

Risk factors for 1-year allograft loss in pediatric heart transplant patients using machine learning: An analysis of the pediatric heart transplant society database

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Abstract

Background: Pediatric heart transplant patients are at greatest risk of allograft loss in the first year. We assessed whether machine learning could improve 1-year risk assessment using the Pediatric Heart Transplant Society database.

Methods: Patients transplanted from 2010 to 2019 were included. The primary outcome was 1-year graft loss free survival. We developed a prediction model using cross-validation, by comparing Cox regression, gradient boosting, and random forests. The modeling strategy with the best discrimination and calibration was applied to fit a final prediction model. We used Shapley additive explanation (SHAP) values to perform variable selection and to estimate effect sizes and importance of individual variables when interpreting the final prediction model.

Results: Cumulative incidence of graft loss or mortality was 7.6%. Random forests had favorable discrimination and calibration compared to Cox proportional hazards with a C-statistic (95% confidence interval [CI]) of 0.74 (0.72, 0.76) versus 0.71 (0.69, 0.73), and closer alignment between predicted and observed risk. SHAP values computed using the final prediction model indicated that the diagnosis of congenital heart disease (CHD) increased 1 year predicted risk of graft loss by 1.7 (i.e., from 7.6% to 9.3%), need for mechanical circulatory support increased predicted risk by 2, and single

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CHD, congenital heart disease; C-statistic, time-dependent concordance statistic; ECMO, extracorporeal membranous oxygenation; eGFR, estimated glomerular filtration rate; MCSD, mechanical circulatory support device; PHTS, Pediatric Heart Transplant Society; PRA, panel reactive antibody; SHAP value, Shapley additive explanation value.

ventricle CHD increased predicted risk by 1.9. These three predictors, respectively, were also estimated to be the most important among the 15 predictors in the final model.

Conclusions: Risk prediction models used to facilitate patient selection for pediatric heart transplant can be improved without loss of interpretability using machine learning.

KEY WORDS

machine learning, pediatric heart transplant

1 | INTRODUCTION

Pediatric patients with end-stage heart failure, consisting of insufficient cardiac output, organ hypoperfusion, and end-organ dysfunction, often require continuous inotropic infusions, mechanical circulatory support, and ultimately cardiac transplantation. Among these, transplantation is the only proven method with prolonged survival. The improvement in transplant outcomes over the past few decades can be attributed to advances in medical management as well as improved patient selection by using models that predict a patient's risk for graft loss or mortality after transplantation.^{1–6} For example, the Improving Pediatric and Adult Congenital Treatments Registry and the Scientific Registry of Transplant Recipients have developed prediction models for mortality after transplant using hierarchical and Bayesian modeling.^{7,8} However, few studies have evaluated whether the prognostic accuracy of risk assessment tools for post-transplant mortality could be improved by using machine learning algorithms. Improving risk prediction for pediatric patients undergoing heart transplant would allow for efficient clinical resource allocation, improved patient counseling and education, as well as individualized approaches to mitigating patient risk, facilitating improvements in precision medicine.

Previous studies have used machine learning techniques to predict risk in adults or combined adult and pediatric transplant outcomes.^{9–15} However, few studies have quantified the importance of variables (i.e., how much each individual variable contributes to the overall predicted risk) selected by machine learning algorithms or have given interpretable summaries of their machine learning models.^{16,17} In the current study, we used data from the pediatric heart transplant society (PHTS) database, a large comprehensive registry of pediatric heart transplant data, to determine if machine learning algorithms could improve risk prediction of 1-year allograft loss in pediatric heart transplant patients compared to traditional statistical modeling. In addition, we used techniques from statistical learning to quantify variable importance and explain the predictions generated by machine learning algorithms.

2 | MATERIALS AND METHODS

2.1 | Patient population

The Pediatric Heart Transplant Society (PHTS) database is based with Kirklin Solutions, Inc on a secure Amazon Web Services server,

and has been collecting data on pediatric patients (age < 18 years) from heart transplant listing since 1993. The PHTS includes 62 participating heart transplant centers from across the United States, Canada, Brazil, and the United Kingdom. Each participating institution maintains their own Institutional Review Board. The data are entered by each PHTS participating institution, and the database is maintained by the PHTS Data Coordinating Center. The Data Coordinating Center performs quality checks and statistical analyses for the approved scientific proposals by the PHTS Scientific Committee. From January 1, 1993, through June 30, 2019, there were 6903 transplant recipients entered into PHTS. For the current analysis, we followed 3787 patients transplanted from 2010 to 2019 for 1-year graft loss free survival. A total of 172 recipient characteristics measured between the time of listing until transplant were included as candidate predictor variables for risk prediction (Tables S1 and S2).

2.2 | Prediction models

In the current study, we applied Cox regression, gradient boosting, axis-based random survival forests, and oblique random survival forests. Gradient boosting (hereafter referred to as boosting) develops an ensemble of weak prediction models sequentially.¹⁸ Each new model in the sequence attempts to correct errors from the previous models. We developed boosting models using decision trees as learners.^{19,20} Random forests are ensembles of de-correlated decision trees that are grown using bootstrapped replicates of the original data.^{21,22} When the trees in a random forest grow new branches using a single predictor (i.e., if $X_1 < 5$, go left, otherwise go right), the forest is called axis-based because the splits of the data appear perpendicular to the axis of the predictor. As most forests are axis based, this is denoted as the standard approach. When the trees use a weighted combination of multiple variables to grow new branches (i.e., if $X_1 + 2 * X_2 < 5$, go left), the forest is called oblique because the splits of the data are neither parallel nor at a right angle to the axis. The difference between axis based and oblique splitting can be seen in the supplemental Figure S1.²³ Oblique random forests often have higher prediction accuracy versus standard random forests, as the additional flexibility in their decision trees can improve their ability to capture complex relationships in the training data.^{24,25} In the current analysis, we fit axis-based and oblique random survival forests.

2.3 | Missing data

Missing values (Table S3) were imputed using the mean and mode of each continuous and categorical variable, respectively, prior to fitting prediction models. Missing values in testing data (i.e., data that were used to assess the accuracy of prediction models) were imputed using the means and modes computed in training data (i.e., data that were used to develop prediction models). While imputation to the mean is not appropriate for statistical inference, this technique has been shown to produce prediction models with Bayes consistency when missing values are non-informative.²⁶

2.4 | Variable selection

When developing prediction models in the current study, we selected 15 of the 167 total variables available in the PHTS to be incorporated as predictors in the model. As we developed a strategy to fit our final prediction model, we applied cross-validation to “tune” the modeling approach. We analyzed the prediction accuracy of models that used 5, 10, 15, 20, 35, 50, and 70 variables identified with differing mechanisms of variable selection. A visual summary of our findings is provided in supplemental Figure S2. Overall, including more predictors improve the prediction accuracy of the machine learning models, but a point of diminishing return appears at the inclusion of >15 predictors. Given the diminishing return in prediction accuracy and favoring simplicity in the final model, we decided to use 15 predictors.

Variable selection was based on SHapley Additive exPlanation (SHAP) values. A SHAP value estimates the contribution of a given predictor variable to a model's prediction for a single observation. Taking the mean of the absolute value of all SHAP values for a single predictor across all observations measures the average absolute contribution of the predictor, and this value can be used to rank predictors from most important (i.e., largest contributor to predictions) to least important (i.e., smallest contributor to predictions). In the current study, we estimated SHAP values using a boosting model, and designated the 15 most important variables from that model as the variables to be included in the Cox regression, boosting, and random forest prediction models.

2.5 | Prediction evaluation

Predictions were evaluated based on discrimination and calibration, as recommended by published guidelines.^{27,28} Discrimination was measured using a time-dependent concordance (C-) statistic,²⁹ with the time of prediction specified as 1-year post-transplant. Calibration was assessed by visualizing the relationship between predicted and observed risk and by computing the expected absolute difference in these two quantities, that is, the integrated calibration index.³⁰ We also computed the index of prediction

accuracy, a metric that combines discrimination and calibration into one value that is useful for comparing overall performance of prediction models.³¹

2.6 | Prediction model selection

To identify a modeling strategy with the highest expected prediction accuracy in external data, we performed cross-validation to compare Cox regression, boosting, and random forests. Briefly, we randomly included 75% of our PHTS cohort into a training set and withheld the remaining 25% as a testing set. We then developed a Cox regression model, a boosting model, an axis-based random forest, and an oblique random forest using the training data, and then evaluated each model's prediction accuracy using the testing data. We repeated this experiment 100 times to account for sampling variability in the procedure (i.e., variability in model performance due to which patients were randomly included in the training and testing sets). We summarize results from this experiment using the median performance for each model, with 25th and 75th percentiles to quantify uncertainty. After identifying which modeling approach had the highest median index of prediction accuracy, we used that approach to fit a final prediction model using the entire cohort as training data (Figures 1 and 2).

2.7 | Prediction model interpretation

We interpret the final prediction model by computing the median (25th percentile, 75th percentile) SHAP value for each predictor used in the model (Figure 3). While the mean absolute SHAP value measures importance, the median of untransformed SHAP values estimates the multi-variable adjusted relationship between a given predictor and the model's predicted risk. We computed the median SHAP value within each category of nominal predictor variables and within subgroups based on a biologically plausible cut-point for continuous predictor variables.³² In a supplemental figure, we plotted SHAP values for each continuous predictor used in the final model as a function of the predictor (Figure S3).

2.8 | Statistical analysis

The 1-year incidence of graft loss or mortality was computed overall and by transplant year. For continuous and categorical variables, characteristics were summarized as median with 25th and 75th percentiles and percentage, respectively. Characteristics were presented for the overall population and stratified by transplant year (Table 1). Analyses were conducted using SAS version 9.4, R version 4.1.1, and a number of open-source R packages.³³⁻³⁷ All R code for the current analysis is publicly available at <https://github.com/bcjaeger/grant-loss>. Data for the current analysis are available by request.

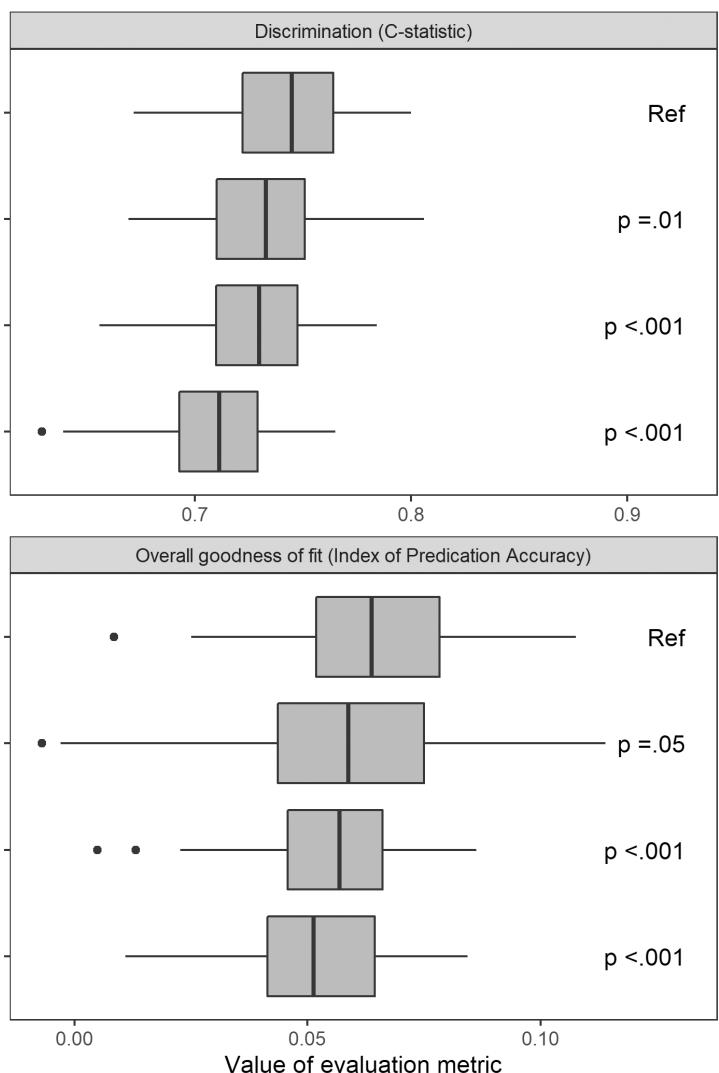


FIGURE 1 Discrimination and overall goodness of fit among four approaches to develop a graft loss prediction model. *p*-Values are computed using the Wilcoxon rank sum test and compare the oblique random survival forest to other approaches. The data summarized in box plots are from 100 independent runs of split sample validation.

2.9 | Institutional review board

This study was approved by the institutional review board maintained by the pediatric heart transplant society and is in compliance with the International Society of Heart and Lung Transplant Ethics statement. All patients whose data are entered into PHTS sign informed consent. No animals were used in this study.

3 | RESULTS

3.1 | Patient characteristics

Patients were 55% male, 65% white, and the median age was 4.9 years at the time of transplant (Table 1). A primary diagnosis of cardiomyopathy was observed in 50% of patients and congenital heart disease in 48% with 35% of those patients carrying a diagnosis of single ventricle heart disease. Before 2014 and after 2017, an estimated 44% and 52% of patients who underwent transplant had congenital heart disease, respectively. The median patient age also increased from 4.4 years before 2014 to 5.5 years after 2017. Of the

included cohort, 47% had undergone cardiac surgery prior to being listed for heart transplantation.

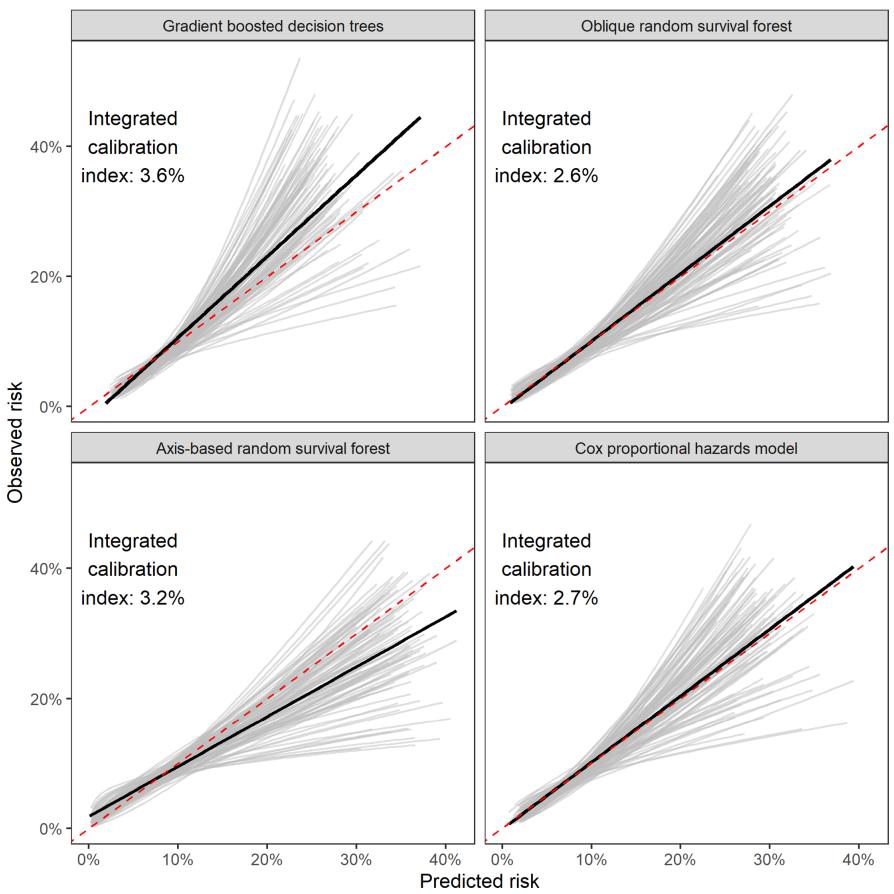
3.2 | Mortality

Overall, 272 of 3787 patients included in the current analysis experienced graft loss or death during the first year following transplant (cumulative incidence: 7.6%, 95% CI 6.7%, 8.5%). Patients diagnosed with congenital heart disease had a 1-year cumulative incidence of 12.5% (95% CI 10.5, 13.6), while those diagnosed with cardiomyopathy had 1-year cumulative incidence of 3.0% (95% CI 2.2, 3.8). The estimated cumulative incidence was highest among patients who required extracorporeal membranous oxygenation (ECMO) at transplant: 29.8% (95% CI 22.7, 36.9).

3.3 | Model selection

Based on 100 replications of a 75/25 split of our data into training/testing sets, the oblique random survival forest had the highest

FIGURE 2 Calibration of fit among four approaches to develop a graft loss prediction model. The gray lines in each panel show a calibration slope plot from 100 independent runs of split sample validation. The black line shows the overall calibration slope plot. Integrated calibration index measures the average absolute difference between predicted and observed probability.



C-statistic, with a median (25th, 75th percentile) of 74.5, (72.2, 76.4), followed by the standard random survival forest with 73.3 (71.0, 75.1) (*p*-value for difference=.01) (Figure 1). The oblique random survival forest also obtained the best estimated calibration with a mean integrated calibration index of 2.6% (Figure 2). The Cox proportional hazards model obtained similar calibration with an integrated calibration index of 2.7%, while the standard random survival forest and boosting models systematically over-estimated and under-estimated risk for patients at higher risk of graft loss, respectively. We therefore used oblique random survival forests as the final machine learning model for our analysis of the entire cohort.

3.4 | Risk factor analysis

Primary etiology, the patient's underlying cardiac diagnosis, was found to have the greatest overall contribution to risk with a mean absolute contribution or Shapley value of 1.63% to 1-year predicted risk of graft loss followed by need for mechanical circulatory support at time of transplant with an absolute mean contribution of 1.4 (i.e., from 5% to 6.4%). These results are delineated in Figure 3 which highlights the variable contributions to predicted risk for the final model using Shapley values. A negative value implies decreased risk whereas a positive value is associated with increased risk contribution. For a patient with average characteristics (i.e., all predictor values are the mean or mode of the respective predictor), a diagnosis

of cardiomyopathy was estimated to lower predicted risk by 1.58, whereas a diagnosis of congenital heart disease was estimated to increase predicted risk by 1.69. Within the group of congenital heart disease patients, a specific diagnosis of single ventricle anatomy was estimated to further increase risk by 1.86. Requiring ECMO at transplant was estimated to increase predicted risk by 10.2, which was the largest estimated contribution of any predictor in the final model.

4 | DISCUSSION

Over the past few decades, outcomes for pediatric heart transplant patients have improved due to advances in medical and surgical management as well as patient selection.¹ There have been notable decreases in waitlist mortality for these patients; however, they remain at higher risk for waitlist mortality than other pediatric solid organ recipients, and adult heart transplant recipients.² Given the limited number of pediatric donor organs available, accurate prediction of patients' risk for adverse outcomes following heart transplantation is of paramount importance.

Prior studies looking at possible recipient contributions to risk for 1-year pediatric heart transplant mortality have suggested that certain variables increase a patient's risk, such as the need for mechanical ventilation or mechanical circulatory support at the time of transplant, smaller patients, and those with other organ

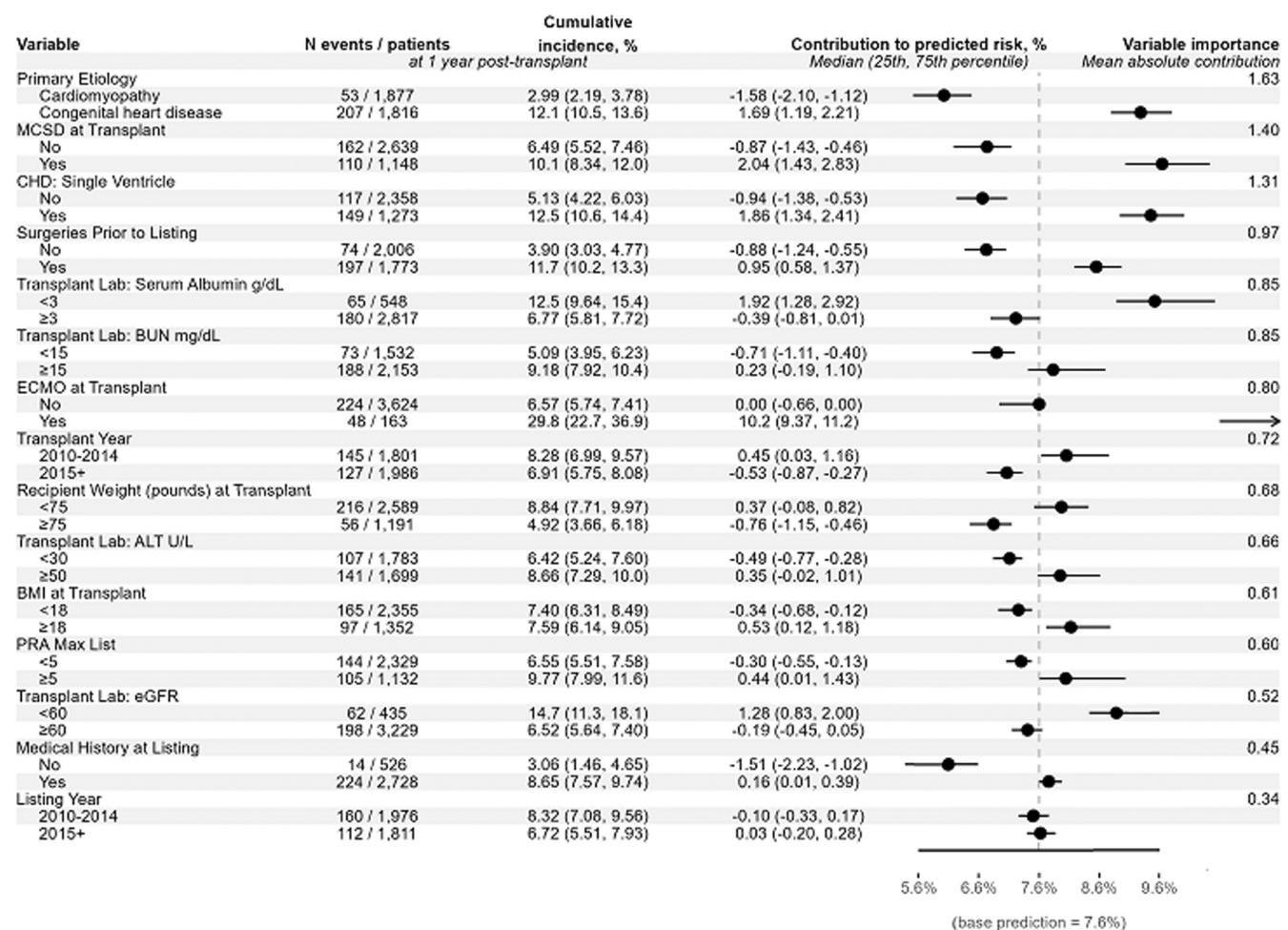


FIGURE 3 Variable contributions to predicted risk for final model. ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CHD, congenital heart disease; ECMO, extracorporeal membranous oxygenation; eGFR, estimated glomerular filtration rate; MCSD, mechanical circulatory support device; PRA, panel reactive antibodies. Shapley additive explanations were used to compute contribution to predicted risk. Variable importance was computed by taking the mean of the absolute values of contributions to predicted risk. Negative Shapley values imply that the variable decreased the overall predicted risk whereas positive Shapley values indicate an increase in risk contribution with that variable.

concerns such as acute renal insufficiency or poor nutrition.³⁻⁶ A prior PHTS database study by Schumacher et al. used logistic regression to look individually at heart transplant patients with an underlying diagnosis of congenital heart disease versus those with cardiomyopathy. They noted that independent recipient predictors of graft loss in patient with cardiomyopathy included year of transplantation, nonwhite race, female sex, diagnosis other than dilated cardiomyopathy, higher blood urea nitrogen, and higher panel reactive antibody. In patients with congenital heart disease, independent predictors of 1 year graft loss included nonwhite race, history of Fontan palliation, ventilator dependence, higher blood urea nitrogen, higher panel reactive antibody, and lower body surface area.⁵ The current study utilizing machine learning algorithms is consistent with prior studies in identifying similar risk factors but has the added benefit of elucidating the degree to which each of these variables is thought to contribute to overall risk, or variable importance. Clinicians routinely attempt to weigh multiple potential risk factors in an individual patient being considered for

heart transplantation in order to gauge the probability of survival. The ability to better understand the weight each individual variable holds would be a unique step forward in risk determination.

4.1 | Future directions

This study shows that machine learning models can be used to improve individualized patient risk prediction which translates into overall improved candidate selection and candidate management while awaiting heart transplant that is more patient-specific and data-driven to transplant survival. In turn, this can also improve cost-effectiveness and organ utilization given the overall imbalance between donor organs and patient needs. Ongoing study looking at additional models to determine how individual variables may influence one another and combine to collectively contribute to overall risk will be important. It will also be prudent to further this study to assess longer term post-transplant outcomes, such as 3-year

TABLE 1 Patient characteristics.

Variable ^a	Overall	Transplant year		
	Overall (N = 3787)	2010–2013 (N = 1400)	2014–2016 (N = 1286)	2017–2019 (N = 1101)
Recipient age (years) at transplant	4.9 (0.74, 13)	4.4 (0.67, 13)	4.9 (0.76, 13)	5.5 (0.88, 13)
Recipient male	55%	53%	56%	57%
Recipient race				
Black	17%	18%	16%	17%
Other	18%	15%	18%	22%
White	65%	67%	66%	62%
Recipient Hispanic or Latino	20%	15%	22%	24%
Primary etiology				
Cardiomyopathy	50%	52%	50%	46%
Congenital heart disease	48%	44%	49%	52%
Single ventricle	35%	27%	38%	43%
Other	2%	4%	1%	2%
BUN mg/dL at transplant	16 (12, 22)	16 (12, 22)	16 (12, 22)	17 (12, 23)
Surgeries prior to listing	47%	44%	48%	49%
MCSD at transplant	30%	28%	28%	36%
ECMO at transplant	4.3%	4.5%	4.7%	3.5%
Albumin g/dL at transplant	3.7 (3.2, 4.2)	3.7 (3.2, 4.2)	3.7 (3.2, 4.2)	3.7 (3.2, 4.2)
eGFR at transplant	97 (76, 124)	95 (73, 120)	96 (76, 122)	103 (80, 131)
ALT U/L at transplant	29 (20, 45)	29 (19, 45)	28 (20, 41)	30 (20, 47)
Recipient weight (pounds) at transplant	35 (17, 94)	33 (16, 95)	35 (17, 93)	39 (18, 97)
Medical history at listing ^b	84%	100%	84%	69%
Listing year	2014 (2012, 2016)	2011 (2010, 2012)	2015 (2014, 2015)	2017 (2017, 2018)
BMI at transplant	17 (15, 20)	17 (15, 19)	17 (15, 19)	17 (15, 20)
PRA max list	0.00 (0.00, 13)	0.00 (0.00, 16)	0.00 (0.00, 13)	0.00 (0.00, 10)

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; ECMO, extracorporeal membranous oxygenation; eGFR, estimated glomerular filtration rate; MCSD, mechanical circulatory support device; PRA, panel reactive antibody.

^aTable values are median (25th percentile, 75th percentile) and percent for continuous and categorical variables, respectively.

^bAdditional medical problems at listing included a history of arrhythmia, cardiac arrest/CPR, diabetes, GI/nutritional issues, heterotaxy/isomerism, malignancy, metabolic disorder, mitochondrial disorder, neurologic concern, pacemaker, peripheral myopathy/neuromuscular disease, prenatal diagnosis, prior transfusions, renal insufficiency, respiratory concerns, shock, syndromes, or other.

mortality or greater to determine if different variables affect longer term mortality greater than short term.

4.2 | Limitations

This study was limited by its retrospective design and the fact that there was some missing registry data, although this was mitigated by limiting analysis to the later eras. The era effect was accounted for by using repeat sampling and thus did not limit the current study.

5 | CONCLUSIONS

Machine learning techniques are advancing risk prediction models in several areas. This study showed that machine learning, specifically,

oblique random survival forests, can be used to better determine the risk of 1-year allograft loss or mortality in pediatric heart transplant patients and that permutation importance can determine individual variable contribution to overall risk which will improve the care of heart transplant patients through improved patient selection and risk factor mitigation.

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CONFLICT OF INTEREST STATEMENT

Ryan Cantor receives partial salary support in his role as lead statistician of the data center for the PHTS Registry. Byron C Jaeger's time working on this manuscript was partially supported by funds from STS HHSN268201100025C (PI: Kirklin). James Kirklin receives

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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