Maximizing Survival Through the Staged Surgical Management of Hypoplastic Left Heart Syndrome and its Related Malformations

By

James M. Meza, M.D.

A thesis submitted in conformity with the requirements for the degree of Master of Science (M.Sc.)
Institute of Medical Science
University of Toronto

© Copyright by James M. Meza, M.D.; 2017
Maximizing Survival Through the Staged Surgical Management of Hypoplastic Left Heart Syndrome and its Related Malformations

James M. Meza, M.D.

Master of Science (M.Sc.)
Institute of Medical Science
University of Toronto
2017

Abstract

Objective: Mortality during 3-stage single ventricle palliation is much greater before vs. after stage-2-palliation (S2P). We investigated how the timing of S2P and post-Norwood events affect survival.

Methods: The optimal timing of S2P was determined with conditional survival analysis. Post-Norwood events and measures, as time-varying covariates (TVC), were used to generate dynamic, patient-level risk profiles.

Results: In low/intermediate-risk infants, performing S2P at ≥3 months old was associated with 89±3% and 82±3% 2-year survival, respectively. In high-risk infants, 2-year survival was ≤63±5% when S2P was performed at ≤6 months old. When accounting for post-Norwood events, weights, and SaO₂, TVCs displaced baseline and operative characteristics. Because risk factors occurred over time, an infant’s mortality risk varied.

Conclusion: S2P should be performed after age 3 months for low/intermediate-risk infants. High-risk infants are unlikely to complete three-stage palliation. By visually depicting risk trajectories, dynamic risk profiles may aid in planning S2P or other interventions.
Acknowledgments

I will always consider my two years as the John W. Kirklin/David Ashburn Fellow as a true privilege. The opportunity to come to the historic Hospital for Sick Children and spend two years learning state-of-the-art research methods from surgical, medical, and analytic leaders in the field has been a career- and life-changing experience for me. The studies that I have undertaken have enabled me to gain insight into complex clinical problems in congenital heart surgery, meet surgeons from across the world, and present these studies at meetings across North America and the world. The skills and insights I have gained over the last two years have changed how I understand outcomes and risk in surgery, which will undoubtedly strengthen my clinical skills as well. I have also truly appreciated that the Congenital Heart Surgeons’ Society Data Center has a palpable mission toward improving the care of children born with congenital heart disease and it has not shied away from performing complex analysis to answer the field’s toughest questions. It is remarkable to me the Society values the potential of a surgical resident who is still half a decade away from a congenital heart surgery fellowship to invest in my education and career through the research training, presentations at national and international meetings, and the opportunity to publish high impact manuscripts.

I must first thank Dr. Brian McCrindle, to whose incomparable mentorship I owe much of my success during the Fellowship. I am grateful for your direct answers to any and all of my questions and your support as I learned to navigate multi-institutional research. It has been a true pleasure work with you.

I also thank my Master’s thesis committee members, including Dr. Chris Caldarone, Dr. Mike Seed, and Dr. Alex Floh for their guidance, their challenges, and investment in my research career.

The time I spent with Dr. Eugene Blackstone and his group at the Cleveland Clinic’s Heart and Vascular Institute was a highlight of my two years as the Fellow. I hope to uphold Dr. Blackstone’s rigor and high standards for research as I continue to develop my academic career. Dr. Blackstone’s dedication to the CHSS and unfailing attendance at the Work Weekends is inspiring. I especially thank Ashley Lowry and Lucy Thuita in Cleveland for their patience and willingness to teach me several techniques that made this manuscript possible.

I’m grateful for Dr William G. Williams and Dr. Bill DeCampli’s leadership of the CHSS Data Center and willingness to always put me in a position to succeed. I’m especially thankful for the
patience and willingness Dr. Williams showed me week after week to discuss study results and ensure that I understood the nuances of the surgical questions and implications of my findings.

The surgeons in the Division of Cardiovascular Surgery at Sick Kids deserve special gratitude from me. The opportunity to attend multi-disciplinary rounds here was a great real-world learning experience that provided context for my research efforts. I’ve truly enjoyed working on various projects with Drs. Chris Caldarone, Glen Van Arsdell, Ed Hickey, Osami Honjo, and Christoph Haller.

From my home program at Duke University Hospital, no one has provided me more guidance and is more responsible for my success here at the K/A Fellow thank Dr. Jake Jaquiss. As my mentor since my intern year, he has consistently challenged me to live up to goal of becoming an academic congenital heart surgeon and has given me invaluable advice over the last five years. He has been an excellent role model as a surgeon, mentor, and investigator.

I’m also grateful to many other surgeons and mentors at Duke. Drs. Allan Kirk and Peter Smith were immediately supportive of my plan to add an additional research year to pursue the K/A fellowship. I thank Dr. Matt Roe at the Duke Clinical Research Institute’s for his support and willingness for me to remain engaged with DCRI fellowship. I finally thank two specific Duke mentors in cardiothoracic surgery, Drs. Betty Tong and Mani Daneshmand, for their support of my career.

The dedication and investment of the CHSS membership in the success of the K/A Fellowship is remarkable, through Work Weekend attendance, abstract and manuscript revision, conference calls, and more. While I have had the privilege of meeting and collaborating with many members, I’m especially grateful to Drs. David Overman, Tara Karamlou, Rick Kim, Jim Kirklin, and Kristine Guleserian for their willingness to help me, frequent feedback, and career guidance.

I have respect and gratitude for the Data Center staff, who are dedicated to the CHSS’ research mission and do so much work to allow me as the Fellow to focus on analysis and productivity. My sincerest thanks to Brenda Chow, Kathryn Coulter, Annette Flynn, Kristina Kovach, Susan MacIntyre, an Arti Singh. I am especially grateful to Sally Cai, for her patience, willingness to teach, and dedication to always finding a way to performing an analysis.

My family, including my mother, father, and brother deserve special mention. They have supported and encouraged my dreams of pursuing a surgical career as long as I can remember.
Their advice and values they instilled continue to shape me as a man and as a surgeon. I will always remember and appreciate the Friday night chats with my brother Jonathan, which were enjoyable and helpful for getting through some long weeks.

Finally and most importantly, I have the sincerest gratitude, respect, and affection for my fiancée, Karina Jordan. She has been unfailingly supportive of me during my two years away from Durham at the Data Center. During this time, I appreciate that we have been able to grow together, travel together, and ultimately decide to spend our lives together.
Contributions

This study was adapted from an upcoming publication in the *Annals of Thoracic Surgery* entitled “The Optimal Timing of Stage-2-Palliation after the Norwood Operation” by Meza et al. 2017. A further abstract and manuscript will be submitted based on this work, concurrent with submission of this thesis.

The author performed all aspects of study design, data analysis, interpretation of results, and manuscript production, with the formal input of the following:

**Brian W. McCrindle, MD, MPH;** Division of Pediatric Cardiology, The Hospital for Sick Children, Toronto, ON, CA: Guidance with study design, analytic approach, interpretation of results, and review of manuscript.

**Christopher A. Caldarone, MD;** Division of Cardiovascular Surgery, The Hospital for Sick Children, Toronto, ON, CA: Guidance with study design, analytic approach, interpretation of results, and review of manuscript.

**Michael Seed, MD;** Division of Cardiology, The Hospital for Sick Children, Toronto, ON, CA: Guidance with interpretation of results and review of manuscript.

**Alejandro Floh, MD;** Division of Critical Care, The Hospital for Sick Children, Toronto, ON, CA: Guidance with interpretation of results and review of manuscript.

**Kristina Kovach, BScN, RN;** Clinical Research Nurse Coordinator, CHSS Data Center, The Hospital for Sick Children, Toronto, ON, CA: Data extraction
# Table of Contents

Acknowledgments .................................................................................................................. iii

Contributions .......................................................................................................................... vi

Table of Contents ................................................................................................................... vii

Abbreviations ........................................................................................................................ xii

List of Tables .......................................................................................................................... xiv

List of Figures .......................................................................................................................... xvi

List of Appendices .................................................................................................................. xix

Chapter 1 Background ............................................................................................................ 1

1.1 Despite 35 years of progress, significant challenges remain ............................................. 1

1.2 HLHS – definition, anatomy, and history ............................................................................ 1

1.3 Pathophysiology ............................................................................................................... 3

1.4 Epidemiology and etiology ............................................................................................... 4

1.5 Presentation and diagnosis ............................................................................................... 4

1.6 Natural history .................................................................................................................. 5

1.7 Management ..................................................................................................................... 6

1.7.1 Comfort care ................................................................................................................. 7

1.7.2 Termination of pregnancy ............................................................................................. 7

1.7.3 Fetal intervention .......................................................................................................... 7

1.7.4 Biventricular repair ....................................................................................................... 8

1.7.5 Heart transplantation ..................................................................................................... 8

1.7.6 Hybrid stage 1 palliation ............................................................................................... 9

1.7.7 Three-stage single ventricle palliation .......................................................................... 10

1.8 Predicting risk after the Norwood operation ..................................................................... 21

1.8.1 Risk stratification of the Norwood operation relative to other congenital cardiac operations ................................................................................................................................. 21
1.8.2 Risk models and predictions for outcomes after the Norwood operation......21
1.8.3 Real time risk assessment following a diagnosis or operation.................22
1.9 The role of the CHSS in congenital heart surgery outcomes research ...........23
1.10 Post-Norwood attrition remains substantial...............................................24

Chapter 2 Research Aims ..................................................................................25

2.1 Challenges in the analysis of the timing of S2P ........................................25
2.2 Dynamic risk assessment during the post-Norwood period may enable data-driven
decision-making.................................................................26
2.3 The CHSS Critical LVOTO Inception Cohort..............................................27
2.4 Aims and Hypotheses ...............................................................................28

Chapter 3 Methods ..........................................................................................29

3.1 Study population........................................................................................29
3.2 Data acquisition...........................................................................................30
3.3 Follow-up .................................................................................................31

3.4 Statistical Analysis......................................................................................31
    3.4.1 Variable preparation ...........................................................................31
    3.4.2 Missing data ......................................................................................32
    3.4.3 Endpoints ...........................................................................................32

3.5 Survival analysis........................................................................................32
    3.5.1 Multiphase parametric risk hazard analysis – background and rationale ......32
    3.5.2 Multivariable risk hazard analysis ......................................................37
    3.5.3 Institutional adjustment ..................................................................38
    3.5.4 Prediction and graphing ...................................................................38
    3.5.5 Risk stratification ............................................................................39

3.6 Analyzing the timing of surgery.................................................................39
3.6.1 Non-parametric conditional survival analysis ........................................39
3.6.2 Parametric conditional survival analysis ..........................................40
3.7 The incorporation of post-operative longitudinal measurements and events into a risk hazard analysis ...................................................................................... 42
  3.7.1 Defining longitudinal data .....................................................................42
  3.7.2 Understanding longitudinal data – mixed effects modeling ...............42
  3.7.3 Defining a time-varying covariate ......................................................44
  3.7.4 Data structure in “typical” analyses vs. those incorporating time-varying covariates .............................................................. 45
  3.7.5 Incorporating time-varying covariates in risk hazard analysis ..........46
  3.7.6 Calculating mortality scores and plotting dynamic risk profiles .......52

Chapter 4 Results ........................................................................................................ 53

  4.1 Baseline pre-operative and echocardiographic characteristics ............53
  4.2 Norwood operative characteristics .......................................................54
  4.3 Outcomes and risk factors after the Norwood operation ....................55
  4.4 Characteristics of the post-Norwood period .......................................57
  4.5 S2P operative characteristics ...............................................................60
  4.6 Outcomes and risk factors for death after S2P ....................................61
  4.7 Conditional survival through the first two stages of single ventricle palliation ....64
  4.8 Risk stratification ....................................................................................66
  4.9 Optimal timing of S2P across risk groups ............................................68
  4.10 Optimal timing of S2P in the presence of specific risk factors ...........73
  4.11 Developing a model for post-Norwood surveillance .........................75
    4.11.1 Longitudinal measures of weight and oxygen after the Norwood operation .75
    4.11.2 Time-related events after the Norwood operation ..........................78
    4.11.3 Outcomes and model for death after Norwood, incorporating time-related events and measures .......................................................... 80
4.11.4 Dynamic risk profiles – overall results ................................................................. 81
4.11.5 Dynamic risk profiles – qualitative assessment .................................................... 83
4.11.6 Risk scores may increase or decrease ................................................................. 83
4.11.7 The effect of time on the magnitude of risk factor effect .................................... 84
4.11.8 The accumulation of multiple risk factors ......................................................... 86

Chapter 5 Discussion ........................................................................................................ 88

5.1 Age at S2P is independently associated with death ..................................................... 88
5.2 Previous analyses of timing fail to account for pre-S2P attrition ............................... 89
5.3 The advantages of parametric conditional survival analysis ........................................ 90
5.4 Accounting for intentionality ...................................................................................... 91
5.5 Optimal timing in low- and intermediate-risk infants ............................................... 91
5.6 The potential benefits of prompt progression to S2P ................................................ 92
5.7 The effect of high-risk features on the timing of S2P ................................................ 93
5.8 Gaining insight into risk over time after the Norwood operation ................................. 95
5.9 Time-varying covariates predominate over baseline characteristics in the risk model ......................................................................................................................... 96
5.10 Novel associations identified when accounting for longitudinal measures and complications .................................................................................................................. 96
5.11 Clinical applications ................................................................................................. 97
5.12 Comparison to other risk scores ............................................................................... 99
5.13 Limitations .................................................................................................................. 100
  5.13.1 Selection bias and non-random patient selection ............................................... 100
  5.13.2 Incomplete risk adjustment and the limits of submitted documentation .......... 101
  5.13.3 Era and institutional effects .................................................................................. 102
  5.13.4 CHSS Critical LVOTO cohort inclusion criteria ............................................... 102
  5.13.5 Surrogate variables ............................................................................................... 102
5.13.6 The risk of death immediately following the Norwood operation is non-zero .................................................................................................................. 103

5.13.7 Memory in dynamic risk profile methodology ........................................ 103

5.14 Conclusions .................................................................................................. 104

Chapter 6 Synthesis – Embracing Complexity ......................................................... 105

6.1 Context within the current of state of outcomes research ............................... 105

6.1.1 Complex clinical questions require embracing complex methodology and nuanced results .............................................................................................................................. 105

6.1.2 The evolution of clinical research with data science – “Big data” and “precision medicine” .............................................................................................................................. 106

6.2 Future directions ............................................................................................. 106

6.2.1 Methodologic extension - multi-state modeling ........................................ 106

6.2.2 Clinical extension – validation and evaluation of dynamic profiles as clinical decision aid .............................................................................................................................. 107

6.2.3 Integration into clinical practice ................................................................. 107

6.2.4 Evaluation .................................................................................................... 108

6.3 Summary ........................................................................................................ 108

References ............................................................................................................ 110

Appendices ........................................................................................................... 126

Copyright Acknowledgements ............................................................................... 132
Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation
AVVR: Atrioventricular valve regurgitation
BSI: Bloodstream infection
CHSS: Congenital Heart Surgeons’ Society
CPAP: Continuous positive airway pressure
EACTS: European Association of Cardiothoracic Surgery
ECC: Extracardiac conduit
ECMO: Extracorporeal membrane oxygenation
FAV: Fetal aortic valvuloplasty
HLHS: Hypoplastic left heart syndrome
ICH: Intracranial hemorrhage
LV: Left ventricle/Left ventricular
LVOTO: Left ventricular outflow tract obstruction
NEC: Necrotizing enterocolitis
MBTS: Modified Blalock-Taussig shunt
MCS: Mechanical circulatory support
NPC-QIC: National Pediatric Cardiology Quality Improvement Collaborative
PA: Pulmonary artery
PDA: Patent ductus arteriosus
PHN: Pediatric Heart Network
PLE: Protein-losing enteropathy
RV: Right ventricle/right ventricular
RVPA: Right-ventricle-to-pulmonary-artery
SaO₂: Arterial oxygen saturation
S2P: Stage-2-palliation
STS: Society of Thoracic Surgeons
SVR: Single Ventricle Reconstruction
T3: Tracking, Trajectory, and Triggering
TVC: Time-varying covariate
WAZ: Weight-for-age z-core
List of Tables

Please note that page numbers are indicated in parentheses following the table title

Chapter 1:
None

Chapter 2:
None

Chapter 3:
None

Chapter 4:
Table 1: Baseline pre-operative and echocardiographic characteristics (53)
Table 2: Norwood operative characteristics (55)
Table 3: Risk factors for death after the Norwood operation (57)
Table 4: Characteristics of the post-Norwood period (58)
Table 5: Interval catheter-based and operative re-interventions on the heart and great vessels during the post-Norwood period (59)
Table 6: Stage-2-palliation operative characteristics (60)
Table 7: Risk factors for death after stage-2-palliation (63)
Table 8: Characteristics of patients undergoing stage-2-palliation by risk group (67)
Table 9: Time-related events after the Norwood operation (79)

Table 10: Risk factors for death after the Norwood operation, incorporating time-related post Norwood measures and events (81)

Table 11: Risk scores on the day of reaching final end state (81)

Chapter 5:

None
List of Figures

Please note that page numbers are indicated in parentheses following the figured title

Chapter 1

Figure 1: The anatomic features of hypoplastic left heart syndrome (2)

Figure 2: The natural history of hypoplastic left heart syndrome (6)

Figure 3: The Norwood operation, surgical anatomy (11)

Figure 4: Stage-2-palliation, surgical anatomy (15)

Figure 5: The timing of stage-2-pallation is a complex decision (18)

Figure 6: The Fontan operation, surgical anatomy (19)

Figure 7: Kaplan-Meier curve for overall survival through single ventricle palliation in patients with hypoplastic left heart syndrome (20)

Figure 8: Daily APACHE-III scores during the first week of ICU admission for two individual patients (22)

Chapter 2

None

Chapter 3

Figure 9: The CHSS Critical LVOTO prospective inception cohort and study population (30)

Figure 10: The relationship between the survival function, hazard function, and cumulative hazard (33)

Figure 11: The decomposition of the hazard function into three phases of risk (35)
Figure 12: Survival analyses (36)

Figure 13: Non-parametric conditional survival curves based on Kaplan-Meier methodology (40)

Figure 14: Parametric conditional survival analysis (41)

Figure 15: Analyzing longitudinal data with mixed effects modeling (43)

Figure 16: The temporal distribution of baseline vs. time-varying covariates (44)

Figure 17: The data set structure with time-related events (45)

Figure 18: Time-varying covariates affect the risk of death after they occur (47)

Figure 19: Segmenting the overall interval under study based upon the occurrence of time-varying covariates (48)

Figure 20: Censoring in survival analysis (50)

Figure 21: Multivariable risk hazard analysis with both baseline and time-varying covariates (51)

Figure 22: Survival and mortality scores (52)

Chapter 4

Figure 23: Outcomes in infants who underwent an initial Norwood operation (56)

Figure 24: Survival after the Norwood operation (56)

Figure 25: Outcomes after stage-2-palliation (61)

Figure 26: The distribution of age at stage-2-palliation (S2P), by mortality status after S2P (62)

Figure 27: Survival after stage-2-palliation (63)

Figure 28: Conditional and non-conditional estimates of survival at two years post-Norwood (64)

Figure 29: The distribution of age at stage-2-palliation (S2P) across risk groups for S2P (67)

Figure 30: The optimal timing of stage-2-palliation in low- and intermediate-risk patients (69)
Figure 31: The optimal timing of stage-2-palliation in high-risk infants (72)

Figure 32: The optimal timing of Stage-2-palliation in patients with specific risk factors (73)

Figure 33: Weight over time after the Norwood operation (76)

Figure 34: Weight-for-age z-scores over time after the Norwood operation (77)

Figure 35: Oxygen saturation (SaO₂) over time after the Norwood operation (78)

Figure 36: Dynamic risk profiles for 360 infants who underwent a Norwood operation (82)

Figure 37: Individual dynamic risk profile for an infant who survived to undergo Stage-2-Palliation 6.6 months post-Norwood (84)

Figure 38: Individual dynamic risk profile for an infant who died 4.7 months post-Norwood (85)

Figure 39: Individual dynamic risk profile for an infant who underwent a heart transplantation 7.1 months post-Norwood and is alive at last follow-up, 7 years later (86)

Chapter 5

Figure 40: Algorithm for the incorporation of the dynamic risk profiles into the management of infants during the post-Norwood period (99)
List of Appendices

Appendix Table 1: Cohort enrollment by institution

Appendix Table 2: Diagnostic criteria for the time-related events and complications after the Norwood operation

Appendix table 3: Indications for stage-2-palliation
Chapter 1
Background

1.1 Despite 35 years of progress, significant challenges remain

The nearly 35 years since the first publication of a palliative procedure for hypoplastic left heart syndrome (HLHS) and its related malformations by Norwood and colleagues have produced tremendous advances in the outcomes of children born with congenital heart disease (Norwood, Lang et al. 1983). Although no longer uniformly fatal during the first weeks of life, the mortality and morbidity rates for the staged surgical management of these lesions are still among the highest in congenital heart surgery and are among the costliest of congenital defects cared for the United States ((CDC) 2003; Jacobs, Jacobs et al. 2012). Although it has been investigated in randomized controlled trials such as the Pediatric Heart Network’s (PHN) Single Ventricle Reconstruction (SVR) Trial, registries such as the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC), and countless single institution studies, substantial questions remain unanswered and many opportunities exist to further improve survival and functional outcomes.

1.2 HLHS – definition, anatomy, and history

HLHS and its related malformations represent a wide spectrum of anatomic defects of the left heart structures that are united by a common pathophysiology – the left heart’s inability to sustain the systemic circulation. HLHS itself is characterized by the underdevelopment, or hypoplasia, of the left heart structures, which can include the left atrium, mitral valve, left ventricle, left ventricular outflow tract, aortic valve, and/or the aorta (Figure 1) (Kouchoukos 2013). The left ventricular myocardium may itself be abnormal, though this is not consistently found. Endocardial fibroelastosis, a fibrotic defect of the endocardium resulting in diastolic ventricular dysfunction, represents another possible severe defect (Lurie 2010).

HLHS is most commonly conceptualized in terms of aortic and/or mitral valvar pathology. The valves can be either stenotic, in which the valve orifice is abnormally narrowed often due to dysfunctional leaflets that do not open normally, or atretic, in which no antegrade blood flow is seen across the valve. Related malformations can include ductal-dependent forms of isolated
critical aortic stenosis, isolated aortic valvar atresia, or “hypoplastic left heart complex” (in which anatomically normal left heart structures are abnormally small such that systemic perfusion is compromised), and others (Tchervenkov, Jacobs et al. 2000).

Figure 1: The anatomic features of hypoplastic left heart syndrome. Infants born with hypoplastic left heart syndrome may demonstrate underdevelopment of any left-sided cardiac structures, from the left atrium to the aorta. In this example, the left ventricle is severely hypoplastic. Systemic perfusion is provided by right-to-left shunting of blood at the patent ductus arteriosus. A left-to-right shunt via an atrial septal defect is necessary for oxygenated blood
returning to the heart via the pulmonary veins can reach the right heart. Reproduced from https://www.cdc.gov/ncbddd/heartdefects/hlhs.html, from the public domain.

Additional cardiac lesions are not common with HLHS, occurring in less than 10% of cases. Possible associated lesions can include an intact atrial septum, anomalous pulmonary venous return, atrial isomerism, interrupted aortic arch, transposition of the great arteries, and atrioventricular septal defect (Rasiah, Ewer et al. 2008). Coronary arterial anomalies, namely connections between ventricular myocardial sinusoids and coronary arteries, can be seen in up to 50% patients with the aortic atresia/mitral stenosis variant (Sauer, Gittenberger-de Groot et al. 1989; Glatz, Fedderly et al. 2008). Non-cardiac anomalies are seen in 28-40% of patients, with central nervous defects among the most common (Galindo, Nieto et al. 2009).

Despite the relatively recent development of management strategies for HLHS and its related malformations, they have been recognized in post-mortem specimens for over 160 years. Canton published the first report of aortic atresia in 1850 (Canton 1850). One hundred years later, the co-occurrence of multiple hypoplastic left heart structures was recognized (Lev 1952). The terminology “hypoplastic left heart syndrome” was first introduced in 1958 by Noonan and Nadas to describe this complex constellation of congenital lesions (Noonan and Nadas 1958).

1.3 Pathophysiology

The anatomic defects of HLHS and its related malformations, namely left ventricular hypoplasia, result in a common pathophysiology in which the left heart is unable to support systemic perfusion. Post-natally, the neonate has “ductal-dependent” systemic circulation, in which the systemic circulation is dependent upon retrograde blood flow from the right ventricle, through the patent ductus arteriosus (PDA), to supply the systemic circulation (Figure 2). The neonate is dependent on this right-to-left shunt, as the normal post-natal closure of the PDA can lead to critical illness, cardiovascular collapse, and death. The prompt initiation of a prostaglandin infusion after birth to maintain ductal patency is essential. The neonate is also dependent upon a second shunt, a left-to-right shunt at the atrial septum, in order for oxygenated blood from the lungs to reach the right ventricle. Patients born with an intact atrial septum often present in extremis due to oxygenation and ventilation failure and require the emergent creation of an atrial-level communication. The initiation of extracorporeal membrane oxygenation (ECMO), for
hemodynamic stabilization and oxygenation, may also be necessary. Mortality in this patient population is high, often near 50% or greater (Rychik, Rome et al. 1999; Vlahos, Lock et al. 2004).

1.4 Epidemiology and etiology

HLHS occurs in approximately 1 in every 4,344 live births in the United States ((CDC) 2016). It represents 2-3% of all congenital heart disease diagnoses and is more often diagnosed in males (Egbe, Uppu et al. 2014). There are no recognized associations with race, ethnicity, geography, seasonality, or several maternal factors such as age, exposures, or parity (Morris, Outcalt et al. 1990; Tikkanen and Heinonen 1994).

The etiology of HLHS is likely multifactorial and is poorly understood. Genetic studies have demonstrated complex associations, specifically with the NKX2.5, NOTCH1, ERBB4, and HAND1 genes. A variety of chromosomal abnormalities have been reported as well, with Jacobsen’s syndrome, a chromosome 11q deletion, being most common (Grossfeld, Mattina et al. 2004; Benson, Martin et al. 2016). During fetal development, blood flow through the cardiac structures is likely critical for proper development. Defects resulting in aortic or mitral valvar stenosis or atresia can limit blood flow across the left heart structures and may limit their development. Animal studies have demonstrated that diminished cardiac blood flow can result in hypoplastic cardiac structures (Sedmera, Hu et al. 2002; Hove, Koster et al. 2003). In an observational study of fetuses diagnosed with aortic valve stenosis, left heart structure growth was severely limited in patients who ultimately were diagnosed with HLHS (Makikallio, McElhinney et al. 2006).

1.5 Presentation and diagnosis

Most infants are diagnosed with HLHS and its related malformations prenatally during the 20-week screening ultrasound. By 20 weeks, the left ventricular hypoplasia can be seen with little difficulty on the four-chamber view. A recent study of the Society of Thoracic Surgeons’ (STS) congenital heart surgery database demonstrated that 67% of cases were detected prenatally, the highest rate of any diagnosis of congenital heart disease. However, substantial geographic variation in the rate of prenatal diagnosis was noted as well (Quartermain, Pasquali et al. 2015).
Diagnosis during pregnancy has many advantages, including allowing time for in-depth counseling of the parents and for arranging delivery at a tertiary or quaternary care institution with expertise in the management of these patients. Prenatal diagnosis is also associated with the presence of fewer preoperative risk factors, though its effect on outcomes is not yet understood (Quartermain, Hill et al. 2016).

An infant who was not diagnosed prenatally will likely not present clinically until the PDA closes, 24 hours to a few days after birth. As the PDA begins to close, the infant can develop signs of congestive heart failure, progressive cyanosis, and feeding intolerance. The infant may even progress to shock and cardiovascular collapse without stabilization. An infant presenting emergently and without a prenatal diagnosis is a much more complex scenario and a wider differential diagnosis must be considered.

1.6 Natural history

HLHS and its related malformations are nearly uniformly fatal without intervention within the first month of life. In a multi-institutional study of patients with aortic atresia, 253 patients underwent single ventricle palliation, 49 underwent heart transplantation, and 21 patients initially did not undergo surgical treatment. By one month following study enrollment, 18/21 (86%) of those who did not undergo any intervention had died. The three survivors crossed over into the group of patients being treated surgically (Figure 2) (Jacobs, Blackstone et al. 1998). In addition, 25% of neonatal deaths in the first week of life were due to a cardiac cause and 15% in the first month were attributable to HLHS (Talner 1998; Reller, Strickland et al. 2008; Fixler, Nembhard et al. 2010).
Figure 2: The natural history of hypoplastic left heart syndrome and its related malformations. Among 21 patients who were not treated surgically (“No Treatment Protocol”), mortality within the first month was extremely high. The three survivors all crossed over into surgical treatment groups. The solid lines represent parametric estimates for survival while the dashed lines represent their 70% confidence limits. The symbols (boxes, circles, and triangles) represent deaths, while the vertical error bars enclose one standard error. Reproduced with permission from (Jacobs, Blackstone et al. 1998). Copyright Elsevier, Inc.

1.7 Management

The management of HLHS and its related malformations has evolved a great deal since the early 1980’s. Currently, three-stage single ventricle palliation, which results in univentricular circulation with the right ventricle providing systemic blood flow and the vena cavae supplying the lungs, is the primary management strategy. However, several alternative methods of
management exist as well and will be briefly reviewed prior to an in depth discussion of single ventricle palliation.

1.7.1 Comfort care

Prior to introduction of the Norwood operation, only comfort care was available. In the modern era, physician respondents to a 2007 survey of 52 centers regarding the management of HLHS indicated that while single ventricle palliation was most often recommended in discussions with the parents, comfort care was also commonly discussed (Wernovsky, Ghanayem et al. 2007). Because of the improvements in the outcomes in single ventricle palliation, offering comfort care has become ethically controversial. Recommendations from both physicians and bioethicists maintain that comfort care should remain an available option, given the long-term neurodevelopmental challenges faced by children after single ventricle palliation (Paris, Moore et al. 2012; Paul, Orfali et al. 2016).

1.7.2 Termination of pregnancy

If HLHS or its related malformations are diagnosed in utero, detailed discussions can be held with the parents regarding the mortality and non-mortality outcomes. Given the significant burdens associated with an infant with HLHS, the elective termination of pregnancy is often presented as a management option, obviating the need to choose between comfort care vs. complex surgical management, with its accompanying risks of morbidity and mortality (Walsh, Verghese et al. 2017). Termination of pregnancy does appear to occur more frequently in pregnancies diagnosed with HLHS vs. other complex congenital cardiac defects, 63% vs. 0-42%, respectively (Khoshnood, De Vigan et al. 2005). The overall rates of termination following fetal diagnosis vary widely across institutions, regions, and countries (Khoshnood, De Vigan et al. 2005; Galindo, Nieto et al. 2009; Beroukhim, Gauvreau et al. 2015).

1.7.3 Fetal intervention

The relief of obstruction to blood flow in utero may enable for the growth of left heart structures, prevent progression to HLHS, and thereby allow for biventricular circulation. Fetal aortic valvuloplasty (FAV) has been studied in patients diagnosed with critical aortic stenosis in utero.
In a single center study of 88 live births who underwent (FAV), biventricular repair was performed in 43% and left heart structures had grown. While early and intermediate survival were greater in that group vs. those who were managed with single ventricle palliation, there was no difference in survival by seven years of age (McElhinney, Marshall et al. 2009). In the European experience with 60 live-born infants who underwent FAV, there was no difference in left heart structure sizes and no difference in mortality observed at four years in infants who underwent FAV vs. those who did not (Gardiner, Kovacevic et al. 2016). Further discussion of this strategy is beyond the scope of this work.

1.7.4 Biventricular repair

In infants with HLHS with a borderline left ventricular size, biventricular repair may be possible. Efforts at “staged ventricular recruitment,” including endocardial fibroelastosis resection with the relief of left ventricular outflow obstruction, have been shown to increase left ventricular dimensions. Some patients have even developed sufficient left ventricular mass to allow for biventricular circulation (Emani, Bacha et al. 2009; Emani, McElhinney et al. 2012). However, the experience with this technique is limited and adverse events, including death, need for heart transplantation, or conversion from biventricular circulation to single ventricle palliation, is not uncommon (Herrin, Zurakowski et al. 2017). While these studies are limited given their lack of controls, further discussion of this strategy is beyond the scope of this work.

1.7.5 Heart transplantation

At the same time as the development of single ventricle palliation, neonatal heart transplantation was developed and implemented for HLHS. Dr. Leonard Bailey of Loma Linda, CA developed an animal model and successfully applied it as single stage, definitive palliation in 1985 (Bailey 1985). Although it results in biventricular circulation, heart transplantation carries with it the risks of long-term immunosuppression (infectious complications, the development of malignancies), rejection, and the eventual need for re-transplantation due to chronic transplant allograft coronary vasculopathy. The Loma Linda group reported the largest experience, with a 14% operative mortality (Razzouk, Chinnock et al. 1996). Waitlist mortality was, as it remains today, a major limitation to this approach, as waitlist mortality in infants continues to be the highest of any age group at 17% (Almond, Thiagarajan et al. 2009). Because of the improvements in
survival, primary heart transplantation is infrequently offered in the contemporary era (Wernovsky, Ghanayem et al. 2007).

In the current era, heart transplantation is most often performed as a salvage operation for patients who have developed complications that preclude continuing with the single ventricle palliation pathway, such as severe, irreversible RV dysfunction. Survival after transplantation is lower in pediatric patients with congenital heart disease compared to other indications (Dipchand, Rossano et al. 2015). Mortality in infants listed for salvage transplantation following the Norwood ranges from 20-50%. This mortality rate is primarily driven by mortality while on the waitlist (Alsoufi, Mahle et al. 2016; Kulkarni, Neugebauer et al. 2016).

1.7.6 Hybrid stage 1 palliation

Hybrid Stage 1 palliation (Hybrid) represents the final additional management strategy for discussion. While not a distinct alternative to single ventricle palliation, the Hybrid can be utilized in addition to or instead of the traditional Norwood operation. It can also bridge an unstable neonate to a decision regarding treatment or to salvage heart transplantation. Because of its technical complexity and need for cardiopulmonary bypass and deep hypothermic circulatory arrest, the Norwood operation places an enormous physiologic stress on an infant. The objective of the Hybrid procedure is to defer these substantial physiologic insults past the neonatal period. It involves the use of cardiac catheterization and conventional surgery. The goals of the operation are identical to the conventional Norwood operation. In the cardiac catheterization lab, a stent is placed in the PDA to provide unobstructed systemic blood flow and a balloon atrial septostomy is performed to ensure unobstructed flow of oxygenated blood from the left atrium to the right heart. Bilateral pulmonary arterial bands are placed in the operating room to balance pulmonary and systemic blood flow by increasing the resistance into the pulmonary circuit and redirect some blood flow into the systemic circuit. The aortic reconstruction is thus delayed until several weeks to months later, when a “comprehensive stage 2” operation is performed, with a concomitant superior cavopulmonary connection. While single center experiences from high-volume centers have shown that outcomes with the Hybrid pathway do not differ from conventional single ventricle palliation, a large, multi-institutional study from the Congenital Heart Surgeons’ Society (CHSS) showed lower survival in those treated with the Hybrid pathway vs. those treated with the Norwood with a RVPA conduit or MBTS (Galantowicz, Cheatham et al. 2008; Baba, Kotani et al. 2012; Schranz, Bauer et al. 2015; Wilder, McCrindle et al. 2017). Wilder and colleagues noted that a survival advantage
existed for patients of low birth weight treated with the Hybrid (Wilder, McCrindle et al. 2017). The Hybrid pathway is now seen a rescue therapy for patients who may be at prohibitive risk for the Norwood operation or as a bridge to heart transplantation, biventricular repair, or another decision. Further discussion of this strategy is beyond the scope of this work.

1.7.7 Three-stage single ventricle palliation

1.7.7.1 Stage 1 - The Norwood operation

The staged surgical palliation of HLHS and its related malformations was developed in the early 1980’s by Norwood and colleagues at the Children’s Hospital of Philadelphia. Several prior attempts with various surgical techniques, such as a right pulmonary artery-to-aorta anastomosis with bilateral branch pulmonary banding, were reported, with poor outcomes (Cayler, Smeloff et al. 1970). In 1983, Norwood and colleagues reported their results with a palliative operation designed to achieve three goals: 1) unimpeded flow of oxygenated blood from the left atrium to the right heart, 2) relief of left-sided outflow obstruction, and 3) balanced blood flow to the pulmonary and systemic circulations (Norwood, Lang et al. 1983). These are accomplished by the performance of: 1) a complete atrial septectomy, 2) reconstruction of the aortic arch with a patch and neo-aorta creation via anastomosis to the main pulmonary artery, and 3) placement of a shunt as a source of pulmonary blood flow following disconnection of the branch pulmonary arteries from the main pulmonary arterial trunk.

In contrast to typical biventricular, in-series circulation, parallel pulmonary and systemic circuits that are both supplied by the right ventricle are created. This aspect importantly highlights that the Norwood operation represents a palliative management strategy, given that the defects are not definitively corrected when single ventricle anatomy and physiology are created. Given the fragility of infants born with HLHS, the Norwood operation is typically performed within the first one or two weeks of life. A large single-center study has shown that delaying surgery, even during the first two weeks of life, was associated with increased risk of morbidity and increased hospital costs (Anderson, Ciarleglio et al. 2015). Notably, arterial oxygen saturation (SaO₂) values are typically 70-85% after the Norwood (Theilen and Shekerdemian 2005).

While a modified Blalock-Taussig shunt (MBTS) was originally described as the source of pulmonary blood flow, a subsequent modification introduced the use of a right-ventricle-to-pulmonary-artery (RVPA) conduit as the source of pulmonary blood flow rather than the MTS
The SVR Trial randomized patients to receive an MBTS or a RVPA conduit and demonstrated superior transplant-free survival at one year in patients with an RVPA conduit (Ohye, Sleeper et al. 2010). However, equivalent transplant-free survival at three years was seen in the two groups (Newburger, Sleeper et al. 2014). In large multi-institutional, observational, propensity-matched study by the CHSS, overall survival at six years was superior for the patients who underwent a Norwood operation with a RVPA conduit vs. a MBTS, 70% vs. 55%, respectively (Wilder, McCrindle et al. 2015). Because a ventriculotomy is required for placement of an RVPA conduit, there is concern that right ventricular (RV) dysfunction could be more prevalent in those infants with an RVPA conduit vs. a MBTS. However, Wilder and colleagues demonstrated that neither RV dysfunction nor atrioventricular valve regurgitation (AVVR) were more prevalent in patients with an RVPA conduit vs. a MBTS.

**Figure 3:** The Norwood operation, surgical anatomy. A. The Norwood operation with a modified Blalock-Taussig shunt. B. The Norwood operation with a right-ventricle-to-pulmonary-artery conduit. Reproduced with permission from (Ohye, Sleeper et al. 2010). Copyright Massachusetts Medical Society.

1.7.7.2 Mortality, morbidity, and risk factors after the Norwood operation

Given the complexity of the Norwood operation and generally high pre-operative risk status of infants born with HLHS, mortality and morbidity after the Norwood operation are high compared to the surgical treatment of other congenital heart defects. The post-operative period following
the Norwood operation represents the highest-risk period for these patients. Single institution studies demonstrate hospital mortality rates of 5-21% (Gaynor, Mahle et al. 2002; Stasik, Gelehrter et al. 2006; Sano, Huang et al. 2009). In the SVR Trial, hospital mortality was 16% (Tabbutt, Ghanayem et al. 2012). In a CHSS multicenter study of patients with aortic atresia and critical aortic stenosis enrolled from 1994-2000, mortality after the Norwood operation but before transition to another end state (inclusive of interstage mortality as well) was 37% (Ashburn, McCrindle et al. 2003).

Complications and re-interventions are common after the Norwood operation. Neurologic complications, including seizures and strokes or intracranial hemorrhages, occur in 4-20% and 5%, respectively (Clancy, Sharif et al. 2005; Gaynor, Jarvik et al. 2006; Tweddell, Ghanayem et al. 2007; Wernovsky, Ghanayem et al. 2007; Hornik, He et al. 2011). At a single center, cardiac arrest post-Norwood occurred in 6% (Hehir, Dominguez et al. 2008). In The SVR Trial, cardiopulmonary resuscitation was required for cardiac arrest in 22% (Tabbutt, Ghanayem et al. 2012). Re-intubation occurred in 13-30 % (Hehir 2008, Hornik 2011). Renal failure has been reported to occur in 8-13% post-Norwood (Tweddell, Ghanayem et al. 2007; Wernovsky, Ghanayem et al. 2007; Tabbutt, Ghanayem et al. 2012). Dialysis was required, temporarily or permanently, in 6% (Hornik, He et al. 2011). Necrotizing enterocolitis (NEC) may occur in up to 18% of patients (Jeffries, Wells et al. 2006). Infectious complications have been reported in approximately 10% of patients, with sepsis reported in 11.5%-17% (Wernovsky, Ghanayem et al. 2007; Hornik, He et al. 2011; Tabbutt, Ghanayem et al. 2012). Unplanned reoperation after the Norwood operation has been reported in 7-12% of patients (Hornik 2011, Alsoufi 2015, Sames-Dolzer 2017). Interventional cardiac catheterization procedures are common, with up to 40% of patients undergoing a catheter procedure after the Norwood at some centers (Reinhardt, De Giovanni et al. 2014).

Risk factors for death and/or other adverse outcomes after the Norwood operation have been extensively studied. Smaller ascending aorta diameter, the presence of genetic abnormalities, lower birth weight, longer duration of cardiopulmonary bypass or deep hypothermic circulatory arrest, requiring ECMO prior to the Norwood, shunt type, prematurity, obstructed pulmonary venous return, lower socioeconomic status, and more have been identified (Ashburn, McCrindle et al. 2003; McGuirk, Griselli et al. 2006; Tabbutt, Ghanayem et al. 2012; Tweddell, Sleeper et al. 2012; Alsoufi, Mori et al. 2015).
1.7.7.3 The interstage period

Following the immediate post-operative period after the Norwood operation, the “interstage” period, or the interval between an infant’s discharge from the hospital and date of Stage-2-palliation (S2P), carries the second-highest risk of mortality. In the SVR Trial, 50 deaths (12%) occurred among the 426 infants who were discharged post-Norwood (Ghanayem, Allen et al. 2012). Because the post-Norwood circulation is in-parallel, there is a constant risk of hemodynamic destabilization and interstage deaths have been noted. These deaths may occur within 24 hours of the first onset of symptoms (Tsao S 2001). Norwood circulation creates several challenges, including volume overloading the right ventricle with venous return from both the systemic and pulmonary circulations, shunt-associated risks, and exposure of the pulmonary vasculature to higher than normal pressures. These risks can lead to poor somatic growth velocity, elevated pulmonary vascular resistance or pulmonary vascular damage, and even sudden death (Vogt, Manlhiot et al. 2007). An infant with Norwood circulation cannot be immediately transitioned to S2P, as the relatively high pulmonary vascular resistance must fall to a level such that blood flow into the lungs can be primarily driven by central venous pressure.

Several strategies have been investigated to mitigate interstage attrition, including earlier S2P and home monitoring programs. The complexity of the decision of the timing of S2P will be discussed following the description of the S2P operation. Home monitoring involves providing parents with a scale and a pulse oximeter to measure weights and oxygen saturation ($\text{SaO}_2$), typically daily or weekly. The parents are instructed to contact a clinician or present to an emergency department if the weight or $\text{SaO}_2$ values are not within specified safe ranges. Interstage home monitoring was pioneered by Ghanayem and colleagues, who reported a decrease in interstage mortality to 2% during their 10-year experience with home monitoring. They also found that S2P was performed earlier when home monitoring was used (Ghanayem, Tweddell et al. 2006). The NPC-QIC study of interstage home monitoring included 50 centers and reported an 8.1% interstage mortality rate and 55% readmission rate (Oster, Ehrlich et al. 2015; Hanke, Joy et al. 2016). While they found that home monitoring was associated with increased weight gain, no association with mortality or readmission was noted (Oster, Ehrlich et al. 2015). Nonetheless, home monitoring and frequent appointments in dedicated high-risk clinics have been commonly adopted (Dobrolet, Nieves et al. 2011).
1.7.7.4 Stage-2-palliation

After the Norwood operation, S2P, or a superior cavopulmonary anastamosis, is performed and in-series circulation is restored. Following the relaxation of the pulmonary vascular resistance (PVR) during the post-Norwood period, the lungs no longer require a high-pressure, ventricular source of blood flow. In addition, it allows for the addressing of residual lesions, such as recoarctation of the aorta, which occurred in 18% of SVR Trial participants (Hill, Rhodes et al. 2013).

Infants are evaluated for candidacy for transitioning to S2P several months after the Norwood operation. Cardiac catheterization has been typically used to assess the ratio of pulmonary blood flow to systemic blood flow (Qp:Qs), pulmonary vascular resistance (PVR), pulmonary arterial sizes, and more. A single study has reported that greater survival has been seen in patients with PVR less than equal to 2 Woods units (Bridges, Jonas et al. 1990). Cardiac catheterization also allows for intervention on lesions such as a stenotic shunt, the balloon dilatation of a recoarctation of the aorta, or the coiling of collateral vessels. Magnetic resonance imaging is another viable assessment modality and can be used in place of or complementary to cardiac catheterization. It also has the added benefit of being non-invasive, when no additional interventions are anticipated (Muthurangu, Taylor et al. 2005; Brown, Gauvreau et al. 2007).

Originally, total cavopulmonary connection was performed after the Norwood operation. S2P was later introduced as an intermediate step for high-risk patients prior to total cavopulmonary connection, or Fontan completion (Bridges, Jonas et al. 1990; Pridjian, Mendelsohn et al. 1993). The addition of S2P, thus establishing three-stage single ventricle palliation, was associated with improved survival following the initial Norwood operation (Forbess, Cook et al. 1997). Currently, two types of S2P are performed, the Hemi-Fontan and the Bidirectional Glenn. Both result in the passive drainage of the superior vena cava (SVC) into the pulmonary arteries. The Hemi-Fontan involves anastomosing the right atrio caval junction to the pulmonary arteries, whereas the Bidirectional Glenn involves disconnecting the SVC from the right atrium and anastomosing it to the pulmonary arteries. The Hemi-Fontan also requires the placement of a patch in order to redirect it into the pulmonary arteries (Figure 4) (Mavroudis and Backer 2003; Stark, de Leval et al. 2006).

S2P re-establishes in-series circulation and, in doing so, decreases the volume load on the systemic right ventricle and facilitates in ventricular remodeling (Rychik, Jacobs et al. 1995;
Jacobs, Rychik et al. 1996). Also, because the MBTS or RVPA conduit is removed, venous blood from the upper body becomes the sole source of pulmonary blood flow. This reduces blood pressure in the pulmonary arteries, since they are no longer supplied directly by the systemic right ventricle, protecting them from systemic pressures and the risk of developing pulmonary vaso-occlusive disease. Following S2P, arterial oxygen saturations are typically 75-85%.

Figure 4: Stage-2-palliation, surgical anatomy. A. The Bidirectional Glenn operation, with the anastomosis of the superior vena cava to the right pulmonary artery. Note that the superior vena cava is in discontinuity with the right atrium. B. The Hemi-Fontan operation, with the anastomosis of the right atrium to the pulmonary artery. The superior vena cava remains in continuity with the right atrium. The heavy arrows in both panels represent the direction of blood flow into the pulmonary arteries, driven passively by central venous pressure. Reproduced from https://www.ctsnet.org/article/superior-cavopulmonary-anastomosis-hemi-fontan-and-bidirectional-glenn, with permission from Dr. Marshall L. Jacobs.
1.7.7.5 Outcomes and risk factors after Stage-2-palliation

Survival after S2P is considerably higher than after the Norwood operation. Over the last 15 years, mortality has ranged from 1-11% in single-center studies (Jaquiss, Ghanayem et al. 2004; Scheurer, Hill et al. 2007; Kogon, Plattner et al. 2008; Friedman, Salvin et al. 2011; Lee, Aiyagari et al. 2012; Francois, Vandekerckhove et al. 2016). In SVR Trial participants, Schwartz and colleagues reported a 4% in-hospital mortality rate (Schwartz, Lu et al. 2014). In a CHSS study of a cohort of patients undergoing single ventricle palliation for critical aortic stenosis and aortic atresia, there was a 7% overall mortality rate after S2P (Ashburn, McCrindle et al. 2003).

Risk factors for death after S2P have been more difficult to determine, given the lower mortality rate after S2P. Instead, investigators have often reported risk factors for combined end points such as death, heart transplantation, and various forms of morbidity. Single-institution studies have identified significant AVVR, RV dysfunction, higher transpulmonary gradient, lower SaO2 at surgery, lower weight at surgery, longer Norwood hospitalization, and greater number of interstage interventions as risk factors (Scheurer, Hill et al. 2007; Kogon, Plattner et al. 2008; Friedman, Salvin et al. 2011; Lee, Aiyagari et al. 2012; Francois, Vandekerckhove et al. 2016).

In the SVR trial, longer length of the Norwood hospitalization, non-elective indication for S2P, and the presence of branch PA stenosis were associated with longer hospital length of stay after S2P (Schwartz, Lu et al. 2014). In the more remote CHSS study, younger age at S2P and concomitant atrioventricular valve repair at the time of S2P were associated with death after S2P (Ashburn, McCrindle et al. 2003).

1.7.7.6 The timing of S2P is a complex decision

The clinical decision of the timing of S2P must integrate multiple interrelated factors, including growth, PVR, SaO2, ventricular function, shunt-dependent pulmonary blood flow, the need for concomitant procedures, and the patient’s overall clinical condition (e.g. if any current medical illness). Although the risk of mortality after S2P is much lower than after the Norwood, the consequences of an incorrect decision must be kept in mind. The failure of S2P, in which the cavopulmonary anastomosis must be taken down and Norwood circulation re-established, represents a dire situation. In multi-institutional studies, S2P was performed at a mean age of 5.3 ± 1.7 months and a median age of 6 months with an absolute range of 1-28 months (Ashburn, McCrindle et al. 2003; Schwartz, Lu et al. 2014).
Earlier transition to S2P offers several potential advantages, as it would reduce the time spent in the unstable parallel circulation created after the Norwood operation. In Norwood circulation, all systemic and pulmonary venous blood returns to the right atrium and thereby to the systemic right ventricle. This anatomic configuration creates a substantial volume and pressure load on the ventricle, which may adversely affect ventricular function. Earlier progression to S2P, with its creation of a superior cavopulmonary shunt would reduce the volume load on the systemic right ventricle and lead to improved myocardial performance (Jacobs, Rychik et al. 1996; Watanabe, Aoki et al. 2008). Shunt-associated risks, namely stenosis and thrombosis, represent major risks that often require re-intervention after the Norwood operation. Re-intervention to relieve shunt or conduit stenosis is not uncommon, and the outcomes following them are generally reassuring (Petit, Gillespie et al. 2006; Vaughn, Moore et al. 2015). Shunt thrombosis represents a potentially devastating complication inherent to any child with a systemic-to-pulmonary shunt. While shunt revision can be performed, the resultant cyanosis may instead prompt progression to S2P. Outcomes in those requiring emergent shunt revision for thrombosis are not encouraging (Desai, Stumper et al. 2009; Bonnet, Petit et al. 2015). Finally, the parallel Norwood circulation exposes the pulmonary arteries to elevated pressures. Progressing to S2P reduces the pressure load on the pulmonary vasculature, once central venous pressure becomes the primary driver of blood into the lungs. However, prior to S2P, the pulmonary PVR must fall to make cavopulmonary connection feasible. Earlier S2P does risk failure due to high PVR. In addition, pulmonary arterial hypoplasia may result from insufficient time for development. Both may be major problems that result in failure of the cavopulmonary shunt and a return to parallel Norwood circulation (Figure 5).

Delaying S2P may also be beneficial. It first allows for potential increased somatic growth of the infant and maturation of the pulmonary arterial tree. It also allows for more time for the PVR decrease. However, the delay does continue to expose the patient to the risks inherent to parallel Norwood circulation and the high risk of death during the interstage period (Figure 5).
Figure 5: The timing of stage-2-palliation is a complex decision. Various factors can affect the decision making regarding the timing of S2P. As depicted by the color gradient, the timing can occur along a spectrum, but also risks additional attrition during the post-Norwood period.

Abbreviations: S2P=Stage-2-palliation

The evidence exploring the timing of S2P is limited to single-institution studies that often simply stratified patients into two groups based on an arbitrary age. Jaquiss and colleagues reported that performing S2P prior to age four months was not associated with higher mortality or lower rate of achieving Fontan completion. But, they did note longer chest tube duration and increased resource utilization of the patients who underwent earlier S2P (Jaquiss, Ghanayem et al. 2004; Jaquiss, Siehr et al. 2006) (Jaquiss 2004, Jaquiss 2008). Petrucci and colleagues reported that S2P was safe to perform as soon as 2 months of age (Petrucci, Khoury et al. 2010).

1.7.7.7 Stage 3 - Fontan completion

The final stage of three-stage single ventricle palliation involves complete connection of the systemic venous circulation to the pulmonary arteries, or total cavopulmonary connection. Following the Fontan operation, all blood flow to the pulmonary arteries is supplied passively by the systemic venous circuit. This procedure was first developed by Dr. Francois Fontan in 1971 for the palliation of children with tricuspid atresia, and later modified in 1988 by Dr. Marc de Leval (Fontan and Baudet 1971). The Fontan operation is performed between two and four years of age, with some centers performing it before the onset of cyanosis or desaturations as the child grows, while others defer the operation until cyanosis or desaturations occur (Hirsch, Goldberg et al. 2008; Salazar, Zafar et al. 2010). The Fontan circuit is currently created in two
ways. In a lateral tunnel Fontan, an intra-atrial baffle directs blood flow from the inferior vena cava (IVC) to the pulmonary arteries (Figure 6A). The lateral tunnel technique may allow for normal somatic growth of the anastomosis. In a Fontan operation with an extracardiac conduit (ECC), the IVC is removed from continuity with the right atrium and a synthetic conduit is used to anastomose the IVC to the pulmonary arteries (Figure 6B). The ECC Fontan operation may be performed without the use of cardiopulmonary bypass and results in lower intra-atrial pressures, which may reduce the likelihood of arrhythmias (Azakie, McCrindle et al. 2001). No analyses have yet definitively demonstrated the superiority of either technique (Fiore, Turrentine et al. 2007; Robbers-Visser, Miedema et al. 2010).

Figure 6: The Fontan operation, surgical anatomy. A. Lateral tunnel Fontan operation, with an intra-atrial baffle directing blood flow from the inferior vena cava to the pulmonary arteries. B. Fontan operation with an extracardiac conduit. Reproduced from http://www.giamberti.it/wp-content/uploads/2014/03/2155-9880-S8-007-g038.gif

Proper context is essential for any discussion of outcomes after the Fontan operation for HLHS, namely that only 50-70% of children born with HLHS will survive to undergo all three stages of single ventricle palliation (Figure 7) (Bove, Ohye et al. 2004; McGuirk, Griselli et al. 2006). While short-term survival after the Fontan operation is often reported at 95% or greater, long-term outcomes are much more variable (Hirsch, Goldberg et al. 2008; Khairy, Fernandes et al. 2008). Some patients are able to survive and thrive into adulthood after the Fontan, with successful pregnancies in women with Fontan circulation now reported (Gouton, Nizard et al. 2015; Zentner, Kotevski et al. 2016). Others may develop significant and life-limiting complications.
during childhood and adolescence, such as systemic RV failure, protein-losing enteropathy (PLE), plastic bronchitis, hepatic fibrosis, thromboembolism, arrhythmias, limited exercise capacity, and obesity. These complications may necessitate additional catheter-based or operative interventions, such as Fontan revision or takedown (surgical conversion to a prior stage of single ventricle palliation, e.g. S2P), permanent pacemaker implantation, or even liver and/or heart transplantation. In a series of 1006 patients with Fontan circulation from Australia and New Zealand, the ten-year freedom from Fontan failure (defined as a composite endpoint of death, heart transplantation, Fontan takedown, the development of PLE, plastic bronchitis, or New York Heart Association class III or IV heart failure) was 79% vs. 92% in patients with HLHS vs. other congenital cardiac lesions, respectively. They also found that a diagnosis of HLHS was independently associated with death (d’Udekem, Iyengar et al. 2014). If Fontan-associated complications such as those described above do develop, freedom from Fontan failure and overall survival are substantially reduced. For example, the five-year freedom from Fontan failure patients who develop PLE is 40-50% (Pundi, Johnson et al. 2015; Allen, Downing et al. 2017).

Figure 7: Kaplan-Meier curve for overall survival through single ventricle palliation in patients with hypoplastic left heart syndrome. The overall survival for all infants undergoing single ventricle palliation is less than 60% by two years after the Norwood operation, the 25th percentile for age at Fontan in this study’s population. The dashed lines represent one standard
1.8 Predicting risk after the Norwood operation

1.8.1 Risk stratification of the Norwood operation relative to other congenital cardiac operations

During single ventricle palliation, most deaths occur during the post-Norwood period (perioperative and interstage periods) and resource utilization is high. Predicting the risk of morbidity and mortality following the Norwood operation is complex. Multiple approaches have been used, including the relative risk stratification of operations, risk models for the Norwood operation, and more advanced real-time predictive algorithms. The Risk Adjustment for Congenital Heart Surgery score was developed in 2002 based on consensus opinion. The Norwood operation was classified as a RACHS category 6 operation, representing the highest risk stratum (Jenkins, Gauvreau et al. 2002). The Aristotle Basic Complexity score was also developed using expert consensus and some empiric data to assign a score to congenital cardiac operations based on an operation’s anticipated mortality rate, anticipated morbidity, and technical difficulty. The Norwood operation’s Aristotle score was 14.5/15, providing a quantitative assessment of its high-risk status (Lacour-Gayet, Clarke et al. 2004). Finally, the Society of Thoracic Surgeons’ (STS) and the European Association of Cardiothoracic Surgery (EACTS) jointly developed a completely data-driven risk model for in-hospital for mortality, the STS-EACTS Congenital Heart Surgery Mortality (STAT) Categories. A Norwood operation is classified as a STAT category 5 operation, the highest category risk for in-hospital mortality (O’Brien, Clarke et al. 2009; Jacobs, Jacobs et al. 2012). It is important to emphasize that all three methods of risk adjustment only include pre-operative or operative factors. None have accounted for events or complications that can occur in the post-Norwood period.

1.8.2 Risk models and predictions for outcomes after the Norwood operation

Previously discussed risk factor analyses have developed general models for morbidity or mortality after the Norwood operation. However, predictions can be generated and graphed only from models that were developed using parametric methods, when values for the risk factors
included in the model are specified (Ashburn, McCrindle et al. 2003; Wilder, McCrindle et al. 2015). While these models are capable of incorporating post-operative events and complications as time-varying covariates, none have yet been included.

1.8.3 Real time risk assessment following a diagnosis or operation

Generating real-time risk predictions over time after an operation or hospital admission is a daunting endeavor. In addition to baseline characteristics (e.g. demographics, initial clinical state) and operative variables, a real-time risk assessment model must account for events or quantitative measurements that occur following the admission or operation. In medicine overall, few such models exist. An example is the Acute Physiology and Chronic Health Evaluation (APACHE). This was developed to predict mortality and length of stay after ICU admission (Knaus, Zimmerman et al. 1981). It has been subsequently revised three times. In its second and third revisions, the correlation of daily APACHE scores with mortality was examined. APACHE-III scores were found to be valid for up to one week after admission and were significantly associated with the risk of overall mortality (Figure 7) (Knaus, Wagner et al. 1991).
Figure 8: Daily APACHE-III scores during the first week of ICU admission for two individual patients. APACHE-III scores represent the daily, predicted risk of in-hospital mortality for two patients admitted with septic shock. The scores were updated based on each day’s clinical parameters that were included in the APACHE-III score. Reproduced with permission from (Knaus, Wagner et al. 1991). Copyright Elsevier, Inc.

Abbreviations: APACHE=Acute physiology and chronic health evaluation, LOS=Length of stay, HLOS=Hospital length of stay

Within cardiac surgery, real-time risk tracking tools are also limited to the ICU setting, in which a plethora of data is available. The Tracking, Trajectory, and Triggering (T3), developed at Boston Children’s hospital, allows for the real-time prediction of an infant’s risk of death, incorporating physiologic monitoring data (Etiometry, Inc., Boston, MA) (Almodovar 2014; Baronov, McManus et al. 2015). It can be used as a decision aid to prompt intervention when an infant’s score rises as their physiologic monitoring data reflects impending deterioration.

1.9 The role of the CHSS in congenital heart surgery outcomes research

The CHSS Data Center was created in 1985 by Drs. John Kirklin and Eugene Blackstone. Given the low incidence of many of congenital heart defects, especially many with high mortality rates, they planned that several institutions would share data regarding their patients into a common database as prospective, diagnosis-based inception cohorts. This combined data would have much greater statistical power and the granularity to identify novel associations. Currently, 11 cohorts exist, of which four are actively enrolling and a 12th is planned to start enrollment in 2018.

Several unique aspects of the CHSS Data Center, in comparison to other clinical research organizations, have allowed for the production of many seminal publications that have helped to define or significantly alter the treatment of patients with various congenital heart defects. First, the Data Center collects clinical data on patients for life, allowing for the longitudinal study of patients with congenital heart disease. The Data Center also performs yearly follow-up with the enrolled patients’ families to obtain mortality status and aid in data collection. Finally, the sophisticated statistical analytic expertise at the Data Center has
facilitated for the performance of analyses capable of answering complex questions that are unique to congenital heart surgery because of the operative complexity, availability of multiple treatment strategies, and complex patient courses.

1.10 Post-Norwood attrition remains substantial

HLHS and its related malformations represent a spectrum of complex congenital cardiac defects that result in functionally univentricular circulation. While they were once uniformly fatal diagnoses, many patients now survive into adulthood. Definitive treatment is not yet possible and various palliative strategies are currently available, with three-stage single ventricle palliation most commonly performed. While outcomes for single ventricle palliation have improved substantially, only 50-70% of infants will survive through all three stages. The post-Norwood period remains especially fraught with risk, as morbidity and mortality is much greater than after S2P. Gaining insight into trajectory of risk during this period and how physician-modifiable factors, such as the timing of S2P, may affect this risk and result in clinically applicable insights.
Chapter 2
Research Aims

2.1 Challenges in the analysis of the timing of S2P

Defining the optimal timing of S2P has proven to be a challenging problem since the introduction of the second stage of three-stage single ventricle palliation. Even analyzing the outcomes after S2P has been limited. Most single center experiences have small study populations and mortality after S2P is low as well. This combination has limited the ability to perform robust risk factor analyses. Even a secondary analysis of the SVR Trial analyzed risk factors for morbidity and increased length of stay, rather than for death after S2P (Schwartz 2012). Finally, infants who transition to S2P are at risk for several competing outcomes with death, including heart transplantation and biventricular repair, which further complicate these analyses.

In addition, infants are at high-risk for death during the interval between the Norwood operation and S2P. As previously discussed, estimates for the mortality after the Norwood operation range from 10-30%. Prior analyses have analyzed survival after S2P and stratified by different ages at operation. However, they do not account for the substantial number of patients who die prior to S2P. While certainly not all of these patients would have been candidates for S2P, their omission does not allow for a robust analysis to determine how to maximize survival through three-stage palliation. In other words, methods to analyze survival through staged surgical procedures have not yet been applied to this problem.

In addition, S2P can be performed for various reasons and understanding a physician’s or team’s intentionality and clinical decision making can be challenging. A wide range of data must be accounted for, including baseline demographic information, diagnosis, and clinical status, the Norwood operative course, the post-operative course, echocardiographic assessments of cardiac function (particularly the atrioventricular valve and right ventricle), cardiac catheterization data (including the pulmonary arterial sizes, development, stenosis, pulmonary vascular resistance, pulmonary-to-systemic blood flow ratio), weights, and more. Incorporating all of this information into a risk factor analysis with limited patients and low event rates after S2P has not yet been possible.
2.2 Dynamic risk assessment during the post-Norwood period may enable data-driven decision-making

Minimizing the duration spent in Norwood circulation may represent one method of maximizing survival after the Norwood operation. However, clinical decision-making does not solely revolve around the timing of S2P, as not all patients will necessarily be candidates for S2P. The Norwood operation is among the most technically complex operations performed in any field of surgery. It results in massive anatomic and physiologic alterations during the neonatal period or early infancy. The immense physiologic stress of the child’s critical congenital cardiac lesion and the adjustment to the sudden transition to Norwood circulation occur within the context of ongoing organ maturation and an extensive systemic inflammatory response. These factors all lead to considerable risks for morbidity and mortality during the post-Norwood period, even when the child will still require at least two more cardiac operations.

Previous analyses have only considered baseline and operative characteristics, without taking into account the events taking place after the Norwood operation. Others have only focused on outcomes in the presence of single complication. The variety of possible complications, from cardiac arrests to developing NEC, is large and their relative impacts on an infants’ ability to survive the post-Norwood period and reach eligibility for S2P are unknown. In addition, large amounts of data, including weights and SaO₂ measurements, are collected from these children during the post-Norwood period. These objective data are used to inform clinical decision-making regarding readmission and/or re-intervention. While the ability to include time-related events in risk modeling has existed, this methodology has not yet been applied to the post-Norwood period. Though similar in approach, the inclusion of longitudinal quantitative data as a time-varying covariate represents a new frontier in risk model development.

Given that the Norwood operation results in wide-ranging changes to an infant’s anatomy and physiology, it is unknown if baseline characteristics or the operative course will continue to affect the risk of mortality over the events that occur post-operatively. Insight into how time-related events and longitudinal measures alter an infant’s risk trajectory during staged surgical management should be integrated with the novel information regarding the optimal timing of S2P. The visualization of changes in an infant’s risk of death over time could provide a tool that makes more nuanced, data-driven decision-making possible.
2.3 The CHSS Critical LVOTO Inception Cohort

Given the low overall prevalence of HLHS and its related malformations, single center reports of outcomes have formed the bulk of the literature regarding this disease. Pooling of the shared experiences of multiple centers represents an effective solution to these limitations. The CHSS initially developed separate prospective inception cohorts for infants born with Critical Aortic Stenosis and Aortic Valve Atresia, enrolled from 1994-2000, which were studied in aggregate in several analyses. However, the desire to study the outcomes of single ventricle palliation vs. biventricular repair in patients with left ventricles of borderline size to support the systemic circulation motivated the creation of a new cohort. It was also intended to include a wider spectrum of anatomic pathology than the previous Critical Aortic Stenosis and Aortic Valve Atresia cohorts.

In 2005, enrollment into the CHSS Critical LVOTO prospective inception cohort began. Specifically, this cohort includes patients with obstruction of the left ventricle such that the left heart cannot support the systemic circulation, and thus all have ductal-dependent circulation (Caldarone 2015). Anatomically, the cohort includes patients with HLHS, critical aortic stenosis, aortic valve atresia, mitral atresia, and anatomically normal but hypoplastic left heart structures (“hypoplastic left heart complex”). These infants have undergone a wide variety of initial treatments, though the majority has undergone single ventricle palliation, starting with a Norwood operation.

The Critical LVOTO cohort collects longitudinal data, from soon after birth onward, including all available operative, clinic, echocardiographic, and cardiac catheterization notes. While the focus of the cohort is certainly to analyze the surgical management of these infants, collecting data beyond operative notes and the perioperative period enables the ascertainment of the effects of surgical management on mid-term and long-term, mortality and morbidity outcomes. In comparison to other multi-institutional studies such as the SVR Trial, this allows for the collection of additional data for ongoing studies, instead of being limited by a pre-defined data collection strategy, i.e. case report forms. Therefore, this detailed information regarding the course of infants with Critical LVOTO, in combination with the CHSS Data Center’s well-known expertise in advanced survival analysis, position the CHSS Data Center to answer the complex question of the optimal timing of S2P, which requires highly detailed operative and non-operative clinical data.
2.4 Aims and Hypotheses

The specific aims and hypotheses of this thesis include the following:

**Aim 1a**: To gain insight into how the age at S2P affects mortality during three-stage single ventricle palliation.

**Hypothesis 1a**: Extremes of age, prior to age three months and after age six months, are associated with higher mortality after S2P.

**Aim 1b**: To determine the optimal timing of S2P that both minimizes pre-S2P attrition and maximizes post-S2P survival.

**Hypothesis 1b**: An optimal timing for S2P exists and depends on patient risk factor profiles.

**Aim 2**: To create a risk model for death after the Norwood operation that incorporates time-related events and longitudinal measurements to predict an individual patient’s instantaneous risk of death.

**Hypothesis 2**: Time-related events and measurements, rather than baseline characteristics, will predominately determine an infant’s instantaneous risk of death during the post-Norwood period.
Chapter 3
Methods

3.1 Study population

The study population was drawn from the CHSS Critical LVOTO prospective inception cohort. Critical LVOTO was specifically defined as a left-sided obstructive lesion that precluded the left heart’s ability to sustain the systemic circulation. Thus, all neonates were dependent on a patent ductus arteriosus so that the right ventricle could provide systemic perfusion (“ductal dependency”). These patients’ anatomic diagnoses included hypoplastic left heart syndrome, anatomically normal but hypoplastic left heart structures (“hypoplastic left heart complex”), aortic valve atresia, critical aortic stenosis, or mitral valve atresia. All included patients were admitted to and underwent their first interventions at a CHSS institution, within their first 30 days of life. From January 1, 2005 through March 6, 2016, 924 neonates were considered for enrollment in the cohort. Of these, 852 fulfilled eligibility criteria and 72 were excluded. Of the 852 eligible, 785 neonates survived to undergo a procedure, of which 534 neonates from 20 institutions underwent an initial Norwood operation (Figure 9). Enrollment by institution is displayed in Appendix Table 1. While the management of patients was deferred to the local, managing physicians, any neonate who underwent another initial procedure, including a Hybrid Stage 1, biventricular repair, isolated aortic arch intervention, heart transplantation, or an interventional cardiac catheter-based procedure (e.g. balloon aortic valvotomy) was excluded from the study population.
The CHSS Critical LVOTO cohort was designed to include broad range of anatomic defects and management strategies, as reflected above. In total 924 neonates were considered for inclusion in the prospective inception cohort, of which 852 were eligible. A “definitive” procedure, or an intervention intended to address the outflow tract obstruction, was performed in 785 with 13 deaths prior to any intervention, and 54 alive without surgical information in the database available for analysis. Of the 785, 655 underwent Stage 1 palliation with the intention to pursue single ventricle palliation, and 534 underwent a Norwood operation as their initial post-natal intervention, which comprise the study cohort.

Abbreviations: BiV=Biventricular, AVR=Aortic Valve Replacement, LVOT=Left Ventricular Outflow Tract, LVOTO=Left Ventricular Outflow Tract Obstruction

3.2 Data acquisition

Patient participation in the study and the submission of medical records were voluntary and confidential. Parental consent was obtained prior to enrollment. The CHSS Data Center and each participating institution obtained Institutional Review Board approval. Following patient enrollment, medical records were sent to the CHSS Data Center by the participating institutions.
Annual cross-sectional follow-up of all enrolled patients was then conducted by CHSS Data Center staff to determine patient mortality status. Participating institutions were annually contacted to provide the latest operative, procedural, and echocardiographic reports, clinic notes, discharge summaries, and more. Data from these reports were then extracted by a single clinical research nurse, as previously described (Lofland, McCrindle et al. 2001).

3.3 Follow-up

Because the primary objective study was to investigate survival through the staged procedures of single ventricle palliation, the median follow-up was calculated following both Norwood and S2P. The median follow-up until transition into the next state after the Norwood operation was 4.6 months (IQR 3.0-5.9). The median follow-up until transition into the next state after S2P was 2.3 years (IQR 1.2-3.0). The most recent cross-sectional follow-up was performed in 2015.

3.4 Statistical Analysis

3.4.1 Variable preparation

Baseline demographic, clinical, Norwood operative, echocardiographic, interventional cardiac catheterization, and various characteristics from the post-Norwood data (including repeated events and repeated measures of weights and oxygen saturations) were summarized. The normality of all variables was queried using the Shapiro-Wilkes test. Categorical variables were presented as percentages and raw frequencies. Continuous variables are presented as means with standard deviations or medians with interquartile ranges, as appropriate. Absolute ranges were reported where of interest. Mathematical transformations were performed in the case that non-linear relationships existed with the outcomes of interest. Echocardiographic measurements were obtained from a Congenital Heart Surgeons’ Society core lab analysis. Echocardiographic measures were standardized as z-scores where applicable or were indexed to body surface area (Pettersen, Du et al. 2008). Weight-for-age z-scores (WAZ) were calculated using the 2000 standards from the World Health Organization. The program used to generate the z-scores was downloaded from https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm. Interval operative and catheter-based re-interventions on the heart and great vessels occurring after the Norwood were incorporated as time-varying covariables. Reoperations on the heart and great vessels
were specifically defined in accordance with the Society of Thoracic Surgeons' Congenital Heart Surgery Database version 3.22. All analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

3.4.2 Missing data

Variables with greater than 50% missing data were excluded from the analysis. For variables with less than or equal to 50% missing data, multiple informative imputation using PROC MI was performed. PROC MI utilizes a Markov-chain Monte Carlo method for variables with an arbitrary pattern of missing-ness. It assumes a multivariate-normal distribution of values and generates five distinct data sets with informatively imputed values (Rubin 1987; Yuan 2010). No outcome variables and no time-related repeated events or continuous measures were imputed.

3.4.3 Endpoints

Two intervals were analyzed, from birth until the end of the Norwood and immediately following the Norwood until the start of the S2P operation. Therefore, there were two primary outcomes of interest: death after the Norwood (without transitioning to another end state) and death after S2P.

3.5 Survival analysis

3.5.1 Multiphase parametric risk hazard analysis – background and rationale

Survival analysis was performed using multiphase parametric risk hazard analysis (Blackstone, Naftel et al. 1986). This method is a type of distributional analysis, in which equations can describe a number of shapes of distribution of the probabilities of events, including Weibull, Rayleigh, Gompertz, exponential, and others. It differs in several substantial ways from the more common non-parametric Kaplan-Meier or semi-parametric Cox proportional hazards techniques. First, this method directly models the cumulative hazard. In Cox proportional hazards analysis, the underlying hazard function is not directly specified. The cumulative hazard, which reflects the accumulation of risk over time, is also equal to the negative logarithm
of the survival function, allowing for simple conversion between the two. It is also the integral of the hazard function, which describes the instantaneous rate of experiencing an event (Figure 10) (Clark, Bradburn et al. 2003). The cumulative hazard domain is attractive because it is unbounded, whereas the survival function is bounded from zero to one. In this analysis, the first step is to derive the cumulative hazard from the survival estimates obtained from the Kaplan-Meier method.

Figure 10: The relationship between the survival function, hazard function, and cumulative hazard. In this example, survival initially decreases (from time 0 to 1), which corresponds to a high early hazard and initial steep rise in cumulative hazard. A more constant rate of attrition is then noted (from time 1-9), with a corresponding constant hazard rate, and constantly increasing cumulative hazard. Survival then decreases again (from time 9-10), with a corresponding increase in hazard rate and cumulative hazard. The cumulative hazard and hazard function functions have been multiplied by 4 and 10, respectively, to be displayed along the same axis as the survival function, which is bounded between 0 and 1. Reproduced with permission from (Blackstone, Naftel et al. 1986). Copyright Taylor & Francis.
Another important difference between parametric survival analysis and traditional methods, such as Cox proportional hazards analysis, is that the proportional hazards assumption need not hold. The proportional hazard assumption states that the effect of a covariate on an individual's hazard for the event of interest is the same at any time during the study period. That is, it is independent of time or does not vary with time. Instead, in parametric survival analysis, up to three distinct phases of risk may be modeled. Therefore, the parametric survival model decomposes the overall hazard into up to three phases multiple phases of risk. The model is thus the sum of the equations that represent the survival distributions. These phases can be referred to as “early,” “constant,” and “late” phases of risk. It is important to note that the terms “early,” “constant,” and “late” reflect mathematical phases of the distribution of events, and do not imply any clinical meaning. It is also important to note that, although up to three phases can be incorporated into the model, all three are not required for model validity.

Each phase has an associated scaling parameter and shaping parameter. The scaling parameter is a log-linear function in which risk factors can be incorporated. The early phase, often described as an initially high and peaking but rapidly decreasing hazard, has a shaping parameter determined by four individual parameters, $m$, $nu$, $t_{1/2}$ (which reflects time to half the total early cumulative hazard), and $delta$. The constant phase, with its constant hazard, is a simple log-linear function, multiplied by $t$. The late phase, with its gradually rising hazard, reflects a generalized version of the Weibull distribution. In addition to its scaling parameter, its shaping parameter is composed of $alpha$, $gamma$, $nu$, and $eta$.

This multiphase paradigm is very useful post-cardiac surgery, as the risk of death is often highest during the initial perioperative period, after large and invasive surgery, and then rapidly dissipates. The patient's risk of death may return to their baseline and be maintained, and the risk of death from underlying comorbidities may predominate. However, as the patient ages, the hazard of death will begin to rise gradually (Figure 11).
Figure 11: The decomposition of the hazard function into three phases of risk. Up to three phases of risk can be resolved using parametric risk hazard analysis. When three phases of risk are present, the early phase corresponds to a period of high risk for the outcome of interest, which rapidly decreases. A constant phase, in which the risk of the outcome of interest is constant, may then be present. A late phase corresponds to a period of increasing risk for the outcome of interest occurring after an early and/or constant phase. All three phases are not required to be present for model validity. The terms “early,” “constant,” and “late” refer to the mathematical distribution of events and do not necessarily correspond with the clinical periods of risk. Reproduced with permission from (Blackstone, Naftel et al. 1986). Copyright Taylor & Francis.
In this analysis, two intervals were analyzed and two parametric models were created: 1) for death after the Norwood as the event of interest, with patients right-censored at the day of progression to S2P, heart transplantation, biventricular repair, or alive at the end of follow-up without transition to another state, and 2) for death after S2P as the event of interest, with right censoring at the day of Fontan completion, heart transplantation, biventricular repair, or alive at the end of follow-up without transition to another state (Figure 12).

**Figure 12: Survival analyses.** The goal of this analysis was to maximize the number of patients who were alive at follow-up after stage-2-palliation (S2P). Two intervals were analyzed during this study, from the Norwood until transition to another end state and from S2P until transition to another state. Two parametric models were created, for death after the Norwood (left) and death after stage-2-palliation (right). Infants are at risk for death after the Norwood and after S2P, with the risk of death much greater after the Norwood than after S2P. The black circles represent the Kaplan-Meier estimates for survival over time with the brackets depicting their 95% confidence limits. The solid red lines represent the parametric model, while the dashed red lines depict the 70% confidence limits.

*Abbreviations: S2P=Stage-2-palliation*
3.5.2 Multivariable risk hazard analysis

Risk factors can be incorporated into the parametric equations for cumulative hazard, as exponential terms in the log-linear scaling functions. As noted above, the proportional hazards assumption need not hold in parametric risk hazard analysis, and each phase represents a separate vector of potential risk factors. If more than one phase is present, unique risk factors may therefore be evaluated or identified for each phase. Regarding the interpretation of the parameter estimates for a given phase of risk, they are analogous to the hazard ratios obtained from Cox proportional hazard analysis. Positive parameter estimates indicate a positive association with the event of interest, while negative parameter estimates reflect a negative, or protective, association with the event of interest.

Candidate risk factors are entered into PROC HAZARD using stepwise backwards selection, with a p-value specified for entry into the model and another specified for retention. However, variables are first subjected to bootstrap aggregation for variable reduction and to aid in selection. Bootstrap aggregation involves the creation of many models, for example, 500. These models are created from analyses of datasets of repeated resampling of the study population with replacement. This resampling is random, with the same sample size as the original study population, which allows for a single patient to be potentially present multiple times within a given resample. Then, the “reliability” of a given variable, or the percentage of the 500 models in which the given variable is present can be determined. A cut off is then set, typically at 50%, below which variables will be excluded from final model building (Sauerbrei and Schumacher 1992; Breiman 1996). The final model is then determined by subjecting the candidate covariates with reliabilities above the set threshold to risk hazard analysis. Multiple imputation can create up to five datasets with candidate covariates for risk hazard analysis. All five data sets are then used to generate the final parameter estimates for the covariates that reached significance in the model by using PROC MIANALYZE.

In this analysis, two multivariable models were created, for each parametric survival model described above. A total of 500 bootstrap resamples was performed for each model, using forward stepwise selection with an initial p=0.10 for entry into the model and p=0.07 for retention. A reliability threshold of 50% was set for the model for death after the Norwood and 25% for death after S2P, because of the smaller population and lower frequency of events (deaths). When building the final model using the bootstrapped list of candidate variables, stepwise forward selection was again used, with p=0.07 for variable entry into the model and p=0.07 for variable retention. Candidate covariates for the model for death after Norwood
included demographic, baseline clinical, echocardiographic, and Norwood operative characteristics. Candidate covariates for the model for death after S2P included characteristics of the Norwood (post-Norwood operation), those from the final echocardiogram prior to S2P, those from the pre-S2P cardiac catheterization, status at the final clinic visit prior to S2P, up until the day of the S2P operation.

### 3.5.3 Institutional adjustment

Case mix is known to vary substantially across institutions performing congenital heart surgery (Pasquali, Wallace et al. 2016). A well-established volume-outcomes relationship in complex congenital heart surgery has also been described, particularly with the Norwood operation (Pasquali, Jacobs et al. 2012). It is therefore critical to account for institutional variation in multivariable modeling. In this analysis, variables representing institutions were entered into the analyses as candidate covariates during bootstrap aggregation and again after final model determination.

### 3.5.4 Prediction and graphing

The parametric risk hazard analysis directly models the cumulative hazard with an equation representing the distribution of events over time and includes a defined set of parameters (risk factors). When risk factor values are specified, the cumulative hazard for the modeled event, and thereby survival, can be predicted as solutions to the multivariable equation. This is accomplished using the PROC HAZPRED. The solutions can then be graphed vs. time, allowing for the creation of risk stratified plots of predicted survival. In addition, nomograms can be plotted, in which survival is displayed as a function of one of the variables in the model, instead of as a function of time. “Summary” or “average” curves were created by generating predicted survival curves for each individual study patient, using their actual values for the variables in the multivariable equations, and then summarized into a single curve.(Sergeant, Blackstone et al. 1997)
3.5.5 Risk stratification

Patients were risk stratified by predicting the cumulative hazard at one year post-S2P using PROC HAZPRED. Patients' actual values were used for the variables identified in the multivariable analyses. The cumulative hazards were ranked into quartiles. The top quartile was classified as high-risk, the second and third as intermediate-risk, and the lowest as low-risk. Representative patients from each risk group were then selected for analyses of survival and timing.

3.6 Analyzing the timing of surgery

3.6.1 Non-parametric conditional survival analysis

Analyzing staged procedures, such as three-stage single ventricle palliation, has proven difficult. Typically, each operation has been analyzed separately, effectively establishing a new time zero for each survival analysis. However, this approach fails to account for attrition between stages. Conditional survival analysis, defined as the likelihood of surviving to time $t$ given survival to time $s$, or $CS = S(t|s)$, represents a viable method to analyze survival through staged procedures. In this analysis, the probability of surviving to two years post-Norwood given survival to S2P [$S(2\text{ years}|S2P)$] was analyzed. Just as non-, semi-, and fully parametric methods are available for traditional survival analysis, these are all available for conditional survival analysis as well. Kaplan-Meier and Cox proportional hazards based methods have been used in various fields such as oncology to estimate the probability of survival to five years after remission given survival to one year after remission (Zabor, Gonen et al. 2013). However, these techniques are only able to include the patients who survived to one year in the analysis, not the entire initial study population (Figure 13). The Nelson cumulative hazard method with left censoring does allow for a conditional survival-type of analysis, in which the conditional event is analyzed as a repeated event. However, the Nelson method is also non-parametric, precluding the incorporation of risk factors (Nelson 1972).
Figure 13: Non-parametric Conditional survival curves based on Kaplan-Meier methodology. The black curve represents the overall Kaplan-Meier estimates for survival in patients diagnosed with Stage III melanoma. Each subsequent colored curve represents conditional survival given survival to 1, 2, 3, or 4 years after diagnosis. Please note that these curves only incorporate information from those patients who survived to each time point. Reproduced with permission from (Zabor, Gonen et al. 2013). Copyright John Wiley and Sons.

3.6.2 Parametric conditional survival analysis

Due to the well-known differences in mortality rates following the Norwood and S2P, Kaplan-Meier or Cox-based methods were deemed inadequate for this analysis. We elected to utilize parametric conditional survival analysis in order to account for all patients who underwent an initial Norwood operation. To perform parametric conditional survival analysis, both multivariable models were used. Survival was first predicted following the Norwood operation (Figure 14, red line) up to the day of the S2P operation (Figure 14, 74±4%, heavy black arrow). Survival was then predicted post-S2P (Figure 14, blue line) and was adjusted for the attrition post-Norwood by multiplying by the survival estimate from Norwood to the day of S2P.
Figure 14: Parametric conditional survival analysis. Parametric risk hazard analysis is composed equations modeling a specified hazard and these equations can be combined to analyze survival through staged operations. In the cumulative hazard domain, these equations can be added. In the survival domain, these equations can be multiplied. In this example, the mean values were specified for all variables in both models. Survival was predicted for a hypothetical patient from the Norwood operation to the day of stage-2-pallation (red line), here at six months (heavy black arrow), which was 85±4%. Survival was then predicted from S2P to two years (blue line), again with all risk factor values set at their mean values, except age at S2P). Each survival estimate after S2P was adjusted for attrition after the Norwood operation by multiplying by the survival estimate at six months (85±4%). The solid lines represent predicted survival from the parametric models described in the results. The dashed lines represent 70% confidence limits. Please note that the y-axis has been truncated to start at 50% for the purpose of this example.
3.7 The incorporation of post-operative longitudinal measurements and events into a risk hazard analysis

3.7.1 Defining longitudinal data

Longitudinal data can be defined in contrast to cross-sectional data. Cross-sectional data are measured at a single time point for every patient. Longitudinal data are measured repeatedly for each patient throughout a study (Diggle, Liang et al. 1994). A simple illustrative example that is applicable to the study would involve assessing weight prior to S2P. A single measurement of weight on the day of S2P for each patient would represent cross-sectional data. The daily weights collected during a home monitoring program for each patient would represent longitudinal data. Longitudinal data can be categorical as well, if an event is measured as occurring vs. not occurring at multiple time points. The overall aggregate occurrence vs. non-occurrence at the end of the study period is not considered longitudinal data. For example, a patient may be readmitted to the hospital multiple times. Cross-sectional data would only represent if the patient was ever re-admitted, with no information regarding the number or timing of readmissions.

3.7.2 Understanding longitudinal data – mixed effects modeling

Longitudinal data from the same patient are likely correlated, whereas values from different patients may not be correlated. The lack of correlation between patients is assumed in cross-sectional data. In order to analyze and understand trends in longitudinal data over time, mixed effects regression modeling is required. Mixed effects models include random and fixed effects, to account for the within-patient correlation of values. The fixed effects refer to potential covariates evaluated as terms in the mixed effects model equation. Random effects use probability distributions to specifically account for within-patient correlation (Diggle, Liang et al. 1994; Rajeswaran and Blackstone 2017).

Figure 15 demonstrates that both the slope and y-intercept three individual patients may vary. Simple linear regression may be used to create linear models for each individual patient (transparent colored lines), but cannot be used to model all data points from every patient, because it cannot account for the within-patient variation. However, a linear mixed effects model can be created, accounting for both random slopes and intercepts, modeling the longitudinal data from multiple patients (thick orange line). Fixed effects constitute the potential covariates,
which determine the slope of each patient’s model and thus, of the overall model. Random effects, using known distributions, account for the varying y-intercepts from multiple patients. Linear mixed effects models were fit using PROC MIXED in SAS.

Figure 15: Analyzing longitudinal data with mixed effects modeling. Individual, hypothetical patient data points for weight are presented as “X.” Hypothetical linear models for each patient are presented as transparent lines. The y-intercepts and slopes for each patient’s linear model are distinct. An overall, hypothetical model, derived from linear mixed effects modeling, is shown as the thick orange line.

It is also possible to model non-linear trends in longitudinal data. Equations for known distributions are used to fit non-linear mixed effects models using PROC NLMIXED in SAS (Rajeswaran 2012). Further discussion of mixed effects modeling is beyond the scope of this work.
3.7.3 Defining a time-varying covariate

The typical variables evaluated in traditional multivariable analyses of surgical outcomes, including baseline clinical, demographic, and operative characteristics, are measured cross-sectionally. These variables remain constant through the course of the time interval under study, or are independent of time. However, a variable, such as requiring mechanical circulatory support (MCS) after an operation, may appear at first to be a post-operative outcome. However, it may also affect a patient’s risk of death post-operatively. Therefore, it can be incorporated into risk hazard analysis as a time-varying covariate (TVC). A TVC is defined as a variable whose value is not constant throughout the study period, or whose value is dependent on time (Kalbfleisch and Prentice 2002; Lee and Wang 2003). Specifically, a TVC must be measured or occur after the start time of the interval under study (Figure 16). Both continuous and categorical data can be incorporated into an analysis as TVC. Continuous data can take the form of repeated measurements of a lab value or other measurement, in which each subsequent measurement is treated as an individual TVC. Categorical data can take the form of the occurrence of an event, such as requiring MCS post-operatively. Repeated occurrences of an event can be treated as a repeating events. TVCs thus represent longitudinal data as well.

![Figure 16: The temporal distribution of baseline vs. time-varying covariates. The values of baseline characteristics do not change throughout the analysis period. In comparison, time-varying covariates, such as whether post-Norwood complications (e.g. reintubation) or](image-url)
measurements (e.g. of weight or O₂ saturation), occur after the start of the interval under study and therefore cannot remain constant throughout the interval under study.

Abbreviations: Re-op=reoperation, RRT=Renal replacement therapy, WAZ=Weight-for-age z-score

### 3.7.4 Data structure in “typical” analyses vs. those incorporating time-varying covariates

In typical survival analysis, the data sets contain one line per patient, containing information such as the patient identifier, event/censoring status, the time interval until the event/censoring, and risk factor values (Figure 17A). When TVCs are present, the data set will contain multiple lines per patient, all with the same patient identifier, overall time interval, event/censoring indicator, and values for any baseline variables (Figure 17B). Each TVC must have a date associated with it, which allows for the calculation of an interval of its occurrence since the start of the analysis.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Death before S2P</th>
<th>Interval from Norwood to end state in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>LV045</td>
<td>37</td>
</tr>
<tr>
<td>23</td>
<td>LV046</td>
<td>183</td>
</tr>
<tr>
<td>24</td>
<td>LV047</td>
<td>113</td>
</tr>
<tr>
<td>25</td>
<td>LV049</td>
<td>152</td>
</tr>
<tr>
<td>26</td>
<td>LV050</td>
<td>114</td>
</tr>
<tr>
<td>27</td>
<td>LV051</td>
<td>108</td>
</tr>
<tr>
<td>28</td>
<td>LV052</td>
<td>44</td>
</tr>
<tr>
<td>29</td>
<td>LV055</td>
<td>29</td>
</tr>
<tr>
<td>30</td>
<td>LV057</td>
<td>141</td>
</tr>
<tr>
<td>31</td>
<td>LV061</td>
<td>67</td>
</tr>
<tr>
<td>32</td>
<td>LV064</td>
<td>202</td>
</tr>
</tbody>
</table>
Figure 17: The data set structure with time-related events. A. Traditional data structure, one line per patient. B. Multiple lines per patient for two patients, with different events on each line and their associated dates. Multiple instances of the same event can also occur. In columns with time-related events, “1” indicates an event occurred and “0” indicates the event did not.

3.7.5 Incorporating time-varying covariates in risk hazard analysis

3.7.5.1 Data set preparation – segmenting of the interval under study by the occurrence of time-varying covariates

When analyzing the effect of TVCs, it is important to remember that the value of the TVC is not constant throughout the time interval under study. Therefore, the TVC can only affect the risk of an outcome once it has occurred and the overall time interval under study must be divided into multiple segments based on the occurrence of TVCs (Figure 18).
Figure 18: Time-varying covariates affect the risk of death after they occur. In the example in this figure, a non-operative readmission occurs after the Norwood operation and before death (green arrow). Its value then changes from 0 to 1, only affecting the risk of death once it has occurred. The arrows, representing the occurrence of a time-related event, are color coded as shown in the list post-Norwood measures and events.

Abbreviations: RRT=Renal replacement therapy

In order to segment the data, the REPEAT macro was used to first calculate the length of the interval from the Norwood to each event (Figure 19A). The length of time between each patient’s time zero and the date of the first event, first to second event, the second to third event, and so forth was then calculated. This continues iteratively until the length of the interval from the day of the final time-varying event to the day of censoring or failure has been accounted for (the time interval between renal replacement therapy initiation, the brown arrow, and death in Figure 18). The sum of the intervals between all events will be equal to the entire length of time between a patient’s entry into the study and their final end state (censoring or failure). Following the creation of these intervals, time-varying covariates can be specifically created, which indicate either the occurrence of an event during a specific time period or a corresponding continuous variable measurement for a given interval (Figure 19B).
### B.

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Interval from Norwood to end state in days</th>
<th>eventpos</th>
<th>Time to event in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>104</td>
<td>LV049</td>
<td>152</td>
<td>Rain t</td>
</tr>
<tr>
<td>105</td>
<td>LV049</td>
<td>152</td>
<td>CPAP</td>
</tr>
<tr>
<td>106</td>
<td>LV049</td>
<td>152</td>
<td>Oxygen</td>
</tr>
<tr>
<td>107</td>
<td>LV049</td>
<td>152</td>
<td>Weight</td>
</tr>
<tr>
<td>108</td>
<td>LV049</td>
<td>152</td>
<td>nocreadm</td>
</tr>
<tr>
<td>109</td>
<td>LV049</td>
<td>152</td>
<td>Oxygen</td>
</tr>
<tr>
<td>110</td>
<td>LV049</td>
<td>152</td>
<td>Weight</td>
</tr>
<tr>
<td>111</td>
<td>LV049</td>
<td>152</td>
<td>Oxygen</td>
</tr>
<tr>
<td>112</td>
<td>LV049</td>
<td>152</td>
<td>Weight</td>
</tr>
<tr>
<td>113</td>
<td>LV049</td>
<td>152</td>
<td>Oxygen</td>
</tr>
<tr>
<td>114</td>
<td>LV049</td>
<td>152</td>
<td>Weight</td>
</tr>
<tr>
<td>115</td>
<td>LV049</td>
<td>152</td>
<td>nocreadm</td>
</tr>
<tr>
<td>116</td>
<td>LV049</td>
<td>152</td>
<td>Oxygen</td>
</tr>
<tr>
<td>117</td>
<td>LV049</td>
<td>152</td>
<td>Weight</td>
</tr>
<tr>
<td>118</td>
<td>LV049</td>
<td>152</td>
<td>Oxygen</td>
</tr>
<tr>
<td>119</td>
<td>LV049</td>
<td>152</td>
<td>Weight</td>
</tr>
<tr>
<td>120</td>
<td>LV050</td>
<td>114</td>
<td>trigs2p</td>
</tr>
<tr>
<td>121</td>
<td>LV050</td>
<td>114</td>
<td>Oxygen</td>
</tr>
<tr>
<td>122</td>
<td>LV050</td>
<td>114</td>
<td>Weight</td>
</tr>
<tr>
<td>123</td>
<td>LV050</td>
<td>114</td>
<td>Oxygen</td>
</tr>
<tr>
<td>124</td>
<td>LV050</td>
<td>114</td>
<td>Weight</td>
</tr>
<tr>
<td>125</td>
<td>LV050</td>
<td>114</td>
<td>nocreadm</td>
</tr>
<tr>
<td>126</td>
<td>LV050</td>
<td>114</td>
<td>ur</td>
</tr>
<tr>
<td>127</td>
<td>LV050</td>
<td>114</td>
<td>Oxygen</td>
</tr>
<tr>
<td>128</td>
<td>LV050</td>
<td>114</td>
<td>Weight</td>
</tr>
<tr>
<td>129</td>
<td>LV050</td>
<td>114</td>
<td>INTCATH</td>
</tr>
<tr>
<td>130</td>
<td>LV050</td>
<td>114</td>
<td>cathAA</td>
</tr>
<tr>
<td>131</td>
<td>LV050</td>
<td>114</td>
<td>recoarc</td>
</tr>
</tbody>
</table>
**Figure 19: Segmenting the overall interval under study based upon the occurrence of time-varying covariates.**

A. Graphical representation of the segmentation of the interval of interest based on the occurrence of time-related events. “D” indicates deaths, “E” indicates the occurrence of a time-related event, and arrows indicate right-censored observations. The REPEAT macro segments the overall interval into individual intervals between the occurrence of each time-related event or longitudinal measurement. B. For the two patients displayed, their overall intervals ("Interval from Norwood to end state in days") has been divided into individual segments ("Time to event in days") based on the occurrence of a time-varying covariate ("eventpo"). “Eventpo” corresponds to “E” in part A. Multiple events occurred on the same day where the “Time to event in days” is equal for different time-varying covariates. Part A was adapted from Kirklin/Barratt-Boyes Cardiac Surgery, Fourth Edition, Chapter 6, page 321, Figure 6-28 (Kouchoukos 2013). Copyright Elsevier, Inc., 2013.

**Abbreviations:** CathAA=Interventional cardiac catheterization on the aorta, CPAP=Continuous positive airway pressure, Eventpo=Occurrence of a post-operative time-related event or longitudinal measure, Intcath=Interventional cardiac catheterization, Nocreadm=Non-operative readmission, Recoarc=Diagnosis of recoarctation of the aorta at cardiac catheterization, Reint=Reintubation, Trsigs2p=Diagnosis of moderate-severe atroventricular valve regurgitation pre-stage-2-palliation, URI=Upper respiratory tract infection.

### 3.7.5.2 Incorporating time-varying covariates using left censoring

Parametric risk hazard modeling allows for the incorporation of TVCs through left censoring (Figure 20). In traditional survival analyses, the censoring of patients who do not experience the event of interest in survival analysis is specifically “right censoring.” In contrast, “left censoring” indicates that an event of interest has occurred before the start of the time interval under analysis (Gomez, Julià et al. 1992).
Censoring is dependent on the time-frame of the analysis. An observation, or patient, can experience a failure, if the event of interest occurs during the study period (Patient 1). If the event does not occur during the study period, then that patient is right-censored (Patient 2). If the event of interest occurs prior to the start of the study, then that patient is left-censored (Patient 3).

When TVCs are included, the starting time of each individual segment is the left censoring time, at which an event occurred that will affect risk over the subsequent intervals. The starting time of the next segment actually reflects time at which an event (the TVC) has already occurred. In this manner, the TVC only exerts its effect on the risk of death after it has occurred. It is also important to note that once a time-related event has occurred, its occurrence is carried forward and affects all subsequent intervals. Patients also remain at risk for repeated events or measurements until their follow-up period ends and are right censored, or experience the event of interest in the study, for example, death (Lee and Wang 2003; Kouchoukos 2013). In PROC HAZARD, left-censoring times can be specified using the statement “LCENSOR”. While baseline variables will remain constant through the interval under study, TVCs can then be evaluated as candidate covariates in the across each interval as they occur (Figure 21A and B). Model building and bootstrapping follow the same procedure as described previously.
Figure 21: Multivariable risk hazard analysis with both baseline and time-varying covariates. A. Baseline characteristics such as the gestational age and the presence of genetic abnormality remain constant throughout the analysis. No time-varying covariates are present in this data set. B. Baseline characteristics (gestational age and the presence of genetic abnormality) remain constant in each interval following segmentation. However, time-varying covariates such as oxygen saturation or a non-operative cardiac readmission do not remain constant and exert their effect after their occurrence (after their “time to event in days”). However, once a time-related event has occurred, e.g. a readmission, its indicator is carried forward so that its occurrence continues to affect the risk of death in subsequent intervals.
### 3.7.6 Calculating mortality scores and plotting dynamic risk profiles

Following model development with the time-related events and measurements, survival can be predicted with PROC HAZPRED. Each patient’s actual values for the risk factors included in the model are used. Because of the segmentation of the interval of study, a survival estimate can be predicted at every occurrence of a TVC. A mortality score was then calculated by subtracting the survival estimate from one (Figure 22). Each individual patient’s mortality score was plotted vs. time since the Norwood operation to create dynamic risk profiles, using R 3.3.2 (R Foundation, Vienna, Austria).

![Figure 22: Survival and mortality scores. A mortality score (1-survival estimate) is generated at every time point at which an event occurs (“time to event in days”).](image.png)
4.1 Baseline pre-operative and echocardiographic characteristics

At the time of the analysis, 534 infants from the CHSS Critical LVOTO prospective inception cohort underwent a Norwood operation as their post-natal intervention and were analyzed in this study. Two-thirds were male. The median gestational age was 38 weeks (IQR 38-39) and the median birth weight was 3.2 kg (IQR 1.6-3.8). A genetic abnormality was diagnosed in 7%. HLHS was most commonly diagnosed by the infants’ treating institutions, in 92%, vs. other forms of LVOTO (Table 1).

On the baseline echocardiogram, extensive left heart hypoplasia and other pathology were observed. The median left ventricular (LV) end diastolic area was small, at 4 mm\(^2\) (IQR 1.5-7.1), with a much larger median right ventricular (RV) end diastolic area of 32 mm\(^2\) (IQR 25.9-36.6). The baseline aortic and mitral valve diameter z-scores were -15.5 (IQR -20.2 - -10.6) and -8.7 (IQR -11.0 - -5.8), respectively. The baseline ascending aorta diameter was 1.4 mm (IQR 0.9-2.3). Neither a ventricular septal defect nor a bilateral superior vena cava was frequently observed, in 13% and 5%, respectively.

Table 1: Baseline pre-operative and echocardiographic characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Overall Cohort (N=534)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>66% (346)</td>
<td>7</td>
</tr>
<tr>
<td>Prenatal diagnosis</td>
<td>73% (383)</td>
<td>12</td>
</tr>
<tr>
<td>Prenatal intervention</td>
<td>1% (4)</td>
<td>159</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.0 (38-39)</td>
<td>37</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.2 (1.6-3.8)</td>
<td>56</td>
</tr>
<tr>
<td>Low birth weight (&lt; 2.5 kg)</td>
<td>16% (87)</td>
<td>*</td>
</tr>
<tr>
<td>Genetic abnormality</td>
<td>7% (41)</td>
<td>4</td>
</tr>
<tr>
<td>White race</td>
<td>84% (363)</td>
<td>104</td>
</tr>
</tbody>
</table>

Primary institutional diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>92% (493)</td>
</tr>
<tr>
<td>Critical aortic stenosis</td>
<td>2% (13)</td>
</tr>
<tr>
<td>Aortic valve atresia</td>
<td>0.6% (4)</td>
</tr>
</tbody>
</table>
Mitral stenosis 0.2% (2)
Mitral atresia 0.2% (2)
Coarctation of the aorta 1% (3)
Interrupted aortic arch 2% (11)
Hypoplastic aortic arch 2% (11)

Baseline echocardiographic characteristics, core lab review

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular end diastolic area (mm²)</td>
<td>4.2 (1.5-7.1)</td>
</tr>
<tr>
<td>Right ventricular end diastolic area (mm²)</td>
<td>32.0 (25.9-36.6)</td>
</tr>
<tr>
<td>Moderate-severe tricuspid valve regurgitation</td>
<td>7% (28)</td>
</tr>
<tr>
<td>Tricuspid valve diameter z-score</td>
<td>-1.7 (-2.9 - -0.4)</td>
</tr>
<tr>
<td>Left pulmonary artery diameter z-score</td>
<td>-0.2 (-0.8-05)</td>
</tr>
<tr>
<td>Right pulmonary artery diameter z-score</td>
<td>-0.5 (-1.1-0.3)</td>
</tr>
<tr>
<td>Moderate-severe mitral valve stenosis</td>
<td>35% (188)</td>
</tr>
<tr>
<td>Mitral valve diameter z-score</td>
<td>-8.7 (-11.0 - -5.8)</td>
</tr>
<tr>
<td>Moderate-severe aortic valve stenosis</td>
<td>34% (127)</td>
</tr>
<tr>
<td>Aortic valve diameter z-score</td>
<td>-15.5 (-20.2 - -10.6)</td>
</tr>
<tr>
<td>Subvalvar LVOT diameter (mm)</td>
<td>1.6 (1.3-2.1)</td>
</tr>
<tr>
<td>Ascending aorta diameter (mm)</td>
<td>1.4 (0.9-2.3)</td>
</tr>
<tr>
<td>VSD</td>
<td>13% (56)</td>
</tr>
<tr>
<td>Bilateral SVC</td>
<td>5% (19)</td>
</tr>
</tbody>
</table>

Categorical data are presented as percentage (raw value). Continuous variables are presented as either means ± standard deviations or as medians (interquartile range), as appropriate. The number of missing variables requiring imputation for inclusion in multivariable hazard analyses is displayed.

Abbreviations: LVOT=Left ventricular outflow tract, SVC=Superior vena cava, VSD=Ventricular septal defect.

*A calculated variable from birth weight

4.2 Norwood operative characteristics

The median age at the Norwood operation was 6 days (IQR 0-48) and the median weight was 3.2 kg (IQR 2.9-3.5) kg. During the Norwood operation, an RVPA conduit was placed in 49% while a MBTS was implanted in 50%. The mean duration of cardiopulmonary bypass was 149.9 ± 45.9 minutes, while the median duration of deep hypothermic circulatory arrest was 8.0 minutes (IQR 4.0-34.0). The median oxygen saturation at the conclusion of the Norwood operation was 80% (IQR 75-85, Table 2).
Table 2: Norwood operative characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall Cohort (N=534)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Norwood (days)</td>
<td>6.0 (0-48)</td>
<td>0</td>
</tr>
<tr>
<td>Shunt type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBTS</td>
<td>49% (263)</td>
<td>0</td>
</tr>
<tr>
<td>RVPA conduit</td>
<td>50% (268)</td>
<td></td>
</tr>
<tr>
<td>Central shunt</td>
<td>1% (3)</td>
<td></td>
</tr>
<tr>
<td>Weight at Norwood (kg)</td>
<td>3.2 (2.9-3.5)</td>
<td>112</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>149.9 ± 45.9</td>
<td>54</td>
</tr>
<tr>
<td>Modified cerebral perfusion utilized</td>
<td>91% (349)</td>
<td>150</td>
</tr>
<tr>
<td>Duration of DHCA (min)</td>
<td>8.0 (4.0-34.0)</td>
<td>76</td>
</tr>
<tr>
<td>Oxygen saturation at end of Norwood operation (%)</td>
<td>80 (75-85)</td>
<td>119</td>
</tr>
</tbody>
</table>

Categorical data are presented as percentage (raw value). Continuous variables are presented as either means ± standard deviations or as medians (interquartile range), as appropriate. The number of missing variables requiring imputation for inclusion in multivariable hazard analyses is displayed.

Abbreviations: CPB=Cardiopulmonary bypass, DHCA=Deep hypothermic circulatory arrest, MBTS=Modified Blalock-Taussig shunt, RVPA=Right-ventricle-to-pulmonary-artery

4.3 Outcomes and risk factors after the Norwood operation

Of the 534 infants who underwent an initial Norwood operation, 70% underwent S2P, 22% died, 2% underwent heart transplantation, 3% underwent biventricular repair, and 3% were alive without transitioning to another end state (Figure 23). A single early phase of risk for death after the Norwood was noted (Figure 24). Factors associated with death after Norwood included undergoing an interval re-operation on the heart and great vessels (incorporated as a time-varying covariate), lower birth weight, lower oxygen saturation at the end of the Norwood operation, having a MBTS placed vs. a RVPA conduit, and a smaller baseline ascending aorta diameter (Table 3).
Figure 23: Outcomes in infants who underwent an initial Norwood operation.

Abbreviations: BVR=Biventricular repair, OHT=Orthotopic heart transplantation, S2P=Stage-2-palliation

Figure 24: Survival after the Norwood operation. A parametric model for the risk of death after the Norwood operation was created. The red line represents the survival function, based on a single early or simplified late phase model, while the dashed red lines represent the 70% confidence limits. The black circles represent the Kaplan-Meier estimates, with their 95% confidence limits.
**Table 3: Risk factors for death after the Norwood operation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Estimate ± SE*</th>
<th>P-Value</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval reoperation on heart and great vessels, time-varying covariable</td>
<td>1.19 ± 0.25</td>
<td>&lt; 0.0001</td>
<td>95%</td>
</tr>
<tr>
<td>Lower birth weight (kg)</td>
<td>8.09 ± 1.64</td>
<td>&lt; 0.0001</td>
<td>93%</td>
</tr>
<tr>
<td>Lower oxygen saturation at the end of the Norwood operation (%)</td>
<td>0.03 ± 0.01</td>
<td>&lt; 0.0001</td>
<td>50%</td>
</tr>
<tr>
<td>MBTS vs. RVPA conduit</td>
<td>0.80 ± 0.20</td>
<td>0.009</td>
<td>64%</td>
</tr>
<tr>
<td>Smaller baseline ascending aortic diameter (mm)</td>
<td>0.38 ± 0.11</td>
<td>0.0006</td>
<td>50%</td>
</tr>
</tbody>
</table>

*The parameter estimates may be interpreted analogously to the log-hazard ratios obtained from Cox proportional hazards analysis because only a single phase of risk is present.

**Abbreviations:** ECMO=Extracorporeal membrane oxygenation, RV=Right ventricular, S2P=Stage-2-Palliation, SE=Standard error

### 4.4 Characteristics of the post-Norwood period

The post-Norwood period was specifically defined as the time following the Norwood operation until transitioning to an end state (death, S2P, etc.), irrespective of hospital discharge. After the Norwood, the median length of stay was 25 days (IQR 16-40). The median duration of mechanical ventilation was 7 days (IQR 5-11). While 30% were diagnosed with gastro-esophageal reflux, fewer than 10% required re-intubation, were re-admitted to the hospital for a respiratory infection, or were diagnosed with necrotizing enterocolitis. The final cardiac catheterization before transitioning to an end state was performed at a median age of 118 days (IQR 84-154) or median length of 28 days (IQR 12-58) days from the catheterization to S2P.

The median Qp:Qs was 1.0 (IQR 0.74-1.32) and the median pulmonary vascular resistance was 1.9 Woods units (1.5-2.5). The median weight-for-age z-score (WAZ) was -1.1 (IQR -2.0 –-0.3). The final echocardiogram before transitioning to an end state was performed at a median age of 96 days (IQR 28–139), or a median interval of 40 days (IQR 11-107) before S2P. Moderate or severe RV dysfunction was diagnosed in 10% and moderate or severe atroventricular valve regurgitation was diagnosed in 22%. The final pre-S2P clinic visit before transitioning to an end state occurred at a median age of 121 days (IQR 93-157) or a median interval of 28 days (IQR 12-58) before S2P. The median WAZ at the final pre-S2P clinic visit was -1.1 (IQR -2.2 – 0.1) and the median oxygen saturation was 80% (IQR 76-83%, Table 4).
Table 4: Characteristics of the post-Norwood period

<table>
<thead>
<tr>
<th>Post-Norwood until day of S2P</th>
<th>Overall Cohort (N=534)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Norwood hospitalization (days)</td>
<td>25 (16-40)</td>
<td>140</td>
</tr>
<tr>
<td>Length of mechanical ventilation (days)</td>
<td>7 (5-11)</td>
<td>120</td>
</tr>
<tr>
<td>Required re-intubation after initial extubation</td>
<td>7% (37)</td>
<td>0</td>
</tr>
<tr>
<td>Required readmission for respiratory infection</td>
<td>5% (25)</td>
<td>0</td>
</tr>
<tr>
<td>Required home oxygen</td>
<td>5% (27)</td>
<td>0</td>
</tr>
<tr>
<td>Underwent tracheostomy</td>
<td>1% (3)</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis of necrotizing enterocolitis</td>
<td>12% (64)</td>
<td>0</td>
</tr>
<tr>
<td>Diagnosis of gastro-esophageal reflux</td>
<td>30% (158)</td>
<td>0</td>
</tr>
<tr>
<td>Pre-S2P cardiac catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at pre-S2P catheterization (days)</td>
<td>118 (84-154)</td>
<td>0</td>
</tr>
<tr>
<td>Interval from catheterization to S2P (days)</td>
<td>28 (12-58)</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>5.5 (4.5-6.3)</td>
<td>96</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td>-1.1 (-2.0 - -0.3)</td>
<td>103</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (Wood units)</td>
<td>1.9 (1.5-2.5)</td>
<td>161</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>1.0 (0.74-1.32)</td>
<td>130</td>
</tr>
<tr>
<td>Coarctation</td>
<td>15% (79)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate-severe right pulmonary artery stenosis</td>
<td>15% (80)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate-severe right pulmonary artery hypoplasia</td>
<td>10% (54)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate-severe left pulmonary artery stenosis</td>
<td>17% (89)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate-severe left pulmonary artery hypoplasia</td>
<td>13% (67)</td>
<td>0</td>
</tr>
<tr>
<td>Pre-S2P echocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at echocardiogram (days)</td>
<td>96 (28 – 139)</td>
<td>0</td>
</tr>
<tr>
<td>Interval from echocardiogram to S2P (days)</td>
<td>40 (11-107)</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.6 (3.5-5.9)</td>
<td>93</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td>-1.2 (-2.0 - -0.5)</td>
<td>103</td>
</tr>
<tr>
<td>Moderate-severe right ventricular dysfunction</td>
<td>10% (51)</td>
<td>0</td>
</tr>
<tr>
<td>Moderate-severe atrioventricular valve regurgitation</td>
<td>22% (117)</td>
<td>0</td>
</tr>
<tr>
<td>Pre-S2P clinic visit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at clinic visit (days)</td>
<td>121 (93-157)</td>
<td>0</td>
</tr>
<tr>
<td>Interval from clinic visit to S2P (days)</td>
<td>28 (12-58)</td>
<td>0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>5.4 (4.8-6.2)</td>
<td>178</td>
</tr>
<tr>
<td>Weight-for-age z-score</td>
<td>-1.1 (-2.2 – 0.1)</td>
<td>204</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>80 (76-83)</td>
<td>212</td>
</tr>
</tbody>
</table>

Categorical data are presented as percentage (raw value). Continuous variables are presented as either means ± standard deviations or as medians (interquartile range), as appropriate.
number of missing variables requiring imputation for inclusion in multivariable hazard analyses is displayed.

Abbreviations: S2P=Stage-2-palliation

During the post-Norwood period and prior to transition to another state, 164 infants underwent 222 interval catheter-based procedures and 50 patients underwent 75 interval re-operations on the heart and great vessels. Re-interventions on the aorta and conduit or shunt were most common (Table 5).

Table 5: Interval catheter-based and operative re-interventions on the heart and great vessels during the post-Norwood period

<table>
<thead>
<tr>
<th>Catheter re-interventions (patients)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balloon dilatation/stenting for recoarctation of aorta</td>
<td>104</td>
</tr>
<tr>
<td>Balloon dilatation/stenting of shunt</td>
<td>55</td>
</tr>
<tr>
<td>Balloon dilatation/stenting of pulmonary arteries</td>
<td>31</td>
</tr>
<tr>
<td>Coil embolization of collaterals</td>
<td>23</td>
</tr>
<tr>
<td>Atrial septostomy/stent</td>
<td>8</td>
</tr>
<tr>
<td>Arrhythmia ablation</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operative re-interventions (patients)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduit/shunt re-operation</td>
<td>25</td>
</tr>
<tr>
<td>Pulmonary arterial reconstruction</td>
<td>11</td>
</tr>
<tr>
<td>Systemic atroioventricular valve repair/replacement</td>
<td>6</td>
</tr>
<tr>
<td>MBTS implantation</td>
<td>6</td>
</tr>
<tr>
<td>Repair of supravalvar aortic stenosis</td>
<td>6</td>
</tr>
<tr>
<td>Permanent pacemaker implantation</td>
<td>6</td>
</tr>
<tr>
<td>ASD creation/enlargement</td>
<td>5</td>
</tr>
<tr>
<td>Neo-aortic valve repair</td>
<td>2</td>
</tr>
<tr>
<td>Repair of aortic re-coarctation</td>
<td>2</td>
</tr>
<tr>
<td>Aortic arch repair</td>
<td>1</td>
</tr>
<tr>
<td>DKS revision</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valvuloplasty</td>
<td>1</td>
</tr>
<tr>
<td>PAPVC repair</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary arterial banding</td>
<td>1</td>
</tr>
<tr>
<td>Removal of intracardiac mass</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are presented as raw frequencies of the interventions. Interventions could be performed more than once during the post-Norwood period.
Abbreviations: ASD=Atrial septal defect, DKS=Damus-Kaye-Stansel, MBTS=Modified Blalock-Taussig shunt, PAPVC=Partial anomalous pulmonary venous return

4.5 S2P operative characteristics

S2P was performed at a median age of 5.3 months (IQR 4.1-6.0) and a median WAZ of -1.1 (IQR -1.1 - 1.0) in 377 (71%) infants. A bidirectional Glenn was performed in 88% of patients. Cardiopulmonary bypass was used in 90% of operations and the mean bypass time was 90.9 ± 46.3 minutes. The S2P operations were relatively evenly distributed throughout all four seasons (Table 6).

Table 6: Stage-2-palliation operative characteristics

<table>
<thead>
<tr>
<th>Underwent S2P (N=377)</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Stage 2 operation</strong></td>
<td>14</td>
</tr>
<tr>
<td>Bidirectional Glenn</td>
<td>88% (318)</td>
</tr>
<tr>
<td>Hemi-Fontan</td>
<td>11% (40)</td>
</tr>
<tr>
<td>Kawashima</td>
<td>1% (4)</td>
</tr>
<tr>
<td><strong>Type of SVC to PA anastomosis</strong></td>
<td>20</td>
</tr>
<tr>
<td>Bilateral</td>
<td>5% (19)</td>
</tr>
<tr>
<td>Unilateral, left</td>
<td>1% (257)</td>
</tr>
<tr>
<td>Unilateral, right</td>
<td>94% (336)</td>
</tr>
<tr>
<td><strong>Age at S2P (months)</strong></td>
<td>5.3 (4.1-6.0)</td>
</tr>
<tr>
<td><strong>Weight at S2P (kg)</strong></td>
<td>6.2 (5.5-6.9)</td>
</tr>
<tr>
<td><strong>Weight-for-age z-score at S2P</strong></td>
<td>-1.1 (-1.1 - 1.0)</td>
</tr>
<tr>
<td><strong>CPB used</strong></td>
<td>97% (344)</td>
</tr>
<tr>
<td><strong>Elapsed time on CPB (min)</strong></td>
<td>90.9 ± 46.3</td>
</tr>
<tr>
<td><strong>Season of S2P</strong></td>
<td>0</td>
</tr>
<tr>
<td>Spring</td>
<td>25% (94)</td>
</tr>
<tr>
<td>Summer</td>
<td>22% (84)</td>
</tr>
<tr>
<td>Fall</td>
<td>25% (95)</td>
</tr>
<tr>
<td>Winter</td>
<td>28% (104)</td>
</tr>
</tbody>
</table>

Categorical data are presented as percentage (raw value). Continuous variables are presented as either means ± standard deviations or as medians (interquartile range), as appropriate. The number of missing variables requiring imputation for inclusion in multivariable hazard analyses is displayed.

Abbreviations: CPB=Cardiopulmonary bypass, PA=pulmonary artery, S2P=Stage-2-palliation, SVC=Superior vena cava
4.6 Outcomes and risk factors for death after S2P

Of the 377 infants who progressed to S2P, 66% subsequently underwent Fontan completion, 10% infants died, 3% underwent heart transplantation, 1% underwent biventricular repair, and 20% were alive without transitioning to another end state (Figure 25). Most deaths occurred in patients who underwent S2P at age six months or less. The distributions of age at S2P in months and outcomes are shown in Figure 26. A single phase of risk for death after S2P was again noted (Figure 27). The risk factors for death after S2P included moderate or severe RV dysfunction on the pre-S2P echocardiogram, younger age at S2P, requiring ECMO after the Norwood operation, and lower weight-for-age z-score at the pre-S2P cardiac catheterization (Table 7).

![Diagram of outcomes after stage-2-pallation]

**Figure 25: Outcomes after stage-2-pallation.**

*Abbreviations: BVR=Biventricular repair, OHT=Orthotopic heart transplantation, S2P=Stage-2-palliation*
Figure 26: The distribution of age at stage-2-palliation, by mortality status after S2P. This histogram represents the distribution of stage-2-palliation (S2P) by mortality status (death at any point after S2P).

Abbreviations: S2P=Stage-2-palliation
Figure 27: Survival after stage-2-pallation. A parametric model for the risk of death after stage-2-pallation was created. The red line represents the survival function, based on a single early or simplified late phase model, while the dashed red lines represent the 70% confidence limits. The black circles represent the Kaplan-Meier estimates, with their 95% confidence limits.

Abbreviations: S2P=Stage-2-palliation

Table 7: Risk factors for death after stage-2-palliation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Estimate ± SE*</th>
<th>P-Value</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-severe RV dysfunction on the pre-S2P echocardiogram</td>
<td>1.74 ± 0.38</td>
<td>&lt; 0.0001</td>
<td>95%</td>
</tr>
<tr>
<td>Younger age at S2P</td>
<td>1.46 ± 0.44</td>
<td>0.0004</td>
<td>71%</td>
</tr>
<tr>
<td>Required ECMO after the Norwood operation</td>
<td>1.39 ± 0.35</td>
<td>&lt; 0.0001</td>
<td>53%</td>
</tr>
<tr>
<td>Greater weight-for-age z-score at the pre-S2P cardiac catheterization</td>
<td>-0.28 ± 0.12</td>
<td>0.02</td>
<td>51%</td>
</tr>
</tbody>
</table>

*Because only a single phase of risk is present, the parameter estimates may be interpreted analogously to the log-hazard ratios obtained from Cox proportional hazards analysis.
4.7 Conditional survival through the first two stages of single ventricle palliation

Survival through the Norwood operation and S2P was predicted for each patient and averaged into a single estimate using parametric conditional survival analysis. At two years post-Norwood, survival through S2P was 73±5% (Figure 2A). As a measure of the validity, the results of parametric conditional survival analysis were compared to results obtained from the non-parametric conditional survival analysis based on Nelson cumulative hazard methodology. Using the Nelson method, two-year survival was 71±2%. Non-conditional Kaplan-Meier estimate for survival at two years post-Norwood was 71±2% (Figure 2B and C).
Figure 28: Conditional and non-conditional estimates of survival at two years post-Norwood. A. Parametric conditional survival at two years post-Norwood, conditional on survival to stage-2-palliation (S2P). The solid line represents a “cohort average,” or the average of curves produced for all 534 infants using their actual risk factor values. The dashed lines represent 70% confidence limits. B. Non-parametric conditional survival, at two years post-Norwood conditional on survival to S2P, using the Nelson cumulative hazard method. The dashed lines represent 70% confidence limits C. Simultaneous plots of parametric and non-parametric, conditional and non-conditional survival analysis are shown. Parametric (black line) and non-parametric (based on Nelson method, red line) conditional survival, two-years post-Norwood conditional on survival to S2P, with dashed lines represent 70% confidence limits. The Kaplan Meier estimates for overall survival after the Norwood operation are depicted by blue circles with bars representing 95% confidence limits (not conditional). Please note that the survival estimates all do not differ based on overlapping confidence limits.

4.8 Risk stratification

Patients were risk-stratified by predicting the cumulative hazard for death at one-year post-S2P and then ranking the infants by cumulative hazard. Patient characteristics differed significantly by risk group, as defined by quartiles. The first quartile was defined as low-risk, the second and third as intermediate-risk, and the fourth as high-risk. High-risk infants included all those diagnosed with moderate or severe RV dysfunction and 84% (37/44) of those who required ECMO after the Norwood operation. These high-risk infants also had the lowest median WAZ (-1.8, IQR -2.7 - -1.2) and underwent S2P at the youngest median age (4.5 months old, IQR 3.2-5.5). Overall, non-time-related mortality was greatest in high-risk patients, at 26 vs. 2% and 6% (p < 0.0001) in low- and intermediate-risk infants, respectively (Table 8). High-risk status was more common in age six months or less, while low risk status became more common after age 4 months (Figure 29).
Table 8: Characteristics of patients undergoing stage-2-palliation by risk group

<table>
<thead>
<tr>
<th></th>
<th>Low Risk (N=95)</th>
<th>Intermediate Risk (N=188)</th>
<th>High Risk (N=94)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at S2P (months)</td>
<td>6.5 (5.6-7.9)</td>
<td>4.8 (4.2-5.6)</td>
<td>4.5 (3.2-5.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Weight-for-age z-score at pre-S2P cardiac catheterization</td>
<td>-0.1 (-0.7-0.8)</td>
<td>-1.2 (-1.9 - -0.4)</td>
<td>-1.8 (-2.7 - -1.2)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Moderate-severe RV dysfunction on pre-S2P echocardiogram</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>26% (24)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Required ECMO post-Norwood</td>
<td>0% (0)</td>
<td>4% (7)</td>
<td>39% (37)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Overall mortality after S2P†</td>
<td>2% (2)</td>
<td>6% (12)</td>
<td>26% (24)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Categorical variables were compared using the chi-square test and continuous variables were compared using the Kruskal-Wallis test.

Abbreviations: ECMO=Extracorporeal membrane oxygenation, RV=Right ventricular, S2P=Stage-2-palliation

† Non-time-related
Figure 27: The distribution of age at stage-2-palliation across risk groups for S2P. This histogram represents the distribution of age at stage-2-palliation by patient risk groups. Risk groups were determined by predicting the cumulative hazard for death at one year post-stage-2-palliation and ranking by cumulative hazard.

Abbreviations: S2P=Stage-2-palliation

4.9 Optimal timing of S2P across risk groups

Optimal timing was determined by plotting nomograms of two-year post-Norwood survival as a function of age at S2P. The optimal timing of S2P differed across patient risk groups. In infants at low and intermediate risk post-S2P, 2-year survival was lowest when S2P was performed at age 2 months (84±5% and 77±6%, respectively). Survival did not differ when S2P was performed at age 4, 6, or 8 months (Figures 30A and 30B). Two-year survival was maximal (89±3% and 82±3%) when performing S2P after age 3 months (Figure 30C). In the high-risk group, when S2P was performed at age 2, 4, 6, or 8 months, 2-year survival was 0±7%, 15±14%, 34±12%, and 46±13%, respectively (Figure 31A). Predicted 2-year survival was ≤63±5% at any age for S2P (Figure 31B).
Figure 30: The optimal timing of stage-2-palliation in low- and intermediate-risk groups.

A. Predicted 2-year, post-Norwood survival over time in a low-risk patient, stratified by age at stage-2-palliation (2, 4, 6, or 8 months old). Patient characteristics: no interval reoperation, birth weight=3.0 kg, right-ventricle-to-pulmonary-artery (RVPA) conduit, oxygen saturation at the end
of the Norwood=89%, baseline ascending aorta diameter=2.5mm, no pre-S2P right ventricular (RV) dysfunction, weight-for-age z-score at the pre-S2P cardiac catheterization (WAZ)=0.1, did not require extracorporeal membrane oxygenation (ECMO) post-Norwood. B. Predicted 2-year, post-Norwood survival over time in an intermediate-risk patient, stratified by age at S2P (2, 4, 6, or 8 months old). Patient characteristics: no interval reoperation, birth weight=3.0 kg, RVPA conduit, oxygen saturation at the end of the Norwood=72%, baseline ascending aorta diameter=2.0mm, no pre-S2P RV dysfunction, WAZ=-1.1, no ECMO post-Norwood. C. Predicted 2-year, post-Norwood survival vs. age at S2P in low- and intermediate-risk patients. Dashed lines represent 70% confidence limits. Patient characteristics are defined in parts A and B.

Abbreviations: S2P=Stage-2-palliation
Figure 31: The optimal timing of stage-2-palliation in high-risk infants. A. Predicted 2-year, post-Norwood survival over time in a high-risk patient, stratified by age at stage-2-palliation (S2P, 2, 4, 6, or 8 months). Patient characteristics: no interval reoperation, birth weight=2.9 kg, right-ventricle-to-pulmonary-artery conduit, oxygen saturation at the end of the Norwood=75%, baseline ascending aorta diameter=1.5mm, pre-S2P right ventricular dysfunction present, weight-for-age z-score at the pre-S2P cardiac catheterization=-1.8, required extracorporeal membrane oxygenation post-Norwood. B. Predicted 2-year, post-Norwood survival vs. age at S2P in a high-risk post-S2P patient. Dashed lines represent 70% confidence limits. Patient characteristics are defined in part A.

Abbreviations: S2P=Stage-2-palliation
4.10 Optimal timing of S2P in the presence of specific risk factors

The effect of specific risk factors on the timing of S2P was investigated further in intermediate-risk infants. Survival was greatest in infants with a RVPA conduit or a MBTS when S2P was performed after age 3 months (82±3% vs. 74±4%) and survival through S2P was lower overall in those with a MBTS (Figure 32A). Undergoing an interval reoperation resulted in lower 2-year survival after age 2 months at S2P, which continued to decrease (≤50±11%, Figure 32B). Survival was ≤61±7% if S2P was performed before age 6 months in those with moderate-severe RV dysfunction (Figure 32C).
Figure 32: The optimal timing of Stage-2-palliation in patients with specific risk factors. A. Predicted 2-year, post-Norwood survival vs. age at S2P, stratified by shunt type. B. Predicted 2-year, post-Norwood survival vs. age at S2P, stratified by interval cardiac reoperation. C.
Predicted 2-year, post-Norwood survival vs. age at S2P, stratified by the presence of moderate-severe pre-S2P right ventricular dysfunction.

Patient characteristics, unless otherwise specified: no interval reoperation, birth weight=3.3 kg, modified Blalock-Taussig shunt, oxygen saturation at the end of the Norwood=80%, baseline ascending aorta diameter=1.5mm, no pre-S2P right ventricular dysfunction, weight-for-age z-score at the pre-S2P cardiac catheterization=-2.0, no extracorporeal membrane oxygenation post-Norwood.

*Abbreviations*: S2P=Stage-2-palliation

### 4.11 Developing a model for post-Norwood surveillance

#### 4.11.1 Longitudinal measures of weight and oxygen after the Norwood operation

Measures of oxygen saturation and weights recorded after the Norwood operation were available for 360 of the 534 (67%) patients included in the study. Baseline measurements were defined as the first measurement of oxygen saturation (SaO₂) taken post-operatively after the Norwood operation and as the weight on the day of the Norwood operation. A total of 963 measures were available for the 360 patients, with a median of 4 measurements (IQR 3-7) per infant. The median interval between measurements was 81 days (IQR 49-123).

The median baseline weight post-Norwood was 3.2 kg (IQR 2.9-3.5) and median final weight was 4.3 kg (IQR 3.2-5.5). The distribution of individual patients’ weight over time post-Norwood is displayed in Figure 31. Mixed effects modeling demonstrated that weight increased linearly over time (Figure 33).

Weight-for-age z-scores (WAZ) were also computed, with a median baseline WAZ of -0.5 (IQR -1.2-0.2) and median final WAZ of -1.2 (IQR -2.2 - -0.5). The distribution of individual patients’ WAZ post-Norwood is displayed in Figure 32. Mixed effects modeling demonstrated that WAZ initially decreased rapidly and non-linearly over time, then eventually stabilizing into a gradual decline (Figure 34).
Figure 33: Weight over time after the Norwood operation. Weights (kg, blue dots) are connected by thin black lines representing an individual patient's weight measurements since the day of the Norwood operation. The thick red line represents the linear mixed effects model, demonstrating a linear increase in weight post-Norwood.
**Figure 34:** Weight-for-age z-scores over time after the Norwood operation. Weight-for-age z-scores (blue dots) are connected by thin black lines representing an individual patient’s Weight-for-age z-scores since the day of the Norwood operation. The thick orange line represents the non-linear mixed effects model demonstrating a non-linear decrease in weight-for-age z-scores post-Norwood.

The median baseline SaO\textsubscript{2} after the Norwood operation was 80% (IQR 75-85) and the median final SaO\textsubscript{2} post-Norwood was also 80% (IQR 75-84). The distribution of individual patients’ SaO\textsubscript{2} over time post-Norwood is displayed in Figure 33. Mixed effects modeling demonstrated that SaO\textsubscript{2} decreased linearly over time (Figure 35).
Figure 35: Oxygen saturation (SaO\textsubscript{2}) over time after the Norwood operation. SaO\textsubscript{2} (blue dots) are connected by thin black lines representing an individual patient’s SaO\textsubscript{2} since the day of the Norwood operation. The thick orange line represents the linear mixed effects model demonstrating a linear decrease in SaO\textsubscript{2} post-Norwood.

4.11.2 Time-related events after the Norwood operation

In total, 1,344 time-related events, which encompassed complications, re-interventions, and diagnoses of cardiac dysfunction, occurred after the Norwood operation for the 360 infants for which weight and SaO\textsubscript{2} measurements were available. The diagnostic criteria for these events can be found in Appendix Table 1. The frequencies of the events, the number of unique patients experiencing each event, and the number of patients with each event who died are summarized in Table 9.
Table 9: Time-related events after the Norwood operation

<table>
<thead>
<tr>
<th>Event</th>
<th># Events*</th>
<th># Patients†</th>
<th># Died‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>12</td>
<td>12</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>11</td>
<td>11</td>
<td>5 (45%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>17</td>
<td>17</td>
<td>6 (35%)</td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCS post-Norwood</td>
<td>75</td>
<td>63</td>
<td>28 (44%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>50</td>
<td>48</td>
<td>26 (54%)</td>
</tr>
<tr>
<td>Interventional catheter procedure</td>
<td>151</td>
<td>127</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>Aorta</td>
<td>44</td>
<td>44</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Atrial septum</td>
<td>8</td>
<td>8</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Coiling of collaterals</td>
<td>16</td>
<td>16</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Conduit/shunt</td>
<td>39</td>
<td>34</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>PA</td>
<td>19</td>
<td>18</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Other</td>
<td>28</td>
<td>7</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>Re-operation on heart and great vessels</td>
<td>35</td>
<td>31</td>
<td>10 (32%)</td>
</tr>
<tr>
<td>Aorta</td>
<td>3</td>
<td>3</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Atrial septectomy</td>
<td>2</td>
<td>2</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Conduit/shunt</td>
<td>11</td>
<td>9</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>PA repair/augmentation/patching</td>
<td>9</td>
<td>8</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Pacemaker placement</td>
<td>4</td>
<td>4</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>AVV repair</td>
<td>5</td>
<td>4</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Other – DKS revision</td>
<td>1</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Non-operative cardiac readmission</td>
<td>146</td>
<td>87</td>
<td>17 (20%)</td>
</tr>
<tr>
<td>Required inotropes during readmission</td>
<td>16</td>
<td>15</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Moderate/severe RV dysfunction on pre-S2P echo</td>
<td>33</td>
<td>33</td>
<td>13 (39%)</td>
</tr>
<tr>
<td>Moderate/severe AVVR on pre-S2P echo</td>
<td>79</td>
<td>79</td>
<td>15 (19%)</td>
</tr>
<tr>
<td>Recoarctation on pre-S2P catheterization</td>
<td>56</td>
<td>56</td>
<td>3 (5%)</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required CPAP</td>
<td>20</td>
<td>19</td>
<td>5 (26%)</td>
</tr>
<tr>
<td>Reintubation</td>
<td>43</td>
<td>43</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>4</td>
<td>4</td>
<td>1 (25%)</td>
</tr>
<tr>
<td><strong>Other operative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation for chylothorax</td>
<td>14</td>
<td>10</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Non-cardiac reoperation</td>
<td>119</td>
<td>90</td>
<td>20 (22%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>44</td>
<td>38</td>
<td>5 (13%)</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>6</td>
<td>5</td>
<td>3 (60%)</td>
</tr>
<tr>
<td><strong>Infectious disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td>51</td>
<td>38</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>Sternal wound infection/mediastinitis</td>
<td>33</td>
<td>28</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Line-associated infection</td>
<td>4</td>
<td>4</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2</td>
<td>2</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
### 4.11.3 Outcomes and model for death after Norwood, incorporating time-related events and measures

A separate model for death after the Norwood operation was created using the 360 patient cohort, in which baseline, echocardiographic, and Norwood operative characteristics, in addition to time-related post-Norwood events and measures of weight and $\text{SaO}_2$ were considered as candidate covariates. It was necessary to use sub-population so that only patients without missing values for the longitudinal measures of weight or oxygen saturation were included. Among the 360 patient sub-population, 282 (78%) underwent S2P, 60 (17%) died, 5 (1%) underwent heart transplantation, and 13 (4%) underwent either biventricular repair or were lost to follow-up. Consistent with the previous model for death after the Norwood, a single phase of risk was again noted. Resuscitated cardiac arrest, the diagnosis of moderate to severe RV dysfunction on the infant’s final echocardiogram, the diagnosis of moderate to severe AVVR on the infant’s final echocardiogram, diagnosis of sepsis, undergoing an operation for a chylothorax, lower $\text{SaO}_2$ (logarithmic transformation), non-operative readmission, having an ischemic stroke, requiring re-intubation after the initial post-Norwood extubation, and smaller weight (inverse transformation) were significantly associated with death after the Norwood operation (Table 10).
Table 10: Risk factors for death after the Norwood operation, incorporating time-related post-Norwood measures and events

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>PE ± STD</th>
<th>P-value</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resuscitated cardiac arrest (TVC)</td>
<td>1.62 ± 0.29</td>
<td>&lt; 0.0001</td>
<td>94%</td>
</tr>
<tr>
<td>Moderate/severe RV dysfunction on final echocardiogram (TVC)</td>
<td>1.53 ± 0.47</td>
<td>0.001</td>
<td>83%</td>
</tr>
<tr>
<td>Moderate/severe AVVR on final echocardiogram (TVC)</td>
<td>1.03 ± 0.46</td>
<td>0.02</td>
<td>74%</td>
</tr>
<tr>
<td>Sepsis diagnosed (TVC)</td>
<td>1.97 ± 0.55</td>
<td>0.0003</td>
<td>65%</td>
</tr>
<tr>
<td>Chylothorax operation (TVC)</td>
<td>1.79 ± 0.52</td>
<td>0.0006</td>
<td>64%</td>
</tr>
<tr>
<td>Lower SaO₂ (TVC, %, logarithmic transformation)</td>
<td>3.40 ± 0.87</td>
<td>0.0001</td>
<td>62%</td>
</tr>
<tr>
<td>Non-operative readmission (TVC)</td>
<td>0.91 ± 0.36</td>
<td>0.01</td>
<td>55%</td>
</tr>
<tr>
<td>Ischemic stroke (TVC)</td>
<td>1.27 ± 0.52</td>
<td>0.01</td>
<td>53%</td>
</tr>
<tr>
<td>Re-intubation (TVC)</td>
<td>0.71 ± 0.36</td>
<td>0.04</td>
<td>51%</td>
</tr>
<tr>
<td>Smaller weight (TVC, kg, inverse transformation)</td>
<td>5.16 ± 2.02</td>
<td>0.01</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Because only a single phase of risk is present, the parameter estimates may be interpreted analogously to the log-hazard ratios obtained from Cox proportional hazards analysis.

Abbreviations: AVVR=Atrioventricular valve regurgitation, RV=Right ventricular, SaO₂=Oxygen saturation, SE=Standard error, TVC=Time-varying covariate

4.11.4 Dynamic risk profiles – overall results

The model was then used to predict a survival estimate (bounded from 0 to 1) at every time point at which a time-related event or longitudinal measurement occurred. A risk score for death was calculated by subtracting each one from each survival estimate. Dynamic risk profiles were then created for every infant by plotting his/her risk score at the occurrence of each time-related event or longitudinal measurement vs. time. Dynamic risk profiles depict an individual infant’s instantaneous risk of death over time and are shown in Figure 36, stratified by final end state. Lines connect the point estimates for the risk scores. Final risk scores differed significantly (Table 11).

Table 11: Risk scores on the day of reaching final end state

<table>
<thead>
<tr>
<th></th>
<th>Stage 2 (n=282)</th>
<th>Dead (n=60)</th>
<th>Transplant (n=5)</th>
<th>Alive (n=13)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality score</td>
<td>6.5 (3.8-14.1)</td>
<td>19.3 (5.2-79.6)</td>
<td>20.3 (18.2-93.8)</td>
<td>6.2 (3.5-11.6)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
Scores presented as medians (IQR) and were compared using the Kruskal-Wallis test.

**Figure 36**: Dynamic risk profiles for 360 infants who underwent a Norwood operation. The instantaneous risk of death is presented as a risk score, or the survival estimate at a given time subtracted from 1. The risk score may increase or decrease. Lines connect risk scores (1-survival point estimates) in which an event occurred. Individual infants are color-coded based on their end state following the Norwood. Stage 2 indicates either a bidirectional Glenn or a Hemi-Fontan. Other indicates a biventricular repair or loss of follow-up.

*Abbreviations: Txp=Heart transplantation*
4.11.5 Dynamic risk profiles – qualitative assessment

An initial review of the individual patient risk profiles demonstrates that several broad groups are present in Figure 36. Among those who progressed to S2P, there is a group whose risk scores remained low and underwent S2P within the expected time from over 3-6 months post-Norwood. The risk scores of another group of those who underwent S2P appeared to rise quickly, with some even oscillating up and down, and underwent S2P between about 3-10 months post-Norwood. Among the infants who died, a group exists whose risk scores remained low, but they died within one-month post-Norwood. The risk scores for another group started low and rose after 1 month post-Norwood, with deaths occurring at about 2 months post-Norwood and after, with much higher risk scores.

4.11.6 Risk scores may increase or decrease

The individual risk profile for an infant who progressed to S2P is shown in Figure 37. The infant was born at 34 weeks' gestation, weighed 2.2kg at birth, and underwent a Norwood operation with an RVPA conduit on day-of-life (DOL) 7. The infant experienced a cardiac arrest 10 days post-Norwood, and then risk score rose to 12%. The infant then was diagnosed with NEC. Although NEC’s association with death post-Norwood did not reach significance such that it would be included in the model, the risk score increased, because time increased. It continued to rise, until a catheter-based procedure on the RVPA conduit at 111 days post-Norwood led to SaO₂ of 80%, dropping the risk of death. The risk then again only rose slightly, as time increased, until a non-cardiac operation, which also did not reach significance in the model. The risk score then increased when the infant was readmitted to the hospital, increased again when the SaO₂ had deteriorated to 67%, and then decreased when the SaO₂ improved to 79% at 178 days post-Norwood. The infant then remained in the hospital and progressed to S2P at 6.6 months post-Norwood, with a final risk score of 39%. The infant was alive at last follow-up, 4.6 years after S2P.
Figure 37: Individual dynamic risk profile for an infant who survived to undergo Stage-2-Palliation at 6.6 months post-Norwood. Lines connect risk scores (1-survival point estimates) in which an event occurred. The black text represents the occurrence of events that were included in the model for death after the Norwood operation, while the purple text indicates the occurrence of an event that was not included in the model.

Abbreviations: Dx=Diagnosis, DOL=Day of life, NEC=Necrotizing enterocolitis, Proc=Procedure RVPA=Right ventricle to pulmonary artery, S2P=Stage-2-palliation, SaO$_2$=Oxygen saturation

4.11.7 The effect of time on the magnitude of risk factor effect

The individual risk profile for an infant who died during the post-Norwood course is shown below in Figure 38. The infant was born at 39 weeks’ gestation, weighed 3.5 kg at birth, and underwent a Norwood operation with an RVPA conduit on DOL 2. The infant’s risk score rose slowly until 60 days of age, when the infant was readmitted after having gained only 0.3 kg and with a 10% decrease in SaO$_2$. While the risk score stabilized until a catheter-based procedure on the RVPA conduit (not included in the model), the infant’s rise core approximately doubled to over 20% when the infant required re-intubation and was diagnosed with a bloodstream
infection at 132 days post-Norwood. The infant then had a cardiac arrest and an ischemic stroke, 3 and 5 days later, respectively, after which the risk score increased substantially to 100%. Soon after, the infants' parents withdrew support, given likely neurologic devastation incurred during the cardiac arrest and persistently positive blood cultures. In comparison to the patient shown in Figure 37, the effect of a cardiac arrest was much greater, given that it happened later in time.

Figure 38: Individual dynamic risk profile for an infant who died 4.7 months post-Norwood. Lines connect risk scores (1-survival point estimates) in which an event occurred. The black text represents the occurrence of events that were included in the model for death after the Norwood operation, while the purple text indicates the occurrence of an event that was not included in the model. Abbreviations: BSI=Bloodstream infection, Cx=Culture, DOL=Day of life, MCS=Mechanical circulatory support, RVPA=Right ventricle to pulmonary artery, SaO₂=Oxygen saturation
4.11.8 The accumulation of multiple risk factors

The individual risk profile for an infant who underwent heart transplantation post-Norwood is shown below in Figure 39. The infant was born at 41 weeks’ gestation, weighed 4 kg at birth, and underwent a Norwood operation with an MBTS on DOL 5. The infant’s risk score stayed low as time progressed through nearly the first two months post-Norwood, until the infant was readmitted to the hospital. However, the risk score increased substantially to over 30%, when the infant suffered a cardiac arrest at four months post-Norwood. While the risk later improved minimally with increase in weight and SaO₂, it did not drop considerably. Then, when the infant was diagnosed with moderate to severe AVVR an RV dysfunction, the risk score to 99%. The infant had been evaluated for heart transplantation during this time, and was transplanted at 7.1 months post-Norwood, with a final risk score of 99%. The patient is alive 7 years later at last follow-up.

Figure 39: Individual dynamic risk profile for an infant who underwent heart transplantation 7.1 months post-Norwood and is alive at last follow-up, 7 years later. Lines connect risk scores (1-survival point estimates) in which an event occurred. The black text represents the occurrence
of events that were included in the model for death after the Norwood operation, while the purple text indicates the occurrence of an event that was not included in the model.

Abbreviations: AVVR=atrioventricular valve regurgitation, DOL=Day of life, HTxp=heart transplantation, MBTS=Modified Blalock-Taussig shunt, RV dysfx=RV dysfunction, SaO$_2$=Oxygen saturation, URI=Upper respiratory tract infection
Mortality during staged surgical palliation for HLHS and its related malformations continues to be high, especially prior to S2P. Given the low prevalence of these conditions, performing high-quality studies has been challenging. In this analysis of a large cohort of infants undergoing the Norwood operation, we sought to determine how to optimally time S2P and then develop a tool to track a patients’ instantaneous risk of death after the Norwood. The timing of S2P is critically important for two reasons: 1) Norwood physiology is inherently much less stable vs. the somewhat more balanced circulation in place after progressing to S2P and 2) it is a physician-modifiable variable. In this study, we have shown that younger age at S2P is independently associated with death after S2P. We also demonstrate that in low/intermediate-risk infants, performing S2P after age 3 months is associated with maximal two-year survival. In high-risk patients, two-year survival was very low, regardless of age at S2P. Finally, using novel methodology, we have developed a tool to depict updatable, instantaneous risk trajectories during the post-Norwood period. These insights obtained from these complex analyses provide evidence to inform data-driven clinical decision making in this high-risk and difficult to study cohort.

5.1 Age at S2P is independently associated with death

The importance of the age at S2P has been investigated in several single center and a few multicenter studies. Most have not analyzed timing directly and are limited by either small sample sizes, analyses of only post-S2P outcomes (without accounting for pre-S2P attrition), or both. Scheurer et al., Kogon et al., and Alsoufi et al. examined the post-S2P outcomes of 270, 167, and 227 patients. None of these analyses found an association between age at S2P and mortality, instead reporting various associations of diagnostic, anatomic or pathophysiologic factors (such as persistently elevated PVR) with death (Scheurer, Hill et al. 2007; Kogon, Plattner et al. 2008; Alsoufi, Manlhiot et al. 2011). In comparison, several other studies did demonstrate an association between age at S2P and the risk of adverse outcomes. In studies of 194 and 557 patients, Friedman et al. and Lee et al. analyzed age at S2P and identified age younger than three months at S2P as associated with death or heart transplantation after S2P (Friedman, Salvin et al. 2011; Lee, Aiyagari et al. 2012). However, they analyzed age as a
categorical variable, dichotomized into younger or older than three months old, in contrast to the analysis of the entire spectrum of age at S2P performed in this study. Recently, in a cohort of 114 patients, Francois et al. demonstrated that age (as a continuous variable) was associated with greater risks for in-hospital mortality, reintubation, and longer ICU length of stay (Francois, Vandekerckhove et al. 2016).

Two analyses of larger populations have also shown apparently contradictory associations between age at S2P and adverse outcomes. A prior CHSS analysis of infants with critical aortic stenosis and aortic atresia enrolled from 1994-2000 did identify younger age at S2P as a risk factor for death, but the authors did not perform a detailed analysis of timing (Ashburn, McCrindle et al. 2003). Schwartz and colleagues examined risk factors for prolonged post-operative length of stay in 393 infants enrolled in the SVR Trial who underwent S2P, identifying a non-elective indication for S2P, among others, but not age at S2P (Schwartz, Lu et al. 2014). “Non-elective indication” is a broad variable that is a composite of many indicators of an infants’ status during the post-Norwood period, including oxygen saturation, weight, status of the shunt, and more. More accurately, it reflects physician decision-making, or physician behavior in response to a patient’s status, and can result in earlier or later S2P.

5.2 Previous analyses of timing fail to account for pre-S2P attrition

Several prior studies have sought to investigate the optimal timing of S2P. All share the limitation - that only post-S2P outcomes were examined and the much higher risk of death pre-S2P was not accounted for. Jaquiss and colleagues examined in- and out-of-hospital mortality in infants who underwent S2P before or after age four months. They found no difference in survival between the two groups, but those who underwent S2P before age 4 months required longer ICU and hospital stays and longer chest tube duration (Jaquiss, Ghanayem et al. 2004). A subsequent study by the same investigators demonstrated that no difference existed in the achievement of Fontan completion between the two groups (Jaquiss, Siehr et al. 2006). Petrucci and colleagues examined outcomes in an even younger group undergoing S2P, those three months of age and younger. While only 20 of the 169 infants included underwent S2P at age three months or younger, they found no difference in outcomes and concluded that S2P in infants as young as two months old is not harmful (Petrucci, Khoury et al. 2010). A recent multicenter analysis of the NPC-QIC data demonstrated that the median age at S2P from 31
centers varies significantly by center. The median of all centers’ median ages at S2P of 155 days (IQR 109-214). This study did indirectly analyze the risk of death pre-S2P, demonstrating that the risk of interstage death was greater among the institutions with median center-specific age at S2P greater than 155 days (Hill, Rudd et al. 2016).

5.3 The advantages of parametric conditional survival analysis

We here have utilized a unique analytic technique to account for the staged procedures of single ventricle palliation, parametric conditional survival analysis. Non-parametric or semi-parametric forms, based on Kaplan-Meier or Cox methods, are more commonly encountered in the literature. They have been applied with increasing frequency across medical and surgical oncology over the last two decades. They have been used to derive valuable prognostic information regarding survival beyond a given earlier time point, e.g. survival to five years, given survival to one year after cancer resection or diagnosis (Zabor, Gonen et al. 2013). In the study of congenital heart disease, conditional survival analysis has been very infrequently applied. Non-parametric conditional survival analysis was used to examine survival after heart transplantation for congenital heart disease (Dipchand, Rossano et al. 2015). Other possible methods, such as splines or locally-weighted scatter plot smoothing (LOESS) regression would have also been useful to explore the relationship between age at S2P with the risk mortality after S2P, especially if it was non-linear. LOESS regression is also unable to account for staged procedures.

To define the optimal timing of S2P, the analysis must balance the attrition during the high-risk post-Norwood as well as the risk of death after S2P. Given that single ventricle palliation involves three consecutive operations with unequal risks of death between each stage, non-parametric conditional survival analysis was inadequate for this study. First, it cannot include all patients in the study population in the conditional analysis, only those that survive to the given event or only those infants who survive to S2P in this study. Non- or semi-parametric methods thereby fail to account for the significant attrition prior to S2P. Using a novel application of this conditional survival, within the parametric domain, we were able to describe more completely survival from the Norwood procedure, through S2P, and to two years post-Norwood.
5.4 Accounting for intentionality

In addition to accounting for staged procedures, the rationale or indication for the timing of progression to S2P needed to be considered as well. S2P can be safely performed electively once the pulmonary vascular resistance has fallen in a patient who has not experienced complications, is growing well, and with stable oxygen saturations. However, clinicians may opt to proceed with “earlier” S2P for reasons such as to address the sudden development of cyanosis, to reduce the volume load on the heart in an infant in heart failure, and other reasons. S2P may be delayed for medical reasons such as the development of an intercurrent respiratory infection, to allow more time for increased caloric intake and somatic growth in an infant failing to thrive, and more. Therefore, it can be argued that infants who require elective vs. “non-elective” progression to S2P represent distinct populations. However, little evidence exists to guide the decision to accelerate or delay S2P. Heterogeneity exists in surgeons’ opinions regarding these “non-elective” cases (Meza, Jaquiss et al. 2017). In this study, we first sought to understand the full spectrum of operative indications for S2P via a thorough chart review. We next strove to include as many variables as possible that could describe each possible non-elective indication for rigorous risk adjustment (Appendix Table 3). Finally, due to likely significant variation in decision-making between surgeons and centers for non-elective S2P, we elected to objectively risk stratify patients for our analysis of timing. Using these strategies, we strove to eliminate the subjectivity associated with elective vs. non-elective progression to S2P and instead to analyze the infants’ clinical status in as much detail as possible.

5.5 Optimal timing in low- and intermediate-risk infants

In low- and intermediate-risk patients, maximal survival at two years post-Norwood was associated with proceeding to S2P after age 3 months. Our results are in agreement with the studies by Jaquiss and colleagues from 2004 and 2006 (Jaquiss, Ghanayem et al. 2004; Jaquiss, Siehr et al. 2006). They are also in accord with a recent study by Barron and colleagues that suggested that in patients without risk factors, earlier S2P is safe, although they neither accounted for pre-S2P attrition nor found an association between age at S2P and the risk of death/heart transplantation (Barron, Haq et al. 2017). On the other hand, our results do not support the conclusions from the study by Petrucci and colleagues that S2P is safe to perform in infants as young as two months old (Petrucci, Khoury et al. 2010). This conclusion is based on the outcomes of 20 patients, a sample size so small that no difference in outcomes
was likely to be detected when this group’s outcomes was compared with the study’s remaining 149 patients. Our data indicate that mortality may be greater if S2P is performed at two months old.

Some surgeons prefer to delay S2P, due to concerns for inadequate somatic growth, pulmonary arterial underdevelopment, or persistently elevated pulmonary vascular resistance. In this analysis, we were unable to determine the optimal oldest age for S2P, as only 25% of infants underwent S2P after 6 months old and, in this upper quartile, only seven of the 38 post-S2P deaths occurred, providing few events for analysis. Also, only 14 infants in this quartile were classified as high-risk, indicating that most who survived this long in Norwood circulation (with its high risk of death) were robust and developed few risk factors.

5.6 The potential benefits of prompt progression to S2P

Although our results do not indicate that delaying S2P is harmful, a compelling case can be made for transitioning out of parallel Norwood circulation as soon as is safe, given the marked decrease in mortality risk following S2P. Several potential non-mortality outcomes may benefit from timely transition to S2P, as well. Growth velocity is substantially impaired after the Norwood operation and returns to a more rapid, though not entirely normal, trajectory following S2P (Vogt, Manlihot et al. 2007; Francois, Bove et al. 2012). The weight-for-age z-score for an infant with Norwood circulation actually declines rapidly in the initial post-operative period and continues to decrease, though more slowly following hospital discharge (Burch, Gerstenberger et al. 2014). Aggressive nutritional support and interstage weight monitoring have been advocated, and have resulted in improved weight gain, but have not affected post-Norwood mortality (Williams, Zak et al. 2011; Oster, Ehrlich et al. 2015). The restoration of less physiologically demanding in-series circulation may aid in improving somatic growth velocity.

Furthermore, HLHS is among the most expensive birth defects cared for in the United States. Both the Norwood hospitalization and interstage period represent especially costly periods (CDC 2003; Danford, Karels et al. 2015). Neither ICU nor overall hospital length of stay increases if S2P is performed before 4 months old (Jaquiss, Siehr et al. 2006). Even though it is impractical and of unknown clinical benefit for these infants to remain hospitalized between the Norwood and S2P, resource use for these infants remains high given that many centers have established both high-risk clinics for weekly appointments during interstage period and home
monitoring programs. Prompt transition to the more stable S2P would allow for the cessation of this intensive resource utilization as soon as it is appropriate.

Finally, the interstage period is very stressful for parents, given their child’s tenuous clinical status, frequent medical appointments, invasive procedures such as cardiac catheterization, and need for home monitoring. High levels of anxiety and depression in the parents of critically ill children have been described, specifically regarding feeding regimens after the Norwood operation (Doering, Moser et al. 2000; Stewart, Dempster et al. 2015). The ability to plan prompt progression to S2P after 3 months and transition out of the unstable Norwood circulation for low- and intermediate-risk infants may be effective in reducing parental anxiety.

5.7 The effect of high-risk features on the timing of S2P

High-risk features significantly reduced survival through the first two stages of single ventricle palliation. RV dysfunction prior to S2P was strongly associated with death. Jean-St-Michel et al. demonstrated that developing RV dysfunction post-Norwood is often associated with failing to complete single ventricle palliation (Jean-St-Michel, Chetan et al. 2016). Although it appears that later S2P would maximize survival in some high-risk patients, this likely reflects length-time bias. However, our data also do not suggest that non-intervention in a deteriorating, high-risk infant would lead to greater survival. By six months, most of the highest-risk patients will have died, thereby increasing the predicted survival estimates. For example, some infants survived long enough to eventually develop RV dysfunction at an older age, e.g. at age seven months. Our results imply that optimally timing S2P for these patients, if they had not yet developed high-risk features, would have been to promptly proceed with S2P after age three months, instead of allowing them to persist in Norwood circulation long enough to develop risk factors for a poor outcome.

Furthermore, when RV dysfunction is present, an optimal time for S2P does not exist. Survival was poor at any age for S2P and was especially low in those who underwent S2P before 6 months old. This situation highlights that transitioning to S2P can address some risk factors, while exacerbating others. Early S2P in the infant who has developed RV dysfunction fails to rescue and may even increase mortality. These patients are at such high risk that the perioperative insult of S2P may be poorly tolerated and the rapid transition of a struggling infant to S2P must be seriously questioned. Survival may instead be maximized by early referral for cardiac transplantation. Outcomes for transplantation as a salvage after Norwood are
encouraging, though waitlist mortality remains high given the current low supply of available organs (Alsoufi, Mahle et al. 2016; Kulkarni, Neugebauer et al. 2016).

It is important to note that the apparent greater survival of high-risk infants when S2P is performed after six months likely reflects that only the more robust of these infants could survive the post-Norwood period long enough to develop risk factors and subsequently undergo S2P after age six months. Those high-risk infants who underwent S2P earlier and died were at such high risk for death that they may have likely died whether S2P was performed or not, which highlights the importance of abandoning single ventricle palliation and instead promptly pursuing transplantation.

Interval cardiac reoperations were associated with high-risk status. This finding stands in contrast with the results of Barron and colleagues. They reported that interstage re-operations restored patients to their expected risk trajectories. A notable weakness of their study is that they did not analyze re-operations as time-related events. We found that interval re-operations, when evaluated as time-varying covariables, were associated with reduced survival and that their negative effect on survival persisted throughout the infants’ course. Reduced survival in patients requiring interstage aortic reconstructions and atrioventricular valve repairs has been reported (Nakata, Fujimoto et al. 2010; Hill, Rhodes et al. 2013). The stress of undergoing additional cardiac surgery must be balanced against the sequelae of unrepaired atrioventricular valve regurgitation or recurrent arch obstruction. Even optimally timing S2P likely results in poor survival and the increased risk persists for S2P at any age. Cardiac transplantation after reoperation, instead of continuing staged palliation, may maximize survival in these high-risk infants.

Finally, shunt choice is an important decision at the surgeon’s discretion. As has been previously demonstrated by the CHSS and Single Ventricle Reconstruction Trial, outcomes are superior with RVPA conduits (Ohye, Sleeper et al. 2010; Wilder, McCrindle et al. 2015). In a single center study of only 58 patients, Rüffer and colleagues noted greater survival in patients with an RVPA conduit until four months old and that the risk of death increased markedly after four months (Ruffer, Arndt et al. 2011). Therefore, they advocated catheterization at two months post-Norwood and progression to S2P by four months. In this analysis, most high-risk patients had a MBTS, which was independently associated with death. Despite the difference in survival, our data do not indicate that optimal timing of S2P differs by shunt type in non-high-risk patients.
5.8 Gaining insight into risk over time after the Norwood operation

The post-Norwood period is fraught with risk and decision making during the post-Norwood period is complex. The development of risk factors during this time can change the trajectory of a patient, to the point that single ventricle palliation is no longer a viable management pathway. To gain insight into how the development of risk factors for death after S2P affect the risk trajectory across the post-Norwood period, we sought to analyze these risk factors in a time-related manner, as time-varying covariates. Then, using dynamic risk profile methodology, we were able to visually depict the effect of risk factors over time.

Several aspects demonstrate this new methodology’s novel analytic capabilities. First, it represents a natural evolution from previous CHSS studies. An analysis from 2013 included a single time-varying covariate, the time-related occurrence of a re-intervention on the conduit, in patients with pulmonary conduits. They demonstrated decrements in pulmonary conduit durability after each re-intervention (Poynter, Eghtesady et al. 2013). In this study, we have incorporated time-related complications, re-interventions, and diagnoses as time-varying covariates, on a larger scale than in previous analyses.

The incorporation of weights and SaO₂ measurements obtained after the Norwood operation represents a completely novel aspect of the analysis. Both weight and SaO₂ provide insight into an infant’s clinical status during the post-Norwood period. Weight more broadly reflects the long-term status of a patient. An infant’s ability to gain weight, especially relative to their age and/or height (i.e. increase his/her WAZ), reflects adequate nutrition and overall health. The inefficiencies of Norwood circulation are therefore not consuming the majority of the infant’s caloric intake and they are not attempting recover from a complication such as an infection. SaO₂ is a more acute indicator of clinical status, with low SaO₂ occurring acutely with shunt thrombosis, more gradually with shunt stenosis or the development of pulmonary vaso-occlusive disease, or with high SaO₂ potentially indicating overcirculation and heart failure. In addition, the NPC-QIC felt that the collection and analysis of SaO₂ were of sufficient value to include as part of the home interstage monitoring initiative. Yet the evidence regarding its association with adverse outcomes is mixed. It must also be highlighted that these measures were incorporated as continuous variables and not artificially categorized. To our knowledge this represents the first use of continuous variables as time-varying covariates.
5.9 Time-varying covariates predominate over baseline characteristics in the risk model

Until now, the majority of studies that have performed traditional multivariable analyses and built models for outcomes after the Norwood operation have only incorporated baseline and operative characteristics, or perhaps one time-varying covariate. In this study, with the incorporation of many time-varying events and longitudinal continuous measures, we have found that the time-related events and measures are predictive than the baseline and operative characteristics in the model. A similar observation was noted in a concurrent analysis of outcomes in adult patients with heart failure who were listed for heart transplantation that employed this methodology. When evaluating measures of serum creatinine and bilirubin, in addition to post-listing time-related complications, baseline and operative characteristics were also not found to be significant in the model for death after listing (E. H. Blackstone, personal communication). It may be tempting to conclude from these results that baseline characteristics do not affect the risk of death after Norwood. We however do not suggest the effects of an infant’s baseline characteristics or operative course should be discounted. The baseline and operative characteristics may instead influence the longitudinal measures and the development of complications post-Norwood.

5.10 Novel associations identified when accounting for longitudinal measures and complications

In our model for death after the Norwood that incorporates the time-related longitudinal measures and events, we have demonstrated several novel associations. As previously noted, previous analyses have not demonstrated an association between $\text{SaO}_2$ and the risk of death post-Norwood or post-S2P. Previous analyses have also been mixed regarding the association of weight or WAZ with outcomes. Barron and colleagues demonstrated that weight on day of S2P was not associated with survival after S2P (Barron, Haq et al. 2017). A single study has examined trends in weight over time following the Norwood, and reported that increasing weight was associated with transplant-free survival. However, this study was substantially limited. While they did account for repeated measures of weights, the authors did not calculate WAZ and were thus unable to determine if patients were gaining weight relative to their age. They also did not perform a time-to-event analysis of the effect of weight gain on survival, as they utilized logistic regression (Evans, Sorkin et al. 2017).
While the development of moderate to severe AVVR and RV dysfunction are well-established risk factors for adverse outcomes post-Norwood, several other novel associations were identified as well. Many events, such as sepsis, renal failure, and re-intubation have been examined as outcomes, but not as potentially associated factors with mortality after the Norwood (Tabbutt, Ghanayem et al. 2012). The impact of bloodstream infections (BSI) on the post-Norwood course has been investigated in a single institution study (Anderson, Ciarleglio et al. 2015). They reported an in-hospital mortality of 9.1% (13/143) in infants with HLHS who developed a BSI, one-third of that seen in our larger cohort, though only in-hospital mortality was reported in this analysis.

Finally, non-operative readmission as a time-varying covariate merits additional consideration. Not only was it significantly associated with death after the Norwood, but 20% of patients who were readmitted ultimately died during the post-Norwood period. Risk factors for readmission after congenital heart surgery have been examined in several series, but the impact of readmission on outcomes has not been directly investigated (Mackie, Gauvreau et al. 2004; Kogon, Jain et al. 2012). The association of non-operative readmission with death and the 20% mortality rate in infants readmitted post-Norwood indicate that readmission may be a surrogate for other ongoing pathology. The purpose of the readmission would be to intervene on this ongoing pathology and to decrease a patient’s risk profile. Readmissions may be temporarily effective for decreasing risk. However, they may ultimately fail to rescue one-fifth of these patients. Further analyses are required to define and understand the patient population who did not benefit from readmission.

### 5.11 Clinical applications

Dynamic risk profiles have potential applications as a clinical decision aid, able to generate updated risk scores whenever an event occurs. They are also dynamic, as the risk score can increase or decrease risk over time, depending on the events occurring or values of the most recent measurements. The risk profiles also demonstrate the effect of the accumulation of risk, or display memory. A physician could then track a patient’s risk trajectory during the post-Norwood course and respond to changes in real-time.

These risk profiles will likely be most useful for patients who develop risk factors for death and see their risk scores rising. A management algorithm incorporating the dynamic risk profiles is proposed in Figure 40. The type of intervention should depend on the type of risk factors that
have become apparent and how they can be addressed. Integrating the new knowledge from the analysis of the optimal timing of S2P is crucial as well. If an infant's risk score is rising, he/she is three months old or older, and has not developed risk factors that cannot be addressed by progressing to S2P, such as RV dysfunction (which portends a grave prognosis after S2P), then performing S2P after medical stabilization would be appropriate. It cannot be overemphasized that progression to S2P should only occur if the specific risk factors would be neutralized by proceeding with S2P, e.g. hypoxemia.

If the infant has developed risk factors that cannot be neutralized by proceeding to S2P (e.g. features of the high-risk group in the timing analysis), or is younger than age three months, then the infant should be strongly considered for listing for heart transplantation, in the absence of other contraindications for heart transplantation. This rescue pathway is illustrated in Figure 33, in which an infant who has developed AVVR and RV dysfunction. This high-risk infant, with a 99% predicted risk of death on the day of heart transplantation, may not have survived the perioperative period if S2P was performed.

Several clinical scenarios could prompt hospitalization without an intent for the surgical interventions described above. In the situation that the patient’s risk score is still relatively low but rising, such as in an infant who is failing to gain weight, hospitalization of the patient and intensification of treatment could be warranted. A patient with a rising risk score over time and seemingly adequate to low SaO₂ measurements from their home monitoring may prompt admission to the hospital for investigation of the status of their shunt and consideration of a catheter-based intervention. In another instance, if an infant has developed risk factors, such as requiring re-intubation and subsequently developing sepsis due to an overwhelming respiratory infection, the infant may not be a candidate for S2P or heart transplantation and must be medically treated. These risk profiles could provide valuable prognostic information for counseling the infants’ parents, especially if the outcome appeared to poor with any intervention or if the infant was not a candidate for any intervention.
Figure 40: Algorithm for the incorporation of the dynamic risk profiles into the management of infants during the post-Norwood period.

Abbreviations: CI=Contraindication, HTxp=Heart transplantation, S2P=Stage-2-palliation

Setting a threshold risk score or increase in risk score over a defined time period that triggers the use of the decision tree described above will likely be necessary. Further investigation is needed to define a clinically relevant threshold.

5.12 Comparison to other risk scores

Little precedent exists for a risk score such as that produced by the dynamic risk profile methodology, especially in cardiac surgery. In adult cardiac surgery, the Society of Thoracic Surgeons score for pre-operative predicted mortality is used to guide decision-making between
traditional surgical aortic valve replacement vs. transcatheter aortic valve replacement (Shahian, He et al.). However, this model is based solely on a patient’s pre-operative characteristics. A single institution study attempted to develop a predictive risk model for in-hospital mortality following the Norwood operation. However, this study was substantially limited, as only pre-operative and intra-operative characteristics were considered, mortality was not analyzed as a time-related phenomenon (logistic regression was used), and only in-hospital mortality was considered (McGuirk, Stickley et al. 2006).

In congenital heart surgery, the T3 system is currently used at two institutions to guide the post-operative management of patients in the pediatric cardiac ICU. This system uses physiologic data drawn from the ICU monitors to aid physicians to avoid preventable clinical deterioration. Its use is limited to within the ICU.

The APACHE score has been used to estimate a patient’s risk of mortality and length of stay in the ICU. The model includes a variety of demographic, diagnosis-specific, and physiologic measures. Originally, these estimates were valid only on the day of admission. However, the use of daily estimates of mortality over the first seven days in the ICU and their correlation with overall mortality were described with APACHE III (Knaus, Wagner et al. 1991). Their utility as a decision aid have been recognized. In a multicenter, inception cohort study, the APACHE-III was validated, with the current day’s APACHE score strongly associated with a patient’s overall risk of death (Wagner, Knaus et al. 1994). The use of daily risk estimates with the current version, APACHE-IV, has not been evaluated.

The T3 and APACHE systems of risk estimations highlight two distinct advantages of the dynamic risk profile methodology. It can be used to monitor risk over time throughout the entire post-Norwood course and is not limited to use only in the ICU or hospital. In addition, the covariates included in the model are commonly tracked measures and well-recognized, easily diagnosed complications. However, both established systems do provide a template for the development, validation, and updating of a risk score to be used as a decision aid.

5.13 Limitations

5.13.1 Selection bias and non-random patient selection

As a prospective cohort study, this analysis is subject to non-random patient selection. Participating institutions’ may have been unable to enroll all eligible infants, perhaps due to
logistical issues. Also, given that infants with HLHS and its related malformations are of great scientific interest to generate new knowledge and improve care, these infants may participate in multiple studies and their parents may have been unwilling to participate in another study. It is important to note that the results of an analysis of prospective inception cohort, such as the CHSS Critical LVOTO cohort analyzed here, can only generate Level II evidence at best (Group 2011). Therefore, only associations, and not causal relationships, can be established from this analysis.

However, it is also unlikely that an effective randomized trial of timing of S2P could be designed to provide meaningful results to a complex question such as the optimal timing of S2P. Several potential obstacles would first include the enrollment of a sufficient number of patients such that the study would be adequately powered given the low incidence and prevalence of HLHS. The effective randomization of patients across a spectrum of ages for S2P would be challenging as well. Finally, equipoise with regard to the timing of S2P may not exist, making designing such a trial ethically unfeasible.

5.13.2 Incomplete risk adjustment and the limits of submitted documentation

Despite our exhaustive approach, the study may be limited by incomplete risk adjustment and unmeasured confounders. While we strove to obtain detailed information on the post-Norwood course, the data available in the medical records for each patient varied considerably and were extracted by a single clinical research nurse. This reality is especially salient for the dynamic risk profiles analysis. Anecdotally, much less complete data, such as only operative notes for the Norwood, S2P, and Fontan, were sent to the CHSS Data Center during the first several years of enrollment in the cohort. More detailed information, including admission and discharge notes, clinic visit notes, serial echocardiographic and cardiac catheterization were eventually submitted, as the cohort matured. This creates an “era effect” for available data, as fewer data points for the continuous measures of weight and SaO₂ and less detailed information regarding the time-related post-Norwood events were available for incorporation into the model for the dynamic risk profiles. Finally, we were dependent on institutional echocardiogram reports, instead of a core lab analysis, for the echocardiographic diagnosis of significant AVVR or RV dysfunction post-Norwood. The limitations of the subjective interpretation of echocardiograms by many cardiologists, characterized by heterogeneous diagnostic and grading criteria for AVVR and RV dysfunction, must be kept in mind. For example, there is known high inter-rater
variability in the interpretation of echocardiograms between sonographers. The diagnostic criteria for RV dysfunction, AVVR, and more is subjective and not uniform, as well.

5.13.3 Era and institutional effects

The CHSS Critical LVOTO cohort has enrolled infants for over 12 years, during which significant changes in the care of infants with HLHS have occurred. The performance of the SVR Trial, the implementation of the NPC-QIC’s interstage home monitoring initiative, and the widespread adoption of afterload reduction all affected outcomes in neonates who underwent the Norwood operation. For example, a single institution reported their experience with interstage monitoring in 2006 (Ghanayem, Tweddell et al. 2006). Currently, over 60 centers participate in the NPC-QIC’s interstage monitoring initiative (Collaborative 2017). Changes in clinical practice in response to these advances likely occurred at different rates across enrolling institutions, which highlights several possible limitations to this analysis, that all management decisions for all enrolled infants were at the discretion of the treating physicians and surgeons and that management strategies evolve over time (though at equal rates among physicians and across centers).

5.13.4 CHSS Critical LVOTO cohort inclusion criteria

It is important to note that the specific anatomic inclusion criteria for the patients analyzed in this study is limited to obstructive lesions of the left heart. However, single ventricle palliation can also be used to palliate lesions with right ventricular hypoplasia ductal-dependent circulation, such as tricuspid atresia. As this cohort did not include patients with left ventricle-dominant single ventricle lesions, we are hesitant to extend these results to that population.

5.13.5 Surrogate variables

Several variables collected for dynamic risk profiling may be broad surrogates for more granular and traditional risk factors. For example, re-operations and re-interventions were analyzed as candidate risk factors, even though the true intention of re-interventions is to address ongoing pathology and decrease the risk of death. In this way, the re-interventions act as surrogates for acquired pathology such as aortic arch recoarctation, shunt stenosis, etc, in place of more
granular measurements, such as aortic arch gradients in cardiac catheterization, shunt diameter narrowing, and more. While the re-intervention may be a statistically-significant risk factor, the circumstances (more granular measurements or indications for the re-intervention) leading to the re-intervention more likely represent the actual cause of risk. The re-intervention is designed to decrease risk, but may also be associated with its own risks for subsequent morbidity and mortality. In addition, the decision to intervene is subjective, and the thresholds for re-intervention likely vary between physicians and institutions. Because of the variable criteria for re-intervention, they may instead more accurately reflect physician behavior and decision making, instead of clinically relevant pathology. We did assume that re-interventions were performed for as clinically indicated, which may introduce bias and uncertainty into this analysis.

5.13.6 The risk of death immediately following the Norwood operation is non-zero

The predominance of the time-related events and longitudinal measures over baseline characteristics highlights an important limitation – that the risk score starts at zero immediately following the Norwood operation. The extensive and complex effects of the Norwood operation on an infant’s anatomy and physiology and the accompanying high risk of death have been extensively reviewed. Therefore, the immediate risk of death cannot start at zero percent. The risk score is only a function of the variables included in the parametric equation, which only included TVCs, none of which had yet occurred immediately after the Norwood.

Future work could address this inconsistency by first developing a model for death without the TVCs. The significant baseline and/or operative variables could then be forced into the model with only TVCs. In this manner, the initial risk of post-operative death, based on baseline and/or operative characteristics could be accounted for, prior to the occurrence of a time-related event.

5.13.7 Memory in dynamic risk profile methodology

Several strengths of this analysis include that the profiles demonstrate the accumulation of risk over time as time increases and that they demonstrate memory – that the effect of previously risk factors continues to affect subsequent risk estimates. It is not yet known how “strong” this memory should be, or if the effect of risk factors should fade or dissipate over time. For example, while the argument can be made that an infant who develops a BSI and is
successfully treated returns to their baseline status. However, a recent analysis by Anderson and colleagues reports that these infants require hospital lengths of stay twice as long as those who did not develop a BSI (Anderson, Ciarleglio et al. 2015). These infants may therefore be qualitatively different as the complication of a BSI may continue to affect their risk of death over time. However, the strength of this effect likely depends on the type of time-related event experienced by an infant. The rate of dissipation of its effect is currently not well understood and may be unique to each type of event. This analysis may present the “least forgiving” case of memory and may reflect the most liberal estimates for death after the Norwood. The presentation of these most liberal estimates may be appropriate for instantaneous predictions of mortality in infants with Norwood circulation, given the well-known high risk for morbidity and mortality during this period.

5.14 Conclusions

The optimal timing of S2P for infants with HLHS and its related malformations depends on the number and type of risk factors present. In low/intermediate-risk patients, survival appears maximized by progressing to S2P after 3 months old. Because of the substantial differences in mortality pre- and post-S2P and the potential benefits to non-mortality outcomes, little is likely to be gained by avoiding timely S2P. We recommend that centers implement protocols in which S2P is planned prior to Norwood hospitalization discharge for as soon as is feasible, but not before 3 months old, to minimize the duration in Norwood circulation, given the potential benefits regarding the preservation of systemic RV function, growth trajectory, cost of care, and parental stress. In high-risk infants, survival appears uniformly poor, regardless of the timing of S2P. As early S2P may increase mortality, prompt consideration of cardiac transplantation may provide their best chance at survival. These insights can be integrated with dynamic risk profiles, which visualize an individual patient’s risk trajectory over time and represent a “state-space characterization” for infants as they proceed through the post-Norwood period. These updatable scores may aid in the management of these high-risk patients, providing personalized, data-driven predictions of risk that can inform decision-making regarding readmission, re-intervention, progression to S2P, or evaluation for heart transplantation.
Chapter 6
Synthesis – Embracing Complexity

6.1 Context within the current of state of outcomes research

6.1.1 Complex clinical questions require embracing complex methodology and nuanced results

The medical and surgical care of children born with HLHS and its related malformations presents one of the most difficult challenges in modern medicine. The field’s knowledge has grown in sixty years from anatomic descriptions from post-mortem specimens to include traditional analyses of outcomes and risk factors, the home monitoring programs, and more. However, even a seemingly simple question of the superiority of the RVPA conduit vs. the MBTS, which the SVR Trial sought to answer, has produced nuanced insights and failed to definitively establish the superiority of one shunt over the other (Ohye, Sleeper et al. 2010).

Modern research questions in congenital heart surgery, such as defining the optimal timing of S2P, are rarely as straightforward as the SVR Trial’s primary aim. Even though traditional biostatistical analytic methods are still the predominant methods employed in studies of clinical outcomes in congenital heart surgery, more advanced methodology is increasingly necessary to avoid oversimplifying the complex clinical realities. As S2P represents the second stage of three-stage single ventricle palliation, methodology that does not integrate the risks pre- and post-S2P is insufficient. How a child arrives at one state (i.e. their clinical course), not just their immediate pre-operative state, likely influences their future outcomes. Single ventricle palliation should instead be thought of and analyzed as a continuum, instead of treating each stage of single ventricle palliation as its own isolated event, independent of the other stages. Conditional survival analysis enabled us to analyze the risk of death across multiple intervals. Our findings also did not yield a simple, overarching conclusion regarding the timing of S2P in all patients undergoing single ventricle palliation. Instead, different conclusions with distinct clinical implications were reached based on patients’ constellations of risk factors.
6.1.2 The evolution of clinical research with data science – “Big data” and “precision medicine”

In the modern era, extremely large amounts of data from disparate sources are generated for each patient from the in-patient and outpatient settings, including demographic, physiologic, pharmacologic, operative, and even genetic data. These multifaceted data have been termed “Big Data” (Health 2017). The exploration and analysis of these data may not be possible with traditional biostatistical analytic methods. Instead, techniques from the interdisciplinary field of data science may be required because of “Big Data’s” volume and complexity. The identification of patterns and insights that affect the management of specific groups or individual patients, or “precision medicine,” is the promise of cutting edge research with “Big Data” (Health 2017).

The application of dynamic risk profile methodology represents the CHSS’ initial analytic effort within the realm of data science. First, information from more diverse data sources (e.g. outpatient clinic notes) with increasingly granularity (e.g. every SaO$_2$ measurement per patient) has been extracted and included. Notably, a single clinical research nurse extracted all of this information. While it does not technically represent “Big Data,” the level of granularity needed for dynamic risk profiles indicates that the CHSS Data Center may soon require automated data extraction from multiple disparate sources.

The use of dynamic risk profiles also signifies a paradigm shift in the study of outcomes and risk factors after congenital heart surgery. In the traditional biostatistical analyses performed by the CHSS, general conclusions were drawn from risk factor analysis of the overall study population and were thought to be representative of that overall study population. Instead, updatable, instantaneous risk estimates for individual patients can be generated. The possible future use to track patient risk trajectories and provide data-driven insights for clinical decision-making would represent a true application of precision medicine to the field of congenital heart surgery and for a high-risk, resource intensive group of patients.

6.2 Future directions

6.2.1 Methodologic extension - multi-state modeling

The staged surgical management of HLHS actually represents multi-state process. Patients are at risk for transitioning to the multiple possible end states after the Norwood operation, including death, S2P, heart transplantation, BVR. The likelihoods or rates of the transitions from the
Norwood to any other end state are also not equal, making them non-homogenous processes. It is also a non-Markov process. The likelihood of a patient transitioning to another state post-Norwood depends on the patients’ current state and on how the patient arrived at the current state (Meira-Machado, de Una-Alvarez et al. 2009).

The application of multi-state modeling to the study of single ventricle palliation represents a natural methodologic extension from conditional survival analysis. The framework for this extension exists within the Blackstone model for the temporal decomposition of hazard. However, this extension would require the de novo mathematical derivation of the system of equations describing multi-state transitions and programming into analysis software.

6.2.2 Clinical extension – validation and evaluation of dynamic profiles as clinical decision aid

6.2.2.1 Model validation

While the development of novel methodology is important to ensure increasingly accurate analysis of complex clinical problems, the implementation of dynamic risk profiles as a clinical decision aid may currently provide information that may alter patient management. However, several potential analytic and logistical challenges must be surmounted. Prior to broader application, the model underlying the dynamic risk profiles will require rigorous validation using an independent data source. The NPC-QIC’s home monitoring program included 50 centers and collected daily or weekly measurements SaO$_2$ and weights (Kugler, Beekman III et al. 2009). In their analysis, Oster and colleagues reported that 92% had daily or weekly SaO$_2$ monitoring and 88% had daily or weekly weight monitoring (Oster, Ehrlich et al. 2015). This registry may provide a more granular source for these continuous data than what could be extracted from the patient chart. In addition, the trends in these continuous variables could be verified using this registry data.

6.2.3 Integration into clinical practice

Following validation, the model will require programming into an electronic medical records system such as the EPIC (Epic Systems Corporation, Verona, WI) electronic health records system (EHR). With integration into an EHR platform, patient data could be
automatically drawn from the medical record and plotted over time, to provide real time estimates for the risk of death or other outcomes during the infant’s post Norwood period. Challenges certainly exist in the execution of this real-world implementation. Funding will be required for the programming of the parametric equation, to generate intervals, identify complications, and create a graphical display, all of which must be integrated into the EHR. While a tool such as the APACHE score is freely available online, EHR integration is crucial for its practical use as a decision aid.

6.2.4 Evaluation

Finally, whether the application of this risk score can decrease mortality during the post-Norwood period must be evaluated using a prospective, randomized, and controlled clinical trial (RCT). Many RCTs of clinical decision aids have been formed over the last two decades. However, most RCTs have evaluated decision aids designed for patients, and not clinicians, and usually for screening, instead of directing management (Man-Son-Hing, Laupacis et al. 1999; Tol-Geerdink, Willem Leer et al. 2013). Importantly, neither the APACHE score nor the T3 monitoring system have been evaluated in a RCT. The possible future RCT to determine the impact a management strategy incorporating dynamic risk profiles (e.g. a specific decision, such as progression to S2P or heart transplantation, based on upon a risk score threshold) on outcomes post-Norwood will likely need to be a multicenter, multinational, cluster randomized trial that includes some of the highest volume centers performing the Norwood operation. It will also require careful study design, distinct from other RCTs in congenital heart surgery, such as the SVR Trial, as heart transplantation was viewed as failure on par with death. In comparison, our data suggests that heart transplantation would be an appropriate rescue strategy for the infant who has developed risk factors that cannot be addressed by progressing to S2P and is on an upward risk trajectory with an increasing likelihood of death.

6.3 Summary

In conclusion, despite substantial progress over the previous 35 years in the care of patients with HLHS and its related malformations, morbidity and mortality remain high compared to other congenital cardiac defects. The care of these infants is complex and the studies performed to gain novel insights and optimize outcomes should account for this complexity. Given the rapid
advancement of analytic methods and the plethora of data available to study these patients, clinically applicable insights should be readily translated into clinical care. The integration of information technology as decision aids into clinical to supplement physicians’ clinical judgment takes advantage of the large amount of available data and represents the application of precision medicine to maximizing survival through three-stage single ventricle palliation.


Almodovar, M. B., D; McManus, M; Butler, E; Laussen, PC (2014). Risk Analytics and Outcome Prediction in Neonates Following Cardiac Surgery. Pediatric Cardiac Intensive Care Society Conference. Miami Beach, FL.


### Appendices

**Appendix Table 1: Enrollment by institution**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Enrolled (n=534)</th>
<th>Reached S2P (n=377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>95</td>
<td>70</td>
</tr>
<tr>
<td>I</td>
<td>63</td>
<td>40</td>
</tr>
<tr>
<td>Q</td>
<td>52</td>
<td>43</td>
</tr>
<tr>
<td>D</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>T</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>M</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>F</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>N</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>H</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>K</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>G</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>S</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>E</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>B</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>O</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>L</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>C</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>J</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>R</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>U</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Abbreviations: S2P=Stage-2-Palliation*
### Appendix Table 2: Diagnostic criteria for time-related events after the Norwood operation

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>Details in note of radiologic evidence of intracranial or intraventricular hemorrhage</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Documentation of infarction, not global ischemic injury or hypoxic ischemic encephalopathy</td>
</tr>
<tr>
<td>Seizure</td>
<td>Clinical diagnosis usually, some electroencephalographically confirmed</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Mechanical circulatory support post-Norwood</td>
<td>Operative note</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>Clinical documentation of cardiac arrest with successful cardiopulmonary resuscitation</td>
</tr>
<tr>
<td>Interventional catheter procedure</td>
<td>Procedure note</td>
</tr>
<tr>
<td>Aorta</td>
<td></td>
</tr>
<tr>
<td>Atrial septum</td>
<td></td>
</tr>
<tr>
<td>Coiling of collaterals</td>
<td></td>
</tr>
<tr>
<td>Conduit/shunt</td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Re-operation on heart and great vessels</td>
<td>Operative note</td>
</tr>
<tr>
<td>Aorta</td>
<td></td>
</tr>
<tr>
<td>Atrial septectomy</td>
<td></td>
</tr>
<tr>
<td>Conduit/shunt</td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td></td>
</tr>
<tr>
<td>Pacemaker placement</td>
<td></td>
</tr>
<tr>
<td>TVR</td>
<td></td>
</tr>
<tr>
<td>Other – DKS revision</td>
<td></td>
</tr>
<tr>
<td>Non-operative readmission</td>
<td>Admission or discharge summary, with indication for admission</td>
</tr>
<tr>
<td>Required inotropes during readmission</td>
<td>Documentation of starting inotropes upon admission to the ICU (epinephrine, norepinephrine, milrinone, or dopamine)</td>
</tr>
<tr>
<td>Moderate/severe RV dysfunction on final echocardiogram before transition to another end state</td>
<td>Echocardiogram note</td>
</tr>
<tr>
<td>Moderate/severe AVVR on final echocardiogram before transition to another end state</td>
<td>Echocardiogram note</td>
</tr>
<tr>
<td>Recoarctation on final cardiac catheterization before transition to another end state</td>
<td>Catheterization note</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
</tr>
<tr>
<td>Required continuous positive airway pressure</td>
<td>Initialization of continuous positive airway pressure therapy in note</td>
</tr>
<tr>
<td>Reintubation</td>
<td>Documented reintubation, after initial post-operative extubation following the Norwood operation</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>Operative note</td>
</tr>
<tr>
<td>Category</td>
<td>Condition</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Other operative</td>
<td>Operation for chylothorax</td>
</tr>
<tr>
<td></td>
<td>Non-cardiac reoperation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal replacement therapy</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>Bloodstream infection</td>
</tr>
<tr>
<td></td>
<td>Sternal wound infection/mediastinitis</td>
</tr>
<tr>
<td></td>
<td>Line-associated infection</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>URI</td>
</tr>
<tr>
<td></td>
<td>UTI</td>
</tr>
</tbody>
</table>
### Appendix Table 3: Indications for stage-2-palliation*

<table>
<thead>
<tr>
<th>Indication</th>
<th>Definition</th>
<th>Specific variables to describe each indication</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective</td>
<td>S2P performed without any factors prompting its planned operative date to be changed. Determined by either a mention of “elective” S2P in the operative note or in the absence of complicating factors in a patient “who had reached good/adequate weight and age for S2P.” Pt may have been “bridged” to an elective S2P by an interval procedure.</td>
<td>Age at S2P, SaO₂ at final clinic visit, cardiac catheterization, and echocardiogram, Weight and WAZ at final clinic visit, cardiac catheterization, and echocardiogram</td>
<td>70% (262)</td>
</tr>
<tr>
<td>Progressive hypoxemia</td>
<td>Stage 2 was performed because of direct description of progressive cyanosis/hypoxemia/desaturations, “outgrowing their shunt,” in the absence of a mechanical or anatomic obstructive lesion</td>
<td>SaO₂ at final clinic visit, cardiac catheterization, and echocardiogram</td>
<td>10% (36)</td>
</tr>
<tr>
<td>Pulmonary blood flow obstruction</td>
<td>Cyanosis/hypoxemia/desaturations attributable to a mechanical issue such as shunt stenosis or an anatomic issue such as PA stenosis</td>
<td>Diagnosis of shunt stenosis or thrombosis Interval operative or catheter-based procedure for the MBTS or RVPA conduit Shunt diameter (mm) Qp:Qs, PVR</td>
<td>8% (29)</td>
</tr>
<tr>
<td>Ventricular dysfunction</td>
<td>S2P performed to address ventricle with deteriorating function</td>
<td>Diagnosis of moderate-severe RV dysfunction on the patient’s final echocardiogram</td>
<td>6% (21)</td>
</tr>
<tr>
<td>Atrioventricular valve regurgitation</td>
<td>S2P performed to address ongoing issue with hemodynamically significant atrioventricular valve regurgitation</td>
<td>Diagnosis of moderate-severe AVVR on the patient’s</td>
<td>1% (4)</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Procedure/Examination</td>
<td>Frequency</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Pulmonary overcirculation</td>
<td>S2P performed to address congestive heart failure due to volume overload</td>
<td>final echocardiogram SaO2 at final clinic visit, cardiac catheterization, and echocardiogram</td>
<td>1% (4)</td>
</tr>
<tr>
<td>Systemic blood flow obstruction</td>
<td>S2P performed to address an obstructive lesion within the systemic circulation such as aortic coarctation or obstruction at any level</td>
<td>Diagnosis of recoarctation on cardiac catheterization Interval operative or catheter-based re-intervention on the aorta</td>
<td>1% (5)</td>
</tr>
<tr>
<td>PA hypoplasia</td>
<td>Alteration in operative planning to allow growth of PA's</td>
<td>PA diameters on final echocardiogram and cardiac catheterization, presence of PA stenosis</td>
<td>0.5% (2)</td>
</tr>
<tr>
<td>Restrictive ASD</td>
<td>S2P performed to augment venous return from the lungs and relieve CHF due to a restrictive ASD restricting mixing of oxygenated and deoxygenated blood in the right atrium</td>
<td>Interval operative or catheter-based re-intervention on the atrial septum SaO2 at final clinic visit, cardiac catheterization, and echocardiogram</td>
<td>0.5% (2)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Alteration in operative planning due to ongoing arrhythmias</td>
<td>N/A</td>
<td>0.3% (1)</td>
</tr>
<tr>
<td>Infection</td>
<td>Alteration in operative planning due to ongoing infectious issues</td>
<td>Admission for respiratory illness Season in which S2P perform</td>
<td>0.3% (1)</td>
</tr>
<tr>
<td>Tracheobronchomalacia</td>
<td>Diagnosis of tracheobronchomalacia</td>
<td>N/A</td>
<td>0.3% (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>No operative note present or unable to understand clinical decision making with the information available.</td>
<td>N/A</td>
<td>2% (9)</td>
</tr>
</tbody>
</table>
Abbreviations: AVVR=Atrioventricular valve regurgitation, MBTS=Modified Blalock-Taussig shunt, PA=Pulmonary artery, RV=Right ventricular, RVPA=Right-ventricle-to-pulmonary-artery, SaO₂=Arterial oxygen saturation, S2P=Stage-2-palliation

*Indications were assigned by a review by a clinical research nurse (Kristina Kovach, BScN, RN), a senior congenital heart surgeon (William G. Williams, MD), and study author (JMM)
Copyright Acknowledgements

Please see several notes below regarding the referenced figures. Formal copyright permission for use for Figures 1, 2, 3, 4, 7, 8, 10, 11, 13, and 19A follow this page.

**Figure 1**: Obtained from the United States Centers for Disease Control and Prevention at [https://www.cdc.gov/ncbddd/heartdefects/hlhs.html](https://www.cdc.gov/ncbddd/heartdefects/hlhs.html). Per its website, “The images are in the public domain and thus free of any copyright restrictions. As a matter of courtesy we request that the content provider (Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities) be credited and notified in any public or private usage of this image.” The CDC was notified via email on May 18, 2017 of this use and a formal declaration that this image is in the public domain follows this page.

**Figure 6**: Obtained from [http://www.giamberti.it/wp-content/uploads/2014/03/2155-9880-S8-007-g038.gif](http://www.giamberti.it/wp-content/uploads/2014/03/2155-9880-S8-007-g038.gif). No copyright was claimed. This figure was cited in a previous work (Justice et al., Utilizing the PCICS Nursing Guidelines in Managing the CICU Patient, WJPCHS, 2015) using this web address.
Thank you for your inquiry to CDC-INFO. We hope you find the following information about using an image of a heart with hypoplastic left heart syndrome for your thesis helpful.

Information and images developed by CDC and presented on the CDC website are works of the U.S. Government. This content may include:

- general text information
- publications for download
- graphs

CDC-generated works (including photographs, graphics, images, videos, PSAs) located on this site are in the public domain. This means that they are meant for public use and are not subject to copyright law protections. Permission is not required for use of public domain items. But, CDC does ask that you credit the agency and contributor whenever the item is used in any publicly distributed media.

You are free to adapt and revise these materials, as long as you distribute the revised materials free of charge. But, if you make changes or revisions, you must remove the CDC name and logo from the materials.

You may also find on the CDC website materials or products that are owned or were created by others. This content may include copyrighted materials and other materials provided by third parties, such as private companies or non-government organizations. These third parties retain all rights, including copyright, to publish or reproduce those documents/images, or to authorize others to do so. This is in accordance with Title 17, Sections 106 through 120 of the U.S. Code. Any copyrighted materials included on the CDC website were used with the permission of the copyright holder and are not in the public domain. These materials remain the property of their respective owners or creators, and should not be reproduced or otherwise used.

Certain Division of Parasitic Diseases and Malaria material are not part of the public domain. Copyrighted material includes: life cycle images of parasites Blastocystis and Pneumocystis, and electron micrograph images of Gnathostoma; if users are interested in publishing these items, they must obtain permission from the original copyright holder.

Content syndication is a way to have CDC.gov content such as podcasts, eCards, Web pages, widgets, microsites, etc., placed on your site. The syndicated content is automatically updated in real time requiring no effort from your development staff to keep the Web pages up to date. You can present CDC Web content in the look and feel of your site and maintain visitors on your site. Content syndication also allows you to integrate CDC Web content and science with localized content. CDC maintains 2 sites for syndication; Content Syndication at: https://tools.cdc.gov

The Content Syndication site provides HTML content for Web pages. The Public Media Health Library provides various media types for syndication including HTML, eCards, podcasts, widgets, infographics, pdfs, buttons, badges, and microsites.

The Public Health Image Library (PHIL) at: https://phil.cdc.gov/phil/home.asp.

Most images found in CDC's PHIL are:

- Royalty-free
- Available for personal, professional, and educational use in electronic or print media, with appropriate citation.

Please credit CDC and the individual photographer, if his or her name is given. If you're using the images in electronic media, please link back to the PHIL site.
Images other than those in the PHIL may have been licensed for use by CDC from a stock photography service. The licensing vendor may prohibit:

• re-publication,
• re-transmission,
• reproduction, or
• other use of the images.

You may submit questions about re-use of specific images via the Contact CDC page on the CDC website.

Data.CDC.gov is a repository for selected API-enabled (can be visualized and syndicated to external sites) CDC data that have been published and made available to the public. Most of these data are already available through various CDC websites and applications. Data.CDC.gov provides a central way to search for and find these data for re-use and provides mechanisms for creating visualizations (e.g., charts, maps, filtered views). These assets are available for download or may be re-used on your Web page with the provided pre-formatted embed code.

For more information on copyright permission, please visit the following CDC websites:

Using CDC.gov: Policies and Regulations
Office of the Associate Director for Communication, Division of Public Affairs
http://www.cdc.gov/Other/policies.html

CDC Online Newsroom: Newsroom Image Library
http://www.cdc.gov/media/subtopic/images.htm

data.CDC.gov
Office of the Associate Director for Communication
https://data.cdc.gov

Content Syndication: Learn More
Office of the Associate Director for Communication
https://tools.cdc.gov/syndication/LearnMore.aspx

Freedom of Information Act (FOIA) Requester Service Center: Reproduction of Copyrighted Materials
Office of the Associate Director for Communication
http://www.cdc.gov/od/foia/

Links to nonfederal organizations are provided as a service. Links are not an endorsement of these organizations or their programs by CDC or the federal government. CDC is not responsible for the content of organization websites found at these links.

Thank you for contacting CDC-INFO. For more information, please call 1-800-CDC-INFO (800-232-4636), visit www.cdc.gov and click on “Contact CDC-INFO,” or go to www.cdc.gov/info. This e-mail was sent from an unmonitored mailbox, and CDC-INFO will not respond to replies sent to this mailbox. If you have questions or comments, please send them via our online form at www.cdc.gov/info.

CDC-INFO is a service of the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR). This service is provided by Verizon and its subcontractors under the Networx Universal contract to CDC and ATSDR.

Thank you,
D.P. 5457

--------- Original Message ----------
From: [cdcinfoforms@cdc.gov]
Sent: 5/18/2017 3:38 PM
To: cdcinfo@cdc.gov
Subject: CDC-INFO: Inquiry
Subject: Image reproduction

From: Clinician

Email Address: james.meza@sickkids.ca

Your Question: To Whom It May Concern:

My name is James Meza, a research fellow at the Hospital for Sick Children in Toronto. I would like to reproduce the image of a heart with hypoplastic left heart syndrome found at https://www.cdc.gov/ncbddd/heartdefects/hlhs.html for inclusion in my Master's thesis and would like to formal permission to do so.

Thank you,
James M. Meza, MD

Optional Information

Name: James Meza
Title: Research Fellow, Division of Cardiovascular Surgery
Organization: The Hospital for Sick Children
Phone: 647-687-4715
Other Email: jamesmeza@gmail.com
Address: 555 University Ave, Toronto, ON, CA

ref:_00DU0YCBU._500t05dswN:ref
This Agreement between James M Meza ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

**License Number** 4112251337506  
**License date** May 18, 2017  
**Licensed Content Publisher** Elsevier  
**Licensed Content Publication** The Journal of Thoracic and Cardiovascular Surgery  
**Licensed Content Title** Intermediate survival in neonates with aortic atresia: A multi-institutional study  
**Licensed Content Author** Marshall L. Jacobs, Eugene H. Blackstone, Leonard L. Bailey  
**Licensed Content Date** September 1998  
**Licensed Content Volume** 116  
**Licensed Content Issue** 3  
**Licensed Content Pages** 15  
**Start Page** 417  
**End Page** 431  
**Type of Use** reuse in a thesis/dissertation  
**Portion** figures/tables/illustrations  
**Number of figures/tables/illustrations** 1  
**Format** both print and electronic  
**Are you the author of this Elsevier article?** No  
**Will you be translating?** No  
**Order reference number**  
**Original figure numbers** Figure 9  
**Title of your thesis/dissertation** Maximizing Survival Through the Staged Surgical Management of Hypoplastic Left Heart Syndrome and its Related Malformations  
**Expected completion date** Jun 2017  
**Estimated size (number of pages)** 150  
**Elsevier VAT number** GB 494 6272 12  
**Requestor Location** James M Meza
INTRODUCTION

1. The publisher for this copyrighted material is Elsevier. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at http://myaccount.copyright.com).

GENERAL TERMS

2. Elsevier hereby grants you permission to reproduce the aforementioned material subject to the terms and conditions indicated.
3. Acknowledgement: If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies. Suitable acknowledgement to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:
"Reprinted from Publication title, Vol / edition number, Author(s), Title of article / title of chapter, Pages No., Copyright (Year), with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]." Also Lancet special credit - "Reprinted from The Lancet, Vol. number, Author(s), Title of article, Pages No., Copyright (Year), with permission from Elsevier."
4. Reproduction of this material is confined to the purpose and/or media for which permission is hereby given.
5. Altering/Modifying Material: Not Permitted. However figures and illustrations may be altered/adapted minimally to serve your work. Any other abbreviations, additions, deletions and/or any other alterations shall be made only with prior written authorization of Elsevier Ltd. (Please contact Elsevier at permissions@elsevier.com). No modifications can be made to any Lancet figures/tables and they must be reproduced in full.
6. If the permission fee for the requested use of our material is waived in this instance, please be advised that your future requests for Elsevier materials may attract a fee.
7. Reservation of Rights: Publisher reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.
8. License Contingent Upon Payment: While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions.
full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and publisher reserves the right to take any and all action to protect its copyright in the materials.

9. Warranties: Publisher makes no representations or warranties with respect to the licensed material.

10. Indemnity: You hereby indemnify and agree to hold harmless publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

11. No Transfer of License: This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without publisher's written permission.

12. No Amendment Except in Writing: This license may not be amended except in a writing signed by both parties (or, in the case of publisher, by CCC on publisher's behalf).

13. Objection to Contrary Terms: Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

14. Revocation: Elsevier or Copyright Clearance Center may deny the permissions described in this License at their sole discretion, for any reason or no reason, with a full refund payable to you. Notice of such denial will be made using the contact information provided by you. Failure to receive such notice will not alter or invalidate the denial. In no event will Elsevier or Copyright Clearance Center be responsible or liable for any costs, expenses or damage incurred by you as a result of a denial of your permission request, other than a refund of the amount(s) paid by you to Elsevier and/or Copyright Clearance Center for denied permissions.

LIMITED LICENSE

The following terms and conditions apply only to specific license types:

15. Translation: This permission is granted for non-exclusive world English rights only unless your license was granted for translation rights. If you licensed translation rights you may only translate this content into the languages you requested. A professional translator must perform all translations and reproduce the content word for word preserving the integrity of the article.

16. Posting licensed content on any Website: The following terms and conditions apply as follows: Licensing material from an Elsevier journal: All content posted to the web site must maintain the copyright information line on the bottom of each image; A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx or the Elsevier homepage for books at https://www.sciencedirect.com/science/journal/xxxxx
Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.
Licensing material from an Elsevier book: A hyper-text link must be included to the Elsevier homepage at [http://www.elsevier.com](http://www.elsevier.com). All content posted to the web site must maintain the copyright information line on the bottom of each image.

**Posting licensed content on Electronic reserve:** In addition to the above the following clauses are applicable: The web site must be password-protected and made available only to bona fide students registered on a relevant course. This permission is granted for 1 year only. You may obtain a new license for future website posting.

17. **For journal authors:** the following clauses are applicable in addition to the above:

**Preprints:**
A preprint is an author's own write-up of research results and analysis, it has not been peer-reviewed, nor has it had any other value added to it by a publisher (such as formatting, copyright, technical enhancement etc.).
Authors can share their preprints anywhere at any time. Preprints should not be added to or enhanced in any way in order to appear more like, or to substitute for, the final versions of articles however authors can update their preprints on arXiv or RePEc with their Accepted Author Manuscript (see below).
If accepted for publication, we encourage authors to link from the preprint to their formal publication via its DOI. Millions of researchers have access to the formal publications on ScienceDirect, and so links will help users to find, access, cite and use the best available version. Please note that Cell Press, The Lancet and some society-owned have different preprint policies. Information on these policies is available on the journal homepage.

**Accepted Author Manuscripts:** An accepted author manuscript is the manuscript of an article that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and editor-author communications.
Authors can share their accepted author manuscript:

- immediately
  - via their non-commercial person homepage or blog
  - by updating a preprint in arXiv or RePEc with the accepted manuscript
  - via their research institute or institutional repository for internal institutional uses or as part of an invitation-only research collaboration work-group
  - directly by providing copies to their students or to research collaborators for their personal use
  - for private scholarly sharing as part of an invitation-only work group on commercial sites with which Elsevier has an agreement
- After the embargo period
  - via non-commercial hosting platforms such as their institutional repository
  - via commercial sites with which Elsevier has an agreement

In all cases accepted manuscripts should:

- link to the formal publication via its DOI
• bear a CC-BY-NC-ND license - this is easy to do
• if aggregated with other manuscripts, for example in a repository or other site, be shared in alignment with our hosting policy not be added to or enhanced in any way to appear more like, or to substitute for, the published journal article.

Published journal article (JPA): A published journal article (PJA) is the definitive final record of published research that appears or will appear in the journal and embodies all value-adding publishing activities including peer review co-ordination, copy-editing, formatting, (if relevant) pagination and online enrichment. Policies for sharing publishing journal articles differ for subscription and gold open access articles:

Subscription Articles: If you are an author, please share a link to your article rather than the full-text. Millions of researchers have access to the formal publications on ScienceDirect, and so links will help your users to find, access, cite, and use the best available version. Theses and dissertations which contain embedded PJAs as part of the formal submission can be posted publicly by the awarding institution with DOI links back to the formal publications on ScienceDirect.

If you are affiliated with a library that subscribes to ScienceDirect you have additional private sharing rights for others' research accessed under that agreement. This includes use for classroom teaching and internal training at the institution (including use in course packs and courseware programs), and inclusion of the article for grant funding purposes.

Gold Open Access Articles: May be shared according to the author-selected end-user license and should contain a CrossMark logo, the end user license, and a DOI link to the formal publication on ScienceDirect.

Please refer to Elsevier's posting policy for further information.

18. For book authors the following clauses are applicable in addition to the above: Authors are permitted to place a brief summary of their work online only. You are not allowed to download and post the published electronic version of your chapter, nor may you scan the printed edition to create an electronic version. Posting to a repository: Authors are permitted to post a summary of their chapter only in their institution's repository.

19. Thesis/Dissertation: If your license is for use in a thesis/dissertation your thesis may be submitted to your institution in either print or electronic form. Should your thesis be published commercially, please reapply for permission. These requirements include permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis and include permission for Proquest/UMI to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission. Theses and dissertations which contain embedded PJAs as part of the formal submission can be posted publicly by the awarding institution with DOI links back to the formal publications on ScienceDirect.

Elsevier Open Access Terms and Conditions
You can publish open access with Elsevier in hundreds of open access journals or in nearly 2000 established subscription journals that support open access publishing. Permitted third party re-use of these open access articles is defined by the author's choice of Creative Commons user license. See our open access license policy for more information.

Terms & Conditions applicable to all Open Access articles published with Elsevier:
Any reuse of the article must not represent the author as endorsing the adaptation of the
article nor should the article be modified in such a way as to damage the author's honour or reputation. If any changes have been made, such changes must be clearly indicated. The author(s) must be appropriately credited and we ask that you include the end user license and a DOI link to the formal publication on ScienceDirect. If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder.

Additional Terms & Conditions applicable to each Creative Commons user license:

**CC BY:** The CC-BY license allows users to copy, to create extracts, abstracts and new works from the Article, to alter and revise the Article and to make commercial use of the Article (including reuse and/or resale of the Article by commercial entities), provided the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, indicates if changes were made and the licensor is not represented as endorsing the use made of the work. The full details of the license are available at [http://creativecommons.org/licenses/by/4.0](http://creativecommons.org/licenses/by/4.0).

**CC BY NC SA:** The CC BY-NC-SA license allows users to copy, to create extracts, abstracts and new works from the Article, to alter and revise the Article, provided this is not done for commercial purposes, and that the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, indicates if changes were made and the licensor is not represented as endorsing the use made of the work. Further, any new works must be made available on the same conditions. The full details of the license are available at [http://creativecommons.org/licenses/by-nc-sa/4.0](http://creativecommons.org/licenses/by-nc-sa/4.0).

**CC BY NC ND:** The CC BY-NC-ND license allows users to copy and distribute the Article, provided this is not done for commercial purposes and further does not permit distribution of the Article if it is changed or edited in any way, and provided the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, and that the licensor is not represented as endorsing the use made of the work. The full details of the license are available at [http://creativecommons.org/licenses/by-nc-nd/4.0](http://creativecommons.org/licenses/by-nc-nd/4.0). Any commercial reuse of Open Access articles published with a CC BY NC SA or CC BY NC ND license requires permission from Elsevier and will be subject to a fee. Commercial reuse includes:

- Associating advertising with the full text of the Article
- Charging fees for document delivery or access
- Article aggregation
- Systematic distribution via e-mail lists or share buttons

Posting or linking by commercial companies for use by customers of those companies.

20. **Other Conditions:**

v1.9

Questions? [customercare@copyright.com](mailto:customercare@copyright.com) or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.
About NEJM Permissions

Submit Your Permission Request Using Rightslink
If you are seeking permission to copy/reproduce/republish content from NEJM and are not the author of that content, you may use the Copyright Clearance Center’s Rightslink® service. Simply visit NEJM.org and locate the article from which you seek to reuse content.

Once you have located and accessed the article you are looking for on NEJM.org:
- Click on the Permission link in the article toolbox (if you are looking at the full-text), or click on the Permissions link in the middle of the page (if you are viewing the abstract or first 100 words of the article because you don't have a subscription)
- The RightsLink® window will pop up, with information about content you have selected.
- Follow the prompts to obtain a free price quote OR
- Sign-in to your existing RightsLink® account, or create an account if you do not already have one, and follow the prompts to secure permission

Confirmation of your permission and a copy of the permission terms and conditions will be sent to you instantly via e-mail for most requests. Some requests may require Publisher review.

If you have questions about using the RightsLink® service, please contact Rightslink® Customer Support at (877) 622-5543 (toll free) or (978) 777-9929, or e-mail customercare@copyright.com.

For other general questions about NEJM Permissions, e-mail permissions@nejm.org.

Permission for Authors
If you are the author of the article that was published in The New England Journal of Medicine (“NEJM”), please visit the NEJM Author Center.

Reuse of Content within a Thesis or Dissertation
Content (full-text or portions thereof) may be used in print and electronic versions of your dissertation or thesis without formal permission from the Massachusetts Medical Society, Publisher of the New England Journal of Medicine.

The following credit line must be printed along with the copyrighted material:
*Reproduced with permission from (scientific reference citation), Copyright Massachusetts Medical Society.

Third-Party Content
Grants of permissions apply only to copyrighted material that the MMS owns, and not to copyrighted text or illustrations for other sources.

Prohibited Uses
The New England Journal of Medicine (and its logo design) are registered trademarks of the Massachusetts Medical Society. We do not grant permission for our logo, cover or brand identity to be used in materials. Permission will not be granted for photographs depicting identifiable individuals.
Hi Jim,

You certainly have my permission to use the figures. We commissioned (i.e. paid) Rachid Idriss to produce these for the CTSNet “article.”

Jazmine is correct in pointing out the “tag” that Rachid put on the pictures, but he really shouldn’t have, since we “bought” them.

The simple approach would be to simply use them, with “Reproduced from XXXX with permission from the author.” You certainly have my permission.

If you’re worried about that approach, I can try to get in touch with Rachid. I haven’t contacted him since 2010. But he still does illustrations for Dr. Mavroudis.

Best,
Marshall

Dr. Jacobs,

I hope you are doing well. I’m nearing the end of my term of as the K/A Fellow and am moving back to NC soon.

I’ve written my thesis and will be defending on June 23rd. I’ve used Figures 6 and 12 from your CTSNet article on cavopulmonary anastomoses (https://www.ctsnet.org/article/superior-cavopulmonary-anastomosis-hemi-fontan-and-bidirectional-glenn) in the background section of my thesis. I contacted CTSNet regarding copyright permissions, but they deferred to you (see email below) to provide permission for me to reproduce those figures. I will need to include this permission as part of the document.

Thank you,
Jim

--
James M. Meza, M.D.
John W. Kirklin/David Ashburn Fellow
Congenital Heart Surgeons’ Society Data Center
The Hospital for Sick Children
555 University Ave
Room 4433, Black Wing
From: Blanch, Jazmine [mailto:jblanch@sts.org]
Sent: Wednesday, May 24, 2017 5:09 PM
To: James Meza <james.meza@sickkids.ca>; Massa, Emily <emassa@sts.org>
Subject: RE: CTSNet copyright question

Dear Dr. Meza:

Thank you for your message. After further review, we noticed the images reference in the article are tagged with a copyright notice from RF Ldriss. Therefore, CTSNet does not own the copyright to these images. We would recommend that you contact the authors Drs. Glenn Pellietier (https://www.ctsnet.org/home/gpellietier) and Marshall Jacobs (https://www.ctsnet.org/home/mjacobs) to secure a license for images referenced in your previous note.

Best,
Jazmine

Jazmine Blanch
Sponsorship & Customer Relations Manager
CTSNet
633 N. St. Clair, 23rd Floor
Chicago, IL 60611
Phone: 312.202.5850
jblanch@ctsnet.org
This Agreement between James M Meza ("You") and BMJ Publishing Group Ltd. ("BMJ Publishing Group Ltd.") consists of your license details and the terms and conditions provided by BMJ Publishing Group Ltd. and Copyright Clearance Center.

License Number 4112270056437
License date May 18, 2017
Licensed Content Publisher BMJ Publishing Group Ltd.
Licensed Content Publication Heart
Licensed Content Title Staged surgical management of hypoplastic left heart syndrome: a single institution 12 year experience
Licensed Content Author S P McGuirk, M Griselli, O F Stumper, E M Rumball, P Miller, R Dhillon, J V de Giovanni, J G Wright, D J Barron, W J Brawn
Licensed Content Date Mar 1, 2006
Licensed Content Volume 92
Licensed Content Issue 3
Type of Use Dissertation/Thesis
Requestor type Individual
Format Print and electronic
Portion Figure/table/extract
Number of figure/table/extracts 1
Description of figure/table/extracts Figure 1
Will you be translating? No
Circulation/distribution 5
Title of your thesis / dissertation Maximizing Survival Through the Staged Surgical Management of Hypoplastic Left Heart Syndrome and its Related Malformations
Expected completion date Jun 2017
Estimated size(pages) 150
Requestor Location James M Meza
555 University Ave
Room 4431
The Hospital for Sick Children
Toronto, ON M5G1X8
Canada
Attn: James M Meza
BMJ Group Terms and Conditions for Permissions

When you submit your order you are subject to the terms and conditions set out below. You will also have agreed to the Copyright Clearance Center's ("CCC") terms and conditions regarding billing and payment. CCC are acting as the BMJ Publishing Group Limited's ("BMJ Group"') agent.

Subject to the terms set out herein, the BMJ Group hereby grants to you (the Licensee) a non-exclusive, non-transferable licence to re-use material as detailed in your request for this/those purpose(s) only and in accordance with the following conditions:

1) **Scope of Licence:** Use of the Licensed Material(s) is restricted to the ways specified by you during the order process and any additional use(s) outside of those specified in that request, require a further grant of permission.

2) **Acknowledgement:** In all cases, due acknowledgement to the original publication with permission from the BMJ Group should be stated adjacent to the reproduced Licensed Material. The format of such acknowledgement should read as follows:

"Reproduced from [publication title, author(s), volume number, page numbers, copyright notice year] with permission from BMJ Publishing Group Ltd."

3) **Third Party Material:** BMJ Group acknowledges to the best of its knowledge, it has the rights to licence your reuse of the Licensed Material, subject always to the caveat that images/diagrams, tables and other illustrative material included within, which have a separate copyright notice, are presumed as excluded from the licence. Therefore, you should ensure that the Licensed Material you are requesting is original to BMJ Group and does not carry the copyright of another entity (as credited in the published version). If the credit line on any part of the material you have requested in any way indicates that it was reprinted or adapted by BMJ Group with permission from another source, then you should seek permission from that source directly to re-use the Licensed Material, as this is outside of the licence granted herein.

4) **Altering/Modifying Material:** The text of any material for which a licence is granted may not be altered in any way without the prior express permission of the BMJ Group. Subject to Clause 3 above however, single figure adaptations do not require BMJ Group's approval; however, the adaptation should be credited as follows:

"Adapted by permission from BMJ Publishing Group Limited. [publication title, author, volume number, pagennumbers, copyright notice year]"

5) **Reservation of Rights:** The BMJ Group reserves all rights not specifically granted in the combination of (i) the licence details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment Terms and Conditions.
Conditions.

6) **Timing of Use:** First use of the Licensed Material must take place within 12 months of the grant of permission.

7) **Creation of Contract and Termination:** Once you have submitted an order via Rightslink and this is received by CCC, and subject to you completing accurate details of your proposed use, this is when a binding contract is in effect and our acceptance occurs. As you are ordering rights from a periodical, to the fullest extent permitted by law, you will have no right to cancel the contract from this point other than for BMJ Group's material breach or fraudulent misrepresentation or as otherwise permitted under a statutory right. Payment must be made in accordance with CCC's Billing and Payment Terms and conditions. In the event that you breach any material condition of these terms and condition or any of CCC's Billing and Payment Terms and Conditions, the license is automatically terminated upon written notice from the BMJ Group or CCC or as otherwise provided for in CCC's Billing and Payment Terms and Conditions, where these apply. Continued use of materials where licence has been terminated, as well as any use of the Licensed Materials beyond the scope of an unrevoked licence, may constitute intellectual property rights infringement and BMJ Group reserves the right to take any and all action to protect its intellectual property rights in the Licensed Materials.

8) **Warranties:** BMJ Group makes no express or implied representations or warranties with respect to the Licensed Material and to the fullest extent permitted by law this is provided on an "as is" basis. For the avoidance of doubt BMJ Group does not warrant that the Licensed Material is accurate or fit for any particular purpose.

9) **Limitation of Liability:** To the fullest extent permitted by law, the BMJ Group disclaims all liability for any indirect, consequential or incidental damages (including without limitation, damages for loss of profits, information or interruption) arising out of the use or inability to use the Licensed Material or the inability to obtain additional rights to use the Licensed Material. To the fullest extent permitted by law, the maximum aggregate liability of the BMJ Group for any claims, costs, proceedings and demands for direct losses caused by BMJ Group's breaches of its obligations herein shall be limited to twice the amount paid by you to CCC for the licence granted herein.

10) **Indemnity:** You hereby indemnify and hold harmless the BMJ Group and their respective officers, directors, employees and agents, from and against any and all claims, costs, proceeding or demands arising out of your unauthorised use of the Licensed Material.

11) **No Transfer of License:** This licence is personal to you, and may not be assigned or transferred by you without prior written consent from the BMJ Group or its authorised agent(s). BMJ Group may assign or transfer any of its rights and obligations under this Agreement upon written notice to you.

12) **No Amendment Except in Writing:** This licence may not be amended except in a writing signed by both parties (or, in the case of BMJ Group, by CCC on the BMJ Group's behalf).

13) **Objection to Contrary Terms:** BMJ Group hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment Terms and Conditions. These terms and conditions, together with CCC's Billing and Payment Terms and Conditions (which to the extent they are consistent are incorporated herein), comprise the entire agreement between you and BMJ Group (and CCC) and the Licensee concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment Terms and Conditions, these terms
and conditions shall control.

14. **Revocation:** BMJ Group or CCC may, within 30 days of issuance of this licence, deny the permissions described in this licence at their sole discretion, for any reason or no reason, with a full refund payable to you should you have not been able to exercise your rights in full. Notice of such denial will be made using the contact information provided by you. Failure to receive such notice from BMJ Group or CCC will not, to the fullest extent permitted by law, alter or invalidate the denial. For the fullest extent permitted by law in no event will BMJ Group or CCC be responsible or liable for any costs, expenses or damage incurred by you as a result of a denial of your permission request, other than refund of the amount(s) paid by you to BMJ Group and/or CCC for denied permissions.

15. **Restrictions to the license:**

15.1 **Promotion:** BMJ Group will not give permission to reproduce in full or in part any Licensed Material for use in the promotion of the following:

a) non-medical products that are harmful or potentially harmful to health: alcohol, baby milks and/or, sunbeds

b) medical products that do not have a product license granted by the Medicines and Healthcare products Regulatory Agency (MHRA) or its international equivalents. Marketing of the product may start only after data sheets have been released to members of the medical profession and must conform to the marketing authorization contained in the product license.

16. **Translation:** This permission is granted for non-exclusive world English language rights only unless explicitly stated in your licence. If translation rights are granted, a professional translator should be employed and the content should be reproduced word for word preserving the integrity of the content.

17. **General:** Neither party shall be liable for failure, default or delay in performing its obligations under this Licence, caused by a Force Majeure event which shall include any act of God, war, or threatened war, act or threatened act of terrorism, riot, strike, lockout, individual action, fire, flood, drought, tempest or other event beyond the reasonable control of either party.

17.1 In the event that any provision of this Agreement is held to be invalid, the remainder of the provisions shall continue in full force and effect.

17.2 There shall be no right whatsoever for any third party to enforce the terms and conditions of this Agreement. The Parties hereby expressly wish to exclude the operation of the Contracts (Rights of Third Parties) Act 1999 and any other legislation which has this effect and is binding on this agreement.

17.3 To the fullest extent permitted by law, this Licence will be governed by the laws of England and shall be governed and construed in accordance with the laws of England. Any action arising out of or relating to this agreement shall be brought in courts situated in England save where it is necessary for BMJ Group for enforcement to bring proceedings to bring an action in an alternative jurisdiction.
Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.
This Agreement between James M Meza ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

License Number 4112270290726
License date May 18, 2017
Licensed Content Publisher Elsevier
Licensed Content Publication CHEST
Licensed Content Title The APACHE III Prognostic System Risk Prediction of Hospital Mortality for Critically III Hospitalized Adults
Licensed Content Author William A. Knaus, Douglas P. Wagner, Elizabeth A. Draper, Jack E. Zimmerman, Marilyn Bergner, Paulo G. Bastos, Carl A. Sirio, Donald J. Murphy, Ted Lotring, Anne Damiano, Frank E. Harrell
Licensed Content Date December 1991
Licensed Content Volume 100
Licensed Content Issue 6
Licensed Content Pages 18
Start Page 1619
End Page 1636
Type of Use reuse in a thesis/dissertation
Intended publisher of new work other
Portion figures/tables/illustrations
Number of figures/tables/illustrations 1
Format both print and electronic
Are you the author of this Elsevier article? No
Will you be translating? No
Order reference number
Original figure numbers Figure 8
Title of your thesis/dissertation Maximizing Survival Through the Staged Surgical Management of Hypoplastic Left Heart Syndrome and its Related Malformations
Expected completion date Jun 2017
Estimated size (number of 150
INTRODUCTION

1. The publisher for this copyrighted material isElsevier. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at http://myaccount.copyright.com).

GENERAL TERMS

2. Elsevier hereby grants you permission to reproduce the aforementioned material subject to the terms and conditions indicated.

3. Acknowledgement: If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies. Suitable acknowledgement to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

"Reprinted from Publication title, Vol./edition number, Author(s), Title of article/title of chapter, Pages No., Copyright (Year), with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]." Also Lancet special credit - "Reprinted from The Lancet, Vol. number, Author(s), Title of article, Pages No., Copyright (Year), with permission from Elsevier."

4. Reproduction of this material is confined to the purpose and/or media for which permission is hereby given.

5. Altering/Modifying Material: Not Permitted. However figures and illustrations may be altered/adapted minimally to serve your work. Any other abbreviations, additions, deletions and/or any other alterations shall be made only with prior written authorization of Elsevier Ltd. (Please contact Elsevier at permissions@elsevier.com). No modifications can be made to any Lancet figures/tables and they must be reproduced in full.

6. If the permission fee for the requested use of our material is waived in this instance, please be advised that your future requests for Elsevier materials may attract a fee.

7. Reservation of Rights: Publisher reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

8. License Contingent Upon Payment: While you may exercise the rights licensed
immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and publisher reserves the right to take any and all action to protect its copyright in the materials.

9. Warranties: Publisher makes no representations or warranties with respect to the licensed material.

10. Indemnity: You hereby indemnify and agree to hold harmless publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

11. No Transfer of License: This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without publisher's written permission.

12. No Amendment Except in Writing: This license may not be amended except in a writing signed by both parties (or, in the case of publisher, by CCC on publisher's behalf).

13. Objection to Contrary Terms: Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

14. Revocation: Elsevier or Copyright Clearance Center may deny the permissions described in this License at their sole discretion, for any reason or no reason, with a full refund payable to you. Notice of such denial will be made using the contact information provided by you. Failure to receive such notice will not alter or invalidate the denial. In no event will Elsevier or Copyright Clearance Center be responsible or liable for any costs, expenses or damage incurred by you as a result of a denial of your permission request, other than a refund of the amount(s) paid by you to Elsevier and/or Copyright Clearance Center for denied permissions.

LIMITED LICENSE

The following terms and conditions apply only to specific license types:

15. Translation: This permission is granted for non-exclusive world English rights only unless your license was granted for translation rights. If you licensed translation rights you may only translate this content into the languages you requested. A professional translator must perform all translations and reproduce the content word for word preserving the integrity of the article.

16. Posting licensed content on any Website: The following terms and conditions apply as
follows: Licensing material from an Elsevier journal: All content posted to the web site must maintain the copyright information line on the bottom of each image; A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx or the Elsevier homepage for books at http://www.elsevier.com; Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

Licensing material from an Elsevier book: A hyper-text link must be included to the Elsevier homepage at http://www.elsevier.com. All content posted to the web site must maintain the copyright information line on the bottom of each image.

**Posting licensed content on Electronic reserve:** In addition to the above the following clauses are applicable: The web site must be password-protected and made available only to bona fide students registered on a relevant course. This permission is granted for 1 year only. You may obtain a new license for future website posting.

17. **For journal authors:** the following clauses are applicable in addition to the above:

**Preprints:**

A preprint is an author's own write-up of research results and analysis, it has not been peer-reviewed, nor has it had any other value added to it by a publisher (such as formatting, copyright, technical enhancement etc.). Authors can share their preprints anywhere at any time. Preprints should not be added to or enhanced in any way in order to appear more like, or to substitute for, the final versions of articles however authors can update their preprints on arXiv or RePEc with their Accepted Author Manuscript (see below).

If accepted for publication, we encourage authors to link from the preprint to their formal publication via its DOI. Millions of researchers have access to the formal publications on ScienceDirect, and so links will help users to find, access, cite and use the best available version. Please note that Cell Press, The Lancet and some society-owned have different preprint policies. Information on these policies is available on the journal homepage.

**Accepted Author Manuscripts:** An accepted author manuscript is the manuscript of an article that has been accepted for publication and which typically includes author-incorporated changes suggested during submission, peer review and editor-author communications.

Authors can share their accepted author manuscript:

- immediately
  - via their non-commercial person homepage or blog
  - by updating a preprint in arXiv or RePEc with the accepted manuscript
  - via their research institute or institutional repository for internal institutional uses or as part of an invitation-only research collaboration work-group
  - directly by providing copies to their students or to research collaborators for their personal use
  - for private scholarly sharing as part of an invitation-only work group on commercial sites with which Elsevier has an agreement

- After the embargo period
  - via non-commercial hosting platforms such as their institutional repository
  - via commercial sites with which Elsevier has an agreement
In all cases accepted manuscripts should:

- link to the formal publication via its DOI
- bear a CC-BY-NC-ND license - this is easy to do
- if aggregated with other manuscripts, for example in a repository or other site, be shared in alignment with our hosting policy not be added to or enhanced in any way to appear more like, or to substitute for, the published journal article.

Published journal article (JPA): A published journal article (PJA) is the definitive final record of published research that appears or will appear in the journal and embodies all value-adding publishing activities including peer review co-ordination, copy-editing, formatting, (if relevant) pagination and online enrichment.

Policies for sharing publishing journal articles differ for subscription and gold open access articles:

**Subscription Articles:** If you are an author, please share a link to your article rather than the full-text. Millions of researchers have access to the formal publications on ScienceDirect, and so links will help your users to find, access, cite, and use the best available version. Theses and dissertations which contain embedded PJAs as part of the formal submission can be posted publicly by the awarding institution with DOI links back to the formal publications on ScienceDirect.

If you are affiliated with a library that subscribes to ScienceDirect you have additional private sharing rights for others' research accessed under that agreement. This includes use for classroom teaching and internal training at the institution (including use in course packs and courseware programs), and inclusion of the article for grant funding purposes.

**Gold Open Access Articles:** May be shared according to the author-selected end-user license and should contain a CrossMark logo, the end user license, and a DOI link to the formal publication on ScienceDirect.

Please refer to Elsevier's posting policy for further information.

18. **For book authors** the following clauses are applicable in addition to the above: Authors are permitted to place a brief summary of their work online only. You are not allowed to download and post the published electronic version of your chapter, nor may you scan the printed edition to create an electronic version. **Posting to a repository:** Authors are permitted to post a summary of their chapter only in their institution's repository.

19. **Thesis/Dissertation:** If your license is for use in a thesis/dissertation your thesis may be submitted to your institution in either print or electronic form. Should your thesis be published commercially, please reapply for permission. These requirements include permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis and include permission for Proquest/UMI to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission. Theses and dissertations which contain embedded PJAs as part of the formal submission can be posted publicly by the awarding institution with DOI links back to the formal publications on ScienceDirect.

**Elsevier Open Access Terms and Conditions**
You can publish open access with Elsevier in hundreds of open access journals or in nearly 2000 established subscription journals that support open access publishing. Permitted third party re-use of these open access articles is defined by the author's choice of Creative
Commons user license. See our open access license policy for more information.

Terms & Conditions applicable to all Open Access articles published with Elsevier:

Any reuse of the article must not represent the author as endorsing the adaptation of the article nor should the article be modified in such a way as to damage the author's honour or reputation. If any changes have been made, such changes must be clearly indicated. The author(s) must be appropriately credited and we ask that you include the end user license and a DOI link to the formal publication on ScienceDirect.

If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder.

Additional Terms & Conditions applicable to each Creative Commons user license:

CC BY: The CC-BY license allows users to copy, to create extracts, abstracts and new works from the Article, to alter and revise the Article and to make commercial use of the Article (including reuse and/or resale of the Article by commercial entities), provided the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, indicates if changes were made and the licensor is not represented as endorsing the use made of the work. The full details of the license are available at http://creativecommons.org/licenses/by/4.0.

CC BY NC SA: The CC BY-NC-SA license allows users to copy, to create extracts, abstracts and new works from the Article, to alter and revise the Article, provided this is not done for commercial purposes and that the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, indicates if changes were made and the licensor is not represented as endorsing the use made of the work. Further, any new works must be made available on the same conditions. The full details of the license are available at http://creativecommons.org/licenses/by-nc-sa/4.0.

CC BY NC ND: The CC BY-NC-ND license allows users to copy and distribute the Article, provided this is not done for commercial purposes and further does not permit distribution of the Article if it is changed or edited in any way, and provided the user gives appropriate credit (with a link to the formal publication through the relevant DOI), provides a link to the license, and that the licensor is not represented as endorsing the use made of the work. The full details of the license are available at http://creativecommons.org/licenses/by-nc-nd/4.0.

Any commercial reuse of Open Access articles published with a CC BY NC SA or CC BY NC ND license requires permission from Elsevier and will be subject to a fee.

Commercial reuse includes:

- Associating advertising with the full text of the Article
- Charging fees for document delivery or access
- Article aggregation
- Systematic distribution via e-mail lists or share buttons

Posting or linking by commercial companies for use by customers of those companies.

20. Other Conditions:

v1.9

Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.
Title: The Decomposition of Time-Varying Hazard into Phases, Each Incorporating a Separate Stream of Concomitant Information
Author: Eugene H. Blackstone, David C. Naftel, Malcolm E. Turner
Publication: Journal of the American Statistical Association
Publisher: Taylor & Francis
Date: Sep 1, 1986

Copyright © 1986 Taylor & Francis

Thesis/Dissertation Reuse Request

Taylor & Francis is pleased to offer reuses of its content for a thesis or dissertation free of charge contingent on resubmission of permission request if work is published.
## JOHN WILEY AND SONS LICENSE
### TERMS AND CONDITIONS

May 18, 2017

This Agreement between James M Meza ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

<table>
<thead>
<tr>
<th>License Number</th>
<th>4112270564609</th>
</tr>
</thead>
<tbody>
<tr>
<td>License date</td>
<td>May 18, 2017</td>
</tr>
<tr>
<td>Licensed Content Publisher</td>
<td>John Wiley and Sons</td>
</tr>
<tr>
<td>Licensed Content Publication</td>
<td>Cancer</td>
</tr>
<tr>
<td>Licensed Content Title</td>
<td>Dynamic prognostication using conditional survival estimates</td>
</tr>
<tr>
<td>Licensed Content Author</td>
<td>Emily C. Zabor, Mithat Gonen, Paul B. Chapman, Katherine S. Panageas</td>
</tr>
<tr>
<td>Licensed Content Date</td>
<td>Aug 1, 2013</td>
</tr>
<tr>
<td>Licensed Content Pages</td>
<td>4</td>
</tr>
<tr>
<td>Type of use</td>
<td>Dissertation/Thesis</td>
</tr>
<tr>
<td>Requestor type</td>
<td>University/Academic</td>
</tr>
<tr>
<td>Format</td>
<td>Print and electronic</td>
</tr>
<tr>
<td>Portion</td>
<td>Figure/table</td>
</tr>
<tr>
<td>Number of figures/tables</td>
<td>1</td>
</tr>
<tr>
<td>Original Wiley figure/table number(s)</td>
<td>Figure 1</td>
</tr>
<tr>
<td>Will you be translating?</td>
<td>No</td>
</tr>
<tr>
<td>Title of your thesis / dissertation</td>
<td>Maximizing Survival Through the Staged Surgical Management of Hypoplastic Left Heart Syndrome and its Related Malformations</td>
</tr>
<tr>
<td>Expected completion date</td>
<td>Jun 2017</td>
</tr>
<tr>
<td>Expected size (number of pages)</td>
<td>150</td>
</tr>
<tr>
<td>Requestor Location</td>
<td>James M Meza</td>
</tr>
<tr>
<td></td>
<td>555 University Ave</td>
</tr>
<tr>
<td></td>
<td>Room 4431</td>
</tr>
<tr>
<td></td>
<td>The Hospital for Sick Children</td>
</tr>
<tr>
<td></td>
<td>Toronto, ON M5G1X8</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
</tr>
<tr>
<td></td>
<td>Attn: James M Meza</td>
</tr>
<tr>
<td>Publisher Tax ID</td>
<td>EU826007151</td>
</tr>
<tr>
<td>Billing Type</td>
<td>Invoice</td>
</tr>
<tr>
<td>Billing Address</td>
<td>James M Meza</td>
</tr>
</tbody>
</table>
TERMS AND CONDITIONS

This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a "Wiley Company") or handled on behalf of a society with which a Wiley Company has exclusive publishing rights in relation to a particular work (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

Terms and Conditions

- The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.

- You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, and any CONTENT (PDF or image file) purchased as part of your order, is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.

- With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner. For STM Signatory Publishers clearing permission under the terms of the STM Permissions Guidelines only, the
terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts. You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

- The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto.

- NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY, INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

- WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.

- You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

- IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, Provisioning, ViewiNG or USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE,
BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

- Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

- The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

- This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

- Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.

- These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

- In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

- WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

- This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

- This Agreement shall be governed by and construed in accordance with the laws of
the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS
Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC BY) License only, the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.

The Creative Commons Attribution License
The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-

Creative Commons Attribution Non-Commercial License
The Creative Commons Attribution Non-Commercial (CC-BY-NC) License permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.(see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License
The Creative Commons Attribution Non-Commercial-NoDerivs License (CC-BY-NC-ND) permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)

Use by commercial "for-profit" organizations
Use of Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee. Further details can be found on Wiley Online Library http://olabout.wiley.com/WileyCDA/Section/id-410895.html

Other Terms and Conditions:

v1.10 Last updated September 2015

Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.
Dear Dr Meza

We hereby grant you permission to reprint the aforementioned material at no charge in your thesis subject to the following conditions:

1. If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies.

2. Suitable acknowledgment to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

“This article was published in Publication title, Vol number, Author(s), Title of article, Page Nos, Copyright Elsevier (or appropriate Society name) (Year).”

3. Your thesis may be submitted to your institution in either print or electronic form.

4. Reproduction of this material is confined to the purpose for which permission is hereby given.

5. This permission is granted for non-exclusive world English rights only. For other languages please reapply separately for each one required. Permission excludes use in an electronic form other than submission. Should you have a specific electronic project in mind please reapply for permission.

6. This includes permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission.

Yours sincerely,

Natalie Qureshi
Global Permissions Manager
Title: Dr. James Meza

Institute/company: The Hospital for Sick Children
Address: 555 University Ave
Post/Zip Code: M5G 1X8
City: Toronto
State/Territory: Ontario
Country: Canada
Telephone: 647-687-4715
Email: james.meza@sickkids.ca

Type of Publication: Book

Book Title: Kirklin/Barrat-Boyes Cardiac Surgery
Book Author: Kouchoukos, Blackstone, Hanley, Kirklin
Book Year: 2013
Book Pages: 324 to 327
Book Chapter number: 6
Book Chapter title: Generating Knowledge from Information, Data, and Analyses

I would like to use: Figure(s)
Quantity of material: Figure 6-28

Excerpts:
Are you the author of the Elsevier material? No
If not, is the Elsevier author involved? No
If yes, please provide details of how the Elsevier author is involved:
In what format will you use the material? Print and Electronic
Will you be translating the material? No
If yes, specify language:
Information about proposed use: Reuse in a thesis/dissertation
Proposed use text:
Additional Comments / Information: Need permissions as soon as possible, thank you!