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Creation of a Quantitative Recipient Risk Index for Mortality Prediction After Cardiac Transplantation (IMPACT)

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Background. No recipient risk index exists predicting short-term mortality after orthotopic heart transplantation (OHT). We utilized United Network for Organ Sharing (UNOS) data to develop a novel quantitative recipient risk score for use in OHT.

Methods. A prospectively collected open cohort of 21,378 primary OHT patients (1997 to 2008) was randomly divided into subgroups. The training cohort (n = 17,079) was used for score derivation and the test cohort (n = 4,299) was used for independent validation. Recipient specific variables associated with 1-year mortality (exploratory p value < 0.2) were incorporated stepwise into a multivariable logistic regression model. The final model contained variables which maximized explanatory power (assessed by pseudo R2, area under the curve, and likelihood-ratio test). A risk index was created by apportioning points approximating the relative impact of variables on 1-year mortality. The Kaplan-Meier method was used to assess impact of risk score on short-term survival.

Results. The 50-point scoring system incorporated 12 recipient specific variables. Derivation and validation cohort scores ranged from 0 to 33 and 0 to 27, respectively (mean 6.1 ± 3.7 and 6.1 ± 3.7). Each point increased the odds of 1-year death by 14% in the derivation cohort (odds ratio 1.14 [1.13 to 1.15], $p < 0.001$) and 15% in the validation cohort (odds ratio 1.15 [1.12 to 1.17], $p < 0001$). One-year survivals in the validation cohort (by increments of 3 points) were the following: 0 to 2 (92.5%); 3 to 5 (89.9%); 7 to 9 (86.3%); and 10 or greater (74.9%); $p < 0.001$. Patients transplanted with risk scores of 20 or higher had 1-year mortality rates greater than 50%.

Conclusions. We present a novel internally validated OHT recipient risk score, which is highly predictive of 1-year mortality. This risk index may prove valuable for patient prognosis, organ allocation, and research stratification in OHT.

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Since Lower and colleagues [1] described their initial technique approximately 50 years ago, orthotopic heart transplantation (OHT) has emerged as the gold standard surgical treatment for patients with end-stage heart failure. The unfortunate reality is that with substantial resource requirements and limited donor supply, OHT cannot be provided to all end-stage heart failure patients. Consequently, outcomes and patient selection are highly scrutinized by payers, the public, and the lay press.

Identification of mortality risk factors is an important focus of outcomes research in OHT. Although donor [2] and institutional factors [3, 4] are frequently cited as contributory, much attention has appropriately focused on optimizing recipient selection [5–8]. Data from large cohorts such as the ISHLT (International Society of Heart and Lung Transplantation) data set provide valuable insight into potentially predictive recipient factors for OHT outcomes [6, 9]. However, no accepted and validated composite tool for assessment of recipient risk prior to and following OHT currently exists.

Our objective was to utilize United Network for Organ Sharing (UNOS) data to create and validate a risk index based solely on recipient factors for accurate prediction of short-term mortality in OHT. The primary goals were to generate a score which combined accuracy, predictive accuracy, and simplicity to aid practitioners in identifying high-risk recipients. We surmise that this index could serve to drive clinical decisions regarding allocation of marginal organs and may prove especially useful in an era of increasing ventricular assist device (VAD) utilization. It further may offer predictive capabilities for recipients and their families and aid in future epidemiologic investigations.

Material and Methods

Data Source

The UNOS provided Standard Transplant Analysis and Research files with donor-specific and follow-up data from

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October 1, 1987 to December 31, 2010. The data set comprises a prospectively collected sample of all thoracic transplantation patients in the United States. No patient or center identifiers were included and the study was granted Institutional Review Board exemption at our institution.

Study Design

We examined all primary, adult (>17 years) OHT patients from January 1997 to December 2008 with follow-up through December 2010, excluding patients receiving simultaneous transplantation of another organ (n = 418) and those with total artificial hearts (n = 46). For validation, the cohort was randomly divided into 2 subcohorts. The training set or derivation cohort comprised 80% of the total sample and the test set or validation cohort comprised the remaining 20%. All score derivation was performed on the training set and then independently validated in the test set. We focused solely on variables specific to the recipient (ie, recipient age) and excluded variables solely involving donors (ie, donor age) or those that involved both donor and recipient (ie, human leukocyte antigen match). We stratified VAD usage into 3 categories; extracorporeal (grouped with extracorporeal membrane oxygenation termed "temporary support"), early-generation paracorporeal and intracorporeal pulsatile flow VADs, and late-generation continuous flow VADs (see legend of Table 1 for full details).The primary endpoint was 1-year post-OHT mortality.

Analysis

The UNOS data set utilized contained 461 variables. All variables with plausibility for predicting 1-year mortality were tested using univariate logistic regression in the derivation sample. Those associated with 1-year mortality on exploratory analysis ($p \leq 0.2$) were incorporated into a multivariable logistic regression model. Spline terms were utilized when appropriate and potential interactions between covariates were thoroughly tested. As models were constructed by casewise deletion, covariates with greater than 15% missing data were excluded.

The final model contained factors that improved the explanatory power as assessed by Akaike information criterion, likelihood ratio test, area under the receiver

Table 1. Baseline Characteristics Among the Derivation and Validation Cohorts

Characteristic	Derivation Cohort (n = 17,079)	Validation Cohort (n = 4,299)	*p* Value[a]
Demographics			
Age (mean ± SD)	52.1 (± 11.9)	51.8 (± 12.1)	0.17
Female	4,048/17,079 (23.7%)	101/4,299 (23.7%)	0.98
Caucasian	12,947/17,007 (76.1%)	3,235/4,285 (75.5%)	0.39
Diagnosis			
Idiopathic	7,050/17,079 (42.1%)	1,809/4,299 (42.1%)	0.34
Ischemic	8,118/17,079 (47.1%)	2,024/4,299 (47.1%)	0.59
Congenital	400/17,079 (2.3%)	106/4,299 (2.5%)	0.63
Other	1,511/17,079 (8.8%)	360/4,299 (8.4%)	0.33
Acuity			
UNOS status I[b]	12,988/17,076 (76.0%)	3,254/4,381 (75.8%)	0.71
HTN	5,579/14,224 (39.2%)	1,414/3,612 (39.1%)	0.93
Diabetes mellitus	3,618/16,718 (21.6%)	857/4,200 (20.4%)	0.08
Creatinine clearance[c]	66.3 (± 25.8)	66.0 (± 25.6)	0.50
Serum bilirubin	1.24 (± 2.11)	1.31 (± 2.27)	0.07
PVR	2.72 (± 1.97)	2.66 (± 1.94)	0.09
Preop mechanical ventilation	456/17,079 (2.7%)	108/4,299 (2.5%)	0.56
Ischemic time (hours)	3.15 (± 1.04)	3.13 (± 1.06)	0.73
Temporary circulatory support[d]	240/17,079 (1.4%)	46/4,299 (1.1%)	0.09
Ventricular assist device			
Early generation[e]	2,298/17,079 (13.5%)	586/4,299 (13.6%)	0.76
Late generation[f]	374/17,079 (2.2%)	87/4,299 (2.0%)	0.5
IABP	927/17,079 (5.4%)	220/4,299 (5.1%)	0.42

[a] *p* value based on the Student *t* test (continuous variables) or χ^2 test (categoric variables). [b] Indicates UNOS status 1a, 1b, or older status 1. [c] based on Cockcroft-Gault calculation: = {[140-age (years)] × weight (kg)/[7.2 × plasma creatinine (mg/dL)]} × (0.85 if female)[Ref 19]. [d] Includes ECMO and [or] extracorporeal VADs; ie, Abiomed BVS5000 (Abiomed, Inc, Danvers, MA), Bio-Medicus (Medtronic Inc, Eden Prairie, MN), TandemHeart (Cardiac Assist, Inc, Pittsburg, PA), and Levitronix/Centrimag(Levitronix, Waltham, MA). [e] Early generation includes para and intracorporeal pulsatile VADs, including Abiomed AB5000, Heartmate I, XE, and XVE, ThortecIVAD (Thoratec Corp, Pleasanton, CA), Toyobo(Toybo Osaka, Japan), Novacor (World Heart Inc, Oakland, CA), Medos (Medos, Stolberg, Germany), and LionHeart (Arrow International Inc, Reading PA). [f] Later generation continuous VADs including Heartmate II, Jarvik (Jarvik Heart Inc, New York, NY), Micromed, Debakey (MicroMed Technology Inc, Houston, TX), and VentrAssist(Ventracor, Sydney, Australia).

ECMO = extracorporeal membrane oxygenation; HTN = hypertension; IABP = intraaortic balloon pump; PVR = pulmonary vascular resistance; UNOS = United Network for Organ Sharing; VADs = ventricular assist devices.

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operating curve, and the Hosmer-Lemeshow goodness of fit test. Automated forward and backward stepwise selection processes and cross validation were employed to determine if the final constructed model was optimal. To assess importance of missing data, multiple imputation (ie, replacement of missing values for variables utilizing bootstrap methods) was carried out on the final model and compared with the model constructed utilizing casewise deletion.

Score Generation

From the final model a 50 point recipient risk score (Index for Mortality Prediction After Cardiac Transplantation [IMPACT]) was created approximating the magnitude of relative odds of 1-year mortality and applied independently to all members of the derivation and validation sets. Cumulative survival was estimated using the Kaplan-Meier method, with censoring for those individuals lost to follow-up or alive at the end of study time (administratively censored). All means are presented with standard deviations, medians with interquartile ranges, and odds ratios with 95% confidence intervals. Statistical analyses were performed with STATA software (v9.2 SE; StataCorp LP, College Station, TX).

Results

Cohort Statistics

A total of 21,378 patients comprised the sample. The mean age was 52.0 ± 12.0 years with 23.7% (n = 5,066) females. A total of 7,421 patients died during the study period (incidence rate of 6.55 deaths/100 person-years). The Kaplan-Meier cumulative incidence of 1-year mortality was 13.2% (n = 2,802). Random stratification yielded a derivation cohort (n = 17,079, 80% of total sample) and validation cohort (n = 4,299, 20% of total sample). The cohorts were predictably similar in key preoperative variables (Table 1).

Variables Examined in the Derivation Cohort

Exploratory univariate logistic regression in the derivation cohort identified 19 recipient variables which significantly increased the risk of 1-year mortality. Of these, 12 met criteria for multivariable inclusion (Table 2). These 12 variables improved the Akaike information criterion and all showed significant likelihood ratio test results ($p < 0.05$). The C-index for the final model was 0.65. Additionally, the nonsignificant Hosmer-Lemeshow χ^2 statistic of 5.21 ($p = 0.73$) indicated that the final model appropriately fit the data.

Examining the associated variables, we observed a strong relationship between those associated with recipient support and mortality. Specifically, those patients who required temporary circulatory support (defined as extracorporeal membrane oxygenation) or extracorporeal VADs (Table 1) comprised 1.4% of the sample (n = 240) but had a 28.9% higher rate of 1-year mortality than those without temporary support (41.8% vs 12.9%, $p < 0.001$) (Fig 1). Patients requiring pre-OHT mechanical ventilation had a 22.3% increased rate of 1-year mortality versus those patients not on mechanical ventilation (35.1% vs 12.8%, $p < 0.001$). Similar trends were seen for dialysis, intraaortic balloon counterpulsation, and other VADs (with the exception of Heartmate II [Jarvik Heart Inc, New York, NY]) (Fig 1).

Score Generation

Using the relative odds generated from the multivariable analysis we assigned points to create a recipient risk score (0 to 50 points) (Table 2). In the derivation cohort, recipient scores were minimally positively skewed in distribution, ranging from 0 to 33, with the mean score 6.1 ± 3.7 points (Fig 2).

The score was confirmed to be associated with risk of 1-year mortality in the derivation cohort when examined on both univariate (odds ratio for 1-year mortality 1.14 [1.13 to 1.15], $p < 0.001$) and multivariable analysis (odds ratio 1.13 [1.12 to 1.14], $p < 0.001$), adjusted for ischemic time and donor age. Each 1-point increase correlated with a 14% increase in the odds of 1-year mortality on unadjusted analysis (Fig 3). The equation for predicted probability of 1-year mortality is provided in Figure 3A along with predicted probabilities of 1-year mortality for scores in the derivation cohort. The correlation coefficient between predicted and observed mortality was 0.95.

Score Validation

In the validation cohort (n = 4,299), scores similarly centered around a mean of 6.1 ± 3.7 and ranged from 0 to 27 (Fig 2). The IMPACT score demonstrated good predictive accuracy when examined as a continuous variable as each 1-point increase predicted a 15% increase in the odds of 1-year mortality on both univariate analysis (OR 1.15 (1.12 to 1.17)], $p < 0.001$) and after adjustment for donor age and ischemic time (OR 1.14 [1.11 to 1.17], $p <$ 0001) (Fig 3). In both the derivation and validation cohorts, predicted mortality conformed to the observed mortality up to a score of approximately 20, where small sample size and outliers skewed the relationship between predicted and observed 1-year mortality (Fig 3).

Survival

When examining Kaplan-Meier survival, recipient risk score (incrementally stratified) again showed accuracy in the derivation cohort and predictive accuracy in the validation cohort as lower risk scores correlated with improved survival. Specifically, in the derivation cohort, those patients with scores 15 or greater had a 34.9% lower 1-year cumulative survival than those in the 0 to 2 point range (92.5% vs 57.6%, $p < 0.001$) (Fig 4). Similarly, the validation cohort showed a 32% lower 1-year cumulative survival for patients with high-risk indices (92.6% vs 60.6%, $p < 0.001$) (Fig 4).

Effect of Donor Age and Ischemic Time

To examine the effect of risk score across a range of donor conditions, recipients were stratified by risk score, donor age, and ischemic time in a pooled analysis (n = 21,378). When the entire cohort was combined

Table 2. Univariate and Multivariable Logistic Regression Used to Generate Recipient Risk Score

Covariates[a]	Univariate Analysis OR (95% CI)	*p* Value	Multivariable Analysis OR (95% CI)	*p* Value[b]	Points Assigned
Age greater than 60	1.29 (1.18–1.43)	<0.001	1.35 (1.21–1.50)	<0.001	3
Bilirubin (serum)					
0–0.99	Reference		Reference		
1–1.99	1.30 (1.17–1.44)	<0.001	1.28 (1.14–1.43)	<0.001	1
2–3.99	1.70 (1.46–1.98)	<0.001	1.49 (1.27–1.75)	<0.001	3
≥4	2.12 (1.85–2.44)	<0.001	1.96 (1.68–2.29)	<0.001	4
Creatinine clearance					
>50 mL/minute	Reference		Reference		0
30–49 mL/minute	1.10 (1.00–1.22)	0.04	1.21 (1.07–1.35)	0.001	2
<30 mL/minute	2.89 (2.32–3.58)	<0.001	2.45 (1.93–3.11)	<0.001	5
Dialysis between listing and transplant	3.11 (2.46–3.94)	<0.001	1.93 (1.49–2.51)	<0.001	4
Female sex	1.18 (1.07–1.31)	0.001	1.39 (1.23–1.57)	<0.001	3
Heart failure etiology					
Ideopathic	Reference		Reference		0
Ischemic	1.26 (1.15–1.39	<0.001	1.30 (1.16–1.45)	<0.001	2
Congenital	2.57 (2.02–3.26)	<0.001	2.80 (2.15–3.65)	<0.001	5
Other	1.25 (1.06–1.47)	0.008	1.22 (1.02–1.46)	0.02	1
Infection	1.68 (1.47–1.91)	<0.001	1.33 (1.16–1.54)	<0.001	3
IABP	1.70 (1.44–2.02)	<0.001	1.26 (1.04–1.53)	0.02	3
Mechanical ventilation prior to transplant	3.69 (3.02–4.51)	<0.001	2.10 (1.66–2.67)	<0.001	5
Race					
Caucasian	Reference		Reference		
African American	1.19 (1.05–1.34)	0.005	1.36 (1.19–1.56)	<0.001	3
Hispanic	1.01 (0.84–1.21)	0.94	1.07 (0.88–1.30)	0.65	0
Other	1.08 (0.81–1.43)	0.61	0.98 (0.72–1.34)	0.90	0
Temporary circulatory support	5.42 (4.08–7.42)	<0.001	3.26 (2.35–4.53)	<0.001	7
Ventricular assist device					
Older gen pulsatile	1.34 (1.19–1.52)	<0.001	1.30 (1.14–1.50)	<0.001	3
New gen continuous (excluding HMII)	1.99 (1.07–3.69)	0.03	2.04 (1.06–3.97)	0.03	5
Heartmate II	1.07 (0.77–1.50)	0.68	1.22 (0.87–1.72)	0.25	0
Total points possible	–	–	–	–	50 points

[a] Variables significant on univariate analysis not meeting criteria for multivariable inclusion (ie, missing data, collinearity, or failure to improve the explanatory power) included education level, HTN, PVR, transfusion prior to transplant, pre-OHT inhaled nitric oxide, panel reactive antibody level, and cachexia (body mass index <18.5). [b] *p* value based on multivariable logistic regression.

CI = confidence interval; HTN = hypertension; IABP = intraaortic balloon pump; OHT = orthotopic heart transplantation; OR = odds ratio; PVR = pulmonary vascular resistance.

in this fashion, 1-year mortality increased in an incremental fashion with increasing donor age and longer ischemic times ($p < 0.001$ for each). The greatest incidence of 1-year mortality occurred for those patients receiving an organ from a donor over age 50 with an ischemic time of greater than 4 hours (mortality = 41.7% [33.4 to 51.2], n = 121) (Table 3).

Comment

In this study we utilized UNOS data to design an easily calculable recipient specific risk index for OHT. Our goals were threefold: (1) Accuracy in the sample from which it was derived; (2) predictive accuracy in an independent sample from which it was not derived; and (3) simplicity, to aid clinicians in assessing recipient risk in real time.

We believe the derived risk index succeeds in these principal aims. We utilized rigorous statistical methods to identify and choose variables which significantly increased the explanatory power of our multivariable logistic model. We employed cross validation, multiple imputation, and automated stepwise methodology to confirm that our variable choices were accurate. To create an index which was understandable and easy to apply, we chose to apportion points that approximated the relative magnitude of the regression coefficients. This strategy provided a practical index that the clinician can rapidly apply when evaluating a potential recipient. The 12 variables which ultimately comprised the 50-point IMPACT score represent those most significantly affecting 1-year mortality for recipients receiving first time heart transplantation.

This strong association is evident by a 14% increase in the odds of death with each 1-point increase in risk score in the derivation cohort. Although this is expected, the relationship was independent of donor

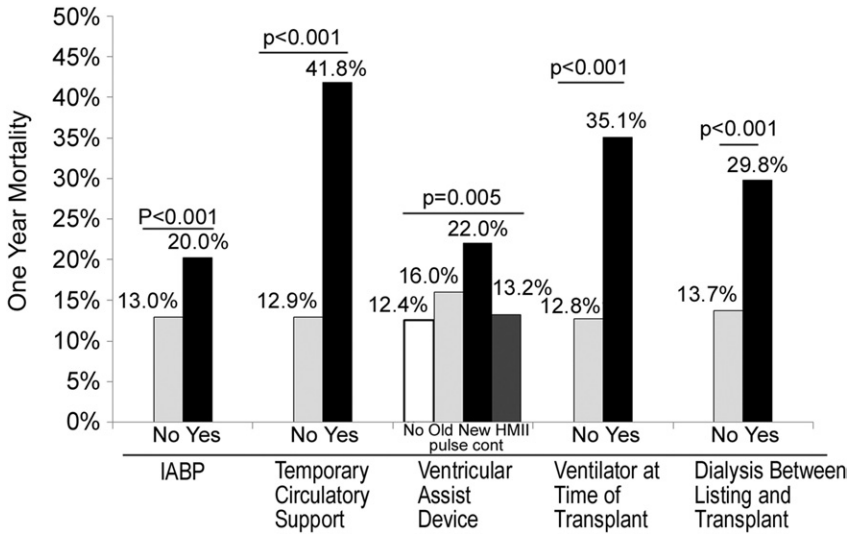


Fig 1. Kaplan-Meier risk of 1-year cumulative mortality by recipient variables. (HMII = Heart Mate II; IABP = intraaortic balloon pump.)

risk, persisting after adjusting for donor age and ischemic time.

More important was the observed association between risk score and mortality in the validation cohort. Specifically, for this group there was also a 15% increase in the odds of death with each 1-point increase in score, which persisted with inclusion of donor age and ischemic time. Risk score in incremental values also were strongly associated with mortality. In the validation cohort, those patients with risk scores of 15 or greater had a Kaplan-Meier 1-year survival of 60.6%, 32% lower than those with risk scores of 0 to 2 points.

In the pooled analysis, ischemic time and donor age in a dichotomous fashion had an additive effect on 1-year mortality. For patients with short ischemic time (<4 hours) and young donors (<50 years), lowest risk patients (0 to 2 points) had a 1-year mortality of 6.3%. This roughly doubled to 15.6% in the high-risk group (≥ 10 points). Similarly, patients receiving hearts from older donors with increased ischemic times also showed a doubling of 1-year mortality when examining those with low versus high IMPACT scores (24.5% vs 41.7%). Although in this study we specifically chose to focus on the recipient irrespective of the donor, the additive influence on mortality for donor and recipient factors may allow addition of donor factors to the recipient risk score in future iterations.

Application of the IMPACT Score

A strength of the derived score is ease of application. There are 50 points, additive in nature, with prediction of 1-year mortality given by a formula in Figure 3A. To provide a clinical example, a young (<60 years) female patient with idiopathic cardiomyopathy, creatinine clearance of 40 mL per minute, without requiring mechanical circulatory support would have an IMPACT score of 5 (3 points for female and 2 points for creatinine clearance). Her expected 1-year survival is 89% (based on the chart in Fig 3). By contrast, a 65-year-old woman with ischemic cardiomyopathy, on a balloon pump, with a recently treated pneumonia would have an IMPACT score of 12 (3 points for female, 2 points for ischemic, 3 points for IABP, 3 points for infection). Her predicted 1-year survival is only 76.6%. In the overall sample, the actual 1-year survival for patients with IMPACT scores of 5 and 12 were 89.0% and 73.1%, respectively, clearly close to the predicted values.

Notable Variables

For the 12 variables used in the index, each strongly predicted recipient 1-year mortality on multivariable analysis. From single and multiinstitutional data, we expected age, bilirubin, creatinine clearance, infection, dialysis, race, gender, heart failure etiology, IABP, tem-

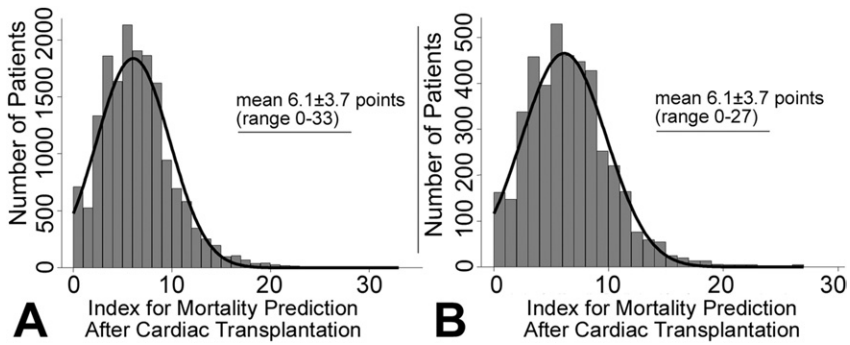
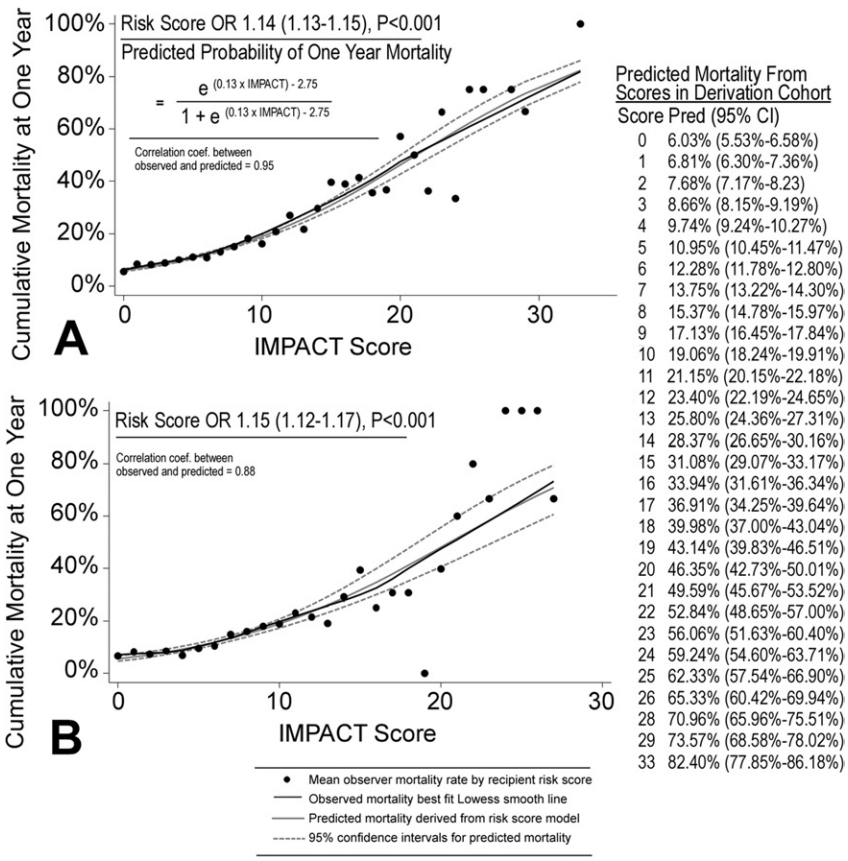


Fig 2. Distribution of recipient risk index in derivation (A) and validation (B) cohorts.



Predicted Mortality From Scores in Derivation Cohort

Score	Pred (95% CI)
0	6.03% (5.53%-6.58%)
1	6.81% (6.30%-7.36%)
2	7.68% (7.17%-8.23)
3	8.66% (8.15%-9.19%)
4	9.74% (9.24%-10.27%)
5	10.95% (10.45%-11.47%)
6	12.28% (11.78%-12.80%)
7	13.75% (13.22%-14.30%)
8	15.37% (14.78%-15.97%)
9	17.13% (16.45%-17.84%)
10	19.06% (18.24%-19.91%)
11	21.15% (20.15%-22.18%)
12	23.40% (22.19%-24.65%)
13	25.80% (24.36%-27.31%)
14	28.37% (26.65%-30.16%)
15	31.08% (29.07%-33.17%)
16	33.94% (31.61%-36.34%)
17	36.91% (34.25%-39.64%)
18	39.98% (37.00%-43.04%)
19	43.14% (39.83%-46.51%)
20	46.35% (42.73%-50.01%)
21	49.59% (45.67%-53.52%)
22	52.84% (48.65%-57.00%)
23	56.06% (51.63%-60.40%)
24	59.24% (54.60%-63.71%)
25	62.33% (57.54%-66.90%)
26	65.33% (60.42%-69.94%)
28	70.96% (65.96%-75.51%)
29	73.57% (68.58%-78.02%)
33	82.40% (77.85%-86.18%)

Fig 3. Observed versus expected (predicted) 1-year mortality with 95% confidence interval (CI) of the predicted mortality (dashed lines) for both derivation (A) and validation (B) cohorts. Equations predicting 1-year mortality provided along predicted mortality for scores in the derivation cohort. (IMPACT = index for mortality prediction after cardiac transplantation; OR = odds ratio.)

porary support, and mechanical ventilation to be associated with short-term mortality [2, 7–12]. The inclusion of VADs in the scoring system is perhaps more controversial. Though some single-center studies have demonstrated improvement in post-OHT survival with VADs compared with historical controls [13, 14], ISHLT registry data suggest that bridge to transplant with assist devices is associated with an approximate doubling in risk of 1-year post-OHT mortality [6, 9]. A recent study by Patlolla and colleagues [15] using UNOS data identified both intracorporeal and extracorporeal VADs to increase the hazard for death within 6 months of transplantation (hazard ratio 1.20 and hazard ratio 1.99 for intracorporeal and extracorporeal, respectively). This position was challenged by Russo and colleagues [16] who identified lower survival with extracorporeal VADs but not those placed intracorporeally.

In this study we chose to stratify VADs into those used for temporary support (extracorporeal, which we grouped with extracorporeal membrane oxygenation), older generation pulsatile, and newer generation continuous flow VADs. We found all types of VADs, with the exception of the Heartmate II continuous flow device, to increase 1-year mortality. Why we have different findings regarding VADs from the study by Russo and colleagues [16] using UNOS data is unclear. One reason may be that our sample spans a greater time period by 5 years and contains 66% more VAD patients (n = 1,193 in excess). Further, Russo and colleagues separated pulsatile flow VADs into paracorporeal and intracorporeal. We did not believe this to be an appropriate division given poor coding of paracorporeal VADs in the UNOS data set and therefore did not stratify in this manner. Notably, when we reran our analysis with this division we did find both intracorporeal and paracorporeal pulsatile VADs similarly to be associated with increased mortality.

Utility of Risk Index in OHT

Clinical risk scores abound for general cardiac surgery patients [17] but not for OHT. The OHT population has a heavy burden of comorbid disease; often surviving on mechanical circulatory support, frequently cared for at high-volume tertiary centers, and requiring highly specialized teams for preoperative, intraoperative, and postoperative care [4]. Predicting risk for this unique population requires a uniquely derived risk score which heretofore has not existed for OHT. Our literature review identified only 1 published abstract, by Segovia and colleagues [18], utilizing 6 variables to predict primary graft failure with no comment on validation.

We believe our index predicting mortality after cardiac transplantation has a role in clinical heart transplantation. Limited resources necessitate proper recipient selection and poor choices are costly from a societal standpoint. The increased use of mechanical circulatory support (particularly for prolonged times as in "bridge to recovery" patients) further places an onus on health providers to identify patients likely to realize maximum benefit from transplan-

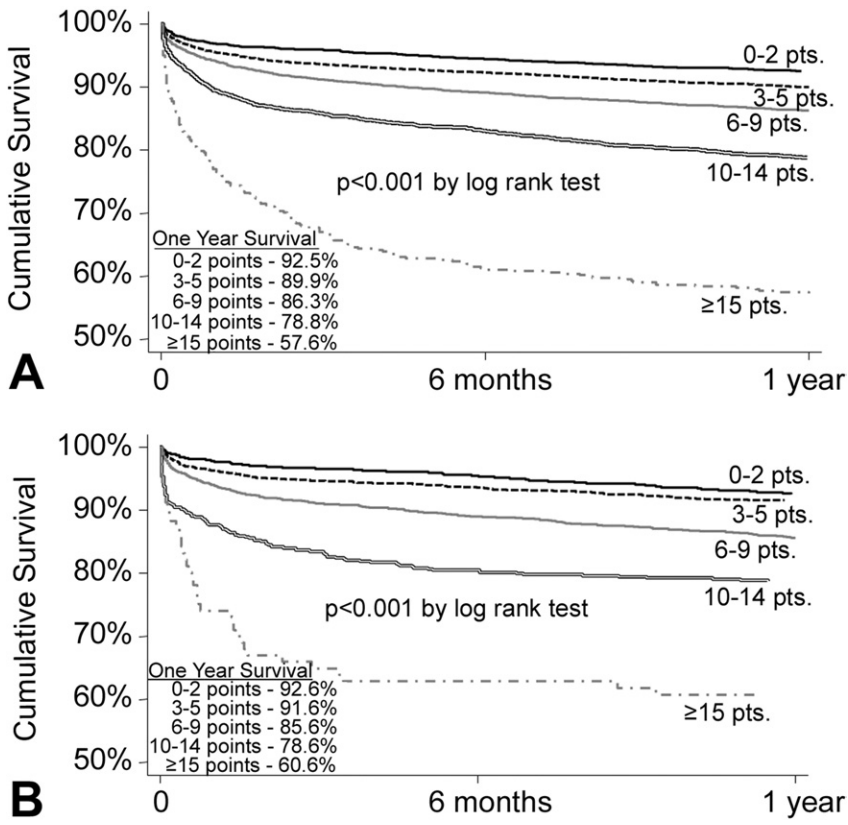


Fig 4. Kaplan-Meier cumulative 1-year survival of recipients in the derivation cohort (A) and validation cohort (B) as stratified by 3-point increments of risk score.

tation. Further, as outcomes become more heavily scrutinized by the public, payers, and press, we will see focus on those factors portending successful OHT outcomes. We believe that our index can add value to the current state of OHT by aiding in organ selection, influencing policy regarding allocation, predicting recipient prognosis, and facilitating future research.

Limitations

Our study has limited follow-up and lack of control of potential confounders. Validation is an important component of clinical scoring systems. We utilized cross validation, with derivation within a random subset and validation in the remainder of the sample. Although we believe our methodology did not introduce bias into the validation, we acknowledge that our recipient index will benefit from external validation in an independent sample. Data regarding VAD type are largely missing in the registry (of all patients listed as having a VAD, only approximately 50% have device type available). We acknowledge that inability to finely discriminate among VAD types limits this study.

Conclusions

We have analyzed over 21,000 OHT recipients to design an easily calculable, 50-point recipient risk index for use in OHT. It was designed to predict 1-year posttransplant mortality, based solely on recipient factors, and proved accurate in the derivation sample with predictive accuracy in the validation sample. This risk index can serve to drive clinical decisions regarding allocation of marginal organs and prove especially useful in an era of increasing

Table 3. Kaplan-Meier Cumulative Risk of 1-Year Mortality With 95% Confidence Intervals, Stratified by Score and Donor Characteristics (n = 21,378)

Group	0–2.9 Points	3–5.9 Points	6–9.9 Points	≥10 Points
Donor age <50 Ischemic time < 4 hours	6.3% (5.4–7.3) n = 2,353	8.9% (8.1–9.7) n = 4,871	12.2% (11.4–13.2) n = 5,181	15.6% (14.3–17.0) n = 1,927
Donor age ≥ 50 Ischemic time < 4 hours	12.9% (9.7–18.9) n = 172	12.4% (9.8–15.6) n = 497	15.6% (12.9–18.9) n = 606	26.4% (21.6–32.2) n = 271
Donor age ≥ 50 Ischemic time ≥ 4 hours	24.5% (15.1–38.4) n = 53	15.7% (10.6–22.9) n = 140	22.0% (17.2–28.0) n = 228	41.7% (33.4–51.2) n = 121

VAD use. It further offers predictive capabilities for recipients and may aid in future epidemiologic investigations.

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DISCUSSION

DR NILOO EDWARDS (Madison, WI): I had two questions. One of them was, I was surprised to see that cachexia was not on your list of variables since that seems to be a fairly strong predictor. The second is what the impact of era is. Since early on, ventricular assist devices [VAD] clearly had a negative effect if you were bridged to transplant. In the current era, most centers, like ours, see no difference in patients who are bridged to transplant with a VAD versus going straight to transplant, meaning that the negative impact of the VAD has gone away. So, since your data set goes back to '97, maybe some of the data was valid but isn't valid.

DR WEISS: Those are both excellent questions. I agree with you that cachexia does impact mortality although its effect is complex. In our analysis of the data set, it seems to impact mortality more for those on the waitlist than those who ultimately undergo transplantation. Why this occurs in unclear. We included cachexia in our exploratory analysis and it didn't ultimately improve our multivariable model, and therefore we didn't include it in the risk score.

Your VAD point is very interesting. Up until recently, I didn't feel that data on VADs was valid within the UNOS [United Network for Organ Sharing] data set. There was so much missing data that we never included VADs in our earlier studies. But in the past three years there has been a much greater increase in the quality of the data available on ventricular assist devices in the UNOS data set and as a result, there have been many studies that have looked at this issue. With that said, data on ventricular assist devices still continues to be problematic in the UNOS data set. Of those patients who have VADs, half of the data on device type is not available. In this study we attempted to discriminate VAD types based on era of usage (ie, older pulsatile flow versus newer continuous flow VADs) and therefore hopefully have addressed concerns regarding era of VADs. We also incorporated time into the analysis and stratified based on era so we feel our results are valid despite the 12-year time period.

DR YOSHIYA TOYODA (Pittsburgh, PA): We all know even low-risk recipients can have a bad outcome if you choose a bad donor. So what are your thoughts on creating such a system, taking into account the donor factors, more detailed donor factors, such as size mismatch, gender mismatch, older donors, or IV [intravenous] drug abuse?

DR WEISS: It is a great question. One of the problems with outcomes analysis is that individual patients are not a database, and studies like this can reveal general trends but may not apply to an individual patient sitting in your office or laying on a hospital bed waiting for transplant. Clearly, the interactions between donor and recipient factors that you are describing are important.

Our goal in creating this risk score was primarily to have a baseline level of risk for an individual recipient irrespective of the donor. We made sure to adjust for ischemic time and donor age to prove that high-risk patients were doing worse beyond being paired with high-risk donors. In future iterations we plan to determine what additional risks there are; whether it be pure donor factors, sex mismatch, size mismatch, as well as institutional factors, volume, surgeon experience, and hospital experience, etcetera, and take those into account. However, since there currently isn't a defined system for assessing baseline recipient risk, this seemed like an appropriate place to start.

DR KEITH B. ALLEN (Kansas City, MO): I congratulate you on your talk. Considering the scarcity of organs and the increased scrutiny that transplant programs have with regard to benchmarking for mortality at one and three years, how do you think this data might play into transplant center selection process for hearts?

DR WEISS: It is a good question. It is also a difficult question and one that really delves more into ethical and political implications as opposed to purely scientific. I should say first that the study was not designed to address the difference between pretransplant wait list survival and posttransplant survival, unlike the lung allocation score for example. By looking purely at post transplant survival there may be missing factors that come into play in a decision whether or not to transplant a patient. With that said, clearly there are patients who are too high acuity to expect a reasonable outcome and there has to be a cutoff. As you pointed out, donor hearts are scarce and will continue to be so until we have tissue generation, as we heard about yesterday. We hope that this score will quantify risk for recipients and allow centers to make responsible decisions regarding who they transplant.

DR HOWARD SONG (Portland, OR): Eric, did your data set include information on patients at the time of listing, and have you worked toward developing some kind of net benefit analysis? If not, can you comment on what some of the barriers to that are since you have worked extensively with the UNOS database?

DR WEISS: The short answer to your question is that yes, we are working on it. The UNOS wait list data is quite good, and this is something that can be developed. The issue is complex because some factors that strongly affect survival on the wait list are different from those that affect survival after transplant, and so teasing out those differences complex. But yes, this is an active area of investigation for us.

DR NICHOLAS G. SMEDIRA (Cleveland, OH): Eric, do you think someone on ECMO [extracorporeal membrane oxygenation] and mechanical ventilation should get 10 points automatically? Isn't that double jeopardy?

DR WEISS: Yes, there is that potential and it is a weakness of this approach which we acknowledge. Because those two risk factors are not mutually exclusive in the data set, there are patients who can have either one or both. For this reason, we kept them separate in the score. We did thoroughly test interactions between all variables and did not find any that significantly affected mortality. You are right though, some of the variables are closely associated but I think the thing to remember is that the score, as it is constructed, strongly and accurately predicts mortality. That's the most important point.