Timing of Transfer and Mortality in Neonates with Hypoplastic Left Heart Syndrome in California

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Abstract
Maternal race/ethnicity is associated with mortality in neonates with hypoplastic left heart syndrome (HLHS). We investigated whether maternal race/ethnicity and other sociodemographic factors affect timing of transfer after birth and whether timing of transfer impacts mortality in infants with HLHS. We linked two statewide databases, the California Perinatal Quality Care Collaborative and records from the Office of Statewide Health Planning and Development, to identify cases of HLHS born between 1/1/06 and 12/31/11. Cases were divided into three groups: birth at destination hospital, transfer on day of life 0–1 (“early transfer”), or transfer on day of life ≥ 2 (“late transfer”). We used log-binomial regression models to estimate relative risks (RR) for timing of transfer and Cox proportional hazard models to estimate hazard ratios (HR) for mortality. We excluded infants who died within 60 days of life without intervention from the main analyses of timing of transfer, since intervention may not have been planned in these infants. Of 556 cases, 107 died without intervention (19%) and another 52 (9%) died within 28 days. Of the 449 included in analyses of timing of transfer, 28% were born at the destination hospital, 49% were transferred early, and 23% were transferred late. Late transfer was more likely for infants of low birthweight (RR 1.74) and infants born to US-born Hispanic (RR 1.69) and black (RR 2.45) mothers. Low birthweight (HR 1.50), low 5-min Apgar score (HR 4.69), and the presence of other major congenital anomalies (HR 3.41), but not timing of transfer, predicted neonatal mortality. Late transfer was more likely in neonates born to US-born Hispanic and black mothers but was not associated with higher mortality.

Keywords Congenital heart disease · Mortality rate · Sociodemographic factors · Patient management · Interhospital transfer

Introduction
Congenital heart disease (CHD) affects approximately 1% of live births in the United States. Hypoplastic left heart syndrome (HLHS) occurs in 13 per 100,000 live births making up 1.2% of congenital heart defects in the United States [1]. While rare, HLHS is one of the most serious forms of congenital heart disease and is still associated with a high mortality rate; recent data estimate neonatal mortality to be between 23 and 30% for HLHS [2–4]. The last four decades have seen remarkable advances in the surgical and postoperative management of infants with HLHS, but there is still important work to be done to further improve survival.

A large body of literature has associated a higher risk of mortality from HLHS and other critical congenital heart disease with certain race/ethnicities [5–13]. A few studies have linked mortality in patients with HLHS to other
sociodemographic factors, such as poverty [4, 5, 14] and insurance status [15]. Patient management factors have also been implicated in neonatal mortality from HLHS, including birth location [3], timing of initial surgery [16, 17], and timing of delivery [18, 19].

Few studies have examined the interplay of sociodemographic factors and management decisions made for infants with HLHS [20]. It is unclear if race/ethnicity or socioeconomic status impact some of these management decisions and contribute to the resulting higher risk of mortality. While patient management decisions can be indirectly linked to interhospital transfer patterns, to our knowledge, no study has directly examined timing of transfer to a surgical center and outcomes. We therefore designed a study to investigate whether maternal, infant, and care-related factors are predictive of transfer after birth and timing of transfer. As a secondary aim, we investigated whether any of these factors are predictive of mortality in infants with HLHS.

Methods

Study Population

We used linked data from two statewide databases on births in California from January 1, 2006, to December 31, 2011. The California Perinatal Quality Care Collaborative (CPQCC) prospectively collects data on infants admitted to participating neonatal intensive care units (NICUs) and includes more than 90% of all NICUs in California (cpqcc.org). CPQCC data were linked with data files from the California Office of Statewide Health Planning and Development (OSHPD) that include linked data on hospital admissions for infants from birth through 1 year of age, birth certificates, and infant death certificates. These OSHPD files are further linked to maternal data including hospitalizations during the pregnancy [21]. Linkage of maternal and infant data is successful for >98% of live births. CPQCC and OSHPD have been linked through 2012; however, the linkage with infant death certificates through 1 year of life is only available through 2011. The OSHPD files include up to 25 diagnostic and 21 procedure ICD-9 codes per hospitalization.

Frohnert et al. previously examined the validity of ICD-9-CM coding for congenital heart disease in a single center and found only 41% of ICD-9-CM coding to accurately reflect the cardiac diagnosis [22]. Additional studies in the adult congenital heart disease population have revealed similar results [23, 24]. Given the more robust nature of data collection for CPQCC, we therefore chose to use CPQCC data to identify the cases for our study [22–24]. Demographic and mortality data were then obtained from OSHPD.

We identified 773 cases that had a CPQCC code for HLHS, 67 of whom could not be linked to OSHPD data and were excluded. Of the remaining 706 infants, 55 survived to 60 days of life without a surgical or catheter-based intervention documented in CPQCC or OSHPD. These 55 infants were excluded since data errors were considered likely (either in the diagnosis or hospital discharge information); based on clinical experience, this outcome is extremely unlikely for a patient with HLHS. One patient underwent a fetal surgery and was also excluded. Of the remaining 650 infants, 556 had complete data on relevant covariates (described below) and were included in analyses (see Supplemental Fig. 1).

Study Outcomes

For the 556 cases, data in CPQCC and OSHPD were queried for a surgical or catheter-based intervention in the first 60 days of life. ICD-9 codes were manually reviewed by the first author to confirm that patients classified as “no intervention” had no evidence of a surgical or catheter-based intervention.

There were 107 infants who died within 60 days of life prior to any intervention being performed. We excluded them from our main analyses of timing of transfer; intervention may not have been performed or even planned in these infants due to the severity of their condition or family choice, which could have affected decisions to transfer them. Our primary goal was to identify factors associated with delays in transfer among infants who ultimately were well enough to undergo surgical repair and were chosen for intervention.

The remaining 449 infants who had an intervention were divided into three groups based on the day of arrival at the hospital where the intervention was performed: those who were born into the same hospital as the intervention (“not transferred”), those who arrived at the intervention hospital on day of life (DOL) 0 or 0 and those who arrived at the intervention hospital on DOL 2 or later. DOL 1 was included for infants born into the same hospital as the intervention (“not transferred”), those who arrived at the intervention hospital on day of life (DOL) 0 or 1, and those who arrived at the intervention hospital on DOL 2 or later. DOL 0–1 therefore represents infants arriving at the intervention hospital within a maximum of 48 h of birth.

The second outcome we examined was infant mortality. Age at death up to 1 year of life was derived from death certificate data and described for all 556 infants. Neonatal mortality was defined as death within 28 days.

Covariates

Descriptive data about the mothers and infants were obtained from infants’ birth certificates. Maternal data included age, race/ethnicity, education, payer, prenatal care, and geocoded residential addresses. Maternal addresses were geocoded.
by the California Environmental Health Tracking Program (CEHTP) Geocoding Service. We then used these geocoded maternal addresses to assign census tracts and determined census tract poverty level using the 2007–2011 American Community Survey Files. Infant data included sex, birthweight, gestational age, and 5-min Apgar score. The presence of other major non-cardiac congenital anomalies was assigned based on CPQCC data (see Supplemental Table 1 for further information).

We assigned hospital level of neonatal care for the birth and intervention hospital. Levels were based on American Academy of Pediatrics guidelines from 2012 [25]. Briefly, level I hospitals are well newborn nurseries; level II units provide care for infants born at greater than 32 weeks’ gestational age and weighing at least 1500 g; level III units provide comprehensive care for infants of all gestational ages and birth weights and include access to a full range of pediatric subspecialties; and level IV units are regional centers with 24-h access to pediatric subspecialty care and the ability to repair complex congenital conditions including cardiac disease.

Analyses

We first describe covariates, overall and then separately among the 107 infants who died prior to intervention and the remaining 449 who did not die prior to intervention. A log-binomial regression model was used to analyze predictors of transfer and generate unadjusted and adjusted estimates of relative risk (RR) among the 449 infants who did not die prior to intervention by comparing cases born into their intervention hospital to cases who were transferred. We then analyzed predictors of early transfer (DOL 0–1) compared to late transfer (DOL ≥ 2). Crude (unadjusted) RRs and RRs adjusted for covariates were estimated from these models. We selected potential covariates for multivariable models a priori, including maternal age, race/ethnicity, education, payer, census tract poverty level, infant birthweight, 5-min Apgar score, and the presence or absence of other congenital anomalies. Gestational age was excluded from multivariable models due to its close association with birthweight and higher unreported data, hospital level of care was excluded due to its close association with transfer patterns, and prenatal care was excluded due to small numbers in one of the groups. A sensitivity analysis was performed including the 107 infants who died within 60 days of life without intervention.

Finally, we conducted Cox proportional hazards analyses to identify predictors of mortality among all 556 cases at 28 days and at 1 year of life. The same covariates from the transfer model were chosen a priori with the addition of infant sex, transfer status, and day of life of arrival at intervention hospital.

This study was approved by the California Committee for the Protection of Human Subjects and Stanford University’s Institutional Review Board. Analyses were performed using SAS 904 (SAS Institute, Inc., Cary, NC).

Results

Of the total cohort of 556 cases, 62% were male, 57% were born to mothers who self-identified as Hispanic, 59% were covered by government insurance, and 32% were born to mothers with less than a high school education (Table 1). Most infants were born at term and at normal weight, and 6% also had non-cardiac congenital anomalies.

Relative to the 449 infants who did not die before intervention, the 107 infants who did tended to have similar sociodemographic characteristics but be higher risk based on clinical factors; i.e., 57% vs. 15% were of low birthweight, 43% vs. 15% were preterm, 48% vs. 5% had low 5-min Apgar scores, and 24% vs. < 5% also had non-cardiac congenital anomalies (Table 1). Of note, 60% of these infants died within the first week of life, compared to 4% of the 449 infants who did not die before intervention.

Hospital Transfer

Of the 449 infants included in analyses of transfer, 124 (28%) were not transferred, 220 (49%) were transferred to the intervention hospital early (DOL 0–1), and 105 (23%) were transferred to the intervention hospital late (DOL ≥ 2) (Table 1). Of the 107 infants who did not have an intervention before they died, < 60% were not transferred, < 35% were transferred early, and < 15% were transferred later (percentages are approximated to mask small cell sizes).

In multivariable analyses comparing the 325 infants who were transferred prior to intervention with the 124 infants born into the intervention hospital, infants born to foreign-born Hispanic mothers were the only group for which the 95% confidence interval excluded 1.0 (RR 0.80) with higher likelihood of being born into a destination center (Table 2). Of the 449 infants who did not have an intervention before they died, < 60% were not transferred, < 35% were transferred early, and < 15% were transferred later (percentages are approximated to mask small cell sizes).

In multivariable analyses comparing late transfers (DOL ≥ 2) with early transfers (DOL 0–1) as the reference group, late transfer was more likely for infants of low birthweight (RR 1.74) and infants born to US-born Hispanic (RR 1.69) and black (RR 2.45) mothers; 95% confidence intervals for these RRs excluded 1.0 (Table 3).

Multivariable analyses were repeated for the total cohort of 556 infants (including the 107 who died prior to intervention), comparing the 369 infants who were transferred to the 187 infants who were not; results were similar to those for the main analyses with one noted exception (Supplemental Tables 2, 3). Low 5-min Apgar score was associated with reduced risk of any transfer and late transfer; the respective...
Table 1  Characteristics of infants with hypoplastic left heart syndrome born in California from 2006 to 2011

|                        | Total % (n = 556) | Infants with interventions % (n = 449) | Infants who died prior to intervention % (n = 107) |
|------------------------|-------------------|----------------------------------------|-----------------------------------------------|
| Infant sex             |                   |                                        |                                               |
| Male                   | 62                | 64                                     | 54                                            |
| Female                 | 38                | 36                                     | 46                                            |
| Birthweight (g)        |                   |                                        |                                               |
| < 2500                 | 23                | 15                                     | 57                                            |
| ≥ 2500                 | 77                | 85                                     | 43                                            |
| Gestational age at birth (weeks) |       |                                        |                                               |
| < 34.0                 | 6                 | < 5                                    | 21                                            |
| 34.0–36.6              | 15                | < 15                                   | 22                                            |
| ≥ 37.0                 | 79                | 85                                     | 57                                            |
| 5-min Apgar scores     |                   |                                        |                                               |
| < 7                    | 13                | 5                                      | 48                                            |
| ≥ 7                    | 87                | 95                                     | 52                                            |
| Major non-cardiac congenital anomalies |     |                                        |                                               |
| Yes                    | 6                 | < 5                                    | 24                                            |
| No                     | 94                | < 100                                  | 76                                            |
| Prenatal care          |                   |                                        |                                               |
| Began 1st or 2nd trimester | <100             | < 100                                  | < 100                                         |
| Began 3rd trimester or none | <5              | < 5                                    | < 5                                           |
| Maternal age (years)   |                   |                                        |                                               |
| < 20                   | 7                 | 7                                      | < 10                                          |
| 20–34                  | 73                | 73                                     | 74                                            |
| ≥ 35                   | 20                | 20                                     | < 20                                          |
| Maternal race/ethnicity|                   |                                        |                                               |
| NH White               | 28                | 29                                     | 23                                            |
| Hispanic-US born       | 23                | 24                                     | 18                                            |
| Hispanic-Foreign born  | 35                | 33                                     | 39                                            |
| NH Asian/Pacific Islander | 5              | < 10                                   | < 5                                           |
| NH Black               | 6                 | < 10                                   | < 10                                          |
| Other                  | 4                 | < 5                                    | < 10                                          |
| Maternal education     |                   |                                        |                                               |
| < High school          | 32                | 31                                     | 36                                            |
| High school degree     | 31                | 31                                     | 32                                            |
| > High school          | 37                | 38                                     | 32                                            |
| Payer                  |                   |                                        |                                               |
| Government             | 59                | 60                                     | 59                                            |
| Non-government         | 41                | 41                                     | 41                                            |
| Census tract poverty level |                |                                        |                                               |
| < 25th percentile      | 21                | 22                                     | 14                                            |
| 25th–75th percentile   | 50                | 49                                     | 55                                            |
| > 75th percentile      | 29                | 29                                     | 31                                            |
| Level of care of birth hospital |     |                                        |                                               |
| Level I/II             | 20                | 20                                     | 20                                            |
| Level III              | 50                | 49                                     | 55                                            |
| Level IV               | 30                | 32                                     | 25                                            |
| Level of care of birth and transfer hospital | |                                        |                                               |
| No transfer            | 34                | 28                                     | 59                                            |
| Level I/II to III/IV   | 18                | 18                                     | 17                                            |
Mortality

Of the 556 cases, 153 (28%) died by 28 days of life and a total of 257 (47%) died by 1 year of age (Table 4). In total, 77 (41%) of infants who were not transferred and 76 (21%) of transferred infants died by 28 days of life. Among the 449 infants who received a surgical or catheter-based intervention, 52 (12%) died by 28 days of life and a total of 150 (33%) died by 1 year of age.

Based on multivariable analysis, mortality by 28 days was more likely for infants of low birthweight (RR 1.50), infants with low 5-min Apgar scores (RR 4.69), and infants with other major non-cardiac congenital anomalies (RR 3.41), and it was less likely for infants born into level IV centers (RR 0.27) and infants who were transferred (RR 0.27 for those who arrived at the destination center on DOL 0–1 and 0.31 for infants who arrived at the destination center on DOL ≥ 2) (Table 5). Unadjusted analyses also found a higher risk of mortality for preterm infants (RR 2.60) and a lower risk of mortality for infants born into level IV centers (RR 0.78) and infants with low 5-min Apgar scores (RR 0.69), and infants with other major non-cardiac congenital anomalies (RR 0.51), and it was less likely for infants born into level IV centers (RR 0.27) and infants who were transferred (RR 0.27 for those who arrived at the destination center on DOL 0–1 and 0.31 for infants who arrived at the destination center on DOL ≥ 2) (Table 5). Unadjusted analyses also found a higher risk of mortality for preterm infants (RR 2.60) and a lower risk of mortality for infants born into level IV centers (RR 0.78) and infants with low 5-min Apgar scores (RR 0.69), and infants with other major non-cardiac congenital anomalies (RR 0.51), and it was less likely for infants born into level IV centers (RR 0.27) and infants who were transferred (RR 0.27 for those who arrived at the destination center on DOL 0–1 and 0.31 for infants who arrived at the destination center on DOL ≥ 2) (Table 5). Unadjusted analyses also found a higher risk of mortality for preterm infants (RR 2.60) and a lower risk of mortality for infants born into level IV centers (RR 0.78) and infants with low 5-min Apgar scores (RR 0.69), and infants with other major non-cardiac congenital anomalies (RR 0.51), and it was less likely for infants born into level IV centers (RR 0.27) and infants who were transferred (RR 0.27 for those who arrived at the destination center on DOL 0–1 and 0.31 for infants who arrived at the destination center on DOL ≥ 2) (Table 5). Unadjusted analyses also found a higher risk of mortality for preterm infants (RR 2.60) and a lower risk of mortality for infants born into level IV centers (RR 0.78) and infants with low 5-min Apgar scores (RR 0.69), and infants with other major non-cardiac congenital anomalies (RR 0.51), and it was less likely for infants born into level IV centers (RR 0.27) and infants who were transferred (RR 0.27 for those who arrived at the destination center on DOL 0–1 and 0.31 for infants who arrived at the destination center on DOL ≥ 2) (Table 5).

Determinants of Hospital Transfer and Its Timing

Our study found a higher likelihood of being born in a destination center among infants born to foreign-born Hispanic mothers. Hospital transfer patterns were otherwise not predicted by maternal demographic data. In a large population-based study of births in Texas from 1996 to 2007, Fixler et al. found no differences in age at referral for treatment of critical congenital heart disease (including HLHS) based on race/ethnicity [13]. To our knowledge, this is the only other study to specifically examine sociodemographic factors as they relate to day of arrival at a cardiac center for neonates with HLHS. The higher likelihood of being born in a destination center for foreign-born Hispanic mothers may reflect geographic patterns of where these mothers live in relation to these hospitals. Further studies are needed to clarify this finding.

A multicenter study in California from 2004 to 2005 found that 61% of infants with HLHS were diagnosed prenatally [26]. The American Heart Association recommends prenatal assignment of postnatal level of care for prenatally diagnosed cardiac lesions, including the more severe forms of HLHS [27]. In practice, many centers will relocate families to be closer to a cardiac center in preparation for delivery of an infant prenatally diagnosed with HLHS, and infants who are prenatally diagnosed are far more likely to be born into the center of intervention [26]. Racial-ethnic differences in transfer patterns found by our study could be related to a

Table 1 (continued)

| Level III/IV to III/IV | Total % (n=556) | Infants with interventions % (n=449) | Infants who died prior to intervention % (n=107) |
|------------------------|-----------------|-------------------------------------|-----------------------------------------------|
| Day of life of arrival at transfer hospital |                  |                                     |                                              |
| No transfer            | 34              | 28                                  | 59                                            |
| Arrived DOL 0–1        | 46              | 49                                  | <35                                           |
| Arrived DOL ≥ 2        | 21              | 23                                  | <15                                           |

Intervention was defined as any ICD-9-CM code for a surgical or catheter-based intervention within 60 days of life for infants who did not die before that time. In order to adhere to OSHPD requirements that cell sizes less than or equal to 15 be suppressed, we present percentages rather than samples sizes and rounded some percentages to the nearest unit of 5%

NH Non-Hispanic

Discussion

In this study of infants born with HLHS in California, 67% of infants were transferred from their birth hospital for intervention and 47% died during infancy. Of the analyzed demographic factors, only the presence of a foreign-born Hispanic mother was associated with decreased likelihood of transfer to a destination hospital. Among infants who were transferred, late transfer (i.e., DOL ≥ 2) was more likely for infants who had low birthweight and were born to US-born Hispanic or black mothers. Mortality was more likely for infants who had low birthweight, low 5-min Apgar scores, and other major non-cardiac congenital anomalies and less likely for infants born into level IV centers and among those who were transferred.

aRRs were 0.6 (0.4–0.8) and 0.3 (0.1–0.9); in the initial analyses, the respective aRRs were 0.7 and 0.6, and their confidence intervals included 1.0.

Discuss the impact of maternal race/ethnicity on the likelihood of transfer and its timing. Explain the implications of these findings for clinical practice and future research.
| Predictor                                         | Not transferred | Transferred | Crude RR of transfer (95% CI) | Adjusted RR of transfer (95% CI) |
|--------------------------------------------------|-----------------|-------------|-------------------------------|---------------------------------|
| Infant sex                                       |                 |             |                               |                                 |
| Male                                             | 68 (n = 124)    | 63          | 0.95 (0.84–1.06)              |                                 |
| Female                                           | 32              | 37          | Reference                      |                                 |
| Birthweight (g)                                  |                 |             |                               |                                 |
| < 2500 g                                         | 15              | 15          | 1.00 (0.85–1.17)              | 1.00 (0.85–1.18)                |
| ≥ 2500 g                                         | 85              | 85          | Reference                      | Reference                       |
| Gestational age at birth (weeks)                 |                 |             |                               |                                 |
| < 37                                             | 15              | 16          | 1.03 (0.88–1.20)              |                                 |
| ≥ 37.0                                           | 86              | 84          | Reference                      |                                 |
| 5-min Apgar scores                               |                 |             |                               |                                 |
| < 7                                              |                 |             |                               |                                 |
| ≥ 7                                              |                 |             |                               |                                 |
| Major non-cardiac congenital anomalies           |                 |             |                               |                                 |
| Yes                                              |                 |             |                               |                                 |
| No                                               |                 |             |                               |                                 |
| Prenatal care                                    |                 |             |                               |                                 |
| Began 1st or 2nd trimester                       |                 |             |                               |                                 |
| Began 3rd trimester or none                      |                 |             |                               |                                 |
| Maternal age (years)                             |                 |             |                               |                                 |
| < 20                                             |                 |             |                               |                                 |
| 20–34                                            |                 |             |                               |                                 |
| ≥ 35                                             |                 |             |                               |                                 |
| Maternal race/ethnicity                          |                 |             |                               |                                 |
| NH White                                         | 23              | 31          | Reference                      | Reference                       |
| Hispanic-US born                                  | 24              | 23          | 0.93 (0.79–1.07)              | 0.86 (0.72–1.02)                |
| Hispanic-Foreign born                            | 40              | 31          | 0.87 (0.75–1.00)              | 0.80 (0.68–0.94)                |
| NH Asian/Pacific Islander                        | < 5             | 6           | 1.02 (0.81–1.28)              | 1.02 (0.78–1.32)                |
| NH Black                                         | < 10            | < 10        | 0.91 (0.69–1.20)              | 0.86 (0.65–1.14)                |
| Other                                            | < 5             | < 5         | 0.94 (0.69–1.30)              | 1.02 (0.75–1.42)                |
| Maternal education                               |                 |             |                               |                                 |
| < High school                                     | 36              | 29          | 0.91 (0.79–1.06)              | 0.90 (0.78–1.05)                |
| High school degree                               | 28              | 32          | Reference                      | Reference                       |
| > High school                                     | 36              | 39          | 0.98 (0.86–1.12)              | 0.96 (0.79–1.15)                |
| Government                                       | 50              | 59          | 1.00 (0.89–1.12)              | 1.04 (0.88–1.25)                |
| Non-government                                    | 40              | 41          | Reference                      | Reference                       |
| Census tract poverty level                       |                 |             |                               |                                 |
| < 25th percentile                                | 23              | 22          | 1.02 (0.88–1.19)              | 0.96 (0.81–1.15)                |
| 25th–75th percentile                             | 52              | 47          | Reference                      | Reference                       |
| > 75th percentile                                | 25              | 31          | 1.08 (0.95–1.23)              | 1.12 (0.98–1.28)                |
| Level of care of birth hospital                  |                 |             |                               |                                 |
| Level I/II                                       |                 |             |                               |                                 |
| Level III                                        |                 |             |                               |                                 |
| Level IV                                         | 89              | 10          | 0.25 (0.18–0.34)              |                                 |

This analysis includes 449 infants; it excludes 107 infants who died and had no evidence of repair. In order to adhere to OSHPD requirements that cell sizes less than or equal to 15 be suppressed, we present percentages rather than samples sizes and rounded some percentages to the nearest unit of 5%.

NH non-Hispanic, RR relative risk, CI confidence interval

*95% CI excludes 1.0
Table 3 Predictors of late (DOL ≥ 2) versus early (DOL 0–1) hospital transfer in infants with hypoplastic left heart syndrome born in California from 2006 to 2011

| Predictor                                      | Early transfer | Late transfer | Crude RR of late transfer (95% CI) | Adjusted RR of late transfer (95% CI) |
|-----------------------------------------------|----------------|---------------|-------------------------------------|---------------------------------------|
| Infant sex                                    |                |               |                                     |                                       |
| Male                                          | 64             | 61            | 0.91 (0.66–1.26)                    |                                       |
| Female                                        | 36             | 39            | Reference                           |                                       |
| Birthweight (g)                               |                |               |                                     |                                       |
| < 2500                                        | 12             | 22            | 1.54 (1.09–2.19)                    | 1.74 (1.20–2.51)                      |
| ≥ 2500                                        | 88             | 78            | Reference                           | Reference                             |
| Gestational age at birth (weeks)              |                |               |                                     |                                       |
| < 37                                          | 17             | < 15          | 0.83 (0.51–1.33)                    |                                       |
| ≥ 37                                          | 83             | < 90          | Reference                           |                                       |
| 5-min Apgar scores                            |                |               |                                     |                                       |
| < 7                                           | < 5            | < 5           | 0.71 (0.26–1.93)                    | 0.56 (0.20–1.58)                      |
| ≥ 7                                           | < 100          | < 100         | Reference                           | Reference                             |
| Major non-cardiac congenital anomalies        |                |               |                                     |                                       |
| Yes                                           | < 5            | < 5           | 0.62 (0.11–3.58)                    | 0.77 (0.13–4.51)                      |
| No                                            | < 100          | < 100         | Reference                           | Reference                             |
| Prenatal care                                 |                |               |                                     |                                       |
| Began 1st or 2nd trimester                    | < 100          | < 100         | Reference                           | Reference                             |
| Began 3rd trimester or none                   | < 5            | < 5           | 1.39 (0.66–2.94)                    |                                       |
| Maternal age (years)                          |                |               |                                     |                                       |
| < 20                                          | 7              | < 10          | 1.22 (0.70–2.11)                    | 1.45 (0.81–2.58)                      |
| 20–34                                         | 76             | 71            | Reference                           | Reference                             |
| ≥ 35                                          | 18             | < 25          | 1.17 (0.80–1.72)                    | 1.05 (0.70–1.58)                      |
| Maternal race/ethnicity                       |                |               |                                     |                                       |
| NH White                                      | 34             | 26            | Reference                           | Reference                             |
| Hispanic-US born                              | 22             | 27            | 1.38 (0.89–2.13)                    | 1.69 (1.04–2.72)                      |
| Hispanic-Foreign born                         | 34             | 25            | 0.96 (0.61–1.53)                    | 1.17 (0.70–1.93)                      |
| NH Asian/Pacific Islander                     | < 10           | < 10          | 1.38 (0.70–2.70)                    | 1.42 (0.72–2.79)                      |
| NH Black                                      | < 5            | < 15          | 2.42 (1.50–3.90)                    | 2.45 (1.41–4.27)                      |
| Other                                         | < 5            | < 10          | 2.04 (1.09–3.83)                    | 1.44 (0.75–2.80)                      |
| Maternal education                            |                |               |                                     |                                       |
| < High school                                  | 31             | 25            | 0.95 (0.61–1.48)                    | 0.97 (0.63–1.50)                      |
| High school degree                            | 34             | 29            | Reference                           | Reference                             |
| > High school                                  | 35             | 47            | 1.35 (0.93–1.96)                    | 1.46 (0.97–2.19)                      |
| Payer                                         |                |               |                                     |                                       |
| Government                                    | 62             | 53            | 0.78 (0.57–1.07)                    | 0.75 (0.51–1.11)                      |
| Non-government                                | 38             | 47            | Reference                           | Reference                             |
| Census tract poverty level                    |                |               |                                     |                                       |
| < 25th percentile                             | 23             | 21            | 0.96 (0.63–1.46)                    | 0.76 (0.48–1.19)                      |
| 25th–75th percentile                          | 48             | 47            | Reference                           | Reference                             |
| > 75th percentile                             | 30             | 32            | 1.08 (0.76–1.54)                    | 1.07 (0.72–1.60)                      |
| Level of care of birth hospital                |                |               |                                     |                                       |
| Level I/II                                     | < 30           | 21            | Reference                           |                                       |
| Level III                                     | 67             | 62            | 1.13 (0.75–1.70)                    |                                       |
| Level IV                                      | < 10           | 17            | 2.07 (1.29–3.31)                    |                                       |

This analysis includes 325 infants who were transferred and underwent intervention. In order to adhere to OSHPD requirements that cell sizes less than or equal to 15 be suppressed, we present percentages rather than samples sizes and rounded some percentages to the nearest unit of 5%.

NH non-Hispanic, RR relative risk, CI confidence interval

*95% CI excludes 1.0
difference in prenatal detection, but prior studies have not directly associated race/ethnicity with prenatal diagnosis [26, 28, 29]. Our datasets do not have information on timing of cardiac diagnosis. However, the vast majority of mothers in our study began prenatal care before the third trimester and HLHS can be diagnosed on routine second trimester ultrasound, suggesting that many of the infants in our study could have been diagnosed prenatally. Many studies have associated race/ethnicity with disparities in prenatal care for all infants, not just those with congenital heart disease; infants born to black mothers have higher rates of preterm birth [30], even when accounting for socioeconomic status [31]. It is unknown if these inequities in prenatal care led to differences in prenatal planning for the mothers in our study.

Timing of transfer was delayed for neonates born to US-born Hispanic and non-Hispanic black mothers. Further studies are needed to determine what types of factors may be responsible for these differences, such as patterns of residential location relative to the location of cardiac centers or differences in management decisions from a clinician or patient perspective. In addition, infants of low birthweight were more likely to be transferred later. This may reflect the correlation between low birthweight and preterm delivery; there is a wide differential diagnosis for preterm infants presenting in extremis and it may take time to make the diagnosis of cardiac disease requiring transfer. This delay may also reflect the time needed to stabilize a low birthweight or preterm infant prior to transfer.

Given the limitations of our datasets, we cannot comment on timing of palliation in patients, but we can posit that delay in transfer may lead to delays in surgical timing. In a single-center study, Anderson, et al. found that delayed surgical timing in infants with HLHS was associated with increased odds of major morbidity and health care costs [17]. In a single-center study in New York from 2005 to 2014, Swartz et al. found a younger age of operation, but longer postoperative length of stay and no difference in mortality for infants requiring cardiac surgery who were born into the cardiac center compared to those who were transferred in [32]. Further investigations are needed to determine if a delay in transfer is associated with other factors such as postoperative length of stay, ventilator days, and morbidities such as sepsis and necrotizing enterocolitis among infants with HLHS. These data were not available for the current analysis.

**Mortality**

Of 556 total cases, 28% died within the first month of life. This is consistent with prior studies of neonatal mortality in HLHS [2–4], but higher than that reported by the multicenter, prospective Single Ventricle Reconstruction (SVR) Trial (11.5%) [33]. Our finding of 47% mortality by 1 year of life is also higher than the 29% 1-year mortality reported by the SVR trial [34].

Despite the association of race/ethnicity with timing of transfer, it was not associated with mortality in our cohort, either in the neonatal period or at 1 year of life. A 2018 study by Peyvandi et al. examined infants with HLHS or dextro-transposition of the great arteries and found that infants with Hispanic mothers had a higher risk of a poor outcome (a composite outcome defined by the authors which included mortality) [35]. The authors did not explore the differences by maternal birthplace. We did not compare all Hispanic mothers to other race/ethnicities.

We did find that transfer was associated with a lower risk of mortality. In contrast to our finding, Morris et al. reported a strong association between birth far from a cardiac center

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**Table 4** Survival among infants born with hypoplastic left heart syndrome in California from 2006 to 2011, based on transfer status and whether they had an intervention

|                      | Not transferred | Early transfer (arrived DOL 0–1) | Late transfer (arrived DOL ≥ 2) | Total |
|----------------------|-----------------|---------------------------------|--------------------------------|-------|
| % (n=187)            | % (n=253)       | % (n=116)                       | n=556                          |       |
| Infants who died before interventiona | 34              | 13                              | 19                             |       |
| Infants who had intervention  | 66              | 87                              | 81                             |       |
| Survived             | 67              | 67                              | 67                             |       |
| Died 0–28 days       | 12              | 12                              | 12                             |       |
| Died 29–365 days     | 21              | 21                              | 22                             |       |
| All infants          | 100             | 100                             | 100                            |       |
| Survived             | 44              | 59                              | 54                             |       |
| Death 0–28 days      | 41              | 21                              | 28                             |       |
| Death 29–365 days    | 14              | 20                              | 19                             |       |

*a Infants who died without intervention within 60 days of life (infants who survived > 60 days without intervention were excluded from the analysis). In order to adhere to OSHPD requirements that cell sizes less than or equal to 15 be suppressed, we present percentages rather than samples sizes and rounded some percentages to the nearest unit of 5%.
Table 5 Predictors of neonatal mortality in infants with hypoplastic left heart syndrome born in California from 2006 to 2011

| Predictor                                                                 | Survived | Died | Crude RR of neonatal mortality (95% CI) | Adjusted RR of neonatal mortality (95% CI) |
|---------------------------------------------------------------------------|----------|------|----------------------------------------|-------------------------------------------|
| Infant sex                                                                |          |      |                                        |                                            |
| Male                                                                      | 64       | 56   | 0.75 (0.55–1.03)                       | 0.90 (0.65–1.26)                          |
| Female                                                                    | 35       | 44   | Reference                               | Reference                                 |
| Birthweight (g)                                                           |          |      |                                        |                                            |
| < 2500                                                                    | 16       | 43   | 3.02 (2.19–4.17)                       | 1.50 (1.01–2.22)                          |
| ≥ 2500                                                                    | 84       | 58   | Reference                               | Reference                                 |
| Gestational age at birth (weeks)                                          |          |      |                                        |                                            |
| < 37                                                                      | 15       | 35   | 2.60 (1.86–3.62)                       |                                            |
| ≥ 37                                                                       | 85       | 65   | Reference                               |                                            |
| 5-min Apgar scores                                                        |          |      |                                        |                                            |
| < 7                                                                       | 5        | 35   | 6.50 (4.64–9.11)                       | 4.69 (3.08–7.16)                          |
| ≥ 7                                                                       | 95       | 65   | Reference                               | Reference                                 |
| Major non-cardiac congenital anomalies                                    |          |      |                                        |                                            |
| Yes                                                                       | < 5      | 18   | 7.79 (5.12–11.8)                       | 3.41 (2.04–5.69)                          |
| No                                                                         | < 100    | 82   | Reference                               | Reference                                 |
| Prenatal care                                                             |          |      |                                        |                                            |
| Began 1st or 2nd trimester                                               | < 100    | < 100 | Reference                               | Reference                                 |
| Began 3rd trimester or none                                               | < 5      | < 5   | 1.44 (0.59–3.50)                       |                                            |
| Maternal age (years)                                                      |          |      |                                        |                                            |
| < 20                                                                      | 7        | < 10  | 0.89 (0.47–1.69)                       | 0.77 (0.39–1.49)                          |
| 20–34                                                                    | 73       | 76   | Reference                               | Reference                                 |
| ≥ 35                                                                      | 20       | < 20  | 0.84 (0.56–1.28)                       | 0.72 (0.47–1.12)                          |
| Maternal race/ethnicity                                                   |          |      |                                        |                                            |
| NH White                                                                  | 29       | 24   | Reference                               | Reference                                 |
| Hispanic-US born                                                          | 25       | 17   | 0.85 (0.52–1.40)                       | 0.80 (0.47–1.36)                          |
| Hispanic-Foreign born                                                     | 33       | 39   | 1.33 (0.88–2.01)                       | 1.27 (0.77–2.09)                          |
| NH Asian/Pacific Islander                                                 | 5        | < 10  | 1.25 (0.58–2.69)                       | 2.11 (0.95–4.65)                          |
| NH Black                                                                  | < 5      | < 10  | 1.85 (1.00–3.42)                       | 1.72 (0.89–3.31)                          |
| Other                                                                     | < 5      | < 10  | 1.81 (0.87–3.75)                       | 0.93 (0.43–2.03)                          |
| Maternal education                                                        |          |      |                                        |                                            |
| < High school                                                             | 31       | 34   | 1.01 (0.68–1.48)                       | 0.93 (0.61–1.43)                          |
| High school degree                                                        | 30       | 33   | Reference                               | Reference                                 |
| > High school                                                             | 39       | 33   | 0.83 (0.56–1.23)                       | 0.74 (0.47–1.15)                          |
| Payer                                                                     |          |      |                                        |                                            |
| Government                                                                | 58       | 63   | 1.18 (0.84–1.63)                       | 1.04 (0.69–1.57)                          |
| Non-government                                                            | 42       | 37   | Reference                               | Reference                                 |
| Census tract poverty level                                                |          |      |                                        |                                            |
| < 25th percentile                                                         | 23       | 14   | 0.62 (0.39–0.99)                       | 0.68 (0.41–1.12)                          |
| 25th–75th percentile                                                      | 49       | 53   | Reference                               | Reference                                 |
| > 75th percentile                                                         | 28       | 33   | 1.04 (0.73–1.48)                       | 0.87 (0.60–1.26)                          |
| Level of care of birth hospital                                           |          |      |                                        |                                            |
| Level I/II                                                                | 20       | 20   | Reference                               | Reference                                 |
| Level III                                                                | 48       | 54   | 1.08 (0.72–1.63)                       | 0.89 (0.57–1.39)                          |
| Level IV                                                                 | 32       | 26   | 0.78 (0.49–1.25)                       | 0.27 (0.15–0.48)                          |
| Transferred before repair                                                 |          |      |                                        |                                            |
| Yes                                                                       | 73       | 50   | 0.42 (0.31–0.58)                       |                                            |
| No                                                                        | 27       | 50   | Reference                               |                                            |
| Day of life of arrival at repair hospital                                  |          |      |                                        |                                            |
and neonatal mortality in neonates with HLHS [3]. Kaltman et al., recently identified an association between maternal proximity to a top 50 cardiac center and better survival in infants with congenital heart disease [36]. However, others have reported no differences in mortality based on birth location for infants with HLHS or other ductal-dependent lesions [11, 12, 37, 38]. The protective effect of transfer found in our study could be explained by a greater propensity for high-risk infants to be delivered into the center of intervention; other studies have confirmed that mothers carrying infants with a prenatal diagnosis of complex congenital heart disease were more likely to deliver in a major cardiac center [26].

**Limitations**

This is a large, population-based study over a 6-year time span in the most populous state in the country and is consistent with prior studies of infants with HLHS. Of the 449 patients included in our primary analysis, the majority were male and of normal birthweight and gestational age, consistent with prior large studies of neonates with HLHS [3, 28]. A total of 33 infants (6%) had a major, non-cardiac congenital anomaly, also consistent with prior studies [28].

Despite these strengths, our study has several limitations. Primarily, the available data are limited in their ability to capture a patient’s diagnosis, prenatal diagnosis status, severity of illness, and interventions. Moreover, validation of the available data was not possible. By using CPQCC data, a prospectively collected dataset, we hoped to define our cases more rigorously than with ICD-9 codes, since CPQCC data are collected within NICUs with clear guidelines. We checked our case ascertainment by confirming OSHPD codes for HLHS. Of the 706 CPQCC cases coded for HLHS, 73% (n = 515) also had an ICD-9-CM code for HLHS (746.700) in OSHPD data. It is also possible that not all patients with HLHS in California were entered into CPQCC data; for example, some neonates that were immediately admitted into a cardiovascular intensive care unit and never entered a NICU may not have been captured.

Additionally, based on the nature of ICD-9 coding in OSHPD, we can only identify timing of transfer based on day of arrival at the cardiac center. For example, an infant born at 11:00 p.m. and transferred at 1:00 a.m. the following morning would be counted as an infant transferred on DOL 1, whereas an infant born at 12:01 a.m. and transferred at 1:00 a.m. the following day would be counted the same way. The definition of transfer also cannot account for transfer to a “co-located” hospital, meaning birth at a women’s hospital affiliated with a certain children’s hospital with a plan for immediate transfer to the children’s hospital; these infants would still be counted as “transferred.” We therefore combined all infants transferred on DOL 0 and 1 into one category, instead of two. A more in-depth evaluation of hospital locations, regional networks, and distance from maternal residence would be informative but not feasible within the scope of the current analysis.

We are also limited in our ability to define the hospital courses of the 107 infants who died prior to any intervention. We did find that the majority of these infants (n = 63, 59%) were not transferred, and the majority (60%) died within the first week of life. Sub-analyses on only these infants who died prior to intervention did not identify significant demographic associations with whether or not they were transferred. Including them in a secondary analysis did not significantly alter our findings (see Supplemental Tables 2, 3, 4). Of note, 24% of these 107 infants carried a diagnosis of an extracardiac malformation compared to < 5% of those who underwent an intervention. These 107 infants may include those who were elected for comfort care only by their families, infants with the most severe forms of the disease, infants who died prior to intervention due to management at lower level centers without access to subspecialty cardiac care, or infants with other cardiac diagnoses. Our struggle to determine what happened to these infants speaks to a lack of “best practices” in the literature of how to deal with such a subgroup, as well as the limited available data.
Despite these limitations, our study is strengthened by the large, racial-ethnically diverse population captured in our analysis and offers new insight into the relationship between transfer patterns and sociodemographic characteristics in infants with HLHS.

Conclusions

Among neonates with HLHS born in California from 2006 to 2011, 67% of infants were transferred from their birth hospital for intervention, 28% died as neonates and 47% died by 1 year of life. Among infants who were transferred to a destination cardiac center, infants born to US-born Hispanic and black mothers were more likely to be transferred late. While we did not associate timing of transfer with mortality, a wealth of prior studies have reported an association between race/ethnicity and mortality. Future studies should further investigate timing of transfer and morbidities in this population and hopefully offer more insight into the factors predicting transfer in infants with HLHS.

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Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflicts of interest or financial ties to disclose.

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