Circulation: Heart Failure

EMERGING INVESTIGATORS

Prediction of Donor Heart Acceptance for Transplant and Its Clinical Implications: Results From The Donor Heart Study

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BACKGROUND: Despite a shortage of potential donors for heart transplant in the United States, most potential donor hearts are discarded. We evaluated predictors of donor heart acceptance in the United States and applied machine learning methods to improve prediction.

METHODS: We included a nationwide (2005–2020) cohort of potential heart donors in the United States (n=73 948) from the Scientific Registry of Transplant Recipients and a more recent (2015–2020) rigorously phenotyped cohort of potential donors from DHS (Donor Heart Study; n=4130). We identified predictors of acceptance for heart transplant in both cohorts using multivariate logistic regression, incorporating time-interaction terms to characterize their varying effects over time. We fit models predicting acceptance for transplant in a 50% training subset of DHS using logistic regression, least absolute shrinkage and selection operator, and random forest algorithms and compared their performance in the remaining 50% (test) of the subset.

RESULTS: Predictors of donor heart acceptance were similar in the nationwide and DHS cohorts. Among these, older age (*P* value for time interaction, 0.0001) has become increasingly predictive of discard over time while other factors, including those related to drug use, infection, and mild cardiac diagnostic abnormalities, have become less influential (*P* value for time interaction, <0.05 for all). A random forest model (area under the curve, 0.908; accuracy, 0.831) outperformed other prediction algorithms in the test subset and was used as the basis of a novel web-based prediction tool.

CONCLUSIONS: Predictors of donor heart acceptance for transplantation have changed significantly over the last 2 decades, likely reflecting evolving evidence regarding their impact on posttransplant outcomes. Real-time prediction of donor heart acceptance, using our web-based tool, may improve efficiency during donor management and heart allocation.

Key Words: donor selection ■ heart transplantation ■ machine learning ■ random forest ■ tissue and organ procurement

New heart transplant (HT) listings in the United States (4588 in 2020) have consistently outpaced the number of transplants performed (3715 in 2020).[1] As a result, many candidates wait several months or longer for transplant and hundreds die annually while waiting. Despite this unmet demand, the majority of potential donor hearts are not used for transplant.[2] Common reasons for nonuse include older donor age, left ventricular (LV) dysfunction or hypertrophy, cardiovascular comorbidities, or other risk factors.[3]

Given these consequences of the donor organ scarcity, high discard rates are justified only if they select out donor risk factors with an adverse impact on posttransplant outcomes. For example, a recent meta-analysis identified a reliable association between donor age and recipient mortality.[4] For other putative risk

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WHAT IS NEW?

- Predictors of donor heart acceptance for transplantation have changed significantly over the last 2 decades.
- Donor age has become increasingly influential while several other factors have become less so, likely reflecting the lack of evidence regarding their impact on posttransplant outcomes.
- Whether a donor will be accepted for heart transplant can be predicted with a high degree of accuracy using a random forest algorithm.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Our novel web-based tool can enable real-time prediction of donor heart acceptance.
- This tool can improve efficiency during donor management, enabling real-time assessment of a given donor's likelihood of being accepted for heart transplant.
- This tool may also be useful to heart transplant centers, in helping inform their decision whether to accept a given donor heart offer.

Nonstandard Abbreviations and Acronyms

AUC	area under the curve
CAD	coronary artery disease
DHS	Donor Heart Study
ET	Eurotransplant
HT	heart transplant
LV	left ventricle
LVH	left ventricular hypertrophy
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OPO	organ procurement organization
OR	odds ratio
SRTR	Scientific Registry of Transplant Recipients
ToP-HAT	Tool to Predict Heart Acceptance for Transplant

factors listed above, such an association is plausible but the evidence is less robust.[5] Naturally, donor heart discard practices should evolve in concert with the evidence base. To judge whether they have requires careful examination of the factors that drive donor heart acceptance (versus discard) and how they have evolved over time.

Critical to the goal of rational donor heart selection is the role played by organ procurement organizations (OPOs), who evaluate and manage potential donors in the hours before their organs are offered for transplant or discarded.[6] OPOs aim to maximize the utilization of viable organs for transplant—an objective that requires complex decisions involving multiple (sometimes competing) priorities. For example, pursuing coronary angiography and serial echocardiograms to evaluate a high-risk donor heart can delay the recovery of other solid organs and potentially compromise their quality.[7] Accordingly, it may be best to defer such intensive cardiac evaluation when the likelihood of yielding a viable donor heart is very low; such a decision is difficult in real time and hinges upon the basic question: how likely is this donor to be accepted for HT?

In this study, we assess current predictors of donor heart acceptance in the United States, how they have changed over the last 2 decades, and whether they reflect evolving evidence on which donor characteristics impact posttransplant outcomes. Second, we apply these predictors using machine learning methods to enable real-time prediction of donor heart acceptance.

METHODS

Data Sources

Our primary data source was the DHS (Donor Heart Study), an observational prospective cohort study of potential heart donors enrolled from February 2015 to May 2020, which has been described previously.[8] The DHS was coordinated at the Stanford University and conducted at 8 OPOs across the United States (listed in the Table). The DHS was approved by the Stanford University Institutional Review Board (protocol 31461) and by the research oversight committee at each participating OPO.

We also used data from the Scientific Registry of Transplant Recipients (SRTR), which includes a record of all donors in the United States from whom at least 1 solid organ was recovered for transplant.[1] The data reported here have been supplied by the Minneapolis Medical Research Foundation as the contractor for SRTR. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the SRTR or the US government. Because of the sensitive nature of these data, the data sets, analytic methods, and study materials cannot be provided directly by us to other researchers for purposes of reproducing the results or replicating the procedure.

These 2 data sources offered complimentary advantages. SRTR's larger sample size and duration were necessary to characterize how predictors of donor heart acceptance have changed over time (as detailed in Inference Models). The DHS characterized contemporary donors in greater detail, allowing more robust prediction of acceptance (as detailed in Prediction Models).

Cohort Definitions

The full DHS cohort was divided randomly in half into equally sized (1:1) derivation (training) and validation (test) subsets. The validation subset is an internal validation data set that was kept separate from the training data. We also defined a nationwide cohort (including both DHS and non-DHS OPOs) that

Table. Descriptive Characteristics of DHS Donors, by Acceptance for Heart Transplantation

	Accepted	Not accepted	SMD
Sample, n (%)	2470 (59.8%)	1660 (40.2%)	
Age, y; mean (SD)	33.6 (10.7)	44.3 (11.8)	0.95
Age, y; categorical			0.89
<35	1385 (56.1%)	384 (23.1%)	
35–49	846 (34.3%)	603 (36.3%)	
50+	239 (9.7%)	673 (40.5%)	
Female	773 (31.3%)	814 (49.0%)	0.37
Hypertension	430 (17.4%)	702 (42.3%)	0.57
Smoking	269 (10.9%)	388 (23.4%)	0.34
Missing	44 (1.8%)	30 (1.8%)	
Diabetes	99 (4.0%)	238 (14.3%)	0.37
Hepatitis C infection	110 (4.5%)	147 (8.9%)	0.18
LV dysfunction			0.46
Mild (LVEF, 40%–49%)	112 (4.5%)	170 (10.2%)	
Moderate-severe (LVEF, <40%)	59 (2.4%)	198 (11.9%)	
LVH			0.40
Mild	243 (9.8%)	272 (16.4%)	
Moderate or severe	72 (2.9%)	176 (10.6%)	
Missing	160 (6.5%)	131 (7.9%)	
Coronary angiogram			1.30
Normal	1048 (42.4%)	410 (24.7%)	
Minor CAD	69 (2.8%)	201 (12.1%)	
Major CAD	2 (0.1%)	100 (6.0%)	
Not performed, low CAD risk	1268 (51.3%)	325 (19.6%)	
Not performed, high CAD risk	83 (3.4%)	624 (37.6%)	
Inotropes or vasopressors	1510 (61.1%)	1104 (66.5%)	0.11
Cause of death			0.61
Anoxia or other	1030 (41.7%)	700 (42.2%)	
Cerebrovascular	398 (16.1%)	631 (38.0%)	
Head trauma	1042 (42.2%)	329 (19.8%)	
Blood type			0.23
O	1238 (50.1%)	721 (43.4%)	
A	901 (36.5%)	638 (38.4%)	
B	286 (11.6%)	203 (12.2%)	
AB	45 (1.8%)	98 (5.9%)	
Any cardiac downtime	182 (7.4%)	144 (8.7%)	0.05
Troponin			0.22
<10×ULN	1684 (68.2%)	982 (59.2%)	
10–100×ULN	612 (24.8%)	472 (28.4%)	
>100×ULN	153 (6.2%)	179 (10.8%)	
Missing	21 (0.9%)	27 (1.6%)	
NT-proBNP, median (IQR)	434 (180–1335)	739 (248–2797)	0.15
Missing	1064 (43.1%)	773 (46.6%)	
Lactate, median (IQR)	1.8 (1.1–3.3)	1.8 (1.2–3.4)	0.02
Missing	1262 (51.1%)	920 (55.4%)	
PHS increased risk	798 (32.3%)	506 (30.5%)	0.05
Cocaine use	1716 (69.5%)	1193 (71.9%)	0.06
Missing	27 (1.1%)	23 (1.4%)	
Weekend/holiday	752 (30.4%)	544 (32.8%)	0.05
Organ procurement organization			0.20
Donor network of Arizona	160 (6.5%)	109 (6.6%)	
Donor network West (California)	433 (17.5%)	246 (14.8%)	
Life Choice Donor Services (Connecticut)	67 (2.7%)	41 (2.5%)	
LifeLink (Georgia)	312 (12.6%)	225 (13.6%)	
Gift of Hope (Illinois)	387 (15.7%)	183 (11.0%)	
New England Donor Services	419 (17.0%)	266 (16.0%)	
Gift of Life Michigan	287 (11.6%)	229 (13.8%)	
LifeGift (Texas)	405 (16.4%)	361 (21.7%)	

The coronary angiogram variable (when performed) was designated as major CAD if any ≥50% large vessel stenosis was noted, as minor CAD if only stenoses ≤50% were noted, and as normal otherwise. Donors with coronary angiogram not performed were classified as low and high CAD risk as detailed in the Supplemental Methods. LVH was defined based on the thickness of the LV posterior wall or intraventricular septum, whichever was greater, and coded as mild (1.2–1.3 cm) and moderate or severe (≥1.4 cm). The PHS increased risk designation identifies donors with risk factors associated with infectious disease transmission. The weekend/holiday indicator variable was based on the date of the first offer of a given donor for transplant (with weekend defined as any Saturday or Sunday and holidays including all US federally designated holidays).

Other variables with missing values (in <1% of the DHS cohort) include diabetes, hypertension, and PHS increased risk.

CAD indicates coronary artery disease; DHS, Donor Heart Study; IQR, interquartile range; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PHS, Public Health Service; SMD, standardized mean difference; and ULN, upper limit of normal.

included all potential heart donors in the United States over a longer period (February 2005 to May 2020).

In each of these cohorts, we included donors aged 18 to 65 years and excluded any with declaration of circulatory death, a history of myocardial infarction, or the absence of a recorded LV ejection fraction. The rationale for these exclusion criteria was to limit each cohort to donors who were at least considered for HT (as opposed to other solid organ transplant only). The construction of each cohort is illustrated with a CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure S1).

Variables

Our outcome variable was donor acceptance for HT. Covariates (listed in the Table) included donor demographics, comorbidities, and diagnostic findings. Covariates were chosen on the basis of (1) data availability (ie, was this factor measured reliably in our data set?) and (2) prior literature (ie, has any prior analysis or guideline document suggested that this factor is or should be associated with donor acceptance for HT?). We focused on those felt to be intrinsic to the donor and excluded those that often reflect clinical management decisions (eg, blood pressure, electrolyte levels). For covariates measured

at multiple time points, we utilized only those obtained at the beginning of donor management, as this is the time at which prediction of donor heart acceptance would have the most clinical utility. Further details on the outcome variable and selected covariates are included in the Supplemental Methods.

Of the 19 donor covariates (not including OPO) listed in the Table, the availability of these differed slightly between the DHS and nationwide cohorts. Specifically, the nationwide cohort (which was characterized using data from SRTR) lacked the following 3 covariates: lactate, NT-proBNP (N-terminal pro-B-type natriuretic peptide), and LV hypertrophy (LVH). Except where otherwise stated below, analyses of the DHS cohort incorporated all 19 donor covariates while those of the nationwide cohort included only 16 of these. The categorization of these variables is detailed in the Table and was consistent in all analyses using both DHS and nationwide cohorts.

Statistical Analysis

Descriptive Analysis

For each cohort, we reported mean and SD for continuous variables and frequencies and proportions for categorical variables. To compare donors by outcome status, we reported standardized mean difference, a comparative measure of effect size between groups. Consistent with prior guidelines, the magnitude of effect was considered small if the standardized mean difference was 0.2 to 0.5, moderate if the standardized mean difference was 0.5 to 0.8, and large if the standardized mean difference was >0.8.[9,10]

Inference Models

Multivariable logistic regression models were fit separately in both the DHS and nationwide cohorts to identify independent associations of each covariate with acceptance for transplant. We fit an additional logistic regression model in the nationwide cohort in which calendar year and interaction terms between calendar year and each covariate were added; the purpose of this model was to assess for changes in the influence of each covariate over time. We used $P<0.05$ as the threshold for statistical significance for both standalone and time-interaction terms in these inference models. We did not apply corrections for multiple comparisons given the models were evaluated for descriptive purposes instead of for hypothesis testing.

In each of these inference models, we accounted for missing donor covariates using multiple imputation, with 5 imputed data sets. Lactate and NT-proBNP were log-transformed before inclusion in logistic regression models. Other covariates were represented as categorical variables as detailed in the Table.

Prediction Models

To develop our prediction model, we compared the performance of 3 machine learning algorithms: logistic regression, random forest, and least absolute shrinkage and selection operator.[11] These 3 candidate algorithms were selected a priori because (1) they each represent a distinct class of prediction algorithm and (2) they are not excessively computationally intensive (which would preclude their incorporation into an online prediction tool). While numerous other prediction algorithms exist (eg, extreme gradient boosting, deep learning), none were evaluated in our study. We used the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement to guide the conduct and reporting of this study.[12] An R-shiny[13] web-based application was created for our final prediction model.

Using the DHS derivation cohort, we constructed prediction models using each of the 3 algorithms and the full set of covariates detailed above. The performance of each was assessed in the DHS validation cohort using model accuracy and area under the curve (AUC). We calculated accuracy using a probability of 50% as the classification threshold. We computed 95% CIs of these AUCs using bootstrapping methods. Calibration plots were also produced to evaluate the algorithms. In each of these prediction models, we accounted for missing donor covariates using multiple imputation, with 5 imputed data sets. We then performed a sensitivity analysis in which prediction models were fit and tested using a temporal split of the DHS cohort (instead of a random 1:1 split as described above); specifically, HTs performed in the years 2015 to 2018 were used as the derivation cohort, and HTs performed in 2019 to 2020 were the validation cohort.

Covariates Included in Each Analysis

The inference models (detailed in Inference Models) included all available donor covariates (19 for the DHS cohort and 16 for the nationwide cohort). The prediction models (derived and validated using the DHS cohort only, as detailed in Prediction Models) included the same covariates with the sole exception of coronary artery disease (CAD). The rationale for this was that while CAD (if known to be present) would certainly impact the likelihood of donor acceptance for HT, the extent of CAD is often unknown at the start of donor management. It is at this time point (ie, the early stages of donor management, before obtaining a coronary angiogram if it is deemed necessary) that we envision our prediction model as having the most utility. CAD was excluded as a covariate from prediction (but not inference) models accordingly.

RESULTS

Donor Characteristics, by Cohort and Outcome Status

Descriptive characteristics of donors in the DHS cohort, including the 59.8% (n=2470) accepted for transplant and the 40.2% (n=1660) not accepted for transplant, are shown in the Table. There were large differences between these 2 subgroups in donor age and coronary angiogram findings and small or moderate differences in several other risk factors. Specifically, accepted donors had mean age of 33.6 years (versus 44.3 for nonaccepted donors) and lower prevalence of CAD, smoking, diabetes, hypertension, cerebrovascular cause of death, LV dysfunction (ie, LV ejection fraction <50%), and LVH.

Similar differences in donor characteristics by acceptance status were found in the nationwide cohort (n=73 948), as detailed in Table S1. However, the proportion accepted for transplant (45.4%; $P<0.001$) was significantly lower in the nationwide (versus DHS) cohort.

Predictors of Acceptance in the DHS and Nationwide Cohorts

Associations between donor characteristics and acceptance for transplant after multivariable adjustment are shown in Figure 1. In both the DHS and nationwide long-term cohorts, factors most strongly associated with nonacceptance for transplant (odds ratio [OR], <0.4 for all) included older age, hepatitis C infection, LV dysfunction, CAD, and blood type AB.

In both cohorts, smaller (ORs, 0.4–0.8) but significant associations with nonacceptance were observed for diabetes, female sex, blood types A and B, hypertension, and troponin >100× the upper limit of normal. Head trauma as the cause of death was associated with a significantly higher likelihood of acceptance in both the DHS (OR, 1.69 [1.34–2.12]) and nationwide long-term (OR, 2.05 [1.95–2.16]) cohorts.

The absence of a coronary angiogram was significantly associated with nonacceptance, although with varying effect size by cohort and presence of CAD risk factors. LVH (measured only in the DHS cohort) was a significant predictor of nonacceptance, both when mild (OR, 0.52 [0.40–0.67]) and when moderate or severe (OR, 0.23 [0.15–0.34]). Other covariates measured only in the DHS cohort, including NT-proBNP (OR per log-unit increase, 0.92 [0.84–0.99]), lactate (OR, 0.88 [0.73–1.06]), and weekend/holiday offers (OR, 0.84 [0.69–1.01]), predicted nonacceptance with varying statistical significance.

Change in Predictors of Acceptance Over Time in the Nationwide Cohort

In a model using time-interaction terms in the nationwide long-term cohort (as detailed in the Methods), several predictors of nonacceptance had decreasing influence over time (had time-interaction terms that were positive and statistically significant). These are indicated by arrows in Figure 1B and include hepatitis C positivity (*P* value for time interaction, <0.0001), mild LV dysfunction (LV ejection fraction, 40%–49%; *P*=0.012), minor CAD (*P*<0.0001), hypertension (*P*=0.028), elevated troponin (>100× upper limit of normal; *P*=0.0029), cocaine use (*P*=0.035), and Public Health Service increased risk (which captures drug use and other high-risk behaviors, as detailed in the Supplemental Methods; *P*=0.0012). In contrast, both age 35 to 49 years (*P* value for time interaction, 0.022) and age ≥50 years (*P*=0.0001) were increasingly predictive of nonacceptance over time.

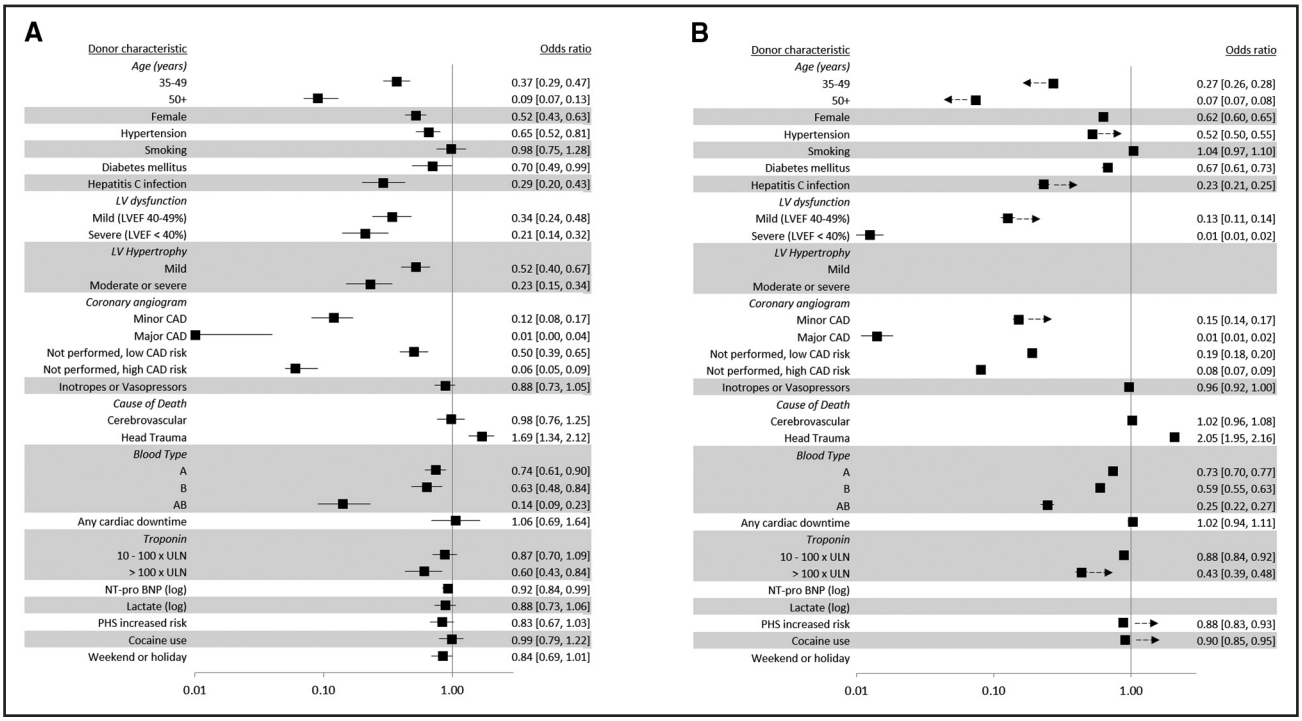

Figure 1. Forest plots of adjusted associations between donor characteristics and acceptance for heart transplant (HT) and their change over time.

A, DHS (Donor Heart Study); **B**, nationwide cohort. Shown are odds ratios and 95% CIs (in brackets) from multivariable logistic regression models as detailed in Methods. Referent groups include age <35 years, normal coronary angiogram, normal left ventricular (LV) function (LV ejection fraction [LVEF], ≥50%), male sex, anoxia or other cause of death, ABO type O, absence of LV hypertrophy, and troponin <10× upper limit of normal (ULN). Arrows in **B** indicate the direction of all statistically significant time interactions. CAD indicates coronary artery disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and PHS, Public Health Service.

Prediction Model Derived From the DHS Cohort

A detailed comparison of performance characteristics between the random forest, logistic regression, and least absolute shrinkage and selection operator–based prediction models is shown in Table S2. In summary, the random forest model outperformed the other algorithms by all metrics, with an accuracy of 0.831 and AUC of 0.908 (95% CI, 0.903–0.914) in the validation set. Its receiver operating characteristic curve and calibration plot are shown in Figure 2. By comparison, the performance metrics of the logistic (AUC, 0.839 [95% CI, 0.832–0.847]) and least absolute shrinkage and selection operator (AUC, 0.832 [95% CI, 0.824–0.840]) models were lower in the validation set. In the sensitivity analysis using a temporal split of the DHS cohort into derivation and validation sets, the performance metrics for the random forest model were slightly lower (accuracy in validation set, 0.800; AUC in validation set, 0.873 [95% CI, 0.866–0.879]) than in the base case analysis using a random (1:1) split.

The random forest algorithm incorporated all 18 candidate predictors (ie, the same 18 predictors that were specified for inclusion in the logistic regression prediction model). As our best-performing model, the random forest model and its 18 predictors were used as the basis for our web-based prediction tool (Tool to Predict Heart Acceptance for Transplant [ToP-HAT]; Figure 3), available at https://qsushiny.shinyapps.io/TOPHAT/.

DISCUSSION

Using the DHS prospective cohort of over 4000 carefully phenotyped potential heart donors, our study evaluated the donor characteristics that determine heart acceptance for transplant. As expected, abnormalities of the potential donor heart itself are most influential, but a wider array of other noncardiac donor characteristics independently predict acceptance (versus discard). We also find that these predictors of donor heart acceptance have changed significantly over the last 2 decades. Together, our findings offer insights into contemporary donor heart selection practices, which warrant scrutiny amid a persistent donor organ shortage.

As a practical extension of these analyses, we present ToP-HAT, a prediction model based on machine learning methods that performed well in a validation cohort.

Evaluation of Donor Heart Selection Practices in the Nationwide Cohort

Any scrutiny of donor heart selection practices must acknowledge the following: there is no scientific consensus regarding which factors should be considered when evaluating a potential donor for HT. Guidelines on heart donor selection (detailed in Table S3) have become less specific over time, granting greater deference to subjective clinical judgement.[6,14,15] The most recent of these (from 2020) focuses on donor age and cardiac diagnostic findings as important to consider but omits the array of noncardiac characteristics cited in prior iterations, a trend reflecting the lack of rigorous evidence regarding their effects on post-HT outcomes.[16]

We find that contemporary donor selection mirrors this guidance; age ≥50 years, severe LV dysfunction (LV ejection fraction, <40%), moderate or severe LVH,

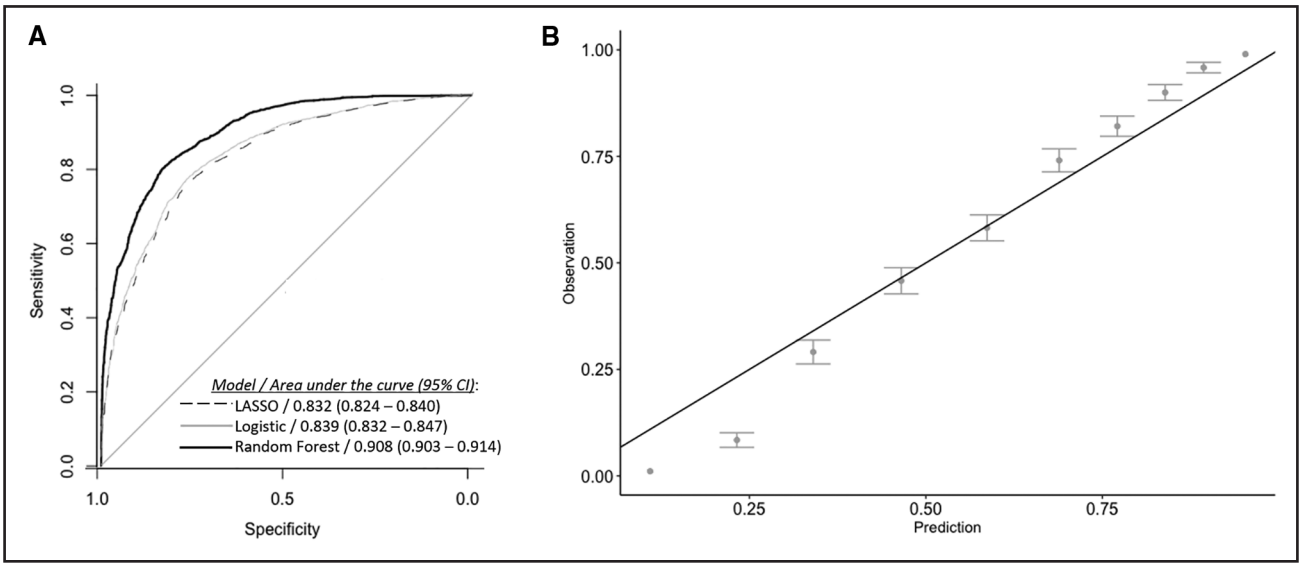

Figure 2. Receiver operating characteristic curves and calibration plot (random forest model only) for prediction models in test data set.

A, Receiver operating characteristic curves; **B**, calibration plot. LASSO indicates least absolute shrinkage and selection operator.

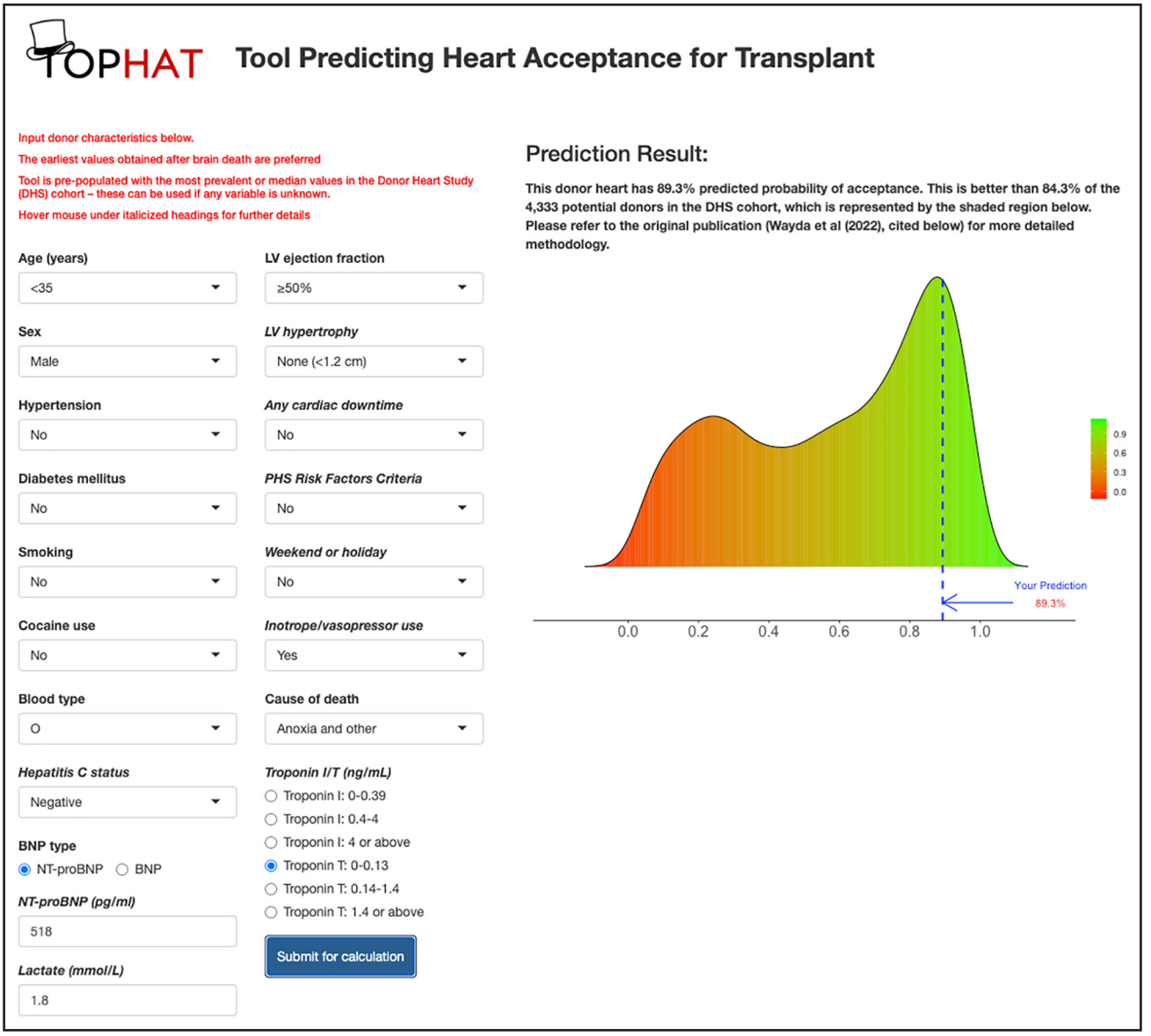

Figure 3. Screenshot of web-based Tool Predicting Heart Acceptance for Transplant (ToP-HAT).
BNP indicates B-type natriuretic peptide; DHS, Donor Heart Study; LV, left ventricle; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and PHS, Public Health Service.

and major CAD were the strongest predictors of nonacceptance. Meanwhile, risk factors related to drug use, which have no independent association with post-HT outcomes[17–20] and have been dropped from the guidelines, have had a diminishing influence on donor heart selection over time.

While agreement between guidelines and practice is always encouraging, exactly how much—and at what threshold—older age should deter donor acceptance is unclear. That donor age >50 years confers a 10-fold reduction in the odds of acceptance—even after adjusting for age-associated risk factors—seems excessive in light of the following: (1) individual centers report excellent outcomes using carefully selected donors over 50 years (ie, those without accompanying risk factors),[21–24] (2) >50-year-old donors are used routinely in other countries (eg, ≈20% of all HTs in the Eurotransplant [ET] consortium),[25] and (3) the age effect appears to be mediated by the presence of other risk factors (eg, CAD and prolonged ischemic time).[26,27]

The profound influence of cardiac diagnostic abnormalities—even in their common and milder forms—warrants similar scrutiny. While the harm posed by severe CAD or severe LVH may be self-evident, the impact of a minor (<50%) stenosis (OR for acceptance, 0.12) or mild hypertrophy (OR, 0.52) on post-HT outcomes is unclear. Donor LV dysfunction also reduces the odds of acceptance by 3-fold to 5-fold—despite prior evidence from the DHS and elsewhere that it is usually reversible and not associated with post-HT outcomes.[28–30] The

dire consequences of the ongoing donor heart scarcity demand further research into which (not whether) donors with these milder or transient abnormalities can safely be used for HT.

Clinical intuition suggests that any adverse effect of donor hypertension or diabetes on post-HT outcomes would be mediated by CAD or LVH. Yet both remain associated with nonacceptance even after multivariate adjustment; by implication, a donor with a completely normal echocardiogram and coronary angiogram will still be penalized by the presence of these comorbidities. Their relevance to donor selection should be further investigated and perhaps explicitly addressed in consensus guidelines.

Our analysis is the first to evaluate the association of donor BNP with acceptance for HT. We find its influence is small but significant (OR, 0.92; P=0.038), perhaps appropriately so, given the virtual absence of data on how to interpret donor BNP levels. Yet we recently found that it predicts the reversibility of donor LV dysfunction[30]; accordingly, the broader prognostic utility of donor BNP and other acute biomarkers warrants further study.

As previously reported, the time span of our analysis (2005–2020) has seen significant improvements in both 1-year (increasing from 88% to 91%) and 5-year (from 75% to 80%) survival among US HT recipients.[31,32] This improvement in post-HT outcomes could (in part) be driven by concurrent improvements in donor selection, including the increasing weight over time given to donor age (which is evidence based[4]) in lieu of other (not evidence based) donor risk factors. But it is equally plausible that these 2 trends are unrelated. The impact of donor risk factors on post-HT outcomes remains one of the most glaring knowledge gaps in the field of HT.

Prediction of Donor Heart Acceptance in the DHS Cohort

We present a novel prediction model to assess the likelihood of donor heart acceptance. Our model is available for real-world application, in the form of the web-based ToP-HAT calculator. Of note, 1 prior study (using a California-only, pre-2010 cohort) demonstrated the potential of random forest to predict donor heart acceptance in the United States.[33] It achieved an AUC of 0.86 in the derivation cohort (no separate validation cohort was used). Strengths unique to our current analysis include (1) the use of a contemporary nationwide cohort; (2) model assessment using a distinct validation cohort; (3) comparison of multiple prediction algorithms; (4) incorporation of novel predictors (which could explain our improved performance, with an AUC of 0.90); and perhaps most importantly, (5) the availability of our model for real-world use in the form of an online tool.

We envision the real-time use of ToP-HAT by OPO teams, as they evaluate and manage potential donors before offering organs for transplant. For context, some potential donors are promptly disqualified from HT due to known heart disease (often as the cause of death); at the other extreme are those with no cardiovascular comorbidities and a reassuring echocardiogram. In between these extremes is a large pool of heart donor candidates whose viability for HT is not immediately clear, perhaps due to risk factors for CAD or an abnormal screening

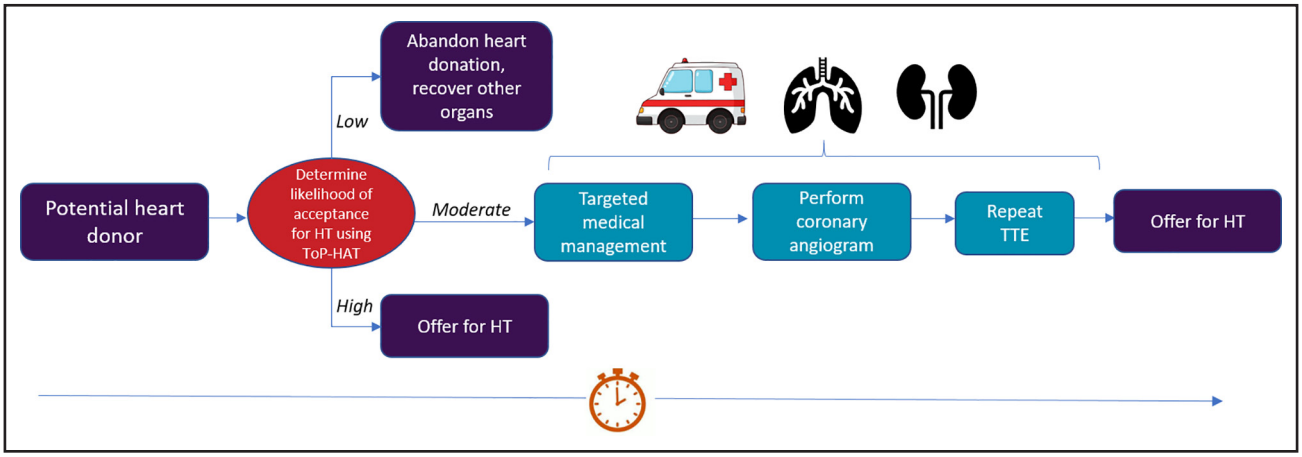

Figure 4. A potential scenario for implementation of Tool Predicting Heart Acceptance for Transplant (ToP-HAT) during donor evaluation.

For many potential donors, their viability for use in heart transplant (HT) is not clear at the early stages of donor management. Making this determination can require extensive cardiac workup including serial echocardiograms or a coronary angiogram; depending on local availability, the latter may require transfer to a different center. The resulting delay in organ recovery is resource intensive, including augmented inotropic therapy and administration of thyroid hormone or corticosteroids, and can compromise the quality of other solid organs, particularly when the donor is hemodynamically unstable. The probability of acceptance for HT—estimated early on using ToP-HAT—can help guide the decision to pursue further cardiac workup. When this probability fails to meet some reasonable threshold, then deferring evaluation for potential HT may be warranted. TTE indicates transthoracic echocardiogram.

echocardiogram. As detailed in Figure 4, whether to pursue (or defer) time-consuming and expensive cardiac evaluation for these donors is a weighty decision and could be guided by use of ToP-HAT.

Our model can also be used by transplant clinicians and centers to supplement their own subjective donor assessment. Those on donor call, evaluating a specific offer might wonder: would other centers be likely to accept this donor? Centers with low donor utilization could ask, are we turning down donors that other centers would elect to accept? ToP-HAT can be used to answer both of these questions.

Study Limitations

While our study utilized distinct patient cohorts for training and validation, these 2 cohorts are random subsets of the same underlying population. Such internal validation can result in overfitting of the model, and prospective deployment of the model in other cohorts may not perform as well. Yet since our cohort was geographically diverse (consisting of 8 OPOs spanning all US regions), we suspect that our model's component predictors and overall performance will translate to non-DHS OPOs in the United States. Unfortunately, external validation of our model in other US populations was not feasible, as there is no large donor cohort data of comparable detail.

We are less confident regarding how our model would perform in a non-US cohort. A recent analysis comparing donor selection practices in the United States and ET—a consortium of 8 European countries—shows that donor acceptance practices differ significantly between these 2 large transplant systems.[34] For example, donor age is a much weaker predictor of nonacceptance in ET than the United States, likely by necessity, given ET's much older pool of potential donors. Thus an ET-derived prediction model, such as the previously published Heart Donor Score,[35] would likely outperform our model in the ET context. However, an update of this score might be warranted, as it was derived from a pre-2010 cohort.

As our study shows, donor acceptance practices are in flux, likely influenced by evolving evidence, by the size and composition of the potential donor (and recipient) pool, and by a myriad of other time- and place-specific factors. Our model does not capture this variation; its predictions reflect aggregate behavior and must be interpreted in the local context. Its use to predict acceptance for declaration of circulatory death donors (excluded from our cohort) is not recommended.

Despite its unprecedented detail, the DHS omits some potentially relevant donor data points (eg, invasive hemodynamic measures, which are not systematically collected during donor management, and specific circumstances of death) that could influence acceptance for HT. Other variables that could influence donor acceptance decisions (but were lacking on our data sets) include suspected malignancy, a potential vegetation seen on echocardiogram, and hypoxemia on the ventilator. Factors related to the many potential recipients of a given donor (eg, size matching and geographic distance between the potential recipients and the donor) could not be included in our analysis (as they would vary widely by recipient for a given donor). For some measured risk factors (eg, cocaine use, diabetes), we lacked data on their severity and duration, which (if known to clinicians at the time of donor selection) could influence acceptance decisions. The omission of some risk factors and incomplete characterization of others constrains the performance of our prediction model, and our identified predictors of acceptance may be partly capturing the influence of these unobserved variables.

In conclusion, our study has (1) evaluated the wide array of factors that determine donor acceptance for HT and (2) developed a model to enable real-time prediction of donor heart acceptance. Both can help improve the efficiency of the organ evaluation and allocation process and can inform clinical practice and policy efforts to safely increase donor heart utilization for HT, thereby granting more patients access to this life-saving therapy.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Supplemental Methods
Tables S1–S3
Figure S1
Reference 36

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