Hypoplastic left heart syndrome (HLHS) and other congenital heart diseases are leading causes of infant mortality in the United States (U.S.). Despite improved survival attributable to operative palliation and advances in postoperative care in recent decades, mortality in infants with HLHS remains high.

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Potentially, prenatal diagnosis and planned delivery near a cardiac surgical center (CSC) should allow prompt stabilization measures and preclude neonatal deterioration. Nonetheless, most studies indicate that prenatal diagnosis of HLHS does not improve survival. Many of these studies, however, did not include infants who died before transfer or before surgery and were limited to large volume hospitals.

None examined the actual importance of delivery location after prenatal diagnosis. Thus, a child diagnosed prenatally but delivered far from a CSC may be at greater risk, because of the complexity of transfer, than a child diagnosed postnatally but delivered near a CSC, where prompt, effective care is available. We hypothesized that infants with HLHS delivered close to a CSC would have lower neonatal mortality than those delivered at greater distances.

We used the Texas Department of State Health Services’ Texas Birth Defects Registry (TBDR) to investigate the association between distance to a CSC at birth and neonatal mortality in 463 infants with HLHS. We also investigated the associations among prenatal diagnosis, CSC HLHS volume, and mortality.

Conclusions—Infants with HLHS born far from a CSC have increased neonatal mortality, and most of this mortality is presurgical. Efforts to improve prenatal diagnosis of HLHS and subsequent delivery near a large volume CSC may significantly improve neonatal HLHS survival.

Key Words: heart defects, congenital hypoplastic left heart syndrome mortality population prenatal diagnosis

Hypoplastic left heart syndrome (HLHS) and other congenital heart diseases are leading causes of infant mortality in the United States (U.S.). Despite improved survival attributable to operative palliation and advances in postoperative care in recent decades, mortality in infants with HLHS remains high.

Background—Most studies have not demonstrated improved survival after prenatal diagnosis of critical congenital heart disease, including hypoplastic left heart syndrome (HLHS). However, the effect of delivery near a cardiac surgical center (CSC), the recommended action after prenatal diagnosis, on HLHS mortality has been poorly investigated.

Methods and Results—Using Texas Birth Defects Registry data, 1999 through 2007, which monitored >3.4 million births, we investigated the association between distance (calculated driving time) from birth center to CSC and neonatal mortality in 463 infants with HLHS. Infants with extracardiac birth defects or genetic disorders were excluded. The associations between prenatal diagnosis, CSC HLHS volume, and mortality were also examined. Neonatal mortality in infants born <10 minutes from a CSC was 21.0%, 10 to 90 minutes 25.2%, and >90 minutes 39.6% (P for trend <0.001). Prenatal diagnosis alone was not associated with improved survival (P=0.14). In multivariable analysis, birth >90 minutes from a CSC remained associated with increased mortality (odds ratio, 2.03; 95% confidence interval, 1.19–3.45), compared with <10 minutes. In subanalysis, birth >90 minutes from a CSC was associated with higher pretransport mortality (odds ratio, 6.69; 95% confidence interval, 2.52–17.74) and birth 10 to 90 minutes with higher presurgical mortality (odds ratio, 4.45; 95% confidence interval, 1.17–17.00). Higher surgical mortality was associated with lower CSC HLHS volume (odds ratio per 10 patients, 0.88; 95% confidence interval, 0.84–0.91).

Conclusions—Infants with HLHS born far from a CSC have increased neonatal mortality, and most of this mortality is presurgical. Efforts to improve prenatal diagnosis of HLHS and subsequent delivery near a large volume CSC may significantly improve neonatal HLHS survival.

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Methods

Patient Population and Study Design

We conducted a retrospective cohort study to evaluate whether increased travel time between the birth location and a CSC was associated with increased neonatal mortality among infants with HLHS. This study used data from the TBDR, which has conducted active, statewide surveillance since 1999. Registry staff review records of all delivery units and pediatric hospitals throughout Texas. They abstract detailed demographic and diagnostic information for infants with a registry-monitored birth defect diagnosed within 1 year of delivery, to Texas-resident mothers. TBDR data are routinely linked to Texas vital records.

The TBDR classifies congenital anomalies using 6-digit birth defect codes that are based on the British Pediatric Association (BPA) Classification of Diseases (1979) and the International Classification of Diseases, ninth revision, clinical modification (1979). We included live births during January 1, 1999 through December 31, 2007 with the codes for HLHS (746.700), aortic atresia (746.480), or hypoplastic left ventricle (746.881). To ensure accurate diagnosis, a pediatric cardiologist (S.A.M.) reviewed available TBDR clinical data. A diagnosis of HLHS required ≥1 of the following:

1. Severe mitral and aortic obstruction, hypoplasia, or atresia and a hypoplastic left ventricle
2. Hypoplastic left heart syndrome diagnosed on echocardiography, cardiac catheterization, cardiac surgical, or pathologic report
3. Left ventricular hypoplasia with evidence of Stage 1 palliation and no more appropriate diagnosis

We excluded infants with alternative primary cardiac diagnoses, including atioventricular septal defect and double outlet or double inlet ventricle. We also excluded twins and infants with gestational age <23 weeks, birthweight <400 grams, or genetic disorders. Patients with either major extracardiac birth defects or more than 3 minor extracardiac birth defects were also excluded. Extracardiac birth defects were carefully catalogued by the TBDR. Major extracardiac birth defects was defined by the National Birth Defects Prevention Network as a congenital abnormality that requires medical or surgical birth defects was defined by the National Birth Defects Prevention Network as a congenital abnormality that requires medical or surgical intervention. To also investigate the relationship between time to CSC and mortality, 3 intermediate outcomes were studied: (1) age at diagnosis, (2) age at Stage 1 palliation (S1P) >3 days of life. All others were included in the unknown group, including those with records using only the term restrictive atrial septum on the echocardiography report, given wide variation in the use of restrictive. CSC HLHS case volume was calculated from the total number of neonates with HLHS present in the registry. Because RAS information was not available in >25% of infants, it was not included in primary analyses. For secondary analyses, RAS was coded as present, absent, or unknown. The present RAS group included those with an atrial septum described as severely restrictive, intact, or who underwent catheter-based atrial septal intervention. Those with absent RAS were those with an atrial septum described as unrestricted, other similar language, or who had no atrial septal descriptors in the echocardiography report but were described throughout the record as clinically stable with no catheter-based atrial septal intervention and Stage 1 palliation (S1P) >3 days of life. All others were included in the unknown group, including those with records using only the term restrictive atrial septum on the echocardiography report, given wide variation in the use of restrictive. CSC HLHS case volume was calculated from the total number of neonates with HLHS presenting to a given CSC, because actual surgical volume was not reliably available in the registry.

Study Variables

Predictor Variable: Driving Time to a Cardiac Surgical Center

The shortest driving time in minutes between the birth hospital and the infant’s CSC was calculated using geocoding software (CDX technologies and Microsoft MapPoint). Although the actual driving time may be slightly different than calculated, given route changes over years and changes throughout a 24-hour period, average daily driving times were used to minimize this variation. Driving time was used instead of distance in miles to a give a more representative picture of possible delays to a CSC, because distances do not account for differences in speed permitted, urban versus rural travel, or volume of traffic. A CSC was defined as a hospital that performed >1 Stage 1 palliation (S1P) during the study period. When the CSC was not clearly identified or death occurred before transfer, either the birth hospital’s usual referral CSC or, in the absence of a referral system, the closest CSC was used. Two infants had no birth hospital listed, and their first echocardiograms were performed 4 and 6 days after birth. Thus, their home addresses were used.

Time to CSC was divided into 3 predetermined groups: <10, 10 to 90, and >90 minutes. Ten minutes was chosen as a cutoff to separate those delivering close versus not close to a CSC. Ninety minutes was chosen as a cutoff at which transport via air ambulance may be considered. The division of travel time into 3 categories was also performed to minimize the effect of subtle changes in travel time that may have occurred over the course of the study.

Covariates

Maternal socioeconomic status was estimated from 2 widely used, validated proxies of socioeconomic status: education level and percent of population living in poverty in the maternal census tract, according to the 2000 U.S. census. When a post office box or a nonmappable rural route was the residential address listed, the street or city was used. For categorical analysis of poverty, a cutoff of ≥20% was used in accordance with the U.S. Census Bureau.

Preterm birth was defined as ≤37 weeks, low birthweight as ≤2500 grams, and small for gestational age as ≤10% of expected weight using published criteria. Birth era was divided into 1999 through 2002 and 2003 through 2007. Presence of total anomalous pulmonary venous return and highly restrictive atrial septal defect/intact atrial septum (RAS) also were noted. Because RAS information was not available in >25% of infants, it was not included in primary analyses. For secondary analyses, RAS was coded as present, absent, or unknown. The present RAS group included those with an atrial septum described as severely restrictive, intact, or who underwent catheter-based atrial septal intervention. Those with absent RAS were those with an atrial septum described as unrestricted, other similar language, or who had no atrial septal descriptors in the echocardiography report but were described throughout the record as clinically stable with no catheter-based atrial septal intervention and Stage 1 palliation (S1P) >3 days of life. All others were included in the unknown group, including those with records using only the term restrictive atrial septum on the echocardiography report, given wide variation in the use of restrictive. CSC HLHS case volume was calculated from the total number of neonates with HLHS present to the given CSC, because actual surgical volume was not reliably available in the registry.

Ascertainment of Mortality

Neonatal mortality (death before age 28 days) was chosen as the primary outcome to minimize the competing effects of socioeconomic status and access to healthcare on postdischarge mortality. Infants were classified as deceased based on the TBDR and Texas vital records. Neonatal death was categorized according to whether it occurred before transfer to a CSC, after arrival at a CSC but before S1P, or after S1P. CSC HLHS case volume was used as a variable in the latter 2 analyses, so only infants with an identifiable CSC were included.

To also investigate the relationship between time to CSC and mortality, 3 intermediate outcomes were studied: (1) age at diagnosis, using the first abstracted postnatal confirmation of HLHS (typically an echocardiogram); (2) presurgical decompensation, determined from review of abstracted data for key phrases (see the online-only Data Supplement); and (3) age at S1P.

Statistical Analysis

Univariable comparisons were performed using the Wilcoxon rank sum or Kruskal-Wallis analysis for continuous variables, and χ², Fisher exact, or χ² trend analyses for categorical data. For associations with categorical variables with ≥2 classes, multiple comparisons were adjusted using Bonferroni correction. Correlations were calculated using Spearman rho.

A multivariable logistic regression model was computed for neonatal mortality outcomes. In the primary analysis, all variables were considered for inclusion if P<0.10 in association with mortality.

For subanalyses evaluating timing of death, the variables noted to be significant in association with overall neonatal mortality were included in the models. For the subanalyses of death before surgery (after arrival at a CSC) and death after surgery, which included CSC HLHS volumes in the models, generalized estimating equation models were computed to accommodate correlation between patients at the same center. P values <0.05 were considered statistically significant.
Results
Of 3,401,057 live births during the study period, 558 met criteria for HLHS (birth prevalence, 1.6 per 10,000 live births). Thirteen were from a twin gestation, and 82 had genetic conditions or extracardiac anomalies, leaving 463 cases for analysis. During 1999 through 2007, nine Texas CSCs performed S1P.

Time to CSC
Time from birthplace to CSC ranged from 0 to 577 minutes: 210 newborns (45.4%), <10 minutes; 147 (31.7%), 10 to 90 minutes; and 106 (22.9%), >90 minutes. Mothers delivering farther from a CSC were less educated and more often lived in a poverty area (Table 1). Thirty percent of mothers delivering >90 minutes from a CSC were born in Mexico, compared with 17% of those delivering <90 minutes from a CSC. Very few black mothers delivered >90 minutes from a CSC.

Prenatal Diagnosis
HLHS was prenatally diagnosed in 39% of newborns, with a higher proportion diagnosed prenatally in the later birth era (49.0% versus 25.5%, \(P<0.001\)). Prenatally diagnosed infants

| Maternal/Infant Characteristics and Intermediate Outcomes by Calculated Driving Time to Cardiac Surgical Center Among Infants With Hypoplastic Left Heart Syndrome, Texas, 1999–2007 |
|---------------------------------|-------------------|-----------------|-------------------|------------------|
| Maternal/child characteristics | All n=463 | <10 Minutes n=210 | 10 to 90 Minutes n=147 | >90 Minutes n=106 | \(P\) Value |
| Preterm, n (%) | 59 (13%) | 22 (10%) | 18 (12%) | 19 (18%) | 0.07 |
| Birthweight <2500 g, n (%) | 50 (11%) | 23 (11%) | 12 (8%) | 15 (14%) | 0.54 |
| SGA, n (%) | 67 (14%) | 32 (15%) | 18 (12%) | 17 (16%) | 0.99 |
| Male sex, n (%) | 303 (65%) | 146 (70%) | 90 (61%) | 67 (63%) | 0.18 |
| Maternal race/ethnicity, n (%) | | | | | <0.001* |
| White | 208 (45%) | 89 (42%) | 77 (52%) | 42 (40%) | |
| Black | 46 (10%) | 28 (13%) | 17 (12%) | 1 (1%) | |
| Hispanic | 199 (43%) | 87 (41%) | 50 (34%) | 62 (58%) | |
| Other | 10 (2%) | 6 (3%) | 3 (2%) | 1 (1%) | |
| Median maternal age, y (IQR) | 26 (22, 31) | 27 (21, 32) | 26 (22, 30) | 25 (21, 29) | 0.28 |
| Maternal education, n (%) | | | | | 0.01 |
| >12th grade | 176 (39%) | 90 (44%) | 53 (36%) | 33 (31%) | |
| 12th grade | 153 (34%) | 68 (33%) | 49 (34%) | 36 (34%) | |
| <12th grade | 127 (28%) | 47 (23%) | 44 (30%) | 36 (34%) | |
| Poverty by census tract ≥20%, n (%) | 144 (31%) | 55 (26%) | 27 (18%) | 62 (58%) | <0.001 |
| Maternal birth country, n (%) | | | | | 0.005* |
| US | 337 (74%) | 149 (73%) | 115 (78%) | 73 (70%) | |
| Mexico | 91 (20%) | 37 (18%) | 23 (16%) | 31 (30%) | |
| Other | 28 (6%) | 18 (9%) | 9 (6%) | 1 (1%) | |
| Birth era, n (%) | | | | | <0.001 |
| 1999–2002 | 200 (43%) | 72 (34%) | 71 (48%) | 57 (54%) | |
| 2003–2007 | 263 (57%) | 138 (66%) | 76 (52%) | 49 (46%) | |
| Prenatal diagnosis – no. (%) | 180 (39%) | 78 (37%) | 38 (26%) | 64 (56%) | <0.001 |
| TAPVR – no. (%) | 15 (3%) | 7 (3%) | 2 (1%) | 6 (6%) | 0.51 |

Intermediate outcomes
Age at diagnosis, n (%) <0.001*
- <1 day | 260 (58%) | 157 (77%) | 58 (42%) | 45 (43%) |
- 1–2 days | 134 (30%) | 36 (18%) | 53 (38%) | 45 (43%) |
- >2 days | 52 (12%) | 10 (5%) | 27 (20%) | 15 (14%) |

Intermediate outcomes reported only for cases in which sufficient data were available. IQR indicates interquartile range (25th percentile, 75th percentile); SGA, small for gestational age; and TAPVR, total anomalous pulmonary venous return.

*Significant difference overall noted in multi-category group; for maternal race/ethnicity: <10 vs 10–90 minutes \(P=0.32\), <10 vs >90 minutes \(P=0.001\), 10–90 vs >90 \(P=0.001\). For maternal birth country: <10 vs 10–90 minutes \(P=0.52\), <10 vs >90 minutes \(P=0.002\), 10–90 vs >90 minutes \(P=0.005\). For age at diagnosis: <10 vs 10–90 minutes \(P<0.001\), <10 vs >90 \(P<0.001\), 10–90 vs >90 \(P=0.53\).
were delivered significantly closer to a CSC, with median time to CSC 2.6 minutes (interquartile range, 1.2–9.9 minutes) versus 28.8 minutes (interquartile range, 10.0–136.3 minutes, \( P<0.001 \)).

**Neonatal Mortality**

Death before age 28 days occurred in 123 infants (26.6%). Mortality was higher in the earlier birth era (Table 2). In crude analysis, increased time to a CSC was associated with increased mortality: \(<10\) minutes, 21.0%; \(10\) to 90 minutes, 25.2%; and \(>90\) minutes, 39.6% \((P\) for trend \(<0.001\), Table 2). This pattern was evident in both birth eras and in both prenatally and postnatally diagnosed infants (Figure 1). In infants diagnosed prenatally, mortality was 22.8% compared to postnatally, 29.0% \((P=0.14\); Table 2).

In multivariable analysis, factors significantly associated with neonatal mortality were time to CSC, low birthweight, and earlier birth year (Table 3). Preterm birth was not included in the multivariable model because of its high correlation with low birthweight.

In subanalyses that adjusted for RAS, the results for time to CSC were similar: 10 to 90 minutes odds ratio \((OR)\) 1.23 \((95\%\) confidence interval \([CI]\), 0.73–2.08); \(>90\) minutes, OR 1.85 \((95\%\ CI, 1.07–3.20\).

To account for the possible effect of parental intention not to treat, we excluded 6 infants who were diagnosed prenatally, delivery \(>90\) minutes from a CSC, and never transferred. The results were similar: 10 to 90 minutes, OR 1.16 \((95\%\ CI\ 0.96–1.42); >90 minutes, OR 1.97 \((95\%\ CI, 1.14–3.38\).

In multivariable analysis, factors significantly associated with neonatal mortality were time to CSC, low birthweight, and earlier birth year (Table 2). In multivariable analysis, factors significantly associated with neonatal mortality were time to CSC, low birthweight, and earlier birth year (Table 3). Preterm birth was not included in the multivariable model because of its high correlation with low birthweight.

**Timing of Death**

Thirty patients (6.5%) died before arriving at a CSC. Pretransport mortality in infants delivered \(>90\) minutes from a CSC was 18.9% compared with those born 10 to 90 minutes \((2.7\%, P<0.001\) and \(<10\) minutes \((2.9\%, P<0.001\), Figure 2). In those prenatally diagnosed, delivery \(>90\) minutes from a CSC was associated with significant pretransport mortality \((28.6\%)\), compared with 7.1% in those born 10 to 90 minutes \((P=0.06\), and 2.2% in those born \(<10\) minutes from a CSC \((P<0.001\).

In multivariable analysis, time to CSC, low birthweight, and birth year remained associated with pretransport neonatal death (Table 3). When RAS was included, the results remained similar: 10 to 90 minutes, OR 0.94 \((95\%\ CI, 0.26–3.47); >90 minutes, OR 6.26 \((95\%\ CI, 2.35–16.70\).

Of 433 newborns arriving at a CSC, 94 (21.7%) died, 15 before undergoing S1P, and 52 after S1P; 27 had insufficiently detailed hospital procedure information abstracted. For presurgical mortality analysis, 384 infants had sufficient information for classification. In those born \(<10\) minutes from a CSC, 3 of 190 (1.6%) patients died before surgery, compared with 8/130 (6.2%) in those born 10–90 minutes, and 4/64 (6.3%) in those born \(>90\) minutes (Figure 2). CSC HLHS volume was inversely correlated with CSC pre-Stage 1 mortality (Spearman rho=−0.498, \(P<0.001\); Figure 3A). In the final multivariable model, time to CSC 10 to 90 minutes was significantly associated with increased pre–Stage 1 mortality, whereas there was a trend towards increased mortality in patients delivered \(>90\) minutes from a CSC and those cared for in lower volume CSCs (Table 3). When RAS was included, the results were similar: 10 to 90 minutes, OR 3.43 \((95\%\ CI, 0.96–12.33); >90 minutes, OR 4.44 \((95\%\ CI, 1.12–17.57\).
Mechanism of Effect of Increased Time to CSC and Mortality

We assessed intermediate outcomes including age at diagnosis (in most cases, time to first echocardiogram), presurgical decompensation, and age at surgery. Age at diagnosis was available for 96% of infants. Although infants born further from a CSC were older at diagnosis (Table 1), older age at diagnosis was not associated with increased mortality (Table 2), even after restricting the analysis to postnatally diagnosed infants ($P=0.50$) or to no RAS ($P=0.74$).

Thirty-five infants had evidence of pre-surgical decompensation (online-only Data Supplement). Infants born further away from a CSC had greater frequency of decompensation (Table 3), even when RAS was included.

Three infants never underwent S1P but were alive at 28 days and ultimately died, 1 underwent S1P in another state, 2 were referred out of state for a primary cardiac transplant, and 1 had no detailed hospital information abstracted and died at 40 days of age.

Evidence of S1P at an identifiable CSC existed for 369 infants. CSC HLHS volume was inversely correlated with S1P mortality (Spearman $\rho=-0.707$, $P<0.001$; Figure 3B). Only low HLHS volume and earlier birth year remained associated with higher S1P mortality in multivariable regression (Table 4), even when RAS was included.

Discussion

This population-based study is the first to examine the interactions among prenatal diagnosis, birth location, and CSC volume in determining neonatal survival in infants with HLHS. Our findings suggest that prenatal diagnosis may reduce mortality if mothers living far from a CSC deliver close to a CSC. Mortality was high in newborns diagnosed prenatally and born far from a CSC, whereas mortality in those diagnosed postnatally but delivered near a CSC was comparable with those prenatally identified born near a CSC. Specifically, we demonstrate that birth near a CSC results in lower pretransport and presurgical mortality. This finding is paramount, because >36% of deaths in our cohort occurred before S1P.

Although longer driving time to a CSC was strongly associated with increased mortality in our cohort, we recognize that (Table 2) even after restricting to no RAS ($P=0.03$). Of note, almost two-thirds (n=22) of infants with decompensation were diagnosed at ≤2 days of life. Of these 22 patients, 2 of 8 (25%) born <10 minutes from a CSC died, whereas 5 of 5 (100%) patients born 10 to 90 minutes from a CSC died, and 8 of 9 (89%) patients born >90 minutes from a CSC died.

Age at surgery was available for 302 of 384 infants undergoing S1P. Infants born further from a CSC were older at surgery (Table 1), but this factor was not associated with mortality (Table 2), even after restricting to no RAS ($P=0.84$).

**Table 3. Multivariable Logistic Regression Models for Overall Neonatal Mortality and Timing-Specific Neonatal Mortality Among Infants With Hypoplastic Left Heart Syndrome, Texas, 1999–2007**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Neonatal Death n=123/4630 (95% CI)</th>
<th>Pretransfer Death n=30/4630 (95% CI)</th>
<th>Pre–Stage 1 Death After Arrival at CSC n=15/384 (95% CI)</th>
<th>Stage 1 Death n=52/3690 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to CSC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 minutes</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>10–90 minutes</td>
<td>1.19 (0.71–1.99)</td>
<td>0.94 (0.26–3.44)</td>
<td>4.45 (1.17–17.00)</td>
<td>0.97 (0.41–2.30)</td>
</tr>
<tr>
<td>&gt;90 minutes</td>
<td>2.03 (1.19–3.45)</td>
<td>6.69 (2.52–17.74)</td>
<td>2.98 (0.81–10.95)</td>
<td>1.11 (0.53–2.35)</td>
</tr>
<tr>
<td>Birthweight &lt;2500g</td>
<td>2.97 (1.57–5.62)</td>
<td>4.83 (1.87–12.51)</td>
<td>2.83 (0.96–8.37)</td>
<td>1.67 (0.83–3.36)</td>
</tr>
<tr>
<td>Birth year</td>
<td>0.83 (0.76–0.91)</td>
<td>0.84 (0.71–0.99)</td>
<td>0.97 (0.84–1.13)</td>
<td>0.82 (0.69–0.96)</td>
</tr>
<tr>
<td>CSC HLHS volume, per 10 patients</td>
<td>0.96 (0.90–1.02)*</td>
<td>0.84 (0.84–0.91)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CSC, cardiac surgical center; HLHS, hypoplastic left heart syndrome; and OR, odds ratio.

*CSC HLHS volume was included for latter 2 timing-specific mortality analyses using mixed generalized estimating equations models.

†Denominator for the group of patients with pre–Stage 1 death is lower than all arriving at a CSC because only patients whose CSC was clearly documented were included.

**Figure 1. Neonatal mortality of infants with hypoplastic left heart syndrome by driving time from birth location to cardiac surgical center (CSC), among birth eras (A) and with prenatal vs postnatal diagnosis (B). Comparison of mortality among birth eras, accounting for time to CSC, $P=0.002$. Comparison of mortality by prenatal diagnosis, accounting for time to CSC, $P=0.90$. Error bars represent 95% confidence intervals.
longer time to CSC may be associated with a more complex risk factor of limited access to care, including lack of prenatal diagnosis and delivery at institutions less experienced with HLHS.

Our study also confirmed the well-known association between CSC volume and S1P mortality.20–22 However, our results suggest that volume may also be inversely related to presurgical mortality. Although in multivariable analysis this association was not statistically significant, the unadjusted data were compelling and the analysis was likely underpowered given the small number of presurgical deaths after arrival at a CSC (n=15). If this association is present, it suggests that not only surgical experience but experience of the multidisciplinary cardiac team accounts for improved survival in these children. This association should be investigated further.

To date, there have been few modifiable risk factors shown to significantly affect mortality in HLHS.20–22 However, the findings in this study suggest that improved fetal detection of HLHS, planned delivery near a CSC, and referral for care at a high-volume institution have the potential to dramatically improve outcomes in HLHS. As an example, in the 2003 to 2007 cohort, for those with a prenatal diagnosis, born <10 minutes from a CSC, and cared for at a large volume CSC, neonatal mortality was 6.3%. For those born in the same era without a prenatal diagnosis, >10 miles from a CSC, and cared for at a low volume CSC, 28-day mortality was 28.9%.

Age at diagnosis (typically the first echocardiogram) was not associated with neonatal mortality. Although this finding is not initially intuitive, it emphasizes the importance of delivery at or near a CSC with a dedicated cardiac team that can provide immediate, effective resuscitation and treatment. Increased frequency of decompensation at increased distance from a CSC was the likely cause of increased mortality in our study, regardless of the age at diagnosis. Hence, improved prenatal diagnosis of HLHS with delivery close to a CSC may decrease neonatal mortality. Cost effectiveness analysis should be done to explore whether universal transfer of mothers living far from a CSC to a nearby birth hospital is reasonable policy, especially in states with a large rural population.

Few studies have investigated the role of birth location in critical congenital heart disease. In 2000, Simpson, et al23 compared neonatal physiology scores in infants with congenital heart disease born at their tertiary care facility with those born at community hospitals, and noted no statistically significant difference. However, a wide variety of lesions, including low mortality lesions such as ventricular septal defect and atrioventricular septal defect, were included in the study. Bennett et al24 investigated the role of birth in a specialty versus nonspecialty hospital on mortality in children with duct-dependent lesions, and demonstrated no statistically significant difference. However, only patients who underwent surgery were included. Our study is consistent with Bennett’s study in showing no statistically significant association between birth far from a CSC and mortality when the sample was limited to only those undergoing surgery.
Our study helps to explain why numerous studies have shown no effect of prenatal diagnosis. First, benefit accrues when prenatal awareness of the diagnosis results in delivery close to a CSC. Those who happened to deliver close may have attenuated the beneficial effect in previous studies. Second, the benefit of prenatal diagnosis is primarily presurgical. Survival bias (the sickest die before arriving and undergoing surgery) is likely present in the majority of previous studies.

**Limitations**

This study was limited by the use of abstracted registry data. However, this registry source is exceptional for its active surveillance for HLHS in all Texas delivery hospitals and pediatric hospitals and extensive data collection. A study of similar content and size cannot be prospectively accomplished.

The use of registry data did not allow us to distinguish families who chose nonintervention, which would result in death. If prenatally-diagnosed mothers chose more often to deliver >10 minutes from a CSC, those with longer times to CSCs would have increased mortality, as our data demonstrate. However, only 42 mothers with a prenatal diagnosis delivered >10 minutes from a CSC. Thirty-six of these infants were transferred to a CSC, suggesting that the families desired care. When excluding the other 6 children, the results were unchanged, confirming that this factor was not responsible for our results. Although families of infants diagnosed postnatally and born far from a CSC may have chosen non-intervention at a higher rate, that factor would not negate our findings, as differential counseling could serve as an additional mechanism of increased mortality with increased distance from a CSC.

Data on termination of pregnancy were not included in this study. The TBDR does collect information on termination of pregnancy in the facilities in which data are collected for births. Although this does not likely include all terminations of pregnancy, only 0.71% of all 1999 through 2007 cases of HLHS in the TBDR, as defined by birth defect code 746.700, were induced terminations. Whereas the primary study variables, time to CSC and neonatal mortality, were universally available, some variables of interest were not, the most important of which was the presence of RAS. Hence, RAS was incorporated into the analyses secondarily and did not significantly alter the effect estimates of time to CSC. Medication use was not available in the birth defects registry, so time to prostaglandin initiation was not evaluated in this study.

The findings of this study may not be applicable in other states or countries with less variation in geography or access to healthcare. However, most states in the United States have even a greater proportion of the population considered rural than Texas. Per the 2010 U.S. Census, 35 states ranked above Texas in proportion of households living rurally. Therefore, we believe a significant proportion of infants with HLHS would benefit from prenatal diagnosis and relocating close to a high-volume CSC.

**Conclusions**

Birth far from a CSC is associated with increased neonatal mortality in HLHS, as is care in a low-HLHS volume CSC. Efforts to improve prenatal diagnosis of HLHS and subsequent delivery near a large volume CSC should significantly improve neonatal HLHS survival. Given that the effect of distance on mortality appears to be at least partially attributable to differential ability to deal with the decompensating infant with HLHS, education of medical teams far from a CSC and advanced telemedicine also have the potential to improve neonatal outcomes.

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**Disclosures**

None.

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There has been significant controversy about the effect of prenatal diagnosis of critical congenital heart disease on mortality, and many large studies have demonstrated no benefit. The authors take a novel approach to this question in neonates with hypoplastic left heart syndrome in 2 ways: (1) they use the Texas Birth Defects Registry, which allows for capture of death prior to transfer to a cardiac surgical center (CSC) and before surgery after transfer, and (2) distance between the birth hospital and a CSC (measured in calculated driving time) is investigated instead of prenatal diagnosis. The results demonstrated that birth >90 minutes from a CSC was associated with increased neonatal mortality compared with <10 minutes away, even when controlling for known risk factors. When timing of death was investigated, the majority of mortality associated with increased distance was pre-transfer and pre-surgical after transfer. Specifically, birth >90 minutes from a CSC was associated with >6-fold higher mortality before transfer than in patients born closer, with a similar effect seen even in those prenatally diagnosed. Birth 10 to 90 minutes from a CSC was associated with higher presurgical mortality after transfer, compared with those born <10 minutes away. The study also confirmed the association between low case volume and higher surgical mortality, and suggested that low case volume may also be associated with higher presurgical mortality. Efforts to improve prenatal diagnosis of hypoplastic left heart syndrome and subsequent delivery near a large volume CSC may therefore significantly improve neonatal survival in infants with hypoplastic left heart syndrome.
Prenatal Diagnosis, Birth Location, Surgical Center, and Neonatal Mortality in Infants With Hypoplastic Left Heart Syndrome
Shaine A. Morris, Mary K. Ethen, Daniel J. Penny, Mark A. Canfield, Charles G. Minard, David E. Fixler and Wendy N. Nembhard

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SUPPLEMENTAL MATERIAL

Appendix

Abstracted notes for each newborn coded as having pre-surgical decompensation

1. “9 day old… progressive respiratory distress syndrome who now has the diagnosis of a hypoplastic left heart syndrome, depressed biventricular function and closing ductus arteriosus which was taken care of with the prostaglandin infusion.”
2. “Active seizures, shows clonic movements of both Lt arm and Lt leg. Imp: seizures secondary to hypoplastic heart syndrome and profound acidosis”
3. “Acute cardiac decompensation requiring inotropic support and mechanical ventilation”
4. “Acute decompensation associated with metabolic acidosis with a lactate level of 22”
5. Autopsy comments: baby was doing fine at birth and was getting ready for transfer due to dusky spells. Expired hours after birth.
6. “Cardiac arrest”
7. “Cardiopulmonary arrest, cardiogenic shock, respiratory failure, profound metabolic acidosis”
8. “Cardiorespiratory arrest”
9. “Congestive heart failure. Procedure: endotracheal intubation, mechanical ventilation, intravenous inotropic support” (upon arrival)
11. “Cyanosis, severe acidosis, and respiratory distress”
12. “Dusky… +gallop… clinical deterioration… acute tubular necrosis”
13. “Grunting and retractions and some difficulty breathing, He also was very lethargic and was tachypneic”
14. “Exploratomy laparotomy” (prior to transfer to CSC)
15. “Lethargic infant having some spontaneous movement”
16. “No spontaneous respiration, floppy and pale”
17. “On arrival, the O2 stats were in the 30-35 range. We intubated this infant and began hand bagging to improve this and then called echo stat for echocardiogram and transferred infant to neonatal ICU for line placement”
18. “Pale, tachypneic, mild-mod resp distress”
19. “Peritonitis, perforated bowel”
20. “Poor perfusion”
21. “Poor tone, cyanotic, grunting”
22. “Pulmonary edema, metabolic acidosis… despite all efforts patient became acidotic due to congenital heart disease. Patient heart rate dropped. Patient expired.”
23. “Pulses are diminished and cap refill 5 seconds.”
24. “Severe cyanosis and acidosis”
25. “Shock”
26. “Shock, massive cardiomegaly and chf”
27. “Status post cardiac arrest”
28. “Status post endotracheal tube placement…pulmonary infiltrates (pre-diagnosis).”
29. “Study was performed on this patient….emergently due hypoxemia”
30. “Tachycardia with heart rate between 150 and 190 variable. The heart is large. The PMI is lateral to the mid-clavicle line. The liver is almost at the bellybutton, about 6cm down.”
32. “The baby was receiving cardiac compression. …the liver was enlarged several cm below the costal margin and firm… poor perfusion to hands and feet”
33. “The infant is lethargic with decreased tone and spontaneous activity as well as decreased response to tactile stimuli.”
34. “The infant is lethargic with decreased tone and spontaneous activity, responsive to tactile stimuli… the skin is ashen and pale/pink with decreased perfusion.
35. “Two-day-old baby who is referred to us… The child is described as being hypoxic and arresting… hypoplastic left heart syndrome with catastrophic presentation, cardiogenic shock”