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MINI-FOCUS ISSUE: END-STAGE HEART FAILURE

Does Survival on the Heart Transplant Waiting List Depend on the Underlying Heart Disease?

Eileen M. Hsich, MD,[a,b] Joseph G. Rogers, MD,[c,d] Dennis M. McNamara, MD, MS,[e] David O. Taylor, MD,[a,b] Randall C. Starling, MD, MS,[a,b] Eugene H. Blackstone, MD,[a,b,f] Jesse D. Schold, PhD[f]

ABSTRACT

OBJECTIVES The aim of this study was to identify differences in survival on the basis of type of heart disease while awaiting orthotopic heart transplantation (OHT).

BACKGROUND Patients with restrictive cardiomyopathy (RCM), congenital heart disease (CHD), or hypertrophic cardiomyopathy (HCM) may be at a disadvantage while awaiting OHT because they often are poor candidates for mechanical circulatory support and/or inotropes.

METHODS The study included all adults in the Scientific Registry of Transplant Recipients database awaiting OHT from 2004 to 2014, and outcomes were evaluated on the basis of type of heart disease. The primary endpoint was time to all-cause mortality, censored at last patient follow-up and time of transplantation. Multivariate Cox proportional hazards modeling was performed to evaluate survival by type of cardiomyopathy.

RESULTS There were 14,447 patients with DCM, 823 with RCM, 11,799 with ischemic cardiomyopathy (ICM), 602 with HCM, 964 with CHD, 584 with valvular disease, and 1,528 in the "other" category (including 1,216 for retransplantation). During median follow-up of 3.7 months, 4,943 patients died (1,253 women, 3,690 men). After adjusting for possible confounding variables including age, renal function, inotropes, mechanical ventilation, and mechanical circulatory support, the adjusted hazard ratios by diagnoses relative to DCM were 1.70 for RCM (95% confidence interval [CI]: 1.43 to 2.02), 1.10 for ICM (95% CI: 1.03 to 1.18), 1.23 for HCM (95% CI: 0.98 to 1.54), 1.30 for valvular disease (95% CI: 1.07 to 1.57), 1.37 for CHD (95% CI: 1.17 to 1.61), and 1.51 for "other" diagnoses (95% CI: 1.34 to 1.69). Sex was a significant modifier of mortality for ICM, RCM, and "other" diagnoses ($p < 0.05$ for interaction).

CONCLUSIONS In the United States, patients with RCM, CHD, or prior heart transplantation had a higher risk for death while awaiting OHT than patients with DCM, ICM, HCM, or valvular heart disease. (J Am Coll Cardiol HF 2016;4:689–97)

From the [a]Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio; [b]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University School of Medicine, Cleveland, Ohio; [c]Division of Cardiology, Duke University, Durham, North Carolina; [d]Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; [e]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and the [f]Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio. This study was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number R56HL125420-01A1. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. John R. Teerlink, MD, served as Guest Editor for this paper.

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ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

CI = confidence interval

DCM = dilated cardiomyopathy

ECMO = extracorporeal membrane oxygenation

HCM = hypertrophic cardiomyopathy

HR = hazard ratio

IABP = intra-aortic balloon pump

ICD = implantable cardioverter-defibrillator

ICM = ischemic cardiomyopathy

LVAD = left ventricular assist device

OHT = orthotopic heart transplantation

RCM = restrictive cardiomyopathy

SRTR = Scientific Registry of Transplant Recipients

TAH = total artificial heart

UNOS = United Network for Organ Sharing

VAD = ventricular assist device

There are few studies comparing the survival of patients with different types of heart disease. Prognosis and the optimal timing to waitlist patients with advanced heart failure for orthotopic heart transplantation (OHT) are especially important among cohorts not easily rescued with inotropes or mechanical circulatory support. Studies have shown that patients with congenital heart disease (CHD) have higher 2-month mortality on the waiting list after multivariate analysis compared with patients without CHD (1) and no survival benefit with ventricular assist device (VAD) support (2). Patients with restrictive cardiomyopathy (RCM) may also be at a disadvantage (3), because VAD support is often not possible with small ventricular cavities. In addition, there is concern that patients with hypertrophic cardiomyopathy (HCM) may have a poor prognosis and may not qualify for high-priority transplantation on the basis of the current allocation system (4). In a national study analyzing survival among patients removed from the heart transplant waiting list, HCM and RCM were among the highest predictors of death (5).

The goal of this study was to evaluate whether the type of heart disease affects mortality while awaiting OHT. Because OHT is a competing outcome, differences in rate of transplantation, United Network for Organ Sharing (UNOS) status at time of transplantation, and use of VAD support were also evaluated. The cohort included all adult patients registered on the national heart transplant waitlist between January 1, 2004, and September 3, 2014.

METHODS

SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS. We used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR database includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network, and has been described elsewhere. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight for the activities of Organ Procurement and Transplantation Network and SRTR contractors. Human error in collecting data is minimized by edit checks, validation of data at the time of entry, and internal verification when there are outliers (6).

PATIENT POPULATION AND UNOS STATUS. We included all adult patients in the SRTR database placed on the waiting list for heart transplantation from January 1, 2004, to September 3, 2014. Patients <18 years of age were excluded because UNOS criteria for listing pediatric patients differed from those for adults (7).

Primary diagnosis was the principal explanatory variable and was categorized on the basis of definitions in the SRTR database: dilated cardiomyopathy (DCM), RCM (idiopathic, amyloid, endocardial fibrosis, sarcoidosis, radiation- or chemotherapy-induced heart disease, and other), ischemic cardiomyopathy (ICM), HCM, valvular heart disease, CHD, and "other" (1,216 prior heart transplantations and 312 "other" diagnoses).

UNOS status was at the time of listing for heart transplantation. UNOS status 1A (high priority) includes patients requiring intra-aortic balloon pumps (IABPs), extracorporeal membrane oxygenation (ECMO), total artificial hearts (TAHs), VADs with device complications, VADs without complications for a total of 30 days, continuous mechanical ventilation, multiple inotropes, or a single high-dose inotrope with continuous hemodynamic monitoring. UNOS status 1B is defined as a patient not meeting criteria for UNOS status 1A but still requiring continuous intravenous inotrope support or VAD support. Finally, UNOS status 2 is for all other active OHT candidates.

OUTCOME MEASURES. The primary endpoint was all-cause mortality, assessed as right-censored time to death, with follow-up censored at the time of heart transplantation. SRTR mortality data are maintained by the transplantation centers and verified with the complete Social Security Death Master File, which is recently available through a specific waiver granted to the SRTR. We also evaluated the cumulative incidence of time to transplantation on the basis of primary diagnosis, censored at the time of last patient follow-up and death.

STATISTICAL ANALYSIS. Baseline characteristics at the time of listing for OHT were stratified by type of heart disease. Continuous variables are expressed as mean ± SD. Categorical variables are expressed as number of patients with frequency (but absolute values were not provided if patient number was <10, to protect the identity of the cohort per SRTR policy). Waitlist survival analysis on the basis of type of heart disease was performed using the Kaplan-Meier method, with censoring for OHT. The primary analysis was based on intention to treat, such that deaths following removal from the waiting list were included in the primary analysis. Multivariable Cox proportional hazards models were created to compare type of

heart disease with DCM to evaluate differences in survival. The proportional hazards assumption for Cox models was evaluated using the proportionality test in PROC PHREG in SAS (SAS Institute, Cary, North Carolina). No deviations from the assumptions were noted in the analyses. Model 1 was adjusted for the following characteristics at the time of listing: age, sex, race (white, black, Hispanic, other), body mass index, insurance (private, Medicare, Medicaid, other), ABO blood type, era (January 1, 2004, to March 31, 2008, vs. April 1, 2008, to September 3, 2014, to account for U.S. Food and Drug Administration approval of left ventricular assist devices [LVADs] in 2008 that could be implanted in smaller patients), history of tobacco use, diabetes mellitus, malignancy, hypertension, prior cerebral vascular accident, peripheral vascular disease, implantable cardioverter-defibrillator (ICD), dialysis, estimated glomerular filtration rate, serum albumin, mean pulmonary artery pressure, cardiac index, mechanical ventilation, ECMO, IABP, inotropes, LVAD, right ventricular assist device ± LVAD or unspecified mechanical circulatory support, and TAH. Model 2 included UNOS status at the time of listing and all variables in model 1 except mechanical ventilation, IABP, ECMO, LVAD, right ventricular assist device, TAH, and inotropes, given that these are collinear variables that define the different UNOS tiers and highly correlate with UNOS status. Multiple imputation was used for missing data, but variables with high proportions of missingness were excluded from the model, including peak oxygen consumption (65% missingness) and antiarrhythmic agents (21% missingness). For multiple imputation, we assumed that data were missing at random. We used the SAS procedure PROC MI and generated 5 models with imputed data followed by use of PROC MIANALYZE to evaluate parameter estimates and measures of variability. As a sensitivity analysis, we generated models excluding patients with VADs at the time of listing to evaluate whether the association of primary diagnoses with outcomes was similar to the model with the entire study population. All analyses were performed using SAS version 9.4. A p value ≤0.05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION. Baseline characteristics of 30,747 adult patients with HF (25% women) awaiting OHT are shown in Table 1. This cohort included 14,447 patients with DCM, 823 with RCM, 11,799 with ICM, 602 with HCM, 964 with CHD, 584 with valvular disease, and 1,528 in the "other" category. Patients with DCM represented the largest subgroup (47% of cohort), with a mean age of 49 years. Compared with the other subgroups, patients with DCM had among the highest use of inotropes, ICDs, and permanent mechanical circulatory support (LVAD, right ventricular assist device ± LVAD, and TAH), and very few of these patients required mechanical ventilation or dialysis. Patients with RCM represented 3% of the SRTR cohort, with a mean age of 53 years. Patients with RCM had the highest percentage of prior malignancy, slightly more patients than most other groups requiring dialysis, and few patients receiving temporary (IABP and ECMO) or permanent mechanical circulatory support or mechanical ventilation. Patients with ICM represented 38% of the cohort. They were older than patients in the other subgroups, with a mean age of 58 years, and were predominately men. Patients with ICM had the highest frequency of diabetes mellitus, peripheral vascular disease, and use of permanent mechanical circulatory support. They also had high use of ICDs, and few required mechanical ventilation. Patients with HCM represented 2% of the cohort, with a mean age 46 years. They were predominately white and had the highest percentage of ICD use, and relatively few patients required mechanical circulatory support (temporary or permanent), inotropes, dialysis, or mechanical ventilation. Patients with valvular cardiomyopathy represented the smallest subgroup (2% of the cohort), with a mean age of 54 years. These patients had among the highest use of antiarrhythmic agents and inotropes and a relatively low frequency of mechanical circulatory support (temporary or permanent), dialysis, or mechanical ventilation. Patients with CHD represented 3% of the entire cohort, were the youngest patients with a mean age of 36 years, and had the lowest values of body mass index. This group was predominately white, with few black patients, had the highest percentage of Medicaid patients, and had the lowest percentage of patients with diabetes mellitus, hypertension, peripheral vascular disease, malignancy, and use of either mechanical circulatory support (temporary and permanent) or inotropes. The other" cardiomyopathy group included mostly patients listed for retransplantation (1,216 with prior OHT and 312 others) and represented 5% of the entire cohort. In this group, patients were relatively young, with a mean age of 45 years, and predominately white, and few had ICDs; they had relatively poor renal function and the highest percentage of temporary mechanical circulatory support (13%), dialysis (9%), and mechanical ventilatory support (10%).

UNOS status at the time of listing varied among the different heart diseases (Table 1). The majority of patients with DCM, ICM, or valvular heart disease were initially listed at the highest priority (UNOS statuses 1A

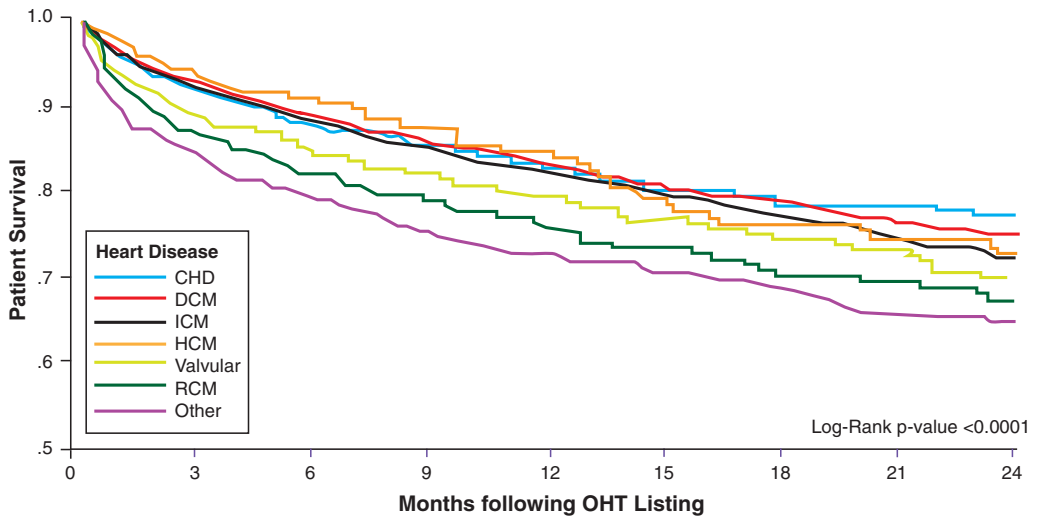
TABLE 1 Baseline Characteristics

	DCM (n = 14,447)	RCM (n = 823)	ICM (n = 11,799)	HCM (n = 602)	Valvular Heart Disease (n = 584)	CHD (n = 964)	Other (n = 1,528)
Female	4,562 (32)	291 (35)	1,556 (13)	231 (38)	208 (36)	385 (40)	535 (35)
Age, yrs	49 ± 13	53 ± 12	58 ± 8	46 ± 14	54 ± 11	36 ± 12	45 ± 15
Race							
White	8,190 (57)	600 (73)	9,380 (80)	489 (81)	396 (68)	795 (82)	1,101 (72)
Black	4,461 (31)	166 (20)	1,210 (10)	52 (9)	105 (18)	82 (9)	247 (16)
Hispanic	1,260 (9)	36 (4)	757 (6)	35 (6)	51 (9)	55 (6)	125 (8)
Other	536 (4)	21 (3)	452 (4)	26 (4)	32 (5)	32 (3)	55 (4)
Insurance							
Private	7,658 (53)	590 (72)	5,994 (51)	411 (68)	327 (56)	584 (61)	877 (57)
Medicare	3,826 (26)	157 (19)	4,142 (35)	110 (18)	170 (29)	152 (16)	400 (26)
Medicaid	2,106 (15)	40 (5)	1,028 (9)	56 (9)	63 (11)	185 (19)	188 (12)
Other	857 (6)	36 (4)	635 (5)	25 (4)	24 (4)	43 (4)	63 (4)
BMI, kg/m^2							
14–19	734 (5)	46 (6)	266 (2)	35 (6)	46 (8)	138 (14)	97 (6)
20–24	3,842 (27)	262 (32)	2,715 (23)	179 (30)	197 (34)	347 (36)	465 (30)
25–29	4,877 (34)	305 (37)	4,727 (40)	207 (34)	233 (40)	269 (28)	527 (34)
30–34	3,457 (24)	167 (20)	3,100 (26)	142 (24)	83 (14)	163 (17)	316 (21)
35–40	1,514 (10)	43 (5)	974 (8)	38 (6)	25 (4)	45 (5)	118 (8)
UNOS status							
1A	3,319 (23)	145 (18)	2,539 (22)	100 (17)	115 (20)	107 (11)	420 (27)
1B	6,089 (42)	212 (26)	4,175 (35)	164 (27)	198 (34)	259 (27)	331 (22)
2	4,421 (31)	439 (53)	4,544 (39)	330 (55)	258 (44)	569 (59)	727 (48)
Inactive	625 (4)	27 (3)	541 (5)	*	13 (2)	29 (3)	50 (3)
ABO blood type							
O	6,685 (46)	349 (42)	4,769 (40)	270 (45)	264 (45)	447 (46)	678 (44)
A	5,073 (35)	314 (38)	4,963 (42)	232 (39)	209 (36)	367 (38)	601 (39)
B	2,050 (14)	124 (15)	1,503 (13)	77 (17)	81 (14)	117 (12)	180 (12)
AB	639 (4)	36 (4)	564 (5)	23 (4)	30 (5)	33 (3)	69 (5)
Era							
1/1/2004–3/31/2008	4,729 (33)	218 (26)	4,431 (38)	195 (32)	245 (42)	339 (35)	523 (34)
4/1/2008–9/3/2014	9,718 (67)	605 (74)	7,368 (62)	407 (68)	339 (58)	625 (65)	1,005 (66)
Tobacco use	5,672 (39)	253 (31)	7,356 (62)	204 (34)	226 (39)	177 (18)	371 (24)
Diabetes mellitus	3,274 (23)	113 (14)	4,518 (38)	47 (8)	98 (17)	67 (7)	308 (20)
Hypertension	5,572 (39)	251 (31)	5,962 (51)	180 (30)	203 (35)	213 (22)	661 (43)
Malignancy	1,090 (8)	109 (13)	664 (6)	*	25 (4)	22 (2)	128 (8)
Prior CVA	655 (5)	26 (3)	619 (5)	29 (5)	30 (5)	55 (6)	66 (4)
PVD	218 (2)	14 (2)	574 (5)	*	*	17 (2)	38 (2)
Dialysis at listing	353 (2)	31 (4)	305 (3)	15 (2)	18 (3)	17 (2)	143 (9)
eGFR, ml/min/1.73 m^2	72 ± 30	66 ± 28	66 ± 26	72 ± 28	65 ± 30	84 ± 35	59 ± 31
Serum albumin, g/dl	3.6 ± 0.7	3.8 ± 0.7	3.7 ± 0.7	3.9 ± 0.7	3.8 ± 0.7	3.9 ± 0.8	3.6 ± 0.7
Mean PAP, mm Hg	30.8 ± 9.7	29.7 ± 8.6	29.8 ± 10.0	30.6 ± 9.7	30.6 ± 9.6	26.4 ± 10.9	26.1 ± 8.4
Cardiac index, l/min/m^2	2.1 ± 0.7	2.1 ± 0.6	2.2 ± 0.6	2.1 ± 0.6	2.3 ± 0.7	2.3 ± 0.7	2.2 ± 0.7
Peak Vo_2, ml/kg/min	12.0 ± 3.5	12.0 ± 3.5	11.7 ± 3.0	11.8 ± 3.5	11.3 ± 3.3	13.0 ± 3.6	12.2 ± 4.2
Antiarrhythmic agents	4,350 (30)	182 (22)	3,800 (32)	176 (29)	203 (35)	274 (28)	259 (17)
ICD	11,112 (77)	378 (46)	8,879 (75)	480 (80)	405 (69)	450 (47)	418 (27)
Inotropes	5,201 (36)	210 (26)	3,449 (29)	157 (26)	183 (31)	226 (23)	407 (27)
LVAD	2,652 (18)	31 (4)	2,314 (20)	22 (4)	46 (8)	30 (3)	63 (4)
RVAD ± LVAD or unspecified	675 (5)	16 (2)	542 (5)	11 (2)	25 (4)	20 (2)	118 (8)
TAH	69 (<1)	*	38 (<1)	*	*	*	16 (1)
IABP	670 (5)	28 (3)	714 (6)	12 (2)	14 (2)	12 (1)	94 (6)
ECMO	88 (1)	*	99 (1)	*	*	17 (18)	103 (7)
Ventilator	316 (2)	12 (2)	394 (3)	10 (2)	20 (3)	26 (27)	150 (10)

Values are mean ± SD or n (%). *n < 10 patients.

BMI = body mass index; CHD = congenital heart disease; CVA = cerebral vascular accident; DCM = dilated cardiomyopathy; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; HCM = hypertrophic cardiomyopathy; IABP = intra-aortic balloon pump; ICD = implantable cardioverter-defibrillator; ICM = ischemic cardiomyopathy; LVAD = left ventricular assist device; PAP = pulmonary artery pressure; PVD = peripheral vascular disease; RCM = restrictive cardiomyopathy; RVAD = right ventricular assist device; TAH = total artificial heart; UNOS = United Network for Organ Sharing; Vo_2 = oxygen consumption.

FIGURE 1 Survival Differences Awaiting Orthotopic Heart Transplantation Stratified by Type of Heart Disease



Kaplan-Meier survival curves while awaiting orthotopic heart transplantation (OHT) according to type of heart disease, with censoring at time of heart transplantation. CHD = congenital heart disease; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; ICM = ischemic cardiomyopathy; other = 1,216 prior heart transplantations and 312 "other" types of heart failure; RCM = restrictive cardiomyopathy; valvular = valvular heart disease.

and 1B). In contrast, the majority of patients with RCM, HCM, and CHD were initially listed at the lowest priority (UNOS status 2). About 50% of those patients with "other" heart diseases were listed as UNOS status 1, and 50% were listed as UNOS status 2.

WAITLIST MORTALITY. A total of 4,943 patients died (1,253 women, 3,690 men) during a median follow-up period of 3.7 months (interquartile range: 0.9 to 12.8 months). Patients with RCM, valvular disease, and "other" diagnoses had worse survival compared with those with all other types of heart disease listed for OHT (Figure 1). Patients with HCM awaiting OHT had the best survival for the first 12 months and survival similar to patients with ICM at 24 months by univariate analysis. After adjusting for multiple confounding variables, patients with RCM compared with those with DCM had the highest risk for mortality, followed by those with "other" diagnoses, CHD, and then valvular disease. Patients with ICM and HCM had better survival than those with the aforementioned heart diseases but a higher risk for death than those with DCM after multivariate analysis (Table 2). The risk for death for patients with RCM (hazard ratio [HR]: 1.70; 95% confidence interval [CI]: 1.43 to 2.02; $p < 0.0001$) and "other" diagnoses (HR: 1.51; 95% CI: 1.34 to 1.69; $p < 0.0001$) compared with that of patients with DCM was higher than IABP (HR: 1.43; 95% CI: 1.28 to 1.60; $p < 0.0001$), inotropes (HR: 1.38; 95% CI: 1.29 to 1.47; $p < 0.0001$), and mechanical ventilation (HR: 1.42; 95% CI: 1.24 to 1.62; $p < 0.0001$) but lower than ECMO (HR: 1.95; 95% CI: 1.61 to 2.36; $p < 0.0001$) (Online Table 1). As a sensitivity analysis, we excluded patients with VADs, and qualitative results were similar to those shown in Table 2. There was an interaction between sex and type of cardiomyopathy (Figure 2), with women at higher risk for death compared with men for ICM ($p < 0.01$) and "other" diagnoses ($p = 0.03$) and lower risk for death compared with men for RCM ($p = 0.048$).

HEART TRANSPLANTATION. The rate of heart transplantation was highest among patients with RCM or HCM and lowest among those with CHD or "other"

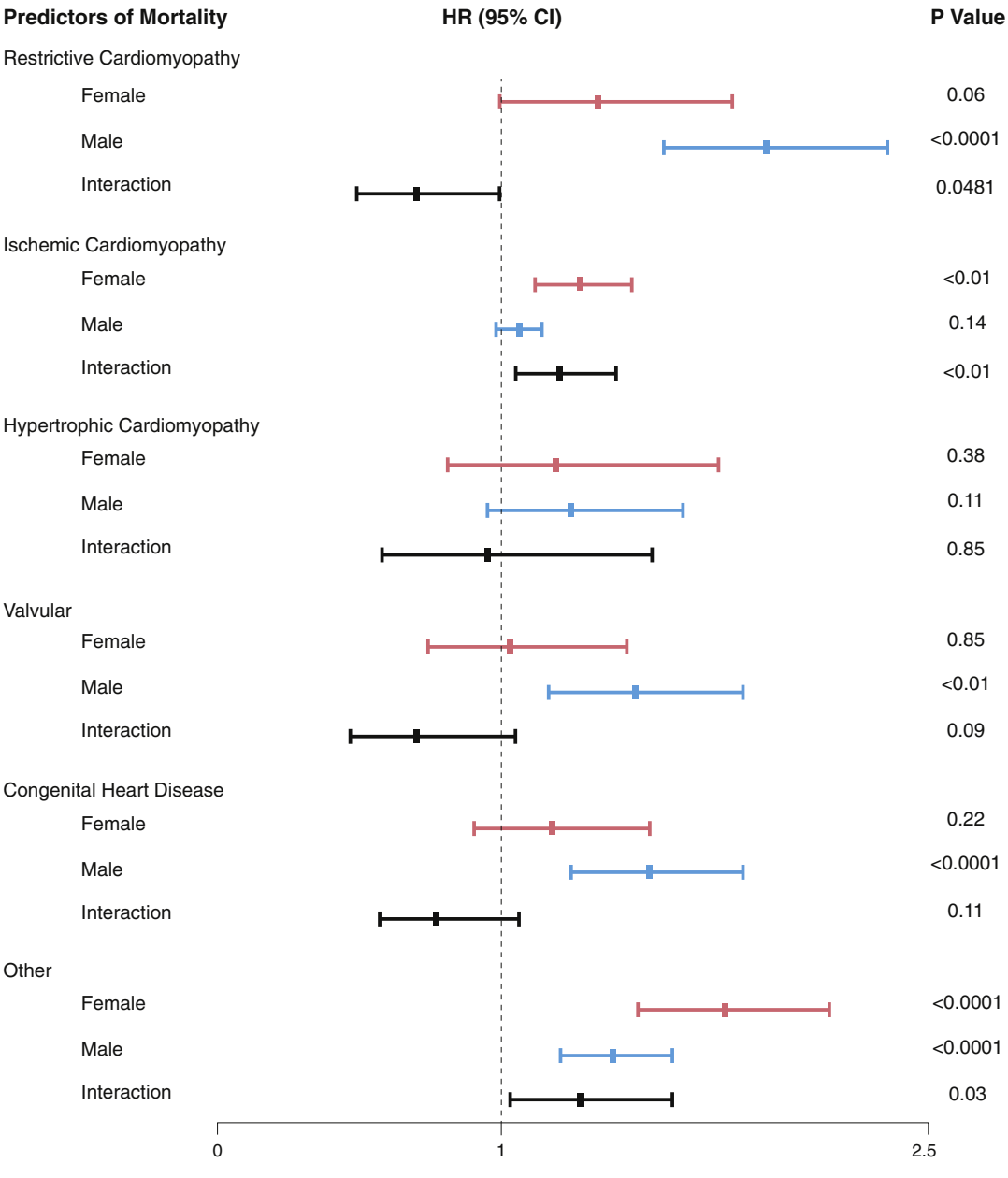
TABLE 2 Multivariate Analysis

	Unadjusted	Adjusted Model 1	Adjusted Model 2
DCM (reference)	–	–	–
RCM	1.50 (1.27–1.77)*	1.70 (1.43–2.02)*	1.80 (1.51–2.13)*
ICM	1.17 (1.10 –1.24)*	1.10 (1.03–1.18)*	1.13 (1.05–1.21)*
HCM	0.99 (0.79–1.24)	1.23 (0.98–1.54)	1.28 (1.02–1.60)*
Valvular heart disease	1.33 (1.10–1.60)*	1.30 (1.07–1.57)*	1.35 (1.12–1.63)*
CHD	0.96 (0.83–1.12)	1.37 (1.17–1.61)*	1.50 (1.28–1.76)*
Other	1.78 (1.60–1.98)*	1.51 (1.34–1.69)*	1.64 (1.46–1.84)*

Values are hazard ratio (95% confidence interval). Model 1 includes sex, age, race, insurance, BMI, ABO blood type, hypertension, era, tobacco use, diabetes mellitus, malignancy, prior CVA, PVD, dialysis, eGFR, albumin, mean PAP, cardiac index, ICD, mechanical ventilation, IABP, ECMO, VAD, TAH, and inotropes and excludes UNOS status. Model 2 includes sex, age, race, insurance, BMI, ABO blood type, hypertension, era, tobacco use, diabetes mellitus, malignancy, prior CVA, PVD, dialysis, eGFR, albumin, mean PAP, cardiac index, ICD, and UNOS status. *$p < 0.05$.

Abbreviations as in Table 1.

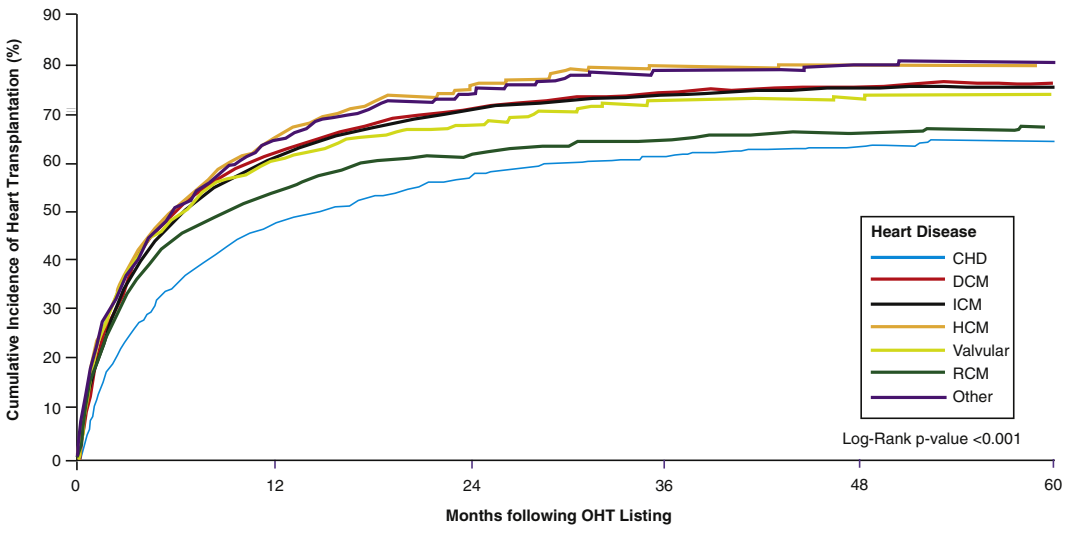
FIGURE 2 Sex Differences in Survival on the Basis of Type of Heart Disease



The risk of being female or male with a given type of heart disease while awaiting heart transplantation was assessed by multivariate Cox proportional hazard analyses adjusting for sex, age, race, insurance, body mass index, ABO blood type, hypertension, era, tobacco use, diabetes mellitus, malignancy, prior cerebral vascular accident, peripheral vascular disease, dialysis, estimated glomerular filtration rate, albumin, mean pulmonary arterial pressure, cardiac index, implantable cardioverter-defibrillator, mechanical ventilation, intra-aortic balloon pump, extra-corporeal membrane oxygenation, ventricular assist device, total artificial heart, and inotropes. The analyses also included possible interactions between female sex and type of heart disease. CI = confidence interval; HR = hazard ratio.

types of heart disease (Figure 3). More than 50% of the study cohort underwent OHT at the conclusion of the study (see Table 3 for data stratified by heart disease). Among the different heart diseases, patients with CHD were less likely to undergo transplantation than those in other subgroups. Most patients at the time of transplant were UNOS status 1A or 1B. Permanent mechanical circulatory support (VAD or TAH) at the time of transplantation was most common in patients with DCM or ICM and least likely in those with CHD or

FIGURE 3 Time to Heart Transplantation Stratified by Type of Heart Disease



Time to heart transplantation among patients on the waiting list, with data stratified by type of heart disease. Abbreviations as in Table 1.

RCM. ECMO was rarely used to bridge patients to transplantation but more likely to be used among those with CHD and "other" types of heart disease. Few patients had mechanical ventilation at the time of transplantation, with those with CHD or "other" diagnoses more likely than those with DCM, RCM, ICM, HCM, or valvular disease.

DISCUSSION

In a large, national transplantation registry, we found differences in adult survival on the basis of type of heart disease while awaiting cardiac transplantation. After adjustment for possible confounding variables, RCM, CHD, and "other" types of heart disease were associated with the highest risk of death compared with DCM. Patients with HCM had a better prognosis but still worse than those with DCM and ICM. There was an interaction between sex and type of heart disease, with women compared with men at higher risk for death with ICM and "other" diagnoses and lower risk for death with RCM.

Our research is the first to document differences in adult outcomes on the basis of type of cardiomyopathy while awaiting heart transplantation. The results for adults with RCM are similar to those in pediatric patients (8). Poor survival among patients with heart diseases such as RCM, CHD, and "other" types may be due to differences in the underlying disease or in the ability to rescue patients with inotropes and permanent mechanical circulatory support while they wait for transplantation. The rate of heart transplantation

TABLE 3 Characteristics at Time of Heart Transplantation

	DCM	RCM	ICM	HCM	Valvular Heart Disease	CHD	Other
OHT	9,616 (67)	540 (66)	7,758 (66)	422 (70)	377 (65)	554 (57)	1,101 (72)
UNOS status							
1A	5,272 (55)	261 (48)	3,866 (50)	200 (47)	174 (46)	236 (43)	507 (46)
1B	3,578 (37)	203 (38)	2,941 (38)	154 (36)	145 (38)	230 (42)	392 (36)
2	766 (8)	76 (14)	951 (12)	68 (16)	58 (15)	87 (16)	202 (18)
LVAD	3,036 (32)	42 (8)	2,413 (31)	46 (11)	53 (14)	28 (5)	132 (12)
RVAD ± LVAD or unspecified	786 (8)	15 (3)	544 (7)	18 (4)	16 (4)	19 (3)	102 (9)
TAH	125 (1)	*	60 (1)	*	*	*	16 (1)
ECMO	60 (1)	*	46 (1)	*	*	11 (2)	30 (3)
Ventilator	163 (2)	*	175 (2)	*	*	20 (4)	59 (5)

Values are n (%). *n < 10 patients.
Abbreviations as in Table 1.

may also have contributed to the higher mortality rate among patients with CHD and "other" types of disease, but not those with RCM.

The current heart transplant allocation system is based on severity of illness, defined by the use of mechanical circulatory support, inotropes, and mechanical ventilation. Patients who do not meet the standard criteria can be listed as high priority by exception if deemed appropriate by their transplantation centers and accepted by the UNOS regional board. However, medical providers have little evidence-based knowledge to request an exception on the basis of type of cardiomyopathy and even less information regarding the risk factors for mortality on the basis of type of heart disease. Without this knowledge, the optimal timing to request high-priority UNOS status remains unknown.

RCM comprises a broad category defined in the SRTR database as idiopathic, amyloidosis, endocardial fibrosis, sarcoidosis, radiation- or chemotherapy-induced heart disease, and other. Prognosis is likely to be different for each of these subgroups and dependent on the underlying cause. However, very limited survival data based on heart disease exist. In a single-center study evaluating only patients with light-chain cardiac amyloidosis (n = 31), 35% of patients died while awaiting OHT (9). Data for patients with cardiac sarcoidosis are limited and confounded by the fact that many are diagnosed after OHT by histological confirmation of the explanted heart (10–12). Few other studies regarding outcomes for type of heart disease are available, yet another SRTR analysis noted findings similar to ours. By univariate analysis, retransplantation had higher 6-month waitlist mortality than RCM among patients listed in 2010 and 2011 (13).

Retransplantation includes patients with allograft vasculopathy, rejection, and unknown causes for allograft failure. In our analysis, this cohort had poor survival while awaiting OHT, had a slower rate of transplantation, and appeared very ill at the time of listing (high frequencies of ECMO, mechanical ventilation, dialysis, and IABP use compared with other subgroups). They were also less likely than the other subgroups to have prophylactic ICDs. There are many possible reasons for the findings and yet few data to support any hypothesis. The degree of illness at the time of listing may reflect the fact that there are no guidelines defining which candidate should be considered for retransplantation and when to relist. Lack of prophylactic ICDs may be due to few heart transplantation patients qualifying for these devices at the time of listing, because current guidelines for prophylactic ICDs are based on "native hearts" with moderate to severe systolic dysfunction (14). Finally, the slow rate of transplantation in this subgroup may have been due to sensitization (suspected but not proved) and/or failure to meet criteria for high-priority status even when ill.

Patients with CHD have been known to constitute a high-risk group while awaiting heart transplantation. Studies have shown that patients with CHD are more likely than those without CHD to be listed at lower status, less likely to receive mechanical circulatory support at the time of listing, less likely to have ICDs, and less likely to undergo heart transplantation (15). Waiting times are significantly longer for patients with CHD compared with those with other diagnoses, which may be related to lower UNOS status at the time of listing and/or sensitization due to blood transfusions during prior surgical procedures (15–17). Poor prognosis on the heart transplant waiting list and slower rates for heart transplantation are therefore not unexpected.

Patients with HCM awaiting OHT have better outcomes than those with most other types of cardiomyopathy, including RCM, which is contrary to the popular belief that this is a disadvantaged group with the current allocation system (4). HCM was once considered a rare disease with a high mortality rate but now is known to be among the most common CHDs, with an adult annual mortality rate of about 0.5% and a "burned-out" phase occurring in 3% of the HCM population. The risk for sudden death is greatest in patients <30 years of age and is reduced with the use of ICDs (18). Because our HCM cohort had a mean age of 46 ± 14 years, they were at lower risk for sudden death. This risk was further reduced with 80% of the cohort having ICDs at the time of listing.

STUDY LIMITATIONS. The validity of the information is dependent on the accuracy of data entry. To reduce human error, SRTR data are assessed by edit checks, validation of data at the time of entry, and internal verification when there are outliers (6). Despite these attempts, critical data such as the type of heart disease may be inaccurate because of misdiagnosis, difficulty with classification when more than 1 diagnosis is known, and failure to standardize the criteria for each subgroup. Misdiagnosis is unlikely to occur with coronary artery disease or CHD. However, it is possible to occur with HCM, because thickening of the ventricle may arise from hypertension or infiltrative diseases. Hypertensive heart disease is more common among blacks and women (19,20), but in our cohort, the HCM subgroup was predominately male (62% men, 38% women), and few were black (9%), making it less likely that a substantial number of patients

with hypertensive heart disease were misdiagnosed with HCM. Infiltrative diseases such as RCM could be mislabeled as HCM. However, the baseline characteristics, including age, for RCM and HCM were very different, as were outcomes, suggesting no significant overlap between the groups. The RCM group may have been mislabeled in the idiopathic and "other" categories, but this is unlikely for the diagnoses of amyloidosis, endocardial fibrosis, sarcoidosis, and radiation- or chemotherapy-induced heart disease. Standardizing the criteria for all heart disease and requesting pathology data post-transplantation will improve accuracy in the future.

CONCLUSIONS

Our research demonstrates a higher mortality rate in the United States for patients awaiting OHT on the basis of etiology of heart disease and sex. Patients with RCM, CHD, or prior heart transplantation had a higher risk for death than those with DCM, ICM, HCM, or valvular heart disease. The current heart allocation system does not address these differences. A revised heart allocation scheme has been proposed that will recognize these subgroups and should account for the disadvantaged.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Eileen M. Hsich, Kaufman Center for Heart Failure, Heart and Vascular Institute, Cleveland Clinic, J3-4, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: hsiche@ccf.org.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For patients awaiting heart transplantation, there are differences in survival on the basis of type of heart disease. Patients with RCM, CHD, or prior transplantation have a higher risk for death than those with DCM, ICM, HCM, or valvular disease.

TRANSLATIONAL OUTLOOK: Our data support a change in the allocation system to prioritize RCM, CHD, and prior heart transplantation over the other types of heart disease. More research is needed to further define the risk factors for these subgroups.

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KEY WORDS cardiac amyloidosis, cardiomyopathy, congenital heart disease, heart failure, heart transplantation, hypertrophic cardiomyopathy

APPENDIX For a supplemental table, please see the online version of this article.