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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Outcomes of Children With Hypoplastic Left Heart Syndrome and Heart Failure on Medical Therapy

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ABSTRACT

BACKGROUND Systemic right ventricle (RV) dysfunction is associated with lower transplant-free survival (TFS) in hypoplastic left heart syndrome (HLHS), but the likelihood of functional improvement and utility of heart failure (HF) medications is not understood.

OBJECTIVES The authors aimed to describe TFS, HF medication use, and surgical interventions in HLHS patients with RV dysfunction with and without subsequent improvement in function.

METHODS The SickKids HF Database is a retrospective cohort that includes all pediatric HLHS patients with RV dysfunction lasting >30 days. We compared TFS, HF medications, and surgical interventions in HLHS patients with and without functional normalization.

RESULTS Of 99 patients with HLHS and RV dysfunction, 52% had normalized function for ≥30 days. TFS at 2 years after dysfunction onset was lower in those without normalization (14% vs 78%, $P < 0.001$). Patients without normalization were less likely to reach target dosing (TD) of HF medications (27% vs 47% on 1 medication at TD, $P < 0.001$) and undergo Fontan completion (7% vs 53%, $P < 0.001$). Clinical factors associated with improved TFS were normalization of function for ≥30 days, onset of dysfunction after bidirectional Glenn, and exposure to ACE inhibition.

CONCLUSIONS Our cohort of HLHS patients with systemic RV dysfunction demonstrated a novel finding of improved TFS in those with functional normalization for ≥30 days. Achieving TD of HF medications was associated with improved outcomes. This may reflect patient stability and tolerance for HF medication more than its therapeutic effect, but it can help inform decisions to proceed with surgical palliation or list for transplant. (JACC Adv 2024;3:100811) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Hypoplastic left heart syndrome (HLHS) continues to carry a significant risk of mortality despite advances in surgical techniques. Recent publications demonstrate 5-year transplant-free survival (TFS) for children born with HLHS ranging from 55% to 75%.[1,2] This has been attributed in part to non-modifiable anatomic factors, including mitral stenosis, aortic atresia subtype,

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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

BB = beta-blocker

BDG = bidirectional Glenn

BTT = Blalock Taussig Thomas

HF = heart failure

HLHS = hypoplastic left heart syndrome

RV = right ventricle

presence of additional cardiac or extracardiac congenital anomalies, and prematurity.[3] However, dysfunction of the systemic right ventricle (RV) remains an independent risk factor for death or transplant.[4-7] These patients also represent a particularly high-risk group for heart transplant[8] with significant waitlist mortality, and thus appropriate risk stratification is needed to guide decision making at each surgical stage.

A portion of HLHS patients will survive and be able to proceed through staged surgical palliation despite RV dysfunction. Given the complexity of underlying ventricular morphology and changes in loading conditions at each surgical stage, predicting the long-term outcomes of patients with HLHS and ventricular dysfunction based on single assessment or short-term follow-up can be misleading. In this context, addressing the impact of improvements in ventricular function over time on TFS and successful surgical palliation is necessary to inform clinical decision-making.

While established guidelines exist for medical management of heart failure (HF) in patients with biventricular physiology and systemic left ventricular dysfunction, the differences between mechanisms of RV and left ventricle failure lead to challenges in extrapolating data on HF medications to pediatric HLHS populations.[9-11] In addition, management of HF in single ventricle patients is intrinsically different than in conventional biventricular patients with ventricular dysfunction, as HF in these patients is caused by a myriad of etiologies often co-existing together, such as ventricular fibrosis, systemic RV myocardial inadequacy, consequences of surgical palliation including ischemia or volume load, and a known predisposition to diastolic HF.[12,13] Conventional HF medication dosing has been explored with no convincing evidence of benefit in pediatric HLHS populations including patients with and without dysfunction.[14-16] However, the relationship between HF medication use in HLHS patients with persistent ventricular dysfunction and TFS is not well understood.

Thus, we aimed to characterize survival outcomes, surgical interventions, and HF medication use in a cohort of HLHS patients with RV dysfunction with and without normalization of systolic function during follow-up. Additionally, we sought to determine clinical factors associated with improved TFS.

METHODS

STUDY DESIGN AND POPULATION. The SickKids HF Database is a retrospective cohort of all patients presenting to the primary center between January 1, 2001, and July 1, 2017, with HF. Our methodology has been described previously.[17] Briefly, patients aged between 0 and 18 years with a diagnosis of HLHS and ventricular dysfunction ≥30 days were considered eligible for inclusion. Patients never seen at SickKids or those who have never had an echocardiogram performed at SickKids were excluded. For the purposes of this study, ventricular dysfunction was defined as a qualitative report of at least mild right ventricular dysfunction as determined by an echocardiogram at time of reporting and lasting >30 days, or where death or transplant occurred within 30 days of onset of dysfunction. The purpose of this distinction was to avoid patients with transient perioperative dysfunction. To facilitate comparative analysis between those with persistent dysfunction and those in whom function normalizes, the overall cohort was divided into 2 subgroups. Normalization of function was defined as normal RV systolic function lasting ≥30 days after dysfunction onset. Echocardiograms where ranges were reported such as mild-moderate were independently reviewed by the principal investigator.

DATA COLLECTION. In order to identify eligible patients, we accessed all echocardiogram reports and surgical records on congenital heart disease patients seen at SickKids between January 1, 2001, and July 1, 2017. Data collection was primarily done by chart review using standard operating procedures for data abstraction and case report forms. Baseline demographics, cardiology-related clinical visits, surgical history, genetic testing, and cardiac testing results were included. Data was collected on use of angiotensin-converting enzyme inhibitor (ACEI), beta-blocker (BB), and mineralocorticoid receptor antagonist, as these represented the standard of care HF medications used during the study period. Target dosing of HF medication was defined, a priori, as ACEI, BB, and mineralocorticoid receptor antagonists prescribed as at least 70% of institutional drug formulary weight-based recommended dosing. Data collection started at the onset of the first period of ventricular dysfunction lasting >30 days and ended at 18 years or sooner in the case of heart transplant, death, or loss of follow-up at SickKids. Outcome of death or heart transplant was also abstracted from the patient chart.

DATA MANAGEMENT AND ANALYSIS. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the Hospital for Sick Children. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Abstracted data was audited regularly by investigators to ensure data validity, completeness, and consistency between abstractors. All discrepancies were resolved at team meetings and, if necessary, review of primary data by investigators.

Our primary outcome was death or transplant. Descriptive statistics were reported using mean (standard deviation), frequency (percentage), or median (Q1-Q3) as appropriate. Differences between patients whose function normalized for ≥30 days and those who did not were analyzed using Mann-Whitney U, Wilcoxon signed-rank, chi-squared, or Fisher tests as appropriate. Kaplan-Meier survival analysis was used to assess TFS. Cox-proportional hazards modeling was used to assess childhood risk factors associated with hazard of death or transplant. Candidate variables were identified based on clinical judgment and univariate analysis. Candidate variable with <80% completeness were excluded. Bootstrap aggregation with resampling (500 resamples) was used for variable selection. Candidate variables that were found in at least 25% of the bootstrap models were subjected to a backward selection with a retention threshold of $P < 0.05$. The level of statistical significance was set at $P = 0.05$. Since this was a descriptive study, no power calculation was completed. The study was approved by the institutional research ethics board prior to commencing data collection, and a waiver of consent was also obtained. Statistical analysis was performed using SAS 9.4 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS OF COHORT. There were 99 patients with HLHS who met the inclusion criteria of having RV dysfunction for a duration ≥30 days during the study period. The median (IQR) age at onset of dysfunction was 2.6 (IQR: 1.0-5.3) months (Table 1). Of this cohort, 51 (52%) met criteria for sustained normalization of RV function during follow-up for a median duration of 3.5 (IQR: 0.8-9.1) years. At the study endpoint, 37 (37%) had normal function.

Most patients developed dysfunction between Norwood and bidirectional Glenn (BDG) procedure (71%), and there was no significant difference in surgical stage at onset of dysfunction between those who had persistent dysfunction and those with normalization of RV function ($P = 0.75$). Of those who developed dysfunction prior to the Glenn procedure and sustained normalization during follow-up, the majority 33/37 (89%) normalized prior to the Glenn procedure. The median time from onset of dysfunction to first normal echocardiogram was 49.0 (IQR: 30.0-133.9) days for those who experienced a period of sustained normalization during follow-up and 50 (IQR: 27.0-333.8) days for those who did not. There was no difference between groups in proportion of patients reported as having at least moderate dysfunction on at least one occasion during follow-up (73% vs 77%, $P = 0.28$).

TRANSPLANT-FREE SURVIVAL. During the study period, there were 22 (46%) deaths and 15 (31%) transplants in the persistent dysfunction cohort, compared with 13 (25%) deaths and 6 (12%) transplants in the cohort with normalization of function for at least 30 days during follow-up ($P < 0.001$) (Table 2).

HF was the most common cause of death accounting for 73% of deaths in the cohort with persistent ventricular dysfunction and 85% of deaths in the cohort with normalization of function for at least 30 days during follow-up ($P = 1.00$). Of those who died from HF, 11/27 (41%) were on extracorporeal membrane oxygenation post-stage 1 palliation, and an additional 4/27 (15%) were Milrinone-dependent after stage 1 surgery and listed for transplant at time of death. Multiorgan dysfunction secondary to HF was documented in 9/27 (33%), and an additional 5/27 (19%) had isolated renal dysfunction, of whom 1 required dialysis. Of our total cohort, 7 died of causes other than HF and documented arrhythmia; these included respiratory failure due to recurrent aspiration and/or lymphangiectasia, diffuse severe hypoxic ischemic encephalopathy, massive pulmonary embolus, and complex multisystem disease with multiple pulmonary arteriovenous malformations. Two patients died suddenly during the interstage period with no autopsy performed and no definitive cause of death ascertained.

The overall TFS for HLHS patients with ventricular dysfunction lasting at least 30 days was 54% at 1 year after onset of ventricular dysfunction (Figure 1A). TFS at 1 year after dysfunction onset was 23% for those

TABLE 1 Baseline Characteristics of Total HLHS Cohort With Ventricular Dysfunction ≥30 Days

	Total Cohort (N = 99)	Dysfunction Cohort (n = 48)	Normalization Cohort (n = 51)	*P* Value
Male	60 (61)	29 (60)	31 (61)	1.00
Age at dysfunction onset (y)	0.22 (0.09-0.44)	0.2 (0.1-0.43)	0.24 (0.09-0.45)	0.88
Birth weight (kg)	3.26 (2.85-3.66)	3.21 (2.8-3.55)	3.35 (2.89-3.71)	0.32
Gestational age <37 wk	9 (9)	4 (8)	5 (10)	0.87
Genetic testing performed	16 (16)	12 (25)	4 (8)	
Genetic disorder	4 (4)			
Status at onset of dysfunction				0.16
Outpatient	15 (15)	9 (19)	6 (12)	
Inpatient (ward)	36 (36)	13 (27)	23 (45)	
Inpatient (ICU)	48 (48)	26 (54)	22 (43)	
Surgical stage at onset of dysfunction				0.75
Prestage 1	6 (6)	3 (6)	3 (6)	
Norwood	70 (71)	36 (75)	34 (67)	
BDG	19 (19)	8 (17)	11 (22)	
Fontan	4 (4)	1 (2)	3 (6)	
Stage 1 procedure				0.21
Norwood/BTT	58 (59)	27 (56)	31 (61)	
Norwood Sano	12 (12)	9 (19)	3 (6)	
Hybrid Stage 1	19 (19)	7 (15)	12 (24)	
Bilateral PA bands	4 (4)	1 (2)	3 (6)	
RV dysfunction grading at onset				0.08
Mild	68 (69)	32 (67)	36 (71)	
Moderate	21 (21)	8 (17)	13 (25)	
Severe	10 (10)	8 (17)	2 (4)	
≥ Moderate tricuspid regurgitation	22 (23)	11 (23)	11 (22)	0.94

Values are n (%) or median IQR). Dysfunction cohort: patients with sustained ventricular dysfunction (≥30 days) without period of normalization of function (≥30 days) during follow-up. Normalization cohort: patients with sustained ventricular dysfunction (≥30 days) with period of normalization of function (≥30 days) during follow-up.

BDG = bidirectional Glenn; BTT = Blalock Taussig Thomas shunt; HLHS = hypoplastic left heart syndrome; ICU = intensive care unit; PA = pulmonary artery.

TABLE 2 Death or Transplant Outcomes in HLHS Patients With Ventricular Dysfunction (≥30 Days) With and Without Period of Normalization of Function (≥30 Days) During Follow-Up

	Total Cohort (N = 990	Dysfunction Cohort (n = 48)	Normalization Cohort (n = 51)	*P* Value
Outcome status				<0.001
Alive and followed	43 (43)	11 (23)	32 (63)	
Transplanted	21 (21)	15 (31)	6 (12)	
Dead	35 (35)	22 (46)	13 (25)	
Cause of death				1.00
Heart failure	27 (77)	16 (73)	11 (85)	
Arrhythmia	1 (3)	1 (5)	0 (0)	
Other	7 (21)	5 (23)	2 (15)	

Values are n (%). Dysfunction cohort: patients with sustained ventricular dysfunction (≥30 days) without period of normalization of function (≥30 days) during follow-up. Normalization cohort: patients with sustained ventricular dysfunction (≥30 days) with period of normalization of function (≥30 days) during follow-up.

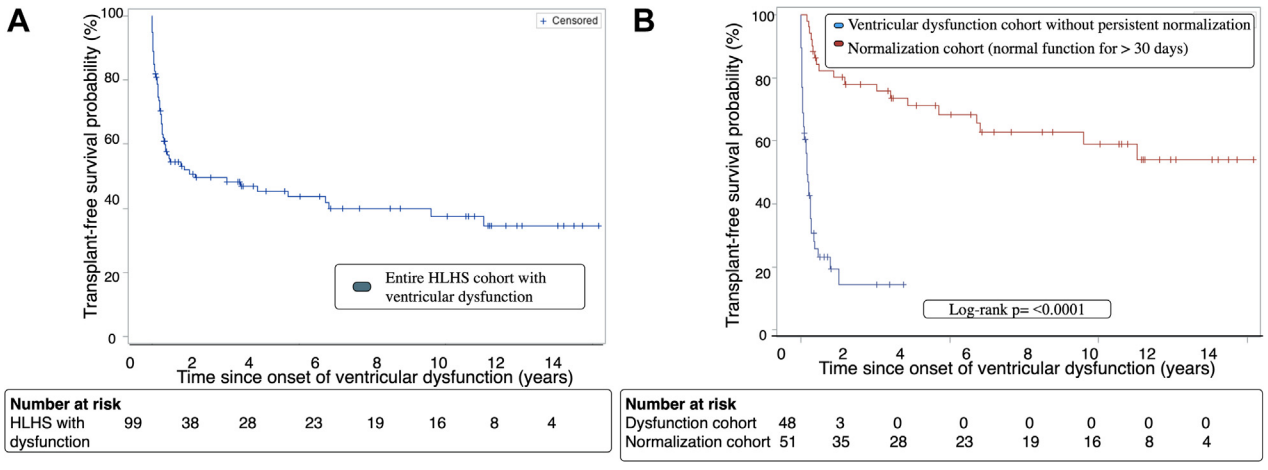
HLHS = hypoplastic left heart syndrome.

with persistent dysfunction and 82% for those with normalization of ventricular function ($P < 0.001$) (Figure 1B).

HEART FAILURE MEDICATIONS USED AFTER DYSFUNCTION ONSET. Fifty-seven patients (58%) of the total cohort reached >70% target dosing in at least one HF medication by study endpoint. Target dosing (>70%) in HF medications was less frequently reached in those with persistent dysfunction than in those with normalization of function, with 27% vs 47% on 1 medication at target dosing ($P < 0.0001$), and 8% vs 27% on 2 medications at target dosing ($P = 0.0004$) (Table 3). ACEI were the most frequently used HF medication in the total cohort with 58% prescribed and 49% achieving target dosing.

SURGICAL INTERVENTIONS AFTER DYSFUNCTION ONSET. Of the total study cohort, 7% underwent Norwood or BTT shunt insertion after onset of

FIGURE 1 Transplant-Free Survival



(A) Transplant-free survival of total cohort of HLHS patients with ventricular dysfunction (≥30 days) was 54% at 1 year after dysfunction onset. (B) Transplant-free survival in HLHS patients with ventricular dysfunction (≥30 days) with and without period of normalization of ventricular function (≥30 days) during follow-up was 23% and 82%, respectively, at 1 year after dysfunction onset. HLHS = hypoplastic left heart syndrome.

ventricular dysfunction, 38% underwent the BDG procedure, and 31% underwent Fontan completion (Table 4). Staged surgical palliation was less frequently reached in those with persistent dysfunction than in those with normalization of ventricular dysfunction, with 18% vs 55% undergoing BDG procedure ($P < 0.001$), and 7% vs 53% undergoing Fontan completion ($P < 0.001$).

There was no significant difference in atrioventricular valve repair (2% vs 12%, $P = 0.12$) or aortic arch intervention (2% vs 10%, $P = 0.21$) after dysfunction onset between the cohort with persistent dysfunction and those with normalization of function. Those with persistent ventricular dysfunction were more likely to require mechanical circulatory support after onset of dysfunction, with 44% vs 18% receiving extracorporeal membranous oxygenation ($P < 0.05$) and 8% vs 0% receiving ventricular assist device ($P = 0.05$).

CLINICAL VARIABLES ASSOCIATED WITH TRANSPLANT-FREE SURVIVAL IN HLHS PATIENTS WITH DYSFUNCTION. Surgical stage at onset of dysfunction. For those who developed dysfunction prior to BDG procedure, 1-year TFS was lower at 44%

TABLE 3 Heart Failure Medication Use After Dysfunction Onset in HLHS Patients With Ventricular Dysfunction (≥30 Days), With and Without Period of Normalization of Function (≥30 Days) During Follow-Up

	Total Cohort (N = 99)	Dysfunction Cohort (n = 48)	Normalization Cohort (n = 51)	*P* Value
1 med at target dose	37 (37)	13 (27)	24 (47)	<0.001
2 meds at target dose	18 (18)	4 (8)	14 (27)	<0.001
3 meds at target dose	2 (2)	0 (0)	2 (4)	0.17
ACEI at any dose	58 (58)	19 (40)	39 (76)	<0.001
ACEI at target dose	49 (49)	14 (29)	35 (69)	<0.001
Beta-blocker at any dose	29 (29)	10 (21)	19 (37)	0.07
Beta-blocker at target dose	14 (14)	2 (4)	12 (24)	0.005
Aldosterone antagonist	27 (27)	6 (13)	21 (41)	0.001

Values are n (%). Dysfunction cohort: patients with sustained ventricular dysfunction (≥30 days) without period of normalization of function (≥30 days) during follow-up. Normalization cohort: patients with sustained ventricular dysfunction (≥30 days) with period of normalization of function (≥30 days) during follow-up.

ACEI = angiotensin-converting enzyme inhibitor; HLHS = hypoplastic left heart syndrome.

TABLE 4 Interventions After Onset of Dysfunction in HLHS Patients With Ventricular Dysfunction (≥30 Days), With and Without Period of Normalization of Function (≥30 Days) During Follow-Up

	Total Cohort (N = 99)	Dysfunction Cohort (n = 48)	Normalization Cohort (n = 51)	*P* Value
Norwood	7 (7)	5 (11)	2 (4)	0.25
BDG	36 (38)	8 (17)	28 (55)	<0.001
Fontan	30 (31)	3 (7)	27 (53)	<0.001
AV valve repair	7 (7)	1 (2)	6 (12)	0.12
Aortic Arch intervention	6 (6)	1 (2)	5 (10)	0.21
ECMO support	30 (30)	21 (44)	9 (18)	0.008
VAD support	4 (4)	4 (8)	0 (0)	0.05

Values are n (%). cohort: patients with sustained ventricular dysfunction (≥30 days) without period of normalization of function (≥30 days) during follow-up. Normalization cohort: patients with sustained ventricular dysfunction (≥30 days) with period of normalization of function (≥30 days) during follow-up.

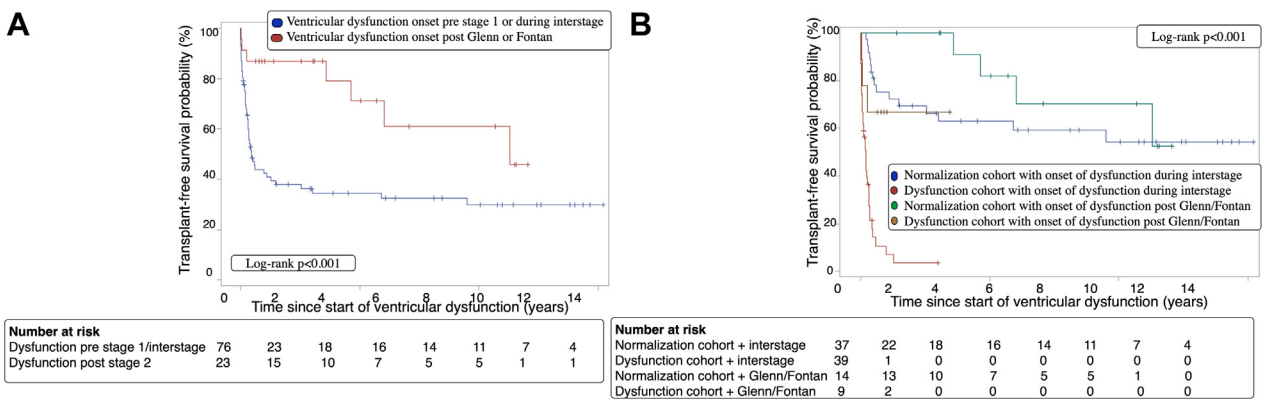
AV = atrioventricular; BDG = bidirectional Glenn; BTT = Blalock Taussig Thomas shunt; ECMO = extracorporeal membranous oxygenation; HLHS = hypoplastic left heart syndrome; VAD = ventricular assist device.

from dysfunction onset, compared to 88% for those who developed dysfunction after the BDG procedure ($P < 0.001$) (Figure 2A). The benefit of having a period of normalization of function was consistent irrespective of surgical stage at onset of dysfunction ($P < 0.001$) (Figure 2B), with 1-year TFS after dysfunction onset of 98% vs 60% for those who develop dysfunction after BDG procedure, compared with 75% vs 10% for those who develop dysfunction prior to BDG procedure.

Heart failure medication use. One-year TFS after dysfunction onset improved incrementally with target dose of HF medications, at 24%, 72%, and 82% on 0, 1, and ≥2 medications at target dosing, respectively ($P < 0.001$) (Figure 3, Central Illustration).

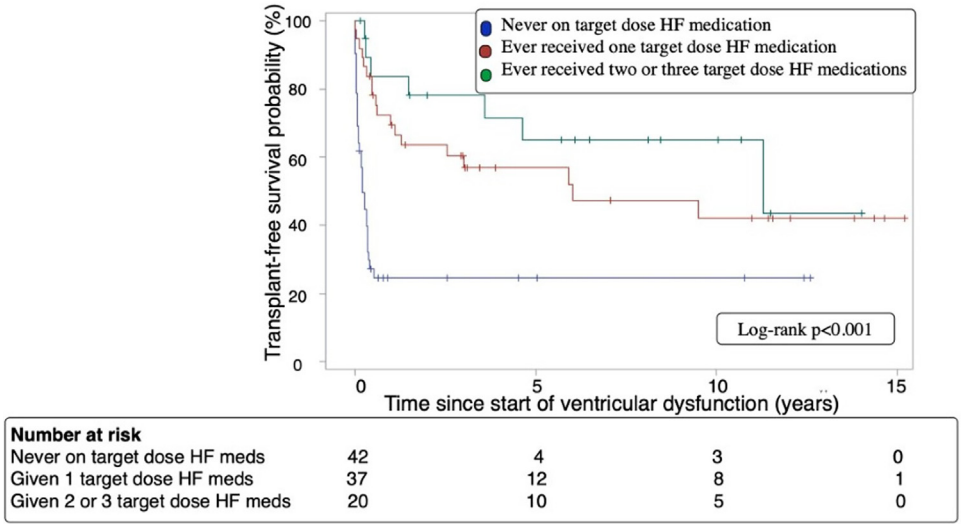
In our total cohort of HLHS patients with ventricular dysfunction, achieving target-dose ACEI correlated with improved 6-month TFS after dysfunction onset from 33% to 70% ($P < 0.01$) (Figure 4A). In those with persistent dysfunction, TFS 6 months after dysfunction onset was 37% for those on target-dose ACEI vs 21% for those on suboptimal dose or none, and in those with normalization of function (≥30 days), 6-month TFS was 94% on target-dose ACEI vs 69% for those on suboptimal dose or none (Figure 4B).

FIGURE 2 Transplant-Free Survival by Surgical Stage at Dysfunction Onset



(A) Transplant-free survival of HLHS patients with ventricular dysfunction (≥30 days) who develop dysfunction prior to Norwood or BDG procedure vs after BDG or Fontan procedure was 44% vs 88%, respectively, at 1 year after dysfunction onset. (B) Transplant-free survival of HLHS patients with ventricular dysfunction (≥30 days) who develop dysfunction prior to Norwood or BDG with and without period of normalization of ventricular function (≥30 days) was 75% and 10%, respectively, at 1 year after dysfunction onset, compared to 98% and 60% for patients with ventricular dysfunction (≥30 days) who develop dysfunction after BDG or Fontan with and without period of normalization of ventricular function (≥30 days). BDG = bidirectional Glenn; HLHS = hypoplastic left heart syndrome.

FIGURE 3 Transplant-Free Survival With Successive Use of Heart Failure Medications at Target Dose



Transplant-free survival of HLHS patients with ventricular dysfunction (≥30 days) on no HF medications at target dose was 24% at 1 year after dysfunction onset, vs 72% for those on 1 HF medication at target dose vs 82% for those on 2 or 3 HF medications at target dose. HF medications = heart failure medications (angiotensin-converting enzyme inhibitor, beta-blocker, or spironolactone); HLHS = hypoplastic left heart syndrome, target dose, at least 70% of recommended dose for age and body weight.

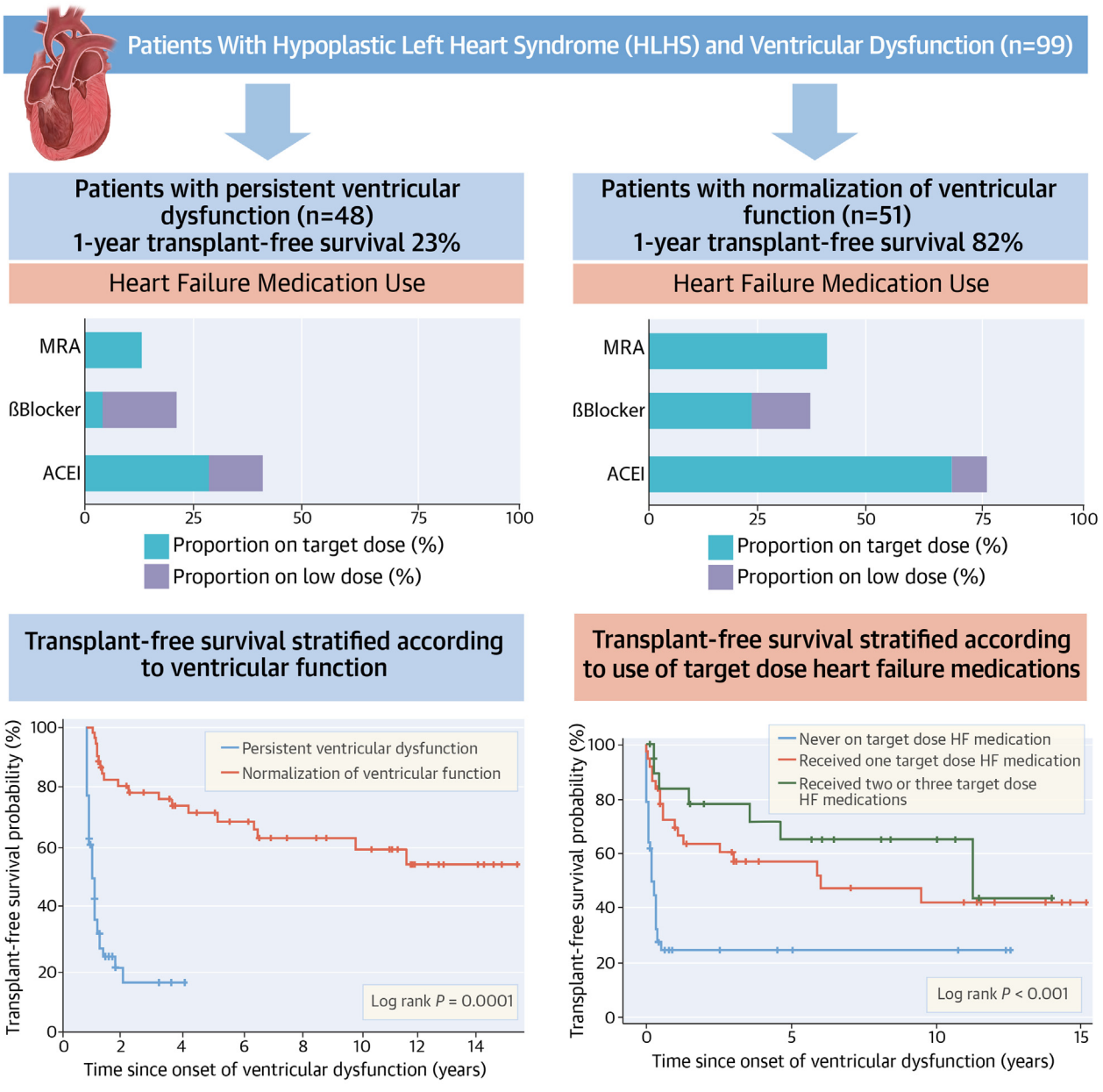
In multivariable regression, the hazard ratio indicated a small decreased risk of composite outcome of death or transplant in those with onset of dysfunction after BDG, normalization of ventricular function for a period of at least 30 days, and exposure to ACEI during follow-up (Table 5). The modifying effect was most significant with ACE inhibitor use, with 38% reduction in risk (95% CI: 21%-70%). Gestational age, weight, genetics, arch intervention, and tricuspid regurgitation were not statistically significant in our cohort.

DISCUSSION

OUTCOMES OF HLHS PATIENTS WITH SUSTAINED RIGHT VENTRICULAR DYSFUNCTION. Our 16-year cohort of HLHS patients with ventricular dysfunction lasting at least 30 days demonstrated a significant reduction in overall survival of 48% at 2 years after dysfunction onset. Patients with HLHS and ventricular dysfunction have previously been demonstrated to be at increased risk of death, transplant, and readmission with HF, particularly those who develop dysfunction during the interstage period.[2,7,18-20] While studies have described peak of dysfunction 3 to 6 months after the Norwood procedure,[2] and variability in functional improvement after ventricular unloading at the time of the BDG procedure,[4,21] the relationship with TFS has not been well studied. The granularity of data included in this study with echocardiograms at multiple time points facilitates a more in-depth understanding of outcomes related to sustained improvement in ventricular function over time. Our data demonstrates a novel finding of improved TFS outcomes and an increased likelihood of successful staged surgical palliation in those who experience a period of normal ventricular function of at least 30 days during follow-up. Interestingly, of those who experienced a period of sustained normalization, most normalized prior to the Glenn procedure. This is likely multifactorial and may relate to time and recovery from surgery, medication use, and optimization of nutrition. Similar to previous data, the population who developed dysfunction during the interstage period remained the most vulnerable cohort,[7,20] and there remains a subgroup of these (11/37) who died or were transplanted and did not proceed through stage 2 palliation despite normalization of function for at least 30 days. However, even in this high-risk group, normalization of function was associated with a significant improvement in TFS.

HEART FAILURE MEDICATION USE IN HLHS PATIENTS WITH RV DYSFUNCTION. Although the therapeutic benefit of a multidrug approach and dose optimization is now widely accepted in the broader HF

CENTRAL ILLUSTRATION **Outcomes of Children With HLHS and Persistent Ventricular Dysfunction (>30 Days)**

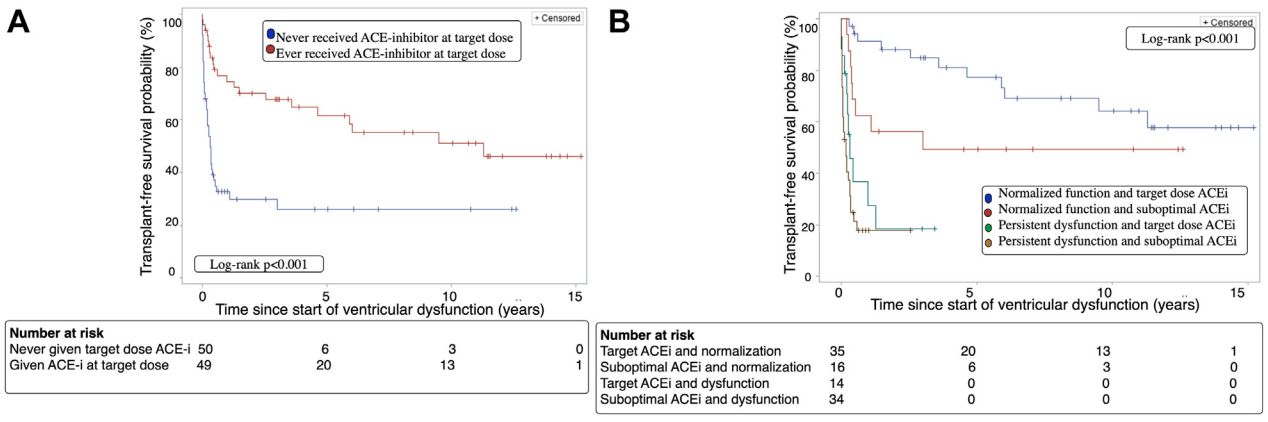


Lynch A, et al. JACC Adv. 2024;3(2):100811.

HLHS = hypoplastic left heart syndrome.

population,[22,23] recent adult HF studies have demonstrated low rates of achieving target dosing in HF medications[24-27] with an associated increased risk of mortality.[24] Similar variability in prescribing practices of HF medications has been demonstrated in pediatric populations.[28,29] Challenges in achieving target dose have impacted prior trials in single ventricle patients,[14] and many prior studies of HF medication efficacy in children did not describe doses achieved.[15] There was a significant association with improved TFS in those on optimal dosing of HF medications in this study, with incremental

FIGURE 4 Transplant-Free Survival With and Without ACE Inhibitor Use



(A) Transplant-free survival of HLHS patients with ventricular dysfunction (≥30 days) on target dose ACEI was 70% at 6 months after dysfunction onset vs 33% for those on suboptimal or no ACEI. (B) Transplant-free survival of HLHS patients with ventricular dysfunction (≥30 days) without period normalization of function on target dose ACEI was 37% at 6 months after dysfunction onset vs 21% for those on suboptimal dose or none, and for those with a period of normalization of function (≥30 days) was 94% for those on target dose ACEI vs 69% for those on suboptimal dose or none. ACEI = angiotensin-converting enzyme inhibitor; HLHS = hypoplastic left heart syndrome; target-dose, at least 70% of recommended dose for age and body weight.

improvements with successive medications. However, the proportion of patients in our cohort achieving target doses in our study was low, and thus the generalizability of this finding warrants further study. Though data are limited and the ability to reach the target dose may simply reflect a more stable hemodynamic profile, we would advocate that the achievement of target dose HF medications should be a consideration when deciding to proceed with staged surgical palliation in HLHS patients with persistent ventricular dysfunction. Given the low-risk profile of these medications, initiating multidrug HF treatment in patients with dysfunction with close monitoring is a reasonable approach.

We further analyzed ACEI use, as it was the most frequently prescribed HF medication in this retrospective cohort. Achieving at least 70% of the recommended target dose of an ACE inhibitor was associated with normalization of function and improved TFS in our cohort of HLHS patients with ventricular dysfunction. Interestingly, the association of target-dose ACEI and improved TFS persisted irrespective of normalization of function. The use of ACEIs in single ventricle patients has been studied with randomized controlled trail and larger retrospective cohorts; however, these studies incorporated an undifferentiated single ventricle cohort, of whom the majority had normal function.[14,15] Carvedilol use in a small subgroup of single ventricle patients with moderate to severe dysfunction also did not show any demonstrable benefit.[16] Additionally, our group has previously described the use of ACEIs and BBs in a smaller cohort of HLHS patients with dysfunction without improvement in short-term survival.[7] The lack of therapeutic effect in these populations compared with our cohort may reflect a different population under study, variable dosing practices, and shorter duration of follow-up. A lower mean ventricular mass-to-volume ratio in interstage patients treated with ACEI has been described.[14] Given the retrospective nature of this study, inferring a causal relationship would be inaccurate, but it is possible that ACE inhibition has an antihypertrophic effect on the volume-loaded single ventricle during the interstage period, which may improve the risk profile of those with pre-existing

TABLE 5 Multivariable Analysis of Clinical Factors Independently Associated With Death or Transplant in HLHS Patients With Ventricular Dysfunction ≥30 Days on Multivariable Analysis

Variable	HR (95% CI)	*P* Value
Surgical stage at onset of dysfunction (post BDG vs prior to BDG)	0.25 (0.11-0.56)	0.001
Normalization of RV function for ≥30 d vs not	0.14 (0.07-0.28)	<0.001
Ever exposed to ACE inhibitor during follow-up vs not	0.38 (0.21-0.70)	0.002

ACEI = angiotensin-converting enzyme inhibitor; BDG = bidirectional Glenn; HLHS = hypoplastic left heart syndrome; RV = right ventricle.

dysfunction.[30] Emerging medications such as sacubitril/valsartan and sodium-glucose co-transporter 2 (SGLT2) inhibitors, now standard of care in adult HF, may play a role in HF management of single ventricle patients in future. Sacubitril/valsartan has recently shown some potential for remodeling of the systemic RV,[31] but its efficacy in patients with single ventricle physiology has yet to be determined.[11]

STUDY LIMITATIONS. There are limitations inherent to the inclusion criteria for this study; only patients with ventricular dysfunction without documented echocardiographic normalization within 30 days were considered eligible for inclusion. The purpose of this was to avoid including patients with transient dysfunction in the postoperative phase or related to intercurrent illness. Those who had intermittent dysfunction for shorter periods than 30 days were not included and may have demonstrated more favorable outcomes. Additionally, those who died or were transplanted within 30 days of dysfunction onset were included to avoid exclusion of those with clinically significant dysfunction resulting in early death or transplant, as we felt this would undermine our ability to address our clinical research question regarding the outcomes of those who develop ventricular dysfunction. In this study, dysfunction was encoded as a binary variable, as this was how inclusion criteria were defined. We therefore did not incorporate duration of dysfunction as a separate variable. Of those included in the study who did not experience a period of sustained normal function ≥30 days, 15 (31%) had normal function documented at least once for a median duration of 0 (IQR: 0-7.3) days compared to 1,266.6 (IQR: 281.1-3,314.2) days in those considered to have sustained normalization. Qualitative measures of function used as inclusion criteria for this study carry an inherent risk of inter-observer variation. However, serial echocardiogram is the mainstay of systemic RV assessment at this institution, and despite increasing data on the utility of advanced functional indices, qualitative assessment remains valid and predominantly used clinically.[32,33] Additionally, using repeated measures methodologies to analyze multiple data points, as in this study, reduces the variance. Echocardiograms reported as 'borderline' or 'near normal' were readjudicated by the principal investigator for inclusion in the 'normalization' or 'persistent dysfunction' cohort. We are unable to quantify the number of echocardiograms readjudicated for this reason. However, mild dysfunction on echocardiogram in isolation did not preclude surgical palliation or guide use of HF medications at our institution, and decision-making was primarily based on clinical status.

Our institution did not routinely utilize biomarkers for HF management during the study period; thus, BNP or NT-proBNP data is not available for this cohort as another marker for ventricular function. This is a retrospective study with inherent survival bias. Analyzing medication utilization in such a cohort is prone to confounding by indication, and we have not gathered details on reasons for not achieving target dosing for HF medications including hemodynamic and laboratory data. As such, we infer that achieving target dose of HF medications is associated with improved ventricular function and survival but should not be considered causative based on this data and may simply reflect a more hemodynamically stable phenotype.

CONCLUSIONS

HLHS patients have limited life expectancy irrespective of surgical strategy or medication use, and in particularly high-risk patients, heart transplant may provide similar survival outcomes with improved quality of life. The novel findings of this study, that those with sustained dysfunction who experience a period of normalization during follow-up have improved survival outcomes and likelihood of successful staged surgical palliation, are of importance to inform surgical decision-making. Additionally, our cohort demonstrated improved outcomes with use of successive HF medications at target dose. While these results do not necessarily infer therapeutic benefit and may simply reflect hemodynamic stability facilitating better medication tolerance, the achievement of therapeutic dosing and the resultant implications for survival should help inform decisions to proceed with surgical palliation or list for transplant.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Ventricular dysfunction in HLHS patients is likely multifactorial in etiology, and while it has been associated with poor outcomes, identifying those patients who may experience improvement in ventricular function over time and successfully proceed through staged surgeries remains a challenge. Our data illustrates that those who achieve target doses of HF medications and have normalized function for >30 days have improved TFS, which should inform surgical decision-making.

TRANSLATIONAL OUTLOOK IMPLICATIONS: Further studies are needed to investigate the efficacy of HF medications in patients with systemic RV.

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