Adverse Outcomes Prediction for Congenital Heart Surgery: A Machine Learning Approach

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Abstract

Objective: Risk assessment tools typically used in congenital heart surgery (CHS) assume that various possible risk factors interact in a linear and additive fashion, an assumption that may not reflect reality. Using artificial intelligence techniques, we sought to develop nonlinear models for predicting outcomes in CHS. Methods: We built machine learning (ML) models to predict mortality, postoperative mechanical ventilatory support time (MVST), and hospital length of stay (LOS) for patients who underwent CHS, based on data of more than 235,000 patients and 295,000 operations provided by the European Congenital Heart Surgeons Association Congenital Database. We used optimal classification trees (OCTs) methodology for its interpretability and accuracy, and compared to logistic regression and state-of-the-art ML methods (Random Forests, Gradient Boosting), reporting their area under the curve (AUC or c-statistic) for both training and testing data sets. Results: Optimal classification trees achieve outstanding performance across all three models (mortality AUC = 0.86, prolonged MVST AUC = 0.85, prolonged LOS AUC = 0.82), while being intuitively interpretable. The most significant predictors of mortality are procedure, age, and weight, followed by days since previous admission and any general preoperative patient risk factors. Conclusions: The nonlinear ML-based models of OCTs are intuitively interpretable and provide superior predictive power. The associated risk calculator allows easy, accurate, and understandable estimation of individual patient risks, in the theoretical framework of the average performance of all centers represented in the database. This methodology has the potential to facilitate decision-making and resource optimization in CHS, enabling total quality management and precise benchmarking initiatives.

Keywords
artificial intelligence, congenital heart surgery, outcomes, statistics-risk analysis/modeling, statistics-survival analysis

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Introduction

Despite great progress achieved in the surgical management of congenital heart disease (CHD), there is still considerable associated risk of death and complications, nonuniformly distributed across specific conditions and treatments. Complications may lead to prolonged length of postoperative mechanical ventilatory support time (MVST) and overall hospital length of stay (LOS). In the context of efforts to promote quality improvements in congenital heart surgery (CHS), large databases of such operations have been developed, along with methodologies seeking to establish benchmarks for surgical results, and to devise risk models for predicting important outcome parameters.1-18 However, methodologies used typically assume that various possible risk factors interact in a linear and additive fashion, an erroneous assumption. Using artificial intelligence techniques, we sought to develop nonlinear models for predicting outcomes in CHS.
of patient-specific is important to be able to make accurate predictions of the risk.

In the quest to achieve improved patient outcomes after CHS, it is crucial that prediction models be transparent and understandable by clinicians. Accordingly, we decided to use ML methods providing interpretability, ranging from population level to individual level, therefore limiting the use of “black box” approaches. Methods providing individual-level interpretability allow understanding of which variables are important for a particular patient, as opposed to other variables (eg, body weight), which may be significant for the population but may indeed be unimportant for an individual. We used a recent breakthrough in ML methodology, the optimal classification trees (OCTs), which can capture nonlinear variable interactions while providing individual-level interpretability.

The entire data set was analyzed for estimating mortality risk and surgical survivors for MVST and LOS. For each of the three models built (mortality, MVST, and LOS), only the preoperatively known patient variables listed in Table 1 are used, with more detailed information provided in Table S2. The data were split into a training set (procedures prior to January 1, 2016, N = 175,239), used to train the ML model, and a test set (procedures on or after January 1, 2016, N = 46,096), that is, data hidden from the model, in order to test the model’s performance on previously “unseen” data. Compared with training data, the test data set describes “future” operations.

The training set was further split (using stratified sampling, ensuring a similar proportion of survivors and nonsurvivors in each subset) to produce a separate validation set, the role of which was to tune algorithm hyperparameters: We select a set of hyperparameters (eg, for OCT models, tree depth, or the minimum number of patients in each leaf), a classification tree was built using training data, and then those hyperparameter values which perform best in the validation set were chosen.

The ML predictive task consists of a binary classification problem aiming to predict one of two possible outcomes for mortality, MVST, and LOS:
For **Mortality**, the binary outcome is whether the patient died in the hospital (or within 30 days) after the procedure or not.

For prolonged **Postoperative MVST** defined as **Time of extubation in ICU (or, time of last extubation in cases of reintubation(s) — Time of end of surgery**, the binary classification problem was to predict whether the duration of MVST was prolonged, selected as being above or below the 85th percentile MSVT (94.5 hours).

For prolonged **LOS**, defined as date of discharge—date of surgery, the binary problem was to predict whether the duration of hospitalization is above or below the selected threshold of 85th percentile (19 days).

### Results

Average mortality is 5.1% in the training, 3.0% in the test, and 4.7% in the overall data sets analyzed. Univariate associations between preoperative variables and mortality in the training set are shown in Table S3. By definition, the average rate for prolonged LOS and prolonged MVST is 15%. For the three models built, the area under the curve was chosen as a metric particularly useful to evaluate binary classification tasks, especially for highly unbalanced data sets, like the one analyzed. Calibration plots for the OCT models in training and testing data are shown in Figure S1.

The importance of each preoperative variable in predicting outcome was also computed and listed in Table S4. The most important risk factors are **procedure** and patient’s age and **weight**. Procedure alone accounts for >50% of the features’ contribution. A short time (<12 days) since the last (of any) prior operation and the presence of any general preoperative risk factors (GPRFs) also contribute significantly to the likelihood of mortality. The remaining factors have marginal significance, with each contributing less than 2% toward the odds of mortality.

The mortality risk model presents itself clearly as a decision tree, shown for the outcome of mortality in Figure 1A. It is possible to follow this tree along its branches to the lowest level terminal leaves, which identify 23 distinct patient cohorts and their respective predicted mortalities. A summary description of an example cohort is presented in Table S5. At each branching step along the decision tree, the combination of factors involved and the logic behind each step is fully transparent. Thus, given the preoperative features of an individual patient, one can read the tree along its branching points and arrive at the predicted risk, as shown in Figure 1B. By direct analogy, the decision trees for predicting MVST and LOS (shown in Figures S3 and S4) are also fully interpretable. Therefore, it becomes clear why our OCT methodology is fully interpretable at the individual patient level.

### Congenital Heart Surgery Adverse Outcome Prediction Tool

The OCT-derived risk models were used to produce a clinician-friendly software tool that aims to permit easy estimation of an individual patient’s risk for a given procedure in the theoretical framework of the average performance of all centers represented in the database. One can input preoperatively available patient information on the smartphone app (Figure S2), leading to the immediate calculation of risk estimates (mortality, prolonged MVST, or prolonged LOS) for the specific patient and the proposed procedure.

### Comment

The ECHSA ECDB was established in 1995, originally as the European Congenital Heart Defects Database and renamed as the European Association for Cardiothoracic Surgery (EACTS) Congenital Database in September 1999, acquiring its current final name in 2015. The ECDB collects data from participating centers regarding pediatric and adult congenital cardiac operations, aiming to assess results for scientific study and to provide tools for individual programs’ own quality improvement efforts. The ECDB has collaborated closely with the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database (CHSD), developing common nomenclature of cardiac defects and identical data fields, enabling sharing data in joint research efforts. The ECDB is fully available online at: https://www.echsacongenitaldb.org/publications/.
Figure 1. A, Mortality decision tree based on the optimal classification tree (OCT) algorithm. Greater intensity of the color in each leaf depicts increased mortality of the cohort. At the root level, the overall mortality rate for 175,239 procedures analyzed in the training data set is 5.1% (note that since the rate is limited to training data prior to 2016, the rate is higher than the overall database average of 4.7%, and of 3.0% in the test data set of 3.0%). The first branch split occurs based on the presence of any general preoperative risk factors (GPRF). If we follow the right branch (no GPRF), we see that the next branching is based on days since previous admission, age, procedure, and weight. If we follow the left branch again, depending on the procedure and age, the mortality can range from 2.8% to 40.2%. It is therefore possible to follow the tree along its branches to the lowest level terminal leaves, which identify 23 patient cohorts and their respective predicted mortalities. At each branching step along the decision tree, the combination of the factors involved and the logic behind each step is fully transparent. Thus, given the preoperative features of an individual patient, one can read the tree along its branching points and arrive at the predicted risk, as shown in B. (B) The prediction of mortality risk (16.2%) for a patient with diagnosis transposition of the great arteries with VSD, weight 3 kg, preoperative ventilation and resolved shock at the time of surgery, age 2 weeks, undergoing an arterial switch operation with VSD closure, is highlighted on the decision tree.
It is established that assessment of surgical results must take into account, on one side, the inherent complexity of the diagnosis, the individual patient’s characteristics, the disease’s severity, and the nature of the procedure, and on the other side, the performance of the surgeon, team, and institution. In this article, we have focused on the impact of various features of the underlying pathologies and preoperative patient characteristics recorded in the ECDB. Important outcomes to study include not only mortality but also the duration of stay in the ICU, on ventilator support (MVST), or in the hospital (LOS). Other quality metrics are also important, as well as costs, which, in turn, are influenced by complications, MVST, and LOS. Such additional outcome metrics along with relevant institutional factors are the focus of further studies by our group.

Major efforts to adjust for “case-mix,” that is, for variability in the inherent risk of various procedures, and to account for effects of variation in patient characteristics, have evolved from initial attempts based on expert consensus (RACHS-I1,12 and Aristotle13,14 methods), to those empirically derived, based on outcome measures provided by real data5-18 (STS-EACTS Mortality Score and Categories, so-called STAT Score and Categories, and STS Morbidity Score and Categories, and use of accurate risk prediction models, such as the STS-CHSD Mortality Risk Model14 and the UK PRAIS2 Model).18 Still, it is recognized that patient factors typically used in these models only explain a small proportion of variation in mortality.16

However, the aforementioned analytical methods, although achieving very high predictive accuracy, are flawed in assuming that various possible risk factors for adverse outcome interact in a linear and additive fashion, an assumption which frequently does not reflect reality. For example, although prematurity and low birth weight are intuitively understood risk factors for CHS, their influence is practically absent in older patients and for most procedures. In recognition of the existence of potential nonlinear interactions of risk factors, the STS-CHSD Mortality Risk Model has included several variables and adjustments, such as condition/age interactions and condition/age/procedure interactions. For example, the effect of Down syndrome was estimated based on age and procedure subgroups, including atroventricular canal repair and single ventricle palliation.14 However, capturing the importance of such interactions required prior manual creation of possible candidates of interactions and use of a Bayesian model to identify groups as similar as possible.

Furthermore, published methods have not provided physicians with a practical tool to predict mortality or morbidity of a given patient with CHD considered for surgery, given his preoperative risk profile.

To circumvent such limitations, we have used AI techniques, which some of us have previously used in other medical applications,19-20 seeking to develop (1) nonlinear models, free from any assumptions regarding the importance and interplay of preoperative variables or their combinations, aiming to predict outcome after CHS and (2), a user-friendly tool enabling clinicians to estimate outcome risks by inputting a specific patient’s characteristics. Thus, we sought to develop models to predict mortality after CHS, and for survivors, to estimate the risk of prolonged MVST and LOS.

Our results demonstrated that OCTs consistently outperformed the simpler linear regression and had similar predictive accuracy (within 1.5%) as the more complex ML models, however, with the significant advantage over the latter of ensuring full interpretability. It is, in fact, a major advantage of OCT methodology that the prediction model generated, presenting itself as a decision tree, is fully transparent. Furthermore, in addition to enabling a clear understanding of how any prediction is reached for an individual patient, the methodology automatically reveals patient cohorts of similar risk. These model features are evident by studying the OCT presented in Figure 1. It is easy to see the influence of each feature (“risk factor”) by following the tree to each successively deeper level. Given the preoperative characteristics of a patient, one can follow the decision “path” along the branches of the tree, understanding at each step the sequential decisions taken, and also comprehend the characteristics of resulting patient cohorts with similar risk, as revealed by the tree’s terminal leaves. The ability to understand the decisions of the OCT algorithm is in advantageous contrast with findings of various studies in similar settings showing the use of “black-box” deep learning solutions.21-27 which, despite higher performance indicators, have architectural inner workings which are obscure not just for clinicians, but for AI experts as well. Such black-box methods cannot provide interpretable explanations of “why” a given patient is assigned a certain outcome risk. The interpretability of our OCT methodology is extremely important since physicians, not typically versed in the complex AI and ML algorithms, need to understand how mathematical models achieve their predictions if they are to trust their results.

The risk factors identified by this analysis are consistent with clinical experience: procedure, age, and weight are the most powerful predictors of aggregate mortality, with significant contributions from the occurrence of a very recent other cardiac operation (<12 days, suggesting an unplanned early procedure possibly addressing some complication), and the presence of any of the various GPRFs listed in Table S2 (such as mechanical circulatory or ventilatory support). Of note, in our model, we have not used the factor of preoperative diagnosis leading to operation because it neither increased model accuracy nor did it result in clinically more useful decision trees.

Interestingly, the contribution to the models’ predicting power of other preoperative variables was very small (eg, case category, cardiopulmonary bypass [CPB] vs non-CPB) or even absent (eg, year of surgery), despite the univariate association of these variables with the outcome (mortality), as shown in Table S3. In this nonlinear analytic system, the importance of such variables is overshadowed by the more powerful predictors listed above, especially when considering the effect of a variable such as year of surgery on procedures with a small
number of yearly observations, which precludes statistical significance.

Several additional points deserve emphasis: Because of well-known progress achieved over the last several years in CHS, particularly with regard to complex high-risk lesions,\textsuperscript{13} we expect the model to overestimate mortality. When we recalibrate the model with a more recent validation set (2016-2017) and show results with validation and testing (2018-2019) calibration plots (Figure 1S), the model still overestimates risks for higher risk procedures, but, its predictions stabilize. In addition, our models still provide correct risk estimation in terms of order as reflected by high AUCs. In other words, AUC is a measure of ordering, not of the absolute magnitude of risk. Thus, although the overall risk in the “new data” is lower than predicted for higher risk procedures, AUC is still high because the order is correct. Clearly, to keep the predictive capacity of the model always current, our plan is to recalculate the model periodically, as new data accumulate.

We emphasize that our model predictions result mathematically from the given data set which is inclusive of data submitted from surgical practices of all ECDB participants, comprising both European and (for 1/3 of data) non-European centers. We did not limit our analysis to European centers, which might have resulted in greater data uniformity and model predictive accuracy, aiming to provide self-assessment tools applicable to all ECDB participating centers.

It is possible that specific predictions of the model regarding particular patients and procedures may well be different if a different data set were analyzed, for example, our European data subset, or the STS-CHSD data reflecting North American practices. Although important lessons could be drawn from such possible future comparative studies, the focus of this study is to establish the new ML methodology of OCTs, not to derive specific clinical lessons from analysis of CHS data for any particular clinical application. In other words, we acknowledge that the emphasis of our current work is to demonstrate the utility of this ML methodology in the evaluation of CHS data in the framework of the total (geographically and temporally heterogeneous) experience recorded in the ECDB. Accordingly, precisely because of this heterogeneity, our presented model is not to be considered “a final product” to be used for assessment by all CHS centers, nor by all ECHSA or European centers. Such applications will obviously require recalculation of the models using the appropriate region-specific and contemporaneous homogeneous data sets.

We also acknowledged that the same data fields are recorded for all patients in the ECDB, it being a registry aiming to record all CHS activity in participating centers. Therefore, the ECDB has not captured all features, which may be important for all pathologies, procedures, and their innumerable combinations. Accordingly, efforts are underway to develop additional data fields to capture important diagnosis and procedure-specific preoperative variables, such as anatomic information of coronary arteries in Transposition of the Great Arteries (TGA) or Tetralogy of Fallot (TOF), and so on.

Future availability of such granular data may well further increase the predictive power of our methodology.

We note that all predictions are made on the procedure instead of on the patient level. Therefore, the cumulative estimated risk for a patient who may undergo multiple procedures would be higher than the individual procedure prediction.

We also note that surgical outcomes do not only depend on the disease, procedure, and patient-specific factors but also on other variables relating to the availability, quality, and organization of necessary health care resources, determined, for example, by geography, center, program size, and so on. The effects of such factors external to the patient were not addressed in this article, but are being analyzed in our continuing research, using the presented methodology, and will be presented in subsequent reports. Consequently, although our current risk calculator provides a user-friendly tool to predict risks of various procedures taking into account individual patient characteristics, we emphasize that such outcome predictions are based on cumulative data of all participating centers and do not reflect any individual center experience and performance level. Accordingly, our current version of the calculator is to be considered as a pilot tool for theoretical general risk prediction and is not intended to advise patients in the context of care provided by individual centers.

Any real-world, real-time model and application used in clinical practice to predict CHS risks requires the use of fairly contemporaneous data to develop the model. Although the models reported in this article demonstrate the potential of ML in the analysis of CHS outcomes, they are not yet ready for actual clinical application in a bedside calculator designed to predict CHS risks in specific centers. However, we hope that our ongoing evolving research, focusing on deep analysis of individual center performance, will allow center-specific predictions. Such more refined models to be developed, based on more homogeneous data subsets and taking into account institutional and possibly surgeon factors, may form the basis of future versions of the calculator which could have more clinical relevance to specific patient counseling.

**Limitations**

This methodology depends on a large number of good quality data, as are those in the ECDB. Although only a minority of data (approximately 14\%) in the ECDB has been subjected to our on-site data verification process (in which independent database auditors visit volunteering centers and perform, on-site, detailed verification of 100\% of submitted data fields and for 100\% of the submitted patients), the outcomes of these verification analyses are regularly updated and published on the ECDB website (https://echsacongenitaldb.org/data_verification_results/), the results to date consistently demonstrating no statistically significant differences between the verified and unverified subsets.\textsuperscript{28} Another limitation is that our analyses have involved a large variety of diagnoses, procedures, and their combinations, with major variation in their frequencies, ranging from relatively common to extremely rare. This
variability precludes having large numbers of data for rare conditions, for which many centers and surgeons may have little or no experience. Accordingly, the terminal leaves of the decision trees indicate frequently heterogeneous patient cohorts of similar risk. Finally, due to the large number of heterogeneous procedures with few observations, we chose not to use procedure-specific but rather cumulative 85th percentile MSVT and LOS. Although this could introduce bias against more complex procedures, auxiliary analyses using procedure-specific MSVT and LOS demonstrated similar model performance for various procedure types (Table S6). Such limitations originating in data heterogeneity are also addressed by our ongoing research analyzing the more common and most clinically important operations, chosen to be, for comparative purposes, the same ten “benchmark operation groups” as introduced by the STS-CHSD analyses. Finally and most importantly, we acknowledge that the wide temporal and geographic heterogeneity of the data on which the models were trained, which likely reflect widely varying patterns of practice and outcomes, precludes the specific application of these models to any one specific regional practice (eg, Europe or North America). However, the same methodology can be easily applied to recalculate the models, for example, using European only data for application in Europe.

Conclusions

In summary, in seeking improved tools for risk prediction in CHS via analysis of the large data set in the ECHSA ECDB, the presented AI and ML-based models of OCTs, which are devoid of assumptions such as risk factor linearity, provide predictive power superior to traditional logistic regression and other competitive ML models, and, due to their intrinsic power, may need fewer variables than traditional methods to achieve accurate statistically significant predictions. Our methods operate entirely objectively, yet their decision-making process is easily understandable at each step. In other words, our approach has the added advantage of full intuitive interpretability of the method and its results, and its predictive models can be easily updated as new data accumulate. Our current risk calculator, based on these models, allows easy estimation of risks for individual patients given different preoperative scenarios, in the theoretical framework of the average performance of all centers represented in the Database.

Our work represents an initial evaluation of powerful ML tools and their application in the estimation of adverse outcome risks after CHS in the context of the challenges and limitations presented by the diverse spectrum of diagnoses, patients, procedures, and important limitations noted, including heterogeneity of patients, procedures, practices, and outcomes in a great variety of ECDB centers across multiple geographic regions, as well as necessary use of “historical” and limited data in developing predictive algorithms. Therefore, we consider the strength of this study to rest more on its focus and demonstration of the potential of the methodology presented, rather than on the actual results and clinical conclusions generated with the current “training” or development data set.

In short, our article demonstrates the potential of ML in the analysis of pediatric and congenital cardiac surgical outcomes. The approach described represents the initial step in an iterative process that will certainly evolve over time. Our methodology, which we plan to develop further to take into account hospital-derived features, has the potential to contribute significantly to quality control initiatives in CHS, opening the door to more precise and transparent benchmarking of outcomes. The current model reported in this article is a preliminary model; this current model is a scientific analysis that is not ready for clinical application. This current model is a general prototype developed based on heterogeneous sources of data, including both geographic heterogeneity and temporal heterogeneity. In order for such a model to be suitable for clinical application, it would need to be recalculated using data from a contemporary interval of time and a geographically proximate source (ie, using only European data rather than global data if the model is to be used clinically in Europe).

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Supplemental Material

Supplemental material for this article is available online.

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