A dynamic Norwood mortality estimation: Characterizing individual, updated, predicted mortality trajectories after the Norwood operation

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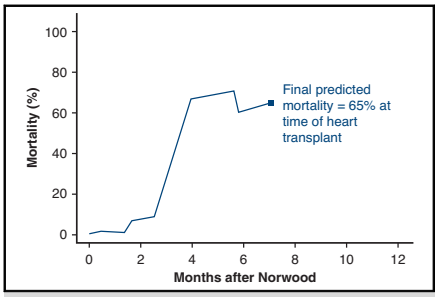
ABSTRACT

Objective: Post-Norwood mortality remains high and unpredictable. Current models for mortality do not incorporate interstage events. We sought to determine the association of time-related interstage events, along with (pre)operative characteristics, with death post-Norwood and subsequently predict individual mortality.

Methods: From the Congenital Heart Surgeons' Society Critical Left Heart Obstruction cohort, 360 neonates underwent Norwood operations from 2005 to 2016. Risk of death post-Norwood was modeled using a novel application of parametric hazard analysis, in which baseline and operative characteristics and time-related adverse events, procedures, and repeated weight and arterial oxygen saturation measurements were considered. Individual predicted mortality trajectories that dynamically update (increase or decrease) over time were derived and plotted.

Results: After the Norwood, 282 patients (78%) progressed to stage 2 palliation, 60 patients (17%) died, 5 patients (1%) underwent heart transplantation, and 13 patients (4%) were alive without transitioning to another end point. In total, 3052 postoperative events occurred and 963 measures of weight and oxygen saturation were obtained. Risk factors for death included resuscitated cardiac arrest, moderate or greater atrioventricular valve regurgitation, intracranial hemorrhage/stroke, sepsis, lower longitudinal oxygen saturation, readmission, smaller baseline aortic diameter, smaller baseline mitral valve z-score, and lower longitudinal weight. Each patient's predicted mortality trajectory varied as risk factors occurred over time. Groups with qualitatively similar mortality trajectories were noted.

Conclusions: Risk of death post-Norwood is dynamic and most frequently associated with time-related postoperative events and measures, rather than baseline characteristics. Dynamic predicted mortality trajectories for individuals and their visualization represent a paradigm shift from population-derived insights to precision medicine at the patient level. (JTCVS Open 2023;14:426-40)



Dynamic predicted mortality post-Norwood for an infant who underwent transplantation.

CENTRAL MESSAGE

Post-Norwood mortality is mostly driven by time-related postoperative events and changes in clinical status. Dynamic individualized prediction models provide insights for post-Norwood risk factors.

PERSPECTIVE

Post-Norwood morbidity and mortality remain high. Current models primarily incorporate preoperative characteristics and lack important postoperative data. A novel dynamic prediction model, which incorporates both preoperative and postoperative time-related data, illustrates individuals' mortality post-Norwood and introduces personalized medicine applied in the field of congenital heart surgery.

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Abbreviations and Acronyms

AVVR = atrioventricular valve regurgitation
CHSS-CRQ = Congenital Heart Surgeons' Society Center for Research and Quality
CLHO = critical left heart obstruction
HLHS = hypoplastic left heart syndrome
Q1-Q3 = first quartile – third quartile
RV = right ventricle
RVPA = right-ventricle-to-pulmonary-artery
SaO2 = arterial oxygen saturation

Despite introduction of home monitoring, afterload reduction with alpha blockade, and other advances in managing hypoplastic left heart syndrome (HLHS) and its related malformations, mortality for infants undergoing the Norwood operation remains substantial at 20% to 30% in large multicenter studies.[1-3] A variety of complications and reinterventions are also common for this population, including neurologic, respiratory, renal, gastrointestinal, and infectious complications.[1,4-9] Unplanned reoperations are performed in 7% to 12% of infants post-Norwood, and transcatheter procedures are performed for up to 40% at some centers.[8,10-12]

Predicting risk of morbidity and mortality after Norwood operations is complex. Risk stratification systems such as the Risk Adjustment for Congenital Heart Surgery score, Aristotle Basic Complexity score, Society of Thoracic Surgeons, and European Association of Cardiothoracic Surgery Congenital Heart Surgery Mortality Categories all predict high hospital mortality after the Norwood.[13-16] All include only preoperative or operative factors; none account for events or complications occurring postoperatively.

Despite availability of sophisticated methods capable of incorporating time-related postoperative events and complications, no risk model has yet included these and quantitative physiologic measures along with preoperative characteristics. The aim of this study was to determine the association of time-related events and longitudinal measures with death post-Norwood, incorporating novel statistical modeling to derive patient-specific dynamic risk profiles. We also sought to illustrate these profiles and determine qualitative trends among the infants.

MATERIALS AND METHODS

Patients

Patients were drawn from the Congenital Heart Surgeons' Society (CHSS) Critical Left Heart Obstruction (CLHO) cohort from 2005 to 2016. CLHO was defined as a left-sided obstructive lesion that precluded the left heart's ability to sustain systemic circulation. Patients' anatomic diagnoses included HLHS, anatomically normal but hypoplastic left heart structures ("hypoplastic left heart complex"), aortic valve atresia, critical aortic stenosis, or mitral valve atresia. Patients were admitted to and underwent their first intervention at a CHSS institution within 30 days of life. Because post-Norwood mortality was the primary objective, any neonate who underwent another initial procedure (eg, hybrid palliation, biventricular repair, isolated aortic arch intervention, heart transplantation, or a transcatheter balloon aortic valvotomy) was excluded.

The Hospital for Sick Children Research Ethics Board approved the protocol (#1000072922) most recently on December 29, 2022, and each participating institution obtained Institutional Review Board approval. Study participation and submission of medical records were voluntary and confidential. Guardians provided informed written consent for participation and publication of study data.

Data

Initial admission medical records and a baseline echocardiogram recording were submitted to the CHSS Center for Research and Quality (CRQ) by institutions after enrollment. Additionally, participating institutions were contacted annually to provide the latest medical records (eg, procedural, clinic, admission, and echocardiography reports). Data were abstracted by a single clinical research nurse at CHSS-CRQ. Abstracted data were assembled from all admission and medical encounters post-Norwood until patients' respective end points. Baseline measurements were defined as the weight on the day of the Norwood operation and the first postoperative arterial oxygen saturation (SaO_2) measurement. Post-Norwood noncardiac adverse events (eg, necrotizing enterocolitis, sepsis, seizures), serial echocardiographic measures of atrioventricular valve regurgitation (AVVR) and right ventricular (RV) dysfunction, operative and transcatheter reinterventions, and all available quantitative measures of weight and SaO_2 from submitted medical records were collected. Moderate or greater RV dysfunction and AVVR from consecutive echocardiographic reports at any timepoint post-Norwood (eg, immediately postoperatively, before hospital discharge post-Norwood, clinic visits, subsequent admissions) were recorded. Annual cross-sectional follow-up and data collection of all eligible patients was conducted to determine patient mortality and clinical status through December 31, 2016, before dataset closure.

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The Institutional Review Board or equivalent ethics committee (Research Ethics Board) of The Hospital for Sick Children approved the study protocol and publication of data (#1000072922; initially approved on December 15, 2004, most recently renewed on December 29, 2022).

Parents/guardians provided informed written consent for publication of the study data.

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Statistical Analyses

Baseline and post-Norwood data (repeated events [eg, serial readmissions] and repeated measures of weights and SaO_2) were summarized. The normality of all variables was queried using Shapiro–Wilk tests. Categorical variables are summarized as frequencies and percentages. Continuous variables are summarized as means with standard deviations or medians with first quartile-third quartile (Q1-Q3), as appropriate. Mathematical transformations (eg, logarithmic, inverse) were performed in the case of nonlinear relationships with respect to mortality. Echocardiographic measurements from baseline anatomic studies performed shortly after birth were obtained from a core laboratory review and were standardized as z-scores where applicable.[17] Weights (z) were calculated using the 2000 weight-for-age z-score standards from the World Health Organization (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm).

Variables with more than 50% missing data were excluded from analyses. For preoperative variables with 50% or less missing data, multiple informative imputation (using a Markov-chain Monte Carlo method yielding 5 datasets) using PROC MI in SAS was performed.[18,19] No time-related variables were imputed.

Mixed Models

Longitudinal quantitative data from the same patient are likely correlated, whereas values from different patients may or may not be correlated. Lack of correlation between patients is assumed in cross-sectional data. To analyze and understand trends in longitudinal data (eg, weight and SaO_2) over time, mixed effects regression modeling was performed. Mixed effects models include random and fixed effects to account for the within-patient correlation of values.[20,21] Linear mixed effects models were fit using PROC MIXED and nonlinear mixed effects models were fit using PROC NLMIXED in SAS.

Survival Analysis

Survival analysis was performed using multiphase, nonproportional parametric risk hazard analysis.[22] The primary end point was all-cause mortality between the Norwood operation (time-zero) and stage 2 palliation. Patients were censored at stage 2 palliation, heart transplantation, or date of last contact for those who had not transitioned to an end point. Before multivariable modeling, both baseline and post-Norwood variables (Tables 1 and 2) were subjected to bootstrap aggregation for variable reduction and to aid in selection. A total of 250 bootstrap resamples were created. Each resample was analyzed within the model using forward stepwise selection and $P = .05$ for retention.[23] Candidate variables that appeared in 30% or more resample analyses ("reliability") were retained and evaluated in the final model. A liberal reliability threshold of 30% was set due to the smaller population and presence of multiple candidate variables and their respective timing.

Risk factors for death post-Norwood were identified using multivariable risk hazard analysis with a statistical significance threshold of P less than .05. Time-related variables, such as requiring mechanical circulatory support post-Norwood, affect a patient's risk of death postoperatively. Therefore, these postoperative, time-related variables were incorporated into risk hazard analysis as time-varying covariates (Table 2). A time-varying covariate is a variable whose value that changes with time.[24,25] Events change from 0 to 1 when they occur; continuous variables change from measurement-to-measurement across time. For analysis, at the time of any change—occurrence of an event of change in a continuous measurement—a step-function change in hazard was assumed to occur, and the magnitude of that change depended on the value and subsequent trajectory of the underlying hazard (Appendix E1). After creation of a final multivariable model, all 5 datasets generated from multiple imputation were used to generate final parameter estimates for the covariates significant in the model using PROC MIANALYZE. All descriptive statistics, mixed effects models, and survival analyses were performed using SAS 9.2 (SAS Institute).

Generating Dynamic Risk Profiles

To display time-varying estimates of risk of death, the equation resulting from the multivariable analysis was solved for each individual patient across time, updating the risk of mortality with the passage of time with occurrence of every event for that patient and every change in value of continuous variables (Video Abstract). For this, at each point in time, the equation generated a value for cumulative hazard that was transformed into a mortality probability as [1 – exp (-cumulative hazard)]. This was accomplished using R 3.3.2 (R Foundation).

RESULTS

Baseline and Norwood Operative Characteristics

Among the 360 infants who underwent the Norwood operation, 63% were male. Median gestational age was 39 weeks (Q1-Q3, 38-39), median birth weight was 3.2 kg (Q1-Q3, 1.6-3.8), and 93% were diagnosed with HLHS. Median age at Norwood operation was 6 days (Q1-Q3, 0-48), 50% with a right-ventricle-to-pulmonary-artery (RVPA) conduit and 50% with a Blalock-Thomas-Taussig shunt. Baseline characteristics are summarized in Table 1.

Time-related Events, Complications, and Diagnoses

In total, 3052 time-related events, which encompassed complications, reinterventions, and diagnoses of cardiac dysfunction, occurred after Norwood operation and before stage 2 palliation, transplantation, or last follow-up. Diagnostic criteria for these events are specified in Table E1. The frequencies of the events, the number of unique patients experiencing each event, and the number of patients with each event who died are shown in Table 2.

Weight and Arterial Oxygen Saturation Post-Norwood

For the 360 patients, 963 weight and SaO_2 measurements were available, with a median of 4 measurements (Q1-Q3, 3-7) per infant. The median interval between measurements was 2.7 months (Q1-Q3, 1.6-4.1).

The median baseline weight measured on the day of Norwood operation was 3.2 kg (Q1-Q3, 2.9-3.5), and the median final weight was 4.3 kg (Q1-Q3, 3.2-5.5). The distribution of individual patients' weight over time post-Norwood is displayed in Figure 1, *A*, which increased linearly over time. Weights (z) were also computed, with median baseline weight (z) of −0.5 (Q1-Q3, –1.2-0.2) and median final weight (z) of −1.2 (Q1-Q3, –2.2, −0.5). The distribution of individual patients' weight (z) post-Norwood is displayed in Figure 1, *B*. Its ensemble average initially decreased rapidly and nonlinearly, and then eventually stabilized into a gradual decline.

Median baseline SaO_2 at Norwood operation was 80% (Q1-Q3, 75-85), and median final SaO_2 post-Norwood was also 80% (Q1-Q3, 75-84). The distribution of

TABLE 1. Demographic, baseline echocardiographic, and Norwood operative characteristics

Characteristic	Overall cohort (N = 360)
Demographic characteristics	
Sex, male	63% (227)
Prenatal diagnosis	71% (253)
Prenatal intervention	1% (4)
Gestational age (wk)	39.0 (38-39)
Birth weight (kg)	3.2 (1.6-3.8)
Genetic abnormality	9% (32)
Primary echocardiographic diagnoses	
HLHS	
Aortic atresia/mitral atresia	34% (123)
Aortic atresia/mitral stenosis	19% (68)
Aortic stenosis/mitral atresia	0.5% (2)
Aortic stenosis/mitral stenosis	19% (69)
Isolated aortic stenosis	8% (27)
Isolated aortic atresia	7% (24)
Isolated mitral stenosis	2% (7)
Isolated mitral atresia	4% (14)
Other	7% (26)
Baseline echocardiographic characteristics, core lab review	
Left ventricular end-diastolic area (mm^2)	4.2 (1.5-7.1)
Right ventricular end-diastolic area (mm^2)	32.0 (25.9-36.6)
Moderate-severe tricuspid valve regurgitation	7% (25)
Tricuspid valve diameter z-score	−1.7 (−2.9, −0.4)
Left pulmonary artery diameter z-score	−0.2 (−0.8-05)
Right pulmonary artery diameter z-score	−0.5 (−1.1-0.3)
Moderate-severe mitral valve stenosis	35% (188)
Mitral valve diameter z-score	−8.7 (−11.0, −5.8)
Moderate-severe aortic valve stenosis	34% (126)
Aortic valve diameter z-score	−15.5 (−20.2, −10.6)
Ascending aorta diameter (mm)	1.4 (0.9-2.3)
Ventricular septal defect	13% (47)
Bilateral superior vena cavae	5% (18)
Norwood operative	
Age at Norwood (d)	6 (0-48)
Shunt type	
Blalock-Thomas-Taussig shunt	50% (179)
RVPA conduit	50% (181)
Weight at Norwood (kg)	3.2 (2.9-3.5)
Duration of cardiopulmonary bypass (min)	149.9 ± 45.9
Modified cerebral perfusion used	91% (328)
Duration of deep hypothermic circulatory arrest (min)	8.0 (4.0-34.0)
Sternum closed at end of Norwood	11% (40)
Oxygen saturation at end of Norwood operation (%)	80 (75-85)

Values are % (n), mean ± standard deviation or median (first quartile – third quartile).
HLHS, Hypoplastic left heart syndrome; *RVPA*, right-ventricle-to-pulmonary-artery.

individual patients' SaO_2 over time post-Norwood is displayed in Figure 1, *C*. Its ensemble average decreased linearly over time.

Outcomes and Risk Factors for Death After the Norwood Operation

Among the 360 infants, 282 (78%) underwent stage 2 palliation, 60 (17%) died, 5 (1%) underwent heart transplantation, and 13 (4%) were alive without transitioning to another state (Figure 2). Few infants (<5) remained admitted post-Norwood throughout stage 2 palliation. Resuscitated cardiac arrest, moderate to severe AVVR on serial echocardiograms, an intracranial complication, a diagnosis of sepsis, longitudinal lower SaO_2, readmission after Norwood hospitalization, smaller baseline ascending aorta diameter, smaller baseline mitral valve diameter z-score, and longitudinal lower weight were significantly associated with death after the Norwood operation (Table 3).

Dynamic Risk Profiles for Individual Infants

Dynamic risk profiles depicting an individual's instantaneous probability of death over time are shown in Figure 3. Lines connect the point estimates for predicted instantaneous probability of death. Median final predicted mortality, on the day of transition to an end point, differed: 4.9% for those who underwent stage 2 palliation, 15.6% for those who died, 16.7% for those who underwent heart transplantation, and 3.7% for those alive without transition ($P < .0001$).

Qualitatively, several groups appear in Figure 3. Among those who progressed to stage 2 palliation, there was a group whose probability of mortality remained low. These patients underwent stage 2 palliation within the expected time frame of 3 to 6 months post-Norwood. Predicted mortality of another group that underwent stage 2 palliation appeared to rise quickly and oscillated. This group transitioned to stage 2 palliation between 3 and 10 months post-Norwood. Among the infants who died, a group existed whose predicted mortality remained low, but died within the first month post-Norwood. Mortality for another group started low and then increased after the first month post-Norwood, with deaths occurring at and after 2 months post-Norwood, with a higher predicted mortality.

Instantaneous Probability of Death May Increase or Decrease

The individual risk profile for a 2.2-kg infant born at 34 weeks' gestation who underwent a Norwood-RVPA on day of life 7 is shown in Figure 2. Cardiac arrest occurred 10 days post-Norwood, and probability of death increased to 11%. The infant was then diagnosed with necrotizing enterocolitis. Although association of necrotizing enterocolitis with death post-Norwood was not statistically significant such that it would be included in the model, predicted mortality increased slightly as time

TABLE 2. Time-related events after the Norwood operation

Event	No. events*	No. patients†	No. died‡
Neurologic			
Intracranial complication (hemorrhage or stroke)	23	23	10 (43%)
Seizure	17	17	6 (35%)
Cardiac			
Mechanical circulatory support post-Norwood	75	63	28 (44%)
Resuscitated cardiac arrest	51	48	26 (54%)
Reinterventions, operative and transcatheter			
Aorta	70	60	4 (7%)
Conduit/shunt	50	41	7 (17%)
Pulmonary arteries	28	22	4 (18%)
Other	35	34	6 (18%)
Moderate or severe right ventricular dysfunction on serial echocardiograms	186	62	18 (29%)
Moderate or severe AVVR on serial echocardiograms	360	127	26 (20%)
Recoarctation on prestage 2 palliation catheterization	57	56	3 (5%)
Respiratory			
Required continuous positive airway pressure	20	19	5 (26%)
Reintubation for respiratory distress	43	43	14 (33%)
Tracheostomy	4	4	1 (25%)
Other			
Readmission after Norwood hospitalization discharge	146	87	17 (20%)
Required inotropes during readmission	16	15	3 (20%)
Discharge after readmission	125	73	15 (21%)
Noncardiac reoperation	133	94	21 (22%)
Gastrointestinal			
Necrotizing enterocolitis	44	38	5 (13%)
Renal			
Renal replacement therapy	6	5	3 (60%)
Infectious disease			
Bloodstream infection	57	40	12 (30%)
Sternal wound infection/mediastinitis	33	28	5 (18%)
Meningitis	2	2	0 (0%)
Sepsis	10	6	4 (67%)
Respiratory tract infection	32	25	10 (40%)
Urinary tract infection	14	12	5 (42%)

AVVR, Atrioventricular valve regurgitation. *Total number of occurrences of the event may occur more than once. †Number of unique patients who experienced at least 1 occurrence of the event. ‡Number of unique patients who experienced at least 1 occurrence of the event and died after the Norwood operation.

post-Norwood increased. It continued to increase until a transcatheter RVPA conduit procedure at 111 days post-Norwood led to SaO_2 of 80%, decreasing the probability of death. Predicted mortality rose again as time increased until a noncardiac operation occurred, which also was not statistically significant in the model. Predicted mortality then increased when the infant was readmitted to the hospital, increased again when the SaO_2 deteriorated to 67%, and then decreased when SaO_2 improved to 79% at 178 days post-Norwood. The infant remained hospitalized and progressed to stage 2 palliation at 6.6 months post-Norwood, with final predicted mortality of 30%. The infant was alive at last follow-up, 4.6 years after stage 2 palliation.

Effect of Time on Risk Factor Magnitude

The individual mortality profile for a 3.5-kg infant born at 39 weeks' gestation who underwent a Norwood-RVPA on day of life 2 is shown in Figure 4, *A*. The infant's predicted mortality increased slowly until 60 days of age, when the infant was readmitted after having grown only 0.3 kg and with a 10% decrease in SaO_2 (80% to 70%). Although predicted mortality stabilized during the period when a transcatheter procedure was performed on the RVPA conduit (variable was not statistically significant therefore not included in the model), the infant's predicted mortality nearly doubled to 18% when the infant required reintubation and was diagnosed with a bloodstream infection at 132 days post-Norwood. The infant had a cardiac arrest and an ischemic

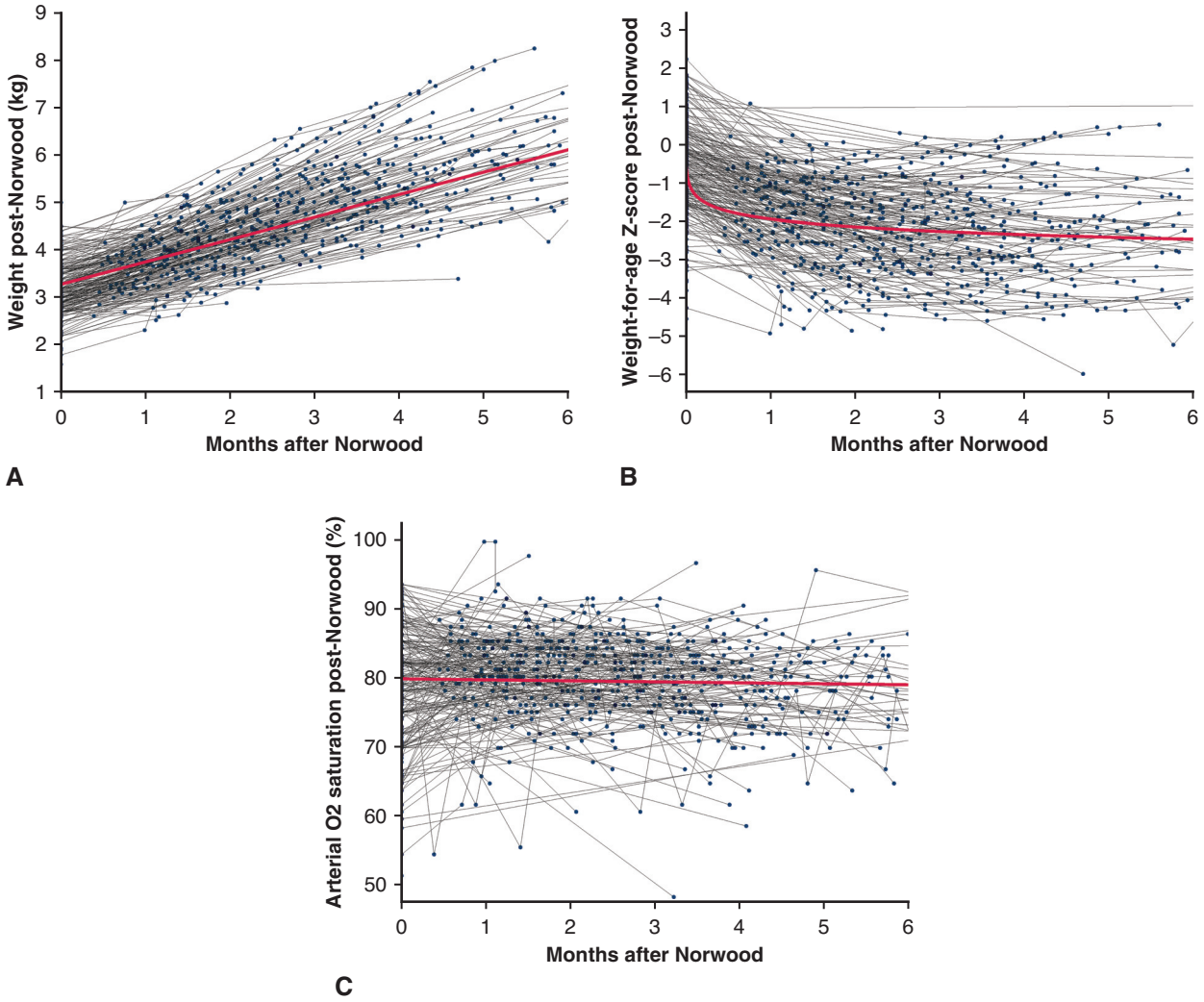


FIGURE 1. Longitudinal measurements of weight (A), weight-for-age z-scores (B), and SaO_2 (C) over time after the Norwood operation. Individual measurements (*blue dots*) are connected by *thin black lines* representing a single patient's serial measurements since the day of the Norwood operation. The *thick red lines* represent linear (A, C) or nonlinear (B) mixed effects models demonstrating the ensemble average for the cohort.

stroke 3 and 5 days later, respectively, after which predicted mortality increased to 99%. Soon after, given the neurologic devastation incurred during the cardiac arrest and persistent bacteremia, support was withdrawn. In comparison with Figure 2, which includes an immediate postoperative cardiac arrest, the cardiac arrest's effect here was greater at this later time interval post-Norwood.

Accumulation of Risk Factors

The individual risk profile for a 4-kg infant born at 41 weeks' gestation who underwent a Norwood with a Blalock-Thomas-Taussig shunt on day of life 5 is shown in Figure 4, *B* (confidence intervals included in Figure E1). The infant's predicted mortality remained low through the first 2 months post-Norwood, until the infant was readmitted at 63 days. However, probability of mortality increased substantially to 66% when the infant had a cardiac arrest at 120 days post-Norwood. Although predicted mortality later decreased with gains in weight and increased SaO_2, it only decreased to 59%. Then, when the infant was diagnosed with moderate or greater AVVR, predicted mortality increased to 65%. Evaluation for heart transplantation occurred during this time, and the infant underwent transplantation at 7.1 months post-Norwood with a final predicted mortality of 65% just before transplantation. The patient is alive 7 years later at last follow-up.

DISCUSSION

The post-Norwood period is fraught with risk, and clinical decisions during this period are complex. Development of risk factors post-Norwood may drastically change

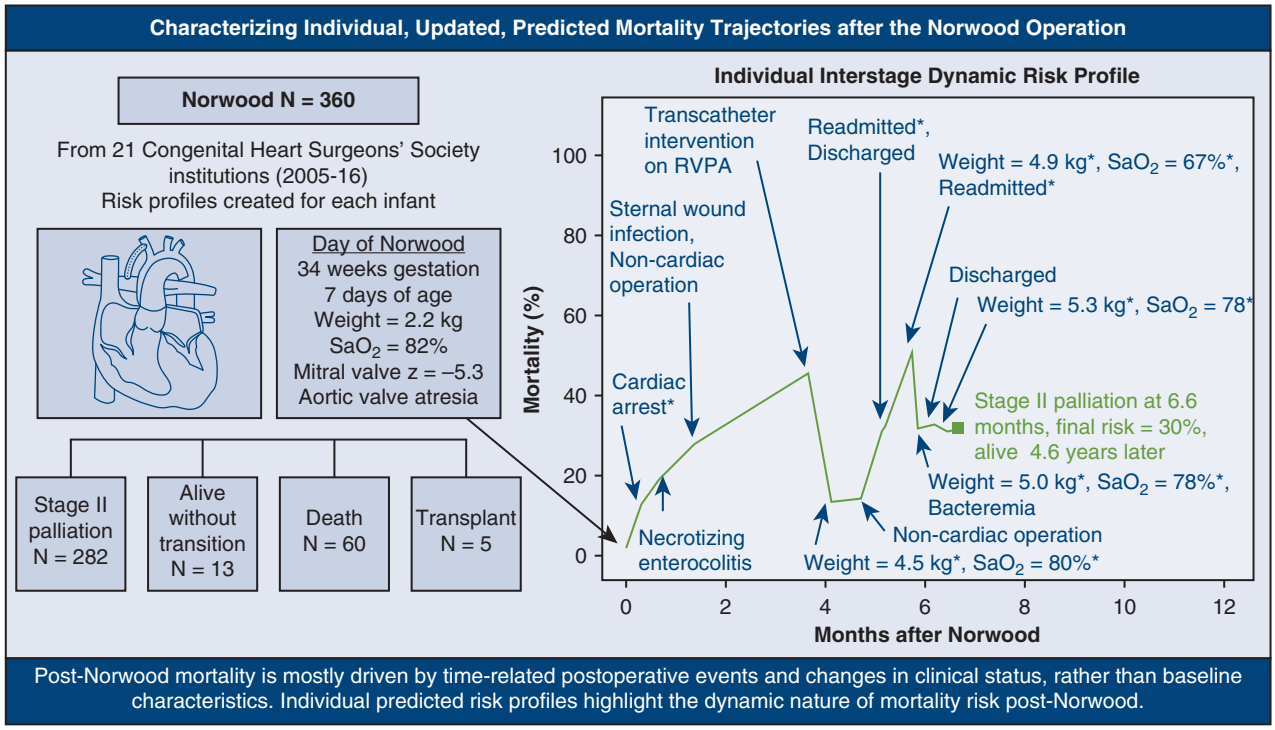


FIGURE 2. Individual dynamic risk profile (*right*) for 1 of 360 infants and their respective end points (*left*) after Norwood operation. The depiction highlights an infant who survived to undergo stage 2 palliation and was alive at last follow-up. The instantaneous risk of death is presented as probability of mortality (%). *The occurrence of events that were significantly associated with mortality. *RVPA*, Right-ventricle-to-pulmonary-artery conduit; *SaO_2*, arterial oxygen saturation.

clinical management and mortality trajectories of a patient. We analyzed these risk factors in a time-related manner and found that they were more frequently associated with death post-Norwood than baseline characteristics. Using dynamic risk profile methodology, we illustrated the effect of risk factors as they occurred over time.

This new methodology represents a natural evolution for individualized knowledge and precision medicine. First, it incorporates immense time-related data from various sources (eg, patient-related characteristics, baseline anatomic measurements, operative details, postoperative complications, reinterventions, serial physiologic data) to construct a model focusing on population-level knowledge. By using this model, individual predictions were created, yielding patient-centered knowledge. Although this methodology is not in the classic realm of machine learning, its tenets mirror the approach.

Time-related Events and Measures

Until now, most studies that have performed traditional multivariable analyses build models for outcomes after the Norwood operation that only incorporate baseline and operative characteristics or perhaps one time-varying covariate.[26] For this study, we found that more time-related events and measures were predictive than baseline and operative characteristics in the model. A similar observation was noted for an analysis that introduced this methodology in outcomes for adults with heart failure who were listed for heart transplantation.[27] When post-listing time-related complications and serial serum creatinine and bilirubin levels included alongside baseline and operative characteristics, baseline factors were not found to be significant in the model for death after listing for transplant.[27] This does not imply that the effects of an infant's baseline characteristics or operative course should be discounted. Instead, baseline and operative characteristics may influence the underlying continuous risk, whereas instantaneous risk is mostly driven by cumulative longitudinal outcome measures and development of adverse events post-Norwood.

We have also demonstrated several novel associations. A previous series reported satisfactory interstage survival by implementing daily physiologic measurements (eg, weight

TABLE 3. Risk factors for death after the Norwood operation

Factors	PE ± SE*	*P* value	Reliability
Resuscitated cardiac arrest†	2.24 ± 0.28	<.0001	98%
Moderate or severe AVVR on serial echocardiograms†	1.18 ± 0.29	<.0001	70%
Intracranial complication (hemorrhage/stroke)†	1.03 ± 0.46	<.0001	60%
Sepsis diagnosed†	2.10 ± 0.57	.0002	58%
Lower SaO_2 (%, logarithmic transformation)†	4.15 ± 0.76	<.0001	67%
Readmission after Norwood hospitalization discharge†	0.90 ± 0.35	.01	40%
Smaller baseline ascending aorta diameter (mm)	0.71 ± 0.21	.0007	38%
Smaller baseline mitral valve diameter z-score	0.07 ± 0.03	.01	30%
Smaller weight (kg, inverse transformation)†	7.47 ± 1.98	.002	34%

PE, Parameter estimate; *SE*, standard error; *AVVR*, atrioventricular valve regurgitation; *SaO_2*, arterial oxygen saturation. *Parameter estimates for a given phase of risk are analogous to the hazard ratios obtained from Cox proportional hazard analysis. Positive parameter estimates indicate a positive association with the event of interest, whereas negative parameter estimates reflect a negative or protective association with the event of interest. Please note that only a single phase of risk was identified. †Time-varying covariate.

and SaO_2) via a home monitoring program;[28] however, no published analyses have demonstrated a time-related association between SaO_2 and the risk of death post-Norwood. Published series have reported inconsistent results regarding the association of weight with outcomes. Barron and colleagues[29] reported that weight on the day of stage 2 palliation was not associated with survival after the operation. Conversely, a single series that examined trends in weight over time after Norwood operation reported increasing weight was associated with transplant-free survival.[30]

Although development of moderate or greater AVVR and RV dysfunction are well-established risk factors for adverse outcomes post-Norwood, several other novel associations were identified. Many events, such as sepsis, renal failure, and reintubation, have been examined as outcomes, but not as potentially associated factors with mortality after Norwood.[1] The effect of bloodstream infection on the post-Norwood course has been investigated in a single-institution study.[31] They reported an in-hospital mortality of 9.1% (13/143) in infants with HLHS who developed a bloodstream infection, one-third of that seen in our larger

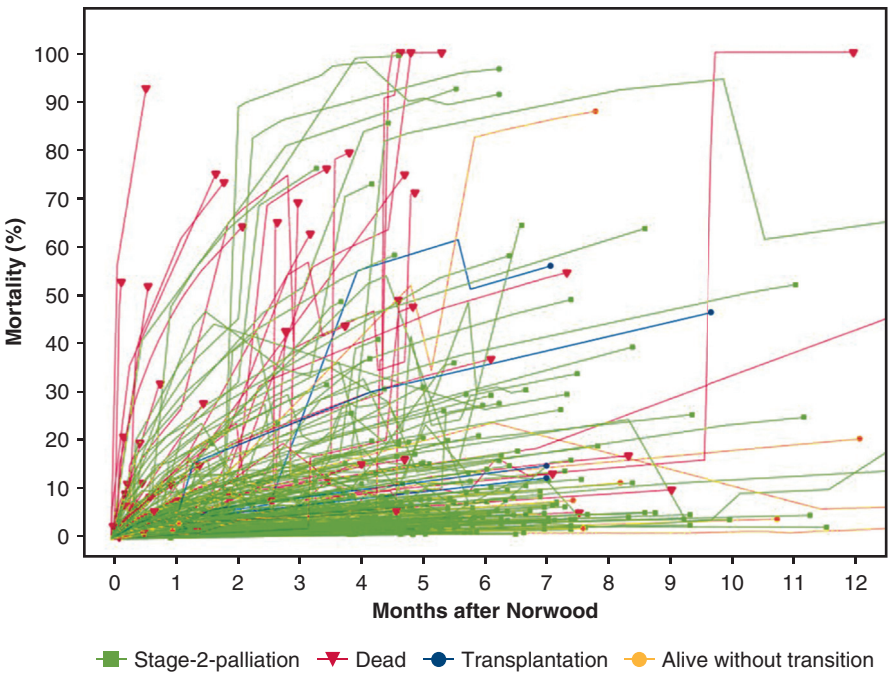
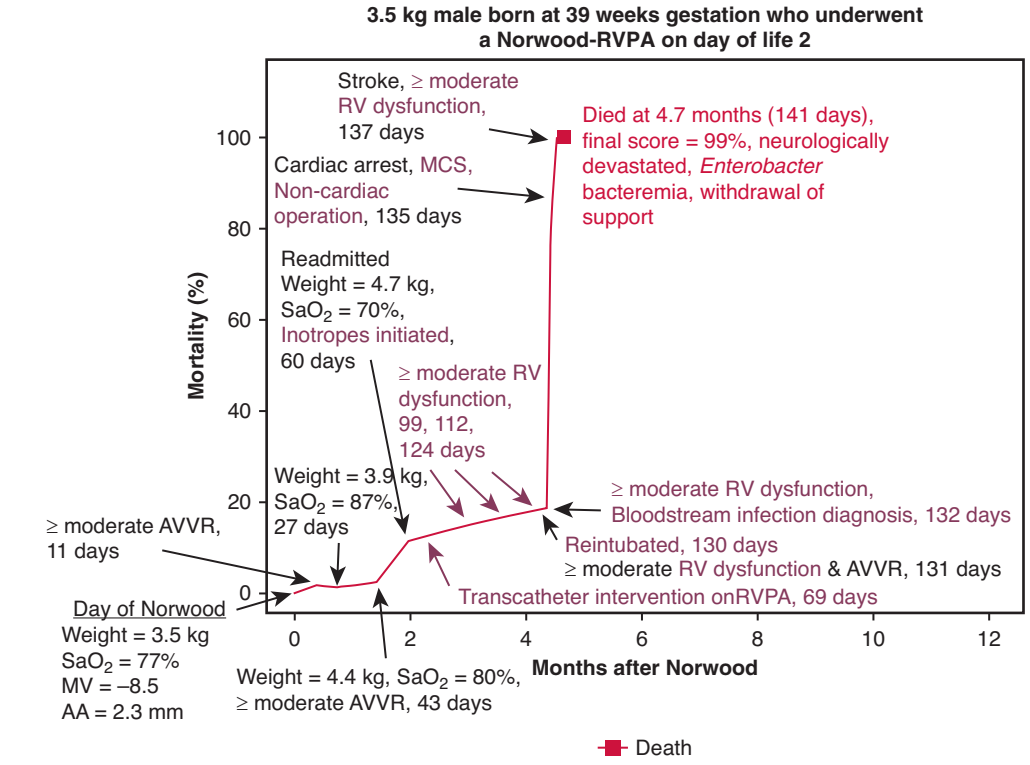
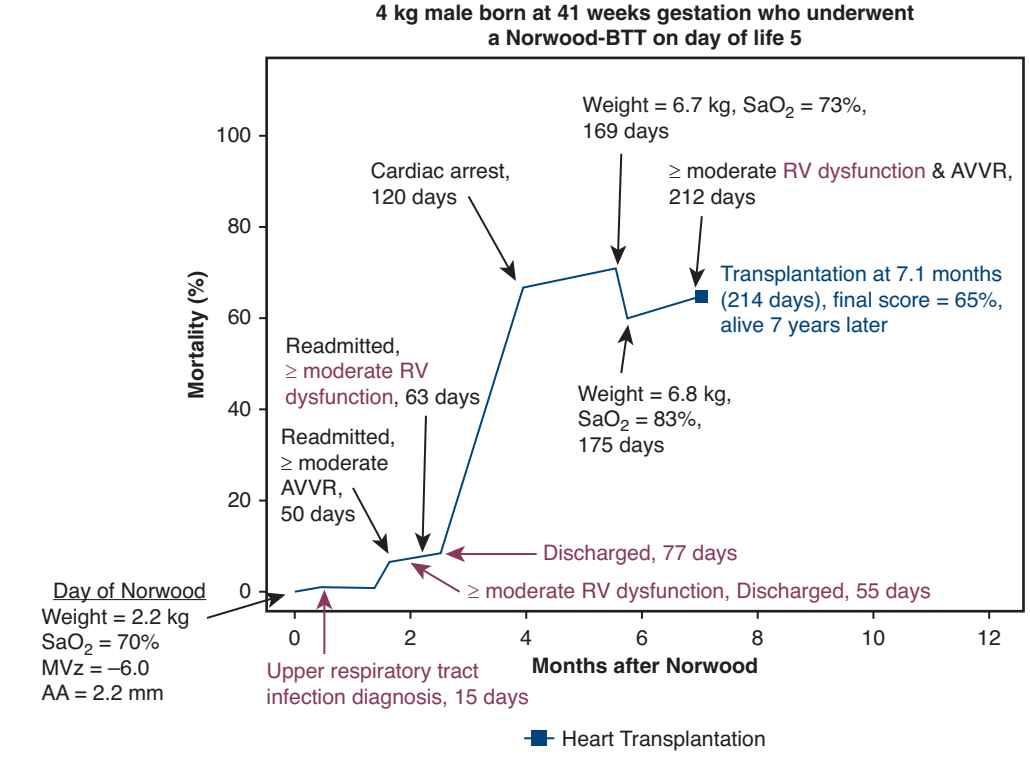


FIGURE 3. Dynamic risk profiles for 360 infants who underwent a Norwood operation. The instantaneous risk of death is presented as probability of mortality (%). Probability of mortality may increase or decrease. *Lines* connect predicted mortality in which an event occurred. Individual infants are color coded based on their end state after the Norwood.



A



B

FIGURE 4. Individual dynamic risk profiles of infants post-Norwood. A, Infant who died after Norwood operation. B, Infant who underwent transplantation and is alive at last follow-up. *Lines* connect predicted mortality in which an event occurred. *Black text* represents the occurrence of events that were significantly associated with mortality and thus included in the model for death after the Norwood operation. *Purple text* indicates the occurrence of an event that was not included in the model. *RVPA*, Right-ventricle-to-pulmonary-artery conduit; *RV*, right ventricle; *MCS*, mechanical circulatory support; *SaO_2*, arterial oxygen saturation; *AVVR*, atrioventricular valve regurgitation; *MVz*, mitral valve z-score; *AA*, Aortic atresia; *BTT*, Blalock-Thomas-Taussig shunt.

cohort, although mortality was not limited to the inpatient setting for our analysis.

Finally, requiring 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 died during the interstage period. Risk factors for readmission after congenital heart surgery have been examined in previous series, but the effect of readmission on outcomes has not been directly investigated.[32,33] The association of nonoperative readmission with death and the 20% mortality in infants readmitted post-Norwood certainly indicate that readmission may be a surrogate for ongoing pathology. The purpose of the readmission ostensibly would be to intervene on this ongoing pathology and to decrease a patient's risk profile. However, its association with death may also imply that readmissions are temporarily effective in decreasing risk, but ultimately fail to rescue one-fifth of these patients. Further analyses are required to define the population of patients who are not benefiting from readmission.

Potential Clinical Applicability and Future Directions

These dynamic risk profiles serve an explanatory role. For this limited cohort, our results highlight the ability for a dynamic risk model to update predicted mortality post-Norwood according to occurrence of events (eg, readmission) or changes in physiologic data (eg, SaO_2). Furthermore, these data underscore the importance of incorporating post-Norwood events when analyzing interstage mortality. For an infant who has developed AVVR and RV dysfunction, predicted mortality (65%) on the day of but before receiving heart transplantation was quantified, which has not previously been performed (Figure 4, *B*). Additionally, decreased predicted mortality after intervention on RVPA and accompanying increased SaO_2 (Figure 2) illustrate the potential influence of shunt-related hypoxia that warrant intervention to improve mortality trajectories while awaiting stage 2 palliation.

Real-life application of an available instantaneously updating dynamic prediction model to guide clinical decisions is far from clinical implementation or integration into an electronic system, but the future potential of such a tool is promising. Further refinements of conceptualization, with defined thresholds and subsequent formal validation using a new cohort, may suggest a need and/or target for reintervention both aimed at reducing individuals' instantaneous probability of mortality while considering the change in status for individual patients. Sourcing data directly from electronic medical records is still a cumbersome process, and human-driven data abstraction is still commonly relied upon. Despite the increasingly widespread use of wearable fitness and health trackers for adults, this has not expanded to infant and pediatric patients. Therefore, serial physiologic measurements in an outpatient setting are also commonly manually recorded, limiting their real-time acquisition. Should real-time data acquisition become more feasible, much work would be required to implement a robust model (for which validation is imperative) into an electronic medical record for clinician use.

Study Limitations

We acknowledge several limitations. Infants were restricted to the CHSS CLHO prospectively enrolled cohort. Data regarding the pre- and post-Norwood course were limited to medical records submitted to the CHSS-CRQ. Clinically important data, such as mode of caloric intake, laboratory values, medications (eg, antiarrhythmics, anticoagulants, diuretics), and presence of supplemental oxygen, were not available. Data from home monitoring programs (eg, serial weight and SaO_2) were not available and able to be included in our analyses. There was variation regarding data by era and institution (fewer medical records were available for early enrollees and certain institutions submitted fewer records). Our multivariable analysis may be limited by unknown confounders. Our analyses were also limited due to small sample size and low frequency of certain events. For infants who died and had no identified risk factors present, their respective instantaneous probability of mortality may be low. Our model is limited to available data and does not account for potentially rare but highly influential risk factors. Finally, our risk model has perfect "memory." The effect of the occurrence of a risk factor is retained and continues to affect subsequent calculations of the hazard function (data carried forward). We have insufficient knowledge of how the effect of occurrence of a complication dissipates or decays with time. Therefore, our estimates for predicted instantaneous mortality may reflect the most "liberal" or dire circumstances for these infants. The rate at which risk dissipates for specific events remains an active area of clinical investigation.

CONCLUSIONS

The application of dynamic risk profile methodology signifies a paradigm shift in the study of outcomes and risk factors after congenital heart surgery. In traditional biostatistical analyses, general conclusions have been drawn from risk factor analysis of the overall study population and were thought to be representative of that study population. Instead, individual instantaneous predicted mortality trajectories, incorporating both preoperative and postoperative data, may now be generated. These data and illustrations represent a true application of precision medicine to the field of congenital heart surgery for a high-risk, resource-intensive group of patients.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: critical left heart obstruction, hypoplastic left heart syndrome, Norwood, precision medicine, prediction, time-varying covariate

APPENDIX E1. STATISTICAL METHODOLOGY INCORPORATING TIME-VARYING COVARIATES

Survival Analyses

Multiphase, nonproportional parametric risk hazard analysis for the primary outcome of all-cause mortality after the Norwood operation (time zero) was performed.[E1] This is a type of distributional analysis for which equations may describe a number of distribution shapes for the probabilities of events. Up to 3 phases of risk may be modeled, although 3 are not required. Each phase is defined by phase-specific shaping and scaling parameters. For this analysis, these shaping parameters were fixed and then candidate variables selected from bootstrap aggregation were entered into the model to perform the multivariable risk hazard analysis.

Time-Varying Covariates

Variables or factors that occur postoperatively after Norwood (ie, after time-zero) may be associated with an increased or decreased likelihood of all-cause mortality. For example, reintervention for stenosis of an RVPA conduit may increase the risk for mortality after Norwood operation. These variables, referred to as "time-varying covariates," are not commonly incorporated in risk models because of their associated complexity. Inclusion of multiple categorical and continuous postoperative time-varying covariates followed by subsequent individual mortality prediction served as the foundation for our methodology. The results provide explanatory data for the fluctuations in risk of death after Norwood operation for individuals. This advanced statistical methodology has been used to assess mortality risk while awaiting heart transplantation for adults with advanced heart failure.[E2] Its application is novel within the field of congenital heart surgery and embarks on the field of precision or individualized medicine for this complex population.[E3]

A time-varying covariate's value is not constant throughout the study period, and instead its value depends on time.[E4,E5] Specifically, a time-varying covariate must be measured or occur after the start time (time-zero) of the interval under study. Both continuous and categorical data may be incorporated into analyses as time-varying covariates. Continuous data can take the form of repeated measurements of arterial oxygen saturation, in which each subsequent measurement and its associated time interval are treated as an individual time-varying covariate. Categorical data can take the form of the occurrence of an event. Repeated occurrences of an event may happen and be included.

Incorporation of time-varying covariates into our parametric hazard analyses was through left censoring (the event of interest occurred before the start time of the interval of interest).[E6] The start time for each individual segment was the left censoring time. Time-varying covariates only exerted their effect on the risk of death after they occurred. Data for both the time-varying covariate and the time of its occurrence were required. To construct the necessary dataset, the overall time interval under study was segmented based on occurrence of the time-varying covariates (Figure E2). The resultant dataset was extensive and had repeated measures (ie, several rows per individual). This longitudinal dataset was crucial to incorporating time-varying covariates in our multivariable hazard analyzes and served as the basis for this methodology.

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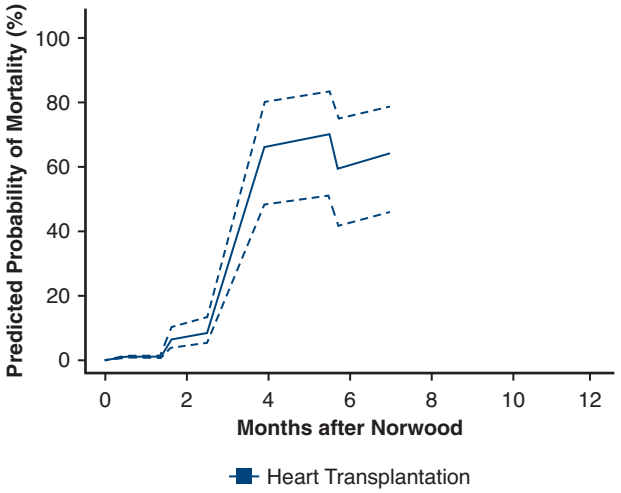

FIGURE E1. Individual dynamic risk profile with corresponding confidence intervals. *Dashed lines* represent 68% confidence limits.

	Baseline Variables		Time-varying Covariates							
Study ID	Gestational age (weeks)	Genetic abnormality	SaO_2 (%)	≥ Moderate AVVR	Conduit Reintervention	Readmission	Death before S2P	Interval under study (days)	Time start (days)	Time to event (days)
CLHO2	41	0	82	0	0	0	0	172	0	11
CLHO2	41	0	82	1	0	0	0	172	11	14
CLHO2	41	0	79	1	0	0	0	172	14	32
CLHO2	41	0	71	1	0	0	0	172	32	54
CLHO2	41	0	67	1	0	0	0	172	54	63
CLHO2	41	0	67	1	1	0	0	172	63	98
CLHO2	41	0	78	1	1	0	0	172	98	109
CLHO2	41	0	78	0	1	0	0	172	109	129
CLHO2	41	0	78	0	1	1	0	172	129	172

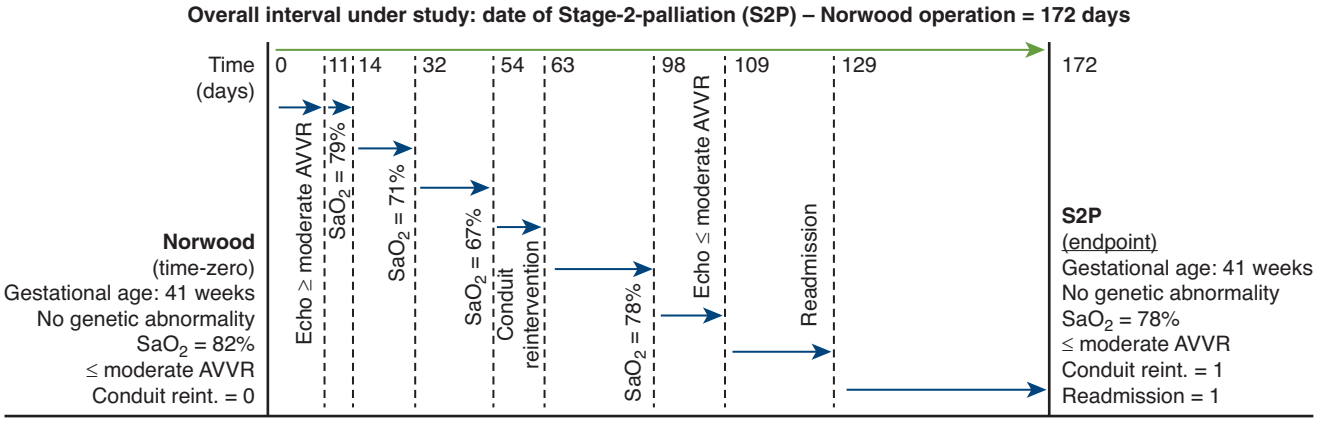

FIGURE E2. Longitudinal dataset example (*top*) for a hypothetical individual "CLHO2." Baseline variables (gestational age and presence of genetic abnormality) occur before Norwood operation and remain constant throughout the interval under study. Time-varying covariates such as SaO_2, AVVR, conduit reintervention, and readmission are not constant and exert their effect after they occur (left censored; after "time to event"). The "time start" describes the beginning of a time-varying covariate. Once a time-varying covariate has occurred, its effect will carry forward in subsequent segmentations indefinitely (eg, conduit reintervention) or until the time-varying covariate changes (eg, SaO_2, AVVR). *SaO_2*, Arterial oxygen saturation; *AVVR*, atrioventricular valve regurgitation.

TABLE E1. Diagnostic criteria for time-related events after Norwood operation

	Diagnostic criteria
Neurologic	
Intracranial complication (hemorrhage or stroke)	Records describe radiographic evidence of intracranial or intraventricular hemorrhage, documentation of infarction, not global ischemic injury or hypoxic ischemic encephalopathy
Seizure	Clinical diagnosis usually, some electro-encephalographically confirmed
Cardiac	
Mechanical circulatory support post-Norwood	Operative report
Resuscitated cardiac arrest	Clinical documentation of cardiac arrest with successful cardiopulmonary resuscitation
Reintervention, operative or transcatheter	Operative or procedure report
Aorta	
Conduit/shunt	
Pulmonary arteries	
Other	Includes atrial septectomy, pacemaker placement, tricuspid valve repair, and more
Moderate or severe right ventricular dysfunction on serial echocardiogram	Echocardiogram report
Moderate or severe AVVR on serial echocardiograms	Echocardiogram report
Recoarctation on final cardiac catheterization before transition to another end state	Catheterization report
Respiratory	
Required continuous positive airway pressure	Initialization of continuous positive airway pressure therapy in records
Reintubation for respiratory distress	Documented reintubation after initial postoperative extubation following Norwood operation
Tracheostomy	Operative report
Other	
Readmission after Norwood hospitalization discharge	Admission or discharge summary, with indication for admission
Required inotropes during readmission	Documentation of starting inotropes upon admission to the ICU (epinephrine, norepinephrine, milrinone, or dopamine)
Discharge after readmission	Discharge summary or clinic note with discharge date
Noncardiac reoperation	Operative report or discharge summary with indication for operation
Gastrointestinal	
Necrotizing enterocolitis	Clinical documentation of diagnosis of necrotizing enterocolitis, medically or surgically treated
Renal	
Renal replacement therapy	Documentation of hemodialysis initiation in progress note or discharge summary
Infectious disease	
Bloodstream infection	Positive blood cultures
Sternal wound infection/mediastinitis	Medical or surgical treatment for sternal wound infection
Meningitis	Positive cerebrospinal fluid culture
Sepsis	Institutional diagnosis of sepsis, with hemodynamic instability
Respiratory tract infection	Clinical diagnosis of upper or lower respiratory infection based on signs or symptoms, often had positive sputum culture
Urinary tract infection	Positive urine culture

AVVR, Atrioventricular valve regurgitation; *ICU*, intensive care unit.