Earlier stage 1 palliation is associated with better clinical outcomes and lower costs for neonates with hypoplastic left heart syndrome

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Objectives: Our aim was to examine the effects of surgical timing on major morbidity, mortality, and total hospital reimbursement for late preterm and term infants with hypoplastic left heart syndrome (HLHS) undergoing stage 1 palliation within the first 2 weeks of life.

Methods: We conducted a retrospective cohort study of infants aged ≥35 weeks gestation, with HLHS, admitted to our institution at age ≤5 days, between January 1, 2003, and January 1, 2013. Children with other cardiac abnormalities or other major comorbid conditions were excluded. Univariable and multivariable analyses were performed to determine the association between age at stage 1 palliation and major morbidity, mortality, and hospital reimbursement.

Results: One hundred thirty-four children met inclusion criteria. Mortality was 7.5% (n = 10). Forty-three percent (n = 58) experienced major morbidity. Median costs were $97,000, in 2013 dollars (interquartile range, $72,000-$151,000). Median age at operation was 5 days (interquartile range, 3-7 days; full range, 1-14 days). All deaths occurred in patients operated on between 4 and 8 days of life. For every day later that surgery was performed, the odds of major morbidity rose by 15.7% (95% confidence interval, 2.5%-30.7%; $P = .018$) and costs rose by 4.7% (95% confidence interval, 0.9%-8.2%; $P < .014$).

Conclusions: Delay of stage 1 palliation for neonates with HLHS is associated with increased morbidity and health care costs, even within the first 2 weeks of life. (J Thorac Cardiovasc Surg 2015;149:205-10)

See related commentary on pages 211-2.

Supplemental material is available online.

Despite significant improvements over the past 2 decades, morbidity and mortality for children with hypoplastic left heart syndrome (HLHS) undergoing stage 1 palliation (S1P) remain high.[1,2] A handful of studies have reported improved morbidity and mortality with earlier age at operation, yet these studies have generally compared standard care to late interventions (after 1-4 weeks).[3-5] It is not known if timing of operation affects clinical outcomes for children with HLHS undergoing routine care. In addition, whereas HLHS is the most expensive birth defect managed in the United States,[6,7] it is not known what effect surgical timing has on costs. We sought to determine the association between the timing of neonatal S1P and mortality, major morbidity, and total in-patient hospital costs, for late preterm and term infants with HLHS.

METHODS

Patients

We performed a retrospective cohort study, including all children aged ≥35 weeks gestation with HLHS admitted to NewYork-Presbyterian/Morgan Stanley Children's Hospital of Columbia University, at age ≤ 5 days, between January 1, 2003, and January 1, 2013. HLHS was defined as a diminutive left ventricle in association with atresia or hypoplasia of the mitral and aortic valves.[8] Children with aortic stenosis or atresia who had adequate left ventricles (such as double inlet left ventricle), as well as those with right-sided disease (such as pulmonary atresia with intact ventricular septum), adequate aortic outflow tracts (such as transposition of the great arteries with mitral atresia), atrioventricular or visceroatrial discordance, total anomalous pulmonary venous return, or atrioventricular septal defects were excluded, even if they underwent single-ventricle palliation. Children were further excluded if they had other major comorbid conditions, were discharged to home before admission to our institution, were taken to the operating room within the first 48 hours of life for a restrictive atrial septum, had positive blood cultures within the first 72 hours of life, or underwent an initial surgery other than the Norwood or Damus-Kaye-Stansel. This study was approved by the Columbia

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication March 25, 2014; revisions received July 1, 2014; accepted for publication July 18, 2014; available ahead of print Sept 16, 2014.

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0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2014.07.094

Abbreviations and Acronyms
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
HLHS = hypoplastic left heart syndrome
S1P = stage 1 palliation

University Medical Center Institutional Review Board, with waiver of informed consent.

Predictor Variables

The primary predictor of interest was age at operation (in days). Demographic variables included sex, birth weight (in kilograms), term gestation (≥37 completed weeks), year of surgery (to reflect surgical era), insurance type (Medicaid or other), and day of the week of birth. Anatomic variables included anatomic subtype (eg, mitral atresia/aortic stenosis, mitral stenosis/aortic stenosis, mitral stenosis/aortic atresia, or mitral atresia/aortic atresia), partial anomalous pulmonary venous return, preoperative tricuspid regurgitation (≥moderate), preoperative right ventricular dysfunction (≥moderate), and the presence of coronary fistulae. Other clinical variables included prenatal diagnosis, transfer from an outside hospital, preoperative diagnostic or therapeutic catheterization, preoperative mechanical ventilation, surgeon, shunt type, and cardiopulmonary bypass (CBP), crossclamp, and deep hypothermic circulatory arrest (DHCA) times. Day of birth was considered in 2 ways. First, it was included in the analysis as a set of 6 indicator variables, with Sunday serving as the reference. Then, it was dichotomized to indicate weekday or weekend (Saturday through Sunday) birth, after examining trends in the association with admission day and morbidity, mortality, and costs.

Surgical Technique and Perioperative Management

All patients were admitted preoperatively and managed postoperatively in the cardiac neonatal intensive care unit. All children received preoperative echocardiograms. The majority received prostaglandin E1. Patients underwent interventional catheterizations for restrictive atrial septum based on the clinical judgment of the inpatient cardiologists; no prespecified atrial gradient was used as a criterion.

All operations were performed by 1 of 4 surgeons at NewYork-Presbyterian/Morgan Stanley Children's Hospital, with an uneven distribution of cases (see Results). In the operating room, all patients underwent median sternotomy, hypothermic CBP, and aortic crossclamp with cold cardioplegic arrest and various amounts of DHCA. All children returned to the neonatal intensive care unit intubated and sedated, on inotropic support as determined by the anesthesiologist.

Primary Outcomes

We considered the primary outcomes of mortality, major morbidity, and costs. Mortality was defined as all-cause mortality before hospital discharge, not limited to 30 days. There was only 1 patient who underwent cardiac transplantation during initial hospitalization. This patient died before discharge and, therefore, was included in the analysis of mortality. Major morbidity was defined as cardiac arrest, extracorporeal membrane oxygenation, systemic infection, necrotizing enterocolitis, seizure, stroke on magnetic resonance imaging with clinical sequellae, postoperative catheterization before discharge, reoperation before discharge, readmission at ≤30 days, or transplant. All patients who died experienced a morbidity before death, and therefore were included in the analyses of major morbidity. Costs were defined as total inpatient hospital reimbursement, based on individual billing records, to most accurately reflect societal costs. All costs were adjusted to January 2013 dollars using the Medical Consumer Price Index (http://www.bls.gov/cpi/#tables). Costs did not include outpatient expenses or physician reimbursement.

Statistical Analysis

All statistical analyses were conducted in SPSS Statistics 21.0 (IBM-SPSS Inc, Armonk, NY) or Stata software, version 13 (StataCorp, College Station, Tex). Clinical and demographic variables were described with standard summary statistics. To assess the marginal associations between predictor variables and mortality or major morbidity, χ^2 or Fisher exact tests were used for categorical variables, and t tests or Wilcoxon rank sum tests were used for continuous variables. To assess the marginal associations between the predictor variables and adjusted costs, Wilcoxon rank sum or Kruskal-Wallis tests were used for categorical variables and Spearman correlations were used for continuous variables.

We hypothesized that the relationship between major morbidity or mortality and age at operation might not be linear. Locally weighted scatterplot smoothing (lowess) was used to determine an appropriate scale to use for age at operation in each model. It was determined that the association between the log odds of mortality and age at operation was best modeled by a quadratic function centered at 5.12 days, whereas the association between the log odds of morbidity and age at operation was best modeled by a linear function.

For major morbidity and mortality, logistic regression models were fit, using generalized estimating equations with exchangeable working correlation structure, to account for possible correlation between children operated on by the same surgeon. Because so few patients in our cohort died, rather than fitting a potentially large multivariable model, we constructed a simpler exploratory model that included only age at operation and age at operation squared. For costs, a linear mixed effects model was first fit to account for possible correlation between children operated on by the same surgeon. The variance component corresponding to the random intercept was estimated to be 0, suggesting that a model without the random intercept was more appropriate. A linear regression model, therefore, was fit for costs, where age at operation was automatically included in the model. To account for the right-skewed nature of costs, costs were log-transformed before entering them into the models, and the top 5% of costs were considered extreme outliers and excluded. Because some children with HLHS undergoing S1P die before discharge and because costs do not accrue postmortem, standard linear regression might incompletely capture the costs to society. Therefore, we also estimated censored regression models that censored the log of costs for patients who died. To examine the influence that small numbers of patients at the tail ends of the distribution for age might have on the results, sensitivity analyses were performed, rerunning multivariable models on the subset of the cohort operated on between the fifth and 95th percentiles for age at operation.

Final multivariable models were determined via a forward stepwise procedure, where age at operation was automatically included in the models. Variables with P values ≤.10 in univariable analyses were evaluated together in multivariable analyses. Other variables were only retained in the final models if their P values met the significance criterion or if their inclusion changed the magnitude of the coefficients for age at operation by ≥10%.

RESULTS

One hundred thirty-four infants met our inclusion criteria. There was a slight male predominance (63% boys). Mean birth weight was 3.10 ± 0.47 kg. The majority of children were born at ≥37 weeks completed gestation (71.3%). Fifty percent of children were covered by