Longitudinal Assessment of Outcome From Prenatal Diagnosis Through Fontan Operation for Over 500 Fetuses With Single Ventricle-Type Congenital Heart Disease: The Philadelphia Fetus-to-Fontan Cohort Study

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Background—Prenatal diagnosis of single ventricle–type congenital heart disease is associated with improved clinical courses. Prenatal counseling allows for optimal delivery preparations and opportunity for prenatal intervention. Expectant parents frequently ask what the likelihood of survival through staged palliation is and the factors that influence outcome. Our goal was specifically to quantify peri- and postnatal outcomes in this population.

Methods and Results—We identified all patients with a prenatal diagnosis of single ventricle–type congenital heart disease presenting between July 2004 and December 2011 at our institution. Maternal data, fetal characteristics, and data from the postnatal clinical course were collected for each patient. Kaplan–Meier curves and multivariate analysis with logistic regression were used to evaluate variables associated with decreased transplant-free survival. Five hundred two patients were identified, consisting of 381 (76%) right ventricle– and 121 left ventricle–dominant lesions. After prenatal diagnosis, 42 patients did not follow up at our center; 79 (16%) chose termination of pregnancy, and 11 had intrauterine demise with 370 (74%) surviving to birth. Twenty-two (6%) underwent palliative care at birth. Among 348 surviving to birth with intention to treat, 234 (67%) survived to at least 6 months post-Fontan palliation. Presence of fetal hydrops, right ventricle dominance, presence of extracardiac anomalies, and low birthweight were significantly associated with decreased transplant-free survival.

Conclusions—In patients with a prenatal diagnosis of single ventricle–type congenital heart disease and intention to treat, 67% survive transplant-free to at least 6 months beyond Fontan operation. An additional 5% survive to 4 years of age without transplant or Fontan completion. Fetuses with right ventricle–dominant lesions, extracardiac anomalies, hydrops, or low birthweights have decreased transplant-free survival. (*J Am Heart Assoc*. 2018;7:e009145. DOI: 10.1161/JAHA.118.009145.)

Key Words: fetal • fetal echocardiography • outcomes research • risk factor • single ventricle

Single ventricle–type congenital heart disease (SVCHD) consists of a spectrum of malformations in which there is significant hypoplasia of either the right or left ventricle with no

anatomical or functional capacity for viability of a 2-ventricle system. Left to its natural course, the condition is lethal in most circumstances. A surgical strategy has evolved over the past 40 years that allows for survival. Staged palliative surgery culminating in the Fontan operation can be undertaken in which the guiding principle is to assign the task of systemic perfusion to the single ventricle while creating a passive pathway for systemic venous return to the pulmonary circulation. Outcomes of individual aspects of staged palliation for SVCHD are well characterized, and long-term survival has increased following improvements in surgical technique and postoperative management.[1–4] Despite the tremendous challenge and effort necessary to create good outcomes for these complex and fragile patients, survival rates at 5 years of age are now reported to approach 70% for patients with hypoplastic left heart syndrome (HLHS) and are slightly higher for patients with dominant single left ventricular (LV) morphology.[5–8]

The changing outcome statistics for SVCHD can be best understood within the context of current advances in

medicine overall. Today, the most common means of initial detection of SVCHD has shifted from identification of neonatal signs of decompensation to prenatal detection in utero. Improvements in obstetrical ultrasound have enabled increased diagnosis of cardiac anomalies in utero, and SVCHD is known to have among the highest prenatal detection rates within congenital heart disease.[9–12] Prenatal diagnosis is associated with a number of benefits, including improved preoperative clinical status before initial surgery, shorter postoperative mechanical ventilator support, and improved long-term neurological outcomes when compared with those diagnosed after birth.[11,13,14] Counseling before birth allows for parental education and preparation for delivery at high-volume tertiary care centers that can provide optimal neonatal management.[15] Infants with a prenatal diagnosis of SVCHD demonstrate improved myocardial function and increased survival following initial surgery.[13,16] In contrast, fetal diagnosis may also increase the viability of newborns with extracardiac risk factors, given that these high-risk patients may not have previously survived to neonatal identification before the era of prenatal diagnosis and fetal care. Despite this shift toward prenatal diagnosis and the likely impact of fetal detection on overall outcome, survival outcomes for prenatally diagnosed patients beyond the initial palliative procedures are not well characterized and have only recently become a subject of study.[17]

Today, prenatal diagnosis is the most common and desired path of entry into the system of care for patients with SVCHD. At prenatal counseling, expectant parents frequently ask:

(1) What is the likelihood that our fetus with SVCHD will be alive after completion of all stages of surgical reconstruction?; and (2) What are the factors that influence the outcome? The purpose of our study is to answer these fundamental questions through longitudinal analysis of a large, single-center cohort of patients prenatally diagnosed with SVCHD. We also characterize outcomes from the earliest point of detection in fetal life through completion of anticipated surgical palliation after Fontan operation.

Methods

Data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The database at the Fetal Heart Program at the Children's Hospital of Philadelphia (CHOP) was searched to identify all patients with a prenatal diagnosis of SVCHD presenting between July 2004 and December 2011. Inclusion diagnosis of SVCHD was determined based on the impression formed by the attending faculty fetal cardiologist who interpreted the fetal echocardiogram and counseled the family. This decision was made because of the fact that some cases may present as borderline between 1- or 2-ventricle-type heart disease, and there are no strict criteria for differentiating these.[18,19] Serial fetal imaging and counseling took place, with multiple assessments performed during the pregnancy in most cases. The fetal cardiologist determined that an SVCHD strategy resulting in a Fontan operation was *strongly* likely as the postnatal management plan, at the latest, by the final fetal encounter before delivery. The time frame of up to 2011 was chosen in order to provide a contemporary cohort for longitudinal analysis from prenatal diagnosis through potential completion of staged palliation with a Fontan operation, which, in our center, typically occurs at ≈2 to 3 years of age.

Approval was obtained through the CHOP Institutional Review Board (CHOP IRB # 15-012216 CR1) for this investigation. The requirement of informed consent was waived. SVCHD included both dominant right ventricular (RV) and dominant LV lesions. Examples of dominant single LV lesions include: double-inlet left ventricle, tricuspid atresia with D-looped ventricles, pulmonary atresia with intact ventricular septum, single left ventricle, and unbalanced atrioventricular canal to the left ventricle. Examples of dominant single RV lesions include: HLHS and unbalanced atrioventricular canal to the right ventricle. Patients presenting with heterotaxy syndrome were characterized according to morphology of the ventricle most likely associated with the aorta and thus assigned the task of perfusing the systemic circulation. All patients included in the study underwent at least 1 complete fetal echocardiogram. Fetuses deemed to have mild ventricular size discrepancies or considered

promising candidates for biventricular repair were excluded. Patients were also excluded if they presented with a prenatal diagnosis from an outside institution or were diagnosed with SVCHD postnatally without prenatal detection.

Maternal variables collected for analysis include maternal age at the time of diagnosis, gravidity and parity, and the presence of singleton pregnancy or multiple gestation. Fetal variables include gestational age at time of initial diagnosis, presence of genetic or chromosomal abnormalities, presence of extracardiac anomalies, heterotaxy syndrome, hydrops, cardiac diagnosis, ventricular systolic dysfunction, atrioventricular valvar regurgitation (based on fetal echocardiogram report), and the presence of fetal arrhythmia. Variables selected as potential risk factors are based on experience and previously reported observations.[20,21] Diagnoses from fetal echocardiography were confirmed by review of postnatal echocardiogram reports. For infants surviving to birth with intention to treat, we collected postnatal variables, including gestational age at birth, birthweight, sex, and type of surgery performed at each stage of palliation. Because not all prenatally diagnosed SVCHD patients went on to have typical staged surgical repair, we broadly defined a "first surgical intervention" or "first operation" to include stage 1 Norwood procedures, aorto-pulmonary shunt only without a Damus–Kaye–Stansel, pulmonary arterial banding, and hybrid procedures. The hybrid procedure was defined by bilateral pulmonary artery band placement and ductal stenting, as an alternative means of providing unobstructed systemic outflow and limited pulmonary blood flow. Second-stage surgical palliations included bidirectional Glenn, bilateral bidirectional Glenn, Kawashima, and hemi-Fontan procedures.[22] Third-stage surgeries included extracardiac conduit and lateral tunnel–type Fontan operations. Additional variables known to affect survival outcome were also collected. Specifically, use of extracorporeal membrane oxygenation post-operatively at any stage, presence of postoperative ventricular dysfunction or AV valve regurgitation, the need for additional cardiac catheterizations outside of anticipated diagnostic preoperative assessment, and any surgeries outside of anticipated staged palliation were variables included in the multivariate analysis.

Analysis was performed for 2 cohorts: (1) all patients presenting with prenatally diagnosed SVCHD and (2) infants who survived to live birth, with intention to treat. Among the entire cohort of patients presenting with prenatally detected SVCHD, outcomes were defined by 4 categories: elective termination of pregnancy (TOP), intrauterine fetal demise, survival to live birth with nonintervention palliative care in which prostaglandin infusion is not administered, and survival to live birth with intention to treat. For infants who survived with intention to treat, the primary outcome was defined as transplant-free survival. Patients who only had one fetal echocardiogram with no further follow up clinical encounters at CHOP were considered lost to follow-up, which we state as having "no follow-up" in the fetal period. Patients who underwent initial postdelivery care or surgical palliation, but who did not receive further care at our center, were considered to have no follow-up in the postnatal period and were censored in the survival analysis as described below.

Statistical Analysis

Descriptive statistics are reported for demographic data and clinical measures. Survival analysis was performed on only patients who survived to birth with intention to treat (n=348). Kaplan–Meier survival curves and log-rank tests were generated to assess the univariate association between time to death or transplant and each of the categorical variables, which were summarized as n (%). Simple Cox regression tests were used to test the bivariate association between time to death or transplant and each of the continuous variables, summarized as median (range). Patients lost to follow-up in the postnatal period were censored at their last known clinical encounter at our institution. Patients surviving to 6 months post-Fontan were censored at that point, and patients on nontraditional surgical pathways were censored at 4 years of age. The 6-month post-Fontan censorship age was used to (1) ensure any adverse postoperative outcomes were captured and (2) maximize the number of patients included in this study who had reached the generally accepted time of 6 months after surgery, by which point full recovery is anticipated. The censorship age of 4 years of age for the nontraditional pathway patients not leading to Fontan completion was selected because it is the approximate average age at which the SVCHD patients were 6 months post-Fontan operation. The variables that were significant at the $P \leq 0.05$ level in univariate analysis were then entered into the final multivariate Cox regression model. Statistical tests were based on a two-tailed test at a 0.05 significance level. All statistical analysis was performed using SAS software (version 9.2; SAS Institute Inc, Cary, NC).

Results

Patient Characteristics

Between July 2004 and December 2011, a total of 502 fetuses with a prenatal diagnosis of SVCHD were evaluated at the Fetal Heart Program at CHOP. HLHS was the most common diagnosis, accounting for 43% of fetuses (Table 1) and 24% were LV dominant lesions, with tricuspid atresia the most common subtype. Median maternal age at fetal diagnosis was 30.1 years, with a range of 15.7 to 46.0 years. Median gestational age at fetal diagnosis was 24.0 weeks,

Table 1. Anatomical Distribution of Single Ventricle Anatomy

Diagnosis	n (%)
HLHS	215 (43)
Unbalanced CAVC to right	57 (11)
Other right-dominant single ventricle	109 (22)
Tricuspid atresia	41 (8)
Double inlet left ventricle	21 (4)
Pulmonary atresia with intact ventricular septum	6 (1.2)
Single left ventricle	2 (<1)
Unbalanced CAVC to left	5 (1)
Other left-dominant single ventricle	46 (9)

CAVC indicates common atrioventricular canal; HLHS, hypoplastic left heart syndrome.

with a range 13.9 to 38.7 weeks. Thirty-six of 502 mothers (7%) had twin gestations; in all cases, only 1 fetus had congenital heart disease. Heterotaxy occurred in 72 patients (14%), with asplenia present 57% of the time. Chromosomal abnormalities were detected in 45 fetuses (9%) and extracardiac abnormalities in 99 cases (20%). Hydrops was noted in 8 fetuses (1.6%). In terms of fetal arrhythmia, third-degree heart block was present in 10 cases, sinus bradycardia in 4, and ventricular tachycardia in 1 case. Incidence of significant fetal ventricular dysfunction or AV valvar regurgitation was relatively low (Table 2); 37 patients (7%) had moderate or severe AV valve regurgitation, and only 6 (1%) had moderate or severe ventricular dysfunction. Among the fetuses with moderate or severe ventricular dysfunction, 3 (50%) had RV dominant lesions. Among those with moderate-to-severe AV valve regurgitation, 33 of 37 patients (89%) had RV dominant lesions. Notably, a total of 8 of the 37 patients also had heterotaxy.

Table 2. Fetal Echocardiogram Functional Characteristics

	n (%)
Atrioventricular valvar regurgitation	
None/trivial	404 (81)
Mild	61 (12)
Moderate	30 (6)
Severe	7 (1)
Ventricular dysfunction	
None	492 (98)
Mild	4 (1)
Moderate	4 (1)
Severe	2 (<1)

Perinatal Outcomes

Of the 502 initial patients, 42 had no follow-up at our institution. Details of the longitudinal outcomes are illustrated in Figure 1. Of the 460 with follow-up, 11 fetuses (2.4%) had intrauterine fetal demise (clinical features are characterized in Table S1). Of 251 mothers diagnosed before 24 weeks gestation, 79 (31%) opted for TOP. Mean gestational age at birth was 38.1 weeks (median, 38.6; range, 26.0–41.6). Of the 370 fetuses surviving to birth, nonintervention palliative care was elected in 22 cases (6%). Clinical characteristics of the fetuses that received palliative care with no intervention are listed in Table S2. Twelve patients with intention to treat died before initial operation (3.4%). A majority of these 12 patients had high-risk hypoplastic left heart lesions or variants thereof (Table S3). Of the 348 patients delivered with intention to treat, there were 5 patients at birth with balanced circulations and no requirement for neonatal surgical interventions, 3 of which survived and 2 who died (Table S4). Additionally, 2 patients underwent biventricular repair, and 1 patient underwent primary orthotopic heart transplant (OHT).

Operative Outcomes

Distribution of operations for each stage are listed in Table 3. A total of 325 patients survived and underwent a first-stage operation. Of these, 41 (12.6%) did not survive to the second stage, and 4 patients underwent OHT. Of the 41 deaths, 14 of these patients died within 7 days of the first-stage operation from associated complications. Three patients who underwent a first operation subsequently underwent biventricular repair, after initial aorto–pulmonary shunt placement. Five patients had no further follow-up at our institution.

Two hundred seventy-two patients proceeded to a second-stage operation. Death between stage 2 and planned stage 3 operations occurred in 19 patients (7%). Two patients had takedown of their superior cavopulmonary anastomoses and conversion to biventricular circulations. There were 2 cases of heterotaxy syndrome, unbalanced common atrioventricular canal, double outlet right ventricle with pulmonary stenosis, and satisfactory oxygen saturations in the 88% to 90% range and are left with superior cavopulmonary (Glenn) physiology. In 3 cases, the decision was made not to proceed with Fontan operation secondary to significantly elevated pulmonary vascular resistances. Four patients underwent OHT. The clinical course of all patients receiving OHT from birth through stage 3 is characterized in Table S5. Eight further patients had no follow-up. A total of 234 patients underwent Fontan operation; average age at time of operation was 3.6±0.9 years.

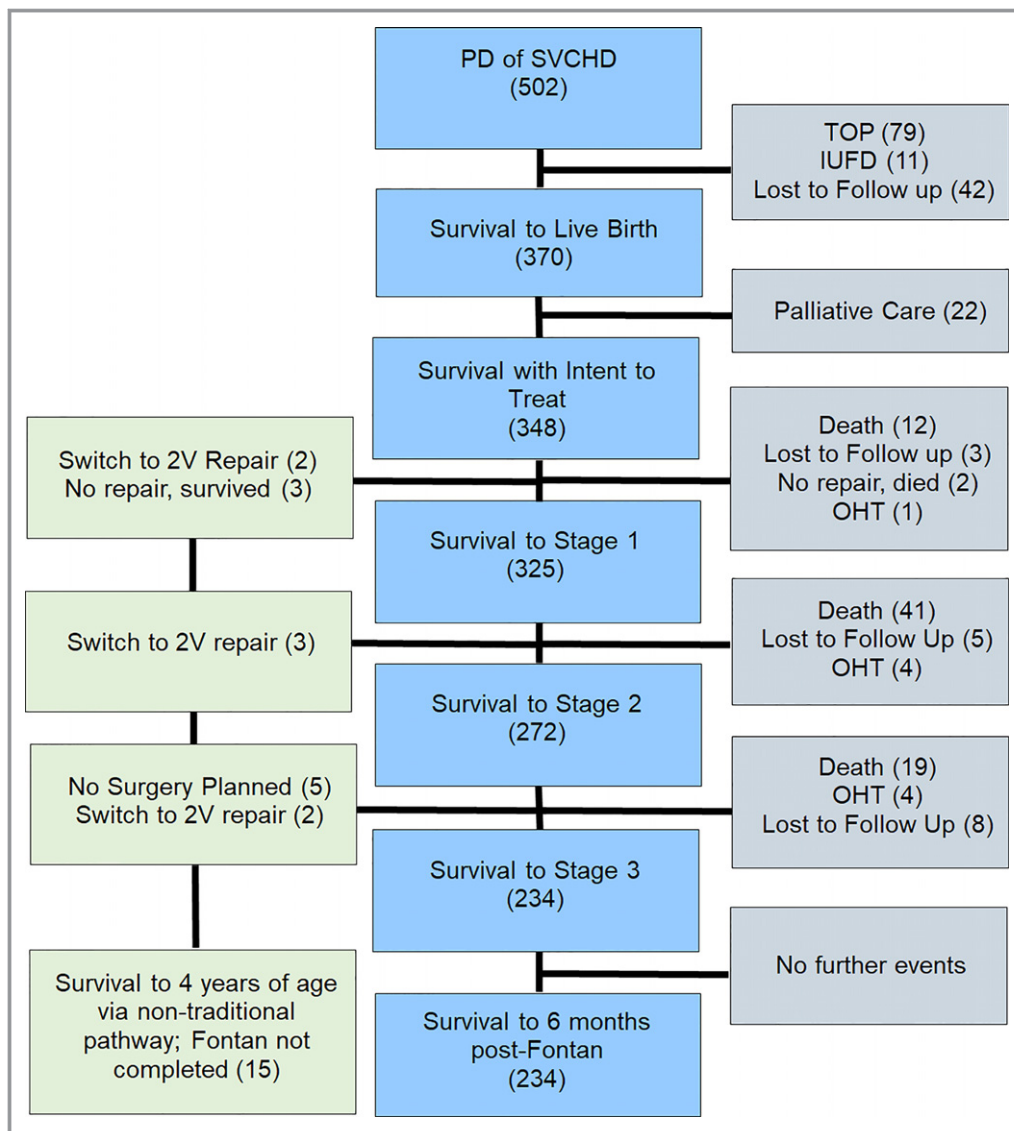Of 502 fetuses with SVCHD, 348 survived to birth with intention to treat, and of these, 234 patients (67%) were alive

Figure 1. Longitudinal outcomes of all prenatally diagnosed fetuses with single ventricle–type congenital heart disease (SVCHD). 2V indicates biventricular; IUFD, intrauterine fetal demise; OHT, orthotopic heart transplant; PD, prenatal diagnosis; TOP, termination of pregnancy.

at least 6 months after their Fontan operation. There were 15 other patients who survived to 4 years of age (3 had balanced circulations without any intervention, 7 had biventricular repairs, and 5 were status post superior cavopulmonary anastomosis without plans for Fontan). This indicates a total of 72% overall transplant-free survival for the intention-to-treat cohort (Figure 2).

Prenatal Risk Factors

Survival analysis was performed using the cohort of fetuses who survived to live birth with intention to treat (n=348). Upon univariate analysis, several prenatal variables were identified as risk factors (Table S6). Fetal cardiac function was strongly associated with hydrops ($P<0.0001$). Because only 8 patients had greater than mild ventricular dysfunction, we excluded this variable from multivariate analysis. Likewise, the presence of a genetic syndrome was dropped from multivariate analysis, because it was strongly associated with extracardiac defects ($P<0.0001$) and birthweight ($P=0.005$).

Multivariate analysis using the significant prenatal variables as well as the aforementioned postnatal variables was performed. Clinical characteristics of the patients who underwent extracorporeal membrane oxygenation at any point and those who had moderate-to-severe ventricular dysfunction or AV valve regurgitation are described in Table S7. This analysis demonstrated that the presence of hydrops, RV dominance, presence of extracardiac anomalies,

Table 3. Distribution of Surgery Type by Stage

	n (%)
Type of first operation	
BT shunt only	53 (16)
PA Band	22 (7)
Stage 1 Norwood with BT shunt	171 (52)
Stage 1 Norwood with Sano modification	45 (14)
Hybrid procedure	7 (2)
Other	27 (8)
Type of second operation	
Bidirectional Glenn	171 (63)
Bilateral Bidirectional Glenn	21 (8)
Hemi-Fontan	61 (22)
Kawashima procedure	9 (3)
Other	10 (4)
Type of third operation	
Extracardiac conduit Fontan	173 (74)
Lateral tunnel Fontan	60 (25)
Other	1 (<1)

BT indicates Blalock–Taussig; PA, pulmonary artery.

Table 4. Multivariate Analysis of Risk Factors Associated With Death/Transplant

Parameter	Hazard Ratio	P Value
Multiple gestation	1.23 (0.5–2.8)	0.62
Presence of hydrops	7.40 (1.7–33.0)	0.01*
RV vs LV dominance	2.38 (1.3–4.4)	0.01*
Extracardiac anomalies	2.12 (1.2–3.6)	0.01*
Low birth weight	1.87 (1.3–2.7)	0.001*
Additional surgeries before/after S1	1.04 (0.7–1.5)	0.86
Catheterization: birth to S1 discharge	1.05 (0.8–1.3)	0.7
ECMO immediately after S1	4.49 (2.2–9.0)	<0.001*

ECMO indicates extracorporeal membrane oxygenation; LV, left ventricle; RV, right ventricle; S1, first stage.
*Statistically significant *P*-values.

after the first surgery were not associated with increased risk of death or transplant.

Discussion

Care for SVCHD starts in prenatal life at the time of ultrasound diagnosis. The hurdles of surgical reconstruction and the challenges of life with a Fontan circulation lead some families to consider termination.[23] As expectant parents consider their options, a common inquiry at prenatal counseling relates to the likelihood of survival through all stages of anticipated surgical reconstruction and what factors contribute to mortality.

Our study offers the benefits of reporting on a large cohort followed longitudinally through multiple nodes of clinical management from a single center with an experience of focused care for SVCHD, thus with relative minimal practice variability. Our contemporary overall transplant-free survival rate (includes 234 Fontan patients and 15 other transplant-free survivors) of 72% in patients with intention to treat is relatively improved compared with studies published in earlier eras.[2,24,25] In addition, we found the incidence of ventricular dysfunction, hydrops, and intrauterine fetal demise to be low. The likelihood of a fetus diagnosed with SVCHD surviving to a viable gestational age is high; however, a number of factors contribute to the potential for postnatal survival.

Rates for termination of pregnancy in HLHS and, more broadly, SVCHD fetuses are variable and multifactorial throughout the world.[17,26,27] Our institution is a large referral center both for prenatal evaluation of complex heart disease and postnatal intervention, likely contributing to a bias toward intention to treat in our overall cohort. Overall termination of pregnancy occurred in 79 subjects of 460 for which there is follow-up (17%); however, of those presenting before 24 weeks gestation, TOP was chosen in approximately one

extracorporeal membrane oxygenation immediately after the first surgical procedure, and low birthweight had a lower rate of transplant-free survival (Table 4). Patients with dominant RV morphology had a lower transplant-free survival rate than those with dominant LV morphology (Figure 3; *P*=0.002), as did patients with extracardiac anomalies versus those without (Figure 4; *P*<0.0001). Notably, unanticipated additional surgeries and number of catheterizations from birth to discharge
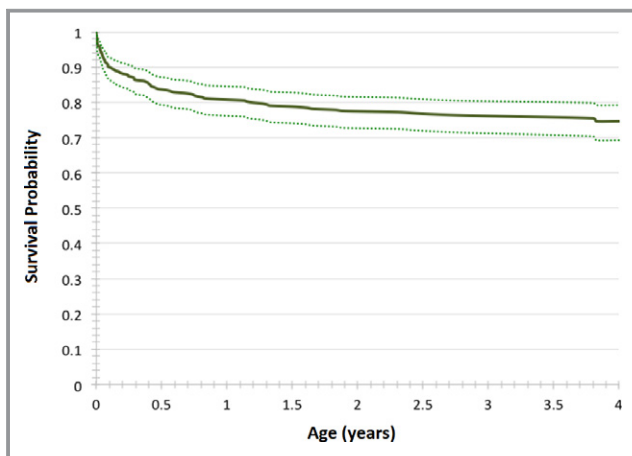

Figure 2. Kaplan–Meier survival curve for overall survival of fetuses with single ventricle-type congenital heart disease with intention to treat.
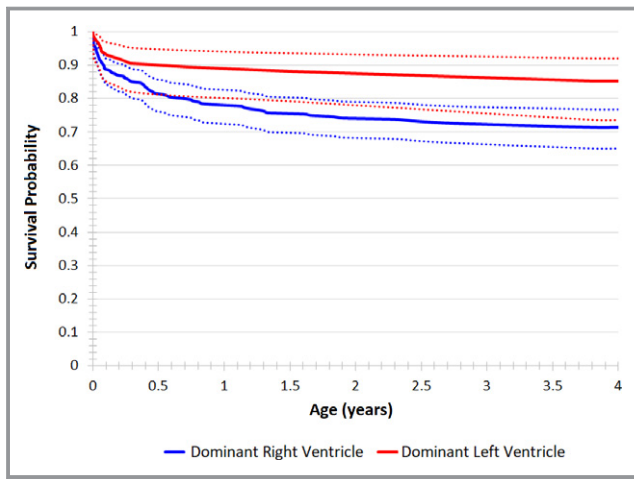
Figure 3. Kaplan–Meier survival curves for dominant right ventricle vs dominant left ventricle anatomy.
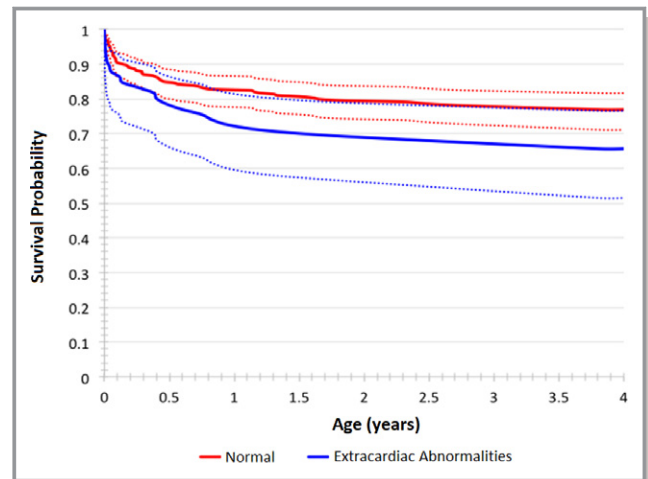

Figure 4. Kaplan–Meier survival curves in patients with extracardiac defects vs without.

third of patients (31%) and nonintervention palliative care in 6%. Fetal diagnosis and transitional care can influence the subsequent course and may offer additional benefits to preoperative survival. All subjects were provided comprehensive fetal care within a single center, with >90% delivering at the Special Delivery Unit at CHOP and the remainder at the adjacent University of Pennsylvania. Thus, our study demonstrates that despite prenatal knowledge of SVCHD, anticipatory planning, optimizing care with little practice variability, and single-team clinical management oversight, a small number (3.4%) will not survive to receive an operation.

Mortality occurs early in the course of care around initial surgery and in the interstage period between stage 1 and stage 2. The interstage period accounted for the largest proportion of deaths by time period, with 12% (41 of 348 patients delivered with intention to treat) expiring in this period. When we look at outcomes at 12 months of life, 64 patients (18%) expired or underwent OHT. In the landmark Single Ventricle Reconstruction trial looking at HLHS patients, rate of death or transplantation at 12 months was 25.6% in the Sano group and 37.3% in the Blalock–Taussig shunt group.[28] Although the superior cavopulmonary circulation is known to be a relatively stable physiology with low mortality rates, 19 of our patients died in this time frame. Operative mortality was low, consistent with previous studies.[29] However, we do cite higher long-term mortality after the second stage, which is likely attributable to the high-complexity patient population typical of a quaternary care center. Over half of these patients developed severe ventricular dysfunction and/or AV valve regurgitation.

We sought to determine risk factors for mortality in our cohort population. Fetuses with RV-dominant lesions, hydrops, extracardiac manifestations, and low birthweights are less likely to experience transplant-free survival to

6 months after Fontan operation in patients undergoing single ventricle palliation or to 4 years of age in nontraditional interventional pathways not leading to Fontan completion. The extracardiac manifestations, which were strongly associated with presence of genetic anomaly, often involved lung, central nervous system, or renal defects, which themselves can potentially be life-threatening, or increase the risk of mortality at surgical reconstruction through organ dysfunction. Similarly, patients with low birthweights have lower transplant-free survival rates. Congenital heart surgical outcomes in low-weight newborns is decreased, with increased morbidity including increased neurological complications and prolonged ventilation times secondary to lung immaturity.[30,31] Postnatal severe AV valve regurgitation and poor ventricular function have previously been thought to be independently associated with poor outcomes with the Norwood operation.[32] In our own prenatal HLHS study, fetuses with tricuspid regurgitation and ventricular dysfunction had total survival of 89% and 25%, respectively.[20] Both characteristics are relatively rare in fetal life; in our study, only 37 (7.4%) fetuses had at least moderate AV valve regurgitation and only 6 (1.1%) patients had moderately or severely diminished ventricular function. Of note, AV valve regurgitation was not associated with worse outcomes in univariate analysis. Outcomes of patients who had any degree of AV valve regurgitation (mild or greater) at any time in postnatal life are characterized in Table S8, along with the outcomes of patients with any degree of ventricular dysfunction at any time postnatally.

We found that patients prenatally diagnosed with SVCHD and dominant LV lesions had superior transplant-free survival rates than those with dominant RV lesions. Possible explanations include: (1) dominant RV lesion surgeries are more complex, often requiring a Norwood procedure for impediment to systemic blood flow, whereas dominant LV lesions

often only require augmentation of pulmonary blood flow; (2) the RV myocardium may have inherent differences in contractility and diastolic function in comparison with the LV myocardium in single ventricles, rendering them less suited to provide systemic pressure; and (3) the tricuspid valve may be at greater risk for incompetence than the mitral valve when at systemic pressure.[33,34] Our survival curves certainly imply that much of the mortality difference occurs before superior cavopulmonary anastomosis, often related to surgical complications along with interstage deaths. The influence of ventricular dominance on survival after the Fontan operation remains a subject of debate and is outside the scope of our study.[5,35,36] Continued longitudinal follow-up of our prenatally diagnosed cohort may answer additional questions related to post-Fontan morbidity and mortality. Although neurodevelopmental outcomes were not studied here, it also remains a subject of much interest and importance.[37,38]

Our study has a number of limitations. The first is that there are no absolute criteria to define single ventricle anatomy, and, as our findings indicate, some lesions are amenable to biventricular repair later in life (7 patients). We thus relied on the impressions of our fetal cardiologists to predict the presence of SVCHD. Second, not all of our patients were screened for chromosomal abnormalities, given that expectant parents sometimes decline amniocentesis. A number of SVCHD patients without dysmorphism or clinical suspicion did not receive genetic analysis in our cohort, although this is changing in the current era of increasing diagnosis of microdeletions and other genetic abnormalities. Our data are thus likely an underestimation of the incidence of genetic abnormalities, which is often included in prenatal counseling.[39] Our rate of TOP is likely an underestimation of the community-wide rate of termination as well, given that many patients referred to our center for evaluation were referred with intention to treat, creating an element of overall population selection bias. Nevertheless, a relatively low rate of TOP in our cohort allows us the unique opportunity to study and discern outcome factors in a large intention-to-treat population. We lost follow-up on 42 subjects (8%), a sizable number of patients, primarily related to return to referring center with no further information on outcomes. Importantly, quality of life of patients with SVCHD is an essential and common concern of expectant parents. The data collected in this study seek to qualify morbidity, but data regarding specific quality-of-life measures are currently most available in patients who have survived after Fontan operation.[40,41] A family's socioeconomic status may have a significant impact on their decisions surrounding peri- and postnatal management, and these data were not examined in this study. Further longitudinal follow-up of this cohort will allow for such analysis as well as the opportunity to explore prenatal factors that may contribute to quality of life throughout the individual's life span.

Conclusion

This is a retrospective, longitudinal study that characterizes the outcomes of fetuses with SVCHD and identifies potential risk factors for morbidity. In this study of patients with a prenatal diagnosis of SVCHD and intention to treat, 67% survive transplant free to at least 6 months beyond Fontan operation. An additional 5% survive to 4 years of age without transplant or Fontan completion, indicating that not all fetuses with SVCHD will travel the traditional pathway to Fontan completion. Among fetuses surviving to birth with intention to treat, those with RV-dominant lesions, extracardiac anomalies, hydrops, or low birthweights have decreased transplant-free survival. Our findings provide sobering data and improve accuracy of prenatal counseling for expectant parents. Further analysis of this cohort may identify modifiable variables related to the maternal-fetal environment that may improve overall survival outcomes.

Disclosures

None.

References

1. Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, Dahl SH, Cannon BC, O'Leary PW, Driscoll DJ, Cetta F. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol*. 2015;66:1700–1710.

2. Fixler DE, Nembhard WN, Salemi JL, Ethen MK, Canfield MA. Mortality in first 5 years in infants with functional single ventricle born in Texas, 1996 to 2003. *Circulation*. 2010;121:644–650.

3. Pearl JM, Nelson DP, Schwartz SM, Manning PB. First-stage palliation for hypoplastic left heart syndrome in the twenty-first century. *Ann Thorac Surg*. 2002;73:331–339.

4. Kogon BE, Plattner C, Leong T, Simsic J, Kirshbom PM, Kanter KR. The bidirectional Glenn operation: a risk factor analysis for morbidity and mortality. *J Thorac Cardiovasc Surg*. 2008;136:1237–1242.

5. Anderson PA, Sleeper LA, Mahony L, Colan SD, Atz AM, Breitbart RE, Gersony WM, Gallagher D, Geva T, Margossian R, McCrindle BW, Paridon S, Schwartz M, Stylianou M, Williams RV, Clark BJ; Pediatric Heart Network Investigators. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. *J Am Coll Cardiol*. 2008;52:85–98.

6. Ghanayem NS, Allen KR, Tabbutt S, Atz AM, Clabby ML, Cooper DS, Eghtesady P, Frommelt PC, Gruber PJ, Hill KD, Kaltman JR, Laussen PC, Lewis AB, Lurito KJ, Minich LL, Ohye RG, Schonbeck JV, Schwartz SM, Singh RK, Goldberg CS; Pediatric Heart Network Investigators. Interstage mortality after the Norwood procedure: results of the multicenter Single Ventricle Reconstruction trial. *J Thorac Cardiovasc Surg*. 2012;144:896–906.

7. Malec E, Januszewska K, Kołz J, Pajak J. Factors influencing early outcome of Norwood procedure for hypoplastic left heart syndrome. *Eur J Cardiothorac Surg*. 2000;18:202–206.

8. Checchia PA, McCollegan J, Daher N, Kolovos N, Levy F, Markovitz B. The effect of surgical case volume on outcome after the Norwood procedure. *J Thorac Cardiovasc Surg*. 2005;129:754–759.

9. Corcoran S, Briggs K, O' Connor H, Mullers S, Monteith C, Donnelly J, Dicker P, Franklin O, Malone FD, Breathnach FM. Prenatal detection of major congenital heart disease—optimising resources to improve outcomes. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:260–263.

10. Montaña E, Khoury MJ, Cragan JD, Sharma S, Dhar P, Fyfe D. Trends and outcomes after prenatal diagnosis of congenital cardiac malformations by fetal echocardiography in a well defined birth population, Atlanta, Georgia, 1990–1994. *J Am Coll Cardiol*. 1996;28:1805–1809.

11. Brown DW, Cohen KE, O'Brien P, Gauvreau K, Klitzner TS, Beekman RH, Kugler JD, Martin GR, Neish SR, Rosenthal GL, Lannon C, Jenkins KJ. Impact of prenatal diagnosis in survivors of initial palliation of single ventricle heart disease: analysis of the National Pediatric Cardiology Quality Improvement Collaborative database. *Pediatr Cardiol*. 2015;36:314–321.

12. Friedberg MK, Silverman NH, Moon-Grady AJ, Tong E, Nourse J, Sorenson B, Lee J, Hornberger LK. Prenatal detection of congenital heart disease. *J Pediatr*. 2009;155:26–31, 31.e1.

13. Tworetzky W, McElhinney DB, Reddy VM, Brook MM, Hanley FL, Silverman NH. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. *Circulation*. 2001;103:1269–1273.

14. Mahle WT, Clancy RR, McGaurn SP, Goin JE, Clark BJ. Impact of prenatal diagnosis on survival and early neurologic morbidity in neonates with the hypoplastic left heart syndrome. *Pediatrics*. 2001;107:1277–1282.

15. Morris SA, Ethen MK, Penny DJ, Canfield MA, Minard CG, Fixler DE, Nembhard WN. Prenatal diagnosis, birth location, surgical center, and neonatal mortality in infants with hypoplastic left heart syndrome. *Circulation*. 2014;129:285–292.

16. Markkanen HK, Pihkala JI, Salminen JT, Saarinen MM, Hornberger LK, Ojala TH. Prenatal diagnosis improves the postnatal cardiac function in a population-based cohort of infants with hypoplastic left heart syndrome. *J Am Soc Echocardiogr*. 2013;26:1073–1079.

17. Beroukhim RS, Gauvreau K, Benavidez OJ, Baird CW, LaFranchi T, Tworetzky W. Perinatal outcome after prenatal diagnosis of single-ventricle cardiac defects. *Ultrasound Obstet Gynecol*. 2015;45:657–663.

18. American Society of Echocardiography statement on fetal echocardiographic screening. *J Am Soc Echocardiogr*. 2014;27:A15.

19. Donofrio MT, Moon-Grady AJ, Hornberger LK, Copel JA, Sklansky MS, Abuhamad A, Cuneo BF, Huhta JC, Jonas RA, Krishnan A, Lacey S, Lee W, Michelfelder EC, Rempel GR, Silverman NH, Spray TL, Strasburger JF, Tworetzky W, Rychik J. Diagnosis and treatment of fetal cardiac disease: a scientific statement from the American Heart Association. *Circulation*. 2014;129:2183–2242.

20. Rychik J, Szwast A, Natarajan S, Quartermain M, Donaghue DD, Combs J, Gaynor JW, Gruber PJ, Spray TL, Bebbington M, Johnson MP. Perinatal and early surgical outcome for the fetus with hypoplastic left heart syndrome: a 5-year single institutional experience. *Ultrasound Obstet Gynecol*. 2010;36:465–470.

21. Tabbutt S, Ghanayem N, Ravishankar C, Sleeper LA, Cooper DS, Frank DU, Lu M, Pizarro C, Frommelt P, Goldberg CS, Graham EM, Krawczeski CD, Lai WW, Lewis A, Kirsh JA, Mahony L, Ohye RG, Simsic J, Lodge AJ, Spurrier E, Stylianou M, Laussen P. Risk factors for hospital morbidity and mortality after the Norwood procedure: a report from the Pediatric Heart Network Single Ventricle Reconstruction trial. *J Thorac Cardiovasc Surg*. 2012;144:882–895.

22. Kawashima Y, Kitamura S, Matsuda H, Shimazaki Y, Nakano S, Hirose H. Total cavopulmonary shunt operation in complex cardiac anomalies. A new operation. *J Thorac Cardiovasc Surg*. 1984;87:74–81.

23. Rychik J. The relentless effects of the Fontan paradox. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2016;19:37–43.

24. Atallah J, Dinu IA, Joffe AR, Robertson CMT, Sauve RS, Dyck JD, Ross DB, Rebeyka IM. Two-year survival and mental and psychomotor outcomes after the Norwood procedure: an analysis of the modified Blalock-Taussig shunt and right ventricle–to–pulmonary artery shunt surgical eras. *Circulation*. 2008;118:1410–1418.

25. Mahle WT, Spray TL, Wernovsky G, Gaynor JW, Clark BJ. Survival after reconstructive surgery for hypoplastic left heart syndrome: a 15-year experience from a single institution. *Circulation*. 2000;102:III136–III141.

26. Allan L, Apfel H, Printz B. Outcome after prenatal diagnosis of the hypoplastic left heart syndrome. *Heart*. 1998;79:371–373.

27. Galindo A, Nieto O, Villagra S, Graneras A, Herraiz I, Mendoza A. Hypoplastic left heart syndrome diagnosed in fetal life: associated findings, pregnancy outcome and results of palliative surgery. *Ultrasound Obstet Gynecol*. 2009;33:560–566.

28. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, Laussen PC, Rhodes JF, Lewis AB, Mital S, Ravishankar C, Williams IA, Dunbar-Masterson C, Atz AM, Colan S, Minich LL, Pizarro C, Kanter KR, Jaggers J, Jacobs JP, Krawczeski CD, Pike N, McCrindle BW, Virzi L, Gaynor JW; Pediatric Heart Network Investigators. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010;362:1980–1992.

29. LaPar DJ, Mery CM, Peeler BB, Kron IL, Gangemi JJ. Short and long-term outcomes for bidirectional Glenn procedure performed with and without cardiopulmonary bypass. *Ann Thorac Surg*. 2012;94:164–171.

30. Rossi AF, Seiden HS, Sadeghi AM, Nguyen KH, Quintana CS, Gross RP, Griepp RB. The outcome of cardiac operations in infants weighing two kilograms or less. *J Thorac Cardiovasc Surg*. 1998;116:28–35.

31. Chang AC, Hanley FL, Lock JE, Castaneda AR, Wessel DL. Management and outcome of low birth weight neonates with congenital heart disease. *J Pediatr*. 1994;124:461–466.

32. Checchia PA, McGuire JK, Morrow S, Daher N, Huddleston C, Levy F. A risk assessment scoring system predicts survival following the Norwood procedure. *Pediatr Cardiol*. 2006;27:62–66.

33. Kaneko S, Khoo NS, Smallhorn JF, Tham EB. Single right ventricles have impaired systolic and diastolic function compared to those of left ventricular morphology. *J Am Soc Echocardiogr*. 2012;25:1222–1230.

34. d'Udekem Y, Xu MY, Galati JC, Lu S, Iyengar AJ, Konstantinov IE, Wheaton GR, Ramsay JM, Grigg LE, Millar J, Cheung MM, Brizard CP. Predictors of survival after single-ventricle palliation: the impact of right ventricular dominance. *J Am Coll Cardiol*. 2012;59:1178–1185.

35. Gentles TL, Mayer JE Jr, Gauvreau K, Newburger JW, Lock JE, Kupferschmid JP, Burnett J, Jonas RA, Castañeda AR, Wernovsky G. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. *J Thorac Cardiovasc Surg*. 1997;114:376–391.

36. Hosein RB, Clarke AJB, McGuirk SP, Griselli M, Stumper O, De Giovanni JV, Barron DJ, Brawn WJ. Factors influencing early and late outcome following the Fontan procedure in the current era. The 'Two Commandments'? *Eur J Cardiothorac Surg*. 2007;31:344–353.

37. Gaynor JW. Neurodevelopmental outcomes in preschool survivors of the Fontan procedure. *J Thorac Cardiovasc Surg*. 2014;147:1276–1283.e5.

38. Sarajuuri A, Jokinen E, Mildh L, Tujulin AM, Mattila I, Valanne L, Lonnqvist T. Neurodevelopmental burden at age 5 years in patients with univentricular heart. *Pediatrics*. 2012;130:e1636–e1646.

39. Song MS, Hu A, Dyhamenahali U, Chitayat D, Winsor EJT, Ryan G, Smallhorn J, Barrett J, Yoo SJ, Hornberger LK. Extracardiac lesions and chromosomal abnormalities associated with major fetal heart defects: comparison of intrauterine, postnatal and postmortem diagnoses. *Ultrasound Obstet Gynecol*. 2009;33:552–559.

40. Uzark K, Zak V, Shrader P, McCrindle BW, Radojewski E, Varni JW, Daniels K, Handisides J, Hill KD, Lambert LM, Margossian R, Pemberton VL, Lai WW, Atz AM. Assessment of quality of life in young patients with single ventricle after the Fontan operation. *J Pediatr*. 2016;170:166–172.e1.

41. Pike NA, Evangelista LS, Doering LV, Koniak-Griffin D, Lewis AB, Child JS. Clinical profile of the adolescent/adult Fontan survivor. *Congenit Heart Dis*. 2011;6:9–17.

SUPPLEMENTAL MATERIAL

Table S1. Clinical characteristics of fetuses with IUFD.

Patient	Diagnosis	Notable characteristics
1	Severe RV hypoplasia	Dilation of Renal Calyces
2	Unbalanced CAVC to Left	Heterotaxy, Complete heart block, Pericardial effusion, Features of noncompaction cardiomyopathy, Moderate AV valve regurgitation
3	HLHS, MA/AA	Lower urinary tract obstruction
4	HLHS, MA/AA	Trisomy 18
5	DORV, LV hypoplasia, arch hypoplasia	Heterotaxy, complete heart block, RV with spongiform changes
6	HLHS, MS/AA	Cystic hygroma, Hydrops
7	Tricuspid Atresia	Twin gestation
8	Unbalanced CAVC to Left with DORV	None
9	Unbalanced CAVC to Right, LV hypoplasia, DORV, Pulmonary Atresia	None
10	Tricuspid Atresia	Hydrops, Severe ventricular dysfunction
11	Unbalanced CAVC to Right	Cystic hygroma, Hydrops

AA- Aortic atresia; AV- atrioventricular; CAVC- Common atrioventricular canal; DORV- Double outlet right ventricle; HLHS- Hypoplastic left heart syndrome; LV- Left ventricle; MA- Mitral atresia; RV- Right ventricle.

Table S2. Characteristics of 22 Live-Born Patients Referred to Palliative Care.

	Anatomy	Genetic Abnormalities	Extracardiac Abnormalities	Note
1	HLHS	Trisomy 13		
2	Unbalanced CAVC to Right		Heterotaxy	
3	Unbalanced CAVC to Left		Congenital diaphragmatic hernia	
4	HLHS	Trisomy 18		
5	HLHS		IUGR, oligohydramnios	Restrictive atrial septum
6	HLHS	Rubenstein Taybi Syndrome		Restrictive atrial septum
7	RV hypoplasia, straddling TV, DORV	Trisomy 18		
8	Unbalanced CAVC to Right	16q deletion	Heterotaxy, corneal opacities, cerebral abnormalities	
9	HLHS		Severe brain malformation	
10	HLHS			Restrictive atrial septum
11	Unbalanced CAVC to Right with RV-Aorta, Pulmonary atresia	Trisomy 18		
12	Hypoplastic LV, MV hypoplasia, aortic arch hypoplasia		Congenital diaphragmatic hernia	
13	HLHS			Born at 27 weeks gestation
14	HLHS			Twin gestation
15	Unbalanced CAVC to Right, single RV		Heterotaxy	Supracardiac TAPVC
16	HLHS	11q deletion (Jacobsen syndrome)		
17	Unbalanced CAVC to Right	Trisomy 18		

18	DORV with MA	Trisomy 18		
19	HLHS			
20	HLHS	Turner Syndrome		
21	DILV			Born at 28 weeks gestation with pulmonary artery aneurysm
22	HLHS	18p deletion	Pulmonary lymphangectasia	Restrictive atrial septum

CAVC- common AV canal defect; DILV- Double inlet left ventricle; DORV- Double outlet right ventricle; HLHS- Hypoplastic left heart syndrome; IUGR- Intrauterine growth restriction; LV- Left ventricle; MV-Mitral Valve; RV- Right ventricle; TAPVC- Total anomalous pulmonary venous connection.

Table S3. Clinical course of patients with intent to treat but death prior initial operation.

Patient	Diagnosis	Clinical course
1	HLHS, restrictive atrial septum	Ventricular fibrillation was induced during sternal incision for hybrid procedure
2	HLHS, restrictive atrial septum	Balloon atrial septostomy attempted, but LA was perforated leading to effusion
3	HLHS, restrictive atrial septum	Underwent intra-atrial stenting, complicated by SIRS, and respiratory failure
4	HLHS, intact atrial septum	Went to OR immediately after birth for atrial septectomy, complicated by anasarca, capillary leak, and junctional bradycardia
5	HLHS	Died intraoperatively during Stage 1 Norwood with Sano modification. Patient noted to have very small ascending aorta (0.5 mm)
6	HLHS with TAPVC	TAPVC repair (confluence to RA, no decompressing vein noted) immediately after birth; operation complicated by pulmonary vein stenosis. Patient noted to have multiple congenital anomalies including microcephaly, congenital brain atrophy with new stroke, butterfly vertebrae, syndactyly.
7	HLHS variant (unbalanced CAVC with arch hypoplasia)	Had prenatal pleural effusions, became increasingly difficult to ventilate despite surfactant
8	HLHS variant (hypoplastic LV, mitral atresia, DORV), restrictive atrial septum	Immediately underwent intraatrial stent placement- Required oscillatory ventilation, became coagulopathic and septic; found to have biliary atresia
9	MA, DORV, heart block	Had complete heart block and hydrops in utero-- when born, had pacing wires placed, but had intractable hypotension
10	HLHS, PAPVR with vertical vein obstruction	Unsuccessful stent placement in vertical vein-- patient died intra-procedure
11	HLHS variant (unbalanced canal to the Right, arch hypoplasia)	Had cardiac arrest during angiography for diagnostic evaluation
12	MA, DORV, intact atrial septum, mixed TAPVC	TAPVC discovered postnatally; also had genetic abnormalities, parents decided to withdraw support

DORV- Double outlet right ventricle; HLHS- Hypoplastic left heart syndrome; LA- Left atrium; MA- Mitral atresia, PAPVR- Partial anomalous pulmonary venous return; OR- Operating room; RA- Right atrium; SIRS- Systemic inflammatory response syndrome. TAPVC- Total anomalous pulmonary venous connection.

Table S4. Clinical outcomes of patients with initial intention to treat who did not require any surgical palliation.

Patient	Diagnosis	Clinical outcome
1	Heterotaxy, Unbalanced CAVC to Right, DORV, Pulmonary stenosis	No surgical interventions indicated to date
2	HLHS with Mowat-Wilson syndrome	Supportive care initially planned, but ductus arteriosus has remained patent and patient survived
3	Tricuspid Atresia, Pulmonary atresia, multiple AP collaterals; with Alagille syndrome	Has undergone several catheterization-based collateral interventions, but continues to have balanced circulation without interventions
4	Heterotaxy, Unbalanced CAVC to Right, Pulmonary atresia, TAPVC, with AP collaterals	Died at 18 months of age at home, etiology unknown
5	Heterotaxy, Unbalanced CAVC to Right, Pulmonary atresia, with AP collaterals, hydrocephalus	Had VP shunt placement and subsequent shunt failure that led to revision, complicated by acute intraventricular hemorrhage and withdrawal of support

AP- aortopulmonary; CAVC- Common atrioventricular canal; DORV- Double outlet right ventricle; TAPVC- Total anomalous pulmonary venous connection; VP- Ventriculoperitoneal.

Table S5. Clinical courses of patients who received orthotopic heart transplant (OHT).

Patient	Diagnosis	Notable characteristics
1	HLHS, MA/AA, Scimitar syndrome, severe TR	Initially had PA bands, and ductal/aortic stents. Had severe TR, transplanted at 5 months of age.
2	HLHS, MA/AA	Initially had Norwood with Sano modification, complicated by ventricular dysfunction, respiratory failure requiring tracheostomy, then underwent Glenn; had severe TR and low normal function, and then eventually underwent OHT.
3	DILV, pulmonary atresia, MAPCAs	Initially underwent unifocalization to RV-PA conduit. Had hypoplastic branch pulmonary arteries; had heart and lung transplant at 15 months of age
4	HLHS, MA/AA	Underwent Stage I and II with progressive heart failure, OHT at 2 years
5	Tricuspid atresia, absent pulmonary valve, ventricular noncompaction, congenital heart block	Underwent bidirectional Glenn, pacemaker placement. Had moderate dysfunction and dilation, and had elevated Glenn pressures. Transplanted at 22 months
6	Tricuspid atresia, absent pulmonary valve syndrome, sub aortic stenosis	OHT at 3 weeks of age; died at 6 years of age.
7	Heterotaxy, CAVC with common ventricle, infradiaphragmatic TAPVC, pulmonary stenosis, pulmonary vein stenosis	Patient had progressive obstruction of all 4 pulmonary veins--had pulmonary hypertension. Patient received heart and lung transplant.
8	HLHS, MS/AA	Underwent bidirectional Glenn, then underwent OHT at 6 years of age for severe ventricular dysfunction
9	HLHS with scimitar syndrome s/p hybrid procedure (atrial stent, bilateral PA banding no PDA for risk of reverse coarctation).	Remained on PGE until OHT at 5 months of age
10	HLHS, MA/AA	Had significant ventricular dysfunction requiring prolonged ventilation including tracheostomy; OHT at 7 months

AA- Aortic atresia; AV- atrioventricular; CAVC- Common atrioventricular canal; DILV- Double inlet left ventricle; DORV- Double outlet right ventricle; HLHS- Hypoplastic left heart syndrome; LV- Left ventricle; MA- Mitral atresia; MAPCA- Major aortopulmonary collateral arteries; OHT- Orthotopic heart transplant; PA- Pulmonary artery; PGE- Prostaglandin E; RV- Right ventricle; TAPVC- Total anomalous pulmonary venous connection; TR- Tricuspid regurgitation

Table S6. Univariate analysis of potential risk factors associated with death/transplant.

Variable	P value
Twin gestation	**<0.0001**
Fetal AV valve regurgitation	0.12
Fetal ventricular function	**0.0083**
Presence of HLHS	**0.0151**
Dominant ventricle morphology (Right vs. Left)	**0.0018**
Presence of Heterotaxy syndrome	0.97
Genetic/chromosomal abnormality	**<0.0001**
Extracardiac anomalies	**0.0014**
Hydrops	**0.0025**
Presence of arrhythmia	0.089
Sex (female vs male)	0.45
Birthweight	**<0.0001**
Gestational age at birth	**0.0051**
Maternal age at diagnosis	0.79

AV- atrioventricular; HLHS- Hypoplastic left heart syndrome.

Table S7. Number of Patients Requiring Extracorporeal Membrane Oxygenation (ECMO).

ECMO	n=		Survival#	
Prior to First Operation	1		0	
After First Operation	25		5	
After Second Operation	4*		0	
After Third Operation	0			
Total	29	(8.3%)**	5	(17.2%)

Transplant free survival 6 months post-Fontan. One patient alive with no anticipated plans for Fontan palliation.
* 1 patient had ECMO after both first and second operations.
**Out of patients surviving to birth with intention to treat.

Table S8. Outcomes of Patients with Any Atrioventricular (AV) Valve Regurgitation (Mild or Greater) and/or Any Ventricular Dysfunction (Mild or Greater) at any time in Postnatal Course.

Outcome	Ventricular Dysfunction	AV Valve Regurgitation
Death Birth-Stage 1	1	7
Death Stage 1-2	15	17
Death Stage 2-3	12	16
Orthotopic heart transplant	4	6
Lost to follow-up:		
Birth-Stage 1		1
Stage 1-2		3
Stage 2-3	4	3
Survival*	62^	99#
Total	98	152

*Survival to 6 months post-Fontan
^Includes 1 patient alive with no plans to undergo Fontan
Includes 4 patients alive with no plans to undergo Fontan and 1 patient not yet 6 months post Fontan.