








ORIGINAL RESEARCH

Impact of Left Ventricular Morphology on Adverse Outcomes Following Stage 1 Palliation for Hypoplastic Left Heart Syndrome: 20 Years of National Data From Sweden

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BACKGROUND: Hypoplastic left heart syndrome is associated with significant morbidity and mortality. We aimed to assess the influence of left ventricular morphology and choice of shunt on adverse outcome in patients with hypoplastic left heart syndrome and stage 1 palliation.

METHODS AND RESULTS: This was a retrospective analysis of patients with hypoplastic left heart syndrome with stage 1 palliation between 1999 and 2018 in Sweden. Patients (n=167) were grouped based on the anatomic subtypes aortic-mitral atresia, aortic atresia-mitral stenosis (AA-MS), and aortic-mitral stenosis. The left ventricular phenotypes including globular left ventricle (Glob-LV), miniaturized and slit-like left ventricle (LV), and the incidence of major adverse events (MAEs) including mortality were assessed. The overall mortality and MAEs were 31% and 41%, respectively. AA-MS (35%) was associated with both mortality (all other subtypes versus AA-MS: interstage-I: hazard ratio [HR], 2.7; $P=0.006$; overall: HR, 2.2; $P=0.005$) and MAEs (HR, 2.4; $P=0.0009$). Glob-LV (57%), noticed in all patients with AA-MS, 61% of patients with aortic stenosis-mitral stenosis, and 19% of patients with aortic atresia-mitral atresia, was associated with both mortality (all other left ventricular phenotypes versus Glob-LV: interstage-I: HR, 4.5; $P=0.004$; overall: HR, 3.4; $P=0.0007$) and MAEs (HR, 2.7; $P=0.0007$). There was no difference in mortality and MAEs between patients with AA-MS and without AA-MS with Glob-LV ($P>0.15$). Patients with AA-MS (35%) or Glob-LV (38%) palliated with a Blalock-Taussig shunt had higher overall mortality compared with those palliated with Sano shunts, irrespective of the stage 1 palliation year (AA-MS: HR, 2.6; $P=0.04$; Glob-LV: HR, 2.1; $P=0.03$).

CONCLUSIONS: Glob-LV and AA-MS are independent morphological risk factors for adverse short- and long- term outcome, especially if a Blalock-Taussig shunt is used as part of stage 1 palliation. These findings are important for the clinical management of patients with hypoplastic left heart syndrome.

Key Words: adverse outcome ■ aortic atresia-mitral stenosis ■ globular left ventricle ■ hypoplastic left heart ■ left ventricular morphology

Hypoplastic left heart syndrome (HLHS) remains a significant cause of morbidity and mortality despite advancements in surgical technique and

perioperative care.¹ Based on valve patency, HLHS is classified into 3 anatomic subtypes: aortic and mitral valve atresia (AA-MA), aortic valve atresia and mitral

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CLINICAL PERSPECTIVE

What Is New?

- In this national hypoplastic left heart syndrome cohort with 20-year follow-up, we demonstrate for the first time that a globular left ventricle phenotype is independently associated with adverse outcomes.
- In addition, patients with a globular left ventricle and/or with aortic atresia-mitral stenosis are at particularly high risk for adverse outcomes if they received a Blalock-Taussig shunt as part of their Norwood stage 1 palliation.

What Are the Clinical Implications?

- Our findings provide an important addition to risk stratification of patients with hypoplastic left heart syndrome, highlighting the need for careful surgical planning and shunt selection at the time of Norwood stage 1.
- In addition, personalized risk assessment depending on left ventricular morphology may allow for a more individualized approach on timing and nature of interstage follow-up.

Nonstandard Abbreviations and Acronyms

AA-MA	aortic atresia-mitral atresia
AA-MS	aortic atresia-mitral stenosis
AS-MS	aortic stenosis-mitral stenosis
BTs	Blalock-Taussig shunt
EFE	endocardial fibroelastosis
Glob-LV	globular left ventricle
IAS	intact atrial septum
IS-I	interstage I
LPW	low preoperative weight
MAEs	major adverse events
RAS	restrictive atrial septum
S1P	stage 1 palliation (Norwood)
sTR	severe tricuspid regurgitation
SVR	Single Ventricle Reconstruction
TCPC	total cavopulmonary connection

valve stenosis (AA-MS), and aortic and mitral valve stenosis (AS-MS). AS-MA is an extremely rare subtype, which typically includes an unrestrictive ventricular septal defect and is therefore not included in the classical types of HLHS.²

The clinical impact of these anatomic subtypes remains debatable. A few early studies suggested worse outcome in patients with AA-MA, presumably because of the severely hypoplastic ascending aorta and the

subsequent risk for decreased myocardial perfusion.³⁻⁵ Later studies suggested higher short- and long-term mortality in patients with AA-MS,⁶⁻⁸ whereas the SVR (Single Ventricle Reconstruction) trial, a large prospective North American multicenter study on 522 patients with single, morphologically right ventricles, could not confirm this finding.⁹

In terms of left ventricular morphology, basically 3 left ventricular phenotypes have been described: (1) a thickened, globular, nonapex-forming LV with endocardial fibroelastosis (EFE) (Glob-LV), (2) a miniaturized, nonapex-forming LV with normal thickness of the myocardium and without EFE, and (3) a slit-like, thin-walled LV.^{10,11}

Glob-LV, the most common left ventricular phenotype, is commonly seen in patients with AA-MS, but also in patients with AS-MS who have minimal outflow from the LV. A miniaturized LV occurs in the AS-MS subtype, with a moderately underdeveloped mitral and aortic valve, whereas a slit-like LV is only encountered in AA-MA.^{10,11}

It has been suggested that, through interventricular interaction, a larger remnant LV in HLHS or a hypertrophied septum may lead to impaired right ventricular (RV) function and/or increased risk for adverse outcome.¹²⁻¹⁵ However, other authors were unable to show such an association.^{9,16}

Interestingly, the potential impact of the slit-like, miniaturized or Glob-LV phenotypes on adverse outcome has to our knowledge not yet been demonstrated.

The introduction of the Sano shunt in 2002 was proposed as a better alternative to the Blalock-Taussig shunt (BTs), although some drawbacks, including longer aortic clamp time and right ventriculotomy, have been described.¹⁷⁻¹⁹ Prior preliminary results of our previous single-center retrospective study of 90 patients with HLHS suggested higher mortality in patients with AA-MS and BTs palliation (abstract presented at the AEPC meeting 2015),²⁰ but the study covered an earlier period starting in 1993, with several inherent biases including significant mortality during the early years of Norwood palliation and the exclusive use of BTs during the 1990s.

The major goal of this study was to investigate the short- and long-term impact of morphological and early surgical risk factors on major adverse outcome in patients with HLHS. We hypothesized that not only the anatomic HLHS subtype, but also the left ventricular phenotype could influence the outcome. Our second hypothesis was that the use of the BTs in infants with certain left ventricular morphological subtypes have further adverse effects on the clinical outcome.

METHODS

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Population

All patients with the anatomic HLHS subtypes AA-MA, AA-MS, and AS-MS who underwent Norwood stage 1 palliation (S1P) at the Skane University Hospital in Lund and the Queen Silvia Children's Hospital, Sahlgrenska University Hospital, Gothenburg (the only 2 tertiary referral centers in Sweden since 1993) between January 1999 and December 2018 were included. Patients with the anatomic subtype AS-MA, ventricular septal defects, or non-HLHS variants with a systemic right ventricle were excluded, because they are not part of the conventional HLHS subtype classification.²

Patients were identified from the local institutional surgical databases and from the SWEDCON (Swedish Registry of Congenital Heart Disease). Informed consent was not required. This study was approved by the Lund University Ethics Committee for human research.

Data were collected by reviewing available postnatal pre- and postoperative echocardiograms, as well as imaging, surgical, and other clinical records including perinatal and demographic data, reinterventions, and postoperative outcome.

Echocardiographic Assessment and Definitions

Echocardiograms were reviewed by a single pediatric cardiologist (K.F.) for anatomic and functional details using videotapes and digital databases including Xcelera (Philips Healthcare, Amsterdam, the Netherlands), SyngoDynamics (Siemens, Erlangen, Germany), or EchoPAC (GE Healthcare, Buckinghamshire, Great Britain), depending on era and center.

The assessment of left ventricular morphology included the anatomic HLHS subtypes and left ventricular phenotypes.

The anatomic HLHS subtypes were defined as follows: AA-MA, no flow across the aortic and mitral valves; AA-MS, no flow across the aortic valve combined with flow across the mitral valve; and AS-MS, flow across the aortic and mitral valve.

The left ventricular phenotypes were defined as follows: (1) Glob-LV: thickened, hypoplastic, nonapex forming LV with a small cavity, and EFE; (2) a miniaturized LV: nonapex-forming LV with normal thickness of the myocardium and without EFE; and (3) a slit-like LV, with a thin parietal LV wall, and a slit-like cavity without EFE. A slit-like LV is even referred to as absent LV, because it is usually not demonstrable by echocardiography. The 3 left ventricular phenotypes are depicted in Figure 1.

A restrictive atrial septum (RAS) was defined as a mean gradient across the atrial septum of ≥ 8 mm Hg and/or small-sized atrial septal defect in patients with

an explicit preoperative clinical presentation indicating RAS.²¹ If no communication between the atria was present, the atrial communication was defined as intact (IAS). Mild-to-moderate RV dysfunction and moderate-to-severe tricuspid regurgitation, qualitatively assessed on the last echocardiogram or echo report before S1P, were noted.

Other Perinatal Factors

In addition to left ventricular morphology, other putative perinatal risk factors included postnatal diagnosis, female sex, prematurity (<37 weeks of gestation), low preoperative (pre-S1P) weight ≤ 2.5 kg, cardiac and extracardiac comorbidity, RV dysfunction before S1P, and RAS/IAS. Early surgical factors included the type of shunt at S1P.

Definition of Outcome Variables

The overall operative mortality for S1P was defined as mortality before hospital discharge or within 30 days after surgery.

Major outcome variables included mortality (interstage [IS]-I, IS-II, post total cavopulmonary connection, and overall mortality) and a combined morbidity-mortality variable called major adverse events (MAEs). The morbidity included in the latter needed a left ventricular assist device or extracorporeal membrane oxygenation, heart transplant, protein-losing enteropathy, and takedown of Glenn or total cavopulmonary connection (for reasons other than conversion to a biventricular circulation).

Statistical Analysis

Data are expressed as median (range). The Mann-Whitney *U* test or Kruskal-Wallis test were used to compare 2 or more subgroups. For categorical variables, a χ^2 test of independence or Fisher exact test was used. Kaplan-Meier curves were applied, and the Wilcoxon log-rank test and Cox regression (95% CI) were used to test for differences in survival and freedom from MAEs between the groups. All risk variables with a *P* value ≤ 0.2 were included in a stepwise multivariate Cox regression model and in a later step removed, if not significant or impacting the estimate of other variables significantly. A sensitivity analysis (forward and backward Wald Cox regression model) was done to verify the results from the stepwise Cox regression model. Interaction between the morphological LV subtypes and type of shunt at S1P was tested in a Cox regression model. A *P* value ≤ 0.05 was considered statistically significant; $P > 0.05$ but < 0.1 was considered a trend. StatView 5.01 for Windows (SAS Institute, Cary, NC) and Statistical Package for Social

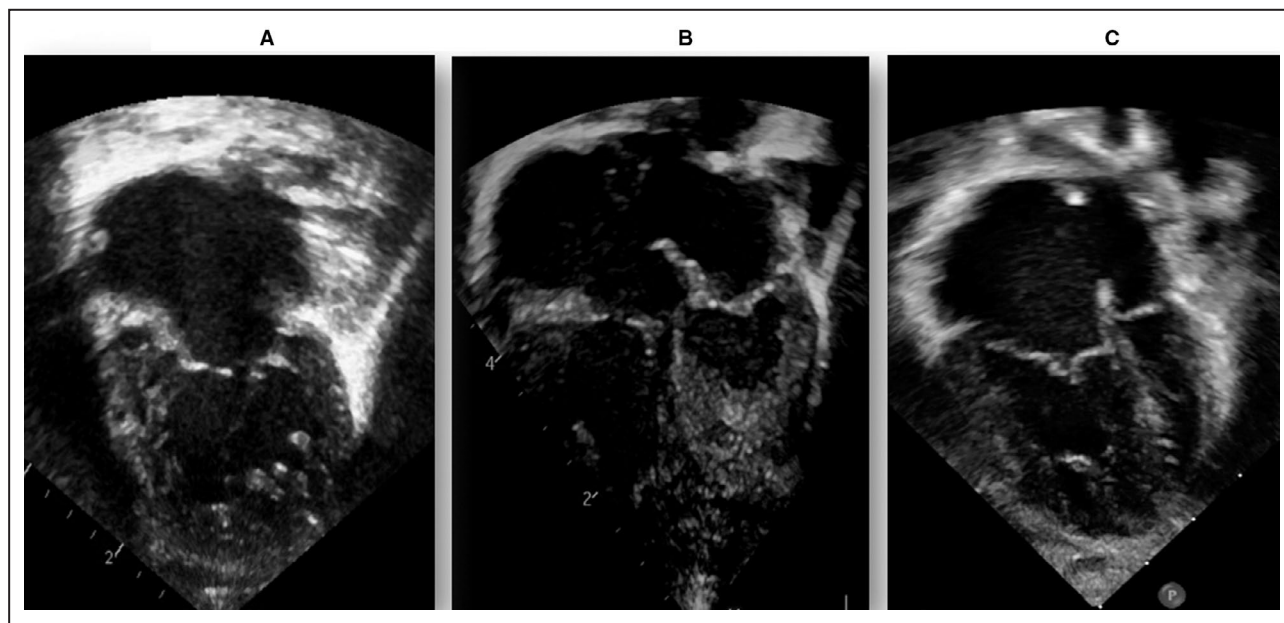


Figure 1. Left ventricular phenotypes.

A, Slit-like left ventricle. **B,** Globular left ventricle. **C,** Miniaturized left ventricle.

Sciences version 25 (IBM, Armonk, NY) were used for data analysis.

RESULTS

Main Characteristics of the Study Cohort

The main characteristics are shown in Table 1. In total, 167 patients met the inclusion criteria. In all patients, the anatomic HLHS subtype and left ventricular phenotype were determined by evaluating pre- or postoperative echocardiograms. In 27 patients, no preoperative echocardiogram was available or echocardiogram quality was suboptimal. In these cases, imaging, surgical, and other clinical notes were used to determine the degree of RAS, tricuspid regurgitation, and RV function before S1P.

Cardiac comorbidity was encountered in 9 patients and included 4 cases with partial or total anomalous pulmonary venous drainage. None of the patients with partial anomalous pulmonary venous drainage or total anomalous pulmonary venous drainage died; 2 of them had MAEs. Extracardiac comorbidity was present in 10 patients and included mainly urogenital anomalies. Forty-six patients (27.5%) underwent S1P with a BTs, which was exclusively used until 2002 when the Sano modification was introduced. The overall operative mortality for S1P was 10.3%. Following S1P, 3 patients remained hospitalized until stage 2. One hundred thirty-three patients (80.6%) went on to the Glenn procedure, and 101 patients (68.2%) had Fontan completion by total cavopulmonary connection.

Left Ventricular Morphology

AA-MA was encountered in 40.7% (n=68) of patients, AA-MS in 34.7% (n=58) of patients, and AS-MS in 24.6% (n=41) of patients. There was no significant difference between these 3 anatomic subtypes with regard to the perinatal variables, although prematurity ($P=0.09$) and cardiac comorbidity ($P=0.08$) tended to be more common in the AA-MA group (Table 1).

A miniaturized LV was present in 9.6% (n=16) of patients, being noticed only in AS-MS. A slit-like LV was encountered in 32.9% (n=55) of patients and only noted in AA-MA. Glob-LV was encountered in 57.5% (n=96) of patients, and present in all patients with AA-MS (n=58), in 61% of patients with AS-MS (n=25), and in 19.1% patients with AA-MA (n=13). Perinatal variables were equally distributed between the 3 left ventricular phenotypes except for female sex, which was most common in patients with a slit-like LV. A BTs was most commonly used in patients with AS-MS (n=19; 46%) and miniaturized LV (n=7; 44%) (Table 2).

Univariate Analysis for Mortality and MAEs

These data are summarized in Table 3.

Perinatal and Surgical Predictors

Among the perinatal variables, low preoperative weight, RV dysfunction before S1P, cardiac comorbidity, RAS/IAS, and female sex were positively associated with IS-I mortality, overall mortality, and/or MAEs.

Palliation with a BTs was associated with IS-I mortality, overall mortality, and MAEs in the univariate analysis

Table 1. Main Characteristics of the Study Cohort Based on the Anatomic Hypoplastic Left Heart Syndrome Subtypes

	Total	AA-MA	AA-MS	AS-MS	P value*
Perinatal variables					
Postnatal diagnosis, n/N (%)	95/167 (56.9)	34/68 (50)	37/58 (63.8)	24/41 (58.5)	0.2
Gestational age, wk	39.0 (32–42)	39.5 (32–42)	39.0 (35–42)	39.0 (37–42)	0.3
Prematurity, n/N (%)	10/167 (6)	7/68 (10.3)	3/58 (5.2)	0/41 (0)	0.09
Female sex, n/N (%)	56/167 (33.5)	29/68 (42.6)	17/58 (35.4)	10/41 (24.4)	0.1
Cardiac comorbidity, n/N (%)	9/167 (5.4)	6/68 (8.8)	0/58 (0)	3/41 (7.3)	0.08
Extracardiac comorbidity, n/N (%)	10/167 (6)	5/68 (7.4)	4/58 (6.9)	1/41 (2.4)	0.5
Restrictive/intact atrial septum, n/N (%)	32/167 (19.2)	10/68 (15)	10/58 (17)	12/41 (29)	0.2
RV dysfunction before S1P, n/N (%)	12/167 (7.2)	4/68 (6.2)	6/58 (10.3)	2/41 (4.9)	0.5
sTR before S1P, n/N (%)	19/167 (11.4)	9/68 (13.2)	7/58 (12.1)	3/41 (7.3)	0.6
Stage 1 palliation					
Age at stage 1, d	6 (1–31)	6 (1–31)	6 (1–17)	6 (1–21)	0.8
Weight at stage 1, kg	3.4 (1.8–4.8)	3.4 (1.8–4.5)	3.4 (2.3–4.5)	3.3 (2.4–4.8)	0.6
Low weight, ≤2.5 kg, n/N (%)	15/167 (8.9)	7/68 (10.3)	7/58 (12)	1/41 (2.4)	0.2
BT shunt, n/N (%)	46/167 (27.5)	7/68 (10.3)	20/58 (34.5)	19/41 (46.3)	<0.0001
Mortality					
Interstage I, n/N (%)	32/165 (19.4)	9/68 (13.2)	19/57 (33.3)	4/40 (10)	0.004
Overall operative, S1P, n/N (%)	17/165 (10.3)	5/68 (7.4)	11/57 (19.3)	1/40 (2.5)	0.02
Interstage II, n/N (%)	15/116 (12.9)	4/49 (8.2)	5/35 (14.3)	6/32 (18.8)	0.6
Post-TCPC, n/N (%)	5/101 (5)	1/45 (2.2)	3/30 (10)	1/26 (3.8)	0.3
Overall, n/N (%)	52/167 (31.1)	14/68 (20.6)	27/58 (46.6)	11/41 (26.8)	0.006
Major adverse events					
ECMO/LVAD, n/N (%)	26/167 (15.6)	10/68 (14.7)	12/58 (20.7)	4/41 (9.8)	0.3
Protein losing enteropathy, n/N (%)	5/167 (3)	3/68 (4.4)	2/58 (3.4)	0/41 (0)	0.4
Takedown Glenn/TCPC, n/N (%)	6/133 (4.5)	2/59 (3.4)	1/38 (2.6)	3/36 (8.3)	0.4
Heart transplant, n/N (%)	10/167 (6)	5/68 (7.4)	2/58 (3.4)	3/41 (7.3)	0.6
Overall, n/N (%)	69/167 (41.3)	20/68 (29.4)	34/58 (58.6)	15/41 (36.6)	0.003

AA-MA indicates aortic atresia-mitral atresia; AA-MS, aortic atresia-mitral stenosis; AS-MS, aortic stenosis-mitral stenosis; BT shunt, Blalock-Taussig shunt; ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; n, number of patients for given variable; N, total number of patients; RV, right ventricular; S1P, stage 1 palliation; sTR, severe tricuspid regurgitation; and TCPC, total cavopulmonary connection.

*P value comparing anatomic hypoplastic left heart syndrome subtypes.

(Table 3). After adjusting for the year of S1P, a BTs was still significantly associated with IS-I mortality (BTs versus Sano shunt: hazard ratio [HR], 2.69 [95% CI, 1.19–6.1]; $P=0.02$), IS-II mortality (HR, 3.9 [95% CI, 1.1–14.4]; $P=0.04$), overall mortality (HR, 3.1 [95% CI, 1.6–5.9]; $P=0.0005$), and MAEs (HR, 2.1 [95% CI, 1.2–3.7]; $P=0.01$).

The year of S1P had a significant influence on overall mortality and MAE in the univariate analysis. When the cohort was grouped on the basis of era (early: 1999–2008 and current: 2009–2010), there were no differences in mortality (IS-I, overall) or MAEs between these 2 groups. Older age at S1P was not associated with adverse outcome (Table 3). Only 9 out of 167 (5.4%) patients had their S1P beyond the age of 14 days.

Left Ventricular Morphology

Patients with AA-MS had the highest IS-I mortality, overall mortality, and MAE as compared with patients with the other 2 anatomic subtypes (Tables 1, Figure 2A and 2B),

whereas AA-MA was associated with the lowest overall mortality and MAEs in the univariate analysis. No significant difference in outcome was noted between AA-MA and AS-MS ($P\geq 0.4$). When adjusting for type of shunt and perinatal variables, AS-MS exhibited the lowest IS-I and overall mortality, again without a significant difference in outcome between AA-MA and AS-MS ($P\geq 0.5$).

A miniaturized LV was linked to the lowest IS-I mortality, overall mortality, and MAEs, whereas Glob-LV was associated with the highest IS-I mortality, overall mortality, and MAEs in the univariate analysis (Tables 2, Figure 2C and 2D).

AA-MS and Glob-LV in the Multivariate Analysis for Mortality and MAE

When including the anatomic subtype AA-MS, type of shunt, and year of S1P as well as significant perinatal variables (RAS/intact atrial septum, low preoperative weight, RV dysfunction before S1P, and cardiac

Table 2. Left Ventricular Phenotypes and Their Association With Adverse Outcome

	Glob-LV, n/N (%)	Miniaturized LV, n/N (%)	Slit-like LV, n/N (%)	P value*
Perinatal variables				
Postnatal diagnosis	60/96 (62.5)	9/16 (56.3)	26/55 (47.3)	0.2
Prematurity	5/96 (5.2)	0/16 (0)	5/55 (9.1)	0.4
Female sex	24/96 (25)	5/16 (31.3)	27/55 (49.1)	0.01
Cardiac comorbidity	4/96 (4.2)	1/16 (6.3)	4/55 (7.3)	0.7
Extracardiac comorbidity	6/96 (6.3)	1/16 (6.3)	3/55 (5.5)	0.9
Restrictive/intact atrial septum	20/96 (20.8)	3/16 (18.8)	9/55 (16.4)	0.8
RV dysfunction before S1P	9/96 (9.4)	0/16 (0)	3/55 (5.5)	0.3
sTR before S1P	10/96 (10.4)	1/16 (6.3)	8/55 (14.5)	0.6
HLHS subtypes				
AA-MA	13/96 (13.5)	0/16 (0)	55/55 (100)	<0.0001
AA-MS	58/96 (60.4)	0/16 (0)	0/55 (0)	
AS-MS	25/96 (26)	16/16 (100)	0/55 (0)	
Stage 1 palliation				
Low preoperative weight	9/96 (9.4)	0/16 (0)	6/55 (10.9)	0.4
BT shunt	36/96 (37.5)	7/16 (43.8)	3/55 (5.5)	<0.0001
Mortality				
Interstage I	27/95 (28.4)	0/15 (0)	5/55 (9.1)	0.002
Overall operative, S1P	14/95 (14.7)	0/15 (0)	3/55 (5.5)	0.08
Interstage II	10/62 (11.3)	1/13 (7.4)	4/41 (9.8)	0.5
Post-TCPC	4/52 (7.7)	0/12 (0)	1/37 (2.7)	0.4
Overall	41/96 (42.7)	1/16 (6.3)	10/55 (18.2)	0.0006
Major adverse events				
ECMO/LVAD	18/96 (18.8)	0/16 (0)	8/55 (14.5)	0.2
Protein losing enteropathy	2/96 (2.1)	0/16 (0)	3/55 (5.5)	0.4
Takedown Glenn/TCPC	3/68 (4.4)	1/15 (6.7)	2/50 (4)	0.9
Heart transplant	5/96 (5.2)	0/16 (0)	5/55 (9.1)	0.4
Overall	51/96 (53.1)	2/16 (12.5)	16/55 (29.1)	0.0007

AA-MA indicates aortic-mitral atresia; AA-MS, aortic atresia-mitral stenosis; AS-MS, aortic-mitral stenosis; BT shunt, Blalock-Taussig shunt; ECMO, extracorporeal membrane oxygenation; Glob-LV, globular left ventricular; LV, left ventricle; HLHS, hypoplastic left heart syndrome; LVAD, left ventricular assist device; n, number of patients for given variable; N, total number of patients; RV, right ventricle; S1P, stage 1 palliation; sTR, severe tricuspid regurgitation; and TCPC, total cavopulmonary connection.

*P value comparing anatomic HLHS subtypes.

comorbidity) and the year of S1P, AA-MS and the use of a BTs remained significantly linked to IS-I mortality, overall mortality, and MAE (Table 4).

Likewise, Glob-LV and the use of a BTs were linked to increased IS-I mortality, overall mortality, and MAEs after adjusting for sex, perinatal variables, and the year of S1P (Table 5). The sensitivity analyses for AA-MS or Glob-LV resulted in similar results.

In a multivariate Cox regression, there was no interaction between AA-MS and shunt type or Glob-LV and shunt type ($P \geq 0.3$ for all). When excluding the 4 patients with partial anomalous pulmonary venous drainage or total anomalous pulmonary venous drainage, Glob-LV, AA-MS, and palliation with a BTs were still associated with adverse outcome in the uni- and multivariate analysis.

Glob-LV With or Without AA-MS

To discriminate between the impact of Glob-LV and AA-MS on mortality and MAEs, we divided our cohort in 3 groups: (1) no Glob-LV/no AA-MS (n=71), (2) Glob-LV/no AA-MS (n=38), and (3) Glob-LV/AA-MS (n=58). There was a significant difference between no Glob-LV/no AA-MS and the other 2 groups in IS-I mortality, overall mortality, and MAEs, with the worst outcome in mortality and MAEs for Glob-LV/AA-MS in the univariate analysis and in overall mortality in the multivariate analysis (Table 6 and Figure 3A and 3B). Similar results were obtained in the sensitivity analyses. However, no significant difference was observed between the Glob-LV/AA-MS and Glob-LV/no AA-MS groups in IS-I mortality (Glob-LV/AA-MS adjusted for year of S1P: HR, 1.8 [95% CI, 0.8–4.1]; $P=0.2$), overall

Table 3. Univariate Analysis for IS-I, Overall Mortality, and Major Adverse Events

	IS-I mortality		Overall mortality		Major adverse events	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
LV morphology						
AA-MS	3.2 (1.6–6.5)	0.001	2.4 (1.4–4.2)	0.002	2.2 (1.4–3.5)	0.001
Glob-LV	4.6 (1.8–11.9)	0.002	3.2 (1.7–6.3)	0.001	2.5 (1.4–4.2)	0.001
Perinatal variables						
Postnatal diagnosis	0.9 (0.5–1.8)	0.8	0.8 (0.5–1.5)	0.6	1.0 (0.6–1.6)	0.9
Prematurity	1.8 (1.1–3.0)	0.01	1.7 (1.1–2.6)	0.01	1.4 (0.9–2.1)	0.1
Female sex	1.6 (0.8–3.2)	0.2	1.3 (1.0–1.7)	0.07	1.7 (1.0–2.7)	0.03
Cardiac comorbidity	1.5 (0.4–6.4)	0.6	1.8 (0.6–4.9)	0.3	2.7 (1.3–6.0)	0.01
Extracardiac comorbidity	1.0 (0.2–4.2)	1	1.0 (0.3–3.2)	1	0.7 (0.2–2.0)	0.5
Restrictive/intact atrial septum	1.0 (0.4–2.3)	0.9	1.8 (1.0–3.3)	0.05	2.3 (1.4–3.8)	0.002
RV dysfunction	3.4 (1.4–8.4)	0.006	2.2 (0.9–5.2)	0.07	2.2 (1.1–4.6)	0.04
sTR before S1P	1.1 (0.4–3.2)	0.8	1.3 (0.6–2.8)	0.6	1.2 (0.6–2.3)	0.7
Stage 1 palliation						
Year of surgery	0.9 (0.9–1.0)	0.06	0.9 (0.9–1.0)	0.08	0.9 (0.9–1.0)	0.2
Early era	1.2 (0.9–1.8)	0.2	1.1 (0.8–1.5)	0.5	1.1 (0.7–1.8)	0.6
Age at stage 1, d	1.0 (1.0–1.1)	0.2	1.0 (0.9–1.1)	0.7	1.0 (0.9–1.1)	0.3
Low preoperative weight, ≤2.5 kg	4.2 (1.9–18.1)	<0.001	3.0 (1.5–6.2)	0.003	2.6 (1.4–5.0)	0.004
BT shunt	2.9 (1.5–5.9)	0.002	3.0 (1.7–5.2)	<0.001	2.0 (1.2–3.3)	0.005

AA-MS indicates aortic atresia-mitral stenosis; BT shunt, Blalock-Taussig shunt; Glob-LV, globular left ventricle; HR, hazard ratio; IS-I, interstage I; LV, left ventricular; RV, right ventricular; S1P, stage 1 palliation; and sTR, severe tricuspid regurgitation.

mortality (HR 1.4 [95% CI, 0.8–2.8]; $P=0.27$), and MAEs (HR, 1.5 [95% CI, 0.8–2.7]; $P=0.2$). There was no interaction between the 3 subgroups of no Glob-LV/no AA-MS, Glob-LV/no AA-MS, and Glob-LV/AA-MS and the type of shunt in the multivariate Cox regression model ($P\geq 0.3$ for all).

Palliation With BTs in Patients With AA-MS or Glob-LV

Patients with AA-MS or Glob-LV who were palliated with a BTs exhibited a significantly higher overall mortality compared with those palliated with Sano shunts, even when corrected for the year of S1P (AA-MS/BTs versus Sano shunt: HR, 2.6 [95% CI, 1.02–6.5]; $P=0.046$; Glob-LV/BTs versus Sano shunt: HR, 2.1 [95% CI, 1.1–4.3]; $P=0.03$) (Figure 3C and 3D).

DISCUSSION

In this 20-year national study from Sweden, we found an independent association of both AA-MS and Glob-LV with adverse outcome in HLHS following S1P. Importantly, a Glob-LV was significantly associated with adverse outcome even in patients without the anatomic subtype AA-MS. To the best of our knowledge, this is the first study reporting independent association

between the Glob-LV phenotype (rather than valvular subtype in isolation) and severe complications. In addition, outcome was particularly poor for patients with a Glob-LV and/or AA-MS who received a BTs as part of their S1P. Again, these findings have not been reported before, and we believe they should be taken into account for both surgical planning and postoperative follow-up.

AA-MS and Adverse Outcome

As in our study, several previous groups have demonstrated a link between AA-MS and both early and late mortality.^{6–8,22,23} Coronary anomalies, including ventriculo-coronary connections and coronary stenosis along with endocardial fibroelastosis and focal calcification, presumably caused by increased intracavitary pressure because of atresia of the left outflow tract, have been documented in autopsy specimens.^{24–26} Theoretically, coronary anomalies could cause ischemia of the right ventricle, leading to RV-dysfunction and eventually sudden death.^{22,23,27,28} However, coronary anomalies are not present in all patients with AA-MS, as clearly demonstrated by earlier autopsy and angiographic studies in which ventriculo-coronary connections were found in only 28% to 56% of cases with AA-MS.^{26,29}

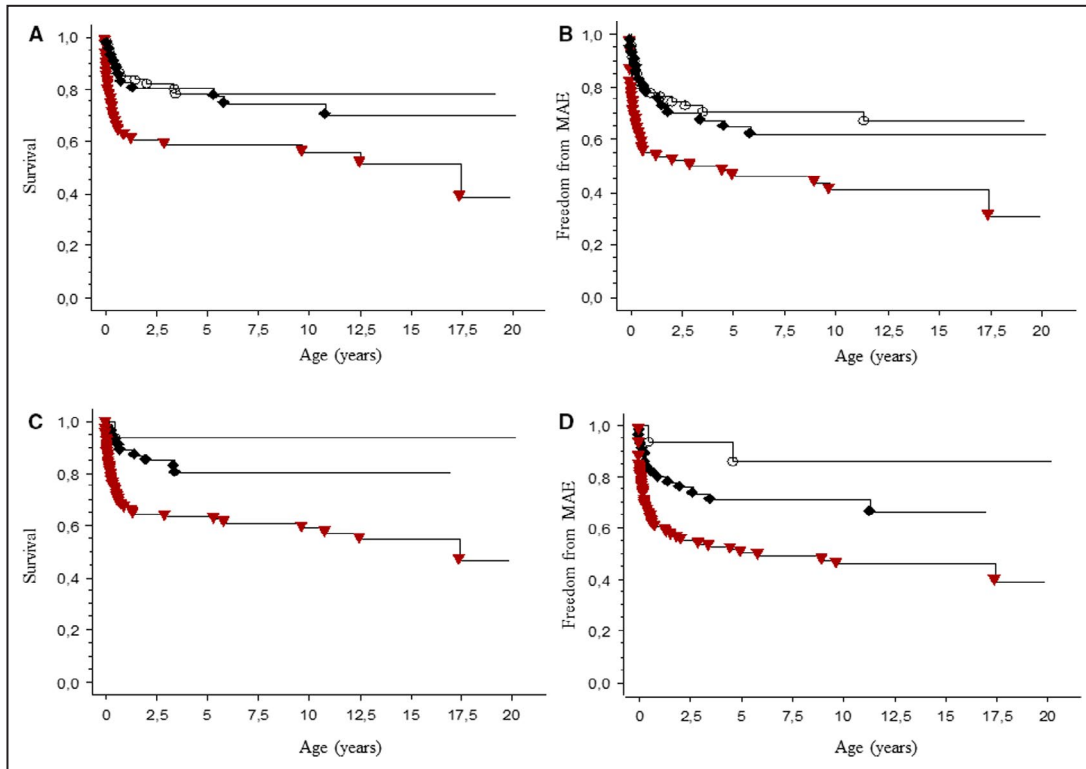


Figure 2. Impact of left ventricular morphology on adverse outcome.

A, Kaplan-Meier analysis of anatomic hypoplastic left heart syndrome (HLHS) subtypes in relation to total survival. Red triangle: aortic atresia-mitral stenosis (AA-MS), black rhomb: aortic stenosis-mitral stenosis (AS-MS), black circle: aortic atresia-mitral atresia (AA-MA). Log-rank test: $P=0.004$. **B**, Kaplan-Meier analysis of anatomic HLHS subtypes in relation to freedom from major adverse events (MAEs). Red triangle: AA-MS, black rhomb: AS-MS, black circle: AA-MA. Log-rank test: $P=0.003$. **C**, Kaplan-Meier analysis of left ventricular phenotypes in relation to total survival. Red triangle: globular left ventricle, black rhomb: slit-like left ventricle, black circle: miniaturized left ventricle. Log-rank test: $P=0.001$. **D**, Kaplan-Meier analysis of left ventricular phenotypes in relation to freedom from MAEs. Red triangle: globular left ventricle, black rhomb: slit-like left ventricle, black circle: miniaturized left ventricle. Log-rank test: $P=0.002$.

Other studies, including the SVR trial, could not demonstrate a link between AA-MS and adverse outcome.^{9,29} Conflicting results on the impact of AA-MS on adverse outcome in HLHS may originate from differences in surgical techniques as well as intra- and perioperative care in different centers as already suggested by other authors.^{9,23}

Left Ventricular Phenotypes and Their Association With Anatomic HLHS Subtypes

The partial association between certain left ventricular phenotypes and anatomic subtypes was demonstrated in 2 previous studies.^{10,11} Our study

Table 4. AA-MS in the Multivariate Analysis

	IS-I mortality		Overall mortality		Major adverse events	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
AA-MS	2.7 (1.3–5.5)	0.006	2.2 (1.3–3.9)	0.005	2.4 (1.4–3.9)	0.0009
Cardiac comorbidity	4.1 (1.7–9.9)	0.002
Restrictive/intact atrial septum	2.1 (1.1–3.9)	0.02	2.2 (1.3–3.8)	0.006
RV dysfunction	4.1 (1.6–10.4)	0.003	3.1 (1.3–7.7)	0.01	3.3 (1.5–7.2)	0.003
Low preoperative weight, ≤ 2.5 kg	5.1 (2.2–11.9)	0.0002	3.9 (1.8–8.3)	0.0004	3.4 (1.7–6.7)	0.0004
BT shunt	2.9 (1.3–6.4)	0.01	3.5 (1.8–6.7)	0.0002	2.5 (1.4–4.4)	0.003
Year of stage 1 surgery	1.0 (0.9–1.1)	0.9	1.0 (0.9–1.0)	0.6	1.0 (0.9–1.0)	0.3

AA-MS indicates aortic atresia-mitral stenosis; BT shunt, Blalock-Taussig shunt; HR, hazard ratio; IS-I, interstage I; and RV, right ventricular.

Table 5. Glob-LV in the Multivariate Analysis

	IS-I mortality		Overall mortality		Major adverse events	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Glob-LV	4.5 (1.6–12.2)	0.004	3.4 (1.7–6.8)	0.0007	2.7 (1.5–4.9)	0.0007
Female sex	2.3 (1.1–4.8)	0.03	2.4 (1.4–4.4)	0.003	1.7 (1.0–2.9)	0.04
Cardiac comorbidity	2.8 (1.1–6.7)	0.02
Restrictive/intact atrial septum	2.0 (1.1–3.5)	0.02
RV dysfunction	3.2 (1.24–8.20)	0.02	3.0 (1.4–6.6)	0.007
Low preoperative weight (≤ 2.5 kg)	5.4 (2.3–12.7)	<0.0001	3.5 (1.6–7.3)	0.001	3.4 (1.7–6.8)	0.0004
BT-shunt	2.3 (1.0–5.2)	0.05	2.9 (1.5–5.5)	0.002	2.0 (1.1–3.5)	0.02
Year of stage 1 surgery	1.0 (0.9–1.1)	0.7	1.0 (0.9–1.1)	0.9	1.0 (0.9–1.0)	0.4

BT shunt indicates Blalock-Taussig shunt; Glob-LV, globular left ventricle; HR, hazard ratio; IS-I, interstage I; and RV, right ventricular.

demonstrated Glob-LV not only in AA-MS and the AS-MS-subtype with critical AS, but also in a few cases with AA-MA. In these cases, MS may have progressed to MA in fetal life, which may explain why this subgroup of patients still exhibits Glob-LV despite the anatomic subtype AA-MA, as previously suggested by Rösner et al.³⁰

However, the embryological formation of HLHS is not yet fully understood. The variability in left ventricular phenotype and the lack of association between left ventricular hypertrophy with the degree of aortic valve stenosis/atresia cannot be explained completely by intracardiac flow disturbances.^{10,11} Crucean et al (2017) and Grossfeld et al (2019)

suggested that LV hypoplasia, in certain cases, may arise from an embryological defect in the ventricular development rather than from intracardiac flow disturbances caused by aortic and/or mitral valve anomalies.^{10,11}

Glob-LV With or Without AA-MS

Our study demonstrated that Glob-LV is associated with poor outcome even in patients without AA-MS. We therefore speculate that the mechanism for poor outcome in patients with Glob-LV can not only be explained by the presence of ventriculo-coronary anomalies, oftentimes encountered in AA-MS. The shape

Table 6. Glob-LV With and Without AA-MS and Association With Adverse Outcome

	IS-I mortality		Overall mortality		Major adverse events	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Univariate						
No Glob-LV/no AA-MS vs						
Glob-LV/no AA-MS	3.2 (1.1–9.9)	0.04	2.6 (1.2–5.7)	0.02	1.9 (1.0–3.8)	0.04
Glob-LV/AA-MS	5.6 (2.1–15.0)	0.001	3.7 (1.8–7.4)	<0.001	2.9 (1.6–5.1)	<0.001
Multivariate						
No Glob-LV/no AA-MS vs						
Glob-LV/no AA-MS	3.1 (0.9–10.3)	0.06	2.6 (1.1–6.3)	0.03	2.0 (1.0–4.1)	0.07
Glob-LV/AA-MS	5.1 (1.8–14.0)	0.002	3.7 (1.8–7.8)	<0.001	3.3 (1.8–6.1)	<0.001
Female sex	2.1 (1.0–4.5)	0.05	2.0 (1.1–3.7)	0.02	1.6 (1.0–2.7)	0.07
Cardiac comorbidity	3.4 (1.4–8.6)	0.009
Restrictive/intact atrial septum	1.8 (1.0–3.5)	0.07	2.0 (1.1–3.6)	0.02
RV dysfunction	3.3 (1.3–8.6)	0.01	2.6 (1.04–6.4)	0.04	3.0 (1.4–6.7)	0.006
Low preoperative weight	5.1 (2.2–12.1)	<0.001	3.9 (1.8–8.3)	0.001	3.3 (1.7–6.6)	0.001
BT shunt	2.5 (1.1–5.7)	0.03	3.0 (1.6–5.9)	0.001	2.1 (1.2–3.8)	0.01
Year of stage 1 surgery	1.0 (0.9–1.1)	0.7	1.1 (1.0–1.1)	0.8	1.0 (1.0–1.1)	0.4

AA-MS indicates aortic atresia-mitral stenosis; BT shunt, Blalock-Taussig shunt; Glob-LV, globular left ventricle; HR, hazard ratio; IS-I, interstage I; and RV, right ventricular.

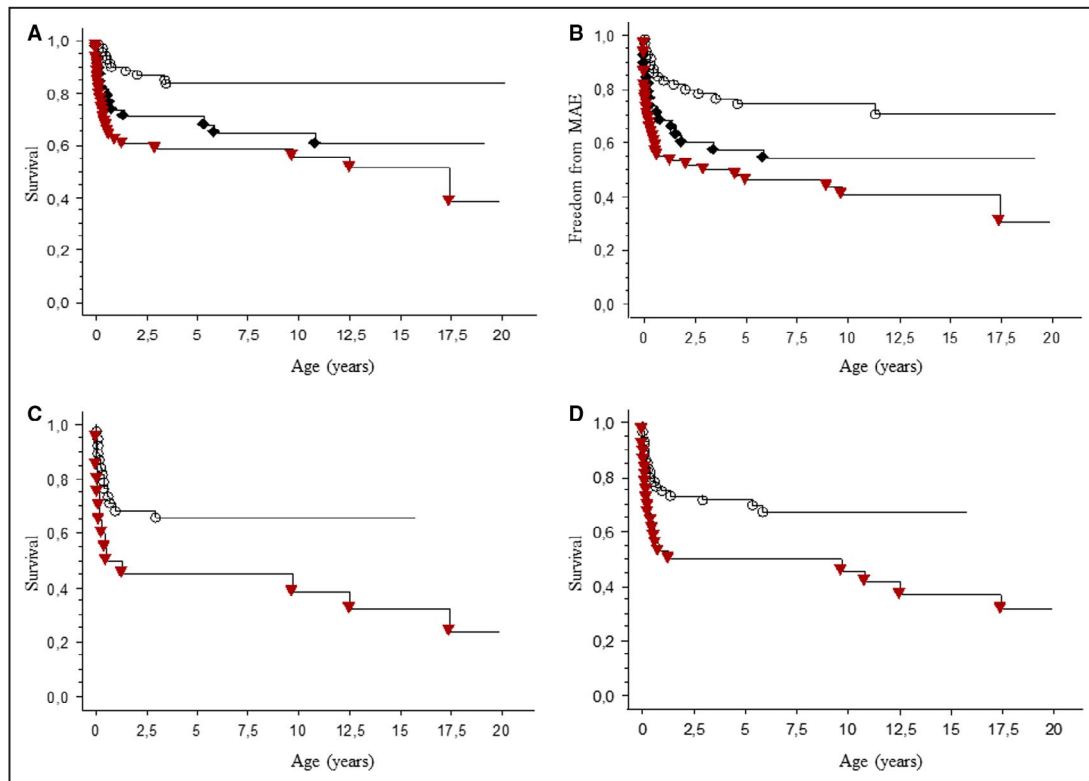


Figure 3. Impact of combined left ventricular morphology on adverse outcome (A and B) and impact of choice of shunt in morphological risk groups on adverse outcome (C and D).

A, Kaplan-Meier analysis of globular left ventricle with and without aortic atresia-mitral stenosis (AA-MS) in relation to total survival. Red triangle: globular left ventricle with AA-MS, black rhomb: globular left ventricle without AA-MS, black circle: all other left ventricular phenotypes and anatomic hypoplastic left heart syndrome (HLHS) subtypes. Log-rank test: $P=0.0006$. **B**, Kaplan-Meier analysis of globular left ventricle with and without AA-MS in relation to freedom from major adverse events (MAEs). Red triangle: globular left ventricle with AA-MS, black rhomb: globular left ventricle without AA-MS, black circle: all other left ventricular phenotypes and anatomic HLHS subtypes. Log-rank test: $P=0.0009$. **C**, Kaplan-Meier analysis of AA-MS and choice of shunt at Norwood stage 1 palliation in relation to total survival. Red triangle: palliation with Blalock-Taussig shunt, black circle: palliation with Sano shunt. Log-rank test: $P=0.03$. **D**, Kaplan-Meier analysis of globular left ventricle and choice of shunt at Norwood stage 1 palliation in relation to total survival. Red triangle: palliation with Blalock-Taussig shunt, black circle: palliation with Sano shunt. Log-rank test: $P=0.002$.

and function of the LV and its impact on RV function might contribute to adverse outcome as well.

LV Size and Left Ventricular Phenotype and Their Impact on Outcome

A few studies have investigated the impact of LV size on RV function and outcome in patients with HLHS, however with conflicting results.^{9,13,14,16}

The majority of these studies divided their cohort in only 2 LV subtypes, those with a remnant LV (corresponding to a miniaturized or Glob-LV) versus those with an absent LV (corresponding the slit-like left ventricular phenotype).^{13,14,16} In 2 of these retrospective studies with few cases ($n=20$ versus 48, respectively), strain of the basal interventricular septum, evaluated by echocardiography or magnetic resonance imaging, was diminished in patients with a remnant

LV^{13,14} and associated with mortality or need of heart transplant.¹⁴

The SVR trial demonstrated better diastolic RV function in patients with absent LV, but could not show any difference in systolic RV function, 1-year transplantation-free survival depending on LV-size, or function in patients with single right ventricles.⁹ Despite its large cohort size and prospective design, this multicenter study had a short follow-up (14 months), and outcome was again related to the presence or absence of a remnant LV. In contrast, our study showed significant results when including both short- and long-term data, and clearly shows that the differences in outcome appear to relate to the left ventricular phenotype, with worst outcome for patients with Glob-LV.

Moreover, 2 retrospective echocardiography studies demonstrated that a hypertrophied interventricular

septum and a larger LV size were important risk factors for adverse outcome in patients with HLHS.^{12,15}

Our results are in agreement with the findings of Rösner et al, who found that a bulging right ventricle (relating to apicolateral hypertrophy of the LV, which corresponds best to our definition of Glob-LV) was associated with regional dysfunction, lower global strain, and adverse outcome compared with patients with a nonbulging right ventricle.³⁰

We assume that the impact of the Glob-LV phenotype on adverse outcome in our study may derive from its negative impact on ventricular septal contractility and subsequently RV function. Coronary anomalies, frequently encountered in Glob-LV/AA-MS, might further deteriorate RV function and hence outcome. In contrast, a miniaturized, nonhypertrophic LV without EFE may impair ventricular septal contractility less, and in some cases even contribute to RV function as already suggested by other authors.^{9,30}

Morphological HLHS Subtypes and Choice of Shunt at S1P

Earlier studies indicated better early outcome in patients palliated with a Sano shunt versus a BTs but no significant difference in the overall survival.^{18,19,31,32} More stable coronary perfusion because of absent diastolic runoff, which is typically encountered after BTs palliation, have been speculated to account for reduced complications early after S1P.³³ However, there are several drawbacks in palliation with Sano shunts including increased need of shunt reinterventions, focal scarring caused by RV ventriculotomy, and shunt regurgitation caused by the valveless conduit. This could lead to later occurrence of RV dysfunction, ventricular aneurysms, and arrhythmias.^{18,33–35} In our study, S1P with a Sano shunt had better early and overall outcome than those palliated with a BTs, with less pronounced mortality during the first year of life. Given the low number of individuals who died late after total cavopulmonary connection, a trustworthy interpretation of these data is not possible.

Our findings are in line with Wilder et al, who reported lower 6-year mortality in a cohort of 454 neonates with HLHS or other left ventricular outflow tract obstructions when palliated with Sano shunts.³⁶

To our knowledge, no other study has yet demonstrated worsened outcome in patients with AA-MS or certain left ventricular phenotypes in relation to the choice of shunt at S1P.

The SVR trial of 549 patients with single right ventricle anomalies indicated increased intermediate term mortality in patients with aortic atresia when operated on with a BTs.³⁷

Two earlier studies could not show a survival benefit in patients with AA-MS, palliated with Sano shunts,

probably because of the small number of included patients with the anatomic subtype AA-MS operated on with a BTs.^{8,38}

The increased risk for adverse outcome in the subgroup of HLHS infants with Glob-LV and/or AA-MS who received a BTs at S1P may be explained by the cumulative effect of 2 risk factors, (1) anatomic substrate leading to impaired systemic RV function by interventricular dynamics and/or the presence of coronary anomalies and (2) coronary steal related to the BTs. Being cognizant of modifiable risk factors is critical for surgical planning and eventually patient outcome.

Limitations

The retrospective design and the exclusive use of a BTs during the 1990s are important limitations. To mitigate the latter, we included only patients with S1P from 1999, when mortality reached a plateau. Despite important benefits arising from centralization of pediatric cardiac surgery to Lund and Gothenburg since 1993, differences in regional surgical techniques and perioperative care might have influenced the short- and long-term outcome. Neither the size nor function of the remnant LV, RV function before or after S1P, nor the presence of coronary ventricular communications were assessed quantitatively. Echocardiograms before S1P were not available or usable in 16% of patients. However, left ventricular morphology was determined in all patients from the postoperative echocardiograms. The lack of association between severe tricuspid regurgitation before S1P and adverse outcome may be a result of a surgical selection bias, because patients with severe tricuspid regurgitation are more often deemed unsuitable for S1P.

The subgroup analysis of patients with Glob-LV with and without AA-MS might be underpowered. A larger prospective study including a detailed functional assessment of the remnant LV and systemic right ventricle is warranted. This may (1) help to understand the mechanism of left ventricular morphology on outcome and (2) determine a potential significant difference in outcome between the 2 subgroups Glob-LV with and without AA-MS.

CONCLUSIONS

The findings of this retrospective nationwide Swedish study demonstrate that both AA-MS and Glob-LV are independently associated with adverse outcome in patients with HLHS. Importantly, the association of Glob-LV with a less favorable outcome was obvious even in patients without the anatomic subtype AA-MS. Furthermore, the outcome in patients with these morphological variants was even worse in those palliated with a BTs. These findings have not been reported

before and should be taken into account for surgical planning as well as postoperative risk stratification and timing of follow-up.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Yabrodi M, Mastropietro CW. Hypoplastic left heart syndrome: from comfort care to long-term survival. *Pediatr Res*. 2017;81:142–149. doi: 10.1038/pr.2016.194
2. Tchervenkov CI, Jacobs JP, Weinberg PM, Aiello VD, Béland MJ, Colan SD, Elliott MJ, Franklin RCG, Gaynor JW, Krogmann ON, et al. The nomenclature, definition and classification of hypoplastic left heart syndrome. *Cardiol Young*. 2006;16:339–368. doi: 10.1017/S104795110600291
3. Jonas RA, Hansen DD, Cook N, Wessel D. Anatomic subtype and survival after reconstructive operation for hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg*. 1994;107:1121–1128; discussion 1127–1128. doi: 10.1016/S0022-5223(94)70389-2
4. Forbess JM, Cook N, Roth SJ, Serraf A, Mayer JE Jr, Jonas RA. Ten-year institutional experience with palliative surgery for hypoplastic left heart syndrome. Risk factors related to stage I mortality. *Circulation*. 1995;92:262–266. doi: 10.1161/01.CIR.92.9.262
5. Jacobs ML. Aortic reconstruction in hypoplastic left heart syndrome—a reappraisal. *J Thorac Cardiovasc Surg*. 2000;120:872–874. doi: 10.1016/j.jacc.2011.09.022
6. Glatz JA, Fedderly RT, Ghanayem NS, Tweddell JS. Impact of mitral stenosis and aortic atresia on survival in hypoplastic left heart syndrome. *Ann Thorac Surg*. 2008;85:2057–2062. doi: 10.1016/j.athoracsur.2008.02.026
7. Furck AK, Uebing A, Hansen JH, Scheewe J, Jung O, Fischer G, Rickers C, Holland-Letz T, Kramer HH. Outcome of the Norwood operation in patients with hypoplastic left heart syndrome: a 12-year single-center survey. *J Thorac Cardiovasc Surg*. 2010;139:359–365. doi: 10.1016/j.jtcvs.2009.07.063
8. Shuhaiber J, Morgan B, Gottliebson W. Survival outcomes following Norwood procedure for hypoplastic left heart. *Pediatr Cardiol*. 2015;36:57–63. doi: 10.1007/s00246-014-0964-9
9. Cohen MS, Dagincourt N, Zak V, Baffa JM, Bartz P, Dragulescu A, Dudlani G, Henderson H, Krawczeski CD, Lai WW, et al. The impact of the left ventricle on right ventricular function and clinical outcomes in infants with single-right ventricle anomalies up to 14 months of age. *J Am Soc Echocardiogr*. 2018;31:1151–1157. doi: 10.1016/j.echo.2018.05.003
10. Crucean A, Alqahtani A, Barron DJ, Brawn WJ, Richardson RV, O'Sullivan J, Anderson RH, Henderson DJ, Chaudhry B. Re-evaluation of hypoplastic left heart syndrome from a developmental and morphological perspective. *Orphanet J Rare Dis*. 2017;12:138. doi: 10.1186/s13023-017-0683-4
11. Grossfeld P, Nie S, Lin L, Wang L, Anderson RH. Hypoplastic left heart syndrome: a new paradigm for an old disease? *J Cardiovasc Dev Dis*. 2019;6. doi: 10.3390/jcdd6010010
12. Son JS, James A, Fan CS, Mertens L, McCrindle BW, Manlihot C, Friedberg MK. Prognostic value of serial echocardiography in hypoplastic left heart syndrome. *Circ Cardiovasc Imaging*. 2018;11:e006983. doi: 10.1161/CIRCIMAGING.117.006983
13. Wang AP, Kelle AM, Hyun M, Reece CL, Young PM, O'Leary PW, Qureshi MY, Nelson TJ, Haile DT, Miller AR, et al. Wanek Family Program for Hypoplastic Left Heart Syndrome Imaging Pipeline. Negative impact of the left ventricular remnant morphology on systemic right ventricular myocardial deformation in hypoplastic left heart syndrome. *Pediatr Cardiol*. 2021;42:278–288. doi: 10.1007/s00246-020-02480-2
14. Forsha D, Li L, Joseph N, Kutty S, Friedberg MK. Association of left ventricular size with regional right ventricular mechanics in hypoplastic left heart syndrome. *Int J Cardiol*. 2020;298:66–71. doi: 10.1016/j.ijcard.2019.07.090
15. Walsh MA, McCrindle BW, Dipchand A, Manlihot C, Hickey E, Caldaroni CA, Van Arsdell GS, Schwartz SM. Left ventricular morphology influences mortality after the Norwood operation. *Heart*. 2009;95:1238–1244. doi: 10.1136/hrt.2008.156612
16. Schlangen J, Fischer G, Steendijk P, Petko C, Scheewe J, Hart C, Hansen JH, Ahrend F, Rickers C, Kramer H-H, et al. Does left ventricular size impact on intrinsic right ventricular function in hypoplastic left heart syndrome? *Int J Cardiol*. 2013;167:1305–1310. doi: 10.1016/j.ijcard.2012.03.183
17. Sano S, Ishino K, Kawada M, Arai S, Kasahara S, Asai T, Masuda Z, Takeuchi M, Ohtsuki S. Right ventricle-pulmonary artery shunt in first-stage palliation of hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg*. 2003;126:504–509; discussion 509–510. doi: 10.1016/S0022-5223(02)73575-7
18. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010;362:1980–1992. doi: 10.1056/NEJMoa0912461
19. Looma RS, Shah PH, Chandrasekar S. Short-term outcome comparison of Norwood procedures with right ventricle to pulmonary artery conduit versus modified Blalock-Taussig shunt: a meta-analysis. *Ann Pediatr Cardiol*. 2011;4:145–149. doi: 10.4103/0974-2069.84653
20. Saphir SMA, Maxedius A, Niemelä J, Liuba P. Perinatal risk factors for mortality after Norwood palliation of hypoplastic left heart syndrome. *Cardiol Young*. 2015;25:16–17.
21. Graziano JN, Heidelberger KP, Ensing GJ, Gomez CA, Ludomirsky A. The influence of a restrictive atrial septal defect on pulmonary vascular morphology in patients with hypoplastic left heart syndrome. *Pediatr Cardiol*. 2002;23:146–151. doi: 10.1007/s00246-001-0038-7
22. Vida VL, Bacha EA, Larrazabal A, Gauvreau K, Dorfman AL, Marx G, Geva T, Marshall AC, Pigula FA, Mayer JE, et al. Surgical outcome for patients with the mitral stenosis-aortic atresia variant of hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg*. 2008;135:339–346. doi: 10.1016/j.jtcvs.2007.09.007
23. Siehr SL, Maeda K, Connolly AA, Tacy TA, Reddy VM, Hanley FL, Perry SB, Wright GE. Mitral stenosis and aortic atresia—a risk factor for mortality after the modified Norwood operation in hypoplastic left heart syndrome. *Ann Thorac Surg*. 2016;101:162–167. doi: 10.1016/j.athoracsur.2015.09.056
24. O'Connor WN, Cash JB, Cottrill CM, Johnson GL, Noonan JA. Ventriculocoronary connections in hypoplastic left hearts: an autopsy microscopic study. *Circulation*. 1982;66:1078–1086. doi: 10.1161/01.CIR.66.5.1078
25. Baffa JM, Chen SL, Guttenberg ME, Norwood WI, Weinberg PM. Coronary artery abnormalities and right ventricular histology in hypoplastic left heart syndrome. *J Am Coll Cardiol*. 1992;20:350–358. doi: 10.1016/0735-1097(92)90101-F
26. Nathan M, Williamson AK, Mayer JE, Bacha EA, Juraszek AL. Mortality in hypoplastic left heart syndrome: review of 216 autopsy cases of aortic

- atresia with attention to coronary artery disease. *J Thorac Cardiovasc Surg.* 2012;144:1301–1306. doi: 10.1016/j.jtcvs.2012.03.013
27. Bartram U, Grunenfelder J, Van Praagh R. Causes of death after the modified Norwood procedure: a study of 122 postmortem cases. *Ann Thorac Surg.* 1997;64:1795–1802. doi: 10.1016/S0003-4975(97)01041-2
 28. Simsic JM, Bradley SM, Stroud MR, Atz AM. Risk factors for interstage death after the Norwood procedure. *Pediatr Cardiol.* 2005;26:400–403. doi: 10.1007/s00246-004-0776-4
 29. Polimenakos AC, Sathanandam SK, Husayni TS, El Zein CF, Roberson DA, Ilbawi MN. Hypoplastic left heart syndrome and aortic atresia-mitral stenosis variant: role of myocardial protection strategy and impact of ventriculo-coronary connections after stage I palliation. *Pediatr Cardiol.* 2011;32:929–939. doi: 10.1007/s00246-011-0017-6
 30. Rosner A, Bharucha T, James A, Mertens L, Friedberg MK. Impact of right ventricular geometry and left ventricular hypertrophy on right ventricular mechanics and clinical outcomes in hypoplastic left heart syndrome. *J Am Soc Echocardiogr.* 2019;32:1350–1358. doi: 10.1016/j.echo.2019.06.003
 31. Azakie A, Martinez D, Sapru A, Fineman J, Teitel D, Karl TR. Impact of right ventricle to pulmonary artery conduit on outcome of the modified Norwood procedure. *Ann Thorac Surg.* 2004;77:1727–1733. doi: 10.1016/j.athoracsur.2003.10.002
 32. Pizarro C, Malec E, Maher KO, Januszewska K, Gidding SS, Murdison KA, Baffa JM, Norwood WI. Right ventricle to pulmonary artery conduit improves outcome after stage I Norwood for hypoplastic left heart syndrome. *Circulation.* 2003;108:155–160. doi: 10.1161/01.cir.0000087390.94142.1d
 33. Riveros Perez E, Riveros R. Mathematical analysis and physical profile of Blalock-Taussig shunt and Sano modification procedure in hypoplastic left heart syndrome: review of the literature and implications for the anesthesiologist. *Semin Cardiothorac Vasc Anesth.* 2017;21:152–164. doi: 10.1177/1089253216687857
 34. Wong J, Lamata P, Rathod RH, Bertaud S, Dedieu N, Bellsham-Revell H, Pushparajah K, Razavi R, Hussain T, Schaeffter T, et al. Right ventricular morphology and function following stage I palliation with a modified Blalock-Taussig shunt versus a right ventricle-to-pulmonary artery conduit. *Eur J Cardiothorac Surg.* 2017;51:50–57. doi: 10.1093/ejcts/ezw227
 35. Fischbach J, Sinzobahamvya N, Haun C, Schindler E, Zartner P, Schneider M, Hraška V, Asfour B, Photiadis J. Interventions after Norwood procedure: comparison of Sano and modified Blalock-Taussig shunt. *Pediatr Cardiol.* 2013;34:112–118. doi: 10.1007/s00246-012-0396-3
 36. Wilder TJ, McCrindle BW, Phillips AB, Blackstone EH, Rajeswaran J, Williams WG, DeCampi WM, Jacobs JP, Jacobs ML, Karamlou T, et al. Survival and right ventricular performance for matched children after stage-1 Norwood: modified Blalock-Taussig shunt versus right-ventricle-to-pulmonary-artery conduit. *J Thorac Cardiovasc Surg.* 2015;150:1440–1450;1452. e1441–1448; discussion 1450–1442. doi: 10.1016/j.jtcvs.2015.06.069
 37. Tweddell JS, Sleeper LA, Ohye RG, Williams IA, Mahony L, Pizarro C, Pemberton VL, Frommelt PC, Bradley SM, Cnota JF, et al. Intermediate-term mortality and cardiac transplantation in infants with single-ventricle lesions: risk factors and their interaction with shunt type. *J Thorac Cardiovasc Surg.* 2012;144:152–159. doi: 10.1016/j.jtcvs.2012.01.016
 38. Murtuza B, Stumper O, Wall D, Stickley J, Jones TJ, Barron DJ, Brawn WJ. The effect of morphologic subtype on outcomes following the Sano-Norwood procedure. *Eur J Cardiothorac Surg.* 2012;42:787–793. doi: 10.1093/ejcts/ezs116