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Age at Referral and Mortality From Critical Congenital Heart Disease

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Age at Referral and Mortality From Critical Congenital Heart Disease

WHAT'S KNOWN ON THIS SUBJECT: Early referral of infants with critical congenital heart disease (CCHD) is recommended to reduce mortality. However, few population-based data have been published showing the relationship between CCHD neonatal mortality and timing of cardiac evaluation at a specialty center.

WHAT THIS STUDY ADDS: In neonates with CCHD, 35% were not evaluated at a cardiac center by 4 days of age. These cases accounted for a significant number of CCHD deaths. This information enhances the rationale for pulse oximetry screening of neonates for CCHD.

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KEY WORDS

congenital heart disease, neonatal mortality, epidemiology, health policy and outcome research

ABBREVIATIONS

CCHD—critical congenital heart disease
CHD—congenital heart disease
CI—confidence interval
HLHS—hypoplastic left heart syndrome
IQR—interquartile range
NH—non-Hispanic
TA—tricuspid atresia
TAPVR—total anomalous pulmonary venous return
TBDR—Texas Birth Defects Registry
TGA—d-transposition of the great arteries
TOF—tetralogy of Fallot

Dr Fixler conceptualized and designed the study and drafted the manuscript; Dr Xu carried out the statistical analyses and reviewed and revised the manuscript; Dr Nembhard contributed to the design of the study and revised the manuscript; Ms Ethen assisted in the design of the data collection instruments, provided the data for statistical analysis, and critically reviewed the manuscript; Dr Canfield directed the data collection, assisted in the design of the data collection instrument, and reviewed the manuscript; and all authors approved the final manuscript as submitted.

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abstract

BACKGROUND AND OBJECTIVE: Newborn pulse oximetry screening is recommended to promote early referral of neonates with critical congenital heart disease (CCHD) and reduce mortality; however, the impact of late referral on mortality is not well defined. The purpose of this population-based study was to describe the association between timing of referral to a cardiac center and mortality in 2360 liveborn neonates with CCHD.

METHODS: Neonates with CCHD born before pulse oximetry screening (1996–2007) were selected from the Texas Birth Defects Registry and linked to state birth and death records. Age at referral was ascertained from date of first cardiac procedure at a cardiac center. Logistic and Cox proportional hazards regression models were used to estimate factors associated with late referral and mortality; the Kaplan-Meier method was used to estimate 3-month survival.

RESULTS: Median age at referral was 1 day (25th–75th percentile: 0–6 days). Overall, 27.5% (649 of 2360) were referred after age 4 days and 7.5% (178 of 2360) had no record of referral. Neonatal mortality was 18.1% (277 of 1533) for those referred at 0 to 4 days of age, 9.0% (34 of 379) for those referred at 5 to 27 days of age, and 38.8% (69 of 178) for those with no referral. No improvement in age at referral was found across the 2 eras within 1996–2007.

CONCLUSIONS: A significant proportion of neonates with CCHD experienced late or no referral to cardiac specialty centers, accounting for a significant number of the deaths. Future population-based studies are needed to determine the benefit of pulse oximetry screening on mortality and morbidity. *Pediatrics* 2014;134:e98–e105

Congenital heart disease (CHD) is one of the common causes of death in infancy.[1–4] Although the outcome has improved over the past decades, morbidity and mortality remain high, especially in infants with critical congenital heart disease (CCHD) in which circulation is dependent on ductal or interatrial shunting.[5–7] A large Swedish population–based study reported that the risk of being discharged with undiagnosed duct-dependent CCHD was 28%.[8] Recently, Peterson et al[9] reported in a US population–based study that 29.5% of 3746 infants with CCHD were diagnosed late, after 3 days of birth. All too frequently such infants are discharged from the nursery without diagnosis, only to be referred to a cardiac center later with severe hypoxemia or in shock. Brown et al[10] reported that neonates with CCHD who presented to Great Ormond Street Hospital in London with cardiac compromise had a 5-fold increase in postoperative mortality. As a result, several investigators evaluated the use of routine pulse oximetry to identify infants with CCHD before discharge from delivery units and reported on its validity.[8,11–17] In the United States, many state legislatures have mandated universal pulse oximetry screening of newborns, which was endorsed by the Secretary of Health and Human Services in 2011. The scientific committees of the American Academy of Pediatrics and the American Heart Association recommended that additional studies be conducted in large diverse populations across a broad range of delivery systems to determine whether pulse oximetry screening in neonates improves outcomes in infants with CCHD.[18] Unfortunately, no US population–based studies have reported the extent that CCHD mortality can be attributed to delays in receiving care at cardiac specialty centers. The purpose of this population-based study was to describe the association of timing of referral to a cardiac center and mortality in neonates with CCHD who were born in Texas during 1996–2007, before routine pulse oximetry screening.

METHODS

Data on cases came 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.[19] This population-based registry collects information on major birth malformations in offspring of Texas-resident mothers. Case finding of all birth defects was conducted by TBDR field staff surveillance in tertiary care centers and birth facilities through review of nursery, obstetric, pediatric, NICU, and surgery logs and discharge diagnoses, followed by review of medical records. The field staff identified birth defect cases among 3 993 668 live births and abstracted diagnostic and survival data from the medical records. Registry cases were linked to their birth and death certificates, as described by Forrester and Canfield.[20] Information on selected sociodemographic factors from vital records (birth and death certificates) was combined with registry data abstracted from medical records. Information on the condition of neonates on admission, detailed surgical data, and type of health care coverage were not available in the TBDR.

Infants with the 7 CCHDs that are considered primary targets for routine pulse oximetry screening by the Advisory Committee for Maternal and Child Health[21] comprised our study population because these defects were most likely to be detected by such screening because of early hypoxemia. These included liveborn infants with hypoplastic left heart syndrome (HLHS), dextrotransposition of the great arteries (TGA), tetralogy of Fallot (TOF), total anomalous pulmonary venous return (TAPVR), pulmonary atresia with intact ventricular septum, truncus arteriosus (truncus), and tricuspid atresia (TA) born to Texas-resident mothers of the 3 most common Texas racial/ethnic groups between January 1, 1996, and December 31, 2007, a period before pulse oximetry screening. Infants of other race/ethnic groups (4.4%) were excluded because of their small numbers, which prevented meaningful analyses. Also excluded were cases with additional cardiac lesions that have atypical outcomes, such as HLHS with TAPVR or unbalanced atrioventricular septal defect, TOF with absent pulmonary valve, TAPVR with heterotaxia, TA with TGA, and TGA with outflow obstruction. Infants with trisomy 13 or 18 were excluded; however, infants with trisomy 21 or significant extracardiac defects were included. Registry information was reviewed by an experienced pediatric cardiologist (D.E.F.) who edited and verified the diagnoses.

We obtained the date of death from the registry records and the Texas death to birth certificate matching performed by the Vital Statistics Unit of the Texas Department of State Health Services. Neonatal mortality was defined as the percentage of liveborn infants with CCHD who died by 27 days of age. The date of referral was defined as the date of the neonate's first postnatal cardiac procedure at a cardiac center, including an echocardiogram (71.3%), cardiac surgery (15.4%), catheterization (9.4%), an electrocardiogram (2.4%), or autopsy (1.0%) as interpreted by an attending pediatric cardiologist or cardiac surgeon. The TBDR had no record of admission to a cardiac center for 178 infants whose diagnoses had been made at facilities other than cardiac centers. The age at referral was defined as the date of referral minus the date of birth (first day of life = 0 days of age). Late referral was defined as after 4 days of age. Logistic

regression was used to calculate crude and adjusted odds ratios with 95% confidence intervals (CIs) to assess the association of maternal and infant factors with referral after 4 days of age, eg, maternal age, maternal race/ethnicity (non-Hispanic [NH]-white, NH-black, Hispanic), maternal education (<12, 12, >12 years), infant gender, birth weight, gestational age, CCHD type, presence of extracardiac defects, birth era (1996–2001 or 2002–2007), and prenatal diagnosis. The Kaplan-Meier method and log rank testing were used to compare the patterns of survival within the first 3 months of life. Cox proportional hazards regression was used to calculate unadjusted and adjusted hazards ratios and 95% CIs. A hazard ratio was considered statistically significant if its 95% CI excluded 1.

The study was approved by the institutional review boards at the University of South Florida, University of Texas Southwestern Medical Center, and the Texas Department of State Health Services.

RESULTS

The total number of selected cases was 2360. Overall, there were 2182 infants whose age at referral could be determined, 27.5% (649 of 2360) were referred after 4 days of age, and 7.5% (178 of 2360) had no TBDR record of referral or admission to a cardiac center. Possible reasons for cases not being admitted may have been death before referral due to an unstable condition, an unrecognized diagnosis, or the parents not wanting referral. Table 1 shows the maternal and infant characteristics of those who were referred. The race/ethnic distribution was 39.0% NH-white, 8.8% NH-black, and 52.2% Hispanic. Although the number of infants born to NH-black mothers was low, the distribution was similar to their frequency in the TBDR of all infants with birth defects.

TABLE 1 Maternal and Infant Characteristics and Age at Referral to a Cardiac Center

	Total *N*	Referral Age									
		0–2 Days		3–4 Days		5–6 Days		7–27 Days		≥28 Days	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
Maternal											
Race/ethnicity											
NH-white	850	538	63.3	71	8.4	45	5.3	94	11.1	102	12.0
NH-black	192	113	58.9	11	5.7	16	8.3	26	13.5	26	13.5
Hispanic	1140	714	62.6	86	7.5	53	4.6	145	12.7	142	12.5
Age											
≤31 years	1650	1042	63.2	122	7.4	87	5.3	193	11.7	206	12.5
32–36 years	332	194	58.4	27	8.1	16	4.8	50	15.1	45	13.6
>36 years	200	129	64.5	19	9.5	11	5.5	22	11.0	19	9.5
Education											
<High school	1215	782	64.4	79	6.5	58	4.8	148	12.2	148	12.2
High school	452	265	58.6	42	9.3	30	6.6	60	13.3	55	12.2
>High school	473	288	60.9	46	9.7	25	5.3	51	10.8	63	13.3
Infant											
Birth weight											
<1500 g	49	31	63.3	1	2.0	2	4.1	6	12.2	9	18.4
1500–2499 g	292	186	63.7	23	7.9	10	3.4	44	15.1	29	9.9
≥2500 g	1839	1147	62.4	144	7.8	102	5.5	215	11.7	231	12.6
Gestational age											
20–31 weeks	70	43	61.4	5	7.1	1	1.4	11	15.7	10	14.3
32–36 weeks	293	184	62.8	19	6.5	13	4.4	45	15.4	32	10.9
37–44 weeks	1704	1071	62.9	135	7.9	94	5.5	191	11.2	213	12.5
Gender											
Male	1298	827	63.7	99	7.6	70	5.4	153	11.8	149	11.5
Female	882	536	60.8	69	7.8	44	5.0	112	12.7	12	13.7
Cardiac diagnosis											
HLHS	557	375	67.3	56	10.1	40	7.2	60	10.8	26	4.7
TGA	407	304	74.7	30	7.4	17	4.2	31	7.6	25	6.1
TOF	344	183	53.2	16	4.7	17	4.9	49	14.2	79	23.0
TAPVR	346	163	47.1	21	6.1	13	3.8	63	18.2	86	24.9
PA-IVS	218	166	76.1	21	9.6	5	2.3	16	7.3	10	4.6
Truncus	174	85	48.9	16	9.2	15	8.6	35	20.1	23	13.2
TA	136	89	65.4	8	5.9	7	5.1	11	8.1	21	15.4
Extracardiac defects											
Absent	1866	1154	61.9	153	8.2	101	5.4	232	12.4	226	12.1
Present	316	211	66.8	15	4.8	13	4.1	33	10.4	44	13.9
Birth era											
1996–2001	807	499	61.8	72	8.9	38	4.7	89	11.0	109	13.5
2002–2007	1375	866	63.0	96	7.0	76	5.5	176	12.8	161	11.7
Prenatal diagnosis											
Yes	328	242	73.8	24	7.3	10	3.0	35	10.7	17	5.2
No	1854	1123	60.6	144	7.8	104	5.6	230	12.4	253	13.6

Data from the TBDR, 1996–2007 (*N* = 2182). HLHS, Hypoplastic left heart syndrome; TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; PA-IVS, pulmonary atresia with intact ventricular septum; Truncus, truncus arteriosus; TA, tricuspid atresia.

The median age of referral was 1 day with the 25th and 75th percentiles, inter-quartile range (IQR) of 0 days, 25th percentile, and 6 days, 75th percentile. Median days of age at referral of NH-whites 1 (IQR 0–5), NH-blacks 1 (0–7) and Hispanics 1 (0–6), did not differ significantly ($P > .127$).

The median (IQR) days of age at referral varied by diagnosis, as follows: for HLHS, 1 (0–4); TGA, 1 (0–3); TOF, 2 (0–22); TAPVR, 3 (1–26); pulmonary atresia with intact ventricular septum, 1 (0–2); truncus, 3 (0–13); and TA, 1 (0–6). We found that later referrals occurred more frequently in infants with TOF, TAPVR, and truncus, which are defects that may not have had apparent cyanosis or signs of heart failure before discharge from the newborn nursery.

Table 2 shows neonatal percentages of mortality by diagnosis and timing of referral. Figure 1 displays longer follow-up outcomes: 3-month survival curves of infants with CCHD according to age at neonatal referral. Early referral was associated with lower 3-month survival. Importantly, in the 178 infants who had no TBDR record of admission to a cardiac center, 27-day mortality was 38.8% and 3-month mortality was 50.6%, as shown in Table 3. These figures may seem lower than expected, possibly due to the fact that the cardiac diagnoses in these cases were based on reports from facilities other than cardiac centers and may be incorrect.

Table 4 shows the results of our logistic regression analysis of potential factors associated with neonatal referral after age 4 days. In multivariable analysis, odds for late referral were higher in NH-blacks, after adjusting for type of CHD and other variables. The presence of a significant extracardiac defect increased the odds of late referral. Odds of late referral did not differ between the 1996–2001 and 2002–2007 eras, indicating no improvement in promptness of referral over the 12-year period.

Table 5 shows the results of our Cox proportional hazards regression analysis of factors associated with neonatal CCHD mortality. In multivariable analysis, increased risk of neonatal mortality was associated with maternal NH-black and Hispanic race/ethnicity, infant female gender, low birth weight, preterm birth, presence of extracardiac defects, and earlier birth era. Prenatal diagnosis was not significantly ($P > .05$) associated with lower mortality risk.

DISCUSSION

This population-based study examined the neonatal outcome of 2360 neonates with selected CCHD born during 1996–2007 in Texas from a racially diverse population of nearly 4 million births. We ascertained the timing of referral of neonates with CCHD (ie, the age at initial evaluation at a cardiac center) and found that 35% failed to have referral by age 4 days, the fifth day of life. We used the age at first cardiac diagnostic or surgical procedure by a cardiac center rather than age at initial diagnosis before referral, because it was judged to be a better measure of promptness of receiving cardiac subspecialty care. Mellander and Sunnegårdh[22] reported that 19.7% of infants with CCHD were diagnosed after discharge from maternity units, and 43% of them were in circulatory shock at time of referral to their cardiac center. Brown et al[10] reported that heart failure and end-organ dysfunction occurred more frequently in infants with CCHD who were discharged from obstetric units compared with those directly referred to their cardiac center. Unfortunately, in our study we were unable to ascertain the condition of the neonate on admission to a cardiac center from the TBDR.

In the population-based study from the Northern Health Region in England (1987–1991), Abu-Harb et al[23] reported the outcome of infants with obstructive left heart malformations. Of 21 infants with HLHS, 14 (67%) were discharged from the hospital with their HLHS undetected. In the United States, several studies have been published in which investigators reviewed population-based records from state health departments to estimate the frequency of unrecognized CCHD. Chang et al[24] examined the California statewide death records for the period 1989–2004 and found 152 cases of CCHD who had no cardiac diagnosis established before autopsy. HLHS accounted for 38% of these undiagnosed cases. In their study of New Jersey hospital discharge records of infants born during 1999–2004 with CCHD, Aamir et al[25] found that 42% (47 of 112) of infants with CCHD were discharged from the birth hospitals without referral to a cardiac center. Using more recent data from the Tennessee Department of Health birth defects file, Liske et al[15] estimated that 15% of infants with critical left heart obstruction were not diagnosed before discharge and one-half of them died. In our population-based study, 18.0% of infants with HLHS were referred between 5 and 27 days of age,

TABLE 2 Timing of Neonatal Referral of CCHD and Neonatal Mortality in Texas Births

Defect	Referral Age								Total	
	0–2 Days		3–4 Days		5–6 Days		7–27 Days			
	Deaths, *n*	Mortality, %	Deaths, *n*	Mortality, %	Deaths, *n*	Mortality, %	Deaths, *n*	Mortality, %	Deaths, *N*	Mortality, %
HLHS	134	35.7	17	30.4	6	15.0	13	21.7	170	32.0
TGA	18	5.9	2	6.7	0	0.0	1	3.2	21	5.5
TOF	11	6.0	0	0.0	1	5.9	3	6.1	15	5.7
TAPVR	25	15.3	1	4.8	0	0.0	2	3.2	28	10.8
PA-IVS	33	19.9	3	14.3	0	0.0	2	12.5	38	18.3
Truncus	21	24.7	2	12.5	2	13.3	4	11.4	29	19.2
TA	9	10.1	1	12.5	0	0.0	0	0.0	10	8.7

Data from the TBDR, 1996–2007. Neonatal mortality indicates infants who died at ages 0–27 days. HLHS, Hypoplastic left heart syndrome; TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; PA-IVS, pulmonary atresia with intact ventricular septum; Truncus, truncus arteriosus; TA, tricuspid atresia.

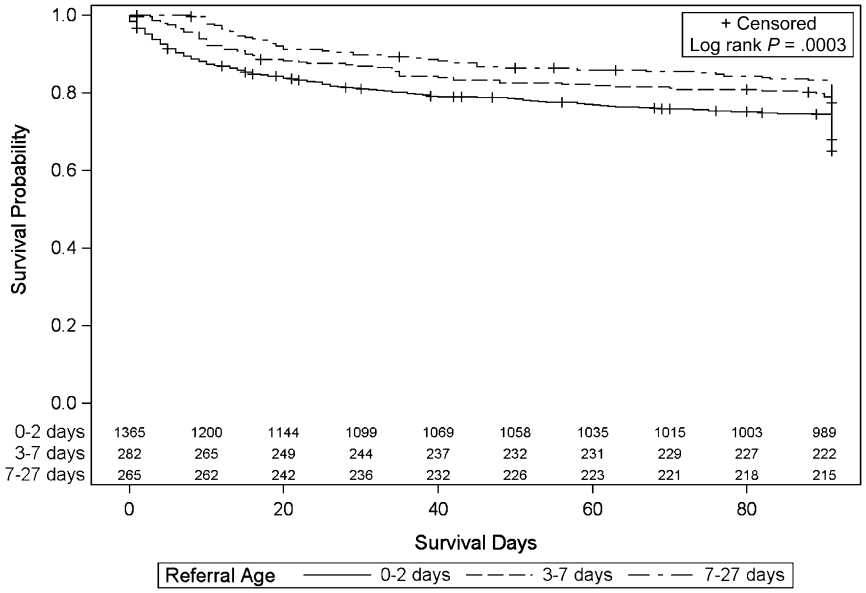

FIGURE 1
Three-month survival in infants with cyanotic CCHD by neonatal age at referral to a cardiac center. Product-limit survival estimates are shown with numbers of subjects at risk.

TABLE 3 Neonatal and 3-Month Mortality in 178 Infants With Cyanotic CCHD Not Admitted to a Cardiac Center

Defect	*N*	Neonatal Mortality (0–27 d)		Three-Month Mortality[a]	
		Deaths, *n*	%	Deaths, *n*	%
HLHS	60	41	68.3	49	81.7
TGA	28	5	17.9	6	21.4
TOF	34	8	23.5	12	35.3
TAPVR	21	6	28.6	9	42.9
PA-IVS	9	3	33.3	5	55.6
Truncus	20	6	30.0	9	45.0
TA	6	0	0.0	0	0.0
Total	178	69	38.8	90	50.6

Data from the TBDR, 1996–2007. HLHS, Hypoplastic left heart syndrome; TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; PA-IVS, pulmonary atresia with intact ventricular septum; Truncus, truncus arteriosus; TA, tricuspid atresia.

[a] Three-month mortality includes neonatal deaths.

which underscores the need to improve early detection of CCHD-affected infants in newborn nurseries.

We found a large variation in the median age at referral within and between the 7 types of CCHD. Functional variants among cases affect the onset of cyanosis or congestive heart failure. Some cases may have delayed closure of their patent ductus and, as such, clinical signs appear late; therefore, delayed referral did not necessarily indicate inappropriate medical management. Other cases may have anatomic variants that lead to early onset of severe circulatory insufficiency; for example, infants with HLHS with an intact atrial septum or infants with obstructed TAPVR who may develop early pulmonary venous hypertension, which impedes pulmonary blood flow even with a widely patent ductus. In addition, anatomic variants such as extreme hypoplasia of the pulmonary arteries or aorta have higher risk of death despite early referral because successful repair may be difficult to achieve. A factor leading to better outcomes in those referred later may be their greater physiologic maturity. Most important, it is likely that the condition of the infant on admission and the severity of the defect were the principal variables affecting neonatal mortality. These variables would explain the higher mortality in cases referred earlier; that is, the more severe cases were recognized earlier, referred earlier, and yet were less likely to survive neonatal surgery.

In this study, the odds of late referral were higher in NH-black infants compared with NH-white infants. Previously published studies reported no racial/ethnic differences in age at referral to pediatric cardiology practices.[26,27] Of note in the current study, racial/ethnic disparities in neonatal mortality were 40% higher in NH-blacks and 26% higher in Hispanics compared with NH-whites. Race/ethnic differences in mortality could be due to variations in morphologic severity of the defect being greater among minorities, but to our knowledge, no studies have described such differences. The timing of surgery could in part explain the differences; however, Chang et al[28] using data from California hospital discharges for 1995–1996 found no difference between whites, blacks, and Asians in age at operation for CHD. A recent study that looked at the effect of race on the timing of surgery for single-ventricle CHD found no racial differences in median age at surgery or length of stay.[7] Nevertheless, other investigators have speculated that unequal access to cardiac specialty care may contribute to racial disparities in outcome because they found that CHD postsurgical mortality was higher in black and Hispanic children after adjusting for income, insurance type, and surgical risk category.[29–32]

Because previous strategies to detect CCHD by routine clinical examination have resulted in many infants being discharged from newborn nurseries before CCHD diagnosis, some governmental agencies and health care centers have adopted a policy of routine pulse oximetry screening of newborns. Several regional and center-specific studies have been published that examine the validity and effectiveness of such universal pulse oximetry screening in reducing delays in

TABLE 4 Risk Factors for Late Referral of Infants With CCHD to a Cardiac Center

	Odds Ratio (95% CI)	
	Crude	Adjusted
Maternal		
Race/ethnicity		
NH-white	Referent	Referent
NH-black	1.24 (0.87–1.77)	1.66 (1.01–2.74)*
Hispanic	1.12 (0.91–1.38)	1.21 (0.88–1.67)
Age		
≤31 years	Referent	Referent
32–36 years	1.26 (0.97–1.64)	1.20 (0.80–1.80)
>36 years	0.81 (0.56–1.16)	0.68 (0.37–1.25)
Education		
12 years	Referent	Referent
<12 years	0.94 (0.74–1.21)	1.02 (0.70–1.48)
>12 years	0.93 (0.69–1.25)	1.02 (0.65–1.60)
Infant		
Diagnosis		
HLHS	Referent	
TGA	0.87 (0.61–1.26)	0.69 (0.44–1.07)
TOF	3.27 (2.38–4.49)*	1.80 (0.92–3.54)
TAPVR	4.12 (3.01–5.63)*	3.91 (2.59–5.90)*
PA-IVS	0.74 (0.46–1.19)	0.84 (0.48–1.47)
Truncus	2.74 (1.85–4.05)*	1.47 (0.74–2.92)
TA	1.69 (1.07–2.66)*	1.11 (0.60–2.03)
Gender		
Male	Referent	Referent
Female	1.18 (0.97–1.44)	1.24 (0.93–1.67)
Birth weight		
≥2500 g	Referent	Referent
<1500 g	1.38 (0.74–2.55)	0.78 (0.22–2.83)
1500–2499 g	1.04 (0.78–1.39)	0.79 (0.45–1.40)
Gestational age		
37–44 weeks	Referent	Referent
20–31 weeks	1.38 (0.82–2.33)	1.40 (0.47–4.14)
32–36 weeks	1.15 (0.86–1.52)	1.01 (0.63–1.62)
Birth era		
1996–2001	Referent	Referent
2002–2007	1.00 (0.82–1.22)	1.15 (0.84–1.57)
Extracardiac defects		
Absent	Referent	Referent
Present	2.16 (1.13–4.15)*	2.42 (1.17–5.05)*
Prenatal diagnosis		
Yes	Referent	Referent
No	1.87 (1.37–2.56)*	1.44 (0.88–2.36)

Late referral indicates referral beyond 4 days of age. Asterisks indicate significant difference from referent. HLHS, Hypoplastic left heart syndrome; TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; PA-IVS, pulmonary atresia with intact ventricular septum; Truncus, truncus arteriosus; TA, tricuspid atresia.

diagnosis; however, few have reported its impact on mortality. In 1 study, de-Wahl Granelli et al[8] compared the outcome of infants with CCHD in 1 region of Sweden where pulse oximetry screening was performed with the outcome in other regions where it was not done. They found the frequency of leaving the hospital undiagnosed was significantly lower in the pulse oximetry screening region than in the other regions, 8% vs 28%. Furthermore, excluding cases requiring Norwood surgery, mortality was significantly lower in those diagnosed before discharge (0.9%) compared with those diagnosed after discharge (18%).

Several limitations of this study should be considered. Most important is the fact that the TBDR does not consistently collect information on the condition of the infant on admission to the cardiac center; hence, the effect of this important potential confounder could not be taken into account. Hemodynamic compromise may occur more frequently in the first few days of life and thereby explain the higher risk of death among infants with early referral. Second, our study addressed only the primary targets for pulse oximetry screening because these defects were most likely to be detected by such screening because of early hypoxemia. Other secondary diagnoses may also be detected, but we wanted to demonstrate how frequently these often clinically apparent cyanotic cases are missed before the adoption of oximetry screening. However, secondary targets of pulse oximetry screening as well as pulmonary disease and sepsis may be detected by routine pulse oximetry screening. Third, we arbitrarily chose referral by age 4 days to examine variables associated with later referral because we felt this timing represented a feasible goal that could be achieved by most delivery centers with routine pulse screening. Fourth, we excluded complex cases having other cardiac malformations that significantly increase complexity and that have atypical outcomes, as well as cases in which missing data prevented determination of age at referral.

The strengths of this study are its population-based cohort design from a period and region representing nearly 4 million births with geographic and racial/ethnic diversity. Also, the diagnoses were collected from an active surveillance of tertiary care centers and a variety of birthing facilities and were verified by an experienced pediatric cardiologist. In addition, the study provides estimates of mortality in infants with CCHD who were not admitted to a cardiac center.

TABLE 5 Risk Factors for Neonatal Mortality Among Infants With CCHD

	Hazard Ratio (95% CI)	
	Crude	Adjusted
Maternal		
Race/ethnicity		
NH-white	Referent	Referent
NH-black	1.54 (1.18–2.00)*	1.40 (1.07–1.83)*
Hispanic	1.22 (1.03–1.44)*	1.26 (1.05–1.51)*
Age		
≤31 years	Referent	Referent
32–36 years	0.92 (0.74–1.14)	0.98 (0.78–1.23)
>36 years	0.95 (0.72–1.25)	0.91 (0.69–1.21)
Education		
12 years	Referent	Referent
<12 years	0.89 (0.74–1.08)	0.96 (0.79–1.17)
>12 years	0.80 (0.67–1.01)	0.81 (0.64–1.02)
Infant		
Diagnosis		
HLHS	Referent	Referent
TGA	0.11 (0.08–0.16)*	0.14 (0.10–0.20)*
TOF	0.29 (0.22–0.37)*	0.18 (0.14–0.24)*
TAPVR	0.23 (0.17–0.30)*	0.22 (0.17–0.30)*
PA-IVS	0.57 (0.45–0.73)*	0.50 (0.40–0.64)*
Truncus	0.61 (0.47–0.79)*	0.44 (0.33–0.57)*
TA	0.26 (0.18–0.39)*	0.20 (0.14–0.31)*
Gender		
Male	Referent	Referent
Female	1.34 (1.15–1.56)*	1.27 (1.09–1.49)*
Birth weight		
≥2500 g	Referent	Referent
<1500 g	5.81 (4.18–8.09)*	4.23 (2.70–6.62)*
1500–2499 g	2.33 (1.93–2.82)*	1.89 (1.53–2.33)*
Gestational age		
37–44 weeks	Referent	Referent
20–31 weeks	3.11 (2.26–4.29)*	1.58 (1.03–2.43)*
32–36 weeks	1.68 (1.37–2.06)*	1.33 (1.07–1.66)*
Birth era		
1996–2001	Referent	Referent
2002–2007	0.79 (0.67–0.92)*	0.65 (0.55–0.77)*
Extracardiac defects		
Absent	Referent	Referent
Present	2.16 (1.85–2.54)*	2.17 (1.41–3.32)*
Prenatal diagnosis		
Yes	Referent	Referent
No	0.66 (0.54–0.80)*	0.84 (0.68–1.03)

Asterisks indicate significant difference from referent. HLHS, Hypoplastic left heart syndrome; TGA, d-transposition of the great arteries; TOF, tetralogy of Fallot; TAPVR, total anomalous pulmonary venous return; PA-IVS, pulmonary atresia with intact ventricular septum; Truncus, truncus arteriosus; TA, tricuspid atresia.

As of October 2013, >25 states had passed legislation mandating routine pulse oximetry screening and many states have such legislation pending. Investigators recently reported that the New Jersey statewide pulse oximetry screening of 72 694 newborns identified 3 newborn infants (1 of 24 231) who had previously unsuspected CCHD.[33] Our study provides information on the timing of referral of CCHD and its associated mortality (Tables 2 and 3), which may be useful in estimating the required sample size for epidemiologic studies to show an effect of pulse oximeter screening on neonatal CCHD mortality. In addition, future studies should also measure other outcome variables such as length of stay and morbidity, because earlier detection may lead to fewer infants developing cardiac decompensation before referral to a cardiac center.

CONCLUSIONS

In this study of CCHD overall, 27.5% (649 of 2360) of neonates were referred after age 4 days and 7.5% (178 of 2360) had no TBDR record of referral. Of the 380 neonatal deaths, 34 occurred in infants referred at age 5 to 27 days and 69 in infants with no referrals of record. Unfortunately, we found no improvement in promptness of referral from 1996–2001 to 2002–2007. Universal screening of newborn infants has been proposed to enhance early diagnosis and timely referral to a cardiac center. Future population-based studies are needed to determine the effect of pulse oximetry screening on outcomes in newborns with CCHD.

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