# Clinical Implications of a Multivariate Stratification Model for the Estimation of Prognosis in Ventricular Septal Defect

David A. Danford, MD[1], Ameeta B. Martin, MD[2], Christopher J. Danford, MD[3], Sheetal Kaul, MD[1], Amanda M. Marshall, MD[1], and Shelby Kutty, MD[1]

**Objectives** To derive and validate a multivariate stratification model for prediction of survival free from intervention (SFFI) in ventricular septal defect (VSD). A secondary aim is for this model to serve as proof of concept for derivation of a more general congenital heart disease prognostic model, of which the VSD model will be the first component.

**Study design** For 12 years, 2334 subjects with congenital heart disease were prospectively and consecutively enrolled. Of these, 675 had VSD and form the derivation cohort. One hundred seven other subjects with VSD followed in another practice formed the validation cohort. The derivation cohort was serially stratified based on clinical and demographic features correlating with SFFI.

**Results** Six strata were defined, the most favorable predicting nearly 100% SFFI at 10 years, and the least favorable, a high likelihood of event within weeks. Strata with best SFFI had many subjects with nearly normal physiology, muscular VSD location, or prior intervention. In the validation cohort, the relation between predicted and actual SFFI at 6 months, 1 year, 2 years, and 5 years follow-up had areas under the receiver operating characteristic curves 0.800 or greater.

**Conclusions** A prediction model for SFFI in VSD has been derived and validated. It has potential for clinical application to the benefit of patients and families, medical trainees, and practicing physicians. *(J Pediatr 2015;167:103-7)*.

Reliable estimates of prognosis in congenital heart disease (CHD) would be of great value to patients, their families, and their physicians. Such information would help keep expectations realistic and would provide a benchmark against which the outcomes of proposed therapies might be compared. Decades ago, when effective therapies were rare, natural history was a meaningful expression of outcome in CHD. In the current era, simple survival analysis often does not convey sufficient prognostic information to be useful,[1,2] and quality adjustment of that survival is complex and controversial.[3-5] CHD care is now characterized by capability to intervene aggressively with acceptable safety in most instances in which the unintervened status is less than ideal. In this context, when such interventions are not arranged, this generally represents acknowledgement that the outcome is "good enough" that we ought not to attempt to alter it further. Survival free from intervention (SFFI) is thereby a modern surrogate for favorable outcome and is an outcome likely of great interest to patients. SFFI in CHD is highly dependent on the lesion,[6-8] and even within a single lesion, SFFI can be quite variable.[1,9-12] For example, in ventricular septal defect (VSD), prognosis is believed to depend on anatomic location,[10,13,14] age,[1,15,16] size of defect, volume of shunt and pulmonary artery pressure,[10,17-20] associated cardiac lesions,[21-24] prior interventional history,[25-28] and even sex.[29-30] The purpose of this study is to derive and validate a multivariate stratification model for prediction of SFFI in VSD. A secondary aim is for the VSD prediction model to serve as proof of concept for derivation of a more general model for prognosis in CHD, of which the VSD model will be the first component.

## Methods

For 12 years, 2334 subjects were prospectively and consecutively enrolled. Inclusion criteria were: (1) an encounter with a single identified practitioner of pediatric cardiology (D.D.) 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 anatomy. Six hundred seventy-five of the subjects had VSD as their highest ranking diagnosis on a hierarchy of CHD diagnoses (**Appendix I**; available at www.jpeds.com), and these form the derivation cohort. There were no specific exclusion criteria.

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| CHD | Congenital heart disease |
| ROC | Receiver operating characteristic |
| SFFI | Survival free from intervention |
| VSD | Ventricular septal defect |

From the [1]University of Nebraska Medical Center College of Medicine, Children's Hospital and Medical Center, Omaha, NE; [2]Department of Cardiology, St. Elizabeth Hospital, Lincoln, NE; and [3]Department of Internal Medicine, Massachusetts General Hospital, Boston, MA

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At enrollment, the following information was recorded: age, sex, anatomic location of the VSD (muscular, perimembranous, doubly committed subarterial, supracristal, or malaligned), 6-dimensional physiologic severity score for hemodynamic burden (**Appendix II**; available at www.jpeds.com) and presence or absence of: (1) trisomy 21; (2) other constellation of deformities, chromosomal abnormality, or inborn error of metabolism; (3) secondary cardiac defect; and (4) prior cardiovascular surgical or catheter mediated intervention. Muscular, perimembranous, supracristal, and doubly committed subarterial defects are identified by the anatomic features reviewed by Minette and Sahn.[31] Defects that extend above the crista supraventricularis are supracristal. Perimembranous defects with outlet extension below the crista are classified as perimembranous. Perimembranous defects with inlet extension are classified as perimembranous, but inlet defects occurring as a component of atrioventricular septal defect are excluded. Malaligned defects are those with either anterior or posterior malalignment of the outlet septum, including those with mitral-aortic fibrous discontinuity, but excluding cases of tetralogy of Fallot or transposition of the great arteries.

Chart review identified for each subject: (1) if and when a surgical or catheter-mediated cardiovascular intervention had been performed since enrollment; (2) the time of the most recent clinical follow-up; and (3) whether or not there had been physician recommended dismissal from cardiology clinical follow-up. Dismissal from follow-up was counted as on-going SFFI. Interventions are not limited to procedures to directly address the VSD, so, for example, pacemaker implantation or surgical removal of an endocarditic lesion on a cardiac valve is counted. Purely medical issues such as nonsurgical management of endocarditis, or hospital admission for medical treatment of congestive heart failure would not be counted.

The same data as were gathered for the derivation cohort were obtained for a validation cohort derived from the practice of a second board certified pediatric cardiologist (A.M.) working independently in another city.

Continuous variables are expressed as means and SDs, and comparisons are made using Student $t$ tests ($P < .05$ considered significant). Dichotomous variables are expressed as proportions of the total, and comparisons are made using $\chi^2$ test ($P < .05$ considered significant). Analysis of time-dependent variables was accomplished using nonparametric right-censored life table analysis with Kaplan-Meier method, and regression with life data (commercially available statistical software package Minitab v 16; Minitab Inc, State College, Pennsylvania). The study protocol was reviewed and approved by the Institutional Review Boards of the University of Nebraska Medical Center and Children's Hospital and Medical Center.

The derivation cohort was divided into 2 subsets at the median estimated risk, using a multivariate regression model for time-dependent SFFI generated assuming a Weibull[32] distribution and using as model terms all those listed in data collection. The 2 subsets were then tested for difference in time-dependent SFFI by right-censored nonparametric Kaplan-Meier method. If the difference was significant ($P < .05$), the subsets were retained for further analysis separate from one another. The process was repeated for the subsets and the sets; thus, generated were tested for time-dependent SFFI differences from all other subsets active in the stratification process. If difference was significant ($P < .05$), the subsets were retained as separate from one another. If the difference was not significant, groups were combined for reanalysis. The process was continued until terminal subsets (strata) were identified because no further divisions or combinations of sets could be made. For each stratum, a final time dependent SFFI curve was produced with right-censored data assuming a Weibull distribution.

Actual SFFI for each member of the validation cohort was determined at 6 months, 1 year, 2 years, and 5 years. The derivation model was then applied to each member of the validation cohort, the predicted SFFI at 6 months, 1 year, 2 years, and 5 years was determined according to stratum. The concordance (c) statistic was used to estimate the area under the receiver operating characteristic (ROC) curve,[33] comparing predicted and actual SFFI at each of the 4 time intervals.

## Results

The clinical and demographic characteristics of the derivation and validation cohorts are compared in **Table I**. The groups were similar in most aspects, however, the validation cohort tended to include younger patients with greater degree of pathophysiologic abnormality, who underwent more interventions.

**Figure 1** shows SFFI as a function of time in the derivation and validation cohorts. Most subjects did not undergo intervention even in the longer term. Most interventions took place in the early months of observation, with a tendency of the curves to flatten at longer follow-up. There were 6 strata defined. Predicted SFFI for VSD displayed in **Figure 2** ranges from almost no likelihood of death or cardiovascular intervention over 10 years (stratum 1) to high likelihood of an event within days to weeks (stratum 6), illustrating the very marked differences in predicted SFFI among the strata in the derivation cohort.

**Figure 3** shows the ROC curves when the derivation cohort is used to predict the validation cohort SFFI at specific times of follow-up. ROC area is 0.800 or greater at each interval, establishing very good validation. **Table II** (available at www.jpeds.com) compares the characteristics of each of strata 1-5 with the characteristics of the higher strata. Consistent with the differences in SFFI demonstrated in **Figure 2**, there were remarkable differences in degree of pathophysiology, VSD location, interventional history, and secondary cardiac defects were identified across strata.

Stratum 1, in which nearly perfect SFFI was found, included more subjects with a very low physiologic severity score (normal or nearly normal hemodynamics) and lower levels of left and right ventricular volume overload, and right