Factors Associated With Interstage Mortality Following Neonatal Single Ventricle Palliation

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Abstract

Background: Several advances have led to improved hospital survival following neonatal palliation (NP) of single ventricle (SV) anomalies. Nonetheless, a number of patients continue to suffer from interstage mortality (ISM) prior to subsequent Glenn. We aim to study patients' characteristics and anatomic, surgical, and clinical details associated with ISM. **Methods:** A total of 453 SV neonates survived to hospital discharge following NP. Competing risk analysis modeled events after NP (Glenn, transplantation, or death) and examined variables associated with ISM. **Results:** Competing risk analysis showed that one year following NP, 10% of patients had died, 87% had progressed to Glenn, 1% had received heart transplantation, and 2% were alive without subsequent surgery. On multivariable analysis, factors associated with ISM were as follows: weight $\leq$2.5 kg (hazard ratio, HR = 2.4 [1.2-4.6], P = .013), premature birth $\leq$36 weeks (HR = 2.0 [1.0-4.0], P = .05), genetic syndromes (HR = 3.2 [1.7-6.1], P < .001), unplanned cardiac reoperation (HR = 2.1 [1.0-4.4], P = .05), and prolonged intensive care unit (ICU) stay >30 days following NP (HR = 2.5 [1.4-4.5], P < .001). Palliative surgery type (shunt, Norwood, band) was not associated with ISM, although aortopulmonary shunt circulation after Norwood was (HR = 5.4 [1.5-19.2] P = .01). Of interest, underlying SV anatomy was not associated with ISM (HR = 1.1 [0.6-2.2], P = .749). **Conclusions:** In our series, ISM following NP occurred in 10% of hospital survivors. As opposed to hospital death, underlying SV anomaly was not associated with ISM. Conversely, several patient factors (prematurity, low weight, and genetic syndromes) and clinical factors (unplanned reoperation and prolonged ICU stay following NP) were associated with ISM. Vigilant outpatient management that is individualized to specific clinical and social needs, taking into account all associated factors, is warranted to improve survival in high-risk patients.

Keywords

single ventricle, Norwood procedure, shunts (indicate location), cavopulmonary anastomosis

Introduction

Multistage palliation is the primary management strategy of neonates born with various single ventricle (SV) cardiac anomalies.[1,2] The neonatal palliation (NP) surgery differs among those patients based on underlying anatomy and associated obstruction of the pulmonary valve, left ventricular outflow tract, or aortic arch. Based on those anatomic considerations, the NP surgery might be a Norwood operation, modified Blalock-Taussig shunt, or pulmonary artery band.[1–5] Historically, the NP operation has been and continues to be associated with the highest hospital mortality risk. Over the past two decades, there has been a remarkable improvement in hospital survival following NP operation owing to several advances in preoperative stabilization, surgical techniques, perfusion strategies, and perioperative care.[2,6] Nonetheless, despite improved hospital survival, patients with SV undergoing NP continue to be at risk of interstage mortality (ISM)

following hospital discharge and prior to reaching the second-stage palliation with the Glenn bidirectional cavopulmonary connection.[7–11] The incidence of ISM has been reported to be between 10% and 20% of hospital survivors following NP and might be related to cardiac etiologies (such as shunt thrombosis, coronary steal, volume loading, arrhythmias, myocardial dysfunction, and residual cardiac lesions) or extracardiac

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etiologies (such as lung disease, pulmonary hypertension, sepsis, aspiration, dehydration, and other organ anomalies).

In the current series, we report events in patients who survived to hospital discharge following NP for various SV cardiac anomalies. We aim to examine the incidence of ISM in the current era and explore associated demographic, anatomic, surgical, and clinical factors linked to increased ISM risk.

Patients and Methods

Inclusion Criteria

From 2002 to 2012, 530 neonates born with SV anomalies underwent NP at Children's Healthcare of Atlanta, Emory University. Our current study patient cohort was comprised of 453 (85.5%) patients who survived the initial hospital admission without requiring heart transplantation following their NP procedure. Patients were identified using our institutional surgical database. Demographic, anatomic, clinical, operative, and hospital details were abstracted from medical records for analysis. Approval of this study was obtained from the hospital's institutional review board and requirement for individual consent was waived for this observational study.

Outpatient Management

Our current outpatient management of patients with SV following NP involves coordinated discharge protocols focusing on extensive parental education and includes advance scheduling of routine diagnostic imaging studies or cardiac catheterization, outpatient home health visits, frequent (weekly) cardiology visits at clinics close to home, routine childhood immunizations, and respiratory syncytial virus prophylaxis. The home health visits occur once to twice a week, and more frequently as needed. During those visits, the home health nurses inspect temperature and other vitals, oxygen saturation, and weight gain and look for signs of dehydration, heart failure, or infection. Additionally, the parents are educated to seek medical attention with the assigned pediatric cardiologist or in the emergency department for any breach of signs and symptoms including vomiting, diarrhea, color change (bluer or paler), fever, difficulty breathing, weight loss, inadequate weight gain, or excessive irritability. There is a low threshold for hospital readmission for any fever >100.5°C, respiratory illness, poor feeding tolerance, weight loss, weight gain less than 5 oz/d, persistent vomiting or diarrhea lasting more than 24 hours, and oxygen saturation 5 to 10 points lower than baseline. Upon

readmission, repeat imaging is performed as deemed necessary to evaluate for any emerging cardiac complication, and supportive care and appropriate treatment of any complicating illness requiring readmission is provided.

Follow-Up

Time-related outcomes were determined from recent office visits documented in Children's Healthcare of Atlanta electronic chart system or from direct correspondence with other pediatric cardiologists outside the system. Follow-up was 93% complete. Mean follow-up duration for our current patient cohort was 7.6 (5.5) years.

Statistical Analysis

Data are presented as means with standard deviation, medians with interquartile ranges (IQRs), or frequencies with percentages as appropriate. Time-dependent outcomes (death, transplantation, and survival to Glenn) after NP were parametrically modeled. Parametric probability estimates for time-dependent outcomes use models based on multiple, overlapping phases of risk. Specifically, the HAZARD procedure (available for use with the SAS system [SAS Institute, Cary, North Carolina] at http://www.clevelandclinic.org/heartcenter/hazard) utilizes maximum likelihood estimates to resolve risk distribution of time-to-event data in up to three phases of risk (early, constant, and late). Competing risk analysis was performed to model the probability over time of each of three mutually exclusive end points after NP: (1) death, (2) heart transplantation, and (3) progression to Glenn, the remaining patients being alive without Glenn or transplantation. Variables potentially influencing the likelihood of outcomes in the competing risks models were sought from demographic, anatomic, surgical, and clinical variables. Multivariable models were created using forward entry of variable. Effects of covariates on the probability of outcomes in the competing risks models were given as hazard ratios (HRs) with 95% confidence intervals. Final models were selected based upon clinically relevant covariates and strongest model fits as indicated by log-likelihood statistics. All statistical analyses were performed using SAS version 9.3 (SAS Institute).

Results

Patients' Characteristics

Between 2002 and 2012, 530 neonates with various SV anomalies underwent NP. After exclusion of patients who died or received heart transplantation during the initial hospital admission following NP, our study's patient cohort contained 453 (85.5%) patients.

Median age at time of NP for those 453 patients was 6 days (IQR: 4-10) and median weight was 3.2 kg (IQR: 2.8-3.5), with 56 (12%) ≤2.5 kg in weight. Overall, there were 57 (13%) who were born prematurely at ≤36 weeks' gestation and 42 (9%) who had genetic syndrome of extracardiac anomaly (not

including heterotaxy syndrome that was considered an individual factor in our analysis). Underlying SV anomaly was hypoplastic left heart syndrome (n = 181, 40%), tricuspid atresia (n = 74, 16%), atrial isomerism (n = 43, 10%), pulmonary atresia with intact ventricular septum (n = 43, 10%), double inlet left ventricle (n = 33, 7%), double outlet right ventricle not amenable to biventricular repair (n = 27, 6%), unbalanced atrioventricular septal defect (n = 20, 4%), mitral atresia (n = 14, 3%), and other (n = 18, 4%). The dominant ventricle morphology was right (n = 255, 56%) and left (n = 174, 38%), with 24 patients (5%) having functional SV with two equally formed ventricles. The NP surgery was Norwood (n = 236, 52% including 178 [39%] who received right ventricle to pulmonary artery shunt and 58 [13%] who received aortopulmonary shunt as source of pulmonary blood flow), modified Blalock-Taussig shunt (n = 147, 32%), and pulmonary artery band (n = 70, 16%, including 28 patients who required simultaneous arch repair at time of band). Following NP, 27 (6%) patients received extracorporeal membrane oxygenator (ECMO) support and 45 (10%) had unplanned cardiac reoperations (not including delayed sternal closure, mediastinal explorations, ECMO procedures, or procedures to treat noncardiac complications such as diaphragm plication or thoracic duct ligation). The duration of mechanical ventilation following NP was 181 (225) hours, while the duration of intensive care unit (ICU) stay was 311 (42) hours. Total postoperative hospital stay was 25 (2) days.

Events Following Hospital Discharge

The events subsequent to hospital discharge following NP are depicted in Figure 1. Among hospital survivors, 46 (10.1%) died prior to Glenn, 7 (1.6%) received heart transplantation, 393 (86.7%) progressed to received Glenn, and 7 (1.6%) were alive without Glenn.

The cause of death in those 46 patients who had ISM was often multifactorial and sometimes unclear. In general, it can be assigned to one of the following categories:

- Inability to proceed to Glenn due to anatomic, hemodynamic, or functional contraindications (eg, poor ventricular of atrioventricular valve function, hypoplastic pulmonary arteries), n = 6.
- Complications following surgical or percutaneous intervention for residual lesions (eg, recurrent coarctation, shunt or pulmonary artery obstruction), n = 6.
- Cardiac arrest with an identified residual surgical lesion (eg, clotted shunt, arch obstruction), n = 7.
- Cardiac arrest at home with no identified residual surgical lesion, n = 6.
- Residual extracardiac complications following NP (eg, postoperative hypoxic brain injury, postoperative respiratory failure requiring tracheostomy), n = 5.
- Extracardiac problems that were not related to NP (eg, complications from abdominal surgery, intracranial anomalies), n = 4.

- Readmission for infectious process (eg, necrotizing enterocolitis, viral pneumonia, endocarditis), n = 6.
- Sudden death at home (unknown), n = 6.

Competing risk models showed that the proportion of patients who underwent Glenn started to rise around three months and peaked around six months after NP. The hazard function for death prior to Glenn was characterized by the presence of an early hazard phase during the initial four months after NP that significantly decreased after that period. The hazard function for heart transplantation was low and steady during the first year following NP. Competing risk analysis showed that at six months after NP, 8% of patients had died, 1% had received heart transplantation, 69% had undergone Glenn, and 22% were alive without Glenn. At one year after NP, 10% of patients had died, 1% had received heart transplantation, 87% had undergone Glenn, and 2% were alive without Glenn (Figure 2).

Factors Associated With ISM

We compared patients' characteristics and anatomic, surgical, and postoperative details between patient who progressed to Glenn (n = 393) and those who had ISM (n = 46). The results are depicted in Table 1. Patients who suffered from ISM were more likely to have been born prematurely, to have low weight at the time of NP, to have associated genetic syndromes of extracardiac anomalies, and to have required unplanned cardiac reoperation following NP. The underlying SV anomaly was not associated with ISM. While there was no significant difference in distribution of Norwood, modified Blalock-Taussig shunt, or pulmonary artery band among the two groups, patients who had ISM were more likely to have received aortopulmonary shunt as source of pulmonary blood supply during the Norwood operation. Finally, patients who had ISM had longer recovery following their NP as evidenced by longer mechanical ventilation and ICU and hospital stays.

Factors associated with ISM were explored and are presented in Table 2. On multivariable analysis, factors associated with increased ISM risk were as follows: weight ≤2.5 kg (HR = 2.4 [1.2-4.6], $P = .013$), premature birth ≤36 weeks (HR = 2.0 [1.0-4.0], $P = .05$), genetic syndromes and extracardiac anomalies (HR = 3.2 [1.7-6.1], $P < .001$), unplanned cardiac reoperation (HR = 2.1 [1.0-4.4], $P = .05$), and prolonged ICU stay >30 days following NP (HR = 2.5 [1.4-4.5], $P < .001$). Neonatal palliation surgery type (shunt vs Norwood vs band) was not associated with ISM, except for Norwood with aortopulmonary shunt (HR = 5.4 [1.5-19.2], $P = .01$). The underlying SV anomaly was not associated with ISM (HR = 1.1 [0.6-2.2], $P = .749$). Extracorporeal membrane oxygenator support at NP was also not associated with ISM (HR = 1.1 [0.4-3.8], $P = .800$).

Discussion

We identified that ISM remained 10% in hospital survivors who have undergone NP during the study period (2002-
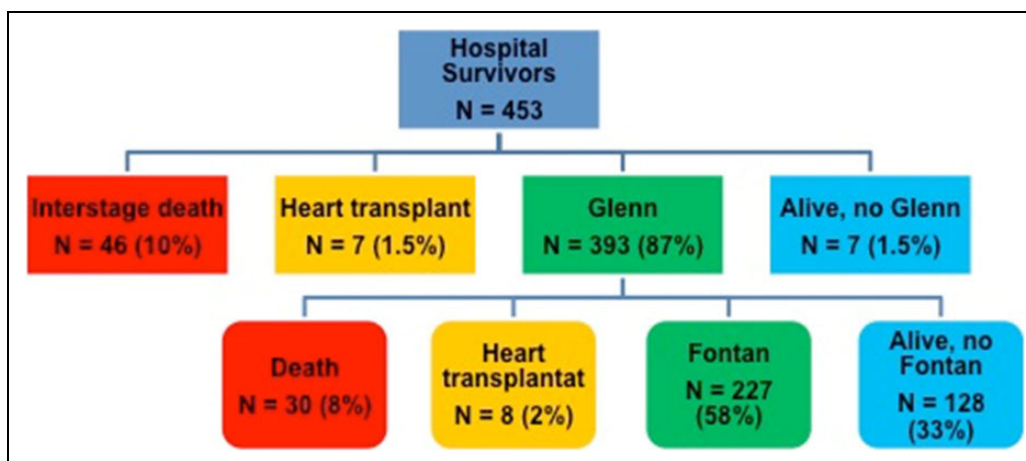
Figure 1. Flowchart depicting events following hospital discharge in neonates who had NP for SV anomalies and survived to hospital discharge. NP indicates neonatal palliation; SV, single ventricle.
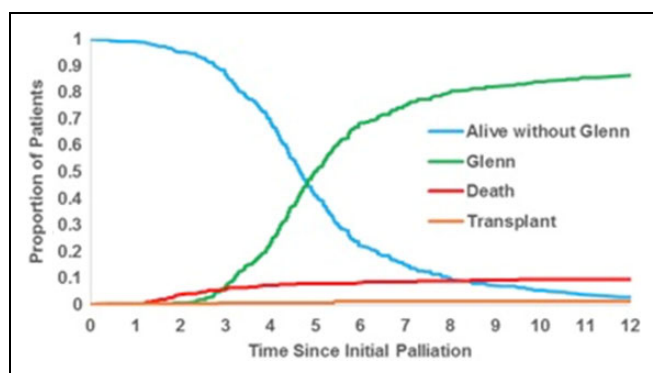

Figure 2. Competing risk analysis of events after NP (death, heart transplantation, and Glenn) in neonates with SV anomalies who survived to hospital discharge (excluding hospital mortalities). NP indicates neonatal palliation; SV, single ventricle.

2012). We identified several demographic, operative, and clinical factors that were associated with increased ISM risk.

Low weight at the time of NP and prematurity were associated with increased ISM. The effect of both prematurity and low weight on hospital mortality following NP has been documented in several previous studies.[9,12–15] This might be due to technical challenges related to small-sized cardiac structures and tissue friability, in addition to postoperative management issues related to organ immaturity, pulmonary dysfunction, and pulmonary hypertension. In addition to increased hospital mortality, both factors have been linked to prolonged recovery and increased complications following NP.[9] Our study demonstrates that the hazard of death persists beyond hospital discharge in those patients, affecting progression toward subsequent Glenn. For example, in our series, ISM was 20% in patients who were ≤2.5 kg in weight versus 9% in those who were >2.5 kg in weight at the time of NP. Similarly, ISM was 18% in patients who were born prematurely at ≤36 weeks' gestation versus 9% in those who were born >36 weeks' gestation. Examination of the effect of those factors on the technical

aspect of repair failed to demonstrate that those patients are more likely to have residual lesions or require unplanned cardiac reoperation.[9] This suggests that organ immaturity in those patients plays a significant role that negatively impacts survival beyond hospital discharge.

Additionally, we found that patients with genetic syndromes and major extracardiac anomalies were at higher risk to suffer from ISM prior to Glenn (22% vs 9%). Neonates with genetic syndromes often have additional factors such as prematurity, low weight, and poor clinical conditions that complicate their recovery and increase their morbidity and mortality following neonatal repair or palliation of congenital heart defects.[16–24] In our study, we demonstrated that the effects of genetic syndromes and major extracardiac anomalies extended beyond hospital discharge following NP and that genetic syndromes and major extracardiac anomalies were significant and independent factors associated with ISM. This is likely related to the associated extracardiac lesions affecting multiple organs and systems (brain, lungs, gastrointestinal, and metabolic) resulting in a more complicated outpatient management and increased risk for noncardiac complications subsequent to hospital discharge. Our analysis did not demonstrate increased residual lesions or need for unplanned reoperation in this group of patients, suggesting again the larger role of associated extracardiac lesions in those patients impacting survival beyond hospital discharge.

Interestingly, we were unable to demonstrate that the underlying SV anomaly was significantly associated with increased ISM. At our institution, we have previously examined the effect of underlying SV anomaly and also dominant ventricle morphology on survival and have demonstrated that SV palliation outcomes varied based on the underlying anomaly.[1,9,25] In those previous studies, we have noted that pulmonary atresia with intact ventricular septum, atrial isomerism, and unbalanced atrioventricular septal defect were associated with the highest hospital mortality and lowest late survival, while double inlet left ventricle and tricuspid atresia were associated with the lowest

Table 1. Difference in Patients' Characteristics, Anatomic and Operative Details, and Hospital Data Between Patients Who Had ISM and Those Who Survived to Receive Glenn.[a]

Characteristic	Received Glenn (N = 393)	Had ISM (N = 46)	P Value
Age (days), median (25th-75th)	6 (4-11)	5 (4-7)	.352
Weight (kg), mean (SD)	3.2 (0.6)	2.9 (0.5)	<.001
Weight <2.5 kg (%)	44 (11.2%)	11 (23.9%)	.014
Female gender (%)	157 (40.0%)	16 (34.8%)	.500
Premature birth ≤36 weeks	46 (11.7%)	10 (21.7%)	.055
Genetic syndrome and extra-cardiac anomaly	29 (7.4%)	11 (23.9%)	<.001
Underlying SV anomaly			
Hypoplastic left heart syndrome	163 (41.5%)	18 (39.1%)	.257
Tricuspid atresia	64 (16.3%)	5 (10.9%)	
Atrial isomerism	39 (9.9%)	3 (6.5%)	
Pulmonary atresia with intact ventricular septum	31 (7.9%)	6 (13.0%)	
Double inlet left ventricle	30 (7.6%)	2 (4.4%)	
Double outlet right ventricle	21 (5.3%)	6 (13.0%)	
Unbalanced atrioventricular septal defect	15 (3.8%)	4 (8.7%)	
Mitral atresia	12 (3.1%)	1 (2.2%)	
Other	18 (4.5%)	1 (2.2%)	
NP procedure			
Modified Blalock-Taussig shunt	122 (31.0%)	17 (37.0%)	.232
Norwood	209 (53.2%)	26 (56.5%)	
Pulmonary artery band	62 (15.8%)	3 (6.5%)	
Norwood type (n = 235)			
Aortopulmonary shunt	45 (21.5%)	12 (46.2%)	.006
Right ventricle to pulmonary artery shunt	164 (78.5%)	14 (53.9%)	
ECMO use at time of NP	22 (5.6%)	3 (6.5%)	1.00
Cardiopulmonary bypass use at NP	236 (60.1%)	29 (63.0%)	.695
Dominant ventricle morphology			
Left	148 (37.7%)	15 (32.6%)	.742
Right	226 (57.5%)	28 (60.9%)	
Both	19 (4.8%)	3 (6.5%)	
Unplanned cardiac reoperation	30 (7.6%)	8 (17.4%)	.033
Total length of stay (days), median (25th-75th)	17 (12-28)	27 (14-52)	<.001
Postoperative ICU length of stay (hours), median (25th-75th)	167 (101-288)	266 (144-544)	.009
Duration of ventilation (hours), median (25th-75th)	103.5 (52.7-202.5)	180.6 (120.3-338.1)	<.001

Abbreviations: ECMO, extracorporeal membrane oxygenator; ICU, intensive care unit; ISM, interstage mortality; NP, neonatal palliation; SD, standard deviation; SV, single ventricle.
[a]Fourteen patients who received heart transplantation or were alive without Glenn were not included.

hospital mortality and highest late survival.[1,9,21,25–27] However, in the current series focusing on ISM in hospital survivors, ISM was comparable among various SV anomaly groups (13% vs 10% in those with pulmonary atresia with intact ventricular septum, atrial isomerism, and unbalanced atrioventricular septal defect compared to other SV anomalies). While this lack of difference might be related to statistical limitation associated with the sample size, this comparable ISM risk also suggests that the maximum impact of underlying SV anomaly is actually on hospital survival following NP.

Our ISM risk following hospital discharge was 5%, 11%, and 12% following pulmonary artery band, Norwood, and modified Blalock-Taussig shunt, respectively. This is an important finding that continues to highlight the fragile physiologic status of SV patients receiving palliation with modified Blalock-Taussig shunt and the associated complications that are related to either coronary steal or shunt thrombosis rendering their ISM risk comparable to those who have

received the more complex Norwood NP operation.[3–5,12,15,28] Factors that have been found to be associated with increased ISM in patients receiving modified Blalock-Taussig shunt include low weight, pulmonary atresia, and cardiopulmonary bypass use.[28] Of relevance, in our series, the use of aortopulmonary versus right ventricle to pulmonary artery shunt as the source of pulmonary blood flow during the Norwood operation was a significant risk factor for ISM (21% vs 8%), which correlates with some other studies in the literature.[29]

Interestingly, the need for ECMO use following NP was not associated with increased ISM in our current series (12% vs 10%). While several series have demonstrated that ECMO use during NP (particularly Norwood) is associated with both high hospital mortality and poor late survival with continuous attrition risk beyond hospital discharge, this has not been the experience at our institution, although our analysis is likely statistically limited by the sample size.[30–32] On the other hand, we found that unplanned cardiac reoperation at the time of NP

Table 2. The Multivariable Risk Analysis Model of Factors Associated With ISM in Hospital Survivors Following NP.

Characteristic	Hazard Ratio	95% CI	P Value
Age	0.99	0.97-1.002	.514
Weight <2.5 kg	2.36	1.20-4.63	.013
Female gender	0.81	0.44-1.48	.494
Premature birth ≤36 weeks	1.98	0.99-3.96	.055
Genetic syndrome and extracardiac anomaly	3.18	1.67-6.12	<.001
Underlying SV anomaly			
Atrial isomerism/unbalanced atrioventricular septal defect	1.24	0.51-2.98	.634
Pulmonary atresia with intact ventricular septum	1.84	0.71-4.77	.210
Hypoplastic left heart syndrome	1.12	0.56-2.22	.749
Other (reference)	–	–	–
NP procedure			
Modified Blalock-Taussig shunt	2.82	0.83-9.63	.098
Norwood	2.62	0.79-8.66	.115
Pulmonary artery band (reference)	–	–	–
NP procedure (including Norwood type)			
Modified Blalock-Taussig shunt	2.82	0.83-9.64	.098
Norwood—aortopulmonary shunt	5.38	1.50-19.23	.010
Norwood—right ventricle to pulmonary artery shunt	1.82	0.52-6.33	.346
Pulmonary artery band (reference)	–	–	–
ECMO use at the time of NP	1.12	0.36-3.78	.800
Cardiopulmonary bypass use at NP	1.17	0.64-2.13	.611
Dominant ventricle morphology			
Left (reference)	–	–	–
Right	1.28	0.68-2.39	.442
Both	1.42	0.42-4.75	.573
Unplanned cardiac reoperation	2.08	0.99-4.37	.052
Prolonged ICU stay (> 30 days)	2.50	1.40-4.47	<.001
Postoperative ICU length of stay, *per 1 day increase*	1.02	1.01-1.02	<.001
Duration of ventilation, *per 1 day increase*	1.03	1.01-1.05	.008

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenator; ICU, intensive care unit; ISM, interstage mortality; NP, neonatal palliation; SV, single ventricle.

was actually associated with higher ISM (21% vs 9%), highlighting the significant effect of residual lesions on both hospital and late survival.

Finally, we found that prolonged recovery following NP is a marker for increased ISM. Patients who suffered from ISM in our series had longer mechanical ventilation and ICU and hospital stay compared to those who properly progressed to receive the subsequent Glenn. Patients who had prolonged ICU stay >30 days were more likely to have ISM (18% vs 8%). Those patients likely have several persisting organ dysfunctions involving the heart (myocardium, valves, or residual lesions) and other organs (neurologic, pulmonary, renal, gastrointestinal, or metabolic) that likely contribute to their higher ISM.[33,34] Therefore, prolonged recovery following NP should be considered an indicator for ongoing risk of attrition and efforts should be made to identify and aggressively treat any correctable cardiac and extracardiac lesion in an effort to improve those patients' outlook.

Our outpatient management protocol has been modified focusing on increased patient education, frequent cardiology visits close to home, scheduled diagnostic tests, and low threshold to admit back to the hospital. Recognizing the ongoing challenges of persistent ISM following NP, several groups have adopted various management protocols for the management of SV patients following NP that ranged from continuous hospital admission until the Glenn bidirectional cavopulmonary connection to intensive home monitoring protocols that rely on daily monitoring of several physiologic variables such as weight and oxygen saturation with home monitors in an effort to early identify life-threatening anatomic lesions and illnesses and permit timely admission and intervention that might ultimately improve survival.[35–38] We selectively use those two approaches in some of our patients, although the majority of our patients currently undergo the outpatient management protocol outlined above. Given that our outpatient management protocol is continuously evolving, and given the great variations among those patients, we were not in a position in the current study to demonstrate a statistically significant improvement in ISM as a result of those management changes. Nonetheless, we feel that our current ISM subsequent to this study period has decreased, underscoring the important role for outpatient management in improving those critical patients' outcomes and the need to individualize outpatient management to specific patient's social and clinical needs, taking into consideration all the associated risk factors affecting ISM.

Declaration of Conflicting Interests

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