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Influence of durable mechanical circulatory support and allosensitization on mortality after heart transplantation

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BACKGROUND: Allosensitization has been shown to negatively affect post-heart transplant (HTx) survival even with a negative crossmatch. Whether allosensitization related to mechanical circulatory support (MCS) is associated with worse post-HTx survival remains controversial.

METHODS: Adult HTx recipients listed in the United Network for Organ Sharing database (July 2006–December 2012) were identified. Multivariate Cox regression assessed the effect of allosensitization on survival. Propensity matching was performed to compare patients who were and were not allosensitized. Kaplan-Meier survival analysis compared matched and unmatched patients in the MCS and medically managed cohorts.

RESULTS: We identified 11,840 HTx recipients, of whom 4,167 had MCS. MCS was associated with allosensitization in multivariate logistic regression. Each different MCS device was associated with worse post-HTx survival in multivariate Cox regression. Allosensitization did not predict post-HTx mortality in MCS patients (hazard ratio, 1.07; 95% confidence interval, 0.89–1.28; $p = 0.48$. Among patients without MCS, allosensitization was associated with post-HTx mortality (hazard ratio, 1.19; 95% confidence interval, 1.03–1.39; $p = 0.02$). Kaplan-Meier analysis revealed equivalent survival in unmatched and matched cohorts when MCS patients who were allosensitized were compared with non-allosensitized MCS patients. Among non-MCS patients, allosensitization was associated with worse survival in unmatched and matched analysis.

CONCLUSIONS: MCS was associated with allosensitization. For MCS patients, allosensitization did not independently predict worse post-HTx outcome. Among non-MCS patients, allosensitization was associated with worse post-HTx survival. Allosensitization appears to be a heterogeneous process influenced by presence of MCS.

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Circulating anti-human leukocyte antigen (anti-HLA) antibodies in transplant recipients are able to react to donor antigens after heart transplantation (HTx). By mixing recipient serum with lymphocytes of known HLA type, the panel reactive antibody (PRA) screen indirectly determines the proportion of potential donor antigens in the greater population to which the patient's pre-formed antibodies may react. A PRA > 10% signifies allosensitization; increasing

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degree of allosensitization has been associated with worse long-term survival and a higher incidence of rejection.[1] Reduction of PRA before transplantation has been linked with improved post-transplant survival.[2]

The introduction of left ventricular assist devices (LVADs) has greatly altered the management of patients awaiting HTx. Use of mechanical circulatory support (MCS) as a bridge to transplantation increased from less than 25% in 2006 to 37% in 2011.[3] Enthusiasm for MCS has been buoyed by evidence for improved survival compared with medically managed patients.[4–6] However, LVAD implantation has been associated with allosensitization.[7–9] The effect of MCS-related allosensitization on survival after HTx has not been delineated. We reviewed the United Network for Organ Sharing (UNOS) database to assess the effect of allosensitization, with or without MCS implantation, on post-transplantation survival.

Methods

Study population and primary end point

This was a retrospective review of deidentified data supplied by the UNOS as the contractor for the Organ Procurement and Transplantation Network. This study was granted an exemption by our Institutional Review Board because no patient identifiers were included. The study's primary end point was post-transplant survival. Patients were censored at the time of last known follow-up.

Statistical analysis

Analyses were conducted with Stata 13 software (StataCorp LP, College Station, TX). Patients were stratified by the presence of MCS—continuous-flow LVAD, pulsatile-flow LVAD, biventricular assist device (BiVAD), total artificial heart (TAH), or right ventricular assist device (RVAD)—at the time of transplant due to the large difference noted in PRA levels in patients with and without MCS. The standardized differences approach compared covariates between allosensitized and non-allosensitized patients to facilitate comparison with subsequent weighted analyses.[10] Means are presented with standard deviations. Hazard ratios (HRs) are presented with 95% confidence intervals (CI). All testing was 2-sided; p-values ≤ 0.05 were considered significant. Because of the exploratory nature of this study, no adjustments were made for multiple comparisons.[11] Post-transplant survival distributions were estimated with the non-parametric Kaplan-Meier method.[12] The log-rank test was used to compare differences between survival distributions in unadjusted analyses.[13] Survival curves were regenerated in a sub-population of matched patients after propensity-score matching, and the stratified log-rank test was used to compare survival curves in matched cohorts.[14,15]

Center volume was included as a covariate in our analyses. During the 77-month study period, centers performing >200 HTxs were considered high volume ($\geq$ 30 transplants/year), and centers performing between 100 and 200 transplants were considered moderate volume (15–29 transplants/year). Cut points were chosen by using a restricted cubic spline analysis.

Missing data

Multiple imputation was used for variables with missing values to avoid list-wise deletion in our multivariable analyses.[16] This was performed in all non-redundant variables by using a regression switching approach with predictive mean matching for continuous and semi-continuous variables, logistic regression for binary variables, and ordered logistic regression for ordinal variables; the model included the event indicator and the Nelson-Aalen estimator of the hazard of death.[17,18] Twenty imputations were performed given our reasonable sample size and moderate amount of missing data.[19] The complete sets of observed values were used as covariates for prediction purposes.

Propensity score matching

Differences in characteristics between allosensitized and non-allosensitized patients were controlled for with propensity score matching.[14] Multivariable logistic regression models that included all available variables at the time of transplant were used to develop a propensity score for patients in each of our 2 propensity-matched comparisons: 1 in patients without MCS (non-MCS) and the other in patients with MCS.[20] To handle missing data, propensity scores were calculated across all imputed data sets ($n = 20$) using the "Across" approach described by Mitra and Reiter[21] and combined according to Rubin's rules.[22] We next performed a 1:1 nearest-neighbor matching algorithm without replacement (using a caliper of 0.01 of the standard deviation of the linear propensity score); balance was achieved in our model by using the standardized differences approach.[10,15]

Cox proportional hazards analysis

A sensitivity analysis was undertaken to corroborate the findings from our propensity score analysis. Cox proportional hazards regression modeling assessed the association of demographic, clinical, transplant center, operative, and donor characteristics with survival after HTx in the non-MCS and MCS cohorts.[23] The proportional hazards assumption was tested by plotting scaled Schoenfeld residuals.[24] Purposeful selection of covariates was used to create the models. Variables hypothesized or previously shown to be of clinical significance in HTx recipients were included along with novel variables that were plausibly significant ($p \leq 0.20$) on bivariable analysis.[25] Variables that were not statistically significant ($p > 0.05$) by the Wald test in our multivariable models but that were plausibly associated with graft survival were included in our final models. Covariate selection was also guided by optimizing the Akaike information criterion.[26]

Panel reactive antibody

In the UNOS data set, Class I and Class II PRA are reported each with "most recent" and "peak" values available. A composite PRA level was created using the highest "most recent" PRA value of Class I or Class II PRA levels. PRA $>10\%$ was considered to be allosensitized.[27]

Results

We identified 11,840 HTx recipients, of whom 4,167 had some form of durable MCS device at the time of transplant, in the study period (July 2006–December 2012). Data were

missing for < 1% of patients for most of the variables analyzed; 4 variables (cardiac index, mean pulmonary artery pressure, organ ischemic time, and donor/recipient cytomegalovirus match) had missing data for 1% to 4% of patients, 2 variables (pulmonary capillary wedge pressure and composite PRA level) had missing data for 5% to 9% of patients, and 2 variables (college education and HLA mismatch) had missing data for ≥10% of patients. Multiple imputation was used to account for missing data. In our unmatched and matched Kaplan-Meier survival analyses, patients without composite PRA level data (5.7% of patients) were excluded; however, these patients were included with an imputed PRA level in our Cox proportional hazards regression analysis.

Demographic data for unmatched and propensity matched patients are listed in Table 1. There were statistically significant differences in baseline characteristics between allosensitized and non-allosensitized patients with and without MCS. The propensity-matching algorithm was able to account for these differences.

Non-MCS patients were separated into patients with and without previous cardiac surgery. Patients with a history of cardiac surgery had a higher composite most recent PRA that was statistically significant. Composite most recent PRA was greater with each device—except isolated RVAD—than non-MCS patients without a history of cardiac surgery (Table 2). Multivariate logistic regression demonstrated that elevated composite most recent PRA ≥ 10% was associated with MCS (odds ratio, 2.01; 95% CI, 1.79–2.27; $p < 0.001$, Table 3). Other factors associated with MCS were male gender, body mass index (BMI) ≥ 35 kg/m^2, idiopathic cardiomyopathy, New York Heart Association Functional Classification IV symptoms, ventilator dependence, extracorporeal membrane oxygenation support, diabetes, later year of transplantation, donor-to-recipient gender match, and organ ischemic time ≥ 4 hours. Negative predictors of MCS were age ≥ 60 years, Hispanic ethnicity, college education, diagnoses other than idiopathic cardiomyopathy with ischemic cardiomyopathy as the reference, inotropic support, intra-aortic balloon pump support, elevated mean pulmonary artery pressure, donor age ≥ 50 years, donor diabetes, and non-identical but compatible ABO type.

Multivariate Cox regression of variables associated with survival in the entire cohort, the sub-set of patients without support, and the sub-set of patients with MCS revealed several variables with heterogeneous effects on survival. Whereas composite most-recent PRA ≥ 10% was not associated with increased hazard for the entire cohort (HR, 1.12; 95% CI, 0.99–1.26; $p = 0.06$), allosensitization was associated with worse post-HTx survival in the sub-set of patients without MCS (HR, 1.18; 95% CI, 1.02–1.37; $p = 0.03$). For patients with MCS, allosensitization did not predict post-transplant mortality (HR, 1.07; 95% CI, 0.89–1.28; $p = 0.48$, Table 4).

Other variables that appeared to have an inconsistent effect between patients with and without MCS were age ≥ 60 years, college education, BMI ≥ 35 kg/m^2, recipient diagnosis, center volume, donor age, donor smoking history, donor diabetes, and gender match. Recipient diagnosis was an independent predictor of post-transplantation survival in patients without MCS with the exception of congenital heart disease but failed to become statistically significant in patients with MCS using ischemic cardiomyopathy as the reference. In addition, patients who underwent transplantation at a moderate-to-high-volume institution had a lower hazard of death than patients who underwent transplantation at an institution with less experience, both in the entire cohort and in the sub-group of patients without MCS; however, this did not hold for the sub-group of patients with MCS. Among patients with MCS, age ≥ 60 had an adverse effect on long-term outcomes, whereas college education and gender match were predictors of improved survival; these were not significant in the non-MCS cohort. BMI ≥ 35 kg/m^2, donor age, donor smoking history, donor diabetes, and previous cardiac surgery each were predictors of worse post-transplantation survival for patients without MCS but did not affect survival in patients with MCS. Previous cardiac surgery was not evaluated in patients with MCS because all patients were considered to have had previous cardiac surgery. Consistent predictors of post-transplantation mortality were African American race, New York Heart Association class IV, extracorporeal membrane oxygenation, ventilator-dependence, renal insufficiency, bilirubin ≥2 mg/dl, and organ ischemic time >4 hours. Private insurance was a consistent predictor of post-transplantation survival.

Multivariate Cox regression using the entire cohort revealed increased hazard with each of the different MCS devices when compared with patients without MCS: continuous-flow LVAD support: HR, 1.26 (95% CI, 1.10–1.44; $p < 0.001$); pulsatile flow LVAD: HR, 1.24 (95% CI, 1.07–1.45; $p = 0.006$); BiVAD: HR, 1.46 (95% CI, 1.19–1.80; $p < 0.001$); TAH: HR, 1.71 (95% CI, 1.20–2.45; $p = 0.003$); and isolated RVAD: HR, 2.10 (95% CI, 1.11–3.96; $p = 0.02$, Table 4). Restricted to the cohort of patients with MCS, the only device associated with increased hazard compared with the other devices was isolated RVAD (HR, 1.94; 95% CI, 1.00–3.74; $p = 0.05$).

Kaplan-Meier survival analysis of post-transplant survival was performed separately in patients with and without MCS at the time of transplant, before and after propensity matching. Unmatched analyses of patients without MCS comparing allosensitized and non-allosensitized patients revealed that survival was worse in allosensitized patients compared with non-allosensitized patients: 87% vs 91% at 1 year and 73% vs 76% at 5 years ($p < 0.001$, Figure 1A). However, post-transplantation survival was equivalent between allosensitized and non-allosensitized patients who had a durable MCS device implanted: 87% vs 87% at 1 year and 68% vs 74% at 5 years ($p = 0.31$, Figure 1B). In matched analysis, allosensitized patients without MCS had worse survival than non-allosensitized patients without MCS: 87% vs 91% at 1 year and 73% vs 76% at 5 years ($p = 0.006$, Figure 1C). Again in matched analysis, there was no difference in survival between allosensitized patients with MCS and non-allosensitized patients: 87% vs 87% at 1 year and 71% vs 68% at 5 years ($p = 0.59$, Figure 1D).

Table 1 Baseline Characteristics of Patients With and Without Mechanical Circulatory Support, Before and After Propensity Score Matching

	Patients without MCS at transplant						Patients with MCS at transplant					
	Unmatched comparison			Matched comparison			Unmatched comparison			Matched comparison		
Variables	PRA $\geq$ 10% (n = 1,226)	PRA $<$ 10% (n = 6,006)	SD	PRA $\geq$ 10% (n = 1,144)	PRA $<$ 10% (n = 1,144)	SD	PRA $\geq$ 10% (n = 976)	PRA $<$ 10% (n = 2,96)	SD	PRA $\geq$ 10% (n = 973)	PRA $<$ 10% (n = 973)	SD
Baseline characteristics												
Age, y	50.4	53.2	0.209	51.0	50.9	0.005	50.6	52.2	0.129	50.6	50.6	0.002
Male gender, %	50	76	0.573	53	51	0.023	66	86	0.485	66	66	0.013
Caucasian race, %	64	70	0.144	64	65	0.007	63	70	0.144	63	62	0.028
African American race, %	23	17	0.155	23	22	0.003	27	19	0.171	27	25	0.031
Hispanic ethnicity, %	9.2	8.4	0.029	9.0	8.7	0.012	5.7	7.3	0.065	5.8	8.6	0.111
College education, %	54	56	0.036	53	53	0.004	54	51	0.045	54	53	0.017
Private insurance, %	53	54	0.027	53	53	0.007	50	51	0.018	51	50	0.004
BMI, kg/m^2	26.0	26.6	0.116	26.1	26.0	0.020	27.4	27.7	0.047	27.4	27.4	0.012
BMI $\geq$ 35 kg/m^2, %	3.3	4.0	0.038	3.3	2.6	0.015	7.8	7.8	0.002	7.7	6.4	0.52
Etiology of heart failure												
Cardiomyopathy, %												
Ischemic/CAD	28	40	0.240	30	29	0.015	36	43	0.137	36	35	0.026
Idiopathic	29	33	0.071	31	32	0.026	40	50	0.006	40	41	0.027
Restrictive	3.5	3.3	0.009	3.6	4.2	0.032	1.2	0.7	0.049	1.2	0.8	0.041
Hypertrophic	3.3	3.0	0.017	3.6	4.7	0.057	1.7	0.9	0.069	1.7	1.3	0.033
Graft dysfunction (re-transplant), %	12	3.3	0.317	8.7	6.9	0.068	1.6	0.8	0.075	1.3	1.7	0.033
Congenital heart disease, %	6.4	3.4	0.138	5.9	6.3	0.018	1.1	0.4	0.088	1.1	0.6	0.055
Functional status, life support												
Status 1a, %	43	40	0.063	43	41	0.028	71	75	0.077	71	73	0.034
Status 1a or 1b, %	89	86	0.105	89	89	0.014	100	100	0.000	100	100	0.000
NYHA class IV, %	51	48	0.059	51	51	0.005	46	38	0.162	46	44	0.029
NYHA class III-IV, %	82	83	0.014	82	82	0.001	78	76	0.049	78	79	0.017
Inotrope support, %	57	55	0.039	58	55	0.056	13	14	0.042	12	14	0.051
IABP support, %	7.3	6.7	0.021	7.1	5.7	0.057	2.2	3.0	0.052	2.2	4.1	0.112
Ventilator support, %	2.7	2.2	0.030	2.4	2.1	0.018	2.5	2.7	0.018	2.5	2.7	0.013
ECMO support, %	1.1	0.8	0.022	0.9	1.1	0.026	1.5	0.7	0.082	1.5	0.9	0.056
MCS, %												
Any	0	0	0.000	0	0	0.000	100	100	0.000	100	100	0.000
Continuous-flow LVAD	0	0	0.000	0	0	0.000	64	64	0.001	65	67	0.041
Pulsatile-flow LVAD	0	0	0.000	0	0	0.000	18	22	0.097	18	16	0.035
BiVAD	0	0	0.000	0	0	0.000	13	11	0.057	13	12	0.016
TAH	0	0	0.000	0	0	0.000	4.8	2.5	0.123	4.6	4.5	0.005
RVAD	0	0	0.000	0	0	0.000	0.4	0.8	0.050	0.4	0.4	0.000

Hemodynamic parameters											
Cardiac index, liters/min/m^2	2.29	2.26	0.046	2.28	2.27	0.009	2.38	2.34	0.058	2.38	2.37	0.021
Mean pulmonary artery pressure, mm Hg	28.8	29.2	0.041	29.0	28.8	0.023	27.8	27.9	0.007	27.8	28.0	0.020
Pulmonary capillary wedge pressure, mm Hg	19.7	19.7	0.009	19.8	19.4	0.042	18.2	18.5	0.029	18.2	18.5	0.039
Renal/liver function, diabetes											
CrCl, ml/min	77.4	80.9	0.107	77.5	78.1	0.017	90.2	92.5	0.060	90.3	89.7	0.015
Dialysis, %	1.9	1.7	0.016	1.8	1.7	0.007	5.2	4.0	0.059	5.0	4.0	0.50
CrCl $<$ 50 ml/min or dialysis, %	21	17	0.105	20	20	0.002	15	13	0.064	15	14	0.024
Diabetes, %	21	26	0.115	22	22	0.007	28	30	0.062	28	29	0.026
Total bilirubin, mg/dl	1.11	1.21	0.068	1.13	1.21	0.063	1.16	1.21	0.018	1.16	1.06	0.052
PRA data											
Composite most recent PRA, %	42.5	0.6	2.147	41.6	0.7	2.107	44.1	0.8	2.217	44.0	0.9	2.207
Transplant center characteristics											
Year of transplant	2010	2009	0.184	2009	2009	0.023	2010	2010	0.073	2010	2010	0.069
Institution listing volume, %											
High	38	36	0.050	37	35	0.051	28	23	0.100	27	25	0.063
Moderate or high	72	71	0.026	72	73	0.018	68	64	0.73	68	67	0.022
Operative characteristics											
Previous cardiac surgery, %	39.4	36.9	0.051	39.8	36.0	0.078	100	100	0.000	100	100	0.000
Bicaval anastomosis, %	76	71	0.115	75	75	0.016	75	70	0.105	75	75	0.012
Organ ischemic time, h	3.23	3.22	0.123	3.22	3.25	0.031	3.33	3.33	0.000	3.33	3.31	0.015
Distance organ transported, miles	194	197	0.016	195	194	0.005	164	178	0.069	165	169	0.022
Local organ (non-regional, non-national) , %	58	55	0.058	57	56	0.012	63	57	0.113	62	62	0.017
Donor characteristics											
Age, years	32.0	31.8	0.014	31.9	32.0	0.006	31.5	30.9	0.051	31.5	31.4	0.003
Smoking history $>$ 20 years, %	15	16	0.034	15	14	0.029	15	15	0.004	15	15	0.006
Diabetes, %	3.2	3.4	0.013	3.2	2.8	0.026	2.9	2.9	0.001	2.9	3.2	0.017
Donor/recipient matching											
Gender match, %	66	73	0.153	67	66	0.026	72	79	0.163	72	74	0.032
Race match, %	48	53	0.101	49	49	0.017	49	53	0.076	49	47	0.037
CMV: donor positive, recipient negative, %	20	23	0.082	20	20	0.014	22	24	0.056	22	21	0.017
Non-identical ABO blood group match (only compatible), %	18	17	0.030	18	17	0.021	14	13	0.017	14	14	0.012
Complete HLA mismatch (all 6 alleles), %	19	24	0.129	20	23	0.077	21	24	0.060	22	20	0.035

BiVAD, biventricular assist device; BMI, body mass index; CAD, coronary artery disease; CMV, cytomegalovirus; CrCl, creatinine clearance; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; MCS, mechanical circulatory support; NYHA, New York Heart Association; PRA, panel reactive antibody; RVAD, right ventricular assist device; SD, standardized difference; TAH, total artificial heart.

Table 2 Panel Reactive Antibody Data, Stratified by Mechanical Circulatory Support Class[a]

Variable	Non-missing data	No MCS without history of cardiac surgery	No MCS with history of cardiac surgery	p[b]	All MCS	p[b]	CF LVAD	p[b]	PF LVAD	p[b]	BiVAD	p[b]	TAH	p[b]	RVAD	p[b]
	No. (%)	(n = 4,533)	(n = 2,699)		(n = 3,932)		(n = 2,532)		(n = 811)		(n = 441)		(n = 121)		(n = 27)	
Most recent PRA																
Class I	11,108 (93.8)	5.0 ± 15.3 0 (0–0)	6.0 ± 17.2 0 (0–1)	0.007	9.2 ± 21.1 0 (0–5)	<0.001	8.8 ± 20.4 0 (0–4)	<0.001	9.0 ± 21.1 0 (0–4)	<0.001	10.4 ± 22.1 0 (0–8)	<0.001	17.6 ± 29.1 2 (0–21.5)	<0.001	4.6 ± 12.6 0 (0–2)	0.90
Class II	10,485 (88.6)	4.4 ± 15.2 0 (0–0)	4.8 ± 16.1 0 (0–0)	0.28	5.4 ± 16.6 0 (0–0)	0.01	5.2 ± 16.2 0 (0–0)	0.04	4.2 ± 14.7 0 (0–0)	0.73	6.2 ± 18.5 0 (0–0)	0.02	13.0 ± 25.2 0 (0–15.5)	<0.001	3.4 ± 10.5 0 (0–1)	0.75
Peak PRA																
Class I	2,720 (23.0)	24.2 ± 26.4 14 (5–34)	29.9 ± 29.6 19 (6–47)	<0.001	34.4 ± 31.1 24 (9–56)	<0.001	33.3 ± 30.6 23 (8–52)	<0.001	38.3 ± 32.7 28 (10–64)	<0.001	34.6 ± 30.9 24 (9–59)	<0.001	39.3 ± 32.3 30 (14–65)	<0.001	10.0 ± 12.4 6 (1–21)	0.15
Class II	1,542 (13.0)	30.8 ± 30.9 18.5 (3–57)	33.5 ± 31.5 23 (6–60)	0.21	34.1 ± 31.1 25 (7–58)	0.17	32.8 ± 30.4 23 (7–56)	0.32	37.3 ± 32.8 30 (4–62)	0.05	36.6 ± 32.1 24 (10–58)	0.14	43.1 ± 35.6 27 (16–78)	0.06	17.4 ± 24.0 6 (4–17)	0.33
Composite most recent PRA, %	11,164 (94.3)	7.38 ± 18.8 0 (0–2)	8.32 ± 20.4 0 (0–3)	0.046	9.1 ± 20.9 0 (0–9)	<0.001	11.2 ± 22.6 0 (0–9)	<0.001	10.4 ± 22.7 0 (0–6)	<0.001	13.0 ± 25.1 0 (0–11)	<0.001	21.4 ± 31.3 4 (0–33)	<0.001	5.7 ± 12.7 0 (0–4)	0.64

BiVAD, biventricular assist device; CF, continuous flow; LVAD, left ventricular assist device; MCS, mechanical circulatory support; PF, pulsatile-flow; RVAD, right ventricular assist device; TAH, total artificial heart.

[a]Mean ± standard deviation is reported along with median (interquartile range).

[b]The p-value compares PRA levels against the baseline: patients without MCS and without prior cardiac surgery.

Table 3 Odds Ratio of Variables Associated With Patients With a Durable Mechanical Circulatory Support Device at Transplantation

Variables	OR (95% CI)	*P*
Demographics		
Age ≥60 years	0.72 (0.65–0.80)	<0.001
Male gender	2.01 (1.79–2.26)	<0.001
Race/ethnicity		
Caucasian	Reference	
African American	1.10 (0.96–1.25)	0.16
Hispanic	0.82 (0.69–0.98)	0.03
Other	0.93 (0.73–1.19)	0.57
College education	0.89 (0.81–0.99)	0.03
Private insurance	1.00 (0.91–1.10)	0.98
BMI ≥35 kg/m^2	1.83 (1.50–2.21)	<0.001
Etiology of heart failure		
Cardiomyopathy		
Ischemic/CAD	Reference	
Idiopathic	1.23 (1.10–1.37)	<0.001
Restrictive	0.10 (0.06–0.15)	<0.001
Hypertrophic	0.34 (0.24–0.48)	<0.001
Graft dysfunction (retransplantation)	0.15 (0.10–0.20)	<0.001
Congenital heart disease	0.24 (0.17–0.35)	<0.001
Functional status, life support		
NYHA class IV	1.32 (1.19–1.45)	<0.001
Inotrope support	0.11 (0.10–0.12)	<0.001
IABP support	0.40 (0.31–0.51)	<0.001
Ventilator support	3.92 (2.90–5.31)	<0.001
ECMO support	1.66 (1.01–2.74)	0.04
Hemodynamic parameters		
Mean pulmonary artery pressure ≥ 30 mm Hg	0.89 (0.81–0.98)	0.02
Renal/liver function, diabetes		
CrCl < 50 ml/min or dialysis	0.98 (0.86–1.12)	0.77
Diabetes	1.12 (1.01–1.24)	0.03
Bilirubin ≥ 2 mg/dl	0.90 (0.78–1.03)	0.13
PRA data		
Composite most recent PRA ≥10%	2.01 (1.79–2.27)	<0.001
Transplant center characteristics		
Year of transplant	1.21 (1.18–1.24)	<0.001
Moderate- or high-volume listing institution	1.03 (0.94–1.13)	0.56
Operative characteristics		
Bicaval anastomosis	0.94 (0.85–1.04)	0.22
Organ ischemic time ≥ 4 hours	1.26 (1.13–1.40)	<0.001
Donor characteristics		
Age ≥ 50 years	0.57 (0.47–0.68)	<0.001
Smoking history > 20 years	1.09 (0.96–1.23)	0.19
Diabetes	0.75 (0.58–0.98)	0.03
Donor/recipient matching		
Gender match	1.15 (1.03–1.28)	0.01
Race match	1.01 (0.92–1.12)	0.78
CMV: donor positive, recipient negative	0.99 (0.88–1.10)	0.79
Non-identical ABO blood group match (only compatible)	0.81 (0.71–0.91)	0.001
Complete HLA mismatch (all 6 alleles)	1.00 (0.89–1.12)	0.98

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CMV, cytomegalovirus; CrCl, creatinine clearance; ECMO, extracorporeal membrane oxygenation;
HLA, human leukocyte antigen; IABP, intra-aortic balloon pump; NYHA, New York Heart Association; PRA, panel reactive antibody.

Discussion

MCS is increasingly being used before HTx. Patients receiving MCS at transplantation were more likely to be allosensitized than patients without MCS, but allosensitization was not associated with an increased risk of post-HTx mortality in patients with MCS. However, MCS itself was an independent predictor of mortality. In non-MCS patients, allosensitization was associated with an increased hazard for mortality after HTx. Among the sub-group of patients receiving MCS, isolated RVAD implantation was associated with the greatest risk of post-transplant mortality.

Table 4 Multivariable Cox Regression of Predictors of Post-Transplant Mortality

	Entire cohort ($N = 11,840$)		Non-MCS cohort ($n = 7,673$)		MCS ($n = 4,167$)	
Variables	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Demographics						
Age $\geq$ 60 years	1.25 (1.13–1.39)	<0.001	1.08 (0.95–1.23)	0.24	1.62 (1.37–1.92)	<0.001
Male gender	0.96 (0.86–1.08)	0.50	0.92 (0.81–1.06)	0.24	1.08 (0.88–1.34)	0.46
Race/ethnicity						
Caucasian	Reference		Reference		Reference	
African American	1.39 (1.23–1.57)	<0.001	1.41 (1.21–1.65)	<0.001	1.38 (1.12–1.69)	0.002
Hispanic	0.98 (0.82–1.17)	0.85	1.07 (0.87–1.33)	0.51	0.78 (0.56–1.08)	0.13
Other	1.05 (0.81–1.35)	0.72	1.18 (0.88–1.59)	0.27	0.80 (0.50–1.29)	0.36
College education	0.84 (0.76–0.93)	<0.001	0.89 (0.79–1.01)	0.06	0.75 (0.64–0.89)	0.001
Private insurance	0.85 (0.78–0.93)	0.001	0.86 (0.76–0.96)	0.008	0.85 (0.73–0.99)	0.04
BMI $\geq$ 35 kg/m^2	1.27 (1.06–1.53)	0.01	1.34 (1.04–1.73)	0.03	1.25 (0.95–1.63)	0.11
Etiology of heart failure						
Cardiomyopathy						
Ischemic/CAD	Reference		Reference		Reference	
Idiopathic	0.78 (0.70–0.87)	<0.001	0.78 (0.67–0.91)	0.002	0.87 (0.73–1.04)	0.12
Restrictive	1.54 (1.18–2.00)	0.001	1.48 (1.13–1.96)	0.005	0.65 (0.20–2.11)	0.47
Hypertrophic	0.69 (0.48–1.00)	0.05	0.64 (0.42–0.97)	0.04	0.98 (0.46–2.09)	0.96
Graft dysfunction (retransplantation)	1.46 (1.18–1.80)	<0.001	1.44 (1.13–1.83)	0.003	1.40 (0.81–2.42)	0.22
Congenital heart disease	1.33 (1.03–1.72)	0.03	1.32 (0.99–1.75)	0.06	1.74 (0.91–3.31)	0.09
Functional status, life support						
NYHA class IV	1.37 (1.24–1.51)	<0.001	1.33 (1.18–1.50)	<0.001	1.47 (1.26–1.73)	<0.001
Inotrope support	0.98 (0.89–1.09)	0.76	0.97 (0.86–1.09)	0.63	1.04 (0.84–1.28)	0.74
IABP support	0.94 (0.78–1.14)	0.52	0.90 (0.72–1.13)	0.37	1.08 (0.74–1.58)	0.69
Ventilator support	1.56 (1.24–1.96)	<0.001	1.53 (1.12–2.09)	0.008	1.61 (1.13–2.29)	0.009
ECMO support	2.64 (1.93–3.61)	<0.001	2.87 (1.91–4.32)	<0.001	2.44 (1.44–2.11)	0.001
MCS						
No MCS	Reference					
Continuous flow LVAD support	1.26 (1.10–1.44)	<0.001			Reference	
Pulsatile flow LVAD support	1.24 (1.07–1.45)	0.006			1.01 (0.83–1.23)	0.91
BiVAD support	1.46 (1.19–1.80)	<0.001			1.20 (0.95–1.53)	0.13
TAH support	1.71 (1.20–2.45)	0.003			1.31 (0.90–1.92)	0.16
RVAD (only) support	2.10 (1.11–3.96)	0.02			1.94 (1.00–3.74)	0.05
Hemodynamic parameters						
Mean pulmonary artery pressure $\geq$ 30 mm Hg	1.10 (1.00–1.20)	0.05	1.08 (0.96–1.21)	0.21	1.13 (0.97–1.32)	0.12
Renal/liver function, diabetes						
CrCl < 50 mL/min or dialysis	1.38 (1.24–1.54)	<0.001	1.33 (1.16–1.52)	<0.001	1.50 (1.24–1.82)	<0.001
Diabetes	1.06 (0.96–1.17)	0.27	1.04 (0.92–1.18)	0.54	1.09 (0.93–1.28)	0.30
Bilirubin $\geq$ 2 mg/dl	1.28 (1.12–1.45)	<0.001	1.21 (1.04–1.42)	0.02	1.40 (1.13–1.73)	0.002

PRA data					
Composite most recent PRA ≥ 10%	1.12 (0.99–1.26)	0.06	1.18 (1.02–1.37)	0.03	1.07 (0.89–1.28)	0.48
Transplant center characteristics					
Year of transplant	0.99 (0.96–1.02)	0.52	0.99 (0.96–1.03)	0.70	0.99 (0.94–1.04)	0.68
Moderate- or high-volume listing institution	0.85 (0.78–0.94)	0.001	0.82 (0.73–0.93)	0.001	0.90 (0.77–1.06)	0.21
Operative characteristics					
Bicaval anastomosis	0.96 (0.87–1.06)	0.43	0.97 (0.86–1.09)	0.62	0.92 (0.79–1.08)	0.32
Previous cardiac surgery	N/A		1.16 (1.02–1.31)	0.02	N/A	
Organ ischemic time, ≥ 4h	1.26 (1.14–1.39)	<0.001	1.27 (1.12–1.45)	<0.001	1.23 (1.05–1.46)	0.01
Donor characteristics					
Age ≥ 50 years	1.37 (1.18–1.59)	<0.001	1.43 (1.20–1.70)	<0.001	1.24 (0.91–1.67)	0.17
Smoking history > 20 years	1.21 (1.08–1.35)	0.001	1.29 (1.12–1.48)	<0.001	1.08 (0.89–1.31)	0.43
Diabetes	1.36 (1.08–1.70)	0.008	1.46 (1.12–1.91)	0.006	1.23 (0.81–1.86)	0.33
Donor/recipient matching					
Gender match	0.86 (0.77–0.95)	0.002	0.89 (0.79–1.01)	0.07	0.78 (0.65–0.93)	0.006
Race match	0.95 (0.86–1.05)	0.34	0.94 (0.83–1.06)	0.31	0.97 (0.82–1.15)	0.73
CMV: donor positive, recipient negative	1.09 (0.98–1.21)	0.13	1.06 (0.92–1.21)	0.42	1.11 (0.93–1.32)	0.25
Non-identical ABO blood group match (only compatible)	0.99 (0.88–1.12)	0.92	1.08 (0.93–1.24)	0.32	0.84 (0.68–1.05)	0.12
Complete HLA mismatch (all 6 alleles)	1.03 (0.92–1.15)	0.64	1.02 (0.89–1.17)	0.76	1.04 (0.86–1.25)	0.68

BiVAD, biventricular assist device; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; CMV, cytomegalovirus; CrCl, creatinine clearance; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; HR, hazard ratio; IABP, intra-aortic balloon pump; MCS, mechanical circulatory support; NYHA, New York Heart Association; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device.

Allosensitization

The results of our analysis are consistent with prior studies showing that LVAD implantation is associated with allosensitization.[8,28] Despite the consistent finding of an association between MCS and allosensitization, the mechanism of sensitization has not been completely delineated. Transfusion of blood products has previously been associated with allosensitization,[29,30] but avoidance of transfusing leukocyte-filtered cellular blood products has not been shown to prevent it.[31] Differences in the immunogenicity of the various devices may play a role, with more contemporary devices potentially posing a lower risk for allosensitization than earlier iterations of VADs.[7,9] The current analysis demonstrated that each form of MCS, except for RVAD, had a continued association with increased risk for allosensitization in a contemporary cohort.

That patients with MCS exhibit a different risk profile associated with allosensitization than those without MCS is not novel per se. A retrospective review of patients bridged to transplantation with a HeartMate XVE (Thoratec Corp, Pleasanton, Calif.) or a HeartMate II (Thoratec Corp) did not reveal differences in post-transplantation survival comparing patients with PRA > 25% and PRA = 0%.[32] The current analysis confirms this finding and goes further by broadening the cohort to compare patients with a variety of support devices.

The difference between device-supported and medically managed patients may be related to the immunogenicity of the device. LVAD-related PRA elevation has been observed to peak early and then decline over the course of support; this has been hypothesized to be a result of the initial interaction between patient blood and the device, followed by mitigation of the immunogenicity of the device secondary to pseudointima formation.[7,33] With this in mind, explantation of the device would significantly reduce the inflammatory milieu contributing to PRA elevation, thus making it a finite process. In contrast, medically treated patients may not have a well-defined reason for PRA elevation, potentially suggesting a durable adverse immunologic response to a transplanted organ. Schaffer et al[2] demonstrated that, on the one hand, reduction in PRA of allosensitized patients before HTx was associated with improved post-transplantation survival in patients without VADs; on the other hand, irreducible PRA was an indicator of poor survival after transplantation.[2] As such, allosensitization appears to be a heterogeneous process, the reversibility of which may be more important than its mere existence.

Durable MCS device implantation and post-transplantation survival

Nativi et al[34] found in an analysis of the International Society for Heart and Lung Transplantation (ISHLT) registry from 2000 to 2008 that the difference in post-transplantation mortality between medically managed and VAD-supported patients was era-dependent. Wozniak et al[6] further determined that among Status 1A patients, the

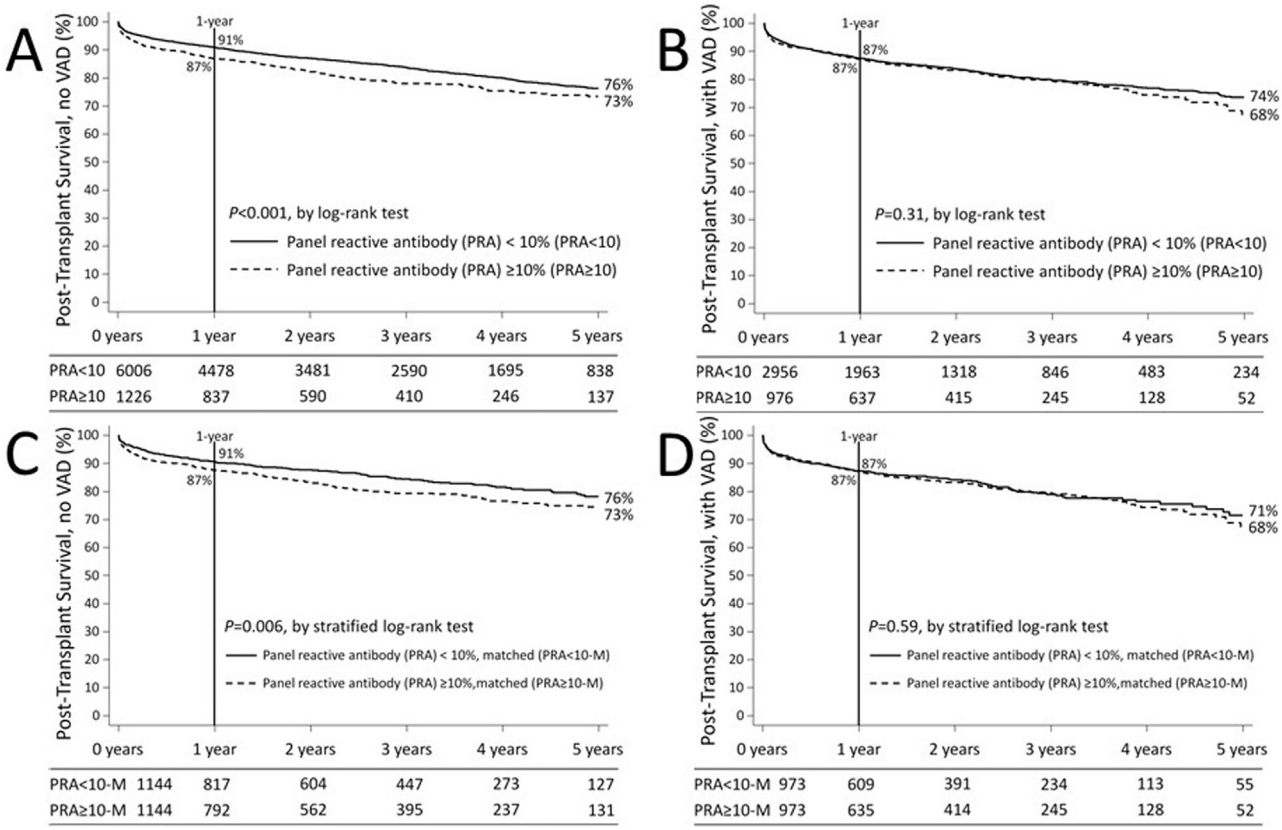

Figure 1 Kaplan-Meier analysis of post-transplant survival, comparing patients with and without elevated most recent composite panel reactive antibody level. (A) Unmatched analysis of patients without mechanical circulatory support (MCS). (B) Unmatched analysis of patients with MCS implanted. (C) Matched analysis of patients without MCS. (D) Matched analysis of patients with MCS implanted.

presence of an isolated LVAD implantation was associated with worse post-transplantation survival before 2008, although survival was similar in the post-2008 era when the medically managed cohort included patients with an intra-aortic balloon pump. These reports suggest the presence of an era effect on the relationship between LVAD and mortality after HTx. Our analysis was limited to a contemporary era (July 12, 2006–December 31, 2012) and was unable to demonstrate an era effect in the entire cohort or each of the sub-groups with and without MCS. In addition, this analysis identified each class of MCS as an independent predictor of post-transplantation mortality suggesting that equivalence has not yet been reached.

This presents a complicated picture. On the one hand, our analysis identified MCS as predictive of post-transplantation mortality. On the other hand, LVAD implantation appears to confer a beneficial effect on waiting list survival compared with medically managed patients.[5,6] Indeed, given the excellent performance of uncomplicated LVAD patients on the waiting list, Dardas et al[5] suggested that they not be afforded elective Status 1A time and even be downgraded from mandatory Status 1B. However, an analysis of waiting list data cannot capture the upfront risk associated with the LVAD operation; that is, not all patients who underwent the initial LVAD operation were eventually wait listed. Moreover, analyses of waiting list data and data at transplantation are unable to include clinical status at the time of MCS implantation unless the device was implanted while on the waiting list. In this way, the decision to implant an LVAD or any other MCS device must be made while considering the risk associated with the operation, the potential waiting list benefit, and the potential effect on post-transplantation survival. In many cases, patients may not survive to transplantation without implantation of a durable MCS device. Overall, appropriate MCS implantation appears to have a net benefit, though further studies must be performed to optimize the timing of implantation and the selection of patients.

Limitations

This was a retrospective review of patients undergoing transplantation using registry data. It is limited by potential inconsistencies in reporting data and completeness. Statistical methods were used to mitigate the effect of missing data in collected variables without increasing the likelihood of introducing spurious positive results. However, this does not account for variables that were not collected. As a result, in-depth analyses of the changes to the immunosuppressive regimen as a result of being allosensitized or the effects of allosensitization on cardiac allograft vasculopathy were not possible because that information was not available in sufficient detail and quality in the UNOS data set. Unfortunately, rejection data were also insufficient to produce a satisfactory analysis of the effect of PRA on

various forms of rejection. Specific HLA-antibody data were not available and could not be correlated with survival or cardiac allograft vasculopathy. Each of these may be worthy of study in a separate analysis. Finally, this analysis does not include patients who died on the waiting list.

The existence of several methods to screen for PRA introduces variability to the measurement of PRA. Use of different tests by different laboratories can produce substantially different PRA levels, resulting in labelling one patient as allosensitized by one laboratory and the same patient as not allosensitized at another laboratory.[35]

Conclusions

Allosensitization is a heterogeneous process that is affected by the presence of MCS. Although PRA screening remains beneficial to identify patients who may require a prospective crossmatch, allosensitization was not an independent predictor of mortality in patients with MCS. MCS was an independent predictor of post-HTx mortality, but this result must be taken cautiously because patients being considered for MCS may otherwise not survive to transplantation. As such, MCS should continue to be used as a bridge to transplantation in appropriately selected patients.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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