The American Journal of Surgery 218 (2019) 737–743

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

The role of estrogen, immune function and aging in heart transplant outcomes

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ARTICLE INFO

Article history:
Received 25 February 2019
Received in revised form
5 May 2019
Accepted 16 July 2019

ABSTRACT

Background: Aging and loss of estrogen suppress immune function, potentially improving survival after orthotopic heart transplant (OHT). The effect of female aging on OHT outcomes is unknown.
Methods: Between 1995 and 2015, 41,299 adult OHT recipients (24.3% women) were studied using a retrospective multi-institutional cohort. Patients were stratified by age and gender into premenopausal (18–39 years), perimenopausal (40–49 years), and postmenopausal (≥50 years) groups. Kaplan-Meier survival analyses and risk-adjusted models examined gender differences across groups at one, five, and ten years.
Results: Kaplan-Meier survival was equivalent for postmenopausal women and men, and lower for premenopausal women than men at all time points ($p \leq 0.05$). Postmenopausal women had higher risk-adjusted five-year survival than premenopausal women (AOR 1.61, 95% CI 1.15–2.25, $p = 0.006$).
Conclusions: Premenopausal women have lower unadjusted survival than men after OHT. Postmenopausal women have significantly better five-year survival than pre-menopausal women. Menopause may contribute to improved survival after OHT.

Introduction

Among orthotopic heart transplant (OHT) recipients, women are a minority. Compared to men, women have an equal incidence of new heart failure diagnosis and rate of heart failure death in the United States, yet receive less than 20% of total heart transplants per year.[1,2] Their odds of survival after OHT are poorly understood, relative to men – data from the United Network for Organ Sharing (UNOS), and multiple single-institution studies, suggest that women have lower one, three and five year survival than men; in contrast, the International Society for Heart and Lung Transplant (ISHLT) data indicates better survival for women.[2–4]

One contributor to survival disparity between the sexes may be the effect of estrogen. Estrogen is a known immune stimulator, inducing B cell activation in humans, and increasing circulating levels of IgG and IgM.[5,6] In patients with autoimmune disease, estrogen increases (and testosterone decreases) circulating levels of autoantibodies.[5] Furthermore, men and postmenopausal women have numerically fewer total B and T cells, when compared to premenopausal women.[5–7] These estrogen effects may confer a mortality benefit after routine cardiac surgical operations, with better outcomes reported among younger women.[8] However, among heart transplant recipients, the amplified immune response seen in younger women may not be desirable.

In addition to increased baseline immunity, women also have a higher incidence of allosensitization - exposure and sensitization to foreign Human Leukocyte Antigens.[9] Allosensitization is measured in transplant candidates by the Panel Reactive Antibody (PRA) assay, and women have higher average percent positive PRA.[10] This predicts a longer time on the transplant waitlist, and correlates to increased likelihood of graft rejection and other complications post-operatively.[11] The higher rate of allosensitization, combined with more robust immune function in the presence of estrogen,

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https://doi.org/10.1016/j.amjsurg.2019.07.007
0002-9610/

leads to a higher incidence of acute rejection for women in comparison to men, especially in the first year after OHT. Women consequently require higher doses of immunosuppression, and are at greater risk of infection-related death.[12–15] Although immune senescence occurs in both genders, the effects of menopause and associated decrement in estrogen on immune function among female OHT recipients have not been described.[16]

In this study, we investigate the effect of menopause on all-cause survival after OHT. We test the hypothesis that the odds of survival after transplant are higher for postmenopausal women than premenopausal women. We also postulate that odds of survival among postmenopausal women following OHT are similar to those of age-matched men.

Methods

Registry source

The United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) database was utilized to identify all adult patients who underwent OHT between 1995 and 2015. Outcomes analysis of this registry was not considered human subjects research, and was exempt from Oregon Health & Science University's Institutional Review.

Study population

De-identified patient data were separated by age and gender. Subsequently, women were stratified into three groups: premenopausal (18–39y), perimenopausal (40–49y), and postmenopausal (≥50y) based on the average age of menopause in the United States.[17] Missing data completely at random underwent case-wise deletion to ensure no missing values prior to analysis.

Statistical analysis

The primary end-point was overall survival at one, five, and ten years following OHT. The strength of association for each variable was measured using appropriate statistical hypothesis testing. The statistical significance of differences in proportions for categorical variables was evaluated by the Pearson χ^2 or Fisher's exact test ($P < 0.05$). The significance of differences in mean values for continuous variables was assessed using single factor analysis of variance models ($P < 0.05$). Survival was analyzed using Kaplan-Meier curves, and results were compared between groups using the log-rank test. Univariable comparisons and separate multivariable regression models were developed to calculate the adjusted odds of survival, by controlling for differences in patient demographics, preoperative characteristics, and operative features. Covariate selections were made *apriori* based upon established literature. Model statistics were computed. The models' predictive capacity to discriminate was measured using the area under the receiver operator curve (AUC). Unadjusted and adjusted odds ratios with 95% confidence intervals were computed. To test that findings were independent of the data, sensitivity analyses were performed, repeating logistic models on randomly generated validation datasets comprising 50% of cases. A decrement of <10% in odds ratio was considered consistent. All data were analyzed using Stata/IC 12.1 (StataCorp LP, College Station, Texas).

Results

Study population

Between 1995 and 2015, 41,299 adult patients underwent OHT (31,251 men and 10,048 women). Table 1 outlines the baseline characteristics of each age group. The premenopausal and

Table 1
Baseline characteristics of study population.

	Age			*P*
	18–39	40–49	≥50	
Number of Patients	6442	7131	27,726	
Women, %	37.5	26.6	20.7	*<0.01*
HF diagnosis, %	79.4	85.4	85.5	*<0.01*
White, %	60.3	65.7	78.1	*<0.01*
US Citizen, %	96.7	97.4	98.1	*<0.01*
BMI, Mean ± SD	25.20 ± 6.4	26.9 ± 5.9	26.5 ± 5.4	*<0.01*
Diabetes, %	4.7	10.3	16.7	*<0.01*
Private Insurance, %	53.7	59.9	54.7	*0.14*
Tobacco use	28%	51%	60%	*<0.01*
Functional status*	5.4 ± 2.4	5.7 ± 2.3	5.8 ± 2.2	*<0.01*
Education level**	3.6 ± 0.9	3.8 ± 1.0	3.9 ± 1.1	*<0.01*
Creatinine, Mean ± SD	1.23 ± 1.2	1.30 ± 1.2	1.37 ± 1.0	*<0.01*
PreOp Dialysis, %	4.4	3.9	2.9	*<0.01*
PreOp Steroids, %	12.0	9.9	8.3	*<0.01*
tBili, Mean ± SD	1.24 ± 2.2	1.17 ± 2.7	1.13 ± 2.7	*<0.01*
PreOp Transfusion, %	24.9	22.6	20.5	*<0.01*
Cerebrovasc Disease, %	3.6	4.0	4.7	*<0.01*
Mean CO (L/min)±SD	3.40 ± 2.0	3.8 ± 1.8	3.9 ± 1.9	*<0.01*
Mean PAP (mmHg) ±SD	38.00 ± 19.0	42.00 ± 18.0	42.00 ± 18.0	*<0.01*
On vent	19.92	18.70%	16.6	*<0.01*
VAD	25.90	24.1	22.3	*<0.01*
Gender Match	67.90	72.5	72.8	*<0.01*
Donor Age	28.5 ± 11.0	30.9 ± 11.8	32.3 ± 12.5	*<0.01*
Ischemic Time	3.0 ± 1.3	2.9 ± 1.2	3.0 ± 1.2	*<0.01*
Donor Diabetes	2.10	2.3	2.7	*<0.01*

Age	18–39		40–49		≥50	
	Men	Women	Men	Women	Men	Women
PRA %, Mean ± SD	2.81 ± 12.4	4.76 ± 17.2	2.70 ± 11.7	*5.44 ± 17.9*	2.23 ± 10.3	4.56 ± 16.8

postmenopausal groups were significantly different in all baseline characteristics except insurance coverage (all $p < 0.01$). Compared to the postmenopausal group, the premenopausal group had more women (37.5% vs 20.7%), fewer Caucasians (60.3% vs 78.1%), fewer patients with diabetes (4.7 vs 16.7%), and more patients who received preoperative steroids (12.0% vs 8.3%) and blood transfusions (24.9% vs 20.5%). This highlights important differences between younger and older populations undergoing heart transplant, alluding to a potentially higher incidence of autoimmune disease (preoperative steroids) and exposure to foreign HLA antigens (transfusions) in the younger population. With regard to baseline levels of allosensitization, percent positive PRA was higher for women compared to men within each age group ($p < 0.01$), but equivalent between post-menopausal and pre-menopausal women ($p = 0.63$).

Kaplan Meier analyses

One, five and ten-year survival curves for men vs women, by age, are shown in Fig. 1. Women 18–39 and 40–49 years had worse survival than age-matched men at all time points ($p < 0.02$ *for all*). Women ≥50 years had equivalent survival to age-matched men at all time points ($p > 0.5$ *for all*).

Unadjusted outcomes

Women 18–39 and 40–49 years had significantly worse survival than men at all time points, while women ≥50 years had equivalent survival compared to men (Supplementary Tables 1–3). Other factors associated with improved survival at one, five and ten years were: preoperative diagnosis of any cardiomyopathy, white race, donor-recipient gender matching, and higher recipient education level ($p < 0.05$ *for all*) (Supplementary Tables 1–3). Unsurprisingly, factors associated with worse survival at all time points included –– lack of private insurance, elevated preoperative creatinine or serum bilirubin levels, preoperative dialysis, blood transfusion or ventilator dependence, increased donor age, longer ischemic time, history of donor alcohol and/or tobacco use, donor diabetes, positive CMV status, postoperative stroke or dialysis requirement, higher PRA%, and graft failure ($p < 0.05$ *for all*) (Supplementary Tables 1–3).

Adjusted outcomes

Postmenopausal women had better adjusted five-year survival than premenopausal women (AOR 1.61, 95% CI 1.15–2.25, $p = 0.006$), however their one and ten-year survival was similar. Among premenopausal patients, female gender was associated with a trend towards worse survival at one and five years (one year: AOR 0.75, 95% CI 0.54–1.01, $P = 0.06$; five year: AOR 0.79, 95% CI 0.55–1.12, $P = 0.18$). Ten year survival was equivalent between premenopausal women and men (AOR 0.98, 95% CI 0.54–1.79, $P = 0.95$) (Tables 2–4; all $AUC > 0.8$). There were no significant differences in adjusted odds of survival between men and women over age 40 (Table 2 through 4; all $AUC > 0.9$). Graft failure was the only factor independently associated with poor survival in all age groups at all time points ($P < 0.001$ *for all*) (see Table 5).

In summary, postmenopausal women had better risk-adjusted five-year survival than premenopausal women. Furthermore, compared to men, postmenopausal women had equivalent survival at all time intervals. Separately, Kaplan-Meier curves and unadjusted models identified premenopausal women to have a

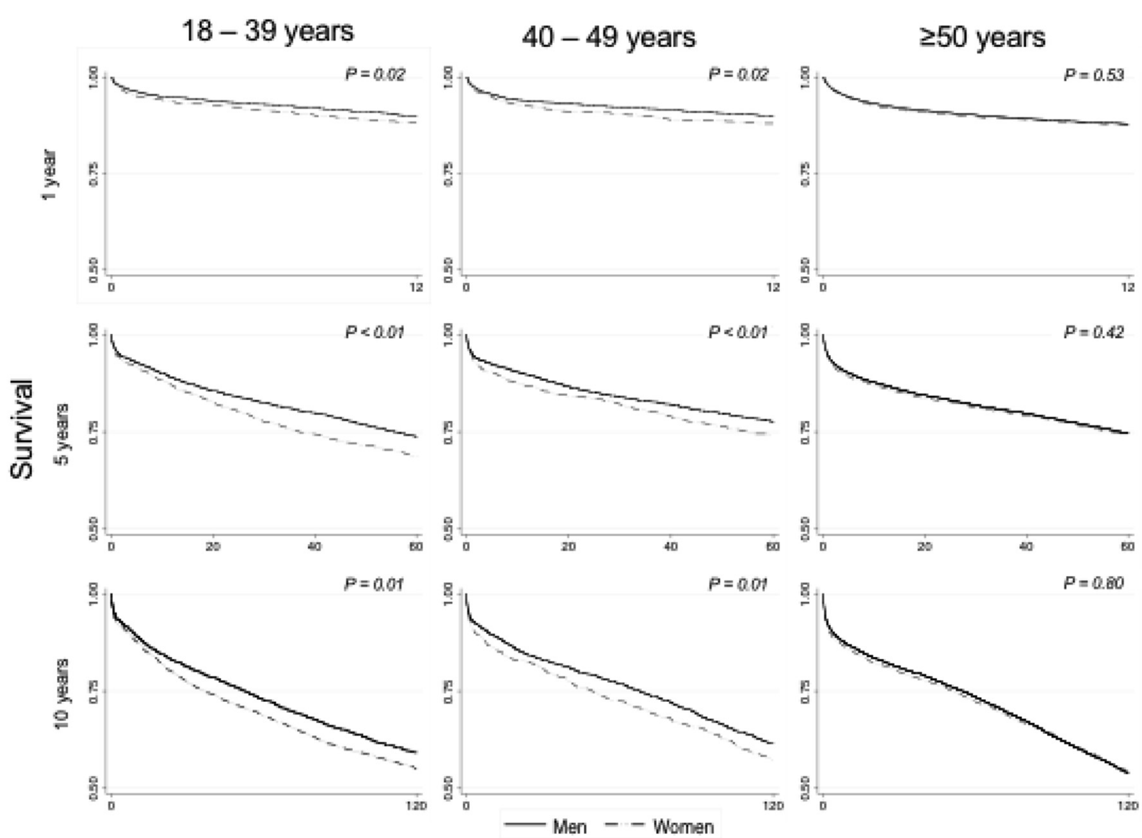

Fig. 1. Kaplan-Meier analyses examining survival between genders across age groups at one, five, and ten years post heart transplant.

Table 2
Risk-adjusted odds of survival by age group and gender.

Women vs Men by Age			
18–39			
	AOR	95% CI	*p*
1 yr	0.75	0.55-1.01	*0.06*
5 yrs	0.78	0.55-1.12	*0.18*
10 yrs	0.98	0.54-1.79	*0.95*
40–49			
	AOR	95% CI	*p*
1 yr	0.83	0.56-1.22	*0.34*
5 yrs	0.83	0.57-1.22	*0.35*
10 yrs	0.69	0.39-1.24	*0.22*
≥50			
	AOR	95% CI	*p*
1 yr	0.88	0.73-1.06	*0.18*
5 yrs	0.99	0.81-1.21	*0.94*
10 yrs	1.22	0.92-1.62	*0.17*
Post- vs Premenopausal Women			
	AOR	95% CI	*p*
1 yr	0.86	.63-1.17	*0.33*
5 yrs	1.61	1.15-2.25	*0.006*
10 yrs	1.11	0.65-1.88	*0.71*

survival disadvantage compared to men. However, following risk adjustment, gender was not independently associated with poor survival.

Sensitivity analysis

Validation datasets comprising 50% of randomly selected cases underwent reanalysis. Models demonstrated <10% decrement in the adjusted odds ratios as independent predictors of survival across all age groups (*Data not shown*).

Discussion

In this study, we shed new light on the complex relationship between gender, aging, and heart transplant outcomes. Foundational studies have shown that women have heightened immune function due to the effect of estrogen; are at higher risk than men of allosensitization, and have higher incidence than men of acute rejection after transplant.[11–14] However, the combined effect of these factors on survival after OHT has not been shown. Furthermore, while aging causes immune senescence, the impact of aging on gender-specific survival after OHT is unknown. To this end, our study is the first to examine outcomes following OHT at short, medium and long-term, comparing men to women stratified by menopausal status. Our data shows that postmenopausal women have superior survival versus premenopausal women at medium term follow-up after OHT. Furthermore, postmenopausal women have equivalent survival to men at all time points after OHT.

Our findings are consistent with contemporary transplant immunology in that: (I) estrogen causes immune upregulation in multiple pathways, (II) women are at higher risk of allosensitization to donor HLA, because of pregnancy, (III) related to this robust

Table 3
Risk-adjusted multivariable model of one-year survival.

	Age											
	18–39				40–49				≥50			
	AOR	95% CI		*p*	AOR	95% CI		*p*	AOR	95% CI		*P*
Recipient Demographics												
Female Gender	0.75	0.55	1.01	*0.06*	0.83	0.56	1.22	*0.34*	0.88	0.73	1.06	*0.18*
HF	1.61	1.08	2.40	*0.02*	0.94	0.56	1.59	*0.82*	1.00	0.79	1.28	*0.98*
White Race	1.34	0.98	1.82	*0.07*	0.94	0.66	1.34	*0.74*	1.09	0.91	1.30	*0.36*
US Citizen	0.75	0.25	2.26	*0.61*	2.66	0.97	1.04	*0.06*	2.14	1.12	4.07	*0.02*
BMI	0.98	0.95	1.01	*0.07*	1.00	0.98	1.04	*0.55*	1.00	0.98	1.01	*0.62*
Diabetes	1.20	0.69	2.09	*0.51*	1.45	0.90	2.31	*0.12*	0.78	0.65	0.93	*0.01*
Patient Tobacco Use	0.98	0.70	1.38	*0.91*	1.47	1.05	2.06	*0.03*	1.15	0.98	1.34	*0.09*
Private Insurance	1.04	0.76	1.41	*0.82*	1.22	0.87	1.72	*0.26*	1.14	0.98	1.32	*0.10*
Functional Status	1.03	0.97	1.10	*0.35*	1.09	1.01	1.18	*0.02*	1.03	0.99	1.06	*0.16*
Education Level	0.99	0.82	1.19	*0.92*	1.02	0.85	1.23	*0.79*	0.98	0.92	1.05	*0.61*
Preoperative Characteristics												
%PRA	1.00	0.99	1.02	*0.98*	1.00	0.98	1.01	0.82	1.01	1.00	1.01	*0.25*
Creatinine	0.97	0.85	1.11	*0.63*	0.90	0.74	1.08	*0.26*	0.93	0.85	1.01	*0.10*
Dialysis	1.29	0.60	2.79	*0.51*	0.54	0.24	1.19	*0.12*	2.01	1.29	3.12	*<0.01*
Steroids	1.33	0.86	2.06	*0.20*	1.40	0.82	2.39	*0.22*	1.41	1.08	1.82	*0.01*
Total Bilirubin	0.99	0.91	1.07	*0.79*	0.97	0.92	1.03	*0.35*	0.93	0.89	0.97	*<0.01*
Transfusions	0.86	0.58	1.28	*0.46*	1.21	0.77	1.91	*0.41*	0.83	0.67	1.03	*0.10*
On Ventilator	0.88	0.57	1.33	*0.53*	1.01	0.61	1.69	*0.96*	0.78	0.62	0.99	*0.04*
VAD	1.17	0.80	1.73	*0.42*	0.44	0.29	0.66	*<0.01*	0.52	0.43	0.63	*<0.01*
History of CVA	0.38	0.18	0.77	*0.01*	1.05	0.51	2.15	*0.89*	0.93	0.68	1.29	*0.68*
Intraoperative Characteristics												
Cardiac Output	1.01	0.93	1.10	*0.78*	1.05	0.96	1.14	*0.33*	1.02	0.98	1.07	*0.35*
PA Pressure	1.01	0.10	1.02	*0.09*	1.00	0.99	1.01	*0.91*	0.99	0.99	1.00	*0.02*
Donor Characteristics												
Gender Match	0.82	0.59	1.13	*0.22*	0.88	0.60	1.30	*0.53*	1.25	1.05	1.47	*0.01*
Donor Age	0.98	0.97	0.99	*<0.01*	0.99	0.99	1.01	*0.85*	0.99	0.99	1.00	*0.04*
Ischemic Time	1.00	0.89	1.13	*0.96*	0.99	0.87	1.13	*0.89*	0.96	0.91	1.03	*0.25*
Donor Diabetes	0.64	0.24	1.69	*0.37*	0.95	0.39	2.31	*0.91*	0.66	0.44	0.99	*0.05*
HLA Mismatch	1.01	0.93	1.10	*0.91*	0.94	0.89	1.03	*0.19*	1.00	0.96	1.04	*0.85*
Postoperative Outcomes												
Stroke	0.42	0.20	0.88	*0.02*	0.29	0.13	0.65	*<0.01*	0.26	0.18	0.37	*<0.01*
Dialysis	0.31	0.20	0.46	*<0.01*	0.13	0.09	0.21	*<0.01*	0.16	0.13	0.19	*<0.01*
Pacemaker Placement	0.64	0.27	1.50	*0.30*	0.91	0.28	2.99	*0.88*	0.93	0.63	1.38	*0.73*
Graft Failure	1.9E-03	4.6E-04	7.5E-03	*<0.01*	6.6E-04	9.1E-05	4.8E-03	*<0.01*	2.8E-04	6.9E-05	1.1E-03	*<0.01*

Table 4
Risk-adjusted multivariable model of five-year survival.

	18–39				40–49				≥50			
	AOR	95% CI		*p*	AOR	95% CI		*p*	AOR	95% CI		*p*
Recipient Demographics												
Female Gender	0.78	0.55	1.12	*0.18*	0.83	0.57	1.22	*0.35*	0.99	0.81	1.21	*0.94*
HF	1.73	1.09	2.76	*0.02*	0.96	0.58	1.58	*0.87*	0.79	0.62	1.01	*0.06*
White Race	1.41	1.00	1.98	*0.05*	1.22	0.86	1.73	*0.27*	1.29	1.06	1.57	*0.01*
US Citizen	0.54	0.18	1.63	*0.28*	0.75	0.24	2.38	*0.63*	1.67	0.77	3.61	*0.19*
BMI	0.98	0.95	1.01	*0.14*	1.01	0.98	1.04	*0.46*	0.99	0.98	1.01	*0.45*
Diabetes	0.83	0.42	1.64	*0.60*	0.99	0.61	1.61	*0.99*	0.74	0.60	0.91	*<0.01*
Patient Tobacco Use	0.83	0.57	1.22	*0.35*	1.25	0.98	1.73	*0.18*	0.99	0.85	1.17	*0.97*
Private Insurance	1.34	0.95	1.89	*0.09*	1.20	0.86	1.68	*0.38*	1.11	0.95	1.29	*0.19*
Functional Status	1.11	1.04	1.20	*<0.01*	1.08	0.99	1.16	*0.07*	1.08	1.04	1.12	*<0.01*
Education Level	1.24	1.00	1.53	*0.05*	0.99	0.82	1.18	*0.89*	0.96	0.89	1.03	*0.29*
Preoperative Characteristics												
%PRA	1.01	0.99	1.02	*0.27*	1.00	0.98	1.01	*0.77*	1.00	0.99	1.01	*0.88*
Creatinine	0.91	0.76	1.08	*0.30*	0.86	0.68	1.09	*0.22*	0.98	0.89	1.07	*0.63*
Dialysis	1.33	0.48	3.65	*0.58*	0.45	0.17	1.23	*0.12*	0.79	0.46	1.37	*0.42*
Steroids	1.66	1.05	2.64	*0.03*	0.89	0.56	1.41	*0.61*	0.87	0.68	1.12	*0.28*
Total Bilirubin	1.02	0.93	1.12	*0.69*	0.99	0.94	1.01	*0.85*	0.94	0.91	0.98	*<0.01*
Transfusions	1.09	0.93	1.12	*0.68*	1.33	0.83	2.14	*0.24*	0.92	0.72	1.19	*0.53*
On Ventilator	1.48	0.88	2.47	*0.14*	1.86	1.06	3.26	*0.03*	0.74	0.56	0.99	*0.04*
VAD	0.74	0.47	1.17	*0.20*	0.35	0.22	0.57	*<0.01*	0.57	0.44	0.74	*<0.01*
History of CVA	1.38	0.61	3.13	*0.44*	1.15	0.56	2.38	*0.70*	1.03	0.73	1.46	*0.87*
Intraoperative Characteristics												
Cardiac Output	1.03	0.94	1.13	*0.53*	1.11	1.02	1.22	*0.02*	1.01	0.96	1.05	*0.74*
PA Pressure	0.99	0.98	1.00	*0.24*	0.99	0.99	1.00	*0.57*	1.00	0.99	1.00	*0.50*
Donor Characteristics												
Gender Match	1.48	1.03	2.14	*0.04*	1.06	0.73	1.54	*0.77*	1.29	1.09	1.55	*<0.01*
Donor Age	0.98	0.96	0.99	*<0.01*	0.99	0.98	1.01	*0.78*	0.99	0.99	1.00	*0.11*
Ischemic Time	0.90	0.79	1.03	*0.12*	0.99	0.87	1.14	*0.94*	0.93	0.87	0.99	*0.02*
Donor Diabetes	0.34	0.09	1.28	*0.11*	1.18	0.48	2.90	*0.72*	0.61	0.38	0.99	*0.05*
HLA Mismatch	0.96	0.88	1.05	*0.34*	0.96	0.89	1.05	*0.38*	1.01	0.97	1.05	*0.62*
Postoperative Outcomes												
Stroke	0.48	0.17	1.34	*0.16*	0.77	0.26	2.26	*0.64*	0.35	0.21	0.58	*<0.01*
Dialysis	0.79	0.45	1.44	*0.46*	0.21	0.12	0.39	*<0.01*	0.34	0.26	0.44	*<0.01*
Pacemaker Placement	1.52	0.59	3.94	*0.39*	0.49	0.14	1.72	*0.27*	0.95	0.63	1.43	*0.80*
Graft Failure	1.9E-03	7.5E-04	4.6E-03	*<0.01*	2.4E-03	1.0E-03	5.7E-03	*<0.01*	3.5E-03	2.3E-03	5.2E-03	*<0.01*

immunity and prior exposure to foreign antigens, women are more likely to experience acute rejection after OHT, and (IV) despite this higher incidence of acute rejection, women have fewer long-term major adverse cardiac events after transplant, and have a lower rate of cardiac related death.

The influence of estrogen on the immune system has been postulated since the late 1960s, when Butterworth et al. demonstrated that women have higher levels of circulating IgG and IgM compared to men.[18] Estrogen is known to increase total number of progenitor B cells, and induce B cell activation.[6,7] Separately, estrogen also upregulates (while testosterone downregulates) autoantibody production, contributing in part to the greater prevalence of autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus in women.[5] Differential expression of estrogen receptors on monocytes, neutrophils, and B and T lymphocyte subsets influence matrikine function.[6,7] Estrogen is also thought to decrease peripheral polymorphonuclear leukocyte and monocyte chemotaxis.[19] Collectively, estrogen mediates both innate and humoral immune mechanisms, and indirectly influences post transplant immunogenic responses. Estrogen-modulated immunity may partially explain our findings of worse survival in premenopausal women. Taking five-year survival as an example, our work indicates that the adjusted odds of survival for women improved with the loss of estrogen in menopause, as the post-menopausal age group had adjusted odds of survival of 1.61 compared to premenopausal women ($P = 0.006$).

In addition to the stimulatory effect of estrogen, adult women of all ages are at baseline higher risk of exposure to foreign antigens and resulting allosensitization than men, due to the effect of previous pregnancy.[9] Furthermore, while red blood cell transfusions are also HLA-sensitizing events (in both genders), women with a history of pregnancy are at greater risk of developing anti-HLA antibodies after transfusion than are men or nulliparous women.[20] For transplant candidates, HLA allosensitization is measured using the panel reactive antibody (PRA) assay, where a higher percent positivity indicates sensitization to a greater number of potential donor antigens.[10,11] The presence of alloantibodies results in a smaller pool of acceptable donor organs, leading to a longer time on the transplant waitlist, as well as increased postoperative complications, including acute rejection and mortality.[11] Our results are consistent with prior reports, in that women of all age groups in our study have a higher %PRA than age-matched men (all $P < 0.01$). Aging did not decrease the level of allosensitization for women in this study, and the postmenopausal and premenopausal age groups had equivalent %PRA.

Consistent with these findings of enhanced innate immunity and increased likelihood of allosensitization, multiple studies have shown a higher likelihood of acute and severe rejection episodes in women than men: In a single-center retrospective review of 520 adult heart transplant patients, Lietz and colleagues reported that female gender was independently associated with shorter interval to first rejection episode, more frequent episodes of rejection, and higher early mortality rates.[14] Not only are episodes of rejection more frequent for women, but Mills and colleagues reported that episodes of rejection in women are more likely to be associated with severe hemodynamic compromise.[15] As a consequence of

Table 5
Risk-adjusted multivariable model of ten-year survival.

	Age											
	18–39				40–49				>50			
	AOR	95% CI		*p*	AOR	95% CI		*p*	AOR	95% CI		*p*
					Recipient Demographics							
Female Gender	0.98	0.54	1.79	*0.95*	0.69	0.39	1.24	*0.22*	1.22	0.92	1.62	*0.17*
HF	1.15	0.53	2.51	*0.72*	0.76	0.38	1.51	*0.43*	0.81	0.59	1.11	*0.20*
White Race	1.65	0.90	3.03	*0.10*	1.21	0.69	2.14	*0.50*	1.14	0.84	1.53	*0.41*
US Citizen	0.15	0.02	1.06	*0.06*	0.69	0.13	3.79	*0.67*	0.68	0.19	2.46	*0.56*
BMI	0.99	0.94	1.05	*0.83*	1.03	0.98	1.07	*0.28*	0.99	0.97	1.01	*0.45*
Diabetes	1.00	0.13	7.80	*1.00*	0.54	0.12	2.51	*0.43*	0.71	0.43	1.17	*0.18*
Patient Tobacco Use	0.31	0.14	0.68	*<0.01*	1.03	0.62	1.71	*0.92*	0.94	0.74	1.18	*0.59*
Private Insurance	1.99	1.09	3.60	*0.03*	1.36	0.79	2.34	*0.26*	1.20	0.97	1.50	*0.10*
Functional Status	1.05	0.91	1.21	*0.47*	0.92	0.80	1.06	*0.27*	1.02	0.96	1.08	*0.52*
Education Level	1.23	0.86	1.78	*0.24*	1.05	0.80	1.37	*0.73*	1.05	0.95	1.17	*0.32*
					Preoperative Characteristics							
% PRA	1.00	0.98	1.02	*0.87*	0.99	0.97	1.01	*0.36*	1.00	0.99	1.01	*0.68*
Creatinine	0.91	0.60	1.38	*0.65*	1.28	0.80	2.04	*0.30*	1.04	0.92	1.17	*0.55*
Dialysis	1.78	0.28	11.19	*0.54*	1.13	0.38	4.60	*0.86*	1.00	0.43	2.32	*1.00*
Steroids	1.74	0.73	4.11	*0.21*	1.93	0.93	4.02	*0.08*	0.79	0.55	1.13	*0.20*
Total Bilirubin	1.03	0.85	1.25	*0.76*	1.00	0.70	1.42	*0.99*	0.97	0.93	1.02	*0.30*
Transfusions	0.82	0.32	2.09	*0.68*	1.00	0.45	2.22	*0.99*	1.13	0.75	1.68	*0.53*
On Ventilator	0.58	0.18	1.86	*0.36*	2.94	1.01	8.58	*0.05*	0.90	0.55	1.49	*0.69*
VAD	0.83	0.28	2.52	*0.75*	0.27	0.11	0.71	*<0.01*	0.86	0.53	1.41	*0.56*
History of CVA	0.53	0.11	2.54	*0.43*	1.34	0.43	4.19	*0.61*	1.17	0.73	1.94	*0.52*
					Intraoperative Characteristics							
Cardiac Output	1.05	0.90	1.23	*0.53*	1.06	0.91	1.22	*0.45*	0.96	0.90	1.03	*0.24*
PA Pressure	1.00	0.98	1.01	*0.69*	1.00	0.98	1.01	*0.55*	1.00	0.99	1.01	*0.75*
					Donor Characteristics							
Gender Match	2.09	1.12	3.88	*0.02*	0.69	0.38	1.24	*0.21*	1.27	0.99	1.63	*0.06*
Donor Age	0.96	0.94	0.99	*<0.01*	0.99	0.97	1.01	*0.55*	1.00	0.99	1.01	*0.70*
Ischemic Time	0.94	0.76	1.16	*0.56*	1.38	1.05	1.57	*0.02*	0.96	0.88	1.05	*0.38*
Donor Diabetes	0.19	0.03	1.26	*0.09*	0.95	0.19	4.85	*0.95*	1.03	0.47	2.28	*0.93*
HLA Mismatch	0.93	0.80	1.07	*0.30*	0.82	0.73	0.93	*<0.01*	1.04	0.98	1.10	*0.17*
					Postoperative Outcomes							
Stroke	0.41	0.07	2.51	*0.34*	1.26	0.25	6.54	*0.79*	0.16	0.06	0.41	*<0.01*
Dialysis	0.78	0.28	2.17	*0.64*	0.20	0.07	0.57	*<0.01*	0.55	0.37	0.82	*<0.01*
Pacemaker Placement	0.59	0.09	3.98	*0.59*	0.12	0.02	0.78	*0.03*	0.82	0.46	1.45	*0.50*
Graft Failure	4.5E-03	1.9E-03	1.1E-02	*<0.01*	7.0E-03	3.5E-03	1.4E-02	*<0.01*	0.01	0.01	0.02	*<0.01*

their robust immune response, and increased severity and frequency of acute rejection, women receive higher doses of immunosuppression and are less likely to be maintained off corticosteroids than men.[13] Our findings are consistent with Foster et al. who demonstrated that young adults (age 17–24 years) are at increased risk for rejection-mediated graft failure after OHT, suggesting they have a robust immune response and require higher amount immunosuppression for treatment.[21] Expanding on this previous work, we are the first to investigate survival following OHT at early, mid and late time points among recipients stratified by gender and menopausal status.

While the higher mid-term mortality following OHT among premenopausal women is sobering, long-term survival among perimenopausal women provides significant encouragement, and is also supported by prior studies. Hiemann and colleagues demonstrated that after the first five years following heart transplant, women were at much lower risk of major adverse cardiac events —— lethal myocardial infarction, sudden cardiac death, graft failure, and cardiac retransplantation (Relative Risk 0.38; 95% Confidence Interval 0.17–0.81).[22] Eifert and colleagues from Munich reported their findings from a single-center among 1000 heart transplant recipients (960 primary + 40 redo), that conditional on survival to 1 year, survival at 10 years was significantly greater for female donors and female recipients (90%) than it was for male donors and male recipients (72%; $P = 0.03$).[23] Consistent with prior studies, we demonstrate that premenopausal women trend towards worse survival than age matched men at one and five years; this survival difference is nonexistent at ten years (adjusted odds of survival 0.98, $P = 0.95$). Furthermore, while postmenopausal women have better survival than premenopausal women at five years (AOR 1.6, $P = 0.006$), their ten-year survivals are equivalent (AOR 1.1, $P = 0.71$).

Limitations

There are several limitations to our work. First, menopause is a continuum rather than a discrete event, and estrogen levels are not collected or recorded in the UNOS database. In this study we apply the average age of menopause in the US to define our cohorts, but acknowledge that some patients in each group will not be accurately classified by these age cutoffs. Next, UNOS STAR is a large database with the potential for miscoding. Coding errors are expected to be homogenously distributed across all groups, thus equally affecting the groups in this evaluation. To exclude errors encountered due to missing data, we analyzed our models using complete case methodology.[24] We observed that variables captured for transplant candidates and recipients changed over time. For example, we were unable to include episodes of acute rejection in our multivariable analysis, as it is not recorded in 42% of recently transplanted patients, and 80% of patients transplanted >10 years ago. Furthermore, institutional level donor management, specific surgical technique and critical care algorithms in post heart transplant care cannot be evaluated by our analysis. Finally, the potential for an unmeasured confounder may remain, which is inherent to the constraints of the UNOS STAR data points. We are unable to adjust for other well-established surgical risk factors such as low perioperative albumin levels or poor nutritional status. Sensitivity analyses of our findings were completed to ensure that our findings were independent of the dataset, but these analyses are similarly impacted by missing data.

Conclusions

We demonstrate that postmenopausal women have equivalent survival to men at one, five and ten years post heart transplant, and superior survival to premenopausal women at five years. Although premenopausal women have a trend towards worse short-term survival than men after heart transplant, in the long-term, their survival is equivalent to men and older women. These new data indicate that women in general, and older women specifically, who historically have not received full attention, deserve equal consideration to men for heart transplant candidacy.

Future directions

Our findings call for a prospective study, correlating preoperative estrogen levels and postoperative outcomes among heart transplant recipients. This will further define the current data, and the complex relationship between estrogen, immunity and transplant outcomes. Our work indicates that if estrogen-mediated risk is modifiable among heart transplant recipients, then survival for young women following transplantation could be improved. Furthermore, as gender has social as well as biologic components, deeper investigations into the impact of gender on interpersonal relationships and behaviors in transplant patients is also indicated to illuminate this topic. Specific areas of interest requiring investigation include —— (i) long-term compliance fatigue (with medications, follow-up testing, biopsies, etc.) among OHT recipients by gender, (ii) types of recipient family support in women vs men, and (iii) overall emotional well-being and perceived control over healthcare outcomes in transplant recipients, by gender.

Funding

This work was supported in part by Health Resources and Services Administration contract 234-2005-37011C. The content is the responsibility of the authors alone and does not reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Conflicts of interest

The authors have no financial conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.07.007.

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