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Hypoplastic right heart with heterotaxy has worse five-year transplant-free survival than the hypoplastic left heart syndrome: a thirteen-year single-centre experience

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Abstract

Background: Outcomes of single ventricle heart defects may be influenced by the morphological type of the hypoplastic ventricle. Recent multi-centre studies have targeted on outcomes of hypoplastic left heart syndrome with limited focus on outcomes of hypoplastic right heart syndrome. We aimed at studying the clinical outcomes of hypoplastic right heart syndrome in the recent era. *Method:* We performed a retrospective analysis of all hypoplastic right heart syndrome patients (n = 153) born between January 2010 and January 2023. Five-year transplant-free survival was compared with hypoplastic left heart syndrome patients without heterotaxy (n = 144) born during the same time. *Results:* Double-inlet left ventricle was the most common anatomic hypoplastic right heart syndrome subtype (n = 39, 25%). Twenty-six (17%) patients with hypoplastic right heart had associated heterotaxy. Five-year transplant-free survival was high for most groups (double inlet left ventricle: 100%, pulmonary atresia: 94%, Ebstein's anomaly: 92%, tricuspid atresia: 90% respectively). The heterotaxy group had worse early outcomes with 3 deaths and 3 heart transplants, before Fontan completion. Heterotaxy was a significant risk factor for death/transplant prior to Fontan completion in hypoplastic right heart syndrome patients (p = 0.03). Patients with hypoplastic right heart syndrome with heterotaxy had significantly worse 5-year transplant-free survival (71%) when compared to hypoplastic right heart syndrome without heterotaxy (95%) and hypoplastic left heart syndrome without heterotaxy (75%), $p < 0.001$. *Conclusions:* Hypoplastic right heart syndrome patients have excellent clinical outcomes and better early childhood survival than hypoplastic left heart syndrome in the current era, except when associated with heterotaxy. The survival advantage conferred by a single left ventricle appears to be negated by heterotaxy syndrome and should be strongly considered during caregiver counselling and medical decision-making.

Introduction

Hypoplastic right heart syndrome (HRHS) encompasses a range of CHD characterised by underdevelopment of right ventricle. The condition, however, is heterogenous, with multiple anatomic subtypes including tricuspid atresia, pulmonary atresia with intact ventricular septum, double inlet left ventricle, Ebstein's anomaly with hypoplastic right ventricle, and heterotaxy syndromes with a hypoplastic right ventricle.[1–6] These conditions are marked by the presence of a systemic left ventricle, which is generally believed to confer survival advantage, compared to the hypoplastic left heart syndrome (HLHS) with a systemic right ventricle.[1–3] A multi-centric trial compared the transplant-free survival following the total cavo-pulmonary anastomosis (commonly known as Fontan operation) between the 1421 HLHS patients and 1615 HRHS patients, born between 1982 to 2003. Patients with HRHS had a higher 20-year transplant-free survival (72%) compared to those with HLHS (52%).[1] Given the overall worse outcomes in HLHS patients, most multi-centric collaboratives such as National Pediatric Cardiology Quality Improvement Collaborative have focused their attention on studying and improving the early childhood outcomes of HLHS infants.[7] However, there are limited data on early childhood survival and outcomes of HRHS patients in the recent era.

Methods

This was a retrospective single centre chart review. Institutional review board approved the study. The objective of our study was to compare early childhood outcomes in different

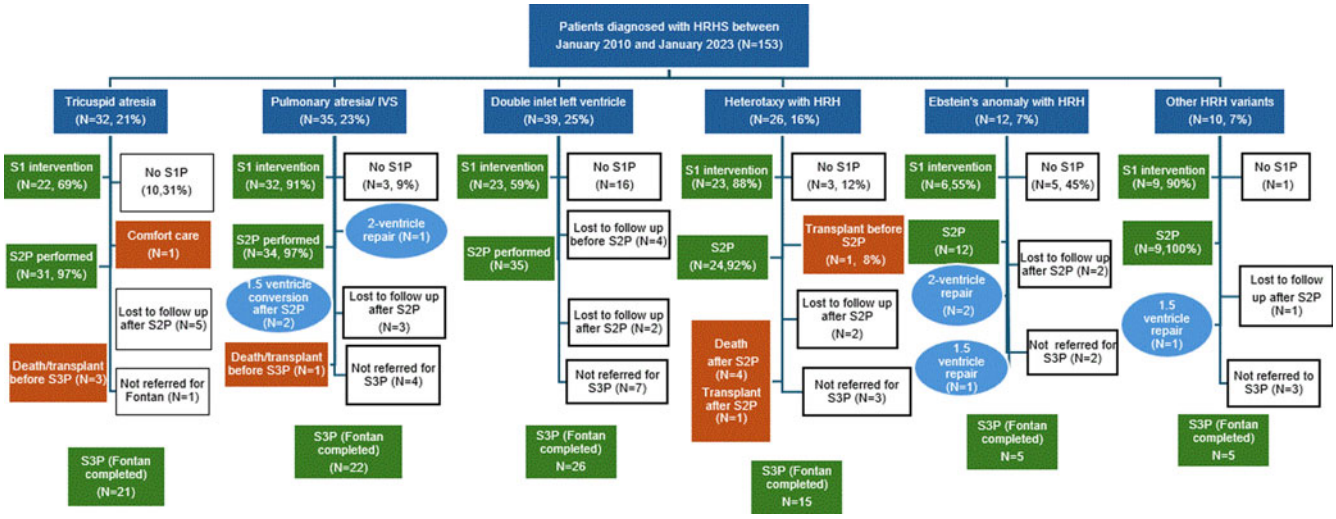

Figure 1. Clinical course and survival to Fontan (Stage 3 palliation) in patients with hypoplastic right heart patients ($N = 153$).

anatomic subtypes of HRHS and to compare the transplant-free survival at 5 years, including survival to Fontan palliation. We also aimed to compare the transplant-free survival in HRHS patients with a cohort of HLHS patients without heterotaxy syndrome, managed at our institute during the study duration. Patients were identified from the cardiothoracic surgical database as well as our institution's single ventricle database. All patients born between January 2010 and January 2023 with the diagnosis of single ventricle CHD (SVCHD) were identified. Patients with morphological systemic left ventricle were categorised as HRHS and their demographic, clinical, surgical and follow-up data from birth to five years were collected and managed using Redcap, University of Arizona. Patients were categorised based on the major anatomic type of HRHS. Patients with systemic right ventricle were classified as HLHS and their survival data was obtained from the institutional surgical registry. Categorical data were compared using the non-parametric tests of significance including Chi-squared analysis, Fischer's exact tests, etc. Continuous data were compared using tests such paired and student *t*-test. A p value <0.05 was considered statistically significant. Survival free of transplant was analysed based on the HRHS anatomical types. Hypoplastic right heart syndrome patients were then divided into those with and without associated heterotaxy syndrome and their survival was compared with the HLHS patients without heterotaxy using the Kaplan–Meier analysis. Data were analysed using the SPSS software version 30.0.

Results

A total of 153 patients with hypoplastic right heart variants were included in this study. Figure 1 shows the distribution of the study subjects into various anatomical forms of HRHS. The most common anatomic variant was double inlet left ventricle ($n = 39$, 25%). About 17% of patients had complex hypoplastic right heart with heterotaxy syndrome ($n = 26$).

The group of patients categorised as "other hypoplastic right heart variants" consisted of six patients with congenital corrected transposition of great arteries (TGA) and one with D-TGA who had either an Ebsteinoid/severely dysplastic tricuspid valve ($n = 4$) or pulmonary atresia ($n = 3$), but all with a hypoplastic morphologic right ventricle. Two patients had severe tricuspid dysplasia (but not atresia) with a hypoplastic right ventricle, who were considered unsuitable for 2-ventricle repair. One patient had an unbalanced, left - dominant atrioventricular canal defect with no associated heterotaxy.

Identifying heterotaxy

At our institute, all patients diagnosed with SVCHD undergo a surveillance abdominal ultrasound at birth and several undergo further testing including chest and heart computer tomography or magnetic resonance imaging and genetic testimg. Heterotaxy was identified based on the diagnostic criteria from the National birth defects prevention study which requires at least 3 out of 8 clinical features; namely presence of characteristic CHD, biliary atresia, abdominal situs anomaly, splenic abnormality, isomerism of bronchi, atrial isomerism and characteristic systemic venous anomaly[8] and using the nomenclature guidelines from the International Nomenclature Committee for Pediatric and Congenital Heart Disease.[9]

Anatomical characteristics

Table 1 details the demographic and anatomic features of the major hypoplastic right heart syndrome subtypes. There was slight female predominance in the Ebstein's anomaly with almost equal sex distribution among the tricuspid atresia and heterotaxy syndrome.

Cardiac position and venous anomalies

Majority ($n = 15$, 60%) of patients with heterotaxy syndrome had dextrocardia. Systemic and pulmonary venous anomalies were common amongst the heterotaxy group, including bilateral superior vena cavae in ($n = 9$,36%), unilateral but left sided superior vena cava ($n = 2$, 8%), interrupted inferior vena cava ($n = 4$,16%), left sided inferior vena cava ($n = 3$,12%) and separate drainage of hepatic veins and inferior vena cava (1, 4%). Due to retrospective nature of the study, adequate data was not available to assess the exact incidence of atrial isomerism.

Atrio-ventricular valves

Anatomically, 40% of patients with pulmonary atresia with intact ventricular septum (PA/IVS) had severely hypoplastic tricuspid valve. While right ventricle sinusoids were noted in most patients, only 2 of them were found to have right ventricle dependent

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Table 1. Demographic and anatomic characteristics of the major hypoplastic right heart syndrome (HRHS) types

Characteristic	Tricuspid atresia ($N = 32$)	Pulmonary atresia with IVS ($N = 35$)	Double inlet left ventricle ($N = 39$)	Heterotaxy syndrome with HRH ($N = 26$)	Ebstein's anomaly with HRH ($N = 12$)
Demographic features					
Females	17 (53%)	13 (37%)	10 (26%)	12 (48%)	6 (60%)
Ethnicity					
• Caucasian	16 (50%)	17 (48%)	24 (62%)	14 (56%)	6 (54%)
• Hispanic	6 (19%)	8 (23%)	6 (15%)	8 (32%)	5 (42%)
• African American	2 (6%)	1 (3%)	4 (10%)	2 (8%)	0
• Asian	3 (9%)	2 (6%)	1 (3%)	0 (0%)	0
• Native American	5 (16%)	7 (20%)	4 (10%)	1(4%)	1 (10%)
Anatomical features					
Systemic venous anomalies	–	–	–	19 (76%)	–
Pulmonary venous anomalies	–	–	1	9 (36%)	–
Atrioventricular (AV) valve anomalies					
• Mitral valve anomalies	–	–	–	–	–
• Tricuspid stenosis/Z score ≤−3)	Tricuspid atresia	14 (40%)	–	–	Displaced TV*
• Unbalanced common AV valve	–	–	–	14 (56%)	–
Great artery relationship					
• Normally related	18 (56%)	32 (91%)	4 (10%)	5 (20%)	12 (100%)
• D-transposed	13 (41%)	1 (3%)	22 (57%)	16 (64%)	–
• L-transposed	1 (3%)	1 (3%)	13 (33%)	4 (16%)	–
Pulmonary stenosis					
• Mild or no stenosis (unobstructed flow)	14 (44%)	Pulmonary atresia	18 (46%)	0 (0%)	5 (45%)
• More than mild stenosis	15 (47%)		15 (38%)	9 (36%)	1 (10%)
• Pulmonary atresia	5 (16%)		4 (10%)	12 (48%)	6 (50%)
Aortic arch obstruction	5 (16%)	0 (0%)	4 (10%)	0 (0%)	1 (10%)

coronary circulation on diagnostic cardiac catheterisation (CC). Majority of patients with heterotaxy syndrome showed some abnormality of the atrio-ventricular valves (88%) and 14 patients (56%) had a common, unbalanced atrio-ventricular valves. Two patients with heterotaxy had a common inlet (8%) and 6 (24%) had atresia of the right sided atrio-ventricular valves. Patients with Ebstein's anomaly had a median displacement of the tricuspid valve ~ 18mm/cm 2. In this group, 8 patients (73%) showing moderate to severe degree of tricuspid valve regurgitation at presentation.

Ventricular septal defect

Most patients with tricuspid atresia (TA) had a ventricular septal defect (VSD), with peri-membranous/outlet defect being the most common subtype. Amongst the patients with double inlet left ventricle, 22 (59%) had a moderate to large (unrestricted) ventricular septal defect, and 11 (29%) had a small ventricular septal defect shunt.

Great arteries

Majority of patients with double inlet left ventricle (DILV) had D-TGA with aorta arising from the rudimentary anterior (right) ventricle; and dependent on the size of the VSD for aortic inflow. Ventricular septal defect was noted to be small in 11 (29%) or about one-third of patients at diagnosis. About 50% of patients with Ebstein's anomaly had significant pulmonary stenosis or atresia. Majority of patients in the heterotaxy group had some restriction to the pulmonary flow ($n = 21$, 84%). Aortic arch obstruction was rare in all subtypes.

Stage 1 intervention

Table 2 and Figure 1 illustrate the clinical course and surgical pathway of these major HRHS types. Transcatheter interventions were commonly performed as the first intervention in patients with pulmonary atresia with intact ventricular septum and less frequently required in other groups. Most HRHS patients, except

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Table 2. Clinical course and outcomes of the major hypoplastic right heart syndrome (HRHS) anatomical types

Characteristic	Tricuspid atresia (*N* = 32)	Pulmonary atresia with intact ventricular septum (*N* = 35)	Double inlet left ventricle (*N* = 39)	Heterotaxy syndrome with HRH (*N* = 26)	Ebstein's anomaly with HRH (*N* = 12)
Stage 1 intervention					
No Stage 1 intervention needed	10 (30%)	3 (9%)	16 (41%)	3 (12%)	5 (45%)
Transcatheter Stage 1 intervention					
PDA stent	1 (3%)	1 (3%)	–	2 (8%)	–
Balloon atrial septostomy	–	20 (57%)	2 (5%)	–	–
Balloon pulmonary valvuloplasty	–	5 (14%)	–	–	1 (10%)
Surgical Stage 1 intervention procedures					
Aorto-pulmonary shunt	19 (58%)	32 (91%)	14 (36%)	14 (56%)	6(54%)
Surgical Pulmonary artery banding	3 (9%)	–	9 (23%)	2 (8%)	1(10%)
DKS anastomosis	5 (15%)	–	9 (23%)	1 (4%)	1(10%)
Arch repair	–	–	2 (5%)	1 (4%)	1(10%)
Uni-focalization of the pulmonary arteries	–	–	2 (5%)	2 (8%)	–
Starnes procedure with tricuspid valve exclusion	–	1 (3%)	–	–	5(45%)
Transannular patch	–	1 (3%)	–	–	–
RVOT construction	–	1 (3%)	–	–	–
TAPVR repair	–	–	–	1 (4%)	–
Subaortic resection	–	–	–	1 (4%)	–
Pre- Stage 2 palliation (S2P) status					
• Death before receiving S2P	1 (3%)	–	–	–	–
• Transplant before receiving S2P	–	–	–	1 (4%)	–
Pre S2P respiratory: Mechanical ventilation/HFNC	3 (9%)	4 (12%)	3 (7%)	5 (20%)	2 (20%)
Pre-S2P echocardiogram					
-Moderate or more atrio-ventricular valve regurgitation	2 (6%)	1 (3%)	3 (7%)	4 (16%)	7 (62%)
-Moderate or worse single LV dysfunction	–	–	1 (3%)	0	–
Pre-S2P haemodynamic data	***N* = 25**	***N* = 29**	***N* = 24**	***N* = 15**	***N* = 9**
Mean pulmonary artery pressure (mean ± SEM)	14.6±0.8	13±0.5	14.5±1	13.5±1	13.7±0.6
LVEDP	7.4±0.7	6.5±0.3	7.3±0.3	8.6±1	7.4±0.4
PVR	2.1±0.3	1.3±0.4	1.3±0.1	1.8±0.3	1.7±0.4
Qp:Qs	1.6±0.2	1.5±0.1	1.6±0.2	1.4±0.2	1.3±0.2
Cardiac index (calculated)	4.1±0.3	3.8±0.2	4.3±0.3	4.8±0.7	3.7±0.5
Significant branch pulmonary artery stenosis	1 (3%)	2 (7%)	–	2 (13%)	4 (37%)
Arch obstruction with arch angioplasty	3 (9%)	–	2 (5%)	–	–
Surgical Stage 2 palliation (S2P)	*N*=31	*N*=34	*N*=35	*N*=24	*N*=12
Weight at surgery in kg (mean ± SEM)	5.9±0.2	6.3±0.1	6.7±0.3	6.3±0.5	6.4±0.9

(*Continued*)

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Table 2. (*Continued*)

Characteristic	Tricuspid atresia (*N* = 32)	Pulmonary atresia with intact ventricular septum (*N* = 35)	Double inlet left ventricle (*N* = 39)	Heterotaxy syndrome with HRH (*N* = 26)	Ebstein's anomaly with HRH (*N* = 12)
Age at surgery in weeks (mean ± SEM)	21±1	22±1.9	28.3±4	27±4	35±10
Type of superior-veno-caval anastomosis					
• Bidirectional Glenn	24 (75%)	32 (97%)	35 (100%)	10 (39%)	11 (92%)
• Hemi-Fontan	1 (3%)	–	–	10 (44%)	–
• Pulsatile Glenn (Pulmonary artery banding)	7 (23%)	–	4 (11%)	1 (4%)	1 (8%)
• Kawashima repair	–	–	–	4 (17%)	–
Additional procedures with S2P					
• DKS anastomosis	2 (6%)	–	5 (14%)	1 (4%)	–
• Arch repair	1 (3%)	–	3 (9%)	–	–
• TAPVR repair	–	–	1 (3%)	–	–
• Pacemaker placement	–	–	1 (3%)	–	1 (8%)
• AV valve repair/surgery	–	–	–	1 (4%)	2 (16%, Starnes)
Major complications after S2P					
Post-S2P ECMO requirement	2 (6%)	–	–	2 (8%)	–
Significant chylothorax needing intervention	3 (9%)	1 (3%)	3 (9%)	3 (12%)	1 (8%)
Death (after S2P)	1 (6%)	2 (6%)	–	4 (17%)	1 (8%)
Cardiac transplant (before S3P)	3 (9%)	–	–	1 (4%)	–
S3P (total cavo-pulmonary anastomosis/Fontan)					
Death/transplant before S3P (total, all stages)	4/32 (12%)	1/35 (3%)	–	6/26 (23%)	1 (8%)
Conversion to 1.5 or 2 ventricle physiology	–	3/35 (9%)	–	–	3/12 (25%)
Lost to follow up before S3P	5	2	6	1	2
Not yet referred for S3P (Fontan completion)	2	4	7	3	1
Unsuitable for S3P palliation, referred for transplant	–	1	–	1	–
S3P (Fontan) completed at last follow up	21	22	26	15	5

for DILV, were palliated with a surgical aorto-pulmonary shunt (most commonly a modified Blalock–Taussig–Thomas) shunt. About 23% of DILV patients and 15% of TA patients had a comprehensive stage 1 palliation (S1P) which included creation of a Damus-Kaye-Stensel (DKS) anastomosis.

Stage 2 interventions

Our institutional surgery of choice for stage 2 palliation (S2P) is superior-cavo- pulmonary anastomosis (SCPA) using direct superior vena cava to PA anastomosis or Glenn anastomosis. Most patient underwent pre-Glenn CC based on our center's practice along with pre-operative echocardiogram. Table 2 shows that most patients were on room air or low respiratory support prior to SCPA, except for the heterotaxy group (20% requiring mechanical ventilation or high flow nasal cannula) prior to S2P. Pre-operative echocardiogram showed persevered single left ventricle function, with about 16% of patients with heterotaxy demonstrating significant AV valve regurgitation. Pre-S2P hemodynamic data revealed overall low pre-Glenn mean pulmonary artery pressure (mPAP). Significant branch PA stenosis was seen frequently in patients with Ebstein's anomaly (37%) and the heterotaxy group (13%).

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Majority of the patients were 5–6 months of age at the time of S2P and weighed about 6 kgs. The most common SCPA technique was bidirectional Glenn with about a fifth of TA patients receiving a pulsatile Glenn (allowing antegrade flow through the native pulmonary artery). Kawashima repair was used in 17% ($N = 4$) of heterotaxy syndrome due to the presence of interrupted IVC with azygous/hemi-azygous connection to the superior vena cava.

Additionally, 8 patients had a comprehensive S2P with DKS anastomosis. Chylothorax needing intervention was the most common post-S2P complication, seen in 9 patients. Two patients from TA group and two from heterotaxy group needed ECMO support.

Post S2P course in the survivors

Three patients in the pulmonary atresia with intact ventricular septum group (8%) and 3 patients in the Ebstein's anomaly group (27%) were able to get conversion to a 2-ventricle or 1.5 ventricle pathway and did not require any further SV palliation. Following S2P, two patients were deemed unsuitable candidates for further SV completion and were referred for OHT. Overall, 94 patients had completed S3P (TCPA /Fontan) palliation at the time of writing this manuscript.

Pre-Fontan or S3P outcomes in hypoplastic right heart syndrome

One patient (in the TA group) was considered unsuitable for SV palliation and died with comfort care. One patient in the heterotaxy group received an orthotopic heart transplant (OHT) and never reached S2P. Eleven patients failed SV palliation pathway after S2P, of whom 6 died and additional 5 patients received an OHT. Details of their clinical course and events leading to death or transplant are outlined in a separate section below.

Details of the patients with hypoplastic right heart syndrome with poor outcomes (death/transplant)

Tricuspid atresia

Overall, 4 patients in this group had death/cardiac transplant and did not undergo Fontan completion. The details of these patients are as follows:

Patient 1: death before S2P

This patient was transferred from an outside facility with a late, postnatal diagnosis at about 8 weeks of age with unrestricted pulmonary blood flow. He was initially palliated with a PDA stent angioplasty; however, he died following stent thrombosis around 3 months of age.

Patient 2: transplant after S2P

This patient's diagnosis included tricuspid atresia, double outlet right ventricle, d-malposed great arteries, large ventricular septal defect and an ASD. He initially underwent S1P with PA banding followed by bidirectional Glenn (SCPA) at 5 months. Post SCPA, he sustained an acute cardiac arrest, leaving him with severe residual mitral regurgitation, left ventricle systolic function and heart failure, which prompted referral for heart transplants. He ultimately received a successful heart transplants at 7 months of age and was alive (12 years of age) at the time of writing of this manuscript.

Patient 3: heart transplant after S2P

This patient was born with tricuspid atresia with D-TGA, ventricular septal defect and hypoplastic right heart . She underwent stage 1 and stage 2 palliation but subsequently developed diffuse left pulmonary artery hypoplasia and compression of left pulmonary veins, making her an unsuitable candidate for Fontan completion. She received heart transplants at 7 years of age and was alive (9 years of age) at the time of writing of this manuscript.

Patient 4: heart transplant after S2P

This patient was born with TA with PA, and an associated genetic anomaly, namely, chromosome 15q11.2 microdeletion syndrome. He underwent stage 1 and stage 2 palliation, however, developed progressive ventricular dysfunction. He received heart transplants at 2 years of age and is alive (8 years) at the time of writing of this manuscript.

Pulmonary atresia with intact ventricular septum

There was no mortality prior to SCPA or definitive surgery. One patient died and did not undergo Fontan completion.

Patient 1: death before S2P

This patient was born with PA/IVS and did not have right ventricle dependent coronary circulation, His initial palliation was pulmonary valve perforation and ballooning via transcatheter route followed by Blalock–Taussig–Thomas shunt. He subsequently developed severe ventricular dysfunction and mitral regurgitation and was never able to wean off mechanical ventilation. His care was subsequently withdrawn, and he died at 3 months of age.

Double inlet left ventricle

There were no deaths or transplant in this group.

Heterotaxy syndrome with hypoplastic right heart syndrome

This group had a high rate of death/transplant ($n = 6$) and only 15 patients had survived to Fontan completion during the study duration. Of these 15 patients, 5 (33%) had already developed signs of Fontan failure and had been referred for heart transplants. Of these, 3 had received heart transplants and 2 had been rejected and deemed unsuitable candidates for heart transplants, and subsequently died, at the time of writing this manuscript. Details of the 6 patients who had poor outcomes prior to Fontan completion are as follows.

Patient 1: death after S2P

This patient's cardiac diagnosis included bilateral superior vena cavas, total anomalous pulmonary venous return, right atrioventricular valve atresia, anteriorly arising aorta with pulmonary atresia, right aortic arch, discontinuous PAs and hypoplastic right ventricle. Following the bilateral bidirectional Glenn anastomosis, this patient was discharged home. However, at about 2 years of age, she was admitted with respiratory failure in the setting of a viral infection and subsequently developed cardiogenic shock and cardiac arrest requiring extracorporeal membranous oxygenation support. Subsequently care was withdrawn.

Patient 2: transplant after S2P and subsequent death

This patient's cardiac diagnosis included interrupted inferior vena cava, unbalanced, left ventricle dominant common atrio-

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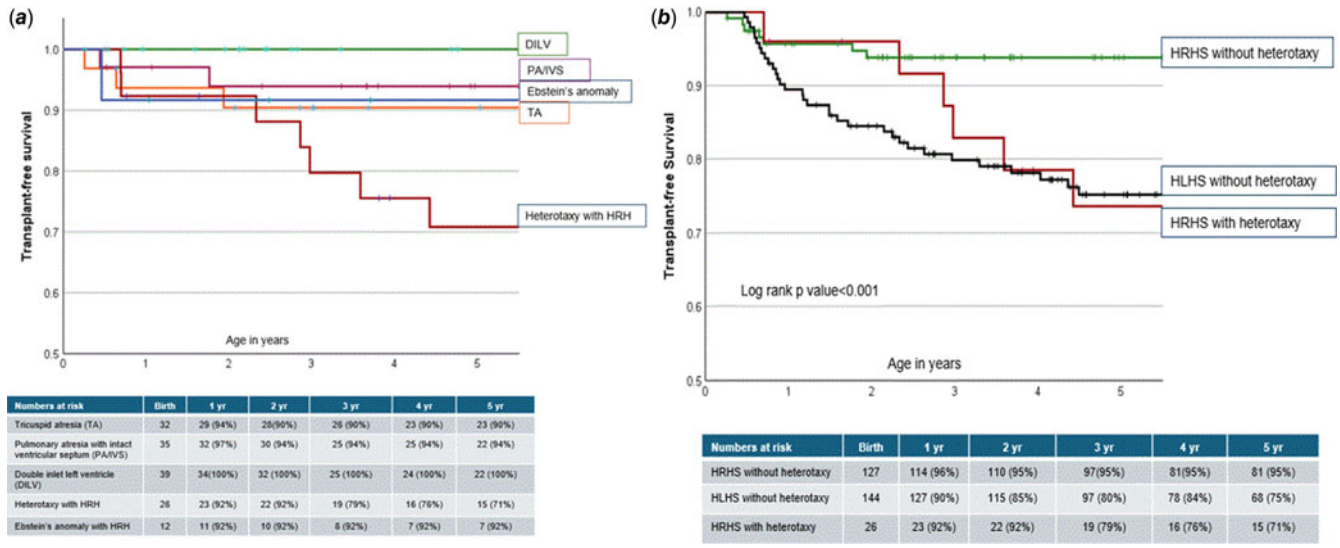

Numbers at risk	Birth	1 yr	2 yr	3 yr	4 yr	5 yr
Tricuspid atresia (TA)	32	29 (94%)	28(90%)	26 (90%)	23 (90%)	23 (90%)
Pulmonary atresia with intact ventricular septum (PA/IVS)	35	32 (97%)	30 (94%)	25 (94%)	25 (94%)	22 (94%)
Double inlet left ventricle (DILV)	39	34(100%)	32 (100%)	25 (100%)	24 (100%)	22 (100%)
Heterotaxy with HRH	26	23 (92%)	22 (92%)	19 (79%)	16 (76%)	15 (71%)
Ebstein's anomaly with HRH	12	11 (92%)	10 (92%)	8 (92%)	7 (92%)	7 (92%)

Numbers at risk	Birth	1 yr	2 yr	3 yr	4 yr	5 yr
HRHS without heterotaxy	127	114 (96%)	110 (95%)	97(95%)	81(95%)	81 (95%)
HLHS without heterotaxy	144	127 (90%)	115 (85%)	97 (80%)	78 (84%)	68 (75%)
HRHS with heterotaxy	26	23 (92%)	22 (92%)	19 (79%)	16 (76%)	15 (71%)

Figure 2. (***a***) comparing transplant-free survival based on HRHS anatomic type. (***b***) comparing transplant-free survival between HRHS with heterotaxy with HLHS and HRHS patients without heterotaxy. HLHS = hypoplastic left heart syndrome; HRHS = hypoplastic left heart syndrome.

ventricular canal, pulmonary atresia, and anomalous pulmonary veins. She initially underwent Blalock–Taussig–Thomas shunt followed by Glenn/Kawashima repair. However, she subsequently developed severe respiratory failure and was referred for heart transplants. She received heart transplants at 7 months of age and died within 2 months of heart transplants.

Patient 3: death after S2P

This patient's cardiac diagnosis consisted of heterotaxy syndrome with unbalanced atrio-ventricular canal, dextrocardia, associated with moderate to severe atrio-ventricular valve regurgitation. Patient tolerated initial palliation with PA Bands and left sided atrio-ventricular valvuloplasty. Bidirectional Glenn was performed at around 4 months of age. Subsequently, she developed progressive, severe ventricular dysfunction and severe atrio-ventricular valve regurgitation and died at an outside hospital at 3.5 years of age.

Patient 4: death after S2P

This was a postnatal diagnosis transferred from outside hospital, and mother left after birth. Her cardiac diagnosis included double outlet, hypoplastic right ventricle with tricuspid atresia, D-malposed great vessels, pulmonary stenosis, and ventricular septal defect who underwent pulsatile Glenn connection. She presented in severe heart failure with severe left ventricle dysfunction and died from heart failure at 2 years of age.

Patient 5: death after S2P

This patient was transferred from outside hospital with post-natal diagnosis of tricuspid atresia with bilateral superior vena cava, pulmonary stenosis, born at term, with dysmorphic features. He also had solitary kidney and brain choroid cyst. He tolerated the initial Blalock–Taussig–Thomas shunt followed by Glenn palliation. Her stage 2 postoperative course was complicated by recurrent, bilateral chylous effusion and renal failure, with peritoneal drain placement, multiple bouts of sepsis with intermittent shock, respiratory failure requiring tracheostomy and chronic ventilation. This patient eventually was discharged to hospice and died at 8 months of age.

Patient 6: transplant after S2P

This patient's diagnoses included right atrial isomerism, unbalanced AVC, total anomalous pulmonary venous return (infra-diaphragmatic), D-TGA with pulmonary atresia, asplenia and dextrocardia. Patient underwent bidirectional Glenn. Patient subsequently developed refractory ventricular dysfunction and heart failure and underwent heart transplants about 4 years of age. Patient was alive (11 y) at the time of writing of this manuscript.

Ebstein's anomaly

Most patients had good outcomes and 3 were able to get converted to a 2-ventricle or 1.5 ventricle circulation. Only one patient died in this group.

Patient 1: death after S2P

This was a 5-month-old transferred from outside hospital with a prenatal diagnosis of Ebstein's anomaly of the tricuspid valve, hypoplastic right heart, and pulmonary atresia. He had hypoplasia of his right lungs. He initially underwent stage 1 palliation with a tricuspid exclusion (Starnes Procedure) with a central aorto-pulmonary shunt placement. His post-operative course was complicated by incessant atrial arrhythmias and persistent oxygen requirement. He underwent stage 2 (Glenn anastomosis) with right atrial reduction; but continued to struggle post-operatively and was unable to wean off mechanical ventilation. He eventually died at 5 months of age from right-sided pneumonia and respiratory failure.

Five-year transplant-free survival in hypoplastic right heart syndrome subtypes

Figure 2A shows the comparative survival free of transplant in HRHS subtypes. Five-year transplant-free survival was high for most groups (double inlet left ventricle: 100%, pulmonary atresia: 94%, Ebstein's anomaly: 92%, tricuspid atresia: 90%). Patients with DILV had the best outcomes with 100% survival at all stages. The worst outcomes were noted in the heterotaxy group. The heterotaxy group had worse outcomes with 3 deaths and 3 heart transplantswithout associated heterotaxy, before Fontan

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completion. The 5-year transplant-free survival in this group was ~ 71%. Heterotaxy was associated with death/transplant in patients with hypoplastic right heart syndrome ($p = 0.03$).

Comparing survival between hypoplastic left heart syndrome and hypoplastic right heart syndrome with and without heterotaxy

We extracted the mortality and transplant data on patients with HLHS diagnosis from our surgical database. Out of the total 193 patients diagnosed with HLHS during the study period (January 2010 to January 2023), 144 (75%) were isolated HLHS without an associated diagnosis of heterotaxy. These patients were compared with HRHS patients. Figure 2B compares the transplant-free survival of HRHS patients with and without heterotaxy with HLHS patients without heterotaxy. A total of 127 patients with HRHS without associated heterotaxy syndrome had excellent one year (96% ± 0.1) and five-year (95% ± 0.2) survival during follow-up. Hypoplastic left heart syndrome cohort did slightly worse than the HRHS group at one-year (90% ± 0.1), however in patients with HLHS who survived infancy, overall survival improved compared to the heterotaxy group. Despite the presence of a systemic left ventricle, patients with HRHS with heterotaxy had significantly worse 5-year transplant-free survival (71% ± 0.1) when compared to HLHS without heterotaxy (75% ± 0.1), log rank $p < 0.001$.

Discussion

Single ventricle heart disease carries a high risk of mortality and lifelong morbidity among survivors. However, advancements in surgical techniques, postoperative care, and routine patient surveillance have led to improved clinical outcomes in recent years.[1–3] While most multicentre collaborations have focused on outcomes in HLHS, there are limited data on early childhood survival in patients with a systemic left ventricle or hypoplastic right heart syndrome.[1–6]

In this large, single-centre study spanning 13 years, we characterise the anatomic features and clinical course of infants with HRHS. We also compare their survival with a contemporaneous cohort of HLHS patients to evaluate the potential survival benefit of a systemic left ventricle. Our analysis demonstrates that the presence of heterotaxy syndrome in HRHS patients negates the survival advantage of a systemic left ventricle, with these patients showing poorer early childhood survival than HLHS patients with a systemic right ventricle.

The single-centre, longitudinal design of our study enables a detailed examination of causes of death and transplant—insights that are often difficult to obtain in multicenter studies. As such, our findings provide a meaningful perspective on the expected outcomes of HRHS in the modern era and may aid in family counselling and surgical decision-making.

Oster et al. conducted a large multicenter study using data from the Pediatric Cardiac Care Consortium, linked with the U.S. National Death Index and the Organ Procurement and Transplant Network through 2014.[1] They analysed outcomes in patients with single-ventricle CHD who were born between 1982 and 2003 and underwent surgical treatment before one year of age. Among the 2,792 individuals who survived to discharge after their first congenital heart surgery without undergoing transplant, 58% had a systemic right ventricle and 85% had a systemic left ventricle. At 20 years post-discharge, transplant-free survival was significantly higher in patients with a systemic left ventricle (72%) compared to those with a systemic right ventricle (52%). This study highlighted the long-term survival advantage of a systemic left ventricle in patients who reached or survived their Fontan completion. However, due to its registry-based design, the study lacked detailed data on the factors contributing to death or transplant before Fontan completion.

Our study addresses this gap by examining anatomical features that may influence survival to Fontan completion in HRHS patients. We found that certain subtypes, such as double-inlet left ventricle, had a 100% survival rate to Fontan completion. Patients with pulmonary atresia with intact ventricular septum and tricuspid atresia also demonstrated high early childhood survival. However, additional patient-specific factors—such as lung hypoplasia, solitary kidney, and chromosomal abnormalities—negatively impacted survival in select cases. In the current era of improved imaging and surgical techniques, about a tenth of pulmonary atresia with intact ventricular septum patients and a quarter of patients with Ebstein's anomaly were able to get conversion to 1.5 to 2 ventricle physiology, thus avoiding the need for further single ventricle palliation, and thus reducing the long-term sequelae of Fontan physiology.

Sittiwangkul et al. reported on 225 patients with tricuspid atresia born between 1971 and 1999, noting substantially lower survival rates at one year (81%) and at ten years (70%).[2] In contrast, our cohort of patients with all tricuspid atresia variants demonstrated markedly improved outcomes, with 1-year and 5-year transplant-free survival rates of 94 and 90%, respectively. These improved results likely reflect advancements in surgical techniques and postoperative care over the past two decades. Another study comparing tricuspid atresia with TGA to double inlet left ventricle patients found superior survival to Fontan among the double inlet left ventricle group (91% vs. 60%). Similarly, in our study, most infants with tricuspid atresia survived through stage II palliation, with only 4 patients (12%) not progressing, and Fontan completion rates were high. Consistent with previous findings, double inlet left ventricle patients in our cohort had the most favourable outcomes, with 100% survival.

A key finding of our study is the significant impact of heterotaxy syndrome in negating the survival advantage typically conferred by a systemic left ventricle in HRHS patients. Among patients without heterotaxy, overall survival across all HRHS subtypes was excellent, with approximately 96% transplant-free survival at 1 year and 94% at 5 years. In contrast, patients with associated heterotaxy syndrome experienced markedly reduced survival, particularly following Glenn (stage 2) palliation. Although their 1-year survival remained high at 96%, it declined substantially to 71% by 5 years.

The progressive increase in mortality among HRHS patients with heterotaxy underscores the complex interplay of associated comorbidities, including splenic dysfunction, feeding difficulties related to intestinal malrotation, abnormal lymphatic development, and the presence of an unbalanced common atrioventricular valve prone to early degeneration. These factors likely contribute to the poorer long-term outcomes observed in this subgroup.

Tanimoto et al.[10] evaluated 279 patients with single-ventricle physiology and heterotaxy syndrome treated between 1978 and 2012, reporting an overall 10-year survival rate of approximately 47%. Notably, the need for neonatal surgery and the presence of total anomalous pulmonary venous return were identified as

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significant risk factors for mortality. Our cohort, drawn from a more contemporary era, had limited long-term follow-up data beyond five years in some patients, precluding robust statistical analysis for long-term outcomes. However, we observed a concerning trend of early Fontan failure within this group. At the time of manuscript preparation, about one-third of all the heterotaxy patients who had completed the Fontan procedure had already shown signs of Fontan failure. Of these, five were referred for transplant evaluation, and two had died after being deemed unsuitable candidates for orthotopic heart transplantation.

Despite the advancement in surgical techniques, and huge international level collaborative initiatives to improve diagnosis and surveillance, recent multicentre studies on HLHS patients have reported comparatively poorer outcomes.[11] The single ventricle reconstruction trial, a large multicentre study, demonstrated transplant-free survival rates of only 59 to 64% at six years of age for patients with HLHS.[10] These numbers would indicate negative influence of single right ventricle morphology on single ventricle outcomes despite the recent advancements.

Our study highlights the critical role of heterotaxy syndrome in negating the survival benefit of a systemic left ventricle in HRHS patients, showing notably worse outcomes in this subgroup. In our cohort, HLHS patients without heterotaxy had better outcomes, with an estimated 5-year transplant-free survival of approximately 75%. Interestingly, when compared to HRHS with heterotaxy, HLHS infants had poorer 1-year survival (91% versus 96%); however, at 5 years, they had better survival than the heterotaxy group (75% versus 71%). This may indicate that the systemic left ventricle (in heterotaxy group) may afford some protection against death during infancy; however, this advantage wanes over time, and HLHS patients who survive infancy, continue to perform better compared to heterotaxy patients despite their systemic right ventricle.

Limitations and strengths

Our study has several limitations. As a retrospective analysis, it is subject to inherent biases. While the overall sample size is large, the relative number of patients within each HRHS subtype remains small, which may limit the generalizability of our findings. Additionally, comprehensive genetic testing was not uniformly performed across the cohort, restricting our ability to fully assess the prevalence and impact of heterotaxy-related genetic variants.

To focus on contemporary management practices, we limited our cohort to patients born after 2010. As a result, follow-up beyond five years was insufficient for many patients, preventing robust conclusions regarding long-term post-Fontan outcomes. Future longitudinal studies are needed to better understand the interaction between heterotaxy and single ventricle morphology over time.

Despite these limitations, the single center design of our study offers distinct advantages. By comparing HRHS and HLHS patients managed at the same institution during the same time period, we have minimised the confounding bias related to variability in surgical technique and institutional practices—challenges often encountered in multicentre studies. This has allowed for a more accurate analysis of survival outcomes and associated risk factors. With a relatively large cohort spanning 13 years, our study provides meaningful insights into early childhood outcomes, including transplant-free survival and mortality causes. This setting also enabled a detailed, case-level review of anatomical subtypes and patient-specific risk factors contributing to poor outcomes. By differentiating among anatomical subtypes of HRHS, the study reveals significant variations in survival, adding clinical granularity that may improve prognostication and applicability to patient care. The inclusion of extracardiac comorbidities offers a holistic view of the multifactorial risks in HRHS management. These findings support nuanced surgical planning and informed family counselling, particularly for patients with heterotaxy syndrome, highlighting the need for individualised treatment strategies.

Conclusion

In summary, this large single-centre study demonstrates that hypoplastic right heart syndrome patients generally experience excellent early childhood survival. However, in those with heterotaxy syndrome, the presence of complex extracardiac comorbidities may offset the survival benefit typically associated with systemic left ventricular morphology. In fact, these patients may have worse outcomes beyond infancy compared to their hypoplastic left heart syndrome counterparts, challenging the assumption that a systemic left ventricle uniformly confers superior prognosis. These findings have important implications for counselling families and for surgical planning in patients with hypoplastic right heart syndrome and heterotaxy.

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Authors contribution. **CM:** data collection and manuscript preparation. **DV**: revision of final manuscript. **DB**: conceptualisation, study design, data collection, data analysis, preparation, and revision of draft and final manuscript.

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