricuspid valve atresia using the Kaplan-Meier method with log-rank tests to estimate survival and found that NH black males and Hispanic males have significantly lower estimates of study endpoint (December 31, 2008) survival probability than NH white males with this defect. After adjusting for maternal age, maternal education, birth weight/gestational age combinations, and number of co-occurring defects covariates in the Cox proportional hazards regression model, we observed statistically significant increased risk of early childhood mortality for NH black children compared to NH white children, and this was because NH black males have 423% increased risk of early childhood mortality compared to NH white males. As shown on Figure 7, the majority of deaths occur within the first year after birth.

Literature findings of 1-year survival for cases of tricuspid valve atresia (Table 14) have been reported at 57% (Samanek 1992) and 46% (Samanek and Voriskova 1999). Our Kaplan-Meier survival estimates for tricuspid valve atresia demonstrate varied survival probabilities: as low as 35.7% (CI 13.0-59.4) in NH black males to 81.0% (CI 56.9-92.4) in NH white males.

We found infant sex and maternal race/ethnicity differences in early childhood mortality for children with tricuspid valve atresia, but no significant differences in pattern of survival. The variables with most influence on the final regression models for were birth weight/gestational age and number of co-occurring defects.

Tricuspid valve atresia inclusion criteria for our study considered the rare cases of tricuspid valve stenosis and were included only if HRV was co-occurring. As such, we did not investigate tricuspid valve atresia as an isolated defect since clinically this defect

does not occur unless it is part of another malformation of the heart. For this reason, our results for tricuspid valve atresia may not be directly comparable to findings of previous studies.

As discussed previously, tricuspid valve atresia is a serious heart defect that can be diagnosed in utero and pregnancy termination may be selected because of this diagnosis. However, prenatal diagnoses of birth defects have been found to be lower among Hispanic and black women (Waller, Pujazon et al. 2000). Our results may be biased away from the null as a result of this effect. Our study did not evaluate severity of defects, paternal race/ethnicity, maternal or paternal environmental factors, family history of congenital heart valve defects, or severity of defects. The possibility exists that there are unidentified factors that explain the disparity in early childhood survival for NH black males.

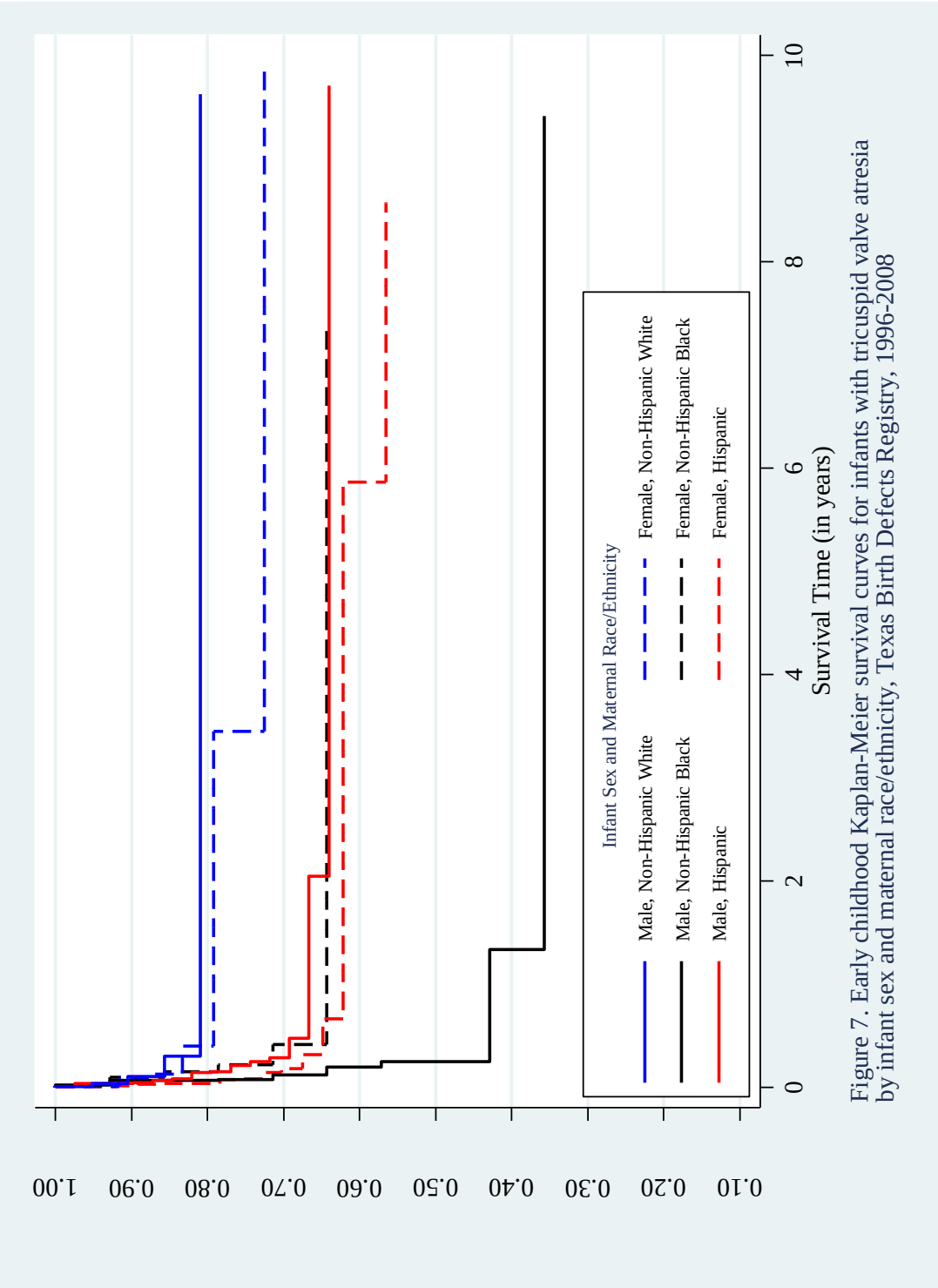

Figure 7. Early childhood Kaplan-Meier survival curves for infants with tricuspid valve atresia by infant sex and maternal race/ethnicity, Texas Birth Defects Registry, 1996-2008

Table 14. Descriptive epidemiology of tricuspid valve defects from published studies, 1985-2010

Author	Study Population	Observation	Estimate (95% CI)
Prevalence Per 10,000 Births			
Nembhard et al. 2010	Texas Birth Defects Registry data for 48,391 singleton infants born between January 1 and December 31, 1996 and diagnosed with major birth defects.	TVA/S in Hispanics	1.10 (0.80-1.63)
		TVA/S in Non-Hispanic Blacks	1.74 (1.31-2.35)
		TVA/S in Non-Hispanic Whites	1.11 (0.91-1.46)
Ferencz et al. 1985	Baltimore-Washington Infant Study of 664 infants born in the study area between 1981 and 1982 and diagnosed with congenital heart disease.	TVA	3.6 (not reported)
Pradat et al. 2003	California, Sweden and France birth defect registry data for 12,932 infants born between 1981 and 1992 with congenital heart defects.	TVA in Asians	0.78 (0.43-1.31)
		TVA in Blacks	0.91 (0.51-1.50)
		TVA in Hispanics	0.49 (0.35-0.64)
		TVA in Whites	0.70 (0.53-0.86)
Prevalence Comparisons for Race/Ethnicity			
Carmichael et al. 2004	California Birth Defects Monitoring Program surveillance data for 2,234,846 infants and fetuses born between 1989 and 1997 with congenital malformations.	Lower risk of TVA/S/insufficiency in foreign-born Hispanics than US-born Hispanics, African-Americans or Whites	ARR=0.7 (0.6-0.8)
Prevalence by Sex			
Lary and Paulozzi 2001	Metropolitan Atlanta Congenital Defects Program data for 28,965 infants born between 1968 and 1995 with at least one major birth defect.	Higher risk of TVA/S in males	RR=1.16 (1.01-1.35)
Samanek 1994	4,409 children born in Bohemia between 1977 and 1984 with congenital heart malformations.	Higher ratio of TVA in boys	Boy to Girl Ratio=1.45:1
Survival Percent			
Samanek 1992	946 Bohemian children with congenital heart disease who died before they were 15 years of age; data were collected between 1952 and 1979.	TVA 1-year survival rate	57% (28-71)
Samanek and Voriskova 1999	5,030 children born in Bohemia between 1980 and 1990 with congenital heart disease. Children were followed until age 15, or until their death before reaching age 15.	TVA 1-year survival rate	46% (30-62)

ARR – Adjusted Relative Risk
RR – Relative Risk
TVA – Tricuspid Valve Atresia
PR – Prevalence Rate
TVA/S – Tricuspid Valve Atresia/Stenosis

Table 15. Descriptive statistics for characteristics of infants with congenital tricuspid valve atresia and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=45)		Non-Hispanic Black (n=28)		Hispanic (n=76)		Total (n=149)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Infants	35	10	14	14	47	29	96	53
Sex								
Male	17 (48.6)	4 (40.0)	5 (35.7)	9 (64.3)	25 (53.2)	14 (48.3)	47 (49.0)	27 (50.9)
Female	18 (51.4)	6 (60.0)	9 (64.3)	5 (35.7)	22 (46.8)	15 (51.7)	49 (51.0)	26 (49.1)
Birth weight/gestational age								
< 37 wk < 1500 grams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (17.2)	0 (0.0)	5 (9.4)
< 37 wk 1500-2499 grams	4 (11.4)	2 (20.0)	0 (0.0)	3 (21.4)	3 (6.4)	5 (17.2)	7 (7.3)	10 (18.9)
< 37 wk ≥ 2500 grams	3 (8.6)	1 (10.0)	0 (0.0)	1 (7.1)	2 (4.3)	3 (10.3)	5 (5.2)	5 (9.4)
≥ 37 wk < 1500 grams	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 37 wk 1500-2499 grams	1 (2.9)	0 (0.0)	2 (14.3)	2 (14.3)	5 (10.6)	3 (10.3)	8 (8.3)	5 (9.4)
≥ 37 wk ≥ 2500 grams	27 (77.1)	7 (70.0)	12 (85.7)	8 (57.1)	37 (78.7)	13 (44.8)	76 (79.2)	28 (52.8)
Number of Defects - Males								
Isolated	0	0	0	0	0	0	0	0
≤ 5	2 (11.8)	1 (25.0)	0 (0.0)	2 (22.2)	3 (12.0)	1 (7.1)	5 (10.6)	4 (14.8)
> 5	15 (88.2)	3 (75.0)	5 (100.0)	7 (77.8)	22 (88.0)	13 (92.9)	42 (89.4)	23 (85.2)
Number of Defects - Females								
Isolated	0	0	0	0	0	0	0	0
≤ 5	2 (11.1)	0 (0.0)	4 (44.4)	2 (40.0)	1 (4.5)	1 (6.7)	7 (14.3)	3 (11.5)
> 5	16 (88.9)	6 (100.0)	5 (55.6)	3 (60.0)	21 (95.5)	14 (93.3)	42 (85.7)	23 (88.5)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 15. Descriptive statistics for characteristics of infants with congenital tricuspid valve atresia and their birth mothers, Texas Birth Defects Registry data for children born 1996 to 2007

Characteristic	Non-Hispanic White (n=45)		Non-Hispanic Black (n=28)		Hispanic (n=76)		Total (n=149)	
	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]	Alive n (%) [a]	Deceased n (%) [a]
Mothers								
Maternal Age (years)								
< 20	5 (14.3)	3 (30.0)	4 (28.6)	1 (7.1)	6 (12.8)	6 (20.7)	15 (15.6)	10 (18.9)
20-29	16 (45.7)	3 (30.0)	10 (71.4)	10 (71.4)	26 (55.3)	16 (55.2)	52 (54.2)	29 (54.7)
30-39	10 (28.6)	4 (40.0)	0 (0.0)	3 (21.4)	14 (29.8)	7 (24.1)	24 (25.0)	14 (26.4)
> 40	4 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (21.3)	0 (0.0)	5 (5.2)	0 (0.0)
Maternal Education								
< High School	6 (17.1)	2 (20.0)	4 (28.6)	1 (7.1)	10 (21.3)	9 (31.0)	20 (20.8)	12 (22.6)
High School	6 (17.1)	4 (40.0)	2 (14.3)	5 (35.7)	10 (21.3)	9 (31.0)	18 (18.8)	18 (34.0)
> High School	12 (34.3)	3 (30.0)	3 (21.4)	4 (28.6)	7 (14.9)	3 (10.3)	22 (22.9)	10 (18.9)
Missing	11 (31.4)	1 (10.0)	5 (35.7)	4 (28.6)	20 (42.6)	8 (27.6)	36 (37.5)	13 (24.5)

[a] Due to rounding effect, percentages may not total 100.0%.

Table 16. Kaplan-Meier (KM) survival estimates with 95% confidence intervals (CIs) and Cox proportional hazards ratios (HRs) for children with congenital tricuspid valve atresia using infant sex as a risk factor, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Female (Reference Group)			Male					
	Alive n	Deceased n	Estimate (95% CI)	Alive n	Deceased n	K-M Estimate (95% CI)	P value	Adjusted HR (95% CI) *	P value
Tricuspid Valve Atresia	49	26	63.1 (49.9-73.6)	47	27	63.5 (51.4-73.3)	0.9023	1.15 (0.64-2.04)	0.6449

Study period 1996 to 2008; Kaplan-Meier estimate of study endpoint (December 31, 2008) survival probability.

CI - Confidence Interval

KM - Kaplan-Meier

HR - Hazard Ratio

* Adjusted for maternal age, maternal education, birth weight/gestational age, infant sex, number of birth defects.

Table 17. Kaplan-Meier (KM) estimates with log-rank test and 95% confidence intervals (CIs) for survival in children with congenital tricuspid valve atresia using maternal race/ethnicity stratified by infant sex as risk factors, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Non-Hispanic White			Non-Hispanic Black			Hispanic			P value †
	Alive n	Deceased n	Survival Estimate (95% CI)	Alive n	Deceased n	Survival Estimate (95% CI)	Alive n	Deceased n	Survival Estimate (95% CI)	
Tricuspid Valve Atresia	35	10	76.9 (61.1-86.9)	14	14	50.0 (30.6-66.6)	47	29	60.5 (48.1-70.9)	0.0615
Female	18	6	72.6 (47.9-87.0)	9	5	64.3 (34.3-83.3)	22	15	56.5 (37.2-71.9)	0.4540
Male	17	4	81.0 (56.9-92.4)	5	9	35.7 (13.0-59.4)	25	14	64.0 (46.9-76.9)	**0.0269** †

Study period 1996 to 2008; Kaplan-Meier estimate of the study endpoint (December 31, 2008) survival probability.

CI - Confidence Interval

KM - Kaplan-Meier

† Statistically Significant at P<0.05

Table 18. Cox-proportional hazards regression model data for risk of mortality in children with congenital tricuspid valve defects using maternal race/ethnicity by infant sex as a risk factor, Texas Birth Defects Registry data for children born 1996 to 2007

Defect	Non-Hispanic White (Reference Group)	Non-Hispanic Black			Hispanic		
	n (%) [a]	n (%) [a]	Adjusted HR (95% CI) [**]	P value [†]	n (%) [a]	Adjusted HR (95% CI) [**]	P value [†]
Tricuspid Valve Atresia	45	28	3.39 (1.41-8.13) [*]	**0.0062** [†]	76	1.43 (0.66-3.10) [*]	0.3689
Female	24 (53.3)	14 (50.0)	0.86 (0.23-3.24)	0.8187	37 (48.7)	0.67 (0.22-2.02)	0.4753
Male	21 (46.7)	14 (50.0)	5.23 (1.33-20.58)	**0.0179** [†]	39 (51.3)	1.33 (0.40-4.41)	0.6412

Study period 1996 to 2008

HR - Hazard Ratio

CI - Confidence Interval

[a] Due to rounding effect, percentages may not total 100.0%.

[†] Statistically Significant at P<0.05

[*] Adjusted for maternal age, maternal education, birth weight/gestational age, infant sex, number of birth defects.

[**] Adjusted for maternal age, maternal education, birth weight/gestational age, number of birth defects; stratified by sex.

CHAPTER 5:

CONCLUSIONS AND RECOMMENDATIONS

The purpose of this study was to determine if the probability of early childhood survival or risk of mortality varies by infant sex or maternal race/ethnicity in children with congenital heart valve defects in order to expand the existing knowledge of the risk factors for these birth defects, and provide public health and clinical practitioners with insight for their efforts to implement improvements in the prevention and treatment of these defects. We were able to meet our study aims; we demonstrated that there were infant sex and maternal racial/ethnic disparities in early childhood survival and risk of mortality for children with congenital heart valve defects.

Our study found that early childhood survival was better for males than females with aortic valve atresia and stenosis. However, after adjusting for confounders, we did not find statistically significant differences in risk of early childhood mortality for either of these defects. We also did not find any differences by race/ethnicity.

For pulmonary valve stenosis we found that early childhood survival was poorer for males than females, and poorer for NH black and Hispanic children than NH white children.

After adjusting for covariates, we determined that NH black children with pulmonary valve atresia and HRV have 193% higher risk of early childhood mortality

than NH white children; this increased risk was because NH black males with this defect have 363% higher risk of early childhood mortality compared to NH white males.

For tricuspid valve atresia we found poorer survival for NH black males and Hispanic males than NH white males. NH black children had 239% increased risk of early childhood mortality than NH white children, and NH black males had 423% increased risk of early childhood mortality than NH white males with tricuspid valve atresia.

The study had several strengths: 1) the results of our study are highly generalizable since the TBDR is a multi-ethnic population-based active surveillance system for all births in Texas; 2) our study had a large sample size, data for 2070 infants with congenital heart valve defects, providing us with adequate study size to observe statistically significant associations by infant sex and maternal race/ethnicity; and 3) verified defect diagnoses improved accuracy of the data.

Our study also had some potential limitations. The numbers of cases of some defects (i.e., aortic valve stenosis or pulmonary valve atresia without HRV) may not have been large enough to observe associations for three racial/ethnic categories after stratifying by infant sex. Perhaps if the study size was larger for these defects, we would have observed statistically significant lower risk of mortality in Hispanic females with aortic valve stenosis compared to NH white females (P=0.0728), or higher risk of mortality in NH black children (P=0.0729) or NH black males (P=0.0570) with pulmonary valve atresia and HRV, compared to NH whites. Power and sample size calculations (Appendix B) indicate power was limited under some conditions. Nonetheless, we observed statistically significant disparities for several defects.

Another potential limitation is that the model included co-occurring birth defects as a continuous variable, but did not differentiate between protective (e.g., patent ductus arteriosus, atrial septal defect, or ventricular septal defect) and deleterious defects. Survival for children with some congenital heart valve defects depends on the presence of another defect to allow blood to flow through the heart. For example: infants with aortic valve atresia may have better chances of survival if patent ductus arteriosus persists; pulmonary valve atresia is commonly present in conjunction with ventricular septal defect; and infants with tricuspid valve atresia may have better chances of survival if patent ductus arteriosus, atrial septal defect, or ventricular septal defect are present. Future studies should assess the effects of protective and deleterious co-occurring defects when adjusting for covariates.

We also did not control for the potential confounding effects of initiation of prenatal care for mothers. Prenatal detection of congenital heart defects has been found to be related to elective termination of pregnancy (Stoll 2002) and varies by race/ethnicity; prenatal diagnoses of birth defects is lower among Hispanic and black women (Waller, Pujazon et al. 2000). As such, it is possible that more NH white mothers had prenatal diagnosis of severe congenital heart defects and elected to terminate the pregnancy more often than NH black or Hispanic mothers. As a result, our results may be biased away from the null as a result of this effect.

We did not include geographic variables in our study. Nembhard, Salemi et al. (2011) used a rural urban commuting area (RUCA) variable in their regression model for determination of hazard ratios. Our data were de-identified, so we did not have access to information necessary to include this variable in our regression models.

We used case inclusion and exclusion criteria that are rather unique to our study. For example, we investigated pulmonary valve atresia with and without HRV. Although our criteria allowed us to observe associations for these specific defects, our findings are not directly comparable with previous investigations. Further, our pediatric-cardiologist verification of defect diagnosis was based on data collected by TBDR personnel, not on direct review of clinical records. Our cardiologist review of the data for defect verification was conducted by an individual expert, not a panel of experts, which may be considered subjective and lacking confirmatory quality assurance of the expert review.

For the combined birth weight and gestational age covariate in our study, one category of this variable (birth weight <1500 grams and gestational age ≥37 weeks) had only one infant meeting these criteria; however, on further evaluation we observed that the gestational age was reported incorrectly. We calculated gestational age using date of birth and date of last menstrual period and found that this infant was less than 37 weeks gestation when born. We corrected the data and as a result there were no children meeting the criteria of birth weight <1500 grams and gestational age ≥37 weeks in our study.

Another covariate in our study was self-reported maternal education, and a considerable portion of our study population had missing information on this variable. We elected to consider "missing" as a variable category in our analysis because there was a possibility of systematic differences in the reasons why a mother may choose to not report level of education completed. We observed high proportions of deceased children for mothers with high school or less than high school education; there was a possibility that the missing information could have biased our determinations toward the null in our adjusted hazard model.

Our study was a population-based retrospective study using TBDR data for all children born in Texas between 1996 and 2007. Our findings are highly generalizable since our data were population-based; however the racial/ethnic demographics of Texas differ from other regions of the United States.

In conclusion, our investigation identified racial/ethnic associations by infant sex that have yet to be reported, and enhanced the findings of previous investigations to advance the understanding of the pathogenesis and etiology of congenital heart valve defects. Our findings provide a foundation for additional research. We recommend a future investigation that includes RUCA variables and considers categories of co-occurring defects and/or protective vs. deleterious defects. Similar studies using active surveillance data for other geographic regions would be useful to determine if disparities are present in other demographic populations.

Disparities in survival probability and risk of mortality indicate genetics may contribute to the outcome. Our study did not investigate paternal variables; future investigations of the contribution of paternal race/ethnicity, family history of congenital heart valve defects, and maternal and paternal environmental exposures may provide useful information to further the understanding of the etiology of these defects.

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APPENDICES

APPENDIX A

TEXAS BIRTH DEFECTS REGISTRY BPA CODES FOR CONGENITAL HEART DEFECTS

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

745 Bulbus Cordis Anomalies and Anomalies of Cardiac Septal Closure

745.000	Common truncus
	Persistent truncus arteriosus
	Absent septum between aorta and pulmonary artery
745.010	Aortic septal defect
	Includes: Aortopulmonary window
	Excludes: Atrial septal defect
745.100	Transposition of great vessels, complete (no VSD)
	D-transposition with no VSD
745.110	Transposition of great vessels, incomplete (with VSD)
	D-transposition with a VSD
	Taussig-Bing syndrome
	Transposition with inlet VSD
	Transposition with perimembraneous VSD
	Excludes: Transposition with muscular VSD
745.120	Corrected transposition of great vessels,
	L-transposition, ventri in version
	Ventricular inversion
	Excludes: Dextrocardia
745.180	Other specified transposition of great vessels
	Includes: Double outlet right ventricle
	Double outlet left ventricle
745.190	Unspecified transposition of great vessels
745.200	Tetralogy of Fallot
	Diagnosis of Tetralogy of Fallot assumes pulmonary valve defects and right ventricular hypertrophy, these defects are not coded separately
745.300	Single ventricle
745.400	Ventricular septal defect
745.400	Roger's disease
745.410	Eisenmenger's syndrome
745.420	Gerbode defect
745.480	Other specified ventricular septal defect (VSD)

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

745.490	Ventricular septal defect (VSD)
745.500	Ostium secundum type atrial septal defect
	Nonclosure of foramen ovale
	Patent foramen ovale (PFO)
745.510	Ostium (septum) secundum defect
	Secundum ASD
	Fossa ovalis atrial septal defect
	Fenestrated ASD
745.520	Lutembacher's syndrome
745.580	Other specified atrial septal defect
745.590	ASD (atrial septal defect)
	Auricular septal defect
	Partial foramen ovale
	PFO vs. ASD
	PFO vs secundum ASD
745.600	Endocardial cushion defects
	Ostium primum defects
	Primum ASD
745.610	Single common atrium, cor triloculare biventriculare
745.630	Common atrioventricular canal 1
	Includes: Complete AV canal defect 1
745.680	Other specified cushion defect
745.690	Endocardial cushion defect, NOS
745.700	Cor biloculare
745.800	Other specified defects of septal closure
745.900	Unspecified defect of septal closure

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

746 Other Congenital Anomalies of Heart

746.000	Anomalies of pulmonary valve Atresia, hypoplasia of pulmonary valve Absent pulmonary valve See 746.995 if valve is not specified (e.g., "pulmonary atresia")
746.010	Stenosis of pulmonary valve Small pulmonary valve See 746.995 if valve not specified (e.g., "pulmonary stenosis") Excludes: Pulmonary infundibular stenosis
746.020	Pulmonary valve insufficiency or regurgitation, congenital
746.080	Other specified anomalies of pulmonary valve Thickened pulmonary valve Dysplastic pulmonary valve Enlarged pulmonary valve Dilated pulmonary valve Bicuspid pulmonary valve Redundant pulmonary valve Dysmorphic pulmonary valve Excludes: Pulmonary infundibular Stenosis (Use 746.830)
746.090	Unspecified anomaly of pulmonary valve
746.100	Anomalies of the tricuspid valve Tricuspid atresia, stenosis, or hypoplasia Right atrioventricular (AV) atresia, stenosis, or hypoplasia Bicuspid right atrioventricular (AV) valve Bicuspid tricuspid valve Cleft right atrioventricular (AV) valve Cleft tricuspid valve Dysplastic right atrioventricular (AV) valve Dysplastic tricuspid valve Small right atrioventricular (AV) valve Small tricuspid valve
746.105	Tricuspid valve insufficiency or regurgitation, congenital Right atrioventricular (AV) valve insufficiency or regurgitation, congenital Tricuspid valve incompetence Excludes: Ebstein's anomaly

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

746.180	Other anomalies of the tricuspid valve
	Abnormal tricuspid valve
	Dilated right atrioventricular (AV) valve
	Dilated tricuspid valve
	Enlarged right atrioventricular (AV) valve
	Enlarged tricuspid valve
	Redundant tricuspid valve
	Right atrioventricular (AV) valve aneurysm
	Thickened right atrioventricular (AV) valve
	Thickened tricuspid valve
	Tricuspid valve aneurysm
	Tricuspid valve prolapse
746.200	Ebstein's anomaly
746.300	Congenital stenosis of aortic valve
	Includes: Congenital aortic stenosis
	Subvalvular aortic stenosis
	Small aortic valve
	Excludes: Supravalvular aortic stenosis
746.400	Congenital insufficiency of aortic valve
	Aortic valve insufficiency or regurgitation, congenital bicuspid aortic valve
	Aortic valve incompetence
746.480	Other specified anomalies of the aortic valves
	Includes: Aortic valve atresia
	Aortic annulus defects
	Hypoplastic aortic valve
	Dysplastic aortic valve
	Thickened aortic valve
	Absent aortic valve
	Dysmorphic aortic valve
	Quadricuspid aortic valve
	Narrow aortic annulus
	Excludes: Supravalvular aortic stenosis
746.490	Unspecified anomalies of the aortic valves
	Abnormal aortic valve

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

746.500	Congenital mitral stenosis
	Congenital left atrioventricular (AV) stenosis
	Thickened mitral valve
	Thickened left atrioventricular (AV) valve
746.505	Absence, atresia, or hypoplasia of mitral valve
	Abnormal mitral valve
	Absence, atresia, or hypoplasia of left atrioventricular (AV) valve
	Cleft left atrioventricular (AV) valve
	Cleft mitral valve
	Double orifice mitral valve
	Dysmorphic mitral valve
	Dysplastic left atrioventricular (AV) valve
	Dysplastic mitral valve
	Left atrioventricular (AV) valve prolapse
	Mitral valve anomaly
	Mitral valve prolapse
	Parachute left atrioventricular (AV) valve
	Parachute mitral valve
746.600	Mitral valve insufficiency or regurgitation, congenital
	Left atrioventricular (AV) valve insufficiency or regurgitation, congenital
746.700	Hypoplastic left heart syndrome
	Diagnosis of hypoplastic left heart syndrome assumes the following diagnoses:
	Hypoplastic left ventricle - 746.881
	Mitral valve anomalies - 746.5 and 746.6
	Aortic valve anomalies - 746.3 and 746.4
	Atresia or hypoplasia of the ascending aorta - 747.210
	When mitral valve or aortic valve are absent/atretic, those defects are diagnosed separately.
	Atresia, or marked hypoplasia of the ascending aorta and defective development of
	the left ventricle (with mitral valve involvement)

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

746.800	Other specified anomalies of the heart
	Dextrocardia without situs inversus (situs solitus)
	Dextrocardia with no mention of situs inversus
	Excludes: Dextrocardia with situs inversus (Use 759.300)
	Dextrocardia with left congenital diaphragmatic hernia
746.820	Cor triatriatum
746.830	Pulmonary infundibular (subvalvular) stenosis
746.840	Trilogy of Fallot
746.850	Anomalies of pericardium
746.860	Anomalies of myocardium
	Cardiomegaly, congenital,
	Cardiomyopathy, congenital
	Cardiomyopathy, hypertrophic
	Rhabdomyoma (heart)
	Ventricular hypertrophy, bilateral 2
	Ventricular septal thickening
	Ventricular septal hypertrophy
	Excludes: Ventricular hypertrophy, unilateral (Use 746.886)
746.870	Congenital heart block
746.880	Other specified anomalies of heart
	Includes: Ectopia (ectopic) cordis (mesocardia), conduction defects,
	Shone's complex
	Tumor of the heart
	Hypoplastic heart
	Long Q-T syndrome
	Left ventricular outflow tract obstruction
	Right ventricular outflow tract obstruction
746.881	Hypoplastic left ventricle
	Excludes: Hypoplastic left heart syndrome
746.882	Hypoplastic right heart (ventricle)
	Uhl's disease
746.883	Hypoplastic ventricle
746.885	Anomalies of coronary artery or sinus
	Dilated coronary sinus
	Excludes: Dilated coronary sinus when there is a left superior vena cava

746.886	Ventricular hypertrophy, unilateral (right or left) Excludes: Ventricular hypertrophy, bilateral
746.887	746.887 Other defects of the atria Hypoplastic atrium Excludes: Congenital Wolfe-Parkinson-White Rhythm anomalies
746.900	Unspecified anomalies of heart Unspecified anomalies of heart valves Truncal valve Truncal valve insufficiency and regurgitation Truncal valve stenosis Narrow truncal valve Single atrioventricular valve Single atrioventricular valve insufficiency and regurgitation
746.910	Anomalous bands of heart
746.920	Acyanotic congenital heart disease, NOS
746.930	Cyanotic congenital heart disease, NOS Blue baby
746.990	Unspecified anomaly of heart: Includes: Congenital heart disease (CHD)
746.995	"Pulmonic" or "pulmonary" atresia, stenosis, or hypoplasia, NOS (no mention of valve or artery)

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

747 Other Congenital Anomalies of Circulatory System

747.000	Patent ductus arteriosus
747.100	Coarctation of aorta
	Preductal (proximal) coarctation of aorta
747.110	Postductal (distal) coarctation of aorta
747.090	Unspecified coarctation of aorta
	Juxtaductal coarctation of aorta
747.200	Other anomalies of aorta
	Atresia of aorta
	Absence of aorta
	Atrophy of aorta
	Pseudotruncus arteriosus
	Stenosis of aorta
747.210	Hypoplasia of aorta
	Tubular hypoplasia of aorta
	Small aorta
	Narrowing of aorta
	Proximal distal transverse arch hypoplasia
	Narrow aortic isthmus
	Hypoplastic aortic arch
747.215	Interrupted aortic arch
747.220	Supra-aortic stenosis (supravalvular)
	Excludes: Aortic valve stenosis, congenital (See 746.300)
747.230	Persistent right aortic arch
747.240	Aneurysm of sinus of Valsalva
747.250	Vascular ring (aorta)
	Double aortic arch
	Includes: Vascular ring compression of trachea
747.260	Overriding aorta
	Dextroposition of aorta
	Malaligned aorta
747.270	Congenital aneurysm of aorta
	Congenital dilatation of aorta
	Enlarged aorta

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

747.280	Other specified anomalies of aorta
	Collateral vessel involving aorta 1
	Pseudocoarctation of aorta
	Elongation of aorta
747.290	Unspecified anomalies of aorta
747.300	Anomalies of pulmonary artery
	Pulmonary artery atresia, absence, or agenesis
	Use 746.995 if artery or valve is not specified
747.310	Pulmonary artery atresia with septal defect
747.320	Pulmonary artery stenosis
	Supravalvular pulmonary stenosis
	Pulmonary artery narrowing
	Use 746.995 if artery or valve is not specified
747.325	Peripheral pulmonary artery stenosis
	Includes: peripheral pulmonic stenosis (PPS)
	pulmonary artery branch stenosis
	peripheral pulmonic stenosis (PPS) murmur
747.330	Aneurysm of pulmonary artery
	Dilatation of pulmonary artery
	Enlarged pulmonary artery
747.340	Pulmonary arteriovenous malformation or aneurysm
747.380	Other specified anomaly of pulmonary artery
	Includes: Pulmonary artery hypoplasia
	Small pulmonary artery
	Overriding pulmonary artery
	Collateral vessel involving pulmonary artery (and not aorta) 1
	Pulmonary vascular or artery sling
747.390	Unspecified anomaly of pulmonary artery
747.400	Anomalies of great veins
	Stenosis of vena cava (inferior or superior)
	Small vena cava (inferior or superior)
747.410	Persistent left superior vena cava
	Bilateral superior vena cava
747.420	(TAPVR) Total anomalous pulmonary venous return
747.430	Partial anomalous pulmonary venous return

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

747.440	Anomalous portal vein termination
747.450	Portal vein - hepatic artery fistula
747.480	Other specified anomalies of great veins
	Enlarged vena cava (inferior or superior)
	Pulmonary vein atresia
	Pulmonary vein stenosis
	Dilated vena cava (inferior or superior)
	Absent vena cava (inferior or superior)
	Interrupted inferior vena cava
	Bilateral inferior vena cava
	Anomalous pulmonary venous return – total/partial not specified
	Small pulmonary veins
	Excludes: Absent left superior vena cava (LSVC) which would be normal
747.490	Unspecified anomalies of great veins
747.500	Absence or hypoplasia of umbilical artery
	Single umbilical artery
	Two-vessel cord
	Umbilical artery hypoplasia
747.600	Other anomalies of peripheral vascular system
	Stenosis of renal artery
747.610	Other anomalies of renal artery
	Absent renal artery
747.620	Arteriovenous malformation (peripheral)
	Excludes: Pulmonary (747.340)
	Cerebral (747.800)
	Retinal (743.510)
747.630	Congenital phlebectasia
	Congenital varix
747.640	Other anomalies of peripheral arteries
	Includes: Aberrant subclavian artery
	Common brachiocephalic trunk
	Aberrant innominate artery
	Absent carotid artery
	Anomalous carotid artery

Table A1. Texas Birth Defects Registry BPA Codes for congenital heart defects

747.650	Other anomalies of peripheral veins
	Hemiazygos vein anomalies
	Hypoplastic innominate vein
	Hypoplastic jugular vein
	Hepatic vein stenosis
747.680	Other anomalies of peripheral vascular system
	Includes: Four vessel umbilical cord
747.690	Unspecified anomalies of peripheral vascular system
747.800	Other specified anomalies of circulatory system
	Arteriovenous (malformation) aneurysm of brain
747.810	Other anomalies of cerebral vessels
	Includes: Anomalies of Vein of Galen
747.880	Other specified anomalies of circulatory system
	Endothelial vessel
	Collateral vessel (not involving aorta or pulmonary artery) 1
	Excludes: Congenital aneurysm:
	Coronary (746.880)
	Peripheral (747.640)
	Pulmonary (747.330)
	Retinal (743.510)
	Ruptured cerebral arteriovenous
	Aneurysm
	Ruptured cerebral aneurysm
747.900	Unspecified anomalies of circulatory system

APPENDIX B:

ESTIMATED POWER CALCULATIONS AND ASSUMPTIONS

The formula used to estimate power for this study is an extension of Schoenfeld's sample-size formula for the proportional-hazards regression model, solved for power (1-β) (Hipwell, Strachan et al. 2000; Shechter, Sharir et al. 2000). We performed power calculations using Power Analysis and Sample Size (PASS) software by NCSS (Kaushik, Leon et al. 2000).

$$N = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{P\,(1-R^2)\,\sigma^2\,B^2}$$

Where N is the sample size; $z_{1-\alpha/2}$ and $z_{1-\beta}$ are standard normal deviates at a two-sided significance level α and power (1-β); P is the overall event rate or proportion of non-censored participants; R^2 is the effect size of covariates on the variable of interest; σ is the standard deviation of the variable of interest; and B is the effect size (log of the hazard ratio).

In order to calculate an estimate of power for this study, several assumptions have been used to select parameter values for inclusion in the formula. Our study was conducted using TBDR data for 2070 singleton infants born between January 1, 1996 and December 31, 2007 with congenital heart valve defects. We found that approximately 48.4% of our cases were Hispanic (1001), 39.8% were non-Hispanic white (824), and 11.8% were non-Hispanic black (245); our study included 219 infants with aortic valve atresia, 300 with had aortic valve stenosis, 124 with pulmonary valve atresia and HRV, 114 with pulmonary valve atresia without HRV, 1323 with pulmonary valve stenosis, and 149 with tricuspid valve atresia.

We calculated the power to detect hazard ratios of 1.5 and 3.0; the significance level, alpha, for our study was 0.05. Since our associations indicate risk or protective exposures, two sided hypotheses were tested.

We calculated power using standard deviation values of 0.5 and 0.7 to show a range of possibilities, and assumed that the outcome was influenced by covariates such that the value of R^2 was assumed to be 0.15. These values were selected as moderate points from a range of potential values.

Based on the study data, estimates of study power were calculated based on three potential scenarios: 1) an event (death) rate of 5%, 2) an event rate of 10%, and 3) an event rate of 40%.

The results of these calculations are presented in Table B1. As shown in the table, estimated study power varies considerably for the various scenarios of our study. Although our study size was fairly small for some of our stratified groups, we were able to observe statistically significant results although the power to detect these results may have been limited.

Table B1. Estimated power for various sample sizes, standard deviations, and event rates

Power	Sample Size (N)	Reg. Coef. (B)	S.D. of X1 (SD)	Event Rate (P)	R-Squared X1 vs Other X's (R2)	Two-Sided Alpha	Beta
0.03811	20	0.4055	0.5	0.05	0.15	0.05	0.96189
0.04802	50	0.4055	0.5	0.05	0.15	0.05	0.95198
0.06154	100	0.4055	0.5	0.05	0.15	0.05	0.93846
0.07304	20	1.0986	0.5	0.05	0.15	0.05	0.92696
0.12318	50	1.0986	0.5	0.05	0.15	0.05	0.87682
0.20396	100	1.0986	0.5	0.05	0.15	0.05	0.79604
0.04498	20	0.4055	0.5	0.1	0.15	0.05	0.95502
0.06154	50	0.4055	0.5	0.1	0.15	0.05	0.93846
0.08552	100	0.4055	0.5	0.1	0.15	0.05	0.91448
0.10679	20	1.0986	0.5	0.1	0.15	0.05	0.89321
0.20396	50	1.0986	0.5	0.1	0.15	0.05	0.79604
0.35999	100	1.0986	0.5	0.1	0.15	0.05	0.64001
0.07618	20	0.4055	0.5	0.4	0.15	0.05	0.92382
0.13051	50	0.4055	0.5	0.4	0.15	0.05	0.86949
0.21836	100	0.4055	0.5	0.4	0.15	0.05	0.78164
0.2989	20	1.0986	0.5	0.4	0.15	0.05	0.7011
0.61976	50	1.0986	0.5	0.4	0.15	0.05	0.38024
0.89306	100	1.0986	0.5	0.4	0.15	0.05	0.10694
0.04473	20	0.4055	0.7	0.05	0.15	0.05	0.95527
0.06103	50	0.4055	0.7	0.05	0.15	0.05	0.93897
0.0846	100	0.4055	0.7	0.05	0.15	0.05	0.9154
0.10547	20	1.0986	0.7	0.05	0.15	0.05	0.89453
0.20075	50	1.0986	0.7	0.05	0.15	0.05	0.79925
0.35398	100	1.0986	0.7	0.05	0.15	0.05	0.64602
0.05593	20	0.4055	0.7	0.1	0.15	0.05	0.94407
0.0846	50	0.4055	0.7	0.1	0.15	0.05	0.9154
0.12873	100	0.4055	0.7	0.1	0.15	0.05	0.87127
0.16921	20	1.0986	0.7	0.1	0.15	0.05	0.83079
0.35398	50	1.0986	0.7	0.1	0.15	0.05	0.64602
0.61106	100	1.0986	0.7	0.1	0.15	0.05	0.38894
0.11128	20	0.4055	0.7	0.4	0.15	0.05	0.88872
0.21487	50	0.4055	0.7	0.4	0.15	0.05	0.78513
0.38024	100	0.4055	0.7	0.4	0.15	0.05	0.61976
0.5181	20	1.0986	0.7	0.4	0.15	0.05	0.4819
0.88701	50	1.0986	0.7	0.4	0.15	0.05	0.11299
0.9942	100	1.0986	0.7	0.4	0.15	0.05	0.0058