Published in final edited form as:

J Pediatr. 2018 January ; 192: 144–151.e1. doi:10.1016/j.jpeds.2017.09.049.

Hearing Loss after Cardiac Surgery in Infancy: an Unintended Consequence of Life-saving Care

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Abstract

Objectives—To investigate the prevalence of hearing loss (HL) after cardiac surgery in infancy, patient and operative factors associated with HL and the relationship of HL to neurodevelopmental outcomes.

Study design—Audiologic and neurodevelopmental (ND) evaluations were conducted on 348 children who had repair of congenital heart disease at Children's Hospital of Philadelphia as part of a prospective study evaluating ND outcomes at 4 years of age. A prevalence estimate was

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The other authors declare no conflicts of interest.

calculated based on presence and type of HL. Potential risk factors and the impact of HL on ND outcomes were evaluated.

Results—The prevalence ($CI_{0.95\%}$) of HL was 21.6% (17.2, 25.9). The prevalence of conductive hearing loss (CHL), sensorineural hearing loss (SNHL), and indeterminate hearing loss (IDHL) were 12.4% (8.8, 16.0), 6.9% (4.1, 9.7) and 2.3% (0.6, 4.0) respectively. Only 18 of 348 subjects (5.2%) had screened positive for HL prior to this study and 10 used a hearing aid. After adjusting for patient and operative covariates, younger gestational age (GA), longer postoperative length of stay (PLOS) and a confirmed genetic anomaly were associated with HL, all $P < .01$. The presence of HL was associated with worse language, cognition and attention, $p < 0.01$.

Conclusions—These findings suggest that the prevalence of HL in preschool children following heart surgery in infancy may be 20-fold higher than in the 1% prevalence seen in the general population. Younger GA, presence of a genetic anomaly and longer PLOS were associated with HL. HL was associated with worse ND outcomes.

Keywords

prevalence; sensorineural; neurodevelopmental; language; cognition; attention

Congenital heart defects (CHDs) are the most common developmental defects and frequently require repair in infancy. As surgical techniques and procedures have improved over the last 25 years, mortality has declined. However, recognition of neurodevelopmental disabilities as an adverse outcome has increased.^{1–3} Understanding the causes of such morbidities is important in helping to mitigate them and improve long-term outcomes.

Hearing loss in childhood has the potential for life-long neurodevelopmental disability, poor language skills and behavioral problems.⁴ There is a paucity of population based data regarding the prevalence of HL in preschool age children, but the best estimates are a prevalence around 1 percent.^{5, 6} Hearing is a pre-requisite for learning spoken language and speech production. When these activities are impaired due to HL, language acquisition is impacted. The Joint Committee on Infant Hearing 2007 identified a series of risk factors associated with HL in childhood.⁷ Many of these also occur in children with CHD, including prolonged intensive care, assisted ventilation, Extracorporeal Membrane Oxygenation (ECMO), and exposure to ototoxic medications.^{8–13} HL and its impact on neurodevelopmental indicators have not been explicitly studied in children with different types of CHD, including those undergoing surgical repair.

The overall purposes of this study were to 1) estimate the prevalence of HL after cardiac surgery in infancy, and 2) evaluate potential risks factors for HL, and 3) investigate the relationship between HL and selected neurodevelopmental indicators.

Methods

This study was a prospective observational study intended to evaluate the effects of Apolipoprotein E (*APOE*) polymorphisms on neurodevelopmental outcomes for preschool-aged patients 4 to 5 years of age following cardiac surgery in the neonatal and infant periods. Between September 1998 and April 2003, 675 eligible infants underwent cardiac surgery.

Twenty-three infants died prior to consent, parents of 102 declined participation, and 550 (81%) were enrolled.¹⁴ Eligible patients were 6 months of age and undergoing surgical treatment of CHD with cardiopulmonary bypass, with or without deep hypothermic circulatory arrest (DHCA). Exclusion criteria included (1) multiple congenital anomalies (2) recognizable genetic or phenotypic syndrome other than chromosome 22q11 microdeletion syndrome, and (3) language other than English spoken in the home. The current study evaluated those patients who completed a standard audiologic evaluation as part of a comprehensive neurodevelopmental evaluation at 4 years of age (2003–2008). The study was approved by the institutional review board at Children's Hospital of Philadelphia. Informed consent was obtained from parents or guardians.

Audiologic evaluations were conducted using standard pediatric assessment methods based on developmental ability. Thresholds were obtained for pure tone air conduction stimuli at frequencies 250 through 8000 Hz in an audiometric booth. Pure tone bone conduction thresholds were obtained when responses to pure tone air conduction signals were poorer than 15 dB HL. Normal hearing sensitivity was defined as response thresholds 15 dB HL. Hearing loss was defined as average pure tone air conduction thresholds 20 dB HL at the following frequencies (500, 1000, 2000), or average pure tone air conduction thresholds 25 dB HL at 2 or more frequencies above 2000 Hz. HL was further classified as conductive or sensorineural (SNHL), conductive hearing loss was defined as pure tone bone conduction thresholds 15 dB HL and pure tone air conduction responses 10 dB or more poorer than the pure tone bone conduction thresholds. SNHL occurred when both pure tone air conduction and pure tone bone conduction thresholds exceeded 15 dB HL, and the difference between the two was 10 dB. HL was classified as indeterminate hearing loss if the subject could not complete the pure tone bone conduction testing necessary (masked or unmasked) due to immaturity or developmental delay, or could only be assessed in a sound field (responses obtained from the better hearing ear, if differences existed between the ears). Degree of hearing loss was determined based on the pure tone average (PTA). Normal hearing sensitivity was defined as PTA between 0–15 dB HL. Hearing loss was defined as PTA >20 dB HL, using the following PTA ranges and descriptors: 21–39 dB HL (mild); 40–54 dB HL (moderate); 55–69 dB HL (moderately-severe); 70–89 dB HL (severe); and, 90 dB HL (profound). High frequency hearing loss (HFHL) was defined as confined to the region at 2000 Hz and above, and using the same descriptors for the average of those responses (ie, “mild high frequency hearing loss”).

Patient-related variables (e.g., age at testing, sex, race, anthropometric measures) and peri-operative variables (e.g., age at surgery, bypass support times, hematocrit, length of stay) were collected from patient records and, patient evaluations and laboratory testing. We were not able to quantify exposure to potentially ototoxic medications.

Patients were evaluated by a genetic dysmorphologist. Chromosome analysis and testing for microdeletion of 22q11 were performed as indicated. Results of the genetic evaluations were classified as normal if no genetic or chromosome abnormality was demonstrated, abnormal if a specific diagnosis was confirmed, and suspect if there was evidence of a genetic syndrome that could not be confirmed.

Language was assessed with the Preschool Language Scale-4 (PLS-4), Auditory Comprehension (AC), Expressive Communication (EC) and Total Language Score (TLS).¹⁵ The Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) was used to assess cognition in children and provides a Full-Scale IQ score.¹⁶ To examine executive functioning and attention the NEuro-PSYchology statue test (NEPSY) was used, targeting inhibition and motor persistence (two components of executive function and attention).¹⁷

Statistical Analyses

Data Analysis occurred in three distinct phases: a descriptive phase, a prevalence phase, and a risk modeling phase.

Measures of central tendency, variability, and association were computed for all relevant variables, for the group as a whole and by hearing loss category. Cardiac diagnosis was coded according to a previously described classification incorporating anatomy and perioperative physiology that has been shown to be predictive of perioperative mortality. Class I is defined as 2 ventricles with no aortic arch obstruction, Class II as 2 ventricles with aortic arch obstruction, Class III as single ventricle with no arch obstruction, and Class IV as single ventricle with arch obstruction.¹⁸ Patients with tetralogy of Fallot (TOF) and transposition of the great arteries are in Class I, whereas patients with hypoplastic left heart syndrome (HLHS) or its variants are in Class IV.

Prevalence estimates for the presence or absence of hearing loss and by each of three identified subtypes (conductive, sensorineural, and indeterminate) were computed complete with 95% confidence intervals.

Three different sets of risk models were specified and tested with presence or absence of hearing loss modeled as a dichotomous outcome. A total of 23 standard logistic regression models and one contingency table (ECMO LVAD) were specified and tested, representing patient-related, peri-operative, and postoperative factors. The single contingency table test for ECMO/LVAD was necessary due to low cell counts in several cells. As a follow-up to the aforementioned models, the percentage of patients with hearing loss who had one or more of the aforementioned risk factors was calculated and compared with those without.

Three secondary analyses were conducted using simple linear regression models to test the relationship between HL and language development (PLS-4 Total Language Score), cognition (WPPSI-III Full-Scale IQ score), and attention/executive function (NEPSY Attention/Executive Function score), respectively (Appendix; available at www.jpeds.com). In each case, HL served as the testable covariate, alone and in the presence of three confounders (GA, genetic anomaly, post-operative length of stay). Due to the non-normative nature of PLS4 and NEPSY scores, transformations were necessary to make them more amenable for analysis. That is, Box-Cox transformations were used in which PLS4 score was raised to a power of 2.06, and NEPSY score was raised to a power of 2.23. All data were analyzed using SAS v9.3.

Results

Of the 550 enrolled patients, the four year evaluation was completed by 381 (78% of eligible) of the 486 patients who were alive and eligible. Baseline characteristics have been previously reported for patients returning for the 4 year evaluation ($n = 381$), those who did not return ($n = 105$), and those who died before age 4 years ($n = 64$).¹⁹ The only significant difference in baseline characteristics between returning and non-returning patients was under-representation of African-Americans in the returning patients (21% vs. 29%). Three hundred and forty-eight patients met entry criteria for the current study, A total of 33 subjects did not receive an audiological examination due to either missing the hearing evaluation ($n = 15$) or an inability to complete the evaluation ($n = 18$). Table 1 lists a more complete presentation of the entire cohort as well as each subgroup.

A total of 75 of the 348 children enrolled in the current study were diagnosed with hearing loss, resulting in a prevalence estimate ($CI_{0.95\%}$) of 21.6% (17.2, 25.9). The prevalence rates of conductive HL, SNHL, and indeterminate HL were 12.4% (8.8, 16.0), 6.9% (4.1, 9.7), and 2.3% (0.6, 4.0), respectively (Figure). Of the 75 children with HL, 50 (67.6%) had mild HL. Of the 24 with SNHL, 12 (50%) had moderate to severe HL and 8 (33.3%) had HFHL. Only 18/348 (5.23%) parents had reported a diagnosis of HL in their infants prior to this evaluation, 10 of whom used hearing technology. This indicates that 80% of those with HL in this cohort had unrecognized and subsequently untreated HL. Deletions of 22q11 were present in 17 subjects (4.9%, 9 with HL [53%]). HL was present in three of eight subjects who required ECMO (37.5%).

Patient factors associated with the presence/absence of a HL were gestational age (term, $p < 0.01$) and presence of a confirmed genetic anomaly ($p < 0.01$). Longer postoperative length of stay (PLOS, ($p < 0.01$)) was the only perioperative factor associated with HL. No other perioperative factors were found to have a statistically significant relationship with HL. However, when considering an adjusted, multiple covariate model, a statistically significant interaction was observed between confirmed genetic anomaly and postoperative length of stay ($p < 0.01$) (Table 2 lists covariates tested). The overall prevalence of HL for those with one or more of these identified risk factors was 36.7% compared with 13.8% in those without.

The mean (SD) PLS-IV Total Language Score for the normal hearing group was 100.8 (15.4), more than half a standard deviation higher than the Total Language score for subjects with HL at 92.4 (20.4). Similarly, the average receptive language score of subjects with normal hearing was 101.2 (15.0) as compared with 93.8 (19.4) for the subjects with HL. Finally, the expressive language scores for the subjects with no hearing loss was 100.1 (14.0) as compared with the 91.9 (19.2) for children with HL. The presence of hearing loss was associated with worse total language (PLS-4) skills alone ($p < 0.01$, $R^2 = 0.03$), and in the presence of the aforementioned covariates ($p < 0.01$, $R^2 = 0.16$). Furthermore, when examined with unadjusted analyses AC and EC were significantly lower in subjects with HL than in subjects without HL.

Statistically significant relationships were observed between HL and two neurodevelopmental outcomes: WPPSI FS IQ score ($p < 0.01$, $R^2 = 0.25$), and NEPSY attention score ($p < 0.01$, $R^2 = 0.19$) after adjusting for genetic anomaly and PLOS. Currently recognized risk factors for adverse ND outcomes were tested for an association with HL. Only younger GA, presence of a genetic anomaly and longer LOS were observed to be significantly associated with HL. Therefore, these three covariates were included as potential confounders when estimating the relationship between HL and our three neurodevelopmental outcomes, PLS-IV Total Language Score, WPPSI FS IQ, and NEPSY Attention score.

Discussion

In this cohort of preschoolers who survived cardiac surgery in infancy, we found the prevalence of HL was 20-fold higher than what is typically seen in this age group. The presence of a genetic anomaly, GA < 37 weeks and longer PLOS were all significantly related to a diagnosis of HL. Importantly, no modifiable operative management factors were associated with an increased risk of HL. A statistically significant interaction was observed between genetic anomaly and PLOS. Lastly, performance measures of cognition, language skills, and attention were all inversely related to an audiologic deficit, after adjustment for genetic anomaly and PLOS.

CHL was diagnosed most frequently and typically results from conditions common among children (i.e. otitis media), once treated, hearing is often restored. For children diagnosed with IDHL a second audiologic evaluation is critical because they could have CHL or SNHL. If left untreated, CHL can impact speech and language, and SNHL can cause significant delays in academic achievement and emotional development. A proportion of our cohort had a history of ECMO or exposure to ototoxic medications, both are related to the diagnosis of SNHL.^{9, 13, 20–22} One-third of the study population with SNHL had HFHL which is typically missed by caregivers. The consequences of such may compromise language acquisition because morphological markers important for speech are perceived at frequencies (1500–1600 Hz) inaudible to those with HFHL.^{23–25}

The prevalence of HL among our cohort was related to the presence of a genetic anomaly, younger GA, and PLOS; suggesting a child's likelihood of HL is associated with both innate and extrinsic factors. Among the spectrum of genetic disorders known to cause congenital defects in children, a small proportion concurrently impacts the cardiac and audiologic systems due to shared developmental origins.²⁶ Specific mutations resulting in heart defects and HL are undoubtedly heterogeneous and multifactorial.²⁷ Many of the genetic syndromes which impact children with CHD (i.e. 22q, Down's Syndrome,) are also associated with hearing loss, however each is the result of a different mutation: this suggests numerous genes may be involved in the presence of HL and CHD. Younger GA is another inherent factor. During the third trimester the brain undergoes a great deal of maturation, but preterm birth places the immature brain at an increased risk of injury.^{28, 29} These insults (ie, periventricular leukomalacia) can be disruptive to the CNS development and may ultimately impact the auditory system.

Our findings are consistent with the risk indicators listed by the Joint Commission on Infant Hearing, which states a neonatal intensive care unit stay greater than 5 days is associated with HL in childhood. During recovery, our cohort spent time in the intensive care unit, an environment plagued with noise of high frequencies and intensities; such stimuli, in excess, contributes to HL. A longer PLOS also serves as a proxy for increased exposure to medication and higher mean drug use.²⁶ In the CHD population, this is particularly relevant to the use of furosemide, an ototoxic agent.^{8, 13} Robertson et al described HL in children with CHD, in the presence of a bolus administration of furosemide. Reports have also described a drug's ototoxicity is related to its duration of use and simultaneous noise exposure.^{13, 21, 30}

It is important to recognize that the onset of HL in this cohort occurred during early language acquisition and, not surprisingly, significantly lower language scores were found. Although most of the HL we diagnosed was mild, this degree of impairment can have an effect on language acquisition; children with bilateral and unilateral HL tend to have lower expressive language scores than their peers.

In our study, the presence of HL was also predictive of cognition scores among preschoolers with CHD. Children with CHD are known to have decreased scores in cognitive examinations, the nature of which is multifactorial.^{2,31,32} Similarly, children with HL are also known to perform less well on such tests.^{33–36} Cognitive tests are language-based and most often administered verbally, relying on a child's ability to use language to answer examination questions. However, when a child's language abilities are diminished, as they often are in children with HL, performance on such tests is impacted. A deficit in spoken and language input due to HL influences a child's ability to receive new concepts and information. Language skills are diminished by HL, ultimately affecting cognition and verbal IQ.

Hyperactivity, behavior difficulties and inattention are morbidities known to occur with increased frequencies in survivors of cardiac surgery. Similarly, children with HL must expend more energy to hear and concentrate, and this overexertion can result in disengagement in their learning and ultimately a decline in attention while in the classroom.³⁷ At times, this population is described as being inattentive and hyperactive, but these behaviors may occur because their HL prohibits them from being sufficiently stimulated.³⁷ In addition to the repercussions of hearing loss, the immaturity of the brain in children with CHD and associated disruption in the formation of neural pathways and can result in the challenges seen in attention.²

This study has a number of limitations. The first being we don't know how many of our participants had hearing loss prior to surgery. We did not collect data on all of the known risk indicators related to the incidence of hearing loss. Information on total exposure to loop diuretics and ototoxic medications, days of assisted mechanical ventilation and presence of a postnatal infection were not available for our analysis. Additionally, some of the conductive hearing loss seen may have been temporary.

The Joint Committee on Infant Hearing has provided a number of recommendations (for example: all infants screened by 1 month of age, infants with a neonatal intensive care unit stay longer than 5 days should have auditory brainstem response examination, and if hearing loss is detected early intervention services should begin by 6 months of age) to ensure those with hearing deficits are detected and receive the necessary care. They suggest infants who have risk indicators for hearing loss have at least one diagnostic audiologic evaluation by 24 to 36 months of age, but ideally, newborns would be screened universally before three months and have necessary interventions by 6 months.⁷ In compliance with the AAP, the Joint Commission on Infant Hearing also recommends regular surveillance of auditory skills and developmental milestones by their medical provider.⁷ Children with CHD appear to be at an elevated risk for HL, further emphasizing the need for the early monitoring and intervention.

It is imperative that children who undergo cardiac surgery at less than six months of age have at least one audiologic evaluation by 24 – 30 months, to evaluate the status of their hearing.⁷ When hearing loss is recognized in a timely manner and children receive the necessary support, we have the potential to modify and improve long-term outcomes.

Acknowledgments

Supported by the Fannie E. Rippel Foundation, an American Heart Association National Grant-in-Aid (9950480N), the National Institutes of Health (HL071834), the National Institute of Neurological Disease and Stroke (1R01NS-072338 [to D.J.L.]) 1R01NS060653 (to D.J.L.), and the June and Steve Wolfson Family Foundation, Philadelphia, Pennsylvania (to D.J.L.).

APPENDIX

The Preschool Language Test-4 is a general test of early language skills for children aged 6 months to 11 years of age. The exam provides a measure of language comprehension and expressive communication. The standard scores are derived based on age and performance. There are three scales: auditory comprehension, expressive communication and a composite total language score, each with a mean of 100, a standard deviation of 15 and are calculated based on the performance on receptive and expressive sections. The test takes less than an hour to administer.

The Weschler Preschool and Primary Scale of Intelligence, Third Edition is a standardized test used to examine intelligence in children ages 3.5 to 7 years old. Used in a research and clinical setting, it typically takes 45 minutes to administer and provides three summary scores and twelve subtest scores. The scores have a mean of 11, standard deviation of 15 and provided measures for full-scale IQ, verbal IQ and performance IQ. Performance tests include object assembly, geometric design, block design, mazes and picture completion. Verbal tests include information, comprehension, arithmetic, vocabulary and similarities. A significant amount of data exists to explain the meaning of the test findings. The WPPSI-revised has proved to have moderate to strong reliability (coefficients for verbal IQ, performance IQ, processing speed, full-scale IQ and general language were 0.92, 0.87, 0.93, 0.92, and 0.90 respectively) and validity (correlation with other cognitive tests in the positive and significant range of 0.74–0.90) in a variety of tests.

The NEPSY (NE-neuro, PSY-psychology) is a developmental neuropsychological assessment tool which was published in 1998. The NEPSY has three subtests used to examine attention and executive function, the statue subset assess inhibition and motor persistence. Each subtests has a mean score of 10 and a standard deviation of 3. Reliability ranges from 0.50 to 0.81. Validity studies indicate that there is a weak correlation between the attention/executive function subtests and the tests of general intelligence. The use of the NEPSY test in a clinical setting on children diagnosed as having ADHD indicated that they score significantly more poorly on tests of attention.

Abbreviations

CHD	Congenital Heart Defects
ECMO	Extracorporeal Membrane Oxygenation
GA	Gestational Age
HL	Hearing Loss
HFHL	High Frequency Hearing Loss
SNHL	Sensorineural Hearing Loss

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Figure.

Distribution of hearing loss seen within our cohort. The first column depicts the total prevalence of hearing loss among our study population. The following columns illustrate the proportion of the three hearing loss diagnoses assigned in this group.

Table 1

Baseline Characteristics for Total Cohort and by HL Category

Variable	Entire Cohort <i>M (SD)</i> <i>n</i> = 381	Hearing Loss <i>M (SD)</i> <i>n</i> = 75	No Hearing Loss <i>M (SD)</i> <i>n</i> = 273	No Test Administered <i>n</i> = 33
Age at testing (yr)	4.8 (0.2)	4.8 (0.2)	4.8 (0.2)	4.8 (0.2)
Age at first surgery (d)	42.4 (53.9)	35.8 (48.5)	44.9 (55.5)	36.4 (51.9)
Birth head circumference (cm)	33.6 (2.1)	33.4 (2.1)	33.7 (1.9)	33.2 (2.9)
Birthweight (kg)	3.1 (0.6)	3.1 (0.7)	3.2 (0.6)	2.9 (0.9)
Hematocrit (%)	27.9 (4.0)	27.3 (3.8)	28.0 (4.1)	28.1 (4.3)
Total bypass time at 1st operation (min)	65.7 (39.3)	61.6 (36.5)	67.0 (40.9)	65.2 (31.0)
Total bypass time at 4-year evaluation (min)	40.8 (62.6)	41.7 (57.7)	39.0 (57.4)	53.7 (103.0)
Total DHCA time at 1st operation (min)	22.3 (23.0)	24.5 (24.0)	21.3 (22.5)	25.3 (24.8)
Total DHCA time at 4-year evaluation (min)	13.2 (24.2)	12.7 (24.6)	13.8 (24.3)	9.9 (22.0)
Pre-operative length of stay (d)	2.2 (3.0)	2.4 (2.4)	2.1 (3.2)	2.5 (2.2)
Post-operative length of stay (d)	12.2 (13.0)	15.8 (17.6)	10.7 (11.3)	15.8 (12.5)
Categorical Variables <i>n</i> (%)				
<i>Sex</i>				
Female (45.4)	165 (43.3)	32 (42.7)	118 (43.2)	15
Male (54.6)	216 (56.7)	43 (57.3)	155 (56.8)	18
<i>Ethnicity</i>				
Black (21.1)	80 (21.0)	9 (12.0)	64 (23.4)	7
White (57.6)	256 (67.2)	58 (77.3)	179 (65.6)	19
Other (21.1)	45 (11.8)	8 (10.7)	30 (11.0)	7
<i>Maternal Education</i>				
Less than high school	19 (5.0)	2 (2.7)	16 (5.9)	1 (3.0)
High School/Some college (54.6)	164 (43.0)	33 (44.0)	113 (41.4)	18
College (36.4)	132 (34.6)	24 (32.0)	96 (35.2)	12
Graduate	64 (16.8)	16 (21.3)	46 (16.8)	2 (6.1)
Missing	2 (0.5)		2 (0.7)	
<i>Socioeconomic Status</i>				
Professional	13 (3.4)	1 (1.3)	11 (4.0)	1 (3.0)
Medium business (12.1)	31 (8.1)	5 (6.7)	22 (8.1)	4
Skilled/Clerical (33.3)	78 (20.5)	13 (17.3)	54 (19.8)	11
Semi-skilled (24.2)	120 (31.5)	25 (33.3)	87 (31.9)	8
Unskilled (27.3)	137 (36.0)	31 (41.3)	97 (35.5)	9
Missing	2 (0.5)		2 (0.7)	

Variable	Entire Cohort <i>M (SD)</i> <i>n</i> = 381	Hearing Loss <i>M (SD)</i> <i>n</i> = 75	No Hearing Loss <i>M (SD)</i> <i>n</i> = 273	No Test Administered <i>n</i> = 33
Gestational Age				
< 37 weeks (21.2)	54 (14.2)	18 (24.0)	29 (10.6)	7
37+ weeks (78.8)	324 (85.0)	56 (74.7)	242 (88.6)	26
Missing	3 (0.80)	1 (1.3)	2 (0.7)	
<i>Diagnostic Class</i>				
2 Ventricles No Arch Obstruction (48.5)	202 (53.0)	37 (49.3)	149 (54.6)	16
2 Ventricles, Arch Obstruction (21.1)	47 (12.3)	12 (16.0)	28 (10.3)	7
1 Ventricle, No Arch Obstruction (15.2)	36 (9.4)	9 (12.0)	22 (8.1)	5
1 Ventricle, Arch Obstruction (15.2)	96 (25.2)	17 (22.7)	74 (27.1)	5
<i>Genetic Evaluation</i>				
Normal (48.8)	296 (77.7)	50 (66.7)	230 (84.2)	16
Suspected (21.2)	32 (8.4)	5 (6.7)	20 (7.3)	7
Confirmed (30.3)	53 (13.9)	20 (26.7)	23 (8.4)	10
<i>APOE Genotype</i>				
E2	44 (11.6)	12 (16.0)	29 (10.6)	3 (9.1)
E3 (75.8)	225 (59.1)	47 (62.7)	153 (56.0)	25
E4 (15.2)	101 (26.5)	16 (21.3)	80 (29.3)	5
Missing	11 (2.9)	0 (0)	11 (4.0)	
Delayed Sternal Closure				
No	340 (89.2)	62 (82.7)	248 (90.8)	30 (0.9)
Yes	41 (10.8)	13 (17.3)	25 (9.2)	3 (9.1)
Intubation requirement before surgery				
No (60.6)	264 (69.3)	50 (66.7)	194 (71.1)	20
Yes (39.4)	117 (30.7)	25 (33.3)	79 (28.9)	13
<i>Additional Operations</i>				
None (57.6)	226 (59.3)	42 (56.0)	165 (60.4)	19
1 (21.2)	46 (12.1)	12 (16.0)	27 (9.9)	7
2 or more (21.2)	109 (28.6)	21 (28.0)	81 (29.7)	7
ECMO and/or LVAD				
Yes (3.0)	9 (2.4)	3 (4)	5 (1.8)	1
No (97.0)	372 (97.6)	72 (96.0)	268 (98.2)	32

Table 2

Single and Multiple Covariate Risk Factor Models for HL

Potential Risk Factors	Single Covariate Models				Best Fitting Multiple Covariate Model			
	β Coef	SEM	Wald χ^2	p-Value	β Coef	SEM	Wald χ^2	p-Value
<i>Patient-related Factors</i>								
Age at Testing (yr)	0.37	0.65	0.33	0.56				
Age at 1 st Surgery (d)	-0.00 *	0.00 *	1.64	0.20				
Birth Head-Circumference (cm)	-0.07	0.06	1.02	0.31				
Birthweight (kg)	-0.29	0.22	1.78	0.18				
Gestational Age (term)	-0.49	0.17	8.69	<0.01	-0.38	0.18	4.52	0.03
Sex (male)	0.01	0.13	0.01	0.93				
Race								
Black	-0.83	0.39	4.66	0.03				
White (Reference)								
Other	-0.19	0.42	0.21	0.65				
Maternal Education								
Less than high school (Reference)								
High school/Some college	-0.21	0.26	0.65	0.42				
College	-0.05	0.27	0.04	0.85				
Graduate	-0.38	0.30	1.65	0.20				
Socioeconomic Status								
Professional	0.86	0.85	1.03	0.31				
Medium Business	0.06	0.46	0.02	0.90				
Skilled/Clerical	0.11	0.34	0.11	0.74				
Semi-skilled	0.29	0.30	0.92	0.34				
Unskilled (Reference)								
Diagnostic Class								
2 Ventricles, No Arch Obstruction (Reference)								
2 Ventricles, Arch Obstruction	0.54	0.39	1.95	0.16				
1 Ventricle, No Arch Obstruction	0.50	0.44	1.31	0.25				
1 Ventricle, Arch Obstruction	-0.08	0.32	0.06	0.81				

Potential Risk Factors	Single Covariate Models				Best Fitting Multiple Covariate Model			
	β Coef	SEM	Wald χ^2	p-Value	β Coef	SEM	Wald χ^2	p-Value
Genetic Anomaly								
Normal (Reference)								
Suspected	0.37	0.35	1.10	0.30	-0.90	0.61	2.17	0.14
Confirmed	-0.88	0.27	10.69	< 0.01	1.39	0.41	11.33	< 0.01
APOE Genotype								
$\epsilon 2$	0.37	0.38	0.93	0.34				
$\epsilon 3$ (Reference)								
$\epsilon 4$	-0.36	0.32	1.26	0.26				
Number of Additional Operations								
0 (Reference)								
1 Operation	0.36	0.25	2.10	0.15				
2 or More Operations	-0.17	0.41	0.69	0.40				
<i>Peri-operative factors</i>								
Hematocrit	-0.04	0.03	1.83	0.18				
Bypass Time, 1 st Operation	-0.00 *	-0.00 *	1.05	0.31				
Total Bypass Time (4yr evaluation)	0.00 *	0.00 *	0.13	0.72				
DHCA Time, 1 st Operation	0.01	0.00 *	1.15	0.28				
Total DHCA time (4yr evaluation)	-0.00 *	0.00 *	0.12	0.73				
Delayed Sternal Closure	0.37	0.18	3.91	0.05				
Intubation	0.10	0.14	0.54	0.46				
Pre-op LOS	0.03	0.04	0.58	0.45				
Post-op LOS	0.02	0.01	7.61	< 0.01	0.03	0.02	3.95	0.05
Post-op LOS * Genetic Anomaly								
LOS * Normal (Reference)					0.03	0.03	1.33	0.25
LOS * Suspected								
LOS * Confirmed					-0.04	0.02	4.86	0.03
Intercept					-1.17	0.36		

Notes. N = 348, Hearing Loss (n = 75), No Hearing Loss (n = 273), SEM = standard error of measurement, LOS = Length of Stay, ECMO/LVAD information was not analyzed using a logistic model due to insufficient cell sizes. For the ECMO/LVAD, a Fisher's Exact Test was used ($p = 0.37$).

* Although two decimal places are used throughout for editorial consistency, additional decimal places are needed for more accurate specificity and will be provided upon request.