Pediatric Heart Transplant Society

Request for Limited De-identified Data Sets for Research Purposes

This packet includes:

- Standard Operating Procedures (SOP)
- Financial Disclosure and Conflict of Interest Form
- Data Request Form
- Research Proposal

Return completed packet to:

Claire Covington
Claire.covington@kirso.net

Analyses will NOT be performed by the PHTS Data Coordinating Center (DCC).
Data will be provided in as SAS files.

Pediatric Heart Transplant Society

Standard Operating Procedures (SOP)

Access & Publications
Instructions on how to access the PHTS database and develop relevant abstracts and manuscripts based on PHTS Data

I. BACKGROUND

The Pediatric Heart Transplant Study (**PHTS**) Group fully supports the use of the PHTS database to improve outcomes for children needing heart transplantation. This document describes the process by which hospitals and surgical groups that generate data for the Database (**Database participants**), as well as others, such as investigators from the private sphere (**Industry**), can submit defined clinical research questions on an ad hoc basis to the PHTS Scientific Committee. Investigators can disseminate these findings to transplant colleagues through peer-reviewed publications, in presentations at scientific meetings, and by adding to the body of knowledge of internal or federally funded quality improvement initiatives.

II. DATA REQUEST FORMS

A. Application

All requests for access to the Database are initiated by completing this form from the PHTS website and then sending the request electronically (via e-mail) to PHTS.

B. Research Question

Completing the request form in its entirety and providing a full description of your study will guarantee that your request will be handled in an efficient and timely manner. Your research question should be clear and specific in regard to 1) variables requested, 2) time period of interest, and 3) how the information will be used (e.g., “for internal research” or “for presentation of clinical trial design to the FDA”). You are strongly encouraged to provide proposed output tables to help statisticians and programmers at the DCC correctly interpret the request parameters. Requesters are also encouraged to describe their projects and how results will be used in language that can be understood by individuals outside their specialty.

It is important to make sure your request is feasible using PHTS data. Data collection forms and data specification documents containing the data fields collected, along with their clinical definitions, are available on the PHTS Web site.

Web Link: https://pediatricheartttransplantsociety.org/2015-forms/

C. Review of request

The PHTS Scientific Committee will review the request and may ask the researcher for more specific details or revisions prior to making a final decision regarding the approval status of the request (yes or no).

Timeliness of Request Submission

The researcher must submit his/her request at least **six months prior** to any anticipated submission deadline that the requester is targeting. This will allow adequate time for the PHTS Scientific Committee to review the request, the DCC to complete the request and forward the dataset to the researcher, the researcher to complete his/her analysis, and the PHTS Scientific Committee to then review the final analysis before submission.

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The PHTS Scientific Committee will review requests based on several key criteria.

1) Is the research question novel and distinct from previous PHTS publications?
2) Are the analytic plan and statistical support sufficient to execute the analysis in a sound manner?
3) Will the research study advance the care of children needing heart transplantation and outcomes post-transplant?

D. Evaluation of the Statistical Analysis Plan (SAP)

The PHTS DCC will review the statistical analysis plan (SAP) and will evaluate the plan according to its ability to provide the statistical analysis necessary to answer the research question. SAPs that are deemed insufficient will be referred back to the researcher.

E. Submitting your Request

E-mail the following completed forms contained in this packet to Claire Finley at claire.covington@kirso.net: SOP, Data Request Form, and Research Proposal. Electronic submission of the Data Request Form is the only method of submission. An e-mail confirming receipt of the request will be returned to the e-mail address from which the data request was submitted.

III. TRANSMISSION OF LIMITED DATA

A. De-identified Data to the Researcher

The PHTS DCC will transmit the de-identified data according to the information security protocol.

All data that are sent to a researcher will be de-identified in 2 specific ways:

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- Patient data: no patient identifiers will be included. This includes all PHI as defined by HIPAA. Therefore, intervals will be substituted for dates.
- Hospital data: no hospital identifiers will be included.
- These datasets will be SAS datasets. Most major statistical packages (applications) have utility programs to translate a SAS dataset.

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B. Data Management

The researcher will be responsible for the data management of the de-identified data that he/she receives. Data management includes linking of the datasets, file management, re-coding of variables for statistical analyses, sub-grouping of the data, calculation of derived variables, etc.

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C. Statistical Analysis of the Data

The researcher will conduct the statistical analysis of the data based on the statistical analysis plan (SAP). **A SAS programmer is required to manage this data.** The PHTS DCC recommends that the researcher work with a knowledgeable SAS programmer with data merging and biostatistical experience.

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IV. Cost

If the PHTS Scientific Committee approves a request from a Database participant the requester will need to pay the DCC to process the request. The fee in these cases goes to the DCC to pay for its overhead and computation and statistical time. The fee set for requests from participating centers in good standing is **$5,000.** The data will only be sent once the payment has been received by the DCC. **If a linkage to another database is required then additional charges will be incurred.**

Members in Good Standing

A member in good standing is defined by the center being compliant in all of the following areas:

- IRB approval up to date and on file at the DCC
- Yearly participation fee paid
- Current on form submission and queries
- Business Associates Agreement (BAA) and Participation Agreement (PA) signed and on file at the DCC

Requests from non PHTS participants

Requests from researchers who do not contribute to the Database and government and industry researchers are priced separately for each project.

Researchers who work for industry or a government organization *or are planning to share data results with industry or a government agency* are always charged a fee for access to information in the Database. The minimum fee set for industry requests is **$10,000.**

V. Statistical Analysis and Data Interpretation for Requests Intended for Publication and/or Presentation

Once the PHTS Scientific Committee approves a request, the assigned DCC statistician will initiate contact with the requester to discuss any remaining needed clarifications. A detailed background literature review and plan for the analysis are important components of requests intended for publication. Preferably these will be present in the original data request submitted. The analysis plan might be expanded and revised during the primary author's discussions with the DCC statistician, with added input from the PHTS Scientific Committee. There may be ongoing communication among the DCC statistician, the clinical reviewer, and the primary author throughout the analysis process, particularly with regard to interpreting the analysis results. Once the project has been approved there should be no additional changes to the analysis plan outside of what has been discussed and approved with the DCC while analysis is in progress.

VI. ABSTRACTS AND MANUSCRIPTS BASED ON PHTS DATA

A. Roles and responsibilities

The majority of requests are initiated with the expectation of submitting one abstract and one manuscript citing the results from the request. This guidance is designed to delineate the responsibilities and expectations of all involved parties related to a PHTS data request.

B. Results of the Analyses: Abstracts, Presentations, Papers

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The researcher is to submit the final abstract, presentation and paper to the PHTS Scientific Committee (via the PHTS DCC) for final review. **The PHTS DCC must have at least 4 weeks to review these materials before they are submitted to a journal or presented at a scientific meeting.** If the PHTS Scientific Committee provides a favorable review then the PHTS DCC will notify the researcher. If the PHTS Scientific Committee provides an unfavorable review of the final abstract, presentation, or paper, then the PHTS Scientific Committee will contact the researcher and PHTS President will serve as final arbiter of the identified issues. The researcher is to use the following sentence for acknowledgement of PHTS data in presentations and manuscripts (not required for abstracts): **"Through an agreement with PHTS, a limited data set of a _____ was obtained. All analyses were**

conducted independently by the authors and not in collaboration with the PHTS."

C. Time limitation on approval of a data request

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Once the researcher receives the data from PHTS, then the researcher has **1 year** to complete the analyses and any resultant manuscript. At the end of 1 year of receipt of data the researcher will return the data to PHTS DCC and destroy any copies that may reside at the researcher's location. **The PHTS DCC requires a dated notice of destroyed data from the center.** If the researcher has not completed the research project within 1 year, then the researcher must submit a new data request and repeat the process stated above.

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No more than 1 scientific abstract and 1 scientific paper can be prepared from any single request. Additional publications and secondary analysis are expressly prohibited.

Writing Group

The suggested size of the writing group is 10-12 members. For proposals that do not require additional data collection, one half of the writing group will be assigned by the PHTS Scientific Committee according to the standard PHTS protocol and using the rotating list of centers. The other half of the writing group will be chosen by the submitting author. There is no obligatory inclusion of member(s) from the PHTS DCC (this is important for some IRBs as they provide the de-identified dataset and maintain responsibility for the key).

For proposals that require supplemental data collection, the writing group members will be chosen from the centers that participate in the supplemental data submission. This will be done by the first and/or senior author in conjunction with the PHTS Scientific Committee.

For proposals that are submitted from more than one investigator at more than one center, one center from the assigned 5-6 centers will be subtracted for each additional center represented on the submission. There will be a minimum of 2 assigned centers from the rotating list for each approved limited dataset.

VII. POLICIES FOR TRANSFERRING AND UTILIZING DE-IDENTIFIED DATA

1. PHTS will only consider 1 limited data set request at a time from a researcher.
2. The researcher has 1 year to complete their analyses based on this request.

3. The researcher may not attempt to merge PHTS data with any other database without the specific approval of the PHTS Scientific Committee in the limited data set approval application process.
4. The researcher may not attempt to identify a patient within the datasets.
5. The researcher may not attempt to identify a hospital within the datasets.
6. The researcher may use the PHTS data for only the purpose stated in his/her request.
7. The researcher may not use the PHTS data for a public comparison of his/her institution's data to the PHTS data.
8. The researcher may not disclose, print, copy, or distribute the data he/she receives to any other entity.

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Penalties to the researcher and the researcher's center will ensue if any of the above polices are not observed. Penalties may include, but not limited to:

- Removal from research projects for a period of time to be specified
- Denial of future limited data set requests for a period of time to be specified

Pediatric Heart Transplant Society

Data Request Form

Data Request for Researchers: Policy and Procedures
Please read, sign, and date this document in order to receive the requested data package. Your data package will contain the following information and will be transferred according to the following policies and procedures:

I. Purpose of the Research Request

The de-identified data that I will receive will accomplish the following research (please attach your research proposal as follows):

- Specific Aims
- Background significance
- Study Design and Methods
- Analytic Methods
- Anticipated Findings

II. Eight de-identified (SAS) datasets

These datasets will contain de-identified PHTS data limited to first heart transplants, unless otherwise requested, within the specified window listed in this SOP.

A. Listing dataset:
- One observation per listed patient.

B. Transplant dataset:
- One observation per first heart transplant.

C. Angiogram dataset:
- One observation per transplanted patient plus an observation for each coronary evaluation captured on Form 04.

D. Rejection dataset:
- One observation per transplanted patient plus an observation for each rejection captured on Form 05.

E. Infection dataset:
- One observation per transplanted patient plus an observation for each infection captured on Form 06.

F. Malignancy dataset:
- One observation per transplanted patient plus an observation for each malignancy captured on Form 07.

G. Follow-up dataset:
- One observation per transplanted patient plus an observation for each follow-up captured on Form 08.

H. MCSD dataset:
- One observation per device captured on Form 15.

III. Data Dictionaries

You will receive a data dictionary describing variables in the datasets as well as annotated forms. This data dictionary will provide a technical data management tool for your data manager. All data elements within these eight datasets have been described according to its SAS specifications. This data management tool will allow your statistician and/or data manager to do all work necessary to fully manage and analyze this PHTS data.

IV. Data Transfer: You will receive the above listed files (# II and # III) via a secure data transfer system (NeoCertified). This system will require a single point of contact to receive the data. Instructions will be given to your point of contact to download your data and additional documentation.

V. Data Consolation

Once we have completed the data transfer listed above, you will then be responsible for all data management and analyses with your requested PHTS data.

Pediatric Heart Transplant Society

Date: December 1, 2024

Requestor Name: Michael A. McCulloch, MD

Requestor Position: Professor of Pediatrics, Division of Pediatric Cardiology

Requestor Hospital: University of Virginia Children's Hospital

Requestor Email: mam3fk@uvahealth.org

Requestor Phone: (434) 872-1143

Relationship to PHTS:

☐ Hospital PI
☒ Hospital Investigator
☐ Other, specify:

Expected Dissemination of the Research Results

Abstract: Abstract or Presentation
Submission Deadline: August 2025

Presentation: Abstract or Presentation
Date: August 2025

Publication: Manuscript
Proposed Journal: Journal of Heart and Lung Transplantation
Anticipated Date: December 2025

Internal Use:

Other:

Pediatric Heart Transplant Society

Data Request Researchers: Policies and Procedures Agreement

I have read, understand, and agree to the entire policy titled “The Transfer of PHTS de-identified data to researchers: Policies and Standard Operating procedure”.

Michael A McCulloch, MD

Print Name

December 1, 2024

Signature Date

Confidentiality Agreement

I agree to use the data that I receive based on this request only for the purposes explicitly stated in this request. I also agree not to disclose, print, copy, or distribute the data that I receive based on this request without appropriate permission from the PHTS DCC.

Michael A. McCulloch, MD

Print Name

December 1, 2024

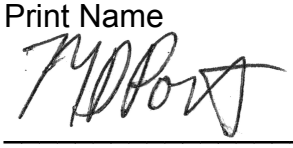
Signature Date

Statistical Support

The following personnel will receive the de-identified data and provide statistical support for this research project.

Michael D. Porter, PhD, University of Virginia School of Data Science, Project Co-PI

Print Name



December 1, 2024

Signature Date

mdp2u@virginia.edu (205) 534-1665

Email Address Work Phone Number

Pediatric Heart Transplant Society

Research Proposal

Title:
Improving Pediatric Donor Heart Utilization with Predictive Analytics

Background:
Background:
Infants and children awaiting heart transplantation experience waitlist mortality rates of approximately 14%.[1,2] Despite this fact, our recent analysis of the 2010-2020 OPTN data demonstrated nearly 90% of all pediatric donor heart *offers* were declined and nearly 40% of these pediatric donor *hearts* were never utilized for children waitlisted in the United States.[3] Further, nearly 2/3 of these non-utilized pediatric donor hearts had normal echocardiograms and over half were utilized for adult or Canadian candidates. When coupled with studies demonstrating worse waitlist survival for patients listed at centers with high refusal rates[4] but no decline in post-transplant outcomes when utilizing organs previously refused by other institutions[5] we contend there is not as much of an issue with pediatric donor availability as with utilization. This is further supported by our findings that more than any donor, candidate, or offer specific variable, the two most important variables predicting whether a specific donor heart would be accepted were how many prior times it had already been refused and a candidate institution's prior year acceptance rates[3]. Collectively, we have interpreted these findings as reinforcing a significant impact of behavioral economics on pediatric donor heart acceptance practices[6,7] despite guidelines suggesting the limited importance of most donor variables in the setting of a normal echocardiogram and donor ischemic times under 6 hours.[7,8]

To continue our work in this field, we have recently secured a 5-year R21/R33 funding from the Agency for Healthcare Research and Quality (AHRQ) with the intent of improving donor utilization and decreasing waitlist mortality without negatively impacting post-transplant outcomes. Our first Specific Aim for the R21 phase of this project is to ***construct and validate predictive models to support transplant offer decision making***. We have already started the process of producing models capable of delivering real-time risk assessments for accept/reject decisions: the probability of a successful outcome if an offered donor heart is transplanted into a specific waitlisted candidate and, if the offer is rejected, the likelihood that the waitlisted candidate would survive for the time predicted until the next offer. The following tables and figures represent a component of our work using the aforementioned OPTN data to both clarify why we are requesting the PHTS data outlined below and to demonstrate the type of analyses we would perform.

We are presently assessing the ability of 5 different models/model types (Logistic Regression using a lasso penalty, LR; Boosted Trees, BT; Boosted Stumps, BT1; Random Forest, RF; and the previously published Choudhry, et al. model[9] CHDY) to predict 1-, 3-, and 5-year post-transplant survival using a variety of donor, candidate and offer

.metric	model	vars	avg	se	min	max	n
<chr>	<fct>	<fct>	<chr>	<chr>	<chr>	<chr>	<int>
roc_auc	lr	cand_LC	0.735	0.003	0.689	0.776	10
roc_auc	lr	all_non_donor_LC	0.732	0.003	0.677	0.764	10
roc_auc	lr	candidate_only	0.729	0.004	0.676	0.806	10
roc_auc	rf	cand_LC	0.729	0.006	0.609	0.815	10
roc_auc	rf	all_non_donor_LC	0.725	0.006	0.613	0.800	10
roc_auc	lr	candidate_ischemic	0.724	0.005	0.663	0.807	10
roc_auc	rf	optimal	0.724	0.006	0.624	0.785	10
roc_auc	lr	all_non_donor	0.723	0.003	0.661	0.760	10
roc_auc	lr	optimal	0.723	0.003	0.658	0.774	10
roc_auc	bt	cand_LC	0.723	0.004	0.670	0.801	10

Table 1. AUROC values for different model and variable types.

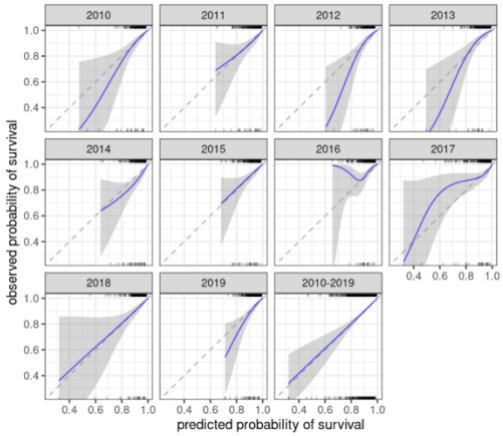


Figure 1. Calibration plots of predicted probabilities using candidate only LR model. Of note, 90% of transplants had predicted 1-year survival >85%.

specific variables. Table 1 demonstrates AUROC values for the top 10 model/variable combinations in predicting 1-year post transplant survival. As is seen in this table and in our 3- and 5-year post-transplant predictions (not shown here), models utilizing only candidate variables consistently outperformed/were not improved with the addition of most donor- (e.g. cause of death, donor infection, history of CPR, vasoactive infusion score) or offer specific (e.g. OPO center, donor hospital, time of day) variables. The relative importance of candidate variable only models are also supported when using log loss and Brier scores to assess predictive performance (not shown here). It should be noted that nearly 90% of accepted offers were associated with a stringent definition of 'normal echocardiograms' (shortening fraction ≥28% and/or ejection fraction ≥55%, no evidence of segmental wall motion abnormalities, no valvar insufficiency >mild) and 68% of all donor ischemic times were less than 4 hours (98% <6 hours), resulting in a relatively narrow range of donor acceptance practice from which to draw these conclusions.

The performance of our 'candidate-only' models are again demonstrated in Figure 1's multiple calibration graphs comparing observed to predicted 1-year post-transplant survival values produced by the candidate only LR model, using 9 of the dataset's 10 years to predict the year shown in each individual graph and the entire cohort in the final graph. It is important to note that although the addition of donor-specific variables (cause of death, CPR history, etc.) did not significantly improve post-transplant survival predictive power, partial effects graphs do demonstrate correlations between 1-year post transplant survival predictions and surrogate measures of donor/candidate size matching (e.g. BMI difference). There was also a very mild association between worse survival and increased donor ischemic time, but only in the very rare transplant recipient who required greater than 6 hours, as seen in Figure 2.

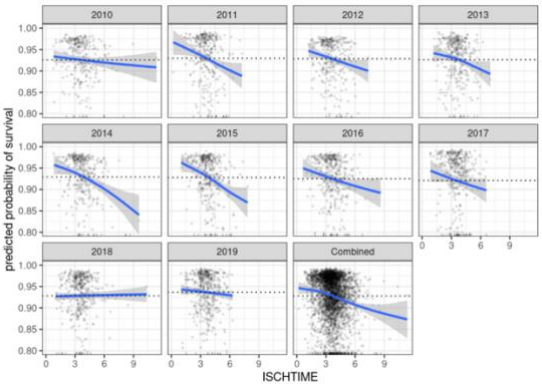


Figure 2. Partial effects plots of donor ischemic time on predicted 1-year post-transplant survival probability. Circles represent individual candidates.

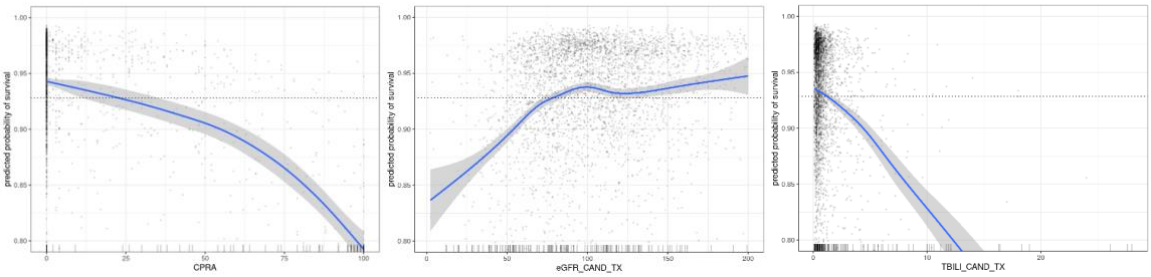


Figure 3. Partial effects plots of candidate cPRA, total bilirubin and eGFR on predicted 1-year post-transplant survival probability. Circles represent individual candidates.

Additional partial effects plots confirmed previously demonstrated associations between worse post-transplant outcomes and both allosensitization (cPRA) and renal (eGFR) or hepatic (total bilirubin) dysfunction, as shown in Figure 3.

Our collective interpretation of the existing scientific literature[7,8,10] our previous work in the field[3,11,12] and the above preliminary data have led us to the following assertions: (1) assuming a normal echocardiogram, donor ischemic time under 6 hours and an 'appropriate' donor/candidate size matching, virtually no other donor- or offer-specific variables significantly impact post-transplant survival; (2) demographic (e.g. cardiomyopathy vs congenital heart disease, size) and potentially modifiable candidate variables (e.g. hepatic/renal failure, cPRA, nutritional status, functional status) have the most direct impact on post-transplant survival; and therefore (3) increasing the granularity of candidate specific data above that available in OPTN may significantly improve our ability to accurately predict post-transplant survival. It is for these reasons we are requesting the PHTS limited data set outlined below and posit the following hypothesis:

Hypothesis / Specific Aims:

Our existing predictive modeling approach for post-transplant survival focused on candidate specific variables will have a significantly increased predictive accuracy when applied to the PHTS dataset as compared to our current OPTN dataset.

Requested Variables (list by form and question number or highlight forms downloaded from the website and submit with this application):

1. Patient Enrollment Form: questions: 1, 3-9, 11 (all subquestions), 13 (all subquestions)
2. Form 1- Listing: 1-4, 5 (all subquestions), 6a (only if U.S. is checked), 6a.iv, 6b, 6b.i, 6b.ii, 6c, 6c.i, 6d, 6e, 6f, 6f.i, 6f.ii, 6g, 7 (all subquestions), 8 (all subquestions), 10c, 10c.i, 10c.ii, 10c.iii, 10d, 10d.i, 10d.i.1, 11 (all subquestions), 12 (all subquestions), 13 (all subquestions), 14 (all subquestions), 15 and 16
3. Form 1T-Transplant: 1, 2 (only need 'None' answer patients), 3 (exclude Heterotopic patients), 4, 5a/5b, 6a.iv, 6b, 6b.i, 6b.ii, 6c, 6c.i, 6d, 6e, 6f, 6f.i, 6f.ii, 6g, 6h, 7 (all subquestions), 8c, 8c.ii, 10, 10a, 10b, 11a, 12 (all subquestions), 13 (all subquestions), 14 (all subquestions), 15 (all subquestions), 16, 16a, 17-19,
4. Form 2- Donor: all questions
5. Form 8- Post Transplant Annual Follow Up: 7b, 4, 5, 15f, 15f.i, 15g, 15g.i

6. Form 10- Death: all questions
7. Form 12- Pre-Transplant Status Report: 1, 1a, 3a, 3b, 5 (all subquestions), 6, 6a, 6b, 7, 7a, 7b,
8. Form 15- Mechanical Circulatory Support Events: all questions

Analyses:

We will apply our current modeling approach to the comparable variables within the PHTS dataset. Our predictive models will be designed to: (i) provide unbiased estimated probabilities and uncertainty assessments; (ii) furnish variable importance scores and explainable predictions; and (iii) be validated with data collected after all models are finalized.

Model post-tx survival: We will assess our current statistical and machine learning models to predict the post-transplant survival for candidate-donor pairs. Leveraging recent advancements in survival modeling, [13–15] we will utilize discrete time formulations to reframe hazard estimation as a Logistic or Poisson regression problem, using loss functions that most modern ML methods can optimize. We will specifically consider Random Forest, Gradient Boosted Trees, Penalized Logistic Regression, and Deep Learning models due to their: great predictive power, ability to capture nonlinear and interaction effects, handling of mixed-type predictor variables, robustness to outliers, and computational efficiency at prediction time. [16–20] We will also implement two specialized survival models (Oblique Random Survival Forests [21] and DeepHit [22]) that have recently been shown to outperform other ML-based survival models. For comparison, we will also include a baseline Cox proportional hazards model. [23,24]

Optimal tuning: The ML models we are considering have many tuning parameters that influence the predictive performance. We will use cross-validation to select the optimal tuning parameters. For the post-transplant survival models, we will use repeated 10-fold cross-validation using outcome stratification to ensure an equal survival distribution in each fold. To help protect against overfitting, we will optimize tuning parameters using grouped Monte Carlo cross-validation, ensuring that all observations from the same candidate are grouped together in the same fold. Each cross-validation process will be repeated iteratively until sufficient evidence is obtained to determine the best tuning parameters.

Variable importance: Complex machine learning models, like the ones we are considering, are not inherently explainable (i.e., it is not obvious how the predictor variables interact to make a prediction). A recent approach, SHAP (SHapley Additive exPlanations), provides a way to estimate the effect each variable has on the prediction, even in black-box machine learning models. [25] Based on concepts from game theory, the SHAP scores estimate a variable's impact by the change in prediction if the feature value was unknown/missing. In other words, the SHAP score estimates how much each variable contributes to the change in model prediction for a given observation. For the specialized survival models, we will use SurvSHAP. [26] We will report the mean absolute value of the SHAP scores over the training data as a variable importance score. [27]

Model Validation: We will validate the performance of the predictive models through cross validation methods, using all but one year of data to predict the standout year of data, repeating 10 times, in addition to repeating this process with multiple separate training and validation subsets. Prediction uncertainty will be estimated using out-of-bag based prediction intervals. [28] Predictive performance will be evaluated using the Concordance Index (C-

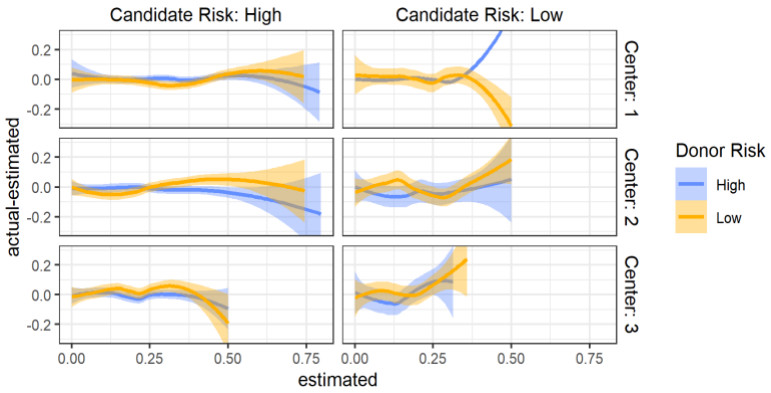


Figure 4: Example calibration plots showing how closely the predictive risk aligns with the true risk across center, donor risk level, and candidate risk level.

statistic), also known as area under the ROC curve (AUROC), and Brier Score. [29] The AUROC measures the model's *discrimination*, or its ability to stratify patients by risk, while the Brier score measures the model's *calibration*, or its ability to make risk predictions that align with the observed risk. [29–31] Since survival models make predictions across time, we will focus on specific time periods of interest to clinicians, including 30-day, 1-year, 3-year, and 5-year post-transplant survival. Based on our current work, we anticipate achieving a validated AUROC of at least 0.70, which is considered an acceptable level of discrimination. [32]

We view a successful, well-calibrated model as one that will assign risk scores that match the true observed proportions (e.g., among patients in the validation set with an estimated risk of 2%, an observed 2 in 100 died within one year after transplant). We will estimate the observed proportion with a scatterplot smoother (e.g, smoothing splines, use of binary outcomes [0 = survival, 1 = death]) and will visually evaluate the resulting calibration plots (Figure 4). [33] In previous work, we assessed calibration as a measure of bias in predictive models of recidivism. [34]

Potential pitfalls and proposed solutions: Because we have already worked extensively with this type of data, [3,35] we are confident that the necessary predictor variables and outcomes can be obtained. We also have significance experience implementing complex cross-validation schemes. [36–40] The predictive performance on the validation data may be substantially worse than expected, indicating that either the predictive models were overfit or the distribution of the validation sample differs from the distribution of the training data. If the validation AUROC is at least 0.70 (i.e., acceptable level of discrimination) [32] but the Brier Score has increased, the issue is likely calibration. Calibration plots will help determine if the issue is due to overfitting or a change in distribution. We do not expect overfitting because of our planned cross-validation approach. A remedy for small changes in distribution is to linearly adjust the predictions. [33]

References:

1. Singh TP, Almond CS, Piercey G, Gauvreau K. Trends in wait-list mortality in children listed for heart transplantation in the United States: era effect across racial/ethnic groups. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*. 2011;11(12):2692-2699. doi:10.1111/j.1600-6143.2011.03723.x
2. Lynn J, Malik T, Montgomery A, et al. Risk Index Predicts Pediatric Heart Allograft Non-Utilization. *Pediatr Transplant*. 2024;28(1). doi:10.1111/petr.14629
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