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ORIGINAL RESEARCH

Decreasing Interstage Mortality After the Norwood Procedure: A 30-Year Experience

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BACKGROUND: The superior cavo-pulmonary connection was introduced at our institution in 1988 for infants undergoing surgery for hypoplastic left heart syndrome. Patients with hypoplastic left heart syndrome remain at high risk for mortality in the time period between the Norwood procedure and the superior cavo-pulmonary connection. The primary objectives of this study were to compare interstage mortality across 4 eras and analyze factors that may impact interstage mortality.

METHODS AND RESULTS: Patients with hypoplastic left heart syndrome who underwent the Norwood procedure, were discharged from the hospital, and were eligible for superior cavo-pulmonary connection between January 1, 1988, and December 31, 2017, were included. The study period was divided into 4 eras based on changes in operative or medical management. Mortality rates were estimated with 95% CIs. Adjusted and unadjusted logistic regression models were used to identify risk factors for mortality. There were 1111 patients who met the inclusion criteria. Overall, interstage mortality was 120/1111 (10.8%). Interstage mortality was significantly lower in era 4 relative to era 1 (4.6% versus 13.4%; P=0.02) during the time that age at the superior cavo-pulmonary connection was the lowest (135 days; P<0.01) and the interstage monitoring program was introduced. In addition, use of the right ventricle to pulmonary artery shunt was associated with decreased interstage mortality (P=0.02) and was more routinely practiced in era 4.

CONCLUSIONS: During this 30-year experience, the risk of interstage mortality decreased significantly in the most recent era. Factors that coincide with this finding include younger age at superior cavo-pulmonary connection, introduction of an interstage monitoring program, and increased use of the right ventricle to pulmonary artery shunt.

Key Words: hypoplastic left heart syndrome ■ interstage monitoring program ■ interstage period

Hypoplastic left heart syndrome (HLHS) and similar structural variants were almost uniformly fatal until the advent of the Norwood procedure (NP).[1] The NP was introduced as the initial surgical palliation in the newborn period and was followed by the Fontan procedure several years later, as a 2-staged palliation. After high mortality rates during the Fontan operation, a 3-staged surgical approach for HLHS was established in 1988 in which the superior cavo-pulmonary connection (SCPC) was completed between the NP and the Fontan.[2]

With this approach, long-term survival for patients with HLHS has significantly improved.[3,4] However, there remains a high risk of mortality in patients with HLHS during the interstage period, between the NP discharge and admission for SCPC, with mortality rates of 5% to 20%.[4–6] One strategy introduced to help reduce interstage mortality was an interstage monitoring program (ISMP),[7] where infants are closely monitored by a dedicated team of healthcare providers and the family. Early results from single center retrospective studies demonstrated dramatic decreases in interstage mortality following initiation of an ISMP.[5,8] Yet controversy remains regarding the efficacy of these programs after a large multicenter study demonstrated no decrease in mortality with ISMPs.[9] Other strategies

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CLINICAL PERSPECTIVE

What Is New?

- The superior cavo-pulmonary connection was introduced at our institution as an interim stage for hypoplastic left heart syndrome in 1988.
- During this 30-year experience, the risk of interstage mortality decreased significantly in the most recent era, from 2011 to 2017.
- This finding corresponds to the performance of the superior cavo-pulmonary connection at an earlier age, increased use of the right ventricle to pulmonary artery shunt, and the introduction of an interstage monitoring program.

What Are the Clinical Implications?

- This study suggests that there may be surgical and clinical strategies that potentially decrease the risk of interstage mortality.
- Further research may help delineate the specific contributions of each intervention to decreasing interstage mortality.

Nonstandard Abbreviations and Acronyms

BT	Blalock Taussig
HLHS	hypoplastic left heart syndrome
ISMP	interstage monitoring program
NP	Norwood procedure
RV-PA	right ventricle to pulmonary artery
SCPC	superior cavo-pulmonary connection

used to decrease interstage mortality included using a right ventricle to pulmonary artery (RV-PA) shunt in place of a modified Blalock Taussig (BT) shunt or decreasing the time between the NP and SCPC; however, the long-term benefits and risks remain unclear.[4,5,10]

The objectives of this study were to examine the overall incidence of interstage mortality during a 30-year period, evaluate interstage mortality across 4 predetermined eras (based on changes in operative or medical management), and analyze the impact of patient characteristics and operative factors on interstage mortality.

METHODS

Study Design

Because of the sensitive nature of the data collected for this study, data will not be available publicly. This was a retrospective chart review that included all patients with HLHS (and variants) who underwent NP, were discharged from the hospital, and were eligible for SCPC between January 1, 1984, and December 31, 2017. Patients excluded were those who underwent 2-ventricle conversion or orthotopic heart transplantation before SCPC, died before Norwood discharge, or underwent SCPC during NP hospitalization. All patients who underwent NP before 1988 were excluded because routine SCPC was not performed at that time. Patients followed at other institutions who were known to be alive at 1 year without information about SCPC were considered survivors. Patients who were discharged alive but with no further follow-up information were excluded. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board for the Protection of Human Subjects; requirement for subject-informed consent was waived because it was not needed for this retrospective study.

The study period was divided into the following 4 eras based on changes in operative or medical management: era 1 (1988–1994, initial use of SCPC), era 2 (1995–2001, change in surgical team), era 3 (2002–2010, introduction of RV-PA shunt), and era 4 (2011–2017, introduction of ISMP). Because of the unique and often theoretically distinct practice patterns associated with each era, the decision was made at the design stage of the study to treat era as a categorical as opposed to an interval or ordinal variable, with conceptually distinct eras for mortality estimates as well as modeling. Data on patient characteristics were abstracted from paper charts, electronic medical records, and clinical registries.

Statistical Analysis

Data analysis proceeded in 3 distinct phases: a descriptive phase in which measures of central tendency, variability, and association were computed for all relevant variables in the data set; an estimation phase in which mortality estimates for interstage deaths were computed and compared by era; and a risk-modeling phase to identify risk factors for interstage mortality among the cohort. All data were analyzed using SAS v9.4 (SAS Institute, Cary, NC).

Descriptive Phase

Descriptive statistics were computed using parametric as well as nonparametric measures of central tendency, variability, and association for all relevant measures to better understand the data. Except for 2 variables, ascending aorta size and gestational age, for which our data were 85% and 93% complete, respectively, missing or incomplete data were minimal (0.2%–0.5%). Hence, no further adjustments were made for missing or incomplete data.

Estimation Phase

Mortality rates were computed for the interstage period (0=alive, 1=deceased) using standard binomial proportions and corresponding 95% CIs overall and by era. Rates across eras were then compared using a logistic regression model with a Tukey–Kramer post hoc adjustment for multiplicity. Average age at SCPC and average age at death were also estimated for the entire cohort and compared by era, complete with empirically derived 95% CIs. Wilcoxon rank-sum tests were used as both an omnibus test in its generalized form (Kruskal–Wallis) and a pairwise follow-up test of significance because of the skewed and non-normative nature of the distributions.

Risk-Modeling Phase

In the risk-modeling phase, 2 sets of logistic regression models were used. In the first set, mortality was regressed onto era as a polychotomous predictor and then onto each of 14 different covariates individually after adjusting for era as the lone confounder for all 1111 patients. A final, best-fitting, multiple covariate model for our primary hypothesis was then selected from among candidate predictors with $P<0.10$, resulting in a model consisting of era, gestational age, and race as testable covariates. A subsequent, secondary analysis was conducted to estimate the impact of shunt type on mortality after adjusting for era as the lone confounder, with era 3 as the new reference group. This cohort included all 526 patients undergoing the NP once the RV-PA shunt was introduced into care. Similar to the primary model, a final, best-fitting logistic regression model was also specified and tested on the reduced sample, with mortality as the outcome and shunt type as the testable covariate and era, gestational age, use of ECMO, and race as informative covariates. This model was then followed up with a simple contingency table test (χ^2) comparing mortality rates between the BT/central shunt group and the RV-PA shunt group for the period in which the RV-PA shunt was available for use. All models tested here were compared and evaluated using model-specific and term-specific Wald (χ^2) statistics as well as Akaike information criterion and log-likelihood comparisons using full and reduced models; all tests were conducted at the unadjusted $\alpha=0.05$ level.

RESULTS

During the study period of January 1, 1984, to December 31, 2017, there were 1772 NPs performed. There were 215 patients who were excluded because they had their NP between 1984 and 1987, before routine interim staging. There were 1193 NP hospital survivors during or after 1988. Of those survivors, 14 were excluded because of biventricular conversion, 2 for orthotopic heart transplantation before NP discharge, 6 for orthotopic heart transplantation before SCPC, and 14 for SCPC before NP discharge. A total of 46 patients were lost to follow-up. Therefore, 1111 patients were available for interstage analysis. Of those, 991 underwent a SCPC and survived, and 120 infants died during the interstage period (after NP discharge without any intervention at <1 year) (Figure 1). If a patient was known to be alive at 1 year but there was no information regarding subsequent operations, he or she was considered a survivor.

The most common diagnosis was HLHS with aortic atresia and mitral atresia (33%) followed by HLHS

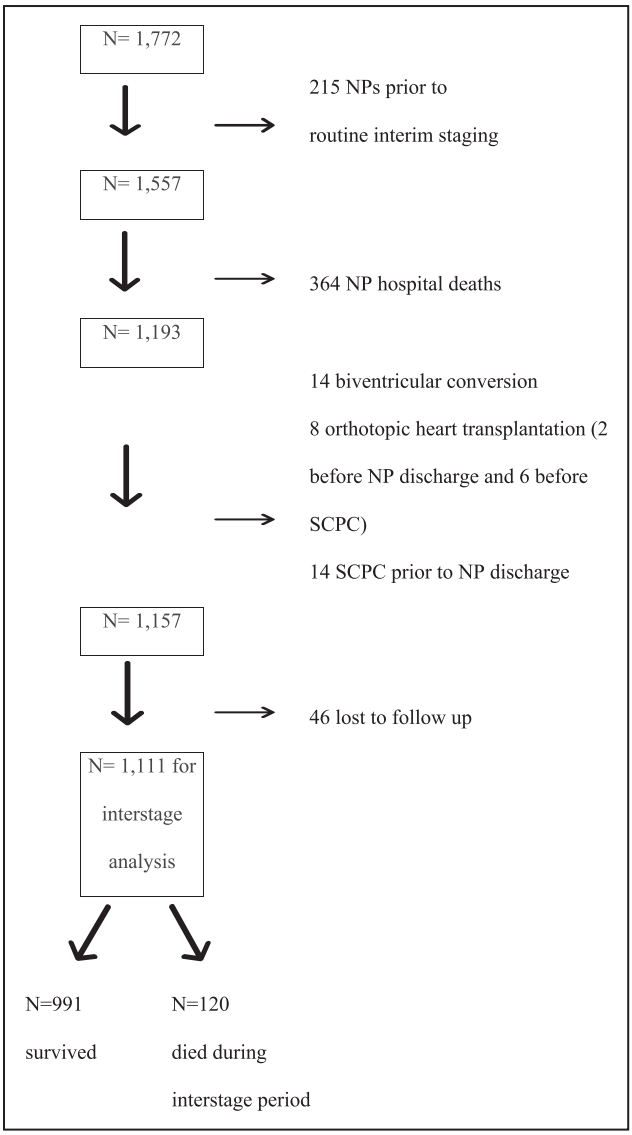

Figure 1. Patient selection.
NP indicates Norwood procedure; and SCPC, superior cavopulmonary connection.

variants (31%). Nearly 12% of patients had a suspected or confirmed genetic abnormality. Anomalous pulmonary venous drainage and significant (moderate or severe) atrioventricular valve regurgitation before the NP were relatively uncommon (4% and 10%, respectively), whereas 13% of our patients had an intact or restrictive atrial septum. The large majority of patients underwent placement of a modified BT or central shunt (83%). Additional patient characteristics are provided in Table 1.

Overall, interstage mortality was 120/1111 (10.8%) and was stable throughout most of the study period, decreasing in the most recent era relative to all others: era 1 (13.4%), era 2 (10.4%), era 3 (11.6%), and era 4

Table 1. Patient Characteristics (N=1111)

Variable	Frequency			No.	Median	Q_{25}, Q_{75}
	No (%)	Yes (%)	Missing			
Ascending aorta, mm				923	3.0	2.0, 5.0
Age at Norwood, d				1111	5.0	3.0, 7.3
Birth weight, g				1041	3.2	2.9, 3.5
CPB time, min				1111	39.0	37.0, 47.0
DHCA time, min				1111	49.0	40.0, 59.0
Gestational age, wk				1029	39.0	38.0, 39.0
LOS, d				1111	19.0	13.0, 31.0
Total support time, min				1111	89.0	79.0, 105.0
Anomalous pulmonary venous drainage	1067 (96.0)	39 (3.5)	5 (0.4)			
Atrioventricular valve regurgitation*	1000 (90.0)	111 (10.0)				
Intact or restrictive atrial septum†	957 (86.1)	149 (13.4)	5 (0.4)			
Era						
1988–1994 (era 1)	352 (31.7)					
1995–2001 (era 2)	230 (20.7)					
2002–2010 (era 3)	355 (32.0)					
2011–2017 (era 4)	174 (15.7)					
Genetic anomaly						
Normal	981 (88.3)					
Suspect/abnormal	130 (11.7)					
Hypoplastic left heart syndrome						
Aortic atresia/mitral atresia	370 (33.3)					
Aortic atresia/mitral stenosis	171 (15.4)					
Aortic stenosis/mitral atresia; Aortic stenosis/mitral stenosis	220 (19.8)					
HLHS variant	348 (31.3)					
Missing	2 (0.2)					
Race						
White	790 (71.1)					
Black	161 (14.5)					
Other	160 (14.4)					
Sex						
Female	412 (37.1)					
Male	699 (62.9)					
Shunt type						
Blalock-Taussig/central	918 (82.6)					
Right ventricle-pulmonary artery	183 (16.5)					
Missing	10 (0.9)					

CPB indicates cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; HLHS, hypoplastic left heart syndrome; LOS, length of stay; Q_{25}, first quartile; and Q_{75}, third quartile.

*Yes=moderate or severe.

†Yes=yes or restrictive.

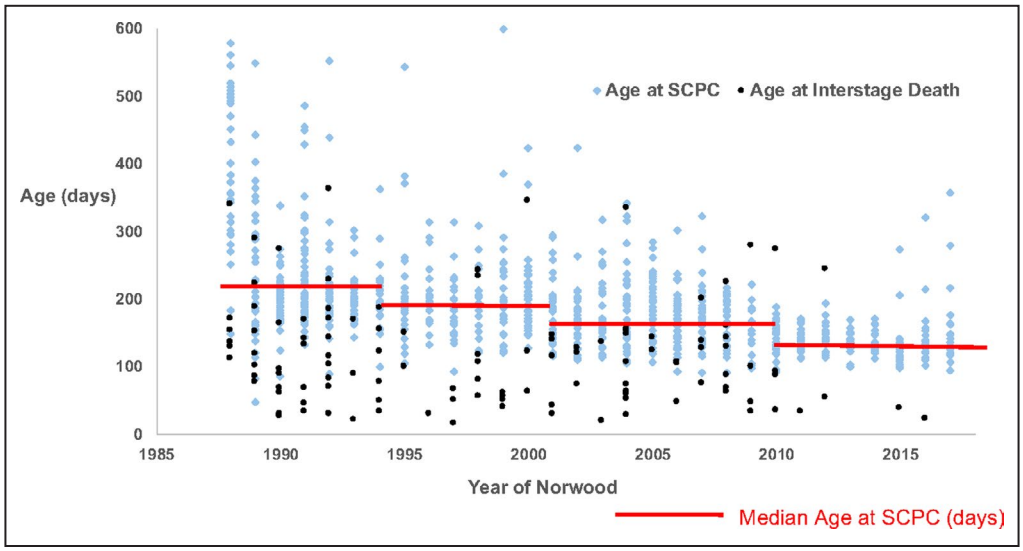

Figure 2. Interstage mortality and median age at SCPC.
SCPC indicates superior cavo-pulmonary connection.

(4.6%) (Figure 2, Table 2). Whereas age at SCPC decreased significantly across the 4 eras (from 208 days in era 1 to 135 days in era 4), there were no statistically significant differences among the 4 eras for age at death (Figure 2, Table 3).

Birth weight, gestational age, length of stay, genetic anomaly, and race (all $P \leq 0.05$) were identified as risk factors for interstage mortality using single covariate adjusted (era) logistic regression models (Table 4). A final, best-fitting, multiple logistic regression model indicated that gestational age ($P=0.04$) and race ($P<0.01$) were both associated with interstage mortality after adjusting for era ($P<0.01$). Importantly, when compared with era 1, era 4 had a significantly lower mortality rate ($P<0.01$), corresponding to both the introduction of the ISMP and the shortest average time period between the NP and SCPC (Tables 3 and 4, Figure 3). A subsequent, secondary analysis was conducted to estimate the relationship between shunt type ($P=0.02$) and interstage mortality after adjusting for era ($P=0.07$): gestational age ($P<0.01$), use of ECMO ($P=0.02$), and race ($P<0.01$); all statistically significant contributors to the final, secondary model. With respect to shunt type, specifically, interstage survival was higher in patients with RV-PA shunts (95.6%) than BT or central shunts (88.0%). RV-PA shunts were first used in era 3 and accounted for 27.4% of shunt types in era 3 and 50.0% of shunt types in era 4.

Table 2. Frequency Counts and Mortality Rates for Entire Cohort and by Era (N=1111)

Years	Norwood Patients' Survival Status at Stage 2		
	Frequency		Mortality Rate*
	Alive	Deceased	n ($CI_{0.95}$)
Entire cohort			
1988–2017	991	120	10.8 (9.0–12.6)
By era			
1988–1994 (era 1)	305	47	13.4 (9.8–16.9)
1995–2001 (era 2)	206	24	10.4 (6.5–14.4)
2002–2010 (era 3)	314	41	11.6 (8.2–14.9)
2011–2017 (era 4)	166	8	4.6 (1.5–7.7)

*Only 1 statistically significant difference was observed among pairwise contrasts for mortality (era 1 vs. era 4; $P=0.02$) using a Tukey–Kramer adjustment for multiple comparisons.

DISCUSSION

This is the largest single-center cohort assessing the risk of mortality during the interstage period after NP discharge and before SCPC for patients with HLHS. During a 30-year time period at our institution, the overall interstage mortality rate was 10.8%, which is similar to other studies, including the multicenter Single Ventricle Reconstruction Trial.[5,11–14] Interestingly, we found that the risk of interstage mortality after NP has decreased significantly in the most recent era. This corresponds to several changes in clinical and surgical management, including the shortest average time period between the NP and SCPC, the introduction of the ISMP program, and an increased use of the RV-PA shunt. No other era for which there was a major alteration in medical or surgical management demonstrated a statistically significant decrease in interstage mortality.

Table 3. Age and Age at Death for Infants Undergoing SCPC

Years	Age at SCPC (d)		Age at Death (d)	
	No.	Median (95% CI)	No.	Median (95% CI)
Entire cohort				
1988–2017	957	179 (174–183)	120	103.5 (84–122)
By era				
1988–1994 (era 1)	298	208 (202–216)	47	118.0 (88–151)
1995–2001 (era 2)	194	189 (183–195)	24	73.0 (55–121)
2002–2010 (era 3)	304	165 (160–170)	41	105.0 (75–135)
2011–2017 (era 4)	161	135 (132–138)	8	43.0 (22–244)

Wilcoxon rank-sum tests for all pairwise comparisons for each variable resulted in statistically significant differences for all ages at SCPC comparisons ($P<0.01$), but not for any age at death comparisons after adjustment for multiplicity. SCPC indicates Superior Cavo-Pulmonary Connection.

Age at SCPC decreased significantly throughout all 4 eras. It is important to note that an integral component of our ISMP is routine scheduling of the SCPC at ≈4 months of age, so the ISMP and earlier time at SCPC are connected. Several studies have shown similar findings, demonstrating that patients with early SCPC have less interstage mortality.[15,16] In addition, a recent study from our institution

Table 4. Single and Multiple Covariate Risk Factor Models for Interstage Mortality, 1988 Through 2017 (N=1111)

Potential Risk Factors	No.	Single Covariate Models*			Best-Fitting Multiple Covariate Model		
		Adjusted for Era			Adjusted for Era		
		β (SE)	OR (95% CI)	*P* Value	β (SE)	OR (95% CI)	*P* Value
Ascending aorta, mm	923	−0.09 (0.06)	0.92 (0.81–1.04)	0.18			
Age at Norwood, d	1111	0.00 (0.00)	1.00 (0.99–1.01)	0.82			
Atrioventricular valve regurgitation (reference: none)	1111	0.08 (0.16)	1.18 (0.64–2.20)	0.59			
Birth weight, kg	1041	−0.43 (0.17)	0.65 (0.46–0.91)	0.01			
Era	1111			0.03			0.01
1988–1994 (reference)							
1995–2001		0.12 (0.19)	0.76 (0.45–1.28)	0.53	0.10 (0.21)	0.65 (0.36–1.17)	0.62
2002–2010		0.24 (0.17)	0.85 (0.54–1.33)	0.16	0.18 (0.17)	0.70 (0.43–1.14)	0.30
2011–2017		−0.76 (0.28)	0.31 (0.14–0.68)	0.01	−0.82 (0.29)	0.26 (0.12–0.57)	0.00
Cardiopulmonary bypass time, min	1111	−0.01 (0.00)	0.99 (0.98–1.00)	0.13			
Deep hypothermic circulatory arrest time, min	1111	−0.01 (0.00)	0.99 (0.98–1.00)	0.17			
Gestational age, wk	1029	−0.12 (0.05)	0.89 (0.80–0.98)	0.02	−0.11 (0.05)	0.90 (0.81–0.99)	0.04
Genetic anomaly (reference: none)	1111	0.27 (0.14)	1.70 (0.99–2.92)	0.05			
Hypoplastic left heart syndrome subtype	1109			0.98			
Aortic atresia/mitral atresia (reference)							
Aortic atresia/mitral stenosis		−0.09 (0.21)	0. 89 (0.49–1.63)	0.68			
Aortic stenosis/mitral atresia; aortic stenosis/mitral stenosis		0.01 (0.18)	0.98 (0.58–1.69)	0.96			
Variant		0.05 (0.16)	1.03 (0.64–1.65)	0.74			
Intact atrial septum (reference: no)	1106	−0.02 (0.14)	0.97 (0.55–1.70)	0.90			
LOS, d	1106	0.01 (0.00)	1.01 (1.00–1.01)	0.01			
Race	1111			<0.01			<0.01
White (reference)							
Black		−0.01 (0.18)	1.57 (0.93–2.65)	0.96	0.04 (0.18)	1.74 (1.02–2.98)	0.82
Other		0.47 (0.17)	2.54 (1.56–4.15)	<0.01	0.47 (0.18)	2.68 (1.60–4.49)	0.01
Sex (reference: female)	1111	−0.03 (0.10)	0.94 (0.63–1.38)	0.74			
Total support time, min	1111	−0.00 (0.00)	1.00 (0.99–1.00)	0.23			

Values reported here as 0.00 were rounded to 2 decimal places for consistency of reporting and to reduce the complexity of the table. LOS indicates length of stay.
*All single covariate models were adjusted for era; however, era was also tested individually as a categorical covariate with no additional adjustments.

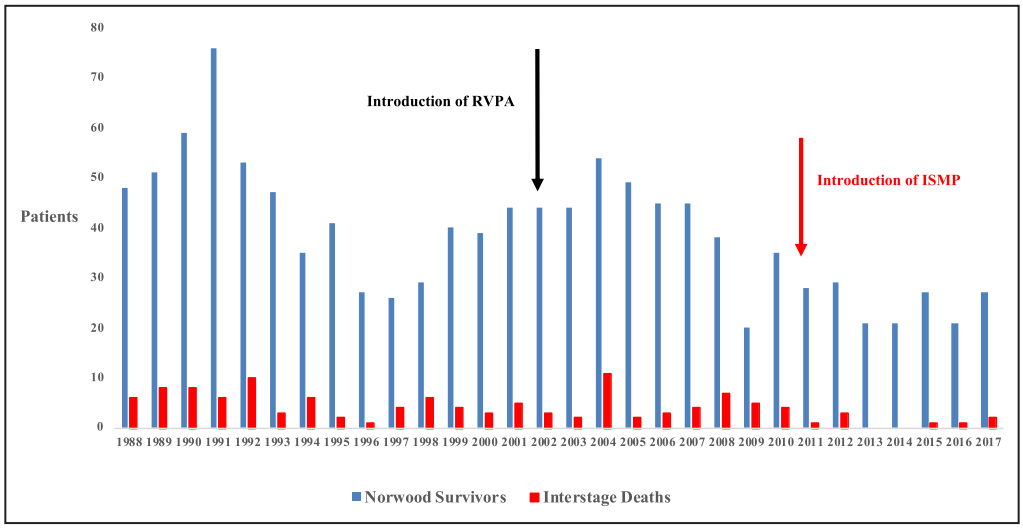

Figure 3. Interstage mortality after the introduction of a right ventricle to pulmonary artery shunt and interstage monitoring.
ISMP indicates interstage monitoring program; and RVPA, right ventricle to pulmonary artery shunt.

found that younger age at SCPC was not associated with higher postoperative mortality or longer length of stay.[16] Not all studies, however, have determined that earlier SCPC is beneficial, and some suggest it does result in longer length of stay.[17] Thus there may be an optimal time that is just long enough and just short enough after NP to benefit the patient. Meza et al suggest that the timing of SCPC is best after 3 months but before 6 months for patients who are not high risk, and others have found that patients who are older at the time of SCPC have worse outcomes at the Fontan operation.[18,19]

This study is consistent with other retrospective, single-center studies that have shown a decrease in interstage mortality following the introduction of an ISMP.[7,20–22] Although the multicenter study by Oster et al using data from the National Pediatric Cardiology Quality Improvement Collaborative did not initially demonstrate a survival benefit with ISMPs, subsequent analyses have shown a benefit.[9,23] To note, we rarely keep patients hospitalized after the Norwood operation during the interstage period, with only 14 patients (1%) during the 30-year period remaining hospitalized before the SCPC operation. This practice did not change with the introduction of the ISMP. This number is less than that reported in the Single Ventricle Reconstruction trial and less than other large pediatric medical centers.[5,24] Our robust ISMP includes daily weight and oxygen saturation measurements as well as mandatory weekly medical follow-up and weekly calls with the dedicated program nurse practitioner and dietician.[16] This rigorous program may account for the discrepancy in findings from this study and previously reported data.

A decrease in interstage mortality with the use of RV-PA shunts compared with BT or central shunts was first reported by Sano et al and has since been confirmed in several studies.[5,25,26] Our subanalysis demonstrated that patients with RV-PA shunts have improved survival compared with BT or central shunts. In addition, there was an increase in use of RV-PA shunts in era 4, during the same time as the initiation of the ISMP and shortest length of time between the NP and SCPC. This topic remains controversial, however, as several other studies have demonstrated no hemodynamic or survival benefit with an RV-PA shunt.[16,27,28]

Independent patient characteristics that have been associated with interstage mortality in other studies were also confirmed in our analysis and include earlier era of operation, lower birth weight, younger gestational age, confirmed or suspected genetic anomaly, race, and longer length of stay. On multivariate analysis, those who were born in an era before the initiation of the ISMP, those who were born at an earlier gestation age, and those who reported a race other than Black or White were still associated with higher interstage mortality. Many of those risk factors represent high-risk cohorts that may require specific management changes, including remaining in the hospital during the interstage period and undergoing an earlier SCPC or a primary hybrid procedure with a more extensive second operation (combined NP and SCPC).

Our study has several limitations. Although this is one of the largest studies of patients who underwent an NP, it is a single-center retrospective study. Despite our significant findings, we cannot determine the relative impact of each individual factor. Some of

the findings that differ from multicenter studies may be attributed to differences in practice at our institution. Because this study spanned 3 decades, there may be other changes in clinical practice for which we did not account that could have affected our findings.

In this cohort, we demonstrated a significant decrease in interstage mortality in the most recent era. This decline in mortality is associated with earlier age at SCPC operation, introduction of an ISMP, and increased use of the RV-PA shunt. Although not causative, these factors may have contributed to the significant decrease in interstage mortality in the most recent era. Because age at SCPC and ISMP in relation to interstage mortality are temporally related, it is not possible to determine their relative contributions to the observed decrease in interstage mortality.

ARTICLE INFORMATION

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Disclosures

None.

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