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Survival Benefit From Transplantation in Patients Listed for Heart Transplantation in the United States

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Objectives The aim of this study was to assess the survival benefit from heart transplantation (HT), defined as reduction in the risks for 90-day and 1-year mortality on undergoing HT close to listing, in candidates stratified by their risk for waiting list mortality.

Background Among patients listed for HT, those at higher risk for death without transplantation are also at higher risk for early post-transplantation mortality.

Methods All patients age ≥18 years listed for HT in the United States from 2007 to 2010 were analyzed. A model was developed to predict the risk for waiting list mortality within 90 days, and listed patients were stratified into 10 risk groups (deciles). All groups were followed for 1 year to assess cumulative 1-year mortality while on the waiting list. Models of 90-day and 1-year post-transplantation mortality were developed using recipient data, and these risks were estimated at listing in all listed candidates.

Results Of 10,159 patients listed for HT, 596 (5.9%) died within 90 days and 1,054 (10.4%) within 1 year without undergoing transplantation. Of 5,720 recipients of transplants with 1-year follow-up, 576 (10.1%) died within 1 year. The risk for death while on the waiting list within 90 days increased from 1.6% to 19% across the 10 risk groups. The survival benefit from HT increased progressively with higher risk for death without transplantation ($p < 0.001$ for trend), but there was no benefit in the first 6 risk groups.

Conclusions The risk for waiting list mortality varies considerably among HT candidates. Although the survival benefit of HT generally increases with increasing risk for waiting list mortality, there is no measurable benefit in many candidates at the lower end of the risk spectrum. (J Am Coll Cardiol 2014;63:1169–78) © 2014 by the American College of Cardiology Foundation

Heart transplantation (HT) is an established therapy for end-stage heart failure (1,2). Although the number of patients listed for HT in the United States continues to increase, the supply of donor hearts remains relatively unchanged (1,3). To minimize mortality in patients awaiting HT, the U.S. allocation policy has prioritized sicker candidates to receive donor hearts since the early days of transplantation (4,5). In the current 3-tier system, a patient may be listed as status 2, 1B, or 1A on the basis of criteria intended to represent increasing medical urgency. These groups are then assigned progressively higher priority during allocation (6). Because not all candidates listed at the highest urgency status (1A) share a similar risk for death while waiting, some experts have argued for a re-examination and revision of the current allocation algorithm (7,8).

See page 1179

Previous studies have suggested that sicker patients among those listed for HT are also at higher risk for post-transplantation mortality (5). Although prioritizing donor hearts to candidates on the basis of transplantation urgency is justified as fairness or justice, whether it is also justifiable on the basis of higher survival benefit to such patients is unknown (9,10). A better understanding of the relationship of the survival benefit from HT with increasing risk for death on the

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JACC Vol. 63, No. 12, 2014
April 1, 2014:1169–78

Abbreviations and Acronyms

HT = heart transplantation

LVAD = left ventricular assist device

OPTN = Organ Procurement and Transplantation Network

UNOS = United Network for Organ Sharing

waiting list will be valuable not only to the physicians caring for patients with heart failure but also to the allocation experts responsible for refining the heart allocation algorithm.

We hypothesized that the survival benefit from HT estimated at the time of listing will be higher in patients at higher risk for death while on the waiting list. The specific objectives of this study were: 1) to risk-stratify patients listed for HT on the basis of their risk for death without HT within 90 days of listing; and 2) to quantify the survival benefit of HT across risk strata of waiting list mortality.

Methods

Study population. We identified all patients aged ≥ 18 years in the Organ Procurement and Transplantation Network (OPTN) database listed for their first HT in the United States between January 1, 2007, and December 31, 2010. The OPTN database includes demographic and clinical information at the time of listing in all HT candidates and at the time of transplantation in all heart transplant recipients in the United States, submitted by transplantation centers. These data are supplemented with death data in patients ever listed for HT (including for patients removed from the waiting list before undergoing HT) from the Social Security Death Master File and are provided to investigators as deidentified data. The Health Resources and Services Administration of the U.S. Department of Health and Human Services provides oversight of the activities of the OPTN contractor, the United Network for Organ Sharing (UNOS). We excluded patients who were listed for heart retransplantation or multiple-organ transplantation. Post-transplantation outcomes were analyzed in study subjects who underwent HT between January 1, 2007 and March 1, 2011. This allowed us to analyze at least 1 year of post-transplantation follow-up in all HT recipients.

Study design and definitions. The primary hypothesis was that the survival benefit from HT estimated at the time of listing would be higher in patients who were at higher risk for death without HT. Survival benefit was quantified on the basis of the estimated 90-day and 1-year risks for death without HT and with HT after listing. We first developed a risk prediction model for 90-day waiting list mortality using clinical data in listed patients and used this model to stratify listed patients into 10 groups (approximate deciles) on the basis of a progressively higher risk for death. We then developed risk prediction models for 90-day and 1-year post-transplantation mortality using clinical data at transplantation in heart transplant recipients. We applied these models to all listed patients at the time of listing and estimated these risks in each of the 10 risk groups at listing. Survival benefit was quantified in each risk group as the reduction in risks for 90-day and 1-year mortality on undergoing HT close to listing.

The primary endpoints were death without HT (while listed or after removal from the list) and death after HT. Demographic and clinical variables were defined at listing to develop the model for death without HT and at transplantation to develop models for death after HT. Race or ethnicity was recorded as reported by the transplantation center and analyzed as white (non-Hispanic white), black (non-Hispanic black), Hispanic, or other. Renal function was analyzed as estimated glomerular filtration rate (ml/min/1.73 m^2) using the Modification of Diet in Renal Disease formula (11,12).

None of the subjects had any missing data for the following variables: age, sex, race or ethnicity, cardiac diagnosis, blood type, hemodynamic support (intra-aortic balloon pump, inotrope support, ventilator, type of mechanical support), medical insurance (Medicaid), UNOS listing status, dialysis, and the dates of listing, transplantation, death, or removal from the waiting list. We imputed glomerular filtration rate values for patients with missing values at listing (0.8%) or at transplantation (0.6%) using a multiple imputation technique and clinical variables at listing and transplantation, respectively.

Statistical analysis. Summary data are presented as median (25th percentile, 75th percentile) or number (percent). Waiting list outcomes in study patients were first assessed using competing outcomes analysis (13,14). Median waiting list time, overall and by listing status, was estimated using the Kaplan-Meier method. A multivariate logistic regression model for 90-day mortality without HT was developed using variables at listing retaining variables significant at the 0.10 level on the basis of a likelihood ratio test. Model discrimination was assessed using the area under the receiver-operating characteristic curve (C-statistic) and calibration using the Hosmer-Lemeshow goodness-of-fit test. The model was internally validated using a bootstrapping technique (200 random samples, 10,159 patients in each sample with replacement). The model was used to quantify the probability of death within 90 days in each listed patient by applying model variables in that patient to the model. Listed patients were stratified into 10 groups on the basis of increasing risk for 90-day mortality without HT (approximate deciles). Observed cumulative 1-year mortality without HT was assessed in each of the 10 risk groups.

We developed risk prediction models for 90-day and 1-year post-transplantation mortality in heart transplant recipients using logistic regression and variable values at transplantation. We internally validated these models using bootstrapping, as outlined previously. We used these models to quantify the probability of 90-day and 1-year post-transplantation mortality at the time of listing in each listed patient by applying variable values at listing to the model. The survival benefit from HT at 90 days was calculated by subtracting the risk for 90-day post-transplantation mortality from the risk for 90-day mortality without HT in each risk group. Survival benefit at 1-year was calculated by subtracting the risk for

1-year post-transplantation mortality from observed 1-year mortality in each risk group. Social factors such as race or ethnicity, education, type of medical insurance, and regional or center characteristics (such as center volume) were not considered in the evaluation of survival benefit and thus in developing risk models.

Data were analyzed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina). All statistical tests were 2-sided, and p values <0.05 were used to define statistical significance.

Results

Study population. During the study period, 10,754 patients age ≥18 years were listed for HT in the United States. Of these, 273 patients were listed for multiple-organ transplantation and 322 for heart retransplantation. The remaining 10,159 patients formed the study cohort. Of these, 4,773 (47%) had dilated cardiomyopathy and 3,704 (37%) had ischemic cardiomyopathy (see Table 1 for baseline characteristics at listing). The median age of the

Table 1 Baseline Characteristics of Patients at Listing by Diagnosis

Variable	Dilated CMP (n = 4,773)	Ischemic CMP (n = 3,704)	Other (n = 1,682)	Total (n = 10,159)	p Value
Age (yrs)					<0.001
18–39	1,130 (24%)	112 (3.0%)	431 (26%)	1,673 (17%)	
40–59	2,529 (53%)	1,771 (48%)	803 (48%)	5,103 (50%)	
60–69	1,058 (22%)	1,699 (46%)	413 (25%)	3,170 (31%)	
≥70	56 (1.2%)	122 (3.3%)	35 (2.1%)	213 (2.1%)	
Men	3,253 (68%)	3,207 (87%)	1,153 (69%)	7,613 (75%)	<0.001
Blood type					<0.001
A	1,691 (35%)	1,575 (43%)	667 (40%)	3,933 (39%)	
B	671 (14%)	452 (12%)	202 (12%)	1,325 (13%)	
O	2,215 (46%)	1,515 (41%)	752 (45%)	4,482 (44%)	
AB	196 (4.1%)	162 (4.4%)	61 (3.6%)	419 (4.1%)	
Listing status					<0.001
1A	964 (20%)	804 (22%)	295 (18%)	2,063 (20%)	
1B	2,149 (45%)	1,315 (36%)	499 (30%)	3,963 (39%)	
2	1,660 (35%)	1,585 (43%)	888 (53%)	4,133 (41%)	
Diabetes					<0.001
Type 1	116 (2.4%)	175 (4.7%)	36 (2.1%)	327 (3.2%)	
Type 2	897 (20%)	1,197 (32%)	246 (15%)	2,340 (23%)	
ICD	3,875 (81%)	2,938 (79%)	1,066 (63%)	7,879 (78%)	<0.001
PAP (mm Hg) (n = 9,331)	31 (24, 38)	30 (23, 38)	29 (21, 36)	30 (23, 38)	<0.001
PWP (mm Hg) (n = 8,964)	21 (15, 27)	20 (14, 26)	20 (14, 25)	20 (15, 27)	<0.001
Ventilation	91 (1.9%)	132 (3.6%)	40 (2.4%)	263 (2.6%)	<0.001
IABP	246 (5.2%)	258 (7.0%)	79 (4.7%)	583 (5.7%)	<0.001
Temporary support					<0.001
ECMO	16 (0.3%)	18 (0.5%)	21 (1.2%)	55 (0.5%)	
Non-ECMO	19 (0.4%)	31 (0.8%)	11 (0.7%)	61 (0.6%)	
Durable support					<0.001
Total artificial heart	26 (0.5%)	12 (0.3%)	8 (0.5%)	46 (0.5%)	
BIVAD	110 (2.3%)	93 (2.5%)	39 (2.3%)	242 (2.4%)	
Pulsatile LVAD	162 (3.4%)	178 (4.8%)	58 (3.4%)	398 (3.9%)	
Continuous-flow LVAD	523 (11%)	396 (11%)	90 (5.4%)	1,009 (9.9%)	
Inotropes	1,770 (37%)	1,146 (31%)	459 (27%)	3,375 (33%)	<0.001
GFR category (ml/min/1.73 m^2)					<0.001
Dialysis	76 (1.6%)	62 (1.7%)	38 (2.3%)	176 (1.7%)	
<30	177 (3.7%)	146 (3.9%)	58 (3.4%)	381 (3.8%)	
30–60	1,795 (38%)	1,632 (44%)	644 (38%)	4,071 (40%)	
≥60	2,725 (57%)	1,864 (50%)	942 (56%)	5,531 (54%)	
Race/ethnicity					<0.001
White	2,725 (57%)	2,953 (80%)	1,272 (76%)	6,950 (68%)	
Black	1,482 (31%)	382 (10%)	223 (13%)	2,087 (21%)	
Hispanic	412 (8.6%)	224 (6.0%)	126 (7.5%)	762 (7.5%)	
Other	154 (3.2%)	145 (3.9%)	61 (3.6%)	360 (3.5%)	

Values are n (%) or median (25th percentile, 75th percentile).

BIVAD = biventricular assist device; CMP = cardiomyopathy; ECMO = extracorporeal membrane oxygenation; GFR = glomerular filtration rate; IABP = intra-aortic balloon pump; ICD = implantable cardiac defibrillator; PAP = pulmonary artery pressure; PWP = pulmonary artery wedge pressure.

JACC Vol. 63, No. 12, 2014
April 1, 2014:1169–78

study cohort was 55 years, 20% were listed at the highest urgency listing status (1A) (6), and 18% were receiving mechanical support (including 2.4% with biventricular assist devices, 14% with durable left ventricular assist devices [LVADs], and 1.1% on temporary mechanical support).

Figure 1 illustrates competing outcomes during the first year after listing in the study cohort. Of 10,159 patients listed for HT, 5,970 (59%) underwent HT, 1,054 (10.4%) died without undergoing HT (695 deaths while on the waiting list, 359 deaths after removal from the list), and 2,759 (27%) were still waiting for HT at 1 year. Of 1,054 deaths without HT, 328 (31%) deaths occurred within 30 days, 596 (57%) within 90 days, and 810 (77%) within 180 days of listing. The median waiting list time to HT was 78 days for the entire cohort, 26 days in patients listed as status 1A, 69 days in patients listed as status 1B, and 155 days in patients listed as status 2. Post-transplantation outcomes were analyzed in 5,720 heart transplant recipients with 1-year follow-up (see Online Table 1 for baseline characteristics at transplantation). Of these, 576 patients (10.1%) died within 1 year of transplantation.

Model for 90-day waiting list mortality. A multivariate risk model for 90-day mortality without HT consisted of 7 risk factors (older age, diagnosis of restrictive cardiomyopathy, listing status 1A or 1B [6], ventilator support, intra-aortic balloon pump, mechanical support, and renal dysfunction) and 1 protective factor (presence of an implantable cardiac defibrillator) (Table 2). The overall model was highly significant (likelihood ratio chi-square = 427.2, Akaike information criterion = 4,538.7). The model's ability to discriminate patients who died within 90 days from those who did not (C-statistic = 0.73) and to calibrate the risk for death (Hosmer-Lemeshow p = 0.23; see Online Figure 1 for predicted vs. observed 90-day mortality among the 10 risk groups) were good. On internal validation by bootstrapping, the area under the receiver-operating characteristic curve in repeated samples ranged from 0.702 to 0.761 (mean 0.732; 95% confidence interval: 0.731 to 0.734). On the basis of this model, the probability of death within 90 days of listing without HT was calculated as: p = (X/X + 1), where X = exp(intercept + coefficient for each variable in Table 2 as it applies to the patient).

Table 2 Risk Prediction Model for 90-Day Waiting List Mortality*

Predictor	Coefficient	Odds Ratio (95% CI)
Age at listing (reference: 18–59 yrs)		
60–69 years	0.22	1.24 (1.0–1.5)
≥70 years	0.72	2.06 (1.3–3.3)
Restrictive CMP	0.78	2.17 (1.4–3.3)
Listing status (reference: status 2)		
1A	1.17	3.22 (2.5–4.2)
1B	0.76	2.14 (1.7–2.7)
Ventilation	1.06	2.88 (2.0–4.1)
Intra-aortic balloon pump	0.52	1.67 (1.3–2.2)
Mechanical support (reference: none)		
BIVAD or TAH	−0.54	0.58 (0.3–1.0)
Continuous-flow LVAD	−0.77	0.46 (0.3–0.7)
Pulsatile LVAD	0.13	1.14 (0.8–1.7)
Temporary support	0.75	2.11 (1.3–3.4)
GFR (reference: ≥60 ml/min/1.73 m^2)		
30–59 ml/min/1.73 m^2	0.46	1.58 (1.3–1.9)
<30 ml/min/1.73 m^2	1.27	3.58 (2.6–4.9)
Dialysis	1.84	6.32 (4.2–9.4)
ICD	−0.21	0.81 (0.7–1.0)
Intercept	−3.77	—

*Includes death in patients who died after removal from the list but within 90 days of listing.
CI = confidence interval; TAH = total artificial heart; other abbreviations as in Table 1.

Using the model, the risk for 90-day mortality without HT increased from 1.6% in the 1st risk group to 19% in the 10th risk group. Table 3 outlines the distribution of model risk factors among the 10 risk groups. Patients in the lowest 2 risk groups were younger, were more likely to have dilated or ischemic cardiomyopathy, were not supported on ventilators or balloon pumps, and had normal renal function at listing. They were either not receiving any mechanical support or were supported with continuous-flow LVADs. Patients in the 3rd and 4th risk groups tended to have only 1 risk factor, such as older age or moderate renal dysfunction. Patients in the 2 highest risk groups included those with multiple risk factors, such as certain types of mechanical support (temporary support, pulsatile LVAD, or biventricular assist device), ventilator support, intra-aortic balloon pump, and moderate or severe renal dysfunction (Table 3).

Models for post-transplantation mortality. Risk prediction models for post-transplantation 90-day mortality and post-transplantation 1-year mortality are shown in Table 4. Risk factors for post-transplantation 90-day mortality included older age, a diagnosis of congenital heart disease, restrictive or ischemic cardiomyopathy, ventilator support,

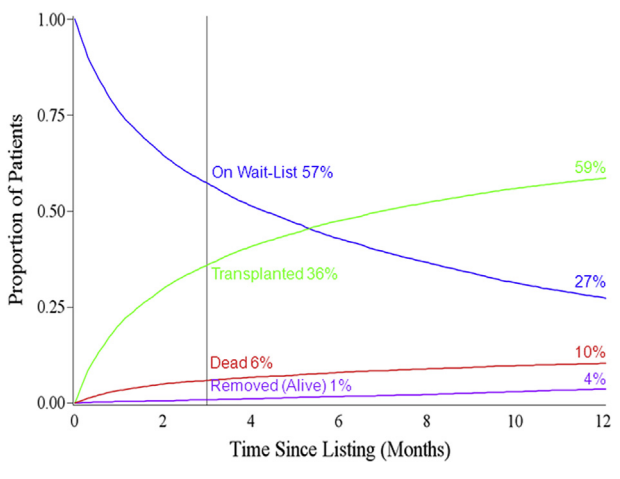

Figure 1 Competing Outcomes After Listing

Competing outcomes during the first year after listing in patients listed for heart transplantation in the United States.

Table 3 Distribution of Risk Factors for Waiting List Mortality Among Risk Groups

	Waiting List Risk Group									
Risk Factor	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Age (yrs)										
18–59	1,387 (21%)	403 (5.9%)	939 (14%)	244 (3.6%)	959 (14%)	410 (6.1%)	962 (14%)	378 (5.6%)	531 (7.8%)	563 (8.3%)
60–69	26 (0.8%)	65 (2.1%)	560 (18%)	697 (22%)	6 (0.2%)	449 (14%)	124 (3.9%)	541 (17%)	351 (11%)	351 (11%)
≥70	0 (0%)	0 (0%)	1 (0.5%)	1 (0.5%)	24 (11%)	2 (0.9%)	58 (27%)	8 (3.8%)	34 (16%)	85 (40%)
Restrictive CMP	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	28 (11%)	54 (21%)	9 (3.5%)	77 (30%)	89 (35%)
Listing status										
1A	0 (0%)	0 (0%)	103 (5%)	96 (4.7%)	0 (0%)	115 (5.6%)	301 (15%)	283 (14%)	547 (27%)	618 (30%)
1B	197 (5%)	137 (3.5%)	131 (3.3%)	85 (2.1%)	954 (24%)	625 (16%)	731 (18%)	577 (15%)	201 (5.1%)	325 (8.2%)
2	1,216 (29%)	331 (8%)	1,266 (31%)	761 (18%)	35 (0.8%)	121 (2.9%)	112 (2.7%)	67 (1.6%)	168 (4.1%)	56 (1.4%)
Ventilator support	0 (0%)	0 (0%)	1 (0.4%)	1 (0.4%)	3 (1.1%)	1 (0.4%)	6 (2.3%)	7 (2.7%)	31 (12%)	213 (81%)
IABP	2 (0.3%)	1 (0.2%)	0 (0%)	15 (2.6%)	8 (1.4%)	14 (2.4%)	13 (2.2%)	27 (4.6%)	113 (19%)	390 (67%)
Mechanical support										
Temporary support	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	2 (1.7%)	0 (0%)	1 (0.9%)	8 (6.9%)	104 (90%)
BIVAD or TAH	4 (1.6%)	3 (1.2%)	32 (13%)	26 (10%)	5 (2.0%)	60 (24%)	22 (8.7%)	30 (12%)	16 (6.3%)	54 (21%)
Pulsatile LVAD	0 (0%)	6 (1.7%)	3 (0.8%)	8 (2.2%)	0 (0%)	48 (13%)	39 (11%)	76 (21%)	106 (29%)	77 (21%)
Continuous LVAD	273 (27%)	142 (14%)	205 (20%)	158 (16%)	4 (0.4%)	80 (8.0%)	56 (5.6%)	20 (2.0%)	43 (4.3%)	25 (2.5%)
None of the above	1,136 (14%)	317 (3.8%)	1,260 (15%)	750 (8.9%)	979 (12%)	671 (8%)	1,027 (12%)	800 (9.5%)	743 (8.8%)	739 (8.8%)
GFR at listing (ml/min/1.73 m^2)										
Dialysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	45 (26%)	131 (74%)
<30	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0 (0%)	51 (13%)	81 (21%)	246 (65%)
30–59	22 (0.5%)	7 (0.2%)	809 (20%)	823 (20%)	5 (0.1%)	157 (3.9%)	745 (18%)	596 (15%)	522 (13%)	385 (9.5%)
≥60	1,391 (25%)	461 (8.3%)	691 (13%)	118 (2.1%)	983 (18%)	703 (13%)	399 (7.2%)	280 (5.1%)	268 (4.8%)	237 (4.3%)
ICD	1,393 (18%)	70 (0.9%)	1,392 (18%)	734 (9.3%)	986 (13%)	478 (6.1%)	995 (13%)	674 (8.6%)	594 (7.5%)	563 (7.1%)

Values are n (%).

Abbreviations as in Tables 1 and 2.

Table 4 Risk Prediction Models for 90-Day and 1-Year Post-Transplantation Mortality

Predictor	Coefficient (90-Day Mortality)	Odds Ratio (95% CI)	Coefficient (1-Year Mortality)	Odds Ratio (95% CI)
Age (reference: 18–59 yrs)				
60–69 yrs	0.48	1.6 (1.3–2.1)	0.37	1.45 (1.2–1.8)
≥70 yrs	0.46	1.6 (0.8–3.1)	0.31	1.36 (0.8–2.3)
Diagnosis				
CHD	1.46	4.3 (2.4–7.7)	1.06	2.87 (1.7–4.8)
Ischemic CMP	0.37	1.5 (1.1–1.8)	0.28	1.32 (1.1–1.6)
Restrictive	0.73	2.1 (1.1–3.9)	0.93	2.54 (1.6–4.0)
Ventilation	0.90	2.5 (1.6–3.9)	0.63	1.88 (1.3–2.8)
Mechanical support (reference: none)				
BIVAD or TAH	0.85	2.4 (1.5–3.6)	0.76	2.13 (1.5–3.0)
LVAD	0.45	1.6 (1.2 2.0)	0.36	1.43 (1.2–1.85)
ECMO	2.21	9.2 (4.6–18.1)	1.70	5.49 (2.9–10.5)
Non-ECMO temporary support	1.54	4.7 (1.8–11.9)	1.45	4.25 (1.9–9.5)
GFR (reference: ≥90 ml/min/1.73 m^2)				
30–59 ml/min/1.73 m^2	0.41	1.5 (1.2–1.9)	0.29	1.34 (1.1–1.6)
<30 ml/min/1.73 m^2	0.65	1.9 (1.1–3.3)	0.55	1.74 (1.1–2.7)
Dialysis	0.92	2.5 (1.4–4.4)	0.96	2.60 (1.7–4.0)
Intercept	−3.69	–	−2.86	–

Abbreviations as in Tables 1 and 2.

mechanical support, and renal dysfunction at transplantation. The overall model was highly significant (likelihood ratio chi-square = 141.3, Akaike information criterion = 2,530.9). The model's ability to discriminate survivors from nonsurvivors (C-statistic = 0.67) and the calibration between predicted and observed mortality (Hosmer-Lemeshow p value = 0.48; see Online Fig. 2 for predicted vs. observed 90-day mortality among the 10 risk groups) were good. Risk factors for post-transplantation 1-year mortality were similar to those for 90-day mortality (Table 3). Although the model was highly significant (likelihood ratio chi-square = 140.0, Akaike information criterion = 3,738.5), its performance was less robust compared with the 90-day model (C-statistic = 0.63, Hosmer-Lemeshow p value = 0.43) (Online Fig. 3).

Survival benefit from HT at listing. Figure 2A illustrates the risks for 90-day mortality without HT and 90-day mortality after transplantation estimated at the time of listing among the 10 risk groups. The survival benefit from HT at 90 days (percent reduction in risk for 90-day mortality) (Fig. 2B) was negative or neutral in the lowest 6 risk groups (risk for post-transplantation mortality higher or similar to risk for waiting list mortality). Survival benefit increased from 1.2% in the 7th risk group to 8.5% in the 10th risk group (risk for waiting list mortality 19.5%, risk for post-transplantation mortality 11%). Overall, the increase in survival benefit across the 10 risk groups was significant ($p < 0.001$ for trend).

Observed 1-year mortality without HT was 5.2% in the lowest risk group and increased progressively to 26.7% in the 10th risk group (Fig. 3A). The risk for 1-year post-transplantation mortality at the time of listing was higher or similar to the observed 1-year mortality (in percent) without HT in the first 6 risk groups (Fig. 3A). Thus, there was no 1-year survival benefit from HT in the first 6 risk groups. Survival benefit increased progressively between the 7th and 10th risk groups (Fig. 3B). For the entire cohort, there was a significant association of survival benefit from HT with increasing risk for death without HT ($p < 0.001$ for trend).

Survival benefit by listing status. The observed 90-day mortality without HT was 3.2%, 6%, and 11% in patients listed as UNOS listing statuses 2, 1B, and 1A, respectively. The observed 1-year mortality without HT was 8.1%, 10.1%, and 14% in these groups, whereas the predicted 1-year post-HT mortality on undergoing HT close to listing was 9.2%, 9.2%, and 10.8%, respectively. Thus, there was no 1-year survival benefit from HT in patients listed as status 2 (−1.1%), whereas status 1A patients derived higher 1-year survival benefit (3.2%) than those listed as status 1B (0.9%).

Discussion

This study had 3 major findings. First, the risk for death within 90 days of listing varied by more than 10-fold among patients listed for HT. Second, patients at higher risk for death without HT were also at higher risk for post-transplantation mortality. However, the risk for post-transplantation mortality increased less sharply, so that there was a higher survival benefit from HT in sicker patients. Third, although the survival benefit from HT generally increased with increasing risk for waiting list mortality, there was no measurable benefit through 1 year after transplantation in many candidates at the lower end of the risk spectrum. These findings suggest that considering

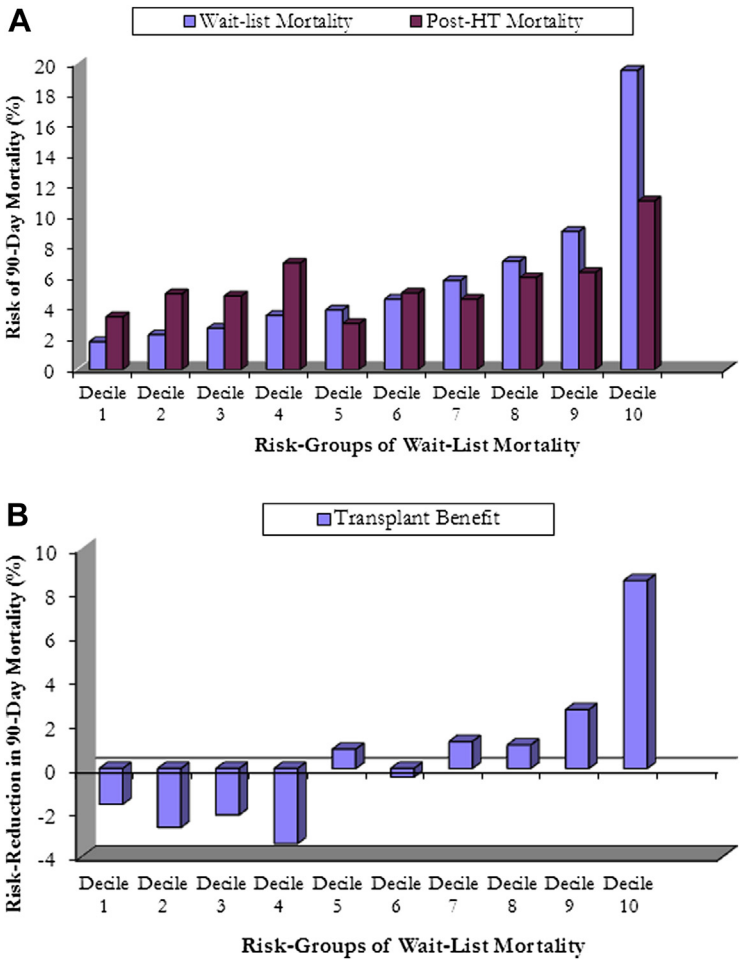

Figure 2 **Predicted Risks for 90-Day Mortality and Survival Benefit Among the 10 Risk Groups**

(A) Predicted risks for 90-day waiting list and 90-day post-transplantation mortality at listing for heart transplantation (HT) in patients with increasing risk for waiting list mortality. **(B)** Survival benefit associated with transplantation in these groups.

survival benefit from HT or improving the stratification of listed patients in prioritizing heart allocation may improve overall outcomes in patients listed for HT. Importantly, these findings support the need for a re-examination and revision of the current heart allocation algorithm in the United States and suggest one possible approach.

Principles of organ allocation. Since the early days of transplantation, the allocation of organs to listed patients has been guided by the principles of justice or fairness and utility or benefit (4,9). After the publication of the final rule in 1998 as a guide to U.S. allocation policy (10), medical urgency became the primary determinant of allocation for all organs. Allocation experts responsible for organ-specific algorithms have applied this guide differently, however. Whereas liver allografts are prioritized to patients with higher scores on a scale that reflects the risk for waiting list death within 90 days of listing (15), the allocation of hearts was changed to a 3-tier system of medical urgency instead of the older 2-tier system (4). Although the current 3-tier system prioritizes sicker candidates for heart allocation, our analysis suggests that estimating the risk for 90-day mortality using listing variables further improves their risk stratification. The final rule also emphasized the importance of avoiding futile transplantations, but only the lung allocation algorithm considers expected post-transplantation survival (and thus survival benefit) at the time of listing in a formal manner (16). The current analysis was inspired by the current lung allocation approach in the United States. The assessment of survival benefit at the time of listing is an essential step in calculating the lung allocation score and is based on the projected 1-year survival on the waiting list (without transplantation) and projected 1-year survival after transplantation, assuming the patient were to receive lungs with the listing characteristics or variables. Once listed, patients change their allocation scores only if the projected risk on either side (on the waiting list or after transplantation)

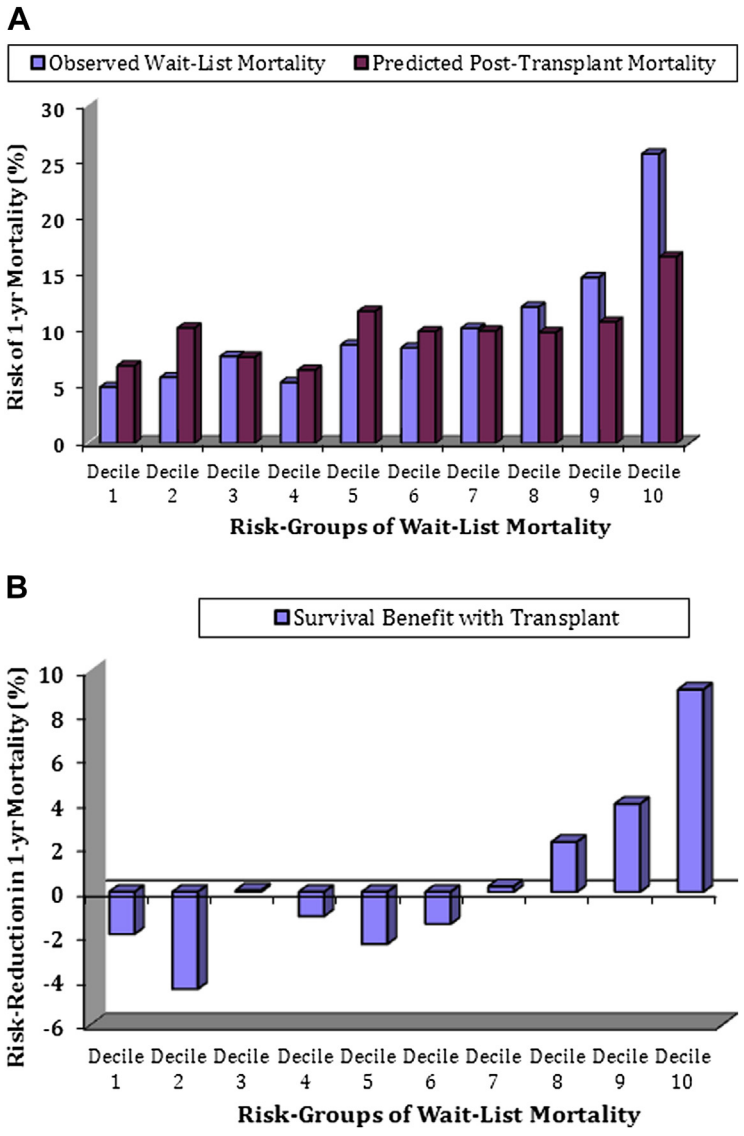

Figure 3 1-Year Mortality Without and With HT and Survival Benefit Among the 10 Risk Groups

(A) Observed 1-year waiting list mortality and predicted 1-year post-transplantation mortality at listing for heart transplantation (HT) in patient-groups with increasing risk for waiting list mortality. **(B)** Survival benefit associated with transplantation in these groups.

has changed, not because of waiting list duration. Because the survival benefit from HT in the present study appeared to be highest in patients most at risk for waiting list death, refining the current allocation algorithm such that it risk-stratifies patients better or considers survival benefit will likely prioritize similar candidates.

Although the major goals in revising the allocation are to lower overall waiting list mortality and to improve access to organs, the potential consequences for all patient groups, including those that might be deprioritized by the revision, are carefully assessed. How a revision will affect resource utilization and costs is also an important consideration. Once a patient is accepted as a candidate by a transplantation center, the overall costs of care include costs while waiting and during the post-transplantation period. Both components are higher, on average, for a higher-risk patient compared with a lower-risk patient. Earlier transplantations in higher-risk patients might lower their costs and resource utilization during pre-transplantation care. Whether the resulting savings will be sufficient to balance the increased system costs of post-transplantation care as more hearts are directed to sicker candidates will require further analysis.

Quantifying survival benefit in listed patients. Several quantitative approaches have been described to predict 1-year survival in patients with heart failure (17–20).

Comparing the expected 1-year survival of a patient on medical therapy with the current post-transplantation outcomes (1) is valuable in determining whether listing for HT should be considered. The analysis of survival benefit in the present study is very different from such comparisons, however, in that it was limited to patients already listed for HT, was applied within the context of the present allocation algorithm, and is much like the calculation of transplantation benefit at the time of listing in lung transplantation candidates, which is then used to determine lung allocation score (16). Our results illustrate that for many patients listed for HT, the real risk for death on the waiting list is not well captured by the present listing system. For example, patients supported with continuous-flow LVADs without complications appear to be at low risk for death without HT but may carry the same allocation priority as patients receiving temporary mechanical support, patients on ventilators, or those with diagnoses of restrictive cardiomyopathy who are often poor candidates for inotropes because of their risk for arrhythmias and for mechanical support because of technical challenges of LVAD implantation related to space constraints in the ventricle (Table 3) (7,8). These findings support the opinion that the current heart allocation algorithm should be amended to stay true to the spirit of the final rule (7,8).

The models to predict the risks for death after listing and in the post-transplantation period were both developed within the study cohort because no such models exist for patients on the waiting list. Furthermore, post-transplantation outcomes have continued to improve in recent years, and the study cohort consisted of very recent patients (1,21,22). It is paramount while assessing survival benefit that the risk periods assessed be identical on the post-listing and the post-transplantation side and that the models consider only those variables that are available at listing (16). We chose a 90-day period for risk stratification of listed patients because it accounted for a majority of waiting list deaths and provided excellent risk stratification of HT candidates by identifying >10-fold variability in the risk for death among groups. It may also be important that it already forms the basis of allocation in another organ (the liver) (15). Because calculating survival benefit at 90 days is unsatisfactory because of the uncertainty of subsequent post-transplantation survival, we also assessed benefit at 1 year, as is routinely done at the time of listing in lung transplantation candidates. Our results suggest that survival benefit at 90 days is a good proxy for 1-year survival benefit.

Study limitations. First, because this study was a retrospective analysis of a national database, there are potential limitations related to data quality in such data sources. It is notable, however, that data submission to UNOS is mandatory at listing and at transplantation, and the submitted data are used for real-time heart allocation. Furthermore, these data are subject to periodic audits by UNOS staff members and are also used for generating center-performance reports. Therefore, some safeguards of data quality are to be expected.

Second, because only variables recorded at listing could be used in evaluating survival benefit, potential risk factors that are currently not collected at listing, such as serum bilirubin and human leukocyte antigen sensitization, cannot be considered in assessing survival benefit.

Third, we were able to assess transplantation benefit only at the time of listing. Because the variable values may change after listing, whether the risk for death without transplantation may be predicted equally well by applying new variable values to the waiting list model or whether the additional knowledge of waiting list duration will improve such predictions is unknown. We were unable to analyze the effect of changes in patient states during the waiting list period because the OPTN database lacks these details. Simulation modeling or in-house analyses at UNOS may be able to evaluate how the waiting duration and change in listing status may alter these risks and the expected survival benefit.

Finally, the estimated risk for waiting list mortality is applicable only in the context of current heart allocation. Any changes in policy that favor the allocation of hearts to sicker patients may reduce their risk for waiting list mortality. Therefore, periodic reappraisal of risk models for waiting list and post-transplantation mortality will be essential to keep such models current.

Conclusions

The risk for waiting list mortality varies considerably among listed patients. Although survival benefit from HT generally increases with increasing risk for death while on the waiting list, there is no benefit through the first post-transplantation year in many candidates at the lower end of the risk spectrum. More complex analyses should consider how the waiting list duration and change in listing status may alter these risks and the expected survival benefit across the risk spectrum. Considering the survival benefit from HT during heart allocation may improve overall outcomes in patients listed for HT.

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Key Words: heart failure ■ heart transplantation ■ risk stratification ■ survival.

APPENDIX

For supplemental figures and tables, please see the online version of this article.