University of Nebraska Medical Center
DigitalCommons@UNMC

Capstone Experience | Master of Public Health

12-2021

Derivation and Validation of a General Predictive Model for Long Term Risks for Mortality and Invasive Cardiovascular Interventions in Congenital Heart Disease

David A. Danford
University of Nebraska Medical Center

Follow this and additional works at: https://digitalcommons.unmc.edu/coph_slce

 Part of the Cardiology Commons, Congenital, Hereditary, and Neonatal Diseases and Abnormalities Commons, Pediatrics Commons, and the Public Health Commons

Recommended Citation

Danford, David A., "Derivation and Validation of a General Predictive Model for Long Term Risks for Mortality and Invasive Cardiovascular Interventions in Congenital Heart Disease" (2021). *Capstone Experience*. 168.
https://digitalcommons.unmc.edu/coph_slce/168

This Capstone Experience is brought to you for free and open access by the Master of Public Health at DigitalCommons@UNMC. It has been accepted for inclusion in Capstone Experience by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

TITLE: Derivation and Validation of a General Predictive Model for Long Term Risks for Mortality and Invasive Cardiovascular Interventions in Congenital Heart Disease

Author: David A. Danford

Institutions: University of Nebraska Medical Center, Criss Heart Center at Children's Hospital and Medical Center, University of Nebraska School of Public Health

ABSTRACT

Introduction. Accurate assessment of prognosis is a key driver of clinical decision making in congenital heart disease (CHD), but is complicated because CHD represents such a diverse collection of conditions. The aim of this investigation is to derive, validate, and calibrate multivariable predictive models for time to surgical or catheter-mediated intervention (INT) in CHD and for time to death in CHD. **Methods.** 4108 unique subjects were prospectively and consecutively enrolled, and randomized to derivation and validation cohorts. Total follow up was 26,578 patient-years, with 102 deaths and 868 INTs. Accelerated failure time multivariable predictive models for the outcomes, based on primary and secondary diagnoses, pathophysiologic severity, age, gender, genetic comorbidities, and prior interventional history, were derived using piecewise exponential methodology. The model predictions were validated, calibrated, and evaluated for sensitivity to changes in the independent variables. **Results.** Model validity was excellent for prediction of both mortality and INT at 4 months, 1 year, 5 years, 10 years, and 22 years (areas under receiver operating characteristic curves ranged from 0.809 to 0.919), and predictions calibrated well with observed outcomes. Although age, gender, secondary diagnoses, and genetic comorbidities were significant independent contributors to the survival and/or freedom from intervention models, predicted outcomes were most sensitive to variations in a composite predictor incorporating primary diagnosis, pathophysiologic severity, and history of prior intervention. An active cohort effect is identified in which predicted mortality and intervention both increased throughout the 22 years of study. **Conclusions.** Time to INT and time to death in CHD can be predicted with accuracy based on clinical variables. The objective predictions available through these models could educate both patient and provider, and inform clinical decision making in CHD.

INTRODUCTION.

Accurate assessment of prognosis is one of the key drivers of clinical decision making. Knowledge of prognosis in congenital heart disease (CHD) is especially complicated because it represents such a diverse collection of conditions. Although some determinants of outcome are known for individual lesions, the degree to which these determinants are shared across specific CHD diagnoses and the ways they interact within and across diagnosis groups remain largely unknown. It is well established that CHD outcomes depend on the specific primary cardiac lesion[1-3], its pathophysiologic severity[4-6], history of prior cardiovascular intervention[5,6], genetic comorbidities such as Down Syndrome[7,8], large chromosome trisomies[9] and other inborn disorders[10,11], and even gender[12,13]. Moreover, general improvements in CHD care have changed outcomes over the years. Therefore, due to a substantial cohort effect, prognosis can depend on the era during which the observations are made[14-16]. Successful surgical or catheter-mediated interventions have, in recent years, become more common and mortality rates have fallen[17], leading many to contend that simple survival analysis no longer conveys a full and useful picture of CHD prognosis[17,18]. Accordingly, both mortality and need for intervention are relevant outcomes for patients with CHD.

Piecewise parametric modelling of time related outcomes is increasingly applied for predictions in medicine in areas such as organ transplant[19,20], oncology[21], neuropsychiatric disorders[22,23], and success or failure of therapies as diverse as antibiotics and contraceptives[24,25]. We are aware of no prior application of this method in CHD. There has, however, been great interest in long-term natural history of individual forms of CHD[26,27], and especially about outcomes after specific surgical or catheter-mediated interventions[3, 16, 28-30]. Although factors associated with survival and/or freedom from intervention are commonly

identified using Kaplan-Meier curves or proportional hazards modeling, general predictive models are not usually subjected to formal independent validation. Identification of factors associated with acute mortality of surgical intervention in CHD have received considerable attention, and there is ample evidence that the RACHS-I stratification scheme, a consensus-based risk adjustment[31] is predictive of in-hospital post-surgical mortality[32,33], other scoring strategies have proven less reliable[34]. A model for acute risk surrounding non-cardiac procedures in patients with CHD has been validated[35]. Although there is some evidence that the more severe strata of RACHS-I are associated with greater ongoing risks for death and re-intervention[36], it is not necessarily clear, that the presumption that risk factors for acute outcome can optimally describe risks in longer term. Among adults with CHD, it has been useful to repurpose a predictive model originally derived for heart failure to identify those at risk for poor outcome in general[37]. Others have derived promising but unvalidated models in an adult CHD population which identify associations of primary diagnosis, interventional history, and disease severity with mortality over time[38,39]. In another unvalidated model of 15-year survival for CHD diagnosed in infancy, mortality risk was independently associated with prematurity, primary and secondary cardiac diagnoses, gender, and noncardiac malformations[40].

A general model to predict individual outcomes within the diverse CHD population has yet to be developed. If a reliable model of this sort were constructed, it is expected that prognostic information available from it would be valuable for patients, their families, and their physicians. The aim of this investigation is to derive, validate, and calibrate multivariable predictive models for time to surgical or catheter-mediated intervention in CHD and for time to death in CHD.

METHODS

Clinical Material. Beginning June 18, 1998 and concluding June 30, 2020, 4108 unique subjects were prospectively and consecutively enrolled. Inclusion criteria were: (1) an encounter with a single identified practitioner of pediatric cardiology in an outpatient clinic for young people with heart disease, working in the larger context of an academic group practice of pediatric cardiology; and (2) the presence of a major or minor anatomic or hemodynamic cardiovascular lesion. There were no specific exclusion criteria. Using a random number table, the subjects were randomized to a derivation cohort, representing 80% of the patients, and a validation cohort, representing 20%. This research was approved by the Institutional Review Board for University of Nebraska Medical Center and Children's Hospital and Medical Center (Omaha).

Data collected. At enrollment, the following information was recorded: age, enrollment date, gender, and presence or absence of: (1) trisomy 21; (2) other constellation of deformities, chromosomal abnormality, or inborn error of metabolism; (3) secondary cardiac defect(s); and (4) prior cardiovascular surgical or catheter mediated interventions. The primary cardiovascular diagnosis was recorded. When more than one diagnosis was present, the primary diagnosis was identified as the highest ranked diagnosis based on a previously-described empiric semi severity-based diagnoses hierarchy[6]. All other cardiovascular diagnoses were recorded, and denoted as secondary. Based on a previously described pathophysiologic severity score for hemodynamic burden[6], the degree of left ventricular volume and pressure overload, right ventricular volume and pressure overload, cyanosis, and systemic ventricular dysfunction were graded as none, mild, moderate, or severe. Chart review identified the times at which two outcomes occurred: (1) death and (2) invasive cardiovascular intervention (surgical or catheter mediated).

Statistical methods.

Descriptive. Central tendencies and spread of continuous variables were described with means and standard deviations. Categorical variables were described with counts and proportions. The two time-dependent outcomes were summarized using the Kaplan-Meier method.

Combining context-dependent predictive variables. Anticipating that the associations of the six pathophysiologic severity variables, diagnosis, and prior intervention to outcome would be complex, and vary widely depending on the combinations in which they exist, the derivation cohort was inspected to see which of these combinations contained 25 or more examples. Twenty-five was chosen based on a two-tailed power calculation which demonstrated that this number would be required for a comparison of Kaplan-Meier curves which would assure detection of Hazard Ratio$\geq$1.75, relative to the remaining members of the derivation cohort, given a reference hazard = 0.4, α=0.05, and power 0.801. Subjects within these groups were assigned a group-specific score based on proportion deceased at 10 years, and this was denoted $DPPI_m$ (**D**iagnosis, **P**athophysiology, **P**rior **I**ntervention, **m**ortality). An analogous procedure yielded scores for intervention $DPPI_i$. For groups represented by fewer than 25 members, and therefore insufficient for confident direct estimation of DPPIi from product-limit estimation, a three-stage process allowed imputation of DPPIi. (1) Using the entire derivation cohort, product-limit estimation provided one approximation of probability of intervention based solely on diagnosis and interventional status (ignoring pathophysiology) or "dpi-based-DPPIi", and another based solely on pathophysiology (ignoring diagnosis and interventional status) or p-based-DPPIi. (2) Based on the 48 DPPI categories for which DPPIi is known, a multiple linear regression was calculated to predict DPPIi from dpi-based-DPPIi, p-based-DPPIi, and their

product. (3) The regression equation was applied to the uncommon categories with small n to estimate DPPIi, and when that estimate exceeded 1.0, a value of 1.0 was applied. An analogous process was applied to estimate DPPIm for members of unusual combination groups (See Appendix).

Scores for **sec**ondary **d**iagnosis relative to **m**ortality ($SECD_m$), and for secondary diagnosis relative to intervention ($SECD_i$) were obtained from 13 categories of secondary cardiac diagnoses, again using 10 year outcomes from Kaplan-Meier curves.

Derivation of predictive models. Parametric survival models were sought for the two time-dependent outcomes of interest, but in the derivation cohort, accelerated failure time assumptions were not fulfilled for exponential models evaluated over the full follow-up duration. Therefore, death rates and intervention rates after enrollment were estimated using piecewise exponential models, stratified using the following intervals: 0 to 4 months, 4 months to 1 year, 1 to 5 years, 5 to 10 years, and 10 to 22 years. Goodness of fit within each segment of the model were tested by plotting the negative log of the survival (or freedom from intervention) against time, and confirming a near linear association. Independent variables from which the freedom from intervention model was built include DPPIi, SECDi, age, gender, date of entry into study, Down syndrome, and other inborn or genetic syndrome. Each segment of the piecewise model was generated by backward selection, with criterion for retention $\alpha = 0.15$. In an analogous fashion the survival model was built starting with independent variables DPPIm, SECDm, age, gender, date of entry into study, Down syndrome, and other inborn or genetic syndrome.

Validation, calibration, and sensitivity analysis of predictive models. Models were validated using a randomly selected 20% of cases which had not been used to derive the model. Receiver operating characteristic (ROC) curves were generated for the survival and freedom

from intervention models at 4 months, 1, 5, 10, and 22 years by plotting sensitivity against 1 minus the specificity of model predictions across the spectrum of predicted outcomes. Areas under the ROC curves were determined and these were reported as a measure of model validity, where 1.0 represents perfect discrimination, 0.7-0.8 acceptable, 0.8-0.9 excellent, and >0.9 outstanding. Survival and freedom from intervention model calibration was evaluated at 4 months, 1, 5, 10, and 22 years in 2 ways. First, Spiegelhalter Z score was calculated, with significance criterion $p>0.05$ suggesting satisfactory calibration. Second, the validation cohort was empirically stratified by predicted outcome at 22 years (threshold probabilities to separate the bins of predicted probability of freedom from cardiovascular intervention: 0.05, 0.20, 0.50, 0.90, and 0.99, and for predicted probability of survival: 0.71, 0.85, 0.90, 0.95, and 0.99), and Kaplan-Meier curves were inspected to obtain observed outcome at 4 months, 1, 5, 10, and 22 years. At each of these timepoints, using data derived from the 6 bins of predicted probabilities, simple linear regression was applied to predict mean observed outcome from mean predicted outcome. These regressions were inspected for slope, intercept, and r^2, to assess model calibration. One-way sensitivity analysis was performed by plotting the variations observed in model output when independent variables were allowed to vary over their ranges. All analyses were performed using SAS 9.4 software (SAS Institute Inc, Cary, NC).

RESULTS

Characteristics of the derivation and validation cohorts. There were 4108 patients included, 3285 in the derivation cohort, and 823 in the validation cohort. The independent variable distributions and the outcomes were comparable between cohorts, and are summarized in Table I. Total follow up time for the entire set of patients was 26,578 patient-years during which there were 102 deaths and 868 invasive cardiovascular interventions. The distribution of primary and secondary diagnoses was similar between the cohorts and appears representative of the broad spectrum of cardiac diagnoses expected in a population of outpatients in a pediatric cardiology clinic (see Tables II and III, respectively). The time-related occurrence of cardiac intervention and death were indistinguishable between the derivation and validation cohorts (Figure 1).

Assembly of compound predictors and assignment of values. Prior to derivation of predictive models, combinations of primary diagnosis, pathophysiologic severity, and prior interventional status (DPPI) were assembled and their observed associations with 10 year outcomes were tabulated for the 48 combinations which represented 25 or more cases in the derivation cohort. These values, derived from Kaplan-Meier estimates of probability of intervention and probability of mortality at 10 years were noted as $DPPI_i$ and $DPPI_m$ scores, respectively. For all other rarer combinations of diagnosis, pathophysiology, and prior interventional history, regardless of how uncommonly they might be expected to occur, DPPIi and DPPIm were imputed (imputation rules in Appendix), allowing the completion of comprehensive tables of $DPPI_i$ and $DPPI_m$ (Tables IV and V, Appendix). There were 13 single or multiple combinations of secondary diagnoses from which intervention and mortality scores

(SECDi and $SECD_m$, respectively) were derived, and are shown in Table VI in the appendix. Because the 13 secondary diagnosis categories were all-inclusive, no imputed value were required.

In the derivation cohort, goodness of fit for the accelerated failure time assumption for the piecewise exponential model was confirmed by establishing linearity of the negative log of survival versus time within intervals: 0 to 4 months, 4 months to 1 year, 1 to 5 years, 5 to 10 years, and 10 to 22 years. Potential predictors were age, time of entry into the study, gender, Down syndrome, and other inborn or genetic syndrome, and (for freedom from intervention model only) $DPPI_i$, $SECD_i$, or (for survival model only) $DPPI_m$, $SECD_m$. Models for time free from cardiovascular intervention, and survival time were generated by backward selection from the models initially including all potential predictors (α to retain = 0.15) are summarized below:

Piecewise Model Equations

(1) $(PFFI_{0.33} = e\text{^}(0.33*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(2) $(PFFI_1 = PFFI_{0.33}*e\text{^}(0.67*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(3) $(PFFI_5 = PFFI_1*e\text{^}(4*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(4) $(PFFI_{10} = PFFI_5*e\text{^}(5*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(5) $(PFFI_{22} = PFFI_{10}*e\text{^}(12*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(6) $(PSURV_{0.33} = e\text{^}(0.33*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(7) $(PSURV_1 = PSURV_{0.33}*e\text{^}(0.67*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(8) $(PSURV_5 = PSURV_1*e\text{^}(4*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(9) $(PSURV_{10} = PSURV_5*e\text{^}(5*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

(10) $(PSURV_{22} = PSURV_{10}*e\text{^}(12*e\text{^}(-(-B_0 + (B_1*X_1) + (B_2*X_2) + (B_3*X_3) \ldots + (B_j*X_j))))$

Where $PFFI_t$ and $PSURV_t$ = model predictions for probability of freedom from intervention and probability of survival at time t, respectively. Values for B and X are given in the table below.

Eqn	Risk*	B_0	B_1	B_2	B_3	B_4	B_5
			X_1	X_2	X_3	X_4	X_5
(1)	High	-2.10	4.24	0.065			
			$DPPI_i$	Age**			
	Low	-53.89	60.43				
			$DPPI_i$				
(2)	High	-1.61	4.59	0.054	-0.23		
			$DPPI_i$	Age	Male		
	Low	6.73					
(3)	High	-0.92	5.14	0.052	-0.29	-0.018	
			$DPPI_i$	Age	Male	EntryT^	
	Low	-34.70	32.29	11.58			
			$DPPI_i$	SEC_i			
(4)	High	-1.04	5.09	0.67	0.40	-0.23	-0.033
			$DPPI_i$	SEC_i	Age	Male	EntryT
	Low	-40.01	36.99	13.92			
			$DPPI_i$	SEC_i			
(5)	High	-0.15	5.03	0.029	-0.22	-0.054	
			$DPPI_i$	Age	Male	EntryT	
	Low	-37.39	46.23	-0.075			
			$DPPI_i$	Age			
(6)	High	-1.89	4.93	0.098			
			$DPPI_m$	EntryT			
	Low	-260.77	269.58				
			$DPPI_m$				
(7)	High	-6.18	12.15	-2.3859			
			$DPPI_m$	Downs			
	Low	7.02	-3.28				
			OtherIG				
(8)	High	-15.80	11.20	11.06			
			$DPPI_m$	SEC_m			
	Low	7.94	-3.04				
			OtherIG				
(9)	High	-0.60	8.01	-0.047	-2.34		
			$DPPI_m$	Age	OtherIG^^		
	Low	-145.78	154.85	-0.083			
			$DPPI_m$	Age			
(10)	High	-4.29	11.01	-0.060	-1.00	-1.52	
			SEC_m	Age	Male	OtherIG	
	Low	8.63					

$DPPI_i$= Diagnosis Pathophysiology Prior Intervention based Intervention Score.
$DPPI_m$ = Diagnosis Pathophysiology Prior Intervention based Mortality Score.
$SECD_i$ = Secondary Diagnosis based Intervention Score.
$SECD_m$ = Secondary Diagnosis based Mortality Score.
*Due to DPPI-dependent variations in the associations of DPPI with outcome, high- and low-risk arms of the models were derived. Intervention Risk is high when DPPIi <0.93, and high risk

intervention model is applied, otherwise low risk model is used. Mortality Risk is high when DPPIm <0.98, and high risk mortality model is applied, otherwise low risk model is used
**Age = age in years
^Entry time if time in years since onset of investigation (June, 1998)
^^otherIG = Other inborn or genetic condition

Calculation of the areas under the receiver operating characteristic (ROC) curves for prediction of actual freedom from cardiovascular intervention in the validation cohort using the PFFI (predicted freedom from intervention) model revealed values 0.893-0.919 throughout the follow-up timeframe, demonstrating the model to be highly valid (Figure 2). PFFI demonstrated a linear relationship between predicted and observed values at each follow-up interval (4 months – 22 years), with slope approximately 1 and intercept close to 0, confirming a well calibrated predictive model. PSURV (predicted survival) was a valid model for prediction of survival across the spectrum of follow-up intervals, as demonstrated by areas under the ROC curve 0.809-0.919 (Figure 3). Significant linear relationships between observed and expected survival were identified at all follow-up intervals, but calibration was considerably best at 5 and 10 years follow-up (high R^2, and linear relation more closely approximating slope of 1 and intercept of 0) than it was at other follow-up intervals.

As expected, predictions of both survival and freedom from intervention were more sensitive to changes in DPPI score than to other predictive variables (Figure 4). Secondary diagnosis score influenced survival more than freedom from intervention. Predicted outcomes varied only minimally with gender (females had slightly more favorable prognosis) and Down syndrome (poorer survival, but no difference in freedom from intervention). Other genetic syndromes demonstrated substantial association with poorer survival, but not with freedom from intervention. Although the effects were relatively small, PSURV was lower, and PFFI was

higher with increasing age. Predicted survival and freedom from intervention were both lower as the study progressed, confirming a cohort effect for both outcomes.

DISCUSSION

Summary of Main Findings. This report describes the derivation and validation of a general predictive model for outcomes in outpatients with CHD based on a large number of subjects observed prospectively for up to 22 years. This model for prediction of survival and freedom from invasive cardiovascular intervention demonstrates excellent validity, and performs well on a clinical sample comprised of CHD outpatients independent of those from which the model was derived. As expected, by far the greatest influence is a combination of primary diagnosis, history of prior intervention, and the nature and severity of pathophysiologic abnormalities. Factors such as age of the patient, gender, secondary cardiac diagnoses, and comorbid genetic conditions are minor contributors to predicted outcomes. Reflecting a practice pattern in which intervention for CHD is generally offered to patients regardless of genetic comorbidities, the model shows that predicted probability of intervention did not vary with these factors, even though predicted mortality did. An active cohort effect is identified in which predicted mortality and intervention both increased throughout the 22 years of study. This is consistent with the expectation that there has been a more aggressive interventional approach to CHD management in recent years. Higher predicted mortality as years passed during this investigation does run contrary to the notion that modern CHD outcomes ought to be better than historical. It is, however, consistent with the concept that more aggressive care is now associated with lower hospital mortality for severe CHD, resulting in greater numbers of fragile short-term survivors entering the outpatient setting for ongoing care. A novel feature of model derivation was to reduce the thousands of possible combinations of diagnosis, history, and pathophysiology into highly predictive continuous scores for risk of mortality and intervention for incorporation in the model.

Important interactions among diagnosis, interventional history, and pathophysiologic severity were thereby accounted for, without introducing a grand multiplicity of interactive predictive terms in the model and without the opacity that would result from using a neural network with unsupervised machine learning to account for them. Moreover, outcome similarities shared across diagnoses and pathophysiologies were successfully incorporated into the model by imputing scores for uncommon combinations.

Potential Applications. Based on simple observations of diagnosis, pathophysiologic severity, prior interventional history, age, gender, genetic comorbidities, and time of entry into the study, the model reported here allows prediction of mortality and need for invasive cardiovascular intervention in outpatients with CHD. Such predictions are potentially of considerable value to frame in quantitative terms expectations for patients with CHD and their families. Specialists in CHD, too, may benefit from an objective means for assessing prognosis, especially when considering intervention for their patients. Should a specialist recommend an intervention when the model predicts minimal probability of mortality or intervention, this should prompt careful consideration of what special circumstances warrant the intervention in that patient at this time. More commonly, we expect that model projections will be concordant with expertise of the specialist, and valuable reassurance regarding the management decision would result from its use. Expertise about prognosis across the spectrum of clinical CHD is uncommon in the broader medical community. Generalists who only occasionally treat patients with CHD may benefit from the cardiovascular prognostic context the model provides. There is also potential educational value for medical trainees for whom the model can provide expectations of how serious a threat is posed by CHD and what factors contribute to the magnitude of that threat.

This rational basis underlying decisions for cardiovascular intervention might, with the insights provided by the model, be more transparent for learners.

Limitations. The model reported here is highly complex, so hand calculation for prediction of outcome for an individual patient is impractical. It would, however be easily automated within a computer application based on equations which comprise the model, thereby allowing simple translation to the clinical setting. The model was derived and validated on the experience with outpatients from a single general pediatric cardiology practice, and so may not generalize to predictions for CHD inpatients or match precisely the experience in other programs and settings. With greater differences in patient characteristics and program practices from the source, greater caution should be exercised as the model is applied. Changes in predicted outcome will probably continue to depend on the era during which patients come under observation, but it cannot be concluded that the cohort effects observed in this investigation will remain stable in perpetuity. Because of this moving target of predicted outcome, model updates will likely be necessary in the future.

Future Directions. Recommendations for intervals of outpatient follow-up in CHD tend not to be data driven, but are generally derived from consensus of expert opinion[41]. Outcome predictions and recommended follow-up intervals likely correlate, although it is not yet known how strong these associations are. We recognize that prognosis for intervention and mortality is not the only basis for follow-up recommendations, however when outcome predictions are inconsistent with the recommendation, the guidance may merit further consideration. Patients'

expectations need to be different when definitive surgery or catheter-mediated treatment for CHD is offered with the likelihood that of a durable good outcome from a single intervention than they would be when serial interventions are necessary. Therefore, there is potential interest, specifically among patients and their families, in the prediction of freedom from second intervention. We plan to use the approach reported here to derive and validate a predictive model for freedom from second intervention. Clinicians tend to think about prognosis as it applies to an individual diagnosis, however many specific conditions in CHD are so rare[42-44] that it is likely even large scale collaborative outcome studies cannot identify with confidence the variables which affect prognosis. Model based predictions might be a satisfactory surrogate for actual outcomes in such conditions, producing estimates for prognosis and accounting for the factors that influence them.

Conclusion. A piecewise exponential model predicting survival and freedom from invasive cardiovascular intervention has been derived which demonstrates excellent validity, and performs well on a clinical sample comprised of CHD outpatients.

Table I.

Clinical Feature		Cohort			p*
		Derivation	Validation	Total	
Left Ventricular Volume Overload	None	1748 (53.2%)	456 (55.4%)	2204 (53.7%)	0.4634
	Mild	1202 (36.6%)	281 (34.4%)	1483 (36.1%)	
	Moderate	293 (8.9%)	72 (8.8%)	365 (8.9%)	
	Severe	42 (1.3%)	14 (1.7%)	56 (1.4%)	
Left Ventricular Pressure Overload	None	2854 (86.9%)	717 (87.1%)	3571 (86.9%)	0.9635
	Mild	389 (11.8%)	94 (11.4%)	483 (11.8%)	
	Moderate	38 (1.1%)	11 (1.3%)	49 (1.2%)	
	Severe	4 (0.1%)	1 (0.1%)	5 (0.1%)	
Right Ventricular Volume Overload	None	2594 (78.9%)	653 (79.3%)	3247 (79.0%)	0.7389
	Mild	393 (12.0%)	97 (11.8%)	490 (11.9%)	
	Moderate	249 (7.6%)	57 (6.9%)	306 (7.4%)	
	Severe	49 (1.5%)	16 (1.9%)	65 (1.6%)	
Right Ventricular Pressure Overload	None	2611 (79.5%)	640 (77.8%)	3251 (79.1%)	0.3043
	Mild	399 (12.2%)	97 (11.8%)	496 (12.1%)	
	Moderate	98 (3.0%)	32 (3.9%)	130 (3.2%)	
	Severe	177 (5.4%)	54 (6.6%)	231 (5.6%)	
Cyanosis	None	3151 (95.9%)	773 (93.9%)	3924 (95.5%)	0.0678
	Mild	55 (1.7%)	18 (2.2%)	73 (1.8%)	
	Moderate	52 (1.6%)	19 (2.3%)	71 (1.7%)	
	Severe	27 (0.8%)	13 (1.6%)	40 (1.0%)	
Systemic Ventricular Dysfunction	None	3203 (97.5%)	806 (97.9%)	4009 (97.6%)	0.5679
	Mild	56 (1.7%)	14 (1.7%)	70 (1.7%)	
	Moderate	22 (0.7%)	3 (0.4%)	25 (0.6%)	
	Severe	4 (0.1%)	0 (0%)	4 (0.1%)	
Gender	Male	1714 (52.2%)	424 (51.5%)	2138 (52.0%)	0.7356
	Female	1571 (47.8%)	399 (48.5%)	1970 (48.0%)	
Down Syndrome	Present	189 (5.8%)	53 (6.4%)	242 (5.9%)	0.4545
	Absent	3096 (94.2%)	770 (93.6%)	3866 (94.1%)	
Other Genetic Syndrome	Present	274 (8.3%)	68 (8.3%)	342 (8.3%)	0.9419
	Absent	3011 (91.7%)	755 (91.7%)	3766 (91.7%)	
Secondary Cardiac Diagnosis	Present	836 (25.5%)	194 (23.6%)	1030 (25.1%)	0.2647
	Absent	2448 (74.5%)	629 (76.4%)	3077 (74.9%)	
Prior Cardiac Intervention	Yes	818 (24.9%)	203 (24.7%)	1021 (24.9%)	0.8854
	No	2466 (75.1%)	620 (75.3%)	3086 (75.1%)	
Age at Enrollment (years; mean±SD)		6.30±7.23	5.74±6.84	6.18±7.16	0.0379
Study Entry Date (years; mean±SD)		8.68±8.46	8.77±6.21	8.70±6.31	0.7318
Death	Yes	82 (2.5%)	20 (2.4%)	102 (2.5%)	0.9133
	No	3203 (97.5%)	803 (97.6%)	4006 (97.5%)	
Intervention	Yes	683 (20.8%)	185 (22.5%)	868 (21.1%)	0.2890
	No	2602 (79.2%)	638 (77.5%)	3240 (78.9%)	
Time followed (years; mean+SD)		6.52±6.96	6.28±6.83	6.47±6.93	0.3639

*p for differences between derivation and validation cohorts, based on chi-square for categorical variables, and 2-tailed Student t-test for continuous variables.

Table II.

Primary Cardiac Diagnosis	Number With		
	Derivation Cohort	Validation Cohort	Total
Muscular Ventricular Septal Defect	479	127	606
Perimembranous Ventricular Septal Defect	366	87	453
Aortic Valve Disease	318	78	396
Pulmonary Valve Disease	268	62	330
Secundum Atrial Septal Defect	226	64	290
Aortic Coarctation	155	52	207
Patent Ductus Arteriosus	131	27	158
Systemic Hypertension, Primary	116	31	147
Tetralogy of Fallot	99	23	122
Mitral Valve Disease	96	14	110
Atrioventricular Septal Defect, Complete	81	21	102
Transposition of the Great Arteries (D)	68	17	85
Kawasaki Disease	64	15	79
Patent Foramen Ovale	63	15	78
Supraventricular Tachycardia	57	14	71
Dilated Cardiomyopathy	53	11	64
Premature Ventricular Contractions	47	15	62
Atrioventricular Septal Defect, Partial	41	12	53
Hypoplastic Left Heart Syndrome	31	13	44
Hypertrophic Cardiomyopathy	31	8	39
Subaortic Stenosis	30	8	38
Aortopathy, Including Marfan	29	5	34
Pulmonary Atresia with Ventricular Septal Defect	28	5	33
Tricuspid Atresia	21	9	30
Tricuspid Valve Dysplasia, NonEbstein	20	8	28
Malalignment Ventricular Septal Defect, including Double Outlet Right Ventricle	22	4	26
Venosus Defects and/or Partially Anomalous Pulmonary Venous Connections	17	8	25
Total Anomalous Pulmonary Venous Connection	21	3	24
Double Inlet Single Ventricle	19	3	22
Premature Atrial Contractions	15	7	22
Subarterial Ventricular Septal Defect	18	3	21
Pulmonary Atresia Intact Ventricular Septum	14	5	19
Ebstein Anomaly	15	4	19
Pulmonary Arterial Branch Stenosis	14	4	18
Transposition of the Great Arteries (L)	14	4	18
Vascular Ring or Right Aortic Arch	15	1	16
Single Ventricle, Other	12	3	15
Supravalve Aortic Stenosis	9	6	15
Cardiac Tumor	11	3	14
Truncus Arteriosus	11	2	13
Pericardial Disease	10	2	12
Hyperlipidemia	9	2	11

The conditions listed above represent 3969 cases, or 96.6% of the sample. Another 65 (1.6%) have one of the following primary diagnoses, and represented more than 5 times in the sample: anomalous coronary arterial origin (6), atrioventricular block (10), coronary fistula (10), interrupted aortic arch (10), long QT syndrome (6), myocarditis (7), primary pulmonary vascular obstructive disease (6), and Wolff-Parkinson-White electrocardiographic pattern without supraventricular tachycardia (10).

Table III.

Secondary Cardiac Diagnosis*	Number With		
	Derivation Cohort	Validation Cohort	Total
Patent Ductus Arteriosus	105	32	137
Aortic Valve Disease	92	23	115
Pulmonary Valve Disease	83	29	112
Secundum Atrial Septal Defect	64	18	82
Mitral Valve Disease	67	7	74
Muscular Ventricular Septal Defect	50	11	61
Patent Foramen Ovale	48	9	57
Perimembranous Ventricular Septal Defect	38	16	54
Supraventricular Tachycardia	34	4	38
Subpulmonary stenosis	30	4	34
Aortic Coarctation	23	7	30
Tricuspid Valve Dysplasia, NonEbstein	22	5	27
Pulmonary Arterial Branch Stenosis	22	3	25
Subaortic Stenosis	19	5	24
Malalignment Ventricular Septal Defect, including Double Outlet Right Ventricle	18	6	24
Premature Ventricular Contractions	19	3	22
Aortopathy, Including Marfan	16	2	18
Arrhythmias, other	15	3	18
Transposition of the Great Arteries (D)	11	2	13
Dilated Cardiomyopathy	8	2	10
Venosus Defects and/or Partially Anomalous Pulmonary Venous Connections	6	3	9
Atrioventricular Septal Defect, Complete	7	1	8
Coronary arterial anomalies, other	4	3	7

*Some patients have more than one secondary diagnosis.

Figure 1

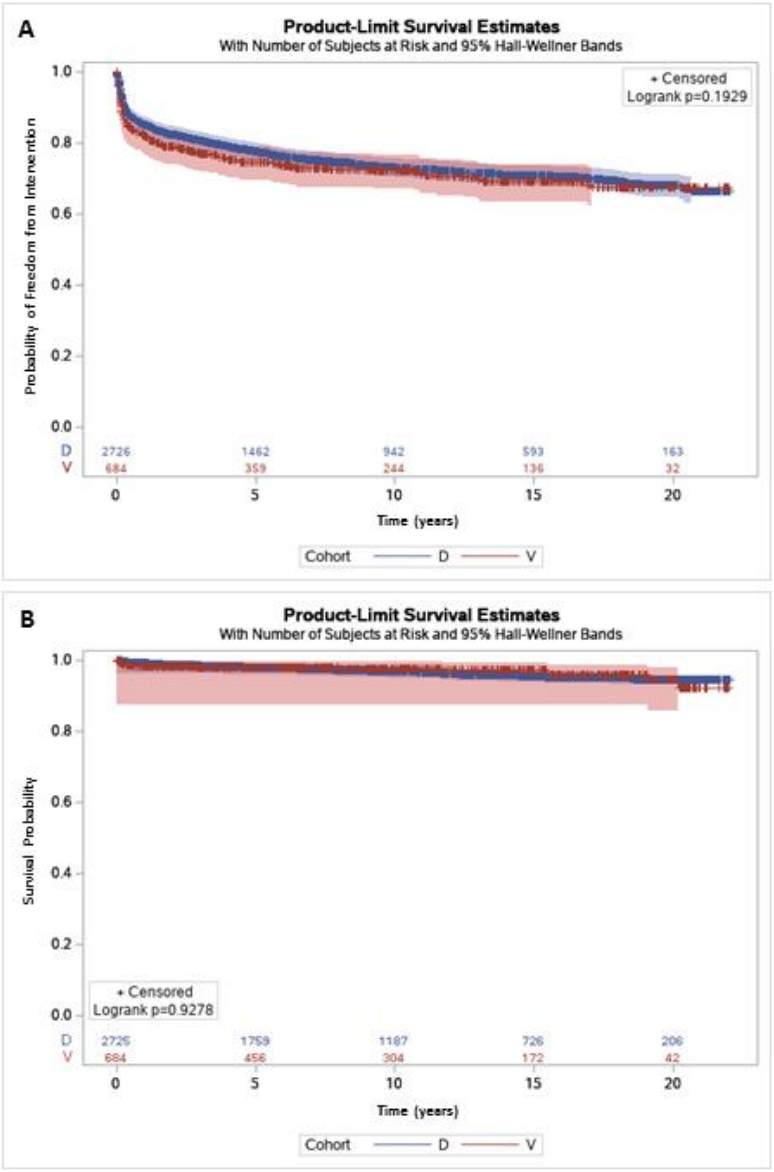
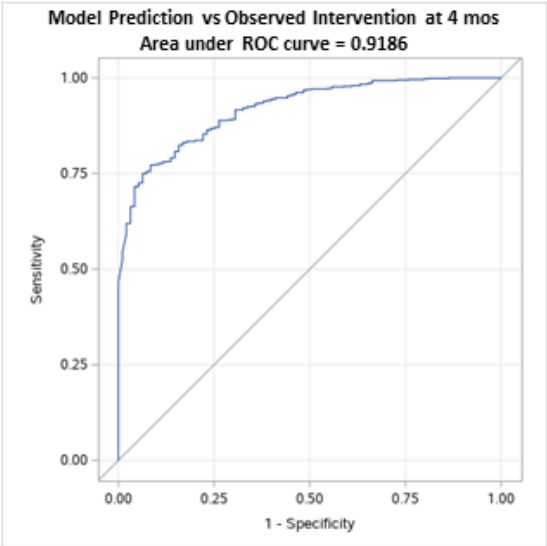

A
Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Hall-Wellner Bands
+ Censored
Logrank p=0.1929
Probability of Freedom from Intervention
1.0
0.8
0.6
0.4
0.2
0.0
D 2726 1462 942 593 163
V 684 359 244 136 32
0 5 10 15 20
Time (years)
Cohort D V
B
Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Hall-Wellner Bands
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
+ Censored
Logrank p=0.9278
D 2726 1759 1187 726 206
V 684 456 304 172 42
0 5 10 15 20
Time (years)
Cohort D V

Figure 2A



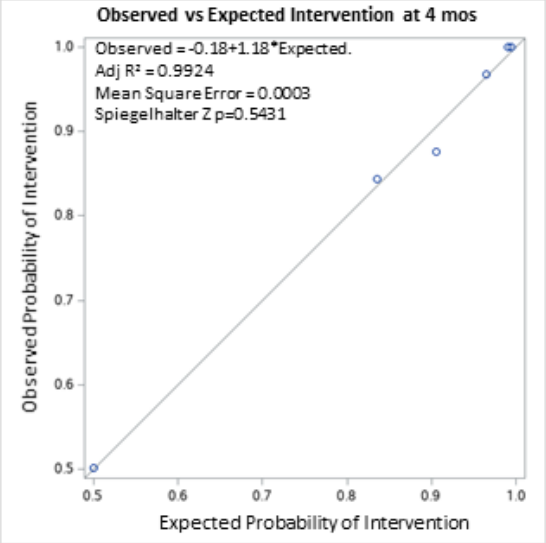
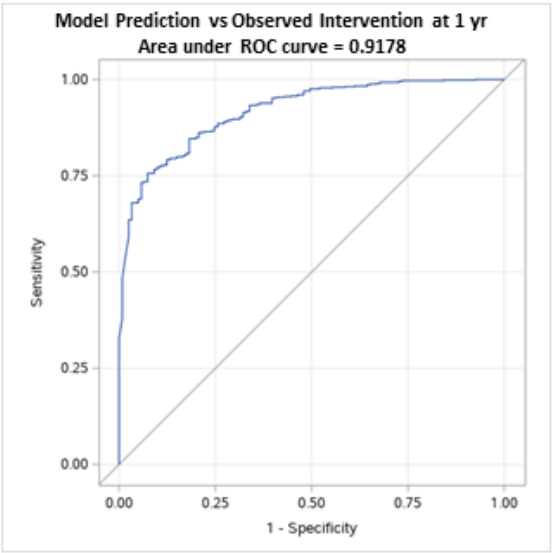


Figure 2B



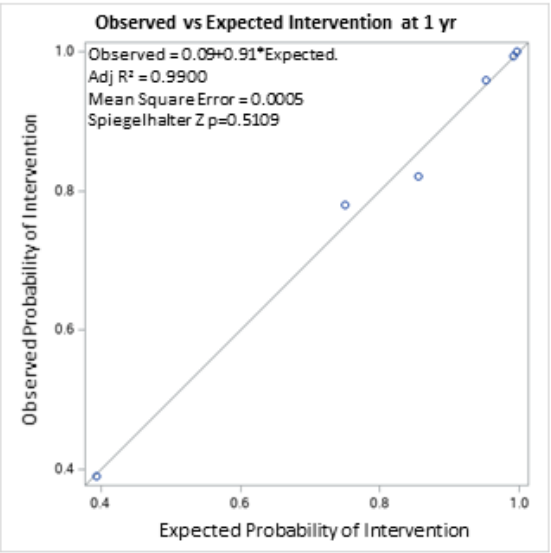
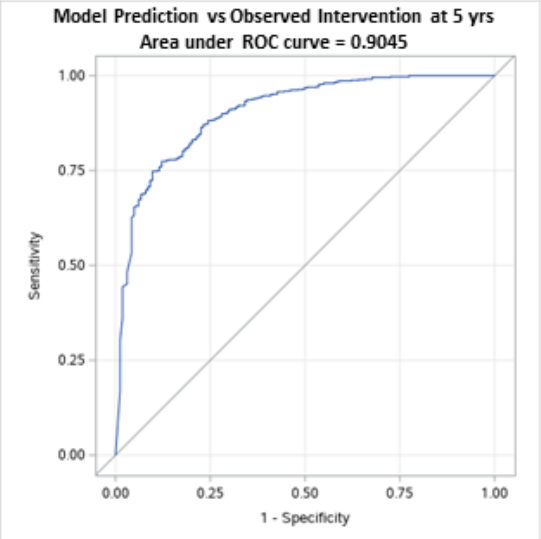


Figure 2C



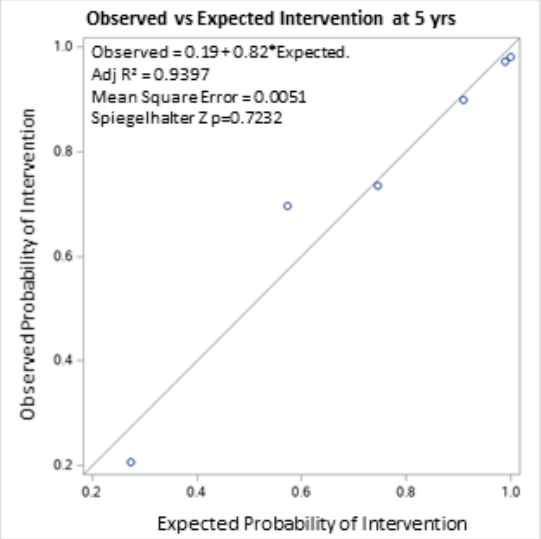
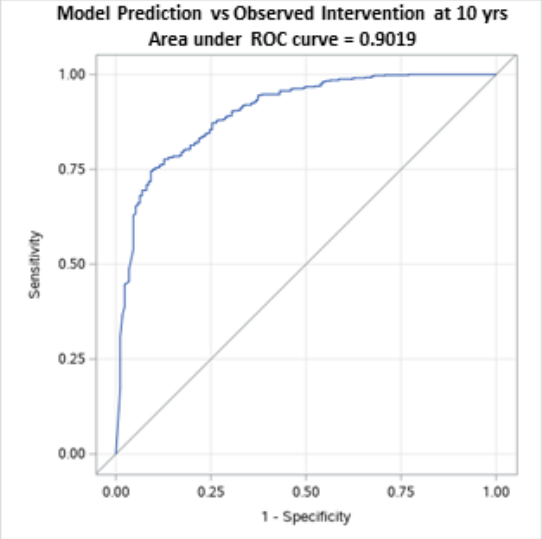


Figure 2D



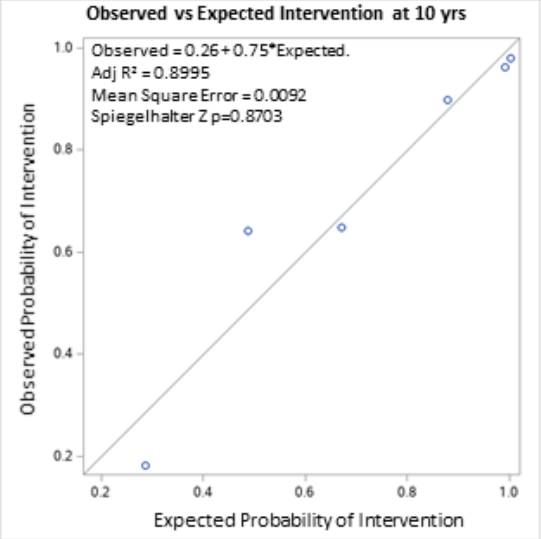
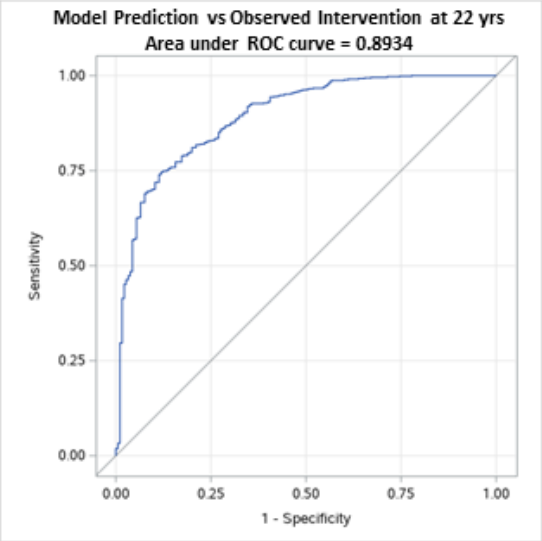


Figure 2E


Model Prediction vs Observed Intervention at 22 yrs
Area under ROC curve = 0.8934
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00

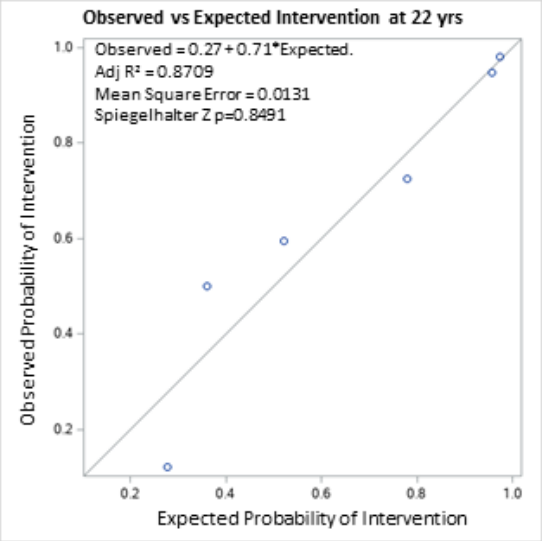
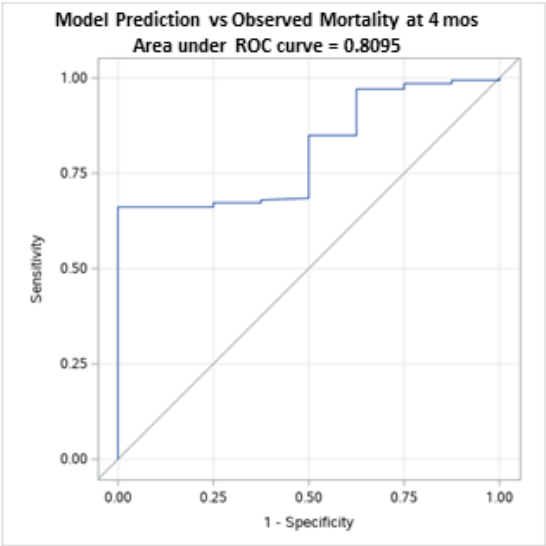

Observed vs Expected Intervention at 22 yrs
Observed = 0.27 + 0.71*Expected.
Adj R² = 0.8709
Mean Square Error = 0.0131
Spiegelhalter Z p=0.8491
Observed Probability of Intervention
Expected Probability of Intervention
0.2
0.4
0.6
0.8
1.0

Figure 3A



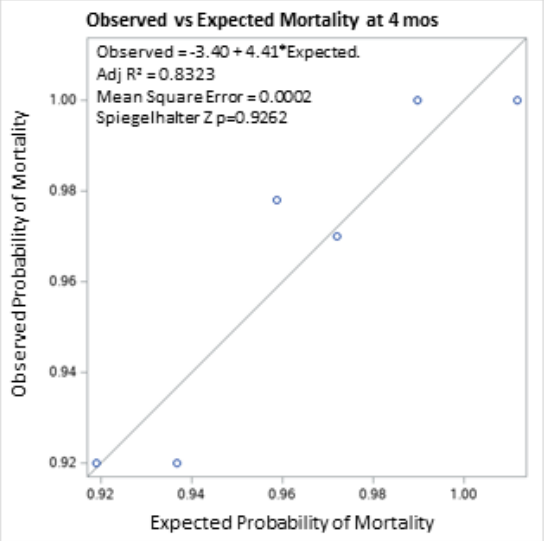
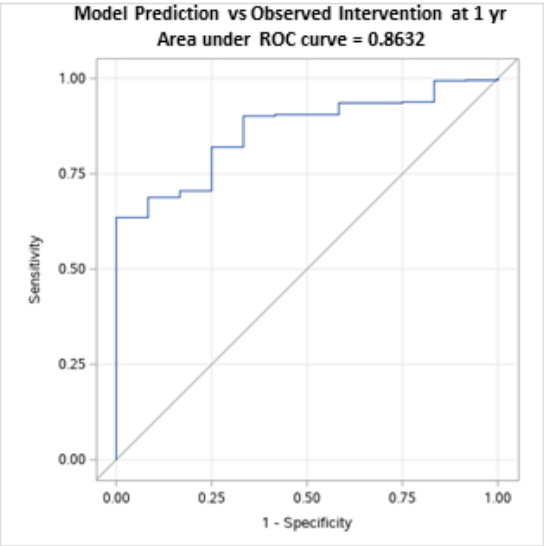


Figure 3B



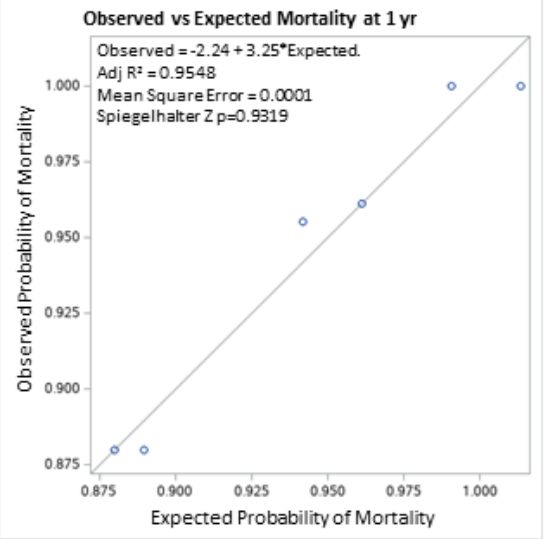
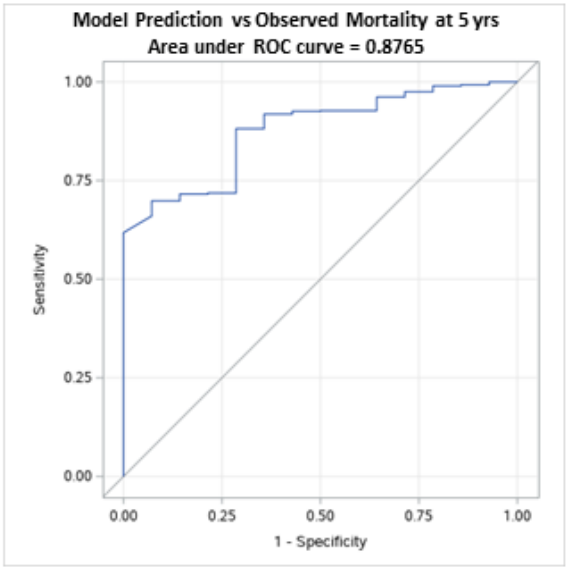


Figure 3C



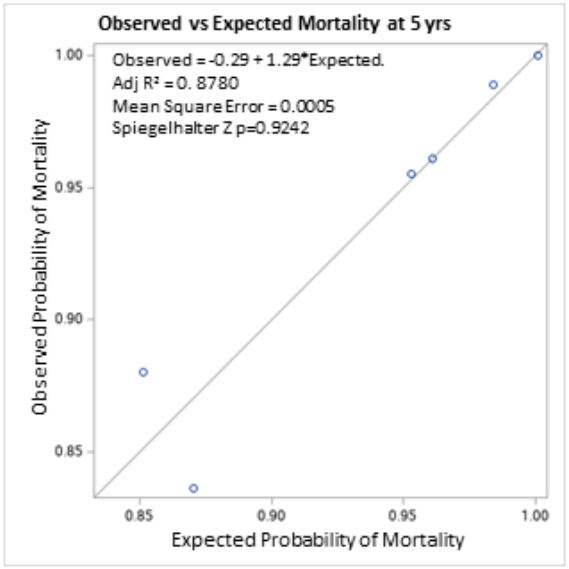
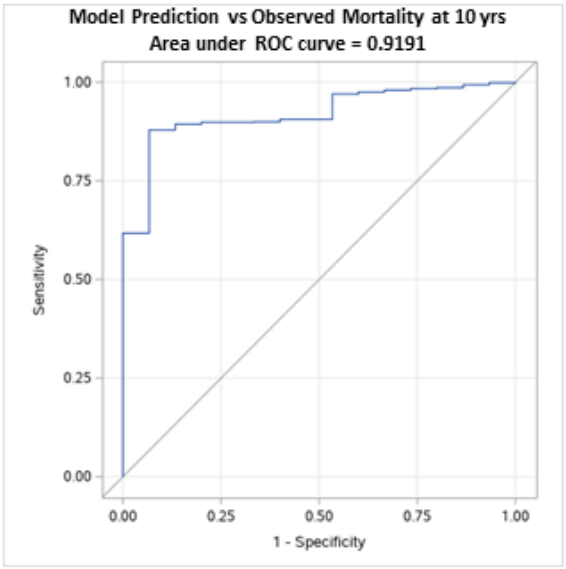


Figure 3D



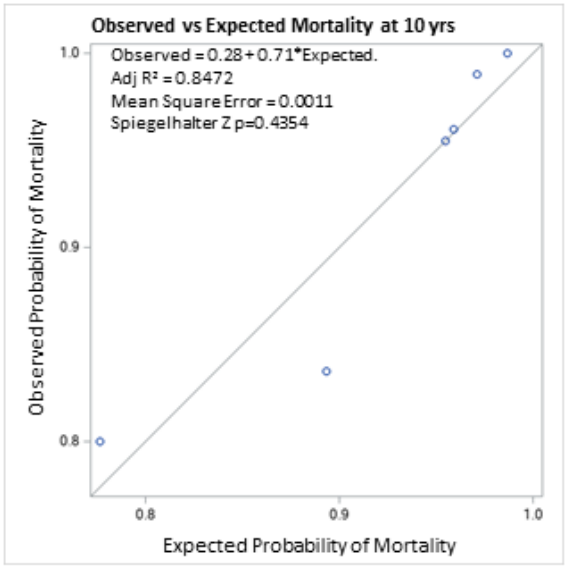
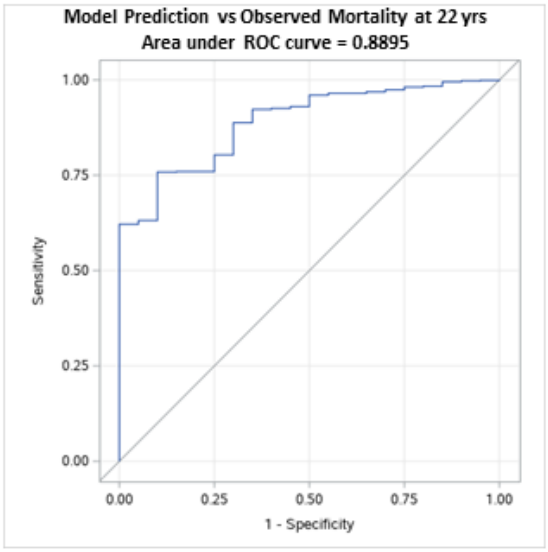


Figure 3E


Model Prediction vs Observed Mortality at 22 yrs
Area under ROC curve = 0.8895
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00

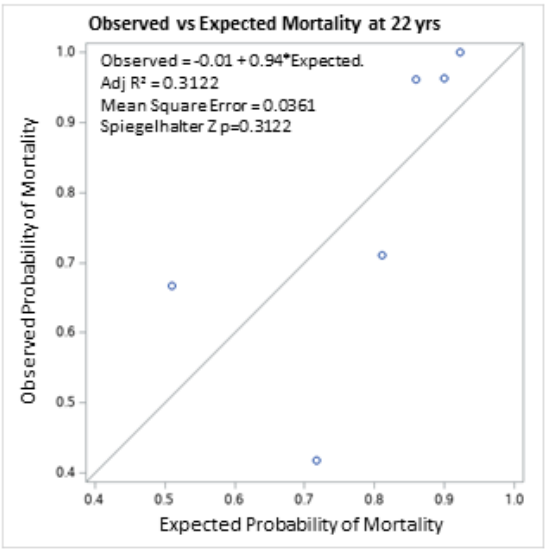

Observed vs Expected Mortality at 22 yrs
Observed = -0.01 + 0.94*Expected.
Adj R² = 0.3122
Mean Square Error = 0.0361
Spiegelhalter Z p=0.3122
Observed Probability of Mortality
Expected Probability of Mortality
0.4
0.5
0.6
0.7
0.8
0.9
1.0

Figure 4

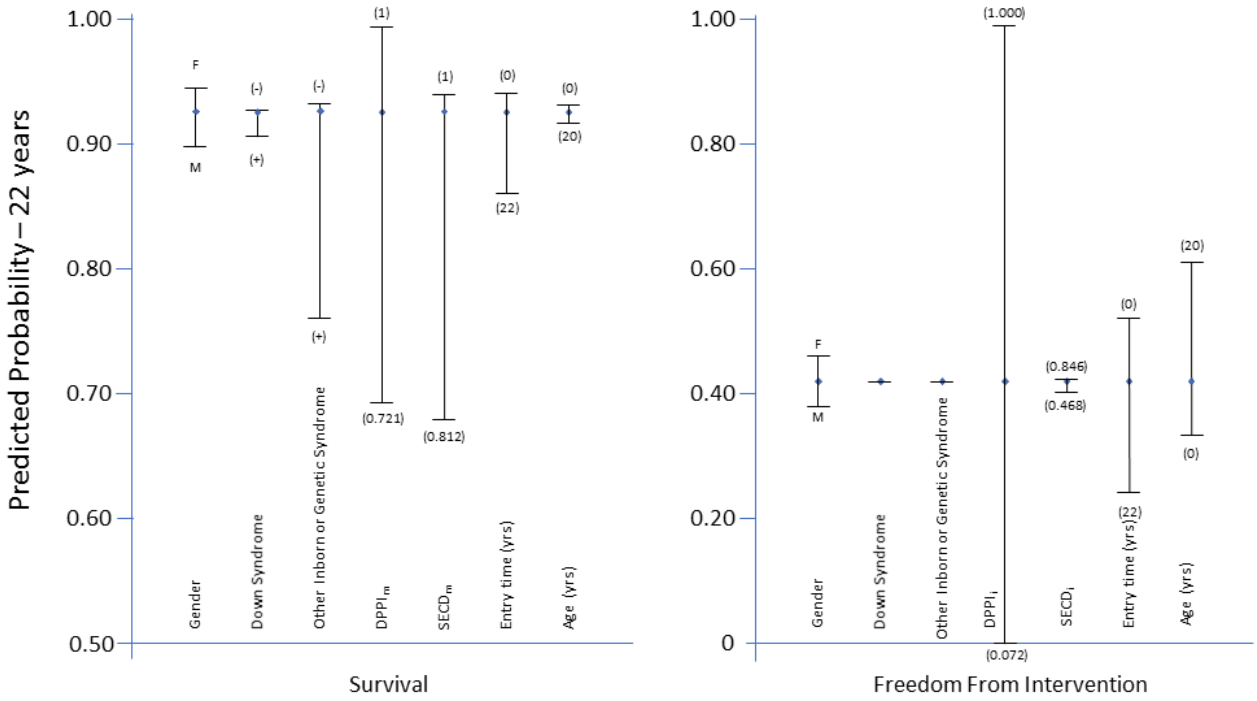

Predicted Probability – 22 years
1.00
0.90
0.80
0.70
0.60
0.50
F
M
(-)
(+)
(-)
(+)
(1)
(0.721)
(1)
(0.812)
(0)
(22)
(0)
(20)
Gender
Down Syndrome
Other Inborn or Genetic Syndrome
DPPIm
SECDm
Entry time (yrs)
Age (yrs)
Survival
1.00
0.80
0.60
0.40
0.20
0
(1.000)
(0.072)
F
M
(0.846)
(0.468)
(0)
(22)
(20)
(0)
Gender
Down Syndrome
Other Inborn or Genetic Syndrome
DPPIi
SECDi
Entry time (yrs)
Age (yrs)
Freedom From Intervention

FIGURE LEGENDS

Figure 1. Kaplan-Meier curves describing time associated freedom from invasive cardiovascular intervention (A), and survival (B). No significant differences are identified between the derivation and validation cohorts.

Figure 2. Validation and calibration of the freedom from invasive cardiovascular intervention model at 4 months (A), 1 year (B), 5 years (C), 10 years (D) and 22 years (E).

Figure 3. Validation and calibration of the survival model at 4 months (A), 1 year (B), 5 years (C), 10 years (D) and 22 years (E).

Figure 4. One way sensitivity analysis for factors associated with probability of survival (A) and freedom from invasive cardiovascular intervention (B) at 22 years. Probability of event changes much more with variation in diagnostic/pathophysiologic/prior intervention score than with changes in any other model components. As mortality is much less common than intervention, note the probability scales are different. Abbreviations: $DPPI_{i/m}$ = diagnosis, pathophysiologic, prior intervention, intervention and mortality models, respectively. $SECD_{i/m}$ = secondary diagnosis, intervention and mortality models, respectively.

REFERENCES

1. Jacobs JP, Jacobs ML, Lacour-Gayet FG, Jenkins KJ, Gauvreau K, Bacha E, Maruszewski B, Clarke DR, Tchervenkov CI, Gaynor JW, Spray TL, Stellin G, O'Bien SM, Elliott MJ, Mavroudis C. Stratification of complexity improves the utility and accuracy of outcomes analysis in a Multi-Institutional Congenital Heart Surgery Database: Application of the Risk Adjustment in Congenital Heart Surgery (RACHS-1) and Aristotle Systems in the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. Pediatr Cardiol. 2009 Nov;30(8):1117-30. doi: 10.1007/s00246-009-9496-0. PMID: 19771463.

2. Jacobs ML, O'Brien SM, Jacobs JP, Mavroudis C, Lacour-Gayet F, Pasquali SK, Welke K, Pizarro C, Tsai F, Clarke DR. An empirically based tool for analyzing morbidity associated with operations for congenital heart disease. J Thorac Cardiovasc Surg. 2013 Apr;145(4):1046-1057.e1. doi: 10.1016/j.jtcvs.2012.06.029. Epub 2012 Jul 24. PMID: 22835225; PMCID: PMC3824389.

3. Karamlou T, McCrindle BW, Blackstone EH, Cai S, Jonas RA, Bradley SM, Ashburn DA, Caldarone CA, Williams WG. Lesion-specific outcomes in neonates undergoing congenital heart surgery are related predominantly to patient and management factors rather than institution or surgeon experience: A Congenital Heart Surgeons Society Study. J Thorac Cardiovasc Surg. 2010 Mar;139(3):569-577.e1. doi: 10.1016/j.jtcvs.2008.11.073. Epub 2009 Nov 11. PMID: 19909989.

4. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galiè N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J. 2014 Mar;35(11):716-24. doi: 10.1093/eurheartj/eht072. Epub 2013 Mar 1. PMID: 23455361.

5. Oliver JM, Gallego P, Gonzalez AE, Garcia-Hamilton D, Avila P, Yotti R, Ferreira I, Fernandez-Aviles F. Risk factors for excess mortality in adults with congenital heart diseases. Eur Heart J. 2017 Apr 21;38(16):1233-1241. doi: 10.1093/eurheartj/ehw590. PMID: 28077469.

6. Danford DA, Martin AB, Danford CJ, Kaul S, Marshall AM, Kutty S. Clinical Implications of a Multivariate Stratification Model for the Estimation of Prognosis in Ventricular Septal Defect. J Pediatr. 2015 Jul;167(1):103-7.e1-2. doi: 10.1016/j.jpeds.2015.04.005. Epub 2015 Apr 30. PMID: 25935817.

7. Evans JM, Dharmar M, Meierhenry E, Marcin JP, Raff GW. Association between Down syndrome and in-hospital death among children undergoing surgery for congenital heart disease: a US population-based study. Circ Cardiovasc Qual Outcomes. 2014 May;7(3):445-52. doi: 10.1161/CIRCOUTCOMES.113.000764. Epub 2014 Apr 22. PMID: 24755908.

8. Peterson JK, Setty SP, Knight JH, Thomas AS, Moller JH, Kochilas LK. Postoperative and long-term outcomes in children with Trisomy 21 and single ventricle palliation. Congenit Heart

Dis. 2019 Sep;14(5):854-863. doi: 10.1111/chd.12823. Epub 2019 Jul 22. PMID: 31332952; PMCID: PMC7329297.

9. Meyer RE, Liu G, Gilboa SM, Ethen MK, Aylsworth AS, Powell CM, Flood TJ, Mai CT, Wang Y, Canfield MA; National Birth Defects Prevention Network. Survival of children with trisomy 13 and trisomy 18: A multi-state population-based study. Am J Med Genet A. 2016 Apr;170A(4):825-37. doi: 10.1002/ajmg.a.37495. Epub 2015 Dec 10. PMID: 26663415; PMCID: PMC4898882.

10. Jernigan EG, Strassle PD, Stebbins RC, Meyer RE, Nelson JS. Effect of Concomitant Birth Defects and Genetic Anomalies on Infant Mortality in Tetralogy of Fallot. Birth Defects Res. 2017 Aug 15;109(14):1154-1165. doi: 10.1002/bdr2.1057. Epub 2017 Jun 19. PMID: 28627098.

11. van Mil S, Heung T, Malecki S, Van L, Chang J, Breetvelt E, Wald R, Oechslin E, Silversides C, Bassett AS. Impact of a 22q11.2 Microdeletion on Adult All-Cause Mortality in Tetralogy of Fallot Patients. Can J Cardiol. 2020 Jul;36(7):1091-1097. doi: 10.1016/j.cjca.2020.04.019. Epub 2020 Apr 26. PMID: 32348848.

12. Farina MA, Hook EB. Apparent sex difference in spontaneous closure of ventricular septal defect. J Pediatr. 1978 Dec;93(6):1065-6. doi: 10.1016/s0022-3476(78)81268-2. PMID: 722432.

13. Sheiner E, Wainstock T, Landau D, Walfisch A. The Association between Sex and Long-Term Pediatric Cardiovascular Morbidity. J Pediatr. 2017 Jan;180:68-73.e1. doi: 10.1016/j.jpeds.2016.09.014. Epub 2016 Oct 13. PMID: 27745861.

14. Tsuda E, Yamada O, Kitano M. Improvement of the outcome in patients with infantile dilated cardiomyopathy over three decades - The usefulness of long-term gradually medical supportive care. J Cardiol. 2019 Aug;74(2):189-194. doi: 10.1016/j.jjcc.2019.02.005. Epub 2019 Mar 12. PMID: 30876708.

15. Oster ME, Lee KA, Honein MA, Riehle-Colarusso T, Shin M, Correa A. Temporal trends in survival among infants with critical congenital heart defects. Pediatrics. 2013 May;131(5):e1502-8. doi: 10.1542/peds.2012-3435. Epub 2013 Apr 22. PMID: 23610203; PMCID: PMC4471949.

16. Kang Y, Kwak JG, Min J, Lim JH, Kim WH. Twenty-Year Experience with Truncus Arteriosus Repair: Changes in Risk Factors in the Current Era. Pediatr Cardiol. 2021 Jan;42(1):123-130. doi: 10.1007/s00246-020-02461-5. Epub 2020 Sep 29. PMID: 32995903.

17. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. J Am Coll Cardiol. 2010 Sep 28;56(14):1149-57. doi: 10.1016/j.jacc.2010.03.085. PMID: 20863956.

18. Anderson BR, Stevens KN, Nicolson SC, Gruber SB, Spray TL, Wernovsky G, Gruber PJ. Contemporary outcomes of surgical ventricular septal defect closure. J Thorac Cardiovasc Surg. 2013 Mar;145(3):641-7. doi: 10.1016/j.jtcvs.2012.11.032. PMID: 23414985.

19. Ying T, Shi B, Kelly PJ, Pilmore H, Clayton PA, Chadban SJ. Death after Kidney Transplantation: An Analysis by Era and Time Post-Transplant. J Am Soc Nephrol. 2020 Dec;31(12):2887-2899. doi: 10.1681/ASN.2020050566. Epub 2020 Sep 9. PMID: 32908001; PMCID: PMC7790214.

20. Miller J, Wey A, Musgrove D, Son Ahn Y, Hart A, Kasiske BL, Hirose R, Israni AK, Snyder JJ. Mortality among solid organ waitlist candidates during COVID-19 in the United States. Am J Transplant. 2021 Feb 23. doi: 10.1111/ajt.16550. Epub ahead of print. PMID: 33621421.

21. Ji SY, Lee J, Lee JH, Lee ST, Won JK, Kim JW, Kim YH, Kim TM, Choi SH, Park SH, Kim Y, Park CK. Radiological assessment schedule for high-grade glioma patients during the surveillance period using parametric modeling. Neuro Oncol. 2020 Nov 1:noaa250. doi: 10.1093/neuonc/noaa250. Epub ahead of print. PMID: 33130858.

22. Heser K, Fink A, Reinke C, Wagner M, Doblhammer G. The temporal association between incident late-life depression and incident dementia. Acta Psychiatr Scand. 2020 Nov;142(5):402-412. doi: 10.1111/acps.13220. Epub 2020 Aug 7. PMID: 32712956.

23. Graff-Radford J, Lesnick T, Rabinstein AA, Gunter J, Aakre J, Przybelski SA, Spychalla AJ, Huston J 3rd, Brown RD Jr, Mielke MM, Lowe VJ, Knopman DS, Petersen RC, Jack CR Jr, Vemuri P, Kremers W, Kantarci K. Cerebral microbleed incidence, relationship to amyloid burden: The Mayo Clinic Study of Aging. Neurology. 2020 Jan 14;94(2):e190-e199. doi: 10.1212/WNL.0000000000008735. Epub 2019 Dec 4. PMID: 31801832; PMCID: PMC6988987.

24. Bradley SEK, Polis CB, Bankole A, Croft T. Global Contraceptive Failure Rates: Who Is Most at Risk? Stud Fam Plann. 2019 Mar;50(1):3-24. doi: 10.1111/sifp.12085. Epub 2019 Feb 21. PMID: 30791104; PMCID: PMC6594038.

25. PRINCIPLE Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet. 2021 Mar 4:S0140-6736(21)00461-X. doi: 10.1016/S0140-6736(21)00461-X. Epub ahead of print. PMID: 33676597.

26. Morris CD, Menashe VD. 25-year mortality after surgical repair of congenital heart defect in childhood. A population-based cohort study. JAMA. 1991 Dec 25;266(24):3447-52. PMID: 1744959.

27. Samánek M, Voríšková M. Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. Pediatr Cardiol. 1999 Nov-Dec;20(6):411-7. doi: 10.1007/s002469900502. PMID: 10556387.

28. Mat Bah MN, Sapian MH, Jamil MT, Alias A, Zahari N. Survival and Associated Risk Factors for Mortality Among Infants with Critical Congenital Heart Disease in a Developing Country. Pediatr Cardiol. 2018 Oct;39(7):1389-1396. doi: 10.1007/s00246-018-1908-6. Epub 2018 May 14. PMID: 29756159.

29. Nelson JS, Pasquali SK, Pratt CN, Yu S, Donohue JE, Loccoh E, Ohye RG, Bove EL, Hirsch-Romano JC. Long-Term Survival and Reintervention After the Ross Procedure Across the Pediatric Age Spectrum. Ann Thorac Surg. 2015 Jun;99(6):2086-94; discussion 2094-5. doi: 10.1016/j.athoracsur.2015.02.068. Epub 2015 Apr 25. PMID: 25921260.

30. Larsen SH, Olsen M, Emmertsen K, Hjortdal VE. Interventional Treatment of Patients With Congenital Heart Disease: Nationwide Danish Experience Over 39 Years. J Am Coll Cardiol. 2017 Jun 6;69(22):2725-2732. doi: 10.1016/j.jacc.2017.03.587. PMID: 28571637.

31. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI. Consensus-based method for risk adjustment for surgery for congenital heart disease. J Thorac Cardiovasc Surg. 2002 Jan;123(1):110-8. doi: 10.1067/mtc.2002.119064. PMID: 11782764.

32. Larsen SH, Pedersen J, Jacobsen J, Johnsen SP, Hansen OK, Hjortdal V. The RACHS-1 risk categories reflect mortality and length of stay in a Danish population of children operated for congenital heart disease. Eur J Cardiothorac Surg. 2005 Dec;28(6):877-81. doi: 10.1016/j.ejcts.2005.09.008. Epub 2005 Oct 19. PMID: 16242940.

33. Nakayama Y, Shibasaki M, Shime N, Nakajima Y, Mizobe T, Sawa T. The RACHS-1 risk category can be a predictor of perioperative recovery in Asian pediatric cardiac surgery patients. J Anesth. 2013 Dec;27(6):850-4. doi: 10.1007/s00540-013-1645-1. Epub 2013 Jun 6. PMID: 23740139.

34. Kang N, Tsang VT, Elliott MJ, de Leval MR, Cole TJ. Does the Aristotle Score predict outcome in congenital heart surgery? Eur J Cardiothorac Surg. 2006 Jun;29(6):986-8. doi: 10.1016/j.ejcts.2006.01.066. Epub 2006 May 4. PMID: 16677819.

35. Faraoni D, Vo D, Nasr VG, DiNardo JA. Development and Validation of a Risk Stratification Score for Children With Congenital Heart Disease Undergoing Noncardiac Surgery. Anesth Analg. 2016 Oct;123(4):824-30. doi: 10.1213/ANE.0000000000001500. PMID: 27529321.

36. Larsen SH, Emmertsen K, Johnsen SP, Pedersen J, Hjortholm K, Hjortdal VE. Survival and morbidity following congenital heart surgery in a population-based cohort of children--up to 12

years of follow-up. Congenit Heart Dis. 2011 Jul-Aug;6(4):322-9. doi: 10.1111/j.1747-0803.2011.00495.x. Epub 2011 Mar 21. PMID: 21418533.

37. Stefanescu A, Macklin EA, Lin E, Dudzinski DM, Johnson J, Kennedy KF, Jacoby D, DeFaria Yeh D, Lewis GD, Yeh RW, Liberthson R, Lui G, Bhatt AB. Usefulness of the Seattle Heart Failure Model to identify adults with congenital heart disease at high risk of poor outcome. Am J Cardiol. 2014 Mar 1;113(5):865-70. doi: 10.1016/j.amjcard.2013.11.043. Epub 2013 Dec 12. PMID: 24411285.

38. Oliver JM, Gallego P, Gonzalez AE, Garcia-Hamilton D, Avila P, Yotti R, Ferreira I, Fernandez-Aviles F. Risk factors for excess mortality in adults with congenital heart diseases. Eur Heart J. 2017 Apr 21;38(16):1233-1241. doi: 10.1093/eurheartj/ehw590. PMID: 28077469.

39. Ombelet F, Goossens E, Apers S, Budts W, Gewillig M, Moons P. Predicting 15-Year Mortality in Adults With Congenital Heart Disease Using Disease Severity and Functional Indices. Can J Cardiol. 2019 Jul;35(7):907-913. doi: 10.1016/j.cjca.2019.04.018. Epub 2019 Apr 26. PMID: 31292090.

40. Knowles RL, Bull C, Wren C, Wade A, Goldstein H, Dezateux C; UKCSCHD (UK Collaborative Study of Congenital Heart Defects) collaborators. Modelling survival and mortality risk to 15 years of age for a national cohort of children with serious congenital heart

defects diagnosed in infancy. PLoS One. 2014 Sep 10;9(8):e106806. doi: 10.1371/journal.pone.0106806. PMID: 25207942; PMCID: PMC4160226.

41. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, Crumb SR, Dearani JA, Fuller S, Gurvitz M, Khairy P, Landzberg MJ, Saidi A, Valente AM, Van Hare GF. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Apr 2;139(14):e637-e697. doi: 10.1161/CIR.0000000000000602. Erratum in: Circulation. 2019 Apr 2;139(14):e831-e832. PMID: 30586768.

42. Ferencz C, Rubin JD, McCarter RJ, Brenner JI, Neill CA, Perry LW, Hepner SI, Downing JW. Congenital heart disease: prevalence at livebirth. The Baltimore-Washington Infant Study. Am J Epidemiol. 1985 Jan;121(1):31-6. doi: 10.1093/oxfordjournals.aje.a113979. PMID: 3964990.

43. Stephensen SS, Sigfusson G, Eiriksson H, Sverrisson JT, Torfason B, Haraldsson A, Helgason H. Congenital cardiac malformations in Iceland from 1990 through 1999. Cardiol Young. 2004 Aug;14(4):396-401. doi: 10.1017/S1047951104004081. PMID: 15680046.

44. Moons P, Sluysmans T, De Wolf D, Massin M, Suys B, Benatar A, Gewillig M. Congenital heart disease in 111 225 births in Belgium: birth prevalence, treatment and survival in the 21st

century. Acta Paediatr. 2009 Mar;98(3):472-7. doi: 10.1111/j.1651-2227.2008.01152.x. Epub 2008 Nov 30. PMID: 19046347.