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Prenatal Diagnosis of Congenital Heart Defects: Impact on 1-year Survival in the Metropolitan Atlanta Congenital Defects Program Cohort

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Epidemiology

_____

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2006

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a thesis submitted to the Faculty of the
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ABSTRACT

Prenatal Diagnosis of Congenital Heart Defects: Impact on 1-year Survival in the Metropolitan Atlanta Congenital Defects Program Cohort

By Christopher H. Kim

Background: Prenatal diagnosis has been shown to improve short-term morbidity in newborns with congenital heart defects (CHDs), but there are conflicting data as to the impact on 1-year survival.

Methods: We performed a population-based, retrospective cohort study of infants with prenatally vs. postnatally diagnosed CHDs between 1994 and 2005 as ascertained by the Metropolitan Atlanta Congenital Defects Program. Among infants with isolated CHDs, we estimated Kaplan-Meier survival probabilities for prenatally vs. postnatally diagnosed infants and determined Cox proportional hazard ratios adjusted for critical CHD status, gestational age, and maternal race/ethnicity.

Results: Of 539,519 live births, 4,366 infants had CHDs (411 prenatally diagnosed). Compared to those with non-critical defects, those with critical defects were more likely to be prenatally diagnosed (57.9% vs. 19.4%, $p<0.001$). Among the 3,065 infants with isolated CHDs, 1-year survival was 77.1% for those prenatally diagnosed (n=201) vs. 96.1% for those postnatally diagnosed (n=2,864) ($p<0.001$). Comparing 1-year survival among those with non-critical CHDs alone (n=2,379) showed no difference between prenatal and postnatal diagnosis (98.0% vs. 98.4%, $p=0.80$) whereas among those with critical CHDs (n=686), prenatally diagnosed infants had significantly lower survival (70.4% vs. 86.0%, $p<0.001$). After adjustment, the hazard ratio for mortality between those with prenatally vs. postnatally diagnosed CHDs was 2.564 (95% CI: 1.78, 3.70).

Conclusion: Prenatal diagnosis is associated with lower 1-year survival for infants with isolated critical CHDs but shows no change for those with isolated non-critical CHDs. Varying disease severity within critical CHD subtypes for prenatal vs. postnatal diagnosis might explain this association.

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Introduction

Fetal echocardiography is widely used in the prenatal diagnosis of congenital heart defects (CHDs). Numerous studies have demonstrated that the prenatal diagnosis of CHDs requiring intervention has a positive effect on the preoperative condition of neonates with severe structural abnormalities as well as a decrease in adverse perioperative events(1-5). These findings have led investigators to suggest that prenatal diagnosis can improve long-term neurological outcomes(2, 3). However, conclusions about the impact of prenatal diagnosis on infant survival have varied.

Conflicting results as to whether prenatal diagnosis leads to decreased preoperative and postoperative mortality have been reported in studies examining hypoplastic left heart syndrome (HLHS)(3, 6, 7) and transposition of the great arteries (TGA)(4, 6). A lack of definitive evidence regarding mortality outcomes may be due in part to the difficulties in obtaining adequate patient numbers when examining specific defects at a single center(1). In addition, few studies have examined survival beyond the perioperative period.

The objective of our study was to examine the 1-year survival of infants with prenatally vs. postnatally diagnosed CHDs in a large population-based cohort. We also sought to determine what factors may lead to differential outcomes in survival between prenatally and postnatally diagnosed infants with CHDs.

Methods

Data Sources

The Centers for Disease Control and Prevention's (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP) is an active population-based surveillance system for major birth defects among infants, fetuses, and children born to residents of the five central counties of metropolitan Atlanta(8). The MACDP was established in 1967 and operates in collaboration with the Georgia Division of Public Health and has approval of the CDC's Institutional Review Board. Medical records for children in whom a birth defect is diagnosed prior to 6 years of age are reviewed, and demographic and clinical information collected.

Cases in the MACDP with International Classification of Diseases, 9th Revision (ICD-9) or modified British Paediatric Association (BPA) codes for CHDs undergo review and classification by clinical experts in pediatric cardiology according to a standard nomenclature adopted from the Society of Thoracic Surgeons and based on current understanding of development morphogenesis(9). All infants in the MACDP identified with a CHD were included in the baseline statistical summary, but infants with multiple defects or defects associated with chromosomal disorders were not included in the Kaplan-Meier survival curves or proportional hazards analyses.

Prenatal echocardiography records were obtained from metropolitan Atlanta area pediatric cardiology clinics. Records were matched to cases in the MACDP. Cases for which no documented prenatal diagnosis existed were assumed to have been diagnosed postnatally. Survival status was determined through review of available clinical records, linkage with vital records from the state of Georgia, or linkage with the National Death

Index (NDI). Echocardiography records were available starting from 1994, and NDI records available through 2006. With 1-year mortality as the primary outcome, the birth cohort was limited to infants born between January 1, 1994 and December 31, 2005.

Covariate Definitions

Potential covariates for the association between timing of diagnosis (prenatal vs. postnatal) and 1-year mortality included critical CHD (CCHD) status (critical vs. non-critical), gestational age at birth (≤36 weeks vs. >36 weeks), neighborhood poverty level (<20% of population in census tract living in poverty vs. ≥20%), birth weight (<2500 grams vs. ≥2500 grams), maternal race/ethnicity (white vs. non-white), and maternal age.

For this study, we defined critical CHDs as 12 defects that are likely to require intervention within the first year of life and/or are likely to be detected by pulse oximetry screening(10). These 12 defects consisted of 7 primary targets [hypoplastic left heart syndrome (HLHS), pulmonary atresia, tetralogy of Fallot (TOF), transposition of the great arteries (TGA), tricuspid atresia, truncus arteriosus, and total anomalous pulmonary venous return (TAPVR)] and 5 secondary targets [coarctation of the aorta (CAA), double outlet right ventricle (DORV), Ebstein's anomaly, interrupted aortic arch (IAA), and single ventricle]. As disease severity is not routinely collected by MACDP, defects such as severe pulmonary stenosis and aortic stenosis were not considered as CCHDs in this study.

Statistical Analysis

Chi-square analyses were performed to compare baseline characteristics of each covariate between the prenatally diagnosed cohort and the postnatally diagnosed cohort. Survival probabilities were estimated using Kaplan-Meier methods, and the log-rank test

used to determine significance ($p<0.05$). Covariates were also analyzed using univariate logistic regression modeling, with death at 1 year as the outcome. Covariates that were significantly different between prenatal and postnatal cohorts, and were also significantly associated with 1-year mortality ($p<0.05$) were identified as potential confounders and included in Cox proportional hazards models to obtain adjusted hazard ratios (aHR) for mortality. The final multivariate models were constructed among cases with isolated CHDs only, and adjusted for maternal race and gestational age at birth. All analyses were performed using SAS 9.3 (Cary, NC).

Results

Of the 539,519 live births in the five counties surveilled by the MACDP from 1994 to 2005, 4,366 were identified as having CHDs. Of these, 411 (9.4%) were diagnosed prenatally. When comparing infants with prenatally vs. postnatally diagnosed CHDs, significant differences were seen with respect to the proportion of infants with CCHDs, gestational age, and maternal race. No significant differences were seen with respect to neighborhood poverty level, low birth weight, or maternal age. All covariates were significantly associated with 1-year mortality by logistic regression. Among all infants, those with CHDs diagnosed prenatally had a significantly greater 1-year mortality rate (33.3%) compared to those diagnosed postnatally (8.9%) (Table 1).

Isolated CHDs accounted for 3,065 of cases in the MACDP from 1994 to 2005. Kaplan-Meier survival curves showed significantly decreased 1-year survival for prenatally vs. postnatally diagnosed CHDs (77.1% vs. 96.1%, $p<0.001$) (Figure 1a). No difference in survival was seen among non-critical CHDs (98.0% vs. 98.4%, $p=0.80$) (Figure 1c), but among critical CHDs, prenatally diagnosed infants had lower 1-year

survival as compared to postnatally diagnosed infants (70.4% vs. 86.0%, p<0.001) (Figure 1b).

These findings were corroborated in the adjusted analysis. When examining 1-year mortality using proportional hazards regression modeling among isolated CHDs, prenatally diagnosed infants had a hazard of mortality 2.564 times greater than postnatally diagnosed infants, after adjustment for CCHD status, gestational age and maternal race (95% CI: 1.780, 3.695). When the analysis was limited to isolated CCHD's, the aHR for prenatally vs. postnatally diagnosed infants was 2.536 (95% CI: 1.739, 3.697). Among non-critical CHDs, the aHR for prenatally vs. postnatally diagnosed infants was 1.004 (95% CI: 0.137, 7.350) (Table 2).

Discussion

We found significantly decreased 1-year survival among infants with prenatally diagnosed CHDs compared to postnatally diagnosed CHDs. Our study thus adds to a growing body of literature in which the survival benefit of prenatal diagnosis is unclear. Despite Tworetzky et al. demonstrating a survival benefit among HLHS infants diagnosed prenatally(7) and Franklin et al. demonstrating benefit for prenatally diagnosed coarctation of the aorta(11), several other studies have failed to demonstrate such benefit. A recent retrospective analysis of 81 HLHS patients from 1999 to 2010 found no survival-to-discharge advantage among the 49 prenatally diagnosed patients(12), a finding that has been similarly demonstrated in other single-center studies with regard to HLHS and TGA(3, 5, 6, 13) as well as pulmonary atresia with intact ventricular septum(14).

Our finding that prenatally diagnosed infants have worse outcomes at 1 year appears to be driven by the higher proportion of CCHDs among the prenatally diagnosed cohort. Similar studies have also attributed the "paradox" of poorer outcomes among prenatally diagnosed CHDs to disease severity(15). A recent study of the Czech Republic's comprehensive CHD registry also found higher rates of prenatal detection of critical CHD forms and high overall mortality among these forms(16). The finding that severe cardiac lesions are more likely to be diagnosed prenatally has been previously reported(5, 14, 17), and can be attributed in part due to the higher likelihood of detecting grossly abnormal anatomy during routine obstetric anatomical scan(18, 19). A previous analysis of CHD outcomes in the MACDP showed significantly higher rates of stillbirth and death prior to 5 years of age among infants with defects that were prenatally diagnosed, reflecting the severity of those conditions(20).

Our definition of CCHDs differs from what other studies may describe as complex or severe, in that we excluded non-isolated CHDs (such as heterotaxy) that might be readily apparent on obstetric scans, and included defects that may only be discernible on visualization of the cardiac outflow tracts, which is not always technically feasible(5). Despite methodological differences in classification of defect severity, our finding that CCHDs were more likely to be diagnosed prenatally—and therefore infants with prenatally diagnosed CHDs have higher 1-year mortality rates—is consistent with other studies that have shown poorer outcomes among infants with lesions that are considered more severe than others. Gedikbasi et al. examined survival rates among Turkish infants with 155 prenatally diagnosed CHDs. When categorized according to the Allan-Huggon grading system, survival among low risk CHDs was 89.2%, moderate risk

66.7%, and high risk 13.5%(21). Chung et al. examined NICU admissions among infants with CHDs classified by severity. “Complex” defects included all cases of atresia and single ventricle physiology, “significant” heart disease included TGA, and TOF, and “simple” defects were those that required no intervention. Among all infants with CHDs admitted to the NICU between 2004-2006, 1-year survival was 73.0% among complex defects, 94.0% among significant, and 100% among simple defects. Although our classification of defects as critical or non-critical serves as a broad comparison of defect severity, we further divided diagnosis timing into three age-at-diagnosis categories. This division can serve as a rough correlate of severity *within* the CCHDs, with prenatal diagnosis representing the most severe defects, diagnosis at greater than 1 day of life the least severe, and postnatal diagnosis before 1 day of life representing moderate severity in this scheme. A Kaplan-Meier survival curve demonstrated increasing 1-year survival ($p<0.001$) with increasing age at diagnosis (Figure 2).

Although our study does not show a 1-year survival benefit associated with prenatal diagnosis, other benefits of prenatal diagnosis have been well described in the context of preoperative condition, with reductions in morbidity such as hypoxemia, need for invasive respiratory support, and metabolic acidosis(1-7, 11-14, 17, 22-24). Early detection has also been shown to allow for better parental counseling and delivery planning(1, 21, 22, 25-27). In addition, several population-based studies from varied international locations have looked at temporal trends in prenatal diagnosis and 1-year survival rates. Increasing rates of prenatal detection over time, in conjunction with increased 1-year survival rates over those eras, have been given as evidence that prenatal echocardiography has led to an overall increase in survival(16, 26, 28, 29), though the

distinction must be made that this increase in survival refers to a comparison between time periods, rather than a comparison of survival between infants with prenatally and postnatally diagnosed defects within a single time period, as is the method of our study.

A major strength of this study is its large and diverse population-based cohort. An acknowledged limitation of many studies examining survival outcomes and prenatal diagnosis of CHDs is the difficulty in obtaining adequate patient numbers in single centers(1, 26). The MACDP is an active case ascertainment system which reviews a wide variety of clinical records in order to obtain accurate reports of birth defects. These reports are then reviewed by a team of pediatric cardiologists and classified in a manner that optimizes accuracy for surveillance and research(30). This large and well-classified system allowed our study to limit analysis to isolated birth defects, thus minimizing the possibility that our findings are due to the poorer outcomes associated with chromosomal abnormalities and extracardiac defects(17, 20, 29).

However, our study is not without limitations. There may have been cases in which prenatal echocardiography was performed at a site that is not covered by the MACDP, and/or birth records were unable to be matched to echocardiographic records. Our need to assume that a lack of echocardiographic data meant a postnatal diagnosis is a potential source of misclassification bias. In addition, our data showed a significantly increased hazard of mortality for prenatally diagnosed infants even after adjusting for critical CHD status. Therefore these findings cannot be explained by the proportion of CCHDs alone. One possible explanation for these findings is the spectrum of severity that may exist within a single defect type (26). Lowenthal and colleagues recently demonstrated that among infants with prenatally diagnosed HLHS, those with any degree

of atrial septal restriction had significantly decreased 2-year survival compared to those without evidence of atrial restriction(31). The MACDP does not contain this level of detail regarding an individual's disease severity, nor does it contain information about clinical course, surgical interventions, or operative mortality. We are therefore unable to assess the influence of these factors on 1-year survival in our cohort.

However, even without specific information regarding surgical interventions and outcomes, our findings can provide some insight into what treatment decisions are made by parents following a prenatal diagnosis of CHD. A number of studies have examined factors that influence parental decision-making regarding treatment options with respect to HLHS(32-36). Advances in surgical technique appear to have led to a decline in physician recommendations for comfort or palliative care alone without surgical intervention(33, 35). Prenatal diagnosis may provide more time and counseling for parents to consider the decision to pursue palliative care over surgical interventions(35, 37), but our findings do not appear to indicate that survival differences between prenatally and postnatally diagnosed infants is due in significant part to more parents choosing palliative care after prenatal diagnosis, as evidenced by differences in survival rates that persisted beyond 1 month of age (Figure 1a, 1b). In addition, one of the most significant predictors of parents choosing palliative care following prenatal diagnosis was the presence of a chromosomal abnormality(32), which we excluded from our analyses. Although it is difficult to assess the impact of prenatal diagnosis on pregnancy termination rates using the MACDP, other investigators have reported relatively stable rates of termination from 1994 and on(28, 29), with isolated CHDs diagnosed prior to 22 weeks gestation a particularly strong indicator for decision to terminate, according to data

from the Paris Registry of Congenital Malformations(38). Possible future areas of investigation may seek to examine the effect of prenatal diagnosis of CHDs on other factors that may influence infant survival, such as delivery timing among term infants(39, 40) as well as mode of delivery(41, 42). Trento and colleagues found that prenatal diagnosis of CHDs is associated with increased odds of scheduled delivery(43). This finding was also seen in the work of Landis et al., which additionally noted an association between prenatally diagnosed CHDs and induction of labor(24). While neither of these studies found a significant effect on short-term mortality, it may be useful to examine these factors in our large population-based cohort.

Conclusion

Fetal echocardiography remains an effective tool in the prenatal detection of congenital heart disease, but 1-year survival among infants with prenatally diagnosed CHDs is lower than that of infants who are postnatally diagnosed, owing to the severity of lesions that can be detected at such an early stage. Therefore, further studies into the impact of prenatal echocardiography on survival should focus on factors that affect morbidity and mortality among the most anatomically severe critical CHDs, and how prenatal detection can influence those factors.

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TABLES

Table 1. Baseline characteristics for prenatally vs. postnatally diagnosed congenital heart defects (CHDs) in Metropolitan Atlanta, Georgia: 1994-2005

	Prenatally Diagnosed (n = 411) N(%)	**Postnatally Diagnosed (n = 3955) N(%)**	**p-Value**
Critical CHD*	238(57.9)	769(19.4)	**<0.001**
Isolated CHD	201(51.0)	2864(75.2)	**<0.001**
Multiple CHD	64(16.2)	428(11.2)	**0.003**
Chromosomal Abnormality	99(25.1)	471(12.4)	**<0.001**
Gestational Age			
<36 Weeks	107(27.4)	997(27.4)	**<0.001**
37-38 Weeks	146(37.3)	957(26.3)	
39-40 Weeks	126(32.2)	1411(38.7)	
>40 Weeks	12(3.1)	279(7.7)	
Neighborhood Poverty Level†			
0.0-4-4.9%	127(32.1)	1295(34.2)	0.64
5.0-9.9%	113(28.5)	1060(28.0)	
10.0-19.9%	100(25.3)	968(25.6)	
>20%	56(14.1)	460(12.2)	
Low Birthweight	120(29.2)	994(25.1)	0.07
Race/Ethnicity			

White, Non-Hispanic	177(43.1)	1765(44.6)	
Black, Non-Hispanic	170(41.4)	1366(34.5)	**0.002**
Hispanic	38(9.3)	612(15.5)	
Other	26(6.3)	212(5.4)	
Maternal Age			
<20	37(9.0)	327(8.3)	
20-24	76(18.5)	730(18.5)	0.14
25-29	82(20.0)	988(25.0)	
30+	216(52.6)	1910(48.3)	
1-Year Mortality	137(33.3)	350(8.9)	**<0.001**

* Defined as seven primary targets (hypoplastic left heart syndrome, truncus arteriosus, tricuspid atresia, total anomalous pulmonary venous return, pulmonary atresia, tetralogy of Fallot, transposition of the great arteries) plus five secondary targets (interrupted aortic arch, coarctation of the aorta, Ebstein's anomaly, single ventricle, double outlet right ventricle)

† Defined by the percentage of residents below poverty level in census tract associated with maternal address

Table 2. Stratified Cox Proportional Hazards Ratios for 1-year Mortality in Infants born with prenatally vs. postnatally diagnosed CHDs: Atlanta, Georgia, 1994-2005

	Hazard Ratio*	95% Confidence Interval	p-Value
All Isolated CHDs†	2.564	1.780, 3.695	**<0.001**
Isolated Non-CCHDs	1.004	0.137, 7.350	0.10
Isolated CCHDs	2.536	1.794, 3.697	**<0.001**

*All Hazard Ratios adjusted for gestational age. Models were stratified by maternal race because it violated the proportional hazards assumption

† Adjusted for CCHDs

FIGURES

Figure 1. One-Year Survival for Infants with isolated Congenital Heart Defects (CHDs) by prenatal vs. postnatal diagnosis: Atlanta, Georgia, 1994-2005. 1a. All CHDs. 1b. Critical CHDs (CCHDs), defined as seven primary targets (hypoplastic left heart syndrome, truncus arteriosus, tricuspid atresia, total anomalous pulmonary venous return, pulmonary atresia, tetralogy of Fallot, transposition of the great arteries) plus five secondary targets (interrupted aortic arch, coarctation of the aorta, Ebstein's anomaly, single ventricle, double outlet right ventricle). 1c. Non-Critical CHDs.

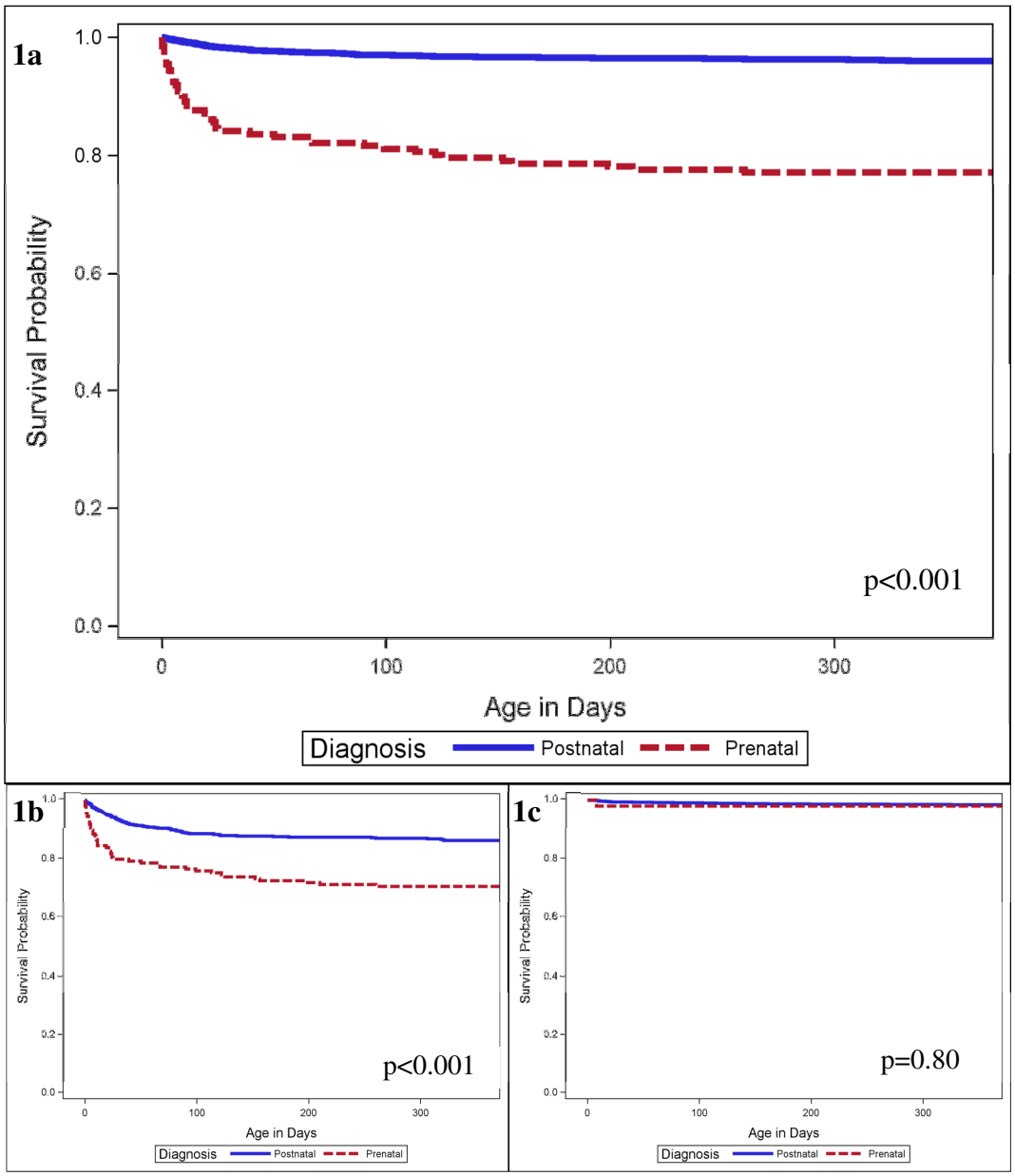

Figure 2. One-Year Survival for Infants with Isolated Critical Congenital Heart Defects (CCHDs) by Age at Diagnosis: Atlanta, Georgia, 1994-2005. 1-year survival among infants with isolated CCHDs diagnosed prenatally was 70.4% (n=152). For infants postnatally diagnosed at less than or equal to 1 day of life, 1-year survival was 82.5% (n=338), and for those diagnosed beyond 1 day of life 1-year survival was 92.0% (n=187).