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Treatment of hypoplastic left heart syndrome: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Background: This meta-analysis aimed to consolidate existing data from randomised controlled trials on hypoplastic left heart syndrome. *Methods:* Hypoplastic left heart syndrome specific randomised controlled trials published between January 2005 and September 2021 in MEDLINE, EMBASE, and Cochrane databases were included. Regardless of clinical outcomes, we included all randomised controlled trials about hypoplastic left heart syndrome and categorised them according to their results. Two reviewers independently assessed for eligibility, relevance, and data extraction. The primary outcome was mortality after Norwood surgery. Study quality and heterogeneity were assessed. A random-effects model was used for analysis. *Results:* Of the 33 included randomised controlled trials, 21 compared right ventricle-to-pulmonary artery shunt and modified Blalock–Taussig-Thomas shunt during the Norwood procedure, and 12 regarded medication, surgical strategy, cardiopulmonary bypass tactics, and ICU management. Survival rates up to 1 year were superior in the right ventricle-to-pulmonary artery shunt group; this difference began to disappear at 3 years and remained unchanged until 6 years. The right ventricle-to-pulmonary artery shunt group had a significantly higher reintervention rate from the interstage to the 6-year follow-up period. Right ventricular function was better in the modified Blalock–Taussig-Thomas shunt group 1–3 years after the Norwood procedure, but its superiority diminished in the 6-year follow-up. Randomised controlled trials regarding medical treatment, surgical strategy during cardiopulmonary bypass, and ICU management yielded insignificant results. *Conclusions:* Although right ventricle-to-pulmonary artery shunt appeared to be superior in the early period, the two shunts applied during the Norwood procedure demonstrated comparable long-term prognosis despite high reintervention rates in right ventricle-to-pulmonary artery shunt due to pulmonary artery stenosis. For medical/perioperative management of hypoplastic left heart syndrome, further randomised controlled trials are needed to deliver specific evidence-based recommendations.

Introduction

Hypoplastic left heart syndrome, characterised by various degrees of underdevelopment of the left ventricle and systemic outflow tract, limits sufficient systemic circulation.[1,2] Hypoplastic left heart syndrome represents 2–9% of CHD cases but accounts for 23% of neonatal deaths from congenital heart malformations.[3,4] Since the Norwood procedure's first description in 1981, significant progress has been made in treating hypoplastic left heart syndrome and related lesions.[1] Over the past 40 years, survival following the Norwood procedure has increased from 0% to >90% at several highly experienced centres.[1] However, considerable morbidity and mortality remain, and evidence to guide optimal care is still evolving.

Staged surgical procedures include stage-I Norwood procedure at birth, stage-II superior cavopulmonary connection, and stage-III Fontan completion at 18–48 months. Although the procedures in the three-stage palliation approach have improved, the stage-I Norwood procedure still carries the highest risk of major complications.[1,5] With innovations to the Norwood procedure, there is renewed interest in the right ventricle-to-pulmonary artery shunt as the source

of pulmonary blood flow rather than the modified Blalock–Taussig-Thomas shunt. Though randomised controlled trials regarding hypoplastic left heart syndrome are rare, the largest multicentre single-ventricle reconstruction trial randomised 555 patients to either right ventricle-to-pulmonary artery shunt or modified Blalock–Taussig-Thomas shunt groups across 15 centres from 2005, and the patients have been closely followed to date for 10–12 years. Other than the surgical strategy of the Norwood operation, hypoplastic left heart syndrome management involves multidisciplinary teams from antenatal diagnosis/counselling, neonatal intensive care, paediatric cardiac surgery/cardiology teams, to lifelong surveillance by adult CHD specialists and transplant teams.

Accordingly, multiple randomised controlled trials have been conducted to overcome its high demanding burden and suggest more reliable evidence. These randomised controlled trials compared shunt strategies for stage-I Norwood palliation, medical treatment, pre- and post-operative intensive care, and nutritional support. In this study, we aimed to conduct a systematic review of the randomised controlled trials in hypoplastic left heart syndrome and provide evidence-based summary recommendations for its treatment.

Materials and method

Literature search and study selection

This systematic review was performed according to a prespecified protocol registered at the International Prospective Register of Systematic Reviews (registration ID: CRD42020190190).[6] We also followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary Table S1). Eligibility criteria were as follows: (1) randomised controlled trials of patients with hypoplastic left heart syndrome, and (2) studies published between January 2005 and September 2021, to reflect the current medical environments with highly improved surgical techniques. We excluded studies that included more than half of the univentricular heart diseases other than hypoplastic left heart syndrome, and articles without clinical data, such as review, letters, or case reports, were also not included. Three electronic databases, PubMed/Medline, EMBASE, and Cochrane, were probed, and search terms are delineated in Supplementary Table S2; Supplementary Figure 1 shows the study selection process. Two authors (AYK and WW) performed the primary search and, if there were discrepancies regarding the inclusion/exclusion of studies, it was discussed with two other investigators (JIS and JWJ) to resolve it.

The initial search yielded 395 results, and 185 studies remained after removing duplicates. A few additional articles were found through manual searches by reviewing references of relevant studies and added to the dataset. When the authors disagreed regarding an article's eligibility or when information in the abstract was insufficient or absent, the full article was reviewed. Finally, the meta-analysis included 33 randomised controlled trials.[5,7–38] When studies originated from the same randomised controlled trial, only the most recent randomised controlled trial publication was included, except for the single-ventricle reconstruction trial, a landmark randomised controlled trial that had the largest prospective cohort of infants with hypoplastic left heart syndrome with longitudinal follow-up.

Data extraction

The primary outcome of interest was all-cause mortality and survival rate at follow-up. The secondary outcomes included reintervention rate, ventricular function, and haemodynamic variables during study period. Other outcomes of single randomised controlled trials were also delineated in this study to demonstrate contemporary progress in this topic: physical and mental development, cardiopulmonary bypass time, ventilator care, myocardial protection, and fluid balance. From the eligible articles, the authors extracted the first author's name, publication year, patient inclusion and exclusion criteria, control group types, follow-up period, and the measured outcomes in terms of either the number of events or number of patients in each arm or mean differences or standardised mean differences and their 95% confidence intervals.

Term definitions and outcome measures

We conducted an analysis by pooling the outcomes based on different time points according to the stage of surgery. Pre-stage-I refers to the fetal/neonatal assessment and management, and stage-I palliation (S1P) is the Norwood procedure. Hybrid procedure was excluded because there were no randomised controlled trials on hybrid S1Ps. Early S1P is defined as the period within 30 days of hospitalisation after S1P surgery, and the interstage as the period between 30 days after Norwood procedure and stage-II palliation (S2P). S2P implies a bidirectional cavopulmonary shunt that is performed at 3–6 months of age. Stage-III palliation (S3P) is the Fontan completion surgery, usually performed at 18–48 months of age. Early mortality includes deaths within 30 days after S1P. Interstage mortality is death after discharge from S1P surgery or 30 days after S1P.

Randomised controlled trial quality assessment

Randomised controlled trial quality was assessed as per the criteria suggested by the Cochrane Collaboration (Supplementary Figure 2).[39] The risk of bias was independently assessed by two reviewers (AYK and WW); any disagreements were resolved by a third reviewer (JIS).

Statistical analysis

The data are presented as counts (percentages) for categorical values or means (standard deviation) for continuous variables. A meta-analysis was performed to estimate the summary effects with a proportion of each variable and 95% confidence interval using a random-effects model. Between-study heterogeneity was evaluated using the I^2 metric of inconsistency and the p-value of the Cochran Q test. I^2 is the ratio of the between-study variance (heterogeneity) to the sum of the within-study and between-study variances, ranging from 0 to 100%. I^2 values of >50% usually indicate significant heterogeneity. As most studies originated from single-ventricle reconstruction trials, I^2 or summary effects were not added if the data were from a single original study. All analyses were conducted using R version 4.1.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Supplementary Table S8 summarises the characteristics of the 33 included randomised controlled trials. The majority (n = 21, 63.6%) of randomised controlled trials compared the source of pulmonary blood flow in the Norwood procedure (right ventricle-to-pulmonary artery shunt versus modified Blalock–Taussig-Thomas shunt),

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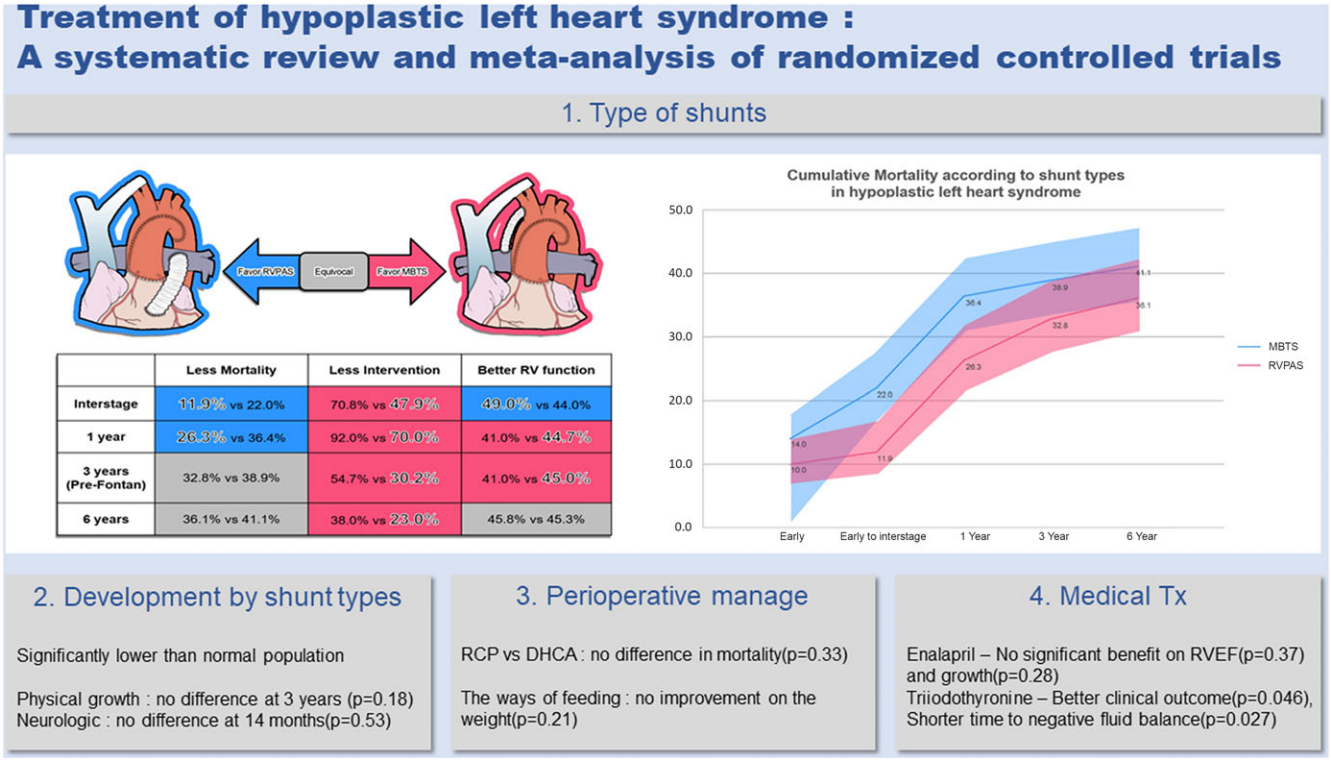

Figure 1. Treatment of HLHS: A systematic review and meta-analysis of RCTs. CI, confidence interval; DHCA, deep hypothermic cardiac arrest; HLHS, hypoplastic left heart syndrome; MBTS, modified Blalock–Taussig-Thomas shunt; OR, odds ratio; RCP, regional cerebral perfusion; RCT, randomised controlled trial; RV, right ventricle; RVEF, right ventricle ejection fraction; RVPAS, right ventricle-to-pulmonary artery shunt; S1P, stage 1 palliation. * RV function described as RVEF (%) by transthoracic echocardiogram.

and the outcome between two shunt types according to periods is described in Figure 1.

Comparison of outcomes between right ventricle-to-pulmonary artery shunt and modified Blalock–Taussig-Thomas shunt

Survival and reintervention (Table 1, Supplementary Table S3 and Figure S3, Figs 1 and 2). Early-to-interstage mortality was higher in modified Blalock–Taussig-Thomas shunt (modified Blalock–Taussig-Thomas shunt = 22%, 95% confidence interval = 17.3–28.0 versus right ventricle-to-pulmonary artery shunt = 11.9%, 95% confidence interval = 8.5–16.8; p = .003). Interstage mortality was also higher in the same group (p < .001), particularly in patients with non-to-mild atrioventricular valve regurgitation (p < .001). A similar finding was observed until the first year after the Norwood procedure (modified Blalock–Taussig-Thomas shunt = 36.4%, 95% confidence interval = 31.1–42.5 versus right ventricle-to-pulmonary artery shunt = 26.3%, 95% confidence interval = 21.6–32.0;
p = .011). However, the significant difference in mortality diminished 3 years after the Norwood surgery (Fig 2).

The reintervention rate at early S1P was not different between modified Blalock–Taussig-Thomas shunt and right ventricle-to-pulmonary artery shunt (p = 0.241). However, the difference became significant after early S1P, and a higher rate was observed in right ventricle-to-pulmonary artery shunt until 6 years (Table 1).

Right ventricular function (Table 2). Supplementary Figures 4–6 describe the results of the meta-analyses of echocardiographic parameters. In early S1P, an improved right ventricle ejection fraction on transthoracic echocardiography was observed in right ventricle-to-pulmonary artery shunt (p < .001). However, the difference was not significant in the subgroup analysis with a three-dimensional echocardiogram. The global right ventricle circumferential strain was decreased in right ventricle-to-pulmonary artery shunt at 14 months (right ventricle-to-pulmonary artery shunt = −12.2 ± 4.2 versus modified Blalock–Taussig-Thomas shunt = −13.4 ± 4.3; p = .05). Pre-Fontan right ventricular remodelling in survivors during the second and third years of life was more favourable in patients with modified Blalock–Taussig-Thomas shunt (right ventricle-to-pulmonary artery shunt = 41.7 ± 7.1% versus modified Blalock–Taussig-Thomas shunt = 44.7 ± 6.0%; p = .007); however, greater improvement of right ventricle ejection fraction was observed in right ventricle-to-pulmonary artery shunt patients from pre-Fontan to 6 years (p = .015). Finally, no significant difference was observed between modified Blalock–Taussig-Thomas shunt and right ventricle-to-pulmonary artery shunt in terms of right ventricle ejection fraction at 6 years.

Haemodynamic variables regarding neoaortic valve size, pulmonary artery size, and tricuspid valve size/function (Supplementary Table 4). Neoaortic valve size was significantly greater in the modified Blalock–Taussig-Thomas shunt patients during early stage-I (5.92 ± 2.94 versus 7.04 ± 3.02; p < .001). However, the difference diminished at 14 months and pre-Fontan evaluation. All indices of neoaortic flow (cardiac index, ejection time, and peak distal arch velocity) were significantly lower in right ventricle-to-pulmonary artery shunt than in modified Blalock–Taussig-Thomas shunt at post-S1P and pre-S2P, but they became similar at 14 months.

The overall pulmonary artery size based on the Nakata index was smaller in the right ventricle-to-pulmonary artery shunt than in the modified Blalock–Taussig-Thomas shunt group (145 versus

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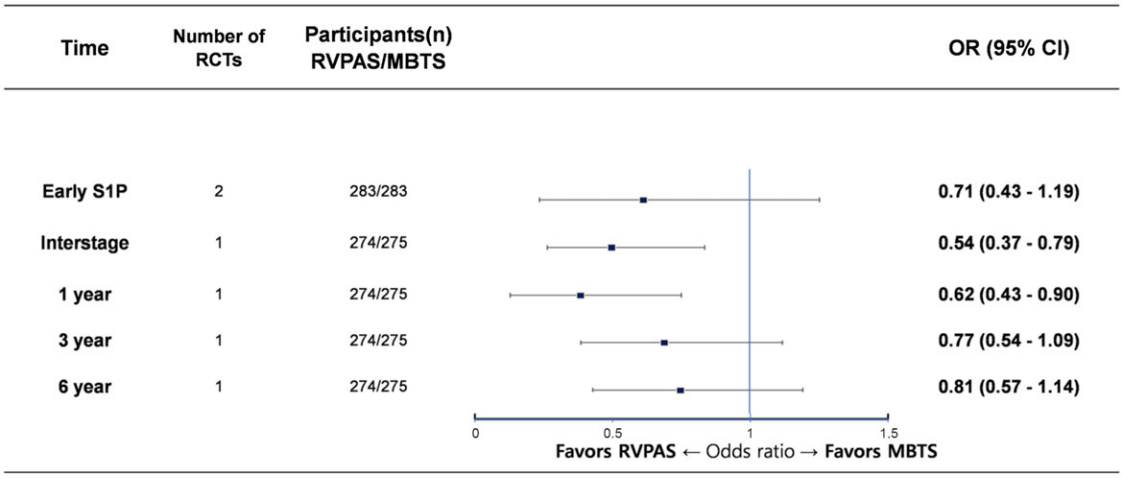

Figure 2. Forest plots of favourable survival comparing RVPAS and MBTS. CI, confidence interval; MBTS, modified Blalock–Taussig-Thomas shunt; OR, odds ratio; RCT, randomised controlled trial; RVPAS, right ventricle-to-pulmonary artery shunt; S1P, stage 1 palliation.

169, respectively; p = .009) before the S2P. When the pulmonary artery branches were compared, the mean diameter of the distal right branches was smaller in the patients with right ventricle-to-pulmonary artery shunt than in those with modified Blalock–Taussig-Thomas shunt. Patients with right ventricle-to-pulmonary artery shunt had greater left pulmonary artery stenosis (right ventricle-to-pulmonary artery shunt = 9.2% versus modified Blalock–Taussig-Thomas shunt = 0.7%; p = .003), smaller mid-main branch pulmonary artery diameters, and lower Nakata indices (right ventricle-to-pulmonary artery shunt = 134 versus modified Blalock–Taussig-Thomas shunt = 164; p < .001) before S2P.

The degree of tricuspid insufficiency was not significantly different between right ventricle-to-pulmonary artery shunt and modified Blalock–Taussig-Thomas shunt with regard to moderate or severe regurgitation at 14 months (23% versus 20%, respectively; p = .88). Both shunts demonstrated a significant decrease in tricuspid valve size from the 14-month to the pre-Fontan period.

Physical and neurologic development (Supplementary Table S5). In terms of physical development, all measurements were significantly lower in patients who underwent the Norwood procedure than in the general population. Although no difference was observed in weight and height between the two shunt types, modified Blalock–Taussig-Thomas shunt patients exhibited less S1P and S2P weight gain. Otherwise, psychomotor development and mental developmental index scores were generally lower in patients who underwent the Norwood procedure than in the general population; the shunt type did not affect the results.

The medical treatment in patients with hypoplastic left heart syndrome (Supplementary Table S6)

The Pediatric Heart Network Infant Single Ventricle Trial examined the use and safety of an angiotensin-converting enzyme inhibitor, enalapril. The benefit of enalapril (target dose 0.4 mg/kg/day) versus placebo showed no significant difference in ventricular ejection fraction, ventricular structure, or clinical heart failure. Another study assessed the effect of continuous infusion of triiodothyronine (0.05 μg/kg/h) in patients undergoing Norwood procedure up to 72 h after cardiopulmonary bypass. The median clinical outcome scores (time until negative fluid balance, sternal closure, or first extubation) and systolic blood pressure were better in patients on triiodothyronine. During S2P, methylprednisolone (30 mg/kg) reduced the inflammatory biomarkers IL-6 and IL-8 and increased the anti-inflammatory cytokine IL-10 from cardiopulmonary bypass to 6 h after surgery, without a significant difference in clinical outcome.[25]

The impact of perioperative strategy on hypoplastic left heart syndrome patients (Supplementary Table S7)

Regional cerebral perfusion during Norwood procedure did not differ in 1-year survival compared to that of deep hypothermic circulatory arrest.[4] Additionally, remote ischaemic preconditioning, nitric oxide usage in the oxygenator during cardiopulmonary bypass, and a single dose of caudal morphine did not improve clinical outcomes. Post-operative prophylactic insertion of a peritoneal dialysis catheter was associated with more adverse events (p = .03) without clinical benefit. Feeding methods did not exhibit a clinical benefit.

Quality assessment

Among the 33 randomised controlled trials, 12 original randomised controlled trials were evaluated for quality. Supplementary Figure 2 show the risk of bias assessment for the included clinical trials. The risk of bias due to incomplete outcome data, selective reporting, and other causes was considered low in all studies.

Discussion

Owing to its rare incidence and limited data for hypoplastic left heart syndrome, it is essential to review the current evidence-based approach to treatment. Management approaches have been adopted solely based on expert consensus and retrospective analysis, rather than on data from prospective randomised controlled trials. Although most studies were derived from the single-ventricle reconstruction trial, the present study was uniquely designed to evaluate all randomised controlled trials involving hypoplastic left heart syndrome and consolidate contemporary clinical practice.

Notably, right ventricle-to-pulmonary artery shunt patients demonstrated a superior 1-year survival compared with that of

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Table 1. Mortality and rate of reintervention in RCTs comparing RVPAS and MBTS in HLHS.

Stage[a]	Author, year	Original trial	Inclusion criteria	Mortality[d]			Reintervention[e]		
				RVPAS	MBTS	p-Value	RVPAS	MBTS	p-Value
Early S1P	Frommelt PC, 2007[12]		HLHS	1/9 (11.1)	1/8 (12.5)	*0.929*			
	Ohye RG, 2010[8]	SVR	HLHS or single-ventricle morphology[g]	28/274 (10.2)	38/275 (13.8)	*0.194*	64/274 (23.4)	77/275 (28.0)	*0.241*
During interstage[b]	Ohye RG, 2010[8]	SVR	HLHS or single-ventricle morphology[g]	**29/243 (11.9)**	**52/236 (22.0)**	***0.003***	**165/233 (70.8)**	**105/219 (47.9)**	***0.008***
During interstage[c]	Ghanayem NS, 2012[16]	SVR	HLHS, survived to discharge from the hospital after S1P	**13/225 (5.8)**	**37/201 (18.4)**	***<0.001***			
			With moderate to severe AVVR	8/48 (16.7)	9/46 (24.3)	*0.792*			
			With none to mild AVVR	**5/176 (2.8)**	**27/153 (17.6)**	***<0.001***			
1 y	Ohye RG, 2010[8]	SVR	HLHS or single-ventricle morphology[g]	**72/274 (26.3)**	**100/275 (36.4)**	***0.011***	**252/274 (92.0)**	**192/275 (70.0)**	***0.003***
	Hill KD, 2013[31]						**60/281 (21.4)[f]**	**37/268 (13.8)[f]**	***0.025***
3 y	Newburger JW, 2014[32]	SVR	HLHS or single-ventricle morphology[g]	90/274 (32.8)	107/275 (38.9)	*0.155*	**(54.7)**	**(30.2)**	***<0.001***
6 y	Newburger JW, 2018[33]	SVR II	HLHS or single-ventricle morphology[g]	99/274 (36.1)	113/275 (41.1)	*0.254*	**(38.0)**	**(23.0)**	***<0.001***

AVVR = atrioventricular valve regurgitation; HLHS = hypoplastic left heart syndrome; HT = heart transplantation; MBTS = modified Blalock–Taussig-Thomas shunt; RCT = randomised controlled trial; RV = right ventricular; RVPAS = right ventricle-to-pulmonary artery shunt; SVR = single-ventricle reconstruction; S1P = stage-I palliation; S2P = stage-II palliation.
Data are presented as n/N (%) or (%).
[a]Stages were classified as follows: early, from the birth to discharge after Norwood operation; interstage, between Norwood discharge and Glenn surgery; 12 months, included post-Glenn surgery.
[b]Between 30 days after S1P and S2P.
[c]Post-discharge after S1P and before S2P.
[d]Included patients who died or underwent heart transplantation.
[e]Total of unintended cardiovascular interventions involving the shunt, pulmonary arteries, or neoaorta.
[f]Intervention for recoarctation.
[g]Included or a related single, morphologic right ventricular anomaly and a planned Norwood procedure.

modified Blalock–Taussig-Thomas shunt patients, and several reasons have been suggested. Modified Blalock–Taussig-Thomas shunt generates continuous forward flow into the pulmonary arteries, leading to diastolic runoff, coronary steal, and an increased pulmonary to systemic blood flow ratio. This physiological response may cause early haemodynamic instability during the interstage period.[5] Several studies reported a greater diastolic runoff in modified Blalock–Taussig-Thomas shunt than in right ventricle-to-pulmonary artery shunt at the early and interstage periods. Lower right ventricle ejection fraction at 14 months was associated with an increased risk of death or transplant in right ventricle-to-pulmonary artery shunt.[28] Although the morbidity during Norwood procedure was similar for both shunt types, fewer right ventricle-to-pulmonary artery shunt patients required early S2P resuscitation for hypoxaemia after S1P.[13] However, the benefit in right ventricle-to-pulmonary artery shunt disappeared after patients underwent further Fontan palliation surgery.[28,29]

The association between the number of cases performed and the outcome has been examined in the context of congenital heart surgery, particularly in relation to the Norwood operation, which has been extensively investigated as a benchmark procedure. Retrospective multi-institutional studies have consistently shown a strong correlation between the volume of Norwood cases performed by both a surgical unit and an individual surgeon and improved survival rates.[40–43] Only site volume showed an interaction with higher volume, decreasing the transplant-free survival advantage of right ventricle-to-pulmonary artery shunt. This finding may reflect the expertise of individual surgeons or institutional experience in the perioperative care of patients with modified Blalock–Taussig-Thomas shunt.[44] Right ventricle-to-pulmonary artery shunt appeared to have a more stable post-operative course and was associated with better early outcomes in centres with less experienced surgeons. However, the use of right ventricle-to-pulmonary artery shunt tended to result in a higher rate of unintended pulmonary artery reintervention.[24]

Developmental impairment was significant in survivors of Norwood procedure compared to that in the healthy population. The impairment was highly associated with intrinsic patient factors and overall morbidity in the first year, rather than with

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Table 2. RV function in RCTs comparing RVPAS and MBTS in HLHS.

Stage[a]	Author, year	Measurements, parameters	No. of RVPAS/MBTS patients	RV parameters (%)		p-Value
				RVPAS	MBTS	
Early stage-I	Frommelt PC, 2007[12]	2D TTE, FAC	7/8	42.0 ± 0.07	35.0 ± 0.05	>0.05
	Ohye RG, 2010[8]	2D TTE, EF	239/241	**48.5 ± 7.6**	**44.5 ± 7.6**	***<0.001***
	Frommelt PC, 2012[15]	2D TTE, EF	198/169	**49.0 ± 7.0**	**44.0 ± 8.0**	***<0.001***
	Marx GR, 2013[20]	3D echocardiogram, EF	111/104	51.4 ± 7.2	52.3 ± 6.7	*0.69*
Interstage	Frommelt PC, 2007[12]	2D TTE, FAC	7/8	37.0 ± 0.07	34.0 ± 0.08	NR
	Ohye RG, 2010[8]	2D TTE, EF	214/181	44.7 ± 8.3	42.9 ± 7.39	*0.07*
	Frommelt PC, 2012[15]	2D TTE, EF	153/127	45.0 ± 9.0	43.0 ± 8.0	*0.07*
	Marx GR, 2013[20]	3D echocardiogram, EF	84/63	47.7 ± 8.4	48.0 ± 7.3	*0.62*
Early stage-II	Frommelt PC, 2007[12]	2D TTE, FAC	7/8	36.0 ± 0.10	34.0 ± 0.09	>0.05
14 months	Ohye RG, 2010[8]	2DTTE, EF	179/184	42.7 ± 8.0	42.7 ± 7.4	*0.97*
	Frommelt PC, 2012[15]	2D TTE, EF	132/104	43.0 ± 8.0	43.0 ± 7.0	*0.91*
	Marx GR, 2013[20]	3D echocardiogram, EF	75/50	46.8 ± 6.4	46.9 ± 7.2	*0.73*
	Hill Gd, 2015[30]	2D TTE, Global RV circumferential strain	98/84	**−12.2 ± 4.2**	**−13.4 ± 4.3**	***0.05***
Between 14 months and Pre-Fontan	Newburger JW, 2014[32]	2D TTE, difference in RVEF	58/56	**-3.25 ± 8.24**	**0.99 ± 8.80**	***0.009***
Pre-Fontan	Newburger JW, 2014[32]	2D TTE, EF	135/123	**41.7 ± 7.1**	**44.7 ± 6.0**	***0.007***
	Frommelt PC, 2014[26]	2D TTE, EF	79/68	**41.0 ± 7.0**	**45.0 ± 6.0**	***0.007***
Between Pre-Fontan and 6 years	Frommelt PC, 2019[41]	2D TTE, difference in RVEF	39/37	**3.90 ± 6.42**	**0.10 ± 6.88**	***0.015***
6 years	Newburger JW, 2018[33]	2D TTE, EF	61/55	46.0 ± 6.0	45.0 ± 6.0	*0.60*
	Frommelt PC, 2019[41]	2D TTE, EF	62/55	45.8 ± 6.4	45.3 ± 6.1	0.68

Data are presented as n/N or mean± (standard deviation).
2D TTE = two-dimensional transthoracic echocardiogram; EF = ejection fraction; FAC = fractional area change; HLHS = hypoplastic left heart syndrome; MBTS = modified Blalock–Taussig-Thomas shunt; RV = right ventricular; RVEF = right ventricular ejection fraction; RVPAS = right ventricle-to-pulmonary artery shunt.
[a]Stages were classified as follows; early stage-I, from the birth to discharge after Norwood procedure; interstage, between Norwood discharge and Glenn surgery; early stage-II, at the discharge after Glenn surgery; pre-Fontan, pre-operative evaluation for Fontan.

perioperative management strategies, including the source of pulmonary blood flow or perfusion strategy.[44]

Although the use of medication for the treatment of hypoplastic left heart syndrome has been scarcely investigated, it remains debatable whether the use of angiotensin-converting enzyme inhibitors, a cornerstone medical therapy for heart failure in hypoplastic left heart syndrome, influences the systemic circulation and ventricular remodelling during the interstage period. The beneficial effect in terms of development remained lower in the renin–angiotensin–aldosterone system gene high-risk group at 14 months, particularly in patients receiving enalapril.[10] A non-randomised study conducted by the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) and an analysis of the single-ventricle reconstruction trial database yielded the conclusion that administering digoxin to patients without arrhythmia during the interstage period was associated with a reduction in mortality, although it was also linked to poorer weight gain during this phase. In a recent consensus-based review conducted in Germany, it was recommended to use diuretics, angiotensin-converting enzyme inhibitors, and, in specific cases, bisoprolol for the management of patients who have a hybrid stage 1 palliation.[45,46] However, there was insufficient data to conclusively confirm these benefits in this analysis

Regarding perioperative management, regional cerebral perfusion and deep hypothermic cardiac arrest did not show a difference in survival benefits. However, regional cerebral perfusion is used routinely for S1P by >80% of surgeons in the United States.[47] Despite the intuitive appeal of regional cerebral perfusion, its effectiveness in providing cerebral protection has not been demonstrated in several neurodevelopmental studies, including

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one randomised controlled trial, two comparative studies, and numerous case series in neonates with hypoplastic left heart syndrome; therefore, it should be used with caution.[30] Furthermore, improvement of clinical management decisions established on evidence-based medicine is crucial. Multicentre randomised controlled trials comparing perioperative strategies are necessary.

The present study had several limitations. The major issue is that most randomised controlled trials originated from the large-scale landmark single-ventricle reconstruction trial due to rare prevalence of hypoplastic left heart syndrome. Although we show several forest plots, only two studies were analysed in them; therefore, results from the single largest trial constitutes the central messages in this meta-analysis. The other included randomised controlled trials had different original trials, but each of them had different outcomes. Therefore, there was not a sufficient number of studies to represent the pooled results. However, this review can assist in understanding randomised controlled trials related to hypoplastic left heart syndrome and suggesting contemporary guidelines based on them. Second, this study could not derive definitive recommendations regarding medical and perioperative care due to the limited number of studies and inconclusive results. Our study should be considered as a tool to understand what we have acquired based on randomised controlled trials about hypoplastic left heart syndrome. Furthermore, evaluation for right ventricular function was mostly based on 2D or 3D echocardiography, which has the inherent limitation of right ventricular view and variation among practitioners. Cardiac MRI should be performed to confirm how right ventricular function changes after the Norwood operation. In addition, this study does not represent the clinical course of patients with non-hypoplastic left heart syndrome morphological right ventricular type functional single ventricle; caution is needed when implementing the results to patients with those conditions.

In conclusion, despite the advantages of right ventricle-to-pulmonary artery shunt during the early period, the two types of shunts applied during the Norwood procedure demonstrated comparable long-term survival despite a high reintervention rate among right ventricle-to-pulmonary artery shunt due to pulmonary artery stenosis. As the number of randomised controlled trials regarding medical/perioperative/ICU management was limited, further multi-institutional randomised controlled trials are required.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1047951123002986

Data availability statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contribution. AYK, JWJ, WW, and JIS designed the study. AYK and WW collected the data. AYK, WW, and JIS performed the statistical analysis. AYK and WW wrote the first draft of this manuscript. All authors had full access to all the study data. All authors reviewed, revised, and approved the final version of the manuscript. The corresponding authors have final responsibility for the decision to submit for publication.

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References

1. Ohye RG, Schranz D, D'Udekem Y. Current therapy for hypoplastic left heart syndrome and related single ventricle lesions. Circulation 2016; 134: 1265–1279.
2. Barron DJ, Kilby MD, Davies B, Wright JG, Jones TJ, Brawn WJ. Hypoplastic left heart syndrome. Lancet 2009; 374: 551–564.
3. Razzouk AJ, Chinnock RE, Gundry SR, et al. Transplantation as a primary treatment for hypoplastic left heart syndrome: intermediate-term results. Ann Thorac Surg 1996; 62: 1–8.
4. Liu Y, Chen S, Zühlke L, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019; 48: 455–463.
5. Ohye RG, Sleeper LA, Mahony L, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. N Engl J Med 2010; 362: 1980–1992.
6. Kim AY, Shin JI, Jung JW. Treatment options of Hypoplastic Left Heart Syndrome A systematic Review. PROSPERO 2020 CRD42020190190 [Internet]. [cited 2021 Dec 21]. Available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020190190.
7. Ghanayem NS, Jaquiss RDB, Cava JR, et al. Right ventricle-to-pulmonary artery conduit versus Blalock-taussig shunt: a hemodynamic comparison. Ann Thorac Surg 2006; 82: 1603–1609, discussion 1609-1610.
8. Frommelt PC, Sheridan DC, Mussatto KA, et al. Effect of shunt type on echocardiographic indices after initial palliations for hypoplastic left heart syndrome: Blalock-Taussig shunt versus right ventricle-pulmonary artery conduit. J Am Soc Echocardiogr 2007; 20: 1364–1373.
9. Hsu DT, Zak V, Mahony L, et al. Enalapril in infants with single ventricle: results of a multicenter randomized trial. Circulation 2010; 122: 333–340.
10. Mital S, Chung WK, Colan SD, et al. Renin-angiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. Circulation 2011; 123: 2353–2362.
11. Frommelt PC, Guey LT, Minich LL, et al. Does initial shunt type for the Norwood procedure affect echocardiographic measures of cardiac size and function during infancy? Circulation 2012; 125: 2630–2638.
12. Ghanayem NS, Allen KR, Tabbutt S, et al. Interstage mortality after the Norwood procedure: results of the multicenter Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2012; 144: 896–906.
13. Newburger JW, Sleeper LA, Bellinger DC, et al. Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the single ventricle reconstruction trial. Circulation 2012; 125: 2081–2091.
14. Tweddell JS, Sleeper LA, Ohye RG, 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.e2.
15. Frommelt PC, Gerstenberger E, et al. Doppler flow patterns in the right ventricle-to-pulmonary artery shunt and neo-aorta in infants with single right ventricle anomalies: impact on outcome after initial staged palliations. J Am Soc Echocardiogr 2013; 26: 521–529.
16. Marx GR, Shirali G, Levine JC, et al. Multicenter study comparing shunt type in the norwood procedure for single-ventricle lesions. Circul Cardiovasc Imag 2013; 6: 934–942.
17. Aiyagari R, Rhodes JF, Shrader P, et al. Impact of pre-stage II hemodynamics and pulmonary artery anatomy on 12-month outcomes in the Pediatric Heart Network Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2014; 148: 1467–1474.
18. Burch PT, Gerstenberger E, Ravishankar C, et al. Longitudinal assessment of growth in hypoplastic left heart syndrome: results from the single ventricle reconstruction trial. J Am Heart Assoc 2014; 3: e000079.

19. Goldberg CS, Lu M, Sleeper LA, et al. Factors associated with neurodevelopment for children with single ventricle lesions. J Pediatr. 2014; 165: 490–496.e8.
20. Ravishankar C, Gerstenberger E, Sleeper LA, et al. Factors affecting Fontan length of stay: results from the Single Ventricle Reconstruction trial. J Thorac Cardiovasc Surg 2016; 151: 669–675.e1.
21. Burch PT, Ravishankar C, Newburger JW, et al. Assessment of growth 6 years after the norwood procedure. J Pediatr 2017; 180: 270–274.e6.
22. Frommelt PC, Gerstenberger E, Cnota JF, et al. Impact of initial shunt type on cardiac size and function in children with single right ventricle anomalies before the fontan procedure: the single ventricle reconstruction extension trial. J Am Coll Cardiol 2014; 64: 2026–2035.
23. Mackie AS, Booth KL, Newburger JW, et al. A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. J Thorac Cardiovasc Surg 2005; 130: 810–816.
24. Kolcz J, Skladzien T, Kordon Z, Rudzinski A, Skalski J. Impact of right ventricle-pulmonary artery conduit placement on pulmonary artery development after the Norwood procedure in hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2012; 42: 218–23, discussion 223-4.
25. Keski-Nisula J, Arvola O, Jahnukainen T, Andersson S, Pesonen E. Reduction of inflammation by high-dose methylprednisolone does not attenuate oxidative stress in children undergoing bidirectional glenn procedure with or without aortic arch or pulmonary arterial repair. J Cardiothorac Vasc Anesth 2020; 34: 1542–1547.
26. Hill GD, Frommelt PC, Stelter J, et al. Impact of initial norwood shunt type on right ventricular deformation: the single ventricle reconstruction trial. J Am Soc Echocardiogr 2015; 28: 517–521.
27. Hill KD, Rhodes JF, Aiyagari R, et al. Intervention for recoarctation in the single ventricle reconstruction trial. Circulation 2013; 128: 954–961.
28. Newburger JW, Sleeper LA, Frommelt PC, et al. Transplantation-free survival and interventions at 3 years in the single ventricle reconstruction trial. Circulation 2014; 129: 2013–2020.
29. Newburger JW, Sleeper LA, Gaynor JW, et al. Transplant-free survival and interventions at 6 years in the SVR trial. Circulation 2018; 137: 2246–2253.
30. Goldberg CS, Bove EL, Devaney EJ, et al. A randomized clinical trial of regional cerebral perfusion versus deep hypothermic circulatory arrest: outcomes for infants with functional single ventricle. J Thorac Cardiovasc Surg. 2007; 133: 880–887.
31. Stuth EAE, Berens RJ, Staudt SR, et al. The effect of caudal vs intravenous morphine on early extubation and postoperative analgesic requirements for stage 2 and 3 single-ventricle palliation: a double blind randomized trial. Paediatr Anaesth. 2011; 21: 441–453.
32. Jones BO, Pepe S, Sheeran FL, et al. Remote ischemic preconditioning in cyanosed neonates undergoing cardiopulmonary bypass: a randomized controlled trial. J Thorac Cardiovasc Surg. 2013; 146: 1334–1340.
33. Ryerson LM, Mackie AS, Atallah J, et al. Prophylactic peritoneal dialysis catheter does not decrease time to achieve a negative fluid balance after the Norwood procedure: a randomized controlled trial. J Thorac Cardiovasc Surg. 2015; 149: 222–228.
34. Spillane NT, Kashyap S, Bateman D, Weindler M, Krishnamurthy G. Comparison of feeding strategies for infants with hypoplastic left heart syndrome: a randomized controlled trial. World J Pediatr Congenit Heart Surg. 2016; 7: 446–453.
35. Jordan LC, Siciliano RE, Cole DA, et al. Cognitive training in children with hypoplastic left heart syndrome: a pilot randomized trial. Prog Pediatr Cardiol 2020; 57: 101185.
36. Johnson JN, Ansong AK, Li JS, et al. Celiac artery flow pattern in infants with single right ventricle following the Norwood procedure with a modified Blalock-Taussig or right ventricle to pulmonary artery shunt. Pediatr Cardiol. 2011; 32: 479–486.
37. Frommelt PC, Hu C, Trachtenberg F, et al. Impact of initial shunt type on echocardiographic indices in children after single right ventricle palliations. Circulation: Cardiovasc Imag 2019; 12: e007865.
38. Mathur K, Hsu DT, Lamour JM, Aydin SI. Safety of enalapril in infants: data from the pediatric heart network infant single ventricle trial. J Pediatr 2020; 227: 218–223.
39. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928–d5928.
40. Hirsch JC, Gurney JG, Donohue JE, Gebremariam A, Bove EL, Ohye RG. Hospital mortality for Norwood and arterial switch operations as a function of institutional volume. Pediatr Cardiol. 2008; 29: 713–717.
41. Pasquali SK, Ohye RG, Lu M, et al. Variation in perioperative care across centers for infants undergoing the Norwood procedure. J Thorac Cardiovasc Surg 2012; 144: 915–921.
42. Checchia PA, McCollegan J, Daher N, Kolovos N, Levy F, Markovitz B. The effect of surgical case volume on outcome after the Norwood procedure. J Thorac Cardiovasc Surg. 2005; 129: 754–759.
43. Hornik CP, He X, Jacobs JP, et al. Relative impact of surgeon and center volume on early mortality following the norwood operation. Ann Thorac Surg. 2012; 93: 1992–1997.
44. Alphonso N, Angelini A, Barron DJ, et al. Guidelines for the management of neonates and infants with hypoplastic left heart syndrome: The European Association for Cardio-Thoracic surgery (EACTS) and the Association for European Paediatric and Congenital Cardiology (AEPC) Hypoplastic Left Heart Syndrome Guidelines Task Force. Eur J Cardio-Thorac Surg 2020; 58: 416–499.
45. Brown DW, Mangeot C, Anderson JB, et al. Digoxin use is associated with reduced interstage mortality in patients with no history of arrhythmia after stage i palliation for single ventricle heart disease. J Am Heart Assoc 2016; 5: e002376.
46. Truong DT, Menon SC, Lambert LM, et al. Digoxin use in infants with single ventricle physiology: secondary analysis of the pediatric heart network infant single ventricle trial public use dataset. Pediatr Cardiol. 2018; 39: 1200–1209.
47. Ohye RG, Goldberg CS, Donohue J, et al. The quest to optimize neurodevelopmental outcomes in neonatal arch reconstruction: the perfusion techniques we use and why we believe in them. J Thorac Cardiovasc Surg 2009; 137: 803–806.

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