Combined ventricular dysfunction and atrioventricular valve regurgitation after the Norwood procedure are associated with attrition prior to superior cavopulmonary connection

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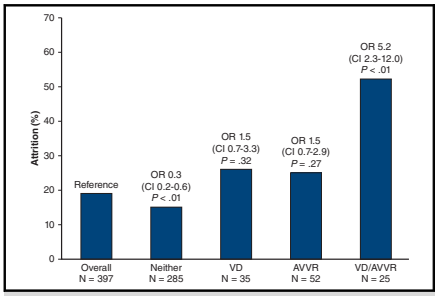
ABSTRACT

Background: Infants with hypoplastic left heart syndrome (HLHS) or a variant are at risk of ventricular dysfunction (VD) and atrioventricular valve regurgitation (AVVR) prior to superior cavopulmonary connection (SCPC). Although the impact of these complications in isolation has been described, their effect in combination on attrition is poorly defined.

Methods: A retrospective observational study of patients with HLHS or variants undergoing a Norwood procedure between 2008 and 2020 at a single center was performed. VD and AVVR were defined as moderate or severe when seen on 2 sequential echocardiograms outside the perioperative period. Attrition was defined as death, listing for heart transplant, or unsuitability for SCPC or transplant. Descriptive statistics and regression models were used for analysis.

Results: A total of 397 patients were included, of whom 75% had HLHS and 57% had received a Blalock-Thomas-Taussig shunt. Isolated VD occurred in 9% of patients, AVVR occurred in 13%, and both occurred in 6%. Attrition prior to SCPC occurred in 19% of the overall cohort, in 52% of patients with combined VD and AVVR (odds ratio [OR], 5.2; 95% confidence interval [CI], 2.3-12.0; $P < .01$), 26% of those with VD (OR, 1.5; 95% CI, 0.7-3.3; $P = .32$), 25% of those with AVVR (OR, 1.5; 95% CI, 0.7-2.9; $P = .27$), and 15% in those with neither (OR, 0.3; 95% CI, 0.2-0.6; $P < .01$). Other factors associated with attrition included prematurity, total bypass time at Norwood, and extracorporeal membrane oxygenation after Norwood, whereas later year of Norwood was protective ($P < .01$ for all).

Conclusions: The presence of combined VD and AVVR markedly increases the likelihood of attrition prior to SCPC, identifying a high-risk group. (JTCVS Open 2023;16:714-25)



Attrition associated with dysfunction and/or atrioventricular valve regurgitation.

CENTRAL MESSAGE

Combined ventricular dysfunction and atrioventricular valve regurgitation after the Norwood operation results in a 5-fold increased risk of attrition prior to superior cavopulmonary connection.

PERSPECTIVE

One in 5 infants with hypoplastic left heart syndrome or variant is at risk of attrition prior to superior cavopulmonary connection (SCPC). The impact of ventricular dysfunction (VD) and atrioventricular valve regurgitation (AVVR) on attrition is poorly defined. We found that combined VD and AVVR increases the likelihood of attrition prior to SCPC by 5-fold, identifying a high-risk group.

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Abbreviations and Acronyms

AV = atrioventricular
AVVR = atrioventricular valve regurgitation
BTT = Blalock-Taussig-Thomas
CI = confidence interval
HLHS = hypoplastic left heart syndrome
OR = odds ratio
PA = pulmonary artery
RV = right ventricle
SCPC = superior cavopulmonary connection
VD = ventricular dysfunction

Since the Norwood operation was initially described in the management of patients with hypoplastic left heart syndrome (HLHS), significant efforts have been made to both study and improve mortality prior to further staged palliation. Previous studies have demonstrated that interstage mortality between Norwood discharge and stage II or superior cavopulmonary connection (SCPC) ranges from 5% to 20%.[1-4] A single-center longitudinal study of interstage mortality rate in these patients between 1988 and 2017 reported that although the overall mortality rate was 10.8%, interstage mortality improved across eras, with a notable improvement in the most recent era of 2011-2017 (mortality rate 4.6%).[4] It has been shown that increased surgical experience with the operation, introduction of interstage monitoring programs, and increasing use of a right ventricle (RV) to pulmonary artery (PA) shunt have contributed to this improvement.[2,4-6] In addition, earlier age at time of SCPC, improvements in perioperative care, and the increasing prevalence of prenatal diagnosis have been hypothesized to affect this decline in mortality. However, although strides have been made in the perioperative, intraoperative, and postoperative care of infants with HLHS and variants, questions about patient-specific contributors to adverse outcomes remain.

Following single ventricle palliation, multiple factors—including volume overload, ventricular dilation, coronary insufficiency, ventricular dysfunction (VD), tricuspid annular dilation, atrioventricular valve regurgitation (AVVR), arrhythmia, recurrent coarctation, and shunt complications—may have important roles in patient outcomes. Multiple studies, including a secondary analysis of the Single Ventricle Reconstruction trial, have demonstrated worse outcomes in patients with ventricular dysfunction, as well as in patients with significant AVVR.[2,6-12] However, there is a paucity of information on isolated versus combined VD and AVVR and its potential impact on worse outcomes. The primary objective of this study was to determine the effect of the combination of VD and AVVR on interstage attrition in this fragile cohort of infants with HLHS or an HLHS variant at Children's Hospital of Philadelphia.

METHODS

Study Design

Using a previously identified cohort of patients who underwent the Norwood procedure at Children's Hospital of Philadelphia between January 2008 and December 2020, additional retrospective clinical data were collected. Inclusion criteria consisted of a diagnosis of HLHS or an HLHS variant based on a review of echocardiography, operative findings, and autopsy reports. An unbalanced atrioventricular (AV) canal was defined as an HLHS variant in our cohort in patients who underwent palliation with a Norwood procedure without subsequent two-ventricle conversion. Characteristics including anatomic subtype (mitral and aortic hypoplasia vs atresia or an HLHS variant), restrictive or intact atrial septum, ascending aorta size, and anomalous pulmonary veins were recorded as well. Patients who underwent a hybrid procedure involving stenting the ductus arteriosus and placing bilateral pulmonary arterial bands or subsequent biventricular repair were excluded. Patients who underwent SCPC prior to discharge from their Norwood hospitalization (ie, those who remained hospitalized in the interstage period) were included. Once eligibility was determined, data were collected from a retrospective review of each patient's electronic medical record and entered into a Research Electronic Data Capture (REDCap) database. All data were analyzed using SAS version 9.4 (SAS Institute). The study protocol was approved by the Children's Hospital of Philadelphia Institutional Review Board (IRB 14-010817; approved June 25, 2014).

Data Collection and Definitions

Data on patient characteristics were abstracted from the electronic medical record, including patient-specific preoperative, operative, and postoperative variables. Data for each patient were collected from birth through time of SCPC, death, transplantation, or decision for no further palliation. Echocardiographic parameters were recorded according to a review of echocardiography reports as they were initially read by pediatric cardiologists with expertise in echocardiography. Images were not primarily reviewed in cases for which a report was unavailable. Qualitative measures of AVVR were used owing to the absence of a standard measurement of severity in pediatrics. Qualitative measures of RV systolic function on echocardiography were also used, given the high degree of variability in routine quantitative measurements, including RV fractional area change.

Significant VD was defined as at least moderately diminished function on 2 sequential echocardiograms outside the immediate 1-week postoperative period. Significant AVVR was similarly defined as at least moderate regurgitation on 2 sequential echocardiograms outside the immediate 1-week postoperative period. No distinction was made between normal and mildly diminished function or between moderately and severely diminished function. Similarly, with the aim of highlighting the impact of AVVR more generally, no distinction was made among patients with none, trivial, and mild AVVR or between patients with moderate and severe AVVR. If at any time during the interstage period a patient met the criteria for significant VD and significant AVVR, they were uniquely defined as having both. These criteria were selected in an effort to capture clinically and physiologically relevant changes.

This study aimed to determine risk factors for the development of AVVR and VD and to evaluate the effect of these clinical findings on attrition following stage 1 palliation, with attrition defined as a composite endpoint of death, listing for transplant, or unsuitability for transplant or further staged palliation after the Norwood operation before undergoing SCPC. Even though most patients met the primary endpoint because of death before SCPC, we chose this broader composite endpoint for Norwood attrition instead of limiting the endpoint to mortality in an attempt to capture all patients who did not meet the criteria for further single

ventricle palliation beyond Norwood surgery. At our institution, there is no standard protocol that precludes offering SCPC, and the decision to proceed down the single ventricle pathway is made by the clinical team, which includes both primary cardiology team members and the pediatric cardiothoracic surgical team. However, since 2004, there has been an increase in the use of hybrid surgery for high-risk patients at our center.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation or median and interquartile range (IQR), and dichotomous variables are reported as count and percentage. Baseline, operative, and postoperative factors were examined in patients with significant dysfunction, those with AVVR, those with dysfunction and AVVR, as well as for attrition. Covariates were limited to patient factors including birth weight, gestational age, age at Norwood, and ascending aorta size; a complete list is provided in Table 1. Three sets of logistic regression models were specified and tested for each outcome individually (ie, VD, AVVR, and VD/AVVR), as well as for the composite of attrition. Single covariate models were created for each outcome, and a best-fitting multiple covariate model was specified for each and tested for statistical significance using the Wald chi-square test. Because of low event rates, a multivariable model was not created for VD or for AVVR. A standard P value <.05 was considered statistically significant. For construction of the multivariable models for the combination of VD/AVVR and attrition, variables were considered for entry into the model at $P < .20$. Covariates were tested for collinearity and were excluded if the Spearman's correlation coefficient, r_s, was >0.40. In the instance of small event rates, the Fisher exact test was used to estimate relationships between the pertinent covariate and each outcome.

RESULTS

Study Cohort

Between January 2008 and December 2020, 413 children with HLHS or an HLHS variant underwent a Norwood procedure. Of these, 10 patients who underwent an initial hybrid procedure and 6 patients who underwent subsequent two-ventricle repair were excluded; thus, 397 patients met the study's inclusion criteria. HLHS was present in 75% of subjects, with a slight predominance of patients who received a Blalock-Thomas-Taussig (BTT) shunt (57%) compared to an RV-PA shunt modification (43%) at the time of the Norwood operation (Table 1).

TABLE 1. Baseline patient characteristics (N = 397)

Characteristic	Value
Age at Norwood, d, median (IQR)	5.2 (4.9)
Birth weight, kg, median (IQR)	3.2 (0.6)
Preterm birth (<37 wk), n (%)	44 (11.1)
Sex, n (%)	
Male	247 (62.2)
Female	150 (37.8)
Race, n (%)	
White	239 (60.4)
Black	51 (12.9)
Other	106 (26.8)
HLHS subtype or variant, n (%)	
Aortic atresia/mitral atresia	141 (35.5)
Aortic atresia/mitral stenosis	83 (20.9)
Aortic stenosis/mitral atresia	12 (3.0)
Aortic stenosis/mitral stenosis	62 (15.6)
Variant	99 (24.9)
Ascending aorta size, mm, median (IQR)	3.6 (2.0)
Intact or highly restrictive atrial septum, n (%)	53 (13.4)
Anomalous pulmonary veins, n (%)	15 (3.8)
Genetic abnormality, n (%)	84 (21.2)
Perioperative characteristics	
Age at Norwood, d, median (IQR)	5.2 (4.9)
Weight at Norwood, kg, median (IQR)	3.2 (0.6)
Year of Norwood, median (IQR)	2013 (2010-2017)
Norwood operation total support time, min, median (IQR)	97 (27.1)
Shunt type, n (%)*	
BTT	228 (57.4)
RV-PA	169 (42.6)
Norwood length of stay, d	41.4 (45.1)
ECMO as a Norwood, n (%)	59 (14.9)
Transcatheter CoA intervention after Norwood, n (%)	86 (21.7)

IQR, Interquartile range; *HLHS*, hypoplastic left heart syndrome; *BTT*, Blalock-Thomas-Tausig; *RV*, right ventricle; *PA*, pulmonary artery; *ECMO*, extracorporeal membrane oxygenation; *CoA*, coarctation of the aorta. *Two patients had both a BTT and an RV-PA and thus were excluded from this analysis.

VD and AVVR

Of the 397 patients in the cohort, 35 (9%) met the criteria for significant VD prior to SCPC, with 46% identified during the Norwood hospitalization and 54% identified after discharge during the interstage period. Compared to the patients without VD, those with VD were more often nonwhite (54% vs 39%; $P = .05$), born prematurely (20% vs 10%; $P = .09$), and had a genetic abnormality (34% vs 20%; $P = .05$). VD occurred in 74% of patients with a BTT shunt compared to 26% of those with an RV-PA conduit ($P = .05$) (Tables E1 and E2). On univariate regression analysis, only younger gestational age (odds ratio [OR], 0.8, 95% confidence interval [CI], 0.65-1.0; $P = .04$) was significantly predictive of dysfunction, whereas birth weight, age at Norwood, weight at Norwood, ascending aorta size, and year of Norwood were not significantly predictive.

Patients with significant AVVR accounted for 13% (n = 52) of the total cohort. In the majority of these patients (62%; n = 32), AVVR was identified prior to Norwood discharge. As shown in Tables E3 and E4, there were no identified predictors of isolated AVVR by single covariate

logistic regression. By Fisher exact testing (necessary owing to small cell sizes), nonwhite race was associated with the presence of AVVR.

The combined VD/AVVR group accounted for 6% (n = 25) of the total cohort. These patients were uniquely identified as having met both criteria for significant VD as well as for AVVR. Of these patients with combined VD/AVVR, 3 patients had both VD and AVVR prior to the Norwood procedure, and approximately one-half of the patients (n = 13) met the criteria for both VD and AVVR prior to Norwood discharge. Smaller ascending aorta size ($P = .02$), younger gestational age ($P < .01$), intact atrial septum ($P = .04$), and nonwhite race ($P = .04$) were predictive of combined VD and AVVR status. Later year of Norwood ($P < .01$) and RV-PA shunt type ($P = .02$) were protective against combined VD/AVVR (Tables E5 and E6). However, only ascending aorta size ($P = .03$) and year of Norwood ($P < .01$) remained statistically significant in the multivariable model.

Outcomes

Attrition prior to SCPC occurred in 19% of the overall cohort (n = 77). Of the patients who met the criteria for attrition after Norwood palliation, 36% had HLHS with aortic atresia and mitral atresia, 27% had an HLHS variant, and 23% had HLHS with aortic atresia and mitral stenosis. There were no significant differences in attrition across HLHS subtypes ($P = .17$) (Table 2). Anomalous pulmonary venous return was associated with Norwood attrition ($P = .01$), as was preterm birth ($P < .01$), but restrictive atrial septum was not ($P = .58$). Attrition after Norwood palliation occurred in 23% of those with a BTT shunt, compared to 15% of those with an RV-PA conduit ($P = .05$). ECMO after Norwood ($P < .01$), earlier year of Norwood ($P < .01$), and longer total support time at Norwood surgery ($P = .02$) were associated with attrition. Transcatheter balloon dilation angioplasty of recoarctation during the Norwood or interstage period was associated with decreased attrition ($P < .01$).

More than one-half (55%) of attrition occurred prior to Norwood hospitalization discharge. Of the patients who met criteria for attrition, 81% (n = 62) died; 18% (n = 14) were listed for transplant, of whom 11 patients died on the waitlist, and 1 patient was determined to not be a candidate for further staged palliation or transplant owing to severe pulmonary vein stenosis. Among those 14 patients listed for transplant, 2 had neither VD nor AVVR, 3 had significant VD, 1 had significant AVVR, and 8 had both significant VD and AVVR. There were 15 deaths within the first 7 days following the Norwood procedure in which echocardiograms by study criteria were excluded and subjects were classified as having neither VD nor AVVR.

In assessing the outcomes among these patients, attrition occurred in 52% of patients with both VD and AVVR, in 26% of those with isolated VD, in 25% of those with isolated AVVR, and in 14% of those without VD or AVVR (Figure 1). Although isolated VD or AVVR was not associated with attrition ($P = .27$ for both), combined VD and AVVR was associated with a 5-fold increased risk of attrition compared to the overall cohort (OR, 5.2; 95% CI, 2.3-12.0; $P < .01$) (Figure 2). Among the 25 patients with combined VD and AVVR, 5 died without being listed for transplant and 8 were listed for transplant, of whom 6 died while awaiting transplant. Twelve patients with combined VD/AVVR went on to undergo SCPC palliation, 1 of whom had an AV valvuloplasty at the time of SCPC.

DISCUSSION

Even though survival has improved for patients with HLHS and HLHS variants undergoing staged palliation, mortality among these children with congenital heart disease remains high.[4,13] The outcomes of this single-center study demonstrate an overall attrition rate prior to SCPC of 19%. In other words, nearly one-fifth of our cohort met the composite endpoint of death, transplant, or unsuitability for SCPC or transplant after the Norwood procedure. We focused on the impact of the presence of VD and AVVR on this outcome. Although there was a trend toward increased attrition when VD or AVVR is present in isolation, there was a 5-fold increase in the odds of attrition in the presence of both.

Previous studies have demonstrated that patients have worse long and short-term outcomes in the presence of significant VD.[2,6,9-11] We identified associations of the presence of a genetic abnormality, nonwhite race, and an RV-PA shunt (vs a BTT shunt) with ventricular dysfunction. Shunt type is of particular interest given the known phenomenon of diastolic runoff in the presence of a BTT shunt, which can lead to decreased coronary perfusion and myocardial ischemia.[14,15] BTT shunt type is known to be associated with interstage mortality, and in a secondary analysis of the Single Ventricle Reconstruction trial, the difference in survival between shunt types within a cohort with RV dysfunction was also significant.[5,6] Kulik and colleagues reported that patients with at least moderately diminished function following Norwood, but in whom the dysfunction resolved, had outcomes that were at least as good as the entire cohort.[9] Furthermore, diminished function on post-Norwood echocardiogram was associated with increased risk of early heart failure, with the highest risk seen in the first year of life.[7] Our study did not find a statistically significant increase in attrition in those with isolated significant dysfunction; however, given the short follow up period, we suspect that the long-term outcomes may be worse in this population compared to those without dysfunction.

TABLE 2. Patient characteristics associated with Norwood attrition

Characteristic	Attrition	No attrition	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Ascending aorta, mm, median (IQR)	2.5 (1.9-4.6)	3.2 (2.0-5.0)	0.87 (0.76-1.00)	.04		
Age at Norwood, d, median (IQR)	4.4 (3.3-6.4)	4.3 (3.0-6.3)	1.02 (0.97-1.06)	.42		
APVR, n (%)						
Yes	7 (47)	8 (53)	?	.01		
No	70 (18)	311 (82)	Reference	-		
Birth weight, kg, median (IQR)	3.0 (2.6-3.5)	3.2 (2.9-3.6)	0.63 (0.40-0.99)	.05		
Coarctation intervention, n (%)						
Yes	7 (8)	79 (92)	?	<.01		
No	70 (23)	241 (77)	Reference	-		
ECMO, n (%)						
Yes	36 (61)	23 (39)	11.30 (6.10-21.00)	<.01	10.79 (5.54-21.00)	<.01
No	41 (12)	297 (88)	Reference	-		
Sex, n (%)						
Male	46 (19)	201 (81)	Reference	-		
Female	31 (21)	119 (79)	1.14 (0.68-1.89)	.62		
Genetic abnormality, n (%)						
Yes	19 (23)	65 (77)	?	.44		
No	58 (19)	255 (81)	Reference	-		
Gestational age, wk, median (IQR)	38 (37-39)	39 (38-39)	0.71 (0.60-0.84)	<.01	0.78 (0.65-0.93)	.01
HLHS subtype, n (%)				.17		
Aortic atresia/mitral atresia	28 (20)	113 (80)	Reference	-		
Aortic atresia/mitral stenosis	18 (22)	65 (78)				
Aortic stenosis/mitral atresia	4 (33)	8 (67)				
Aortic stenosis/mitral stenosis	6 (10)	56 (90)				
HLHS variant	21 (21)	78 (79)				
Intact atrial septum, n (%)						
Yes	12 (23)	41 (77)	?	.58		
No	65 (19)	279 (81)	Reference	-		
Race, n (%)				.01		
White	31 (13)	208 (87)	Reference	-		
Black	11 (22)	40 (78)				
Other	35 (33)	71 (67)				
Shunt type, n (%)						
BTT	52 (23)	175 (77)	Reference	-		
RV-PA	25 (15)	143 (85)	0.59 (0.35-1.00)	.05		
Weight at operation, kg median (IQR)	3.0 (2.7-3.5)	3.2 (2.8-3.6)	0.66 (0.43-1.03)	.07		
Total support time at Norwood, min, median (IQR)	100 (80-119)	87 (79-104)	1.02 (1.01-1.02)	<.01	1.01 (1.00-1.02)	.02
Year of Norwood, median (IQR)	2012 (2009-2015)	2014 (2010-2017)	0.89 (0.83-0.96)	<.01	0.88 (0.81-0.95)	<.01

OR, Odds ratio; *CI*, confidence interval; *IQR*, interquartile range; *APVR*, anomalous pulmonary venous return; *ECMO*, extracorporeal membrane oxygenation; *HLHS*, hypoplastic left heart syndrome; *BTT*, Blalock-Taussig-Thomas; *RV*, right ventricle; *PA*, pulmonary artery.

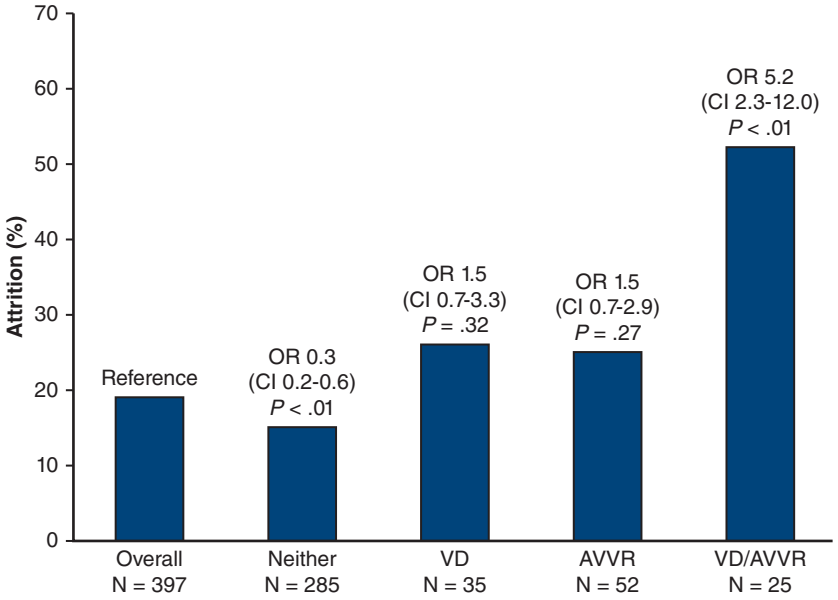

FIGURE 1. Attrition associated with the presence of significant ventricular dysfunction (*VD*) and/or atrioventricular valve regurgitation (*AVVR*). The overall cohort was the reference group for comparison. *OR*, Odds ratio; *CI*, confidence interval.

The tricuspid valve or common AV valve is vulnerable after the Norwood operation and is exposed to greater volumes and variable loading conditions. The mechanisms of AVVR seen in HLHS and its variants are known to be multifactorial, including abnormalities of the tricuspid valve, such as leaflet clefts, dysplasia, prolapse, and annular dilatation.[16] Annular dilation results from volume loading of the systemic right ventricle, which can lead to ventricular

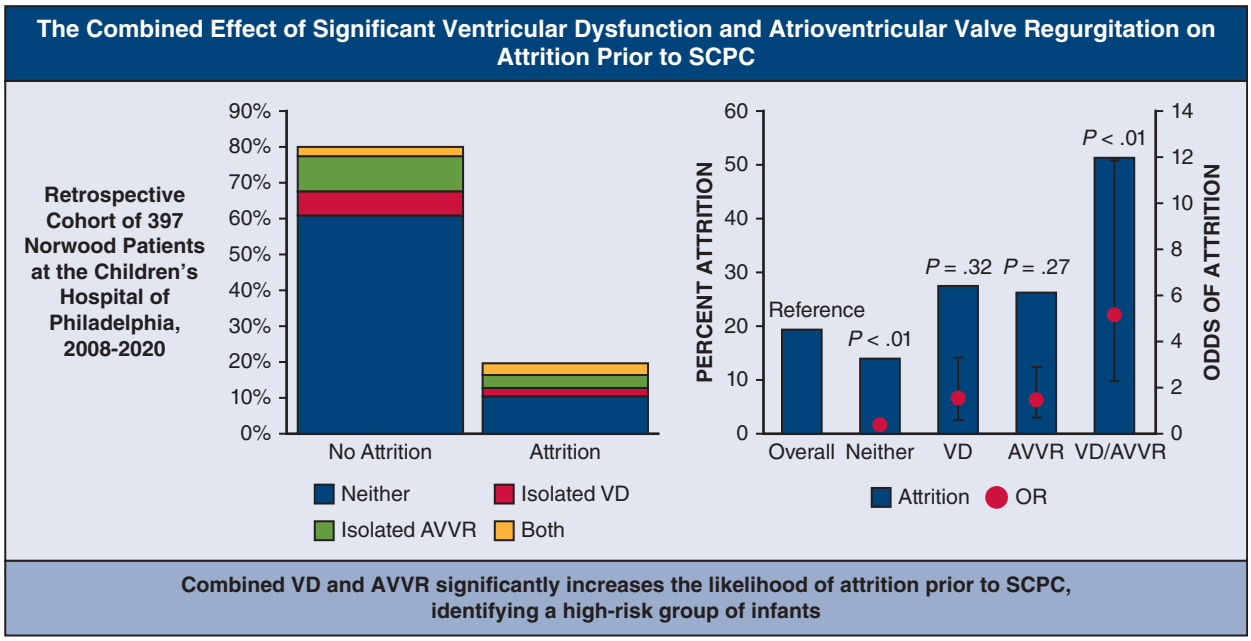

FIGURE 2. Graphical abstract. *SCPC*, Superior cavopulmonary connection; *VD*, ventricular dysfunction; *AVVR*, atrioventricular valve regurgitation; *OR*, odds ratio.

dilatation along with changes in geometry. Ultimately, the ventricular changes can lead to progressive valvular regurgitation and VD and the clinical picture of heart failure. AVVR is an frequently studied entity in these patients given the potential for surgical intervention. Surgical intervention for relief of AVVR remains a challenge, and the need for a valve operation between Norwood and SCPC has been identified as an independent risk factor for mortality.[17,18] Furthermore, the durability of AV valve repair in single-ventricle patients has been shown to be poor, with recurrent significant AVVR seen in up to 81% of these patients and need for a repeat valvuloplasty or valve replacement in 21%.[16] Patients with early success of valve interventions can experience late failure owing to lack of recovery after a decrement in ventricular function postoperatively.[19,20]

Numerous studies have sought to better identify and define which single-ventricle patients are at risk for poor outcomes and may benefit from earlier transplant evaluation. Our study adds to the growing body of literature by identifying a uniquely high-risk group of patients, those with both VD and AVVR identified early in their lifetimes. Although interactions between dysfunction and AVVR have been studied, to our knowledge no previous study has directly compared these groups with respect to attrition. In our study, greater ascending aorta size and later year of Norwood were protective against attrition. It could be hypothesized that larger ascending aorta size is more likely to be associated with a patent aortic valve and hence less tenuous coronary perfusion. Furthermore, the general trend toward improved attrition over time is likely due to the robust attention given to the interstage cohort through the Interstage Single Ventricle Monitoring Program,[21] as home monitoring programs have been widely shown to improve interstage outcomes, although this would not have impacted the development of VD or AVVR. Additionally, the use of hybrid surgery for high-risk patients has been increasing since 2004, and thus the population undergoing the Norwood operation changed during the study period. With these data, we can better describe in detail the longitudinally accrued morbidity in the lifetime of patients with HLHS or its variants undergoing Norwood palliation.

Limitations

Limitations of this study include its single-center and retrospective nature. For patients born during these earlier years, data collection relied on digitalization of paper records. However, for the data included in this study, there was a minimal amount of missing data, with complete records for 99.8% of the data (9111 observed of 9131 total data points). Data were complete on all study endpoints as well as for 14 of 18 total predictors, with only 1 covariate—ascending aorta size—having more than 2 missing data points (4%; 16 of 397 missing). Surgical and care practices also changed markedly changed over the study period. The earlier years overlapped with enrollment of patients into the Single Ventricle Reconstruction trial, and the use of the RV-PA shunt has broadened greatly since that time. More recently, patients judged too high risk are more frequently undergoing hybrid procedures rather than our typical approach with a Norwood procedure. One of the major limitations of this study was that echocardiographic images were not primarily reviewed; rather, measurements of VD and AVVR were recorded from qualitative assessments in the reports. Owing to the limited number of patients in each category, we were unable to further stratify patient cohorts beyond moderate/severe dysfunction and moderate/severe AVVR for our outcome analysis. Similarly low was the number of patients who underwent valvuloplasty either before or at the time of SCPC, limiting our ability to evaluate the impact of valvuloplasty on outcomes. Given the relatively short period over which the outcomes could be met, the lead time between onset and identification of AVVR or VD also might have affected outcomes. Also relevant is that the short patient specific study period (ie, Norwood procedure to SCPC) and single-center inclusion resulted in a low number of patients meeting each outcome and subsequently limited our analyses. Because of this already limited time frame and so as not to capture early attrition, only the immediate postoperative week was eliminated from our analysis. Patients who died within 1 week of the Norwood were classified as having neither VD nor AVVR, because echocardiograms during this period were excluded from the analysis by design. If any of these subjects had moderate or greater VD or AVVR and were to be reclassified, it would strengthen the findings of this study.

CONCLUSIONS

Following the Norwood procedure, our cohort had a 19% incidence of attrition, defined as death, transplant, or unsuitability for further stage palliation, prior to the SCPC. We found that although patients with isolated VD or AVVR tended to have greater rates of attrition, the presence of both VD and AVVR was associated with marked increases in mortality, transplant, and unsuitability for SCPC. Additional data are needed to evaluate how patients who have recovery of function and/or improvement in AVVR differ from those with persistence of either or both, and whether there is a cumulative effect with each insult. Further studies are needed to better assess which patients are likely to progress to Fontan completion versus those likely to benefit from earlier consideration for transplant.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or

reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: Norwood, attrition, dysfunction, regurgitation

TABLE E1. Logistic regression model results for VD (N = 397)

Potential risk factors	With VD		Without VD		Single covariate logistic regression models			
	n	Median (IQR)	n	Median (IQR)	n	β (SE)*	OR (95% CI)	*P* value
Ascending aorta, mm	34	4.0 (2.0-5.1)	347	3.0 (2.0-5.0)	381	0.04 (0.09)	1.04 (0.88-1.24)	.62
Age at Norwood, d	35	4.4 (3.0-6.4)	362	4.3 (3.0-6.3)	397	0.00 (0.03)	1.00 (0.94-1.07)	.88
Birth weight, kg	35	3.1 (2.7-3.4)	362	3.2 (2.8-3.6)	397	−0.18 (0.32)	0.84 (0.45-1.56)	.57
Gestational age, wk	35	38.0 (37.0-39.0)	362	39.0 (38.0-39.0)	397	−0.22 (0.11)	0.80 (0.65-1.00)	.04
Weight at surgery, wk	35	3.2 (2.7-3.4)	362	3.2 (2.8-3.6)	397	−0.21 (0.31)	0.81 (0.44-1.49)	.50
Total support time at Norwood, min	35	86.0 (82.0-102.0)	362	88.0 (79.0-109.0)	397	−0.01 (0.01)	0.99 (0.97-1.01)	.20
Year of Norwood	35	2012 (2010-2015)	362	2013 (2010-2017)	397	−0.06 (0.05)	0.94 (0.86-1.03)	.20

VD, Ventricular dysfunction; *IQR*, interquartile range; *SE*, standard error; *OR*, odds ratio; CI, confidence interval. *Values reported here as 0.00 were rounded to 2 decimal places for consistency of reporting and to reduce the complexity of the table.

TABLE E2. Summary statistics for VD (N = 397)

Variable*	With VD, *f* (%)	Without VD, *f* (%)	*P* value
Anomalous pulmonary veins			.63
No	33 (94.3)	348 (96.4)	
Yes	2 (5.7)	13 (3.6)	
Sex			.86
Female	14 (40.0)	136 (37.6)	
Male (Ref)	21 (60.0)	226 (62.4)	
Genetic abnormality			.05
Abnormal	12 (34.3)	72 (19.9)	
Normal	23 (65.7)	290 (80.1)	
HLHS subtype or variant			.35
Aortic atresia/mitral atresia (ref)	17 (48.6)	124 (34.2)	
Aortic atresia/mitral stenosis	5 (14.3)	78 (21.6)	
Aortic stenosis/mitral atresia		12 (3.3)	
Aortic stenosis/mitral stenosis	3 (8.6)	59 (16.3)	
Variant	10 (28.6)	89 (24.6)	
Intact atrial septum			.80
No (Ref)	30 (85.7)	314 (86.7)	
Yes/restrictive	5 (14.3)	48 (13.3)	
Preterm birth			.09
No	28 (80.0)	325 (89.8)	
Yes	7 (20.0)	37 (10.2)	
Race			.05
White (Ref)	16 (45.7)	223 (61.8)	
Black	9 (25.7)	42 (11.6)	
Other	10 (28.6)	96 (27.6)	
Shunt type			.05
BTT (Ref)	26 (74.3)	201 (55.8)	
RV-PA	9 (25.7)	159 (44.2)	

VD, Ventricular dysfunction; *Ref*, reference group; *HLHS*, hypoplastic left heart syndrome; *BTT*, Blalock-Taussig-Thomas; *RV*, right ventricle; *PA*, pulmonary artery. *Categorical variables not amenable for modeling owing to low cell counts and percentages.

TABLE E3. Logistic regression model results for AVVR (N = 397)

Potential risk factor	With AVVR		Without AVVR		Single covariate logistic regression model			*P* value
	N	Median (IQR)	n	Median (IQR)	n	β (SE)*	OR (95% CI)	
Ascending aorta, mm	50	3.4 (2.0-5.7)	331	3.0 (2.0-5.0)	381	0.07 (0.07)	1.07 (0.93-1.24)	.35
Age at Norwood, d	52	4.2 (2.7-6.3)	345	4.3 (3.0- 6.3)	397	0.02 (0.02)	1.02 (0.98-1.07)	.32
Birth weight, kg	52	3.4 (3.0-3.6)	345	3.2 (2.8-3.5)	397	0.32 (0.27)	1.38 (0.82-2.34)	.23
Gestational age, wk	52	39.0 (37.5-39.0)	345	39.0 (38.0-39.0)	397	0.04 (0.11)	1.04 (0.84-1.28)	.72
Shunt type (Ref. BTT)					395	−0.05 (0.15)	0.90 (0.50-1.64)	.74
Weight at surgery, kg	52	3.3 (2.9-3.6)	345	3.2 (2.8-3.5)	397	0.28 (0.26)	1.33 (0.80-2.21)	.28
Total support time at Norwood, min	52	99.0 (83.0-116.0)	345	87.0 (78.0-106.0)	397	0.01 (0.00)	1.01 (1.00-1.02)	.16
Year of Norwood	52	2012 (2010-2017)	345	2013 (2010-2017)	397	−0.00 (0.04)	1.00 (0.92-1.08)	.91

AVVR, Atrioventricular valve regurgitation; *IQR*, interquartile range; *SE*, standard error; *OR*, odds ratio; *CI*, confidence interval; *Ref*, reference; *BTT*, Blalock-Taussig-Thomas. *Values reported here as 0.00 were rounded to 2 decimal places for consistency of reporting and to reduce the complexity of the table.

TABLE E4. Summary statistics for AVVR (n = 397)

Categorical variable*	With AVVR, *f* (%)	Without AVVR, *f* (%)	*P* value
Anomalous pulmonary veins			1.00
No	50 (96.2)	331 (96.2)	
Yes	2 (3.8)	13 (3.8)	
Sex			.88
Female	19 (36.5)	131 (38.0)	
Male (Ref)	33 (63.5)	214 (62.0)	
Genetic anomaly			.47
Abnormal	13 (25.0)	71 (20.6)	
Normal	39 (75.0)	274 (79.4)	
HLHS subtype or variant			.54
Aortic atresia/mitral atresia (Ref)	15 (28.8)	126 (36.5)	
Aortic atresia/mitral stenosis	10 (19.2)	73 (21.2)	
Aortic stenosis/mitral atresia	1 (1.9)	11 (3.2)	
Aortic stenosis/mitral stenosis	8 (15.4)	54 (15.7)	
Variant	18 (34.6)	81 (23.5)	
Intact atrial septum			.08
No (Ref)	41 (78.8)	303 (87.8)	
Yes/restrictive	11 (21.2)	42 (12.2)	
Preterm birth			1.00
No	47 (90.4)	306 (88.7)	
Yes	5 (9.6)	39 (11.3)	
Race			.02
White (Ref)	35 (67.3)	204 (59.3)	
Black	1 (1.9)	50 (14.5)	
Other	16 (30.8)	90 (26.2)	
Shunt type			.74
BTT (Ref)	31 (59.6)	196 (57.1)	
RV-PA	21 (40.4)	147 (42.9)	

AVVR, Atrioventricular valve regurgitation; *Ref*, reference group; *HLHS*, hypoplastic left heart syndrome; *BTT*, Blalock-Taussig-Thomas; *RV*, right ventricle; *PA*, pulmonary artery. *Categorical variables not amenable for modeling owing to low cell counts and percentages.

TABLE E5. Logistic regression model results for combined VD and AVVR (N = 397)

Potential risk factor	With VD and AVVR		Without VD and AVVR		Single covariate logistic regression models				Multiple covariate logistic regression model ($R^2 = 0.05$)			
	n	Median (IQR)	n	Median (IQR)	n	β (SE)*	OR (95% CI)	*P*	*n*	β (SE)	OR (95% CI)	*P*
Ascending aorta, mm	24	2.0 (1.6-2.9)	357	3.2 (2.0-5.0)	381	−0.33 (0.14)	0.72 (0.55-0.95)	.02	381	−0.30 (0.14)	0.74 (0.56-0.97)	.03
Age at Norwood, d	25	4.4 (3.0-5.5)	372	4.3 (3.0-6.3)	397	−0.02 (0.05)	0.98 (0.88-1.09)	.71				
Birth weight, kg	25	3.4 (2.6-3.7)	372	3.2 (2.8-3.5)	397	−0.14 (0.37)	0.87 (0.42-1.80)	.70				
Gestational age, wk	25	38.0 (37.0-39.0)	372	39.0 (38.0-39.0)	397	−0.33 (0.12)	0.72 (0.57-0.91)	<.01				
Weight at surgery, kg	25	3.3 (2.8-3.8)	372	3.2 (2.8-3.5)	397	−0.03 (0.36)	0.97 (0.48-1.97)	.93				
Total support time at Norwood, min	25	90.0 (79.0-114.0)	372	87.5 (79.0-107.0)	397	−0.00 (0.01)	1.00 (0.99-1.02)	.98				
Year of Norwood	25	2010 (2008-2013)	372	2014 (2010-2017)	397	−0.22 (0.07)	0.80 (0.70-0.92)	<.01	381	−0.21 (0.07)	0.81 (0.71-0.93)	<.01
Intercept									381	426.2 (139.5)		

VD, Ventricular dysfunction; *AVR*, atrioventricular valve regurgitation; *IQR*, interquartile range; *SE*, standard error; *OR*, odds ratio; *CI*, confidence interval. *Values reported here as 0.00 were rounded to 2 decimal places for consistency of reporting and to reduce the complexity of the table.

TABLE E6. Summary statistics for combined VD and AVVR (N = 397)

Categorical variable*	With VD and AVVR, *f* (%)	Without VD and AVVR, *f* (%)	*P* value
Anomalous pulmonary veins			1.00
No	24 (96.0)	357 (96.2)	
Yes	1 (4.0)	14 (3.8)	
Sex			.29
Female	12 (48.0)	138 (37.1)	
Male (Ref)	13 (52.0)	234 (62.9)	
Genetic anomaly			.45
Abnormal	7 (28.0)	77 (20.7)	
Normal	18 (72.0)	295 (79.3)	
HLHS subtype or variant			.72
Aortic atresia/mitral atresia (ref)	11 (44.0)	130 (35.0)	
Aortic atresia/mitral stenosis	5 (20.0)	78 (21.0)	
Aortic stenosis/mitral atresia		12 (3.2)	
Aortic stenosis/mitral stenosis	5 (20.0)	57 (15.3)	
Variant	4 (16.0)	95 (25.5)	
Intact atrial septum			.04
No (Ref)	25 (100.0)	319 (85.8)	
Yes/restrictive	0 (0.00)	53 (14.2)	
Preterm birth			.18
No	20 (80.0)	333 (89.5)	
Yes	5 (20.0)	39 (10.5)	
Race			.04
White (Ref)	10 (40.0)	229 (61.7)	
Black	3 (12.0)	48 (12.9)	
Other	12 (48.0)	94 (25.3)	
Shunt type			.02
BTT (Ref)	20 (80.0)	207 (56.0)	
RV-PA	5 (20.0)	163 (44.0)	

VD, Ventricular dysfunction; *AVVR*, atrioventricular valve regurgitation; *Ref*, reference; *HLHS*, hypoplastic left heart syndrome; *BTT*, Blalock-Taussig-Thomas; *RV*, right ventricle; *PA*, pulmonary artery. *Categorical variables not amenable for modeling owing to low cell counts and percentages.