ORIGINAL ARTICLE

Donor and recipient age matching in heart transplantation: analysis of the UNOS Registry

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SUMMARY

The association of donor and recipient age with survival following adult heart transplantation has not been well characterized. The purpose of this study was to examine the impact of the relationship between donor and recipient age on post-transplant survival. We retrospectively reviewed the 2005–2018 UNOS heart transplant database for all adult recipients undergoing first-time isolated heart transplantation. The impact of donor and recipient age on survival was analyzed with Cox proportional hazards modeling using restricted cubic splines. A total of 25 480 heart transplant donor and recipient pairs met inclusion criteria. Unadjusted and adjusted Cox proportional hazards modeling demonstrated a near-linear association between increasing donor age and decreased survival; in addition, older and younger recipient age was associated with decreased survival. After adjustment, there was no significant interaction between donor and recipient age. Older donors decreased survival similarly in both older and younger recipients. Increasing donor age and both younger and older recipient age are independently associated with worsened post-heart transplant survival. The relationship between donor and recipient age does not significantly affect survival following heart transplant.

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Key words
age matching, donor age, heart transplantation, recipient age

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Introduction

Heart transplantation remains the gold standard therapy for end-stage heart failure. The demand for donor organs exceeds the limited supply, and therefore, the proper allocation of available allografts is of vital importance. Heart transplantation is performed for recipients of a wide age range with varying comorbidities. Similarly, allografts are procured from donors with a large age range. Several studies in the literature, largely single-institution analyses, have attempted to characterize the impact of both donor and recipient age on post-transplant outcomes, with conflicting results [1–4]. Studies of outcomes following kidney transplantation have suggested a synergistic effect between donor and recipient age on graft survival; however, the relationship between donor and recipient age in heart transplantation remains poorly elucidated [5].

The aim of this study was to characterize the relationship between donor and recipient age as well as to analyze the impact of age on survival following heart transplantation. We hypothesized that younger recipient age would be protective against the deleterious effects of older donor age.

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Materials and methods

Data source

The United Network for Organ Sharing (UNOS) provided Standard Transplant Analysis and Research files with deidentified deceased donor and recipient transplant data from October 1987 through March 2018. The database includes prospectively collected donor and recipient demographic and transplant data for all organ transplants performed in the United States. This study was deemed exempt by Duke University's Institutional Review Board.

Study population

We retrospectively reviewed the UNOS database for all first-time, adult (age ≥18), heart transplant recipients between 2005 and 2018 and their associated donors. Multiorgan transplants were excluded from analysis.

Data analysis

Baseline donor and recipient demographic and clinical characteristics were presented as median [interquartile range (IQR)] for continuous variables and percent (count) for categorical variables, unless otherwise specified. The associations between age, both donor and recipient, and post-transplant recipient survival were assessed using adjusted Cox proportional hazards models, with all continuous variables including age modeled using restricted cubic splines (RCS). The use of RCS is a well-validated methodology that permits the creation of regression models using continuous variables (e.g., donor and recipient age) through smoothly joined polynomial functions without the assumption of linearity [6,7]. For the purpose of identifying independent predictors of decreased survival, while controlling for potential confounders, multivariable models included both donor and recipient age functions as well as donor and recipient characteristics selected *a priori* based upon clinical experience and availability within the dataset. Relevant covariates included donor gender, race, ejection fraction (EF), and graft ischemic time; and recipient gender, donor/recipient gender mismatch, race, BMI, donor/recipient BMI ratio, history of diabetes, IV antibiotic requirement in the prior two weeks, medical condition at transplant (i.e., not hospitalized, hospitalized, or in the intensive care unit), heart failure etiology, serum creatinine and bilirubin, IV inotrope, and mechanical circulatory support requirement, as well as year of transplant. To account for within-center clustering, transplant center ID was entered into the multivariable models as a cluster variable. Models were performed as complete case analyses (all variables <1.5% missing). A subgroup landmark analysis was performed among patients who survived at least 90 days to examine outcomes independent of perioperative complications. In addition, a sensitivity analysis was performed with donor and recipient populations dichotomized into older and younger cohorts based upon qualitative inflection points from the prior splines analysis.

Two-sided *P*-values ≤0.05 were considered statistically significant unless otherwise indicated. All statistical analyses were performed using R version 3.5.1 (Vienna, Austria).

Results

A total of 25 480 heart transplant donor and recipient pairs met inclusion criteria during the study period. Baseline demographic and clinical characteristics of recipients and donors are presented in Tables 1 and 2, respectively. The median age of recipients was 56 (IQR 46–63) years, while the median age of donors was 30 (IQR 22–41) years. The bivariate distribution of donor and recipient age is presented in Fig. 1. 28.3% (n = 7207) of recipients were being treated in an intensive care unit prior to transplant, and 40.7% (n = 10 368) were supported with a durable ventricular assist device.

One-, 5-, and 10-year survival of the overall cohort was 90.1%, 77.9%, and 61.3%, respectively. The association between donor and recipient age with survival was initially modeled with unadjusted Cox proportional hazards regression and restricted cubic splines. Donor age demonstrated an approximately linear relationship with survival, with increasing age correlated with increasing mortality (Fig. 2). Recipient age, however, demonstrated an inflection point around age 47–50, with decreasing age among young recipients and increasing age among older recipients correlated with worsened survival (Fig. 3).

To account for potential confounders and identify independent predictors of survival, an adjusted Cox proportional hazards model was created (Table 3), with continuous variables including donor and recipient age modeled using restricted cubic splines. The interaction between donor and recipient age (Fig. 4) was found to be insignificant ($P > 0.05$) and was subsequently excluded from the final model. After adjustment, increasing donor age as well as increasing recipient age above 47–50 was associated with worsened survival, while decreasing recipient age below 47–50 was also associated with worsened survival. Additionally, other

Table 1. Baseline recipient characteristics

Variable	n = 25 480
Male gender	74.7% (19 043)
Donor/recipient gender mismatch	
No mismatch	75.0% (19 102)
Female donor/male recipient	14.3% (3649)
Male donor/female recipient	10.7% (2729)
Age	56 (46–63)
BMI	27.0 (23.7–30.6)
Donor/recipient BMI ratio	0.98 (0.85–1.15)
Ethnicity	
White	67.4% (17 176)
Black	20.3% (5169)
Hispanic	8.0% (2030)
Others	4.3% (1105)
Recipient history	
Diabetes	27.1% (6892)
Malignancy	7.6% (1908)
Cerebrovascular disease	5.3% (1360)
Heart failure etiology	
Ischemic cardiomyopathy	34.0% (8664)
Nonischemic cardiomyopathy	50.0% (12 750)
Others	16.0% (4066)
Recipient creatinine (median, IQR)	1.2 (0.9–1.5)
Recipient bilirubin (median, IQR)	0.8 (0.5–1.2)
Pretransplant status	
Intensive care unit	28.3% (7207)
Hospitalized (non-ICU)	15.8% (4021)
Not hospitalized	55.9% (14 250)
Medical therapy	
IV antibiotics in two weeks before transplant	10.2% (2588)
IV inotropes at transplant	38.4% (9774)
Ventilator support at transplant	1.6% (396)
IABP at transplant	5.9% (1494)
ECMO support at transplant	0.6% (152)
VAD at transplant	40.7% (10 368)
ABO blood type	
A	40.8% (10 397)
B	14.6% (3716)
AB	5.6% (1437)
O	39.0% (9930)
Days on waitlist (median, IQR)	92 (26–257)
Year of transplant (median, IQR)	2012 (2008–2015)
Year of transplant	
2005–2009	8609 (33.8%)
2010–2013	7440 (29.2%)
2014–2018	9431 (37.0%)

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; VAD, ventricular assist device.

Table 2. Baseline donor characteristics

Variable	n = 25 480
Donor male gender	71.1% (18 123)
Donor age (median, IQR)	30 (22–41)
Donor BMI (median, IQR)	26.2 (23.1–30.1)
Donor ethnicity	
White	64.9% (16 541)
Black	15.9% (4048)
Hispanic	16.2% (4137)
Others	3.0% (754)
Donor history	
Cigarette use	14.3% (3631)
Cocaine use	16.7% (4256)
Alcohol abuse	15.9% (4043)
Diabetes	3.3% (847)
Hypertension	14.6% (3723)
Cancer	1.6% (395)
Donor cause of death	
Anoxia	22.6% (5746)
Cerebrovascular/stroke	20.4% (5190)
Head trauma	54.2% (13 819)
CNS tumor	0.7% (176)
Others	2.2% (548)
ABO blood type	
A	36.1% (9187)
B	11.0% (2797)
AB	2.2% (568)
O	50.7% (12 928)
Ejection fraction (median, IQR)	60 (55–65)
Graft ischemic time (hours, median, IQR)	3.2 (2.4–3.8)

BMI, body mass index; CNS, central nervous system; IQR, interquartile range.

identified independent predictors of worse survival included black donors, increasing graft ischemic time, decreasing donor/recipient BMI ratio, black recipients, recipient diabetes, ischemic cardiomyopathy as the etiology of heart failure, VAD at transplant, IV antibiotics in the prior two weeks, and increasing serum creatinine and bilirubin at the time of transplant. Transplants performed in 2012 or later as well as transplant candidates who were being treated outside of an intensive care unit prior to transplant independently predicted improved overall survival. On subgroup landmark analysis limited to recipients who survived at least 90 days following transplant (n = 22 983), increasing donor age was again associated with decreased survival. Similarly, increasing recipient age over 47–50 predicted decreased survival while increasing recipient age under 47–50 predicted improved survival. Again, there was no significant interaction between donor and recipient age.

A sensitivity analysis was performed with older and younger donors defined as those above and below age 30, respectively, and older and younger recipients defined as those above and below age 50, respectively (Table S1). On unadjusted Kaplan–Meier survival

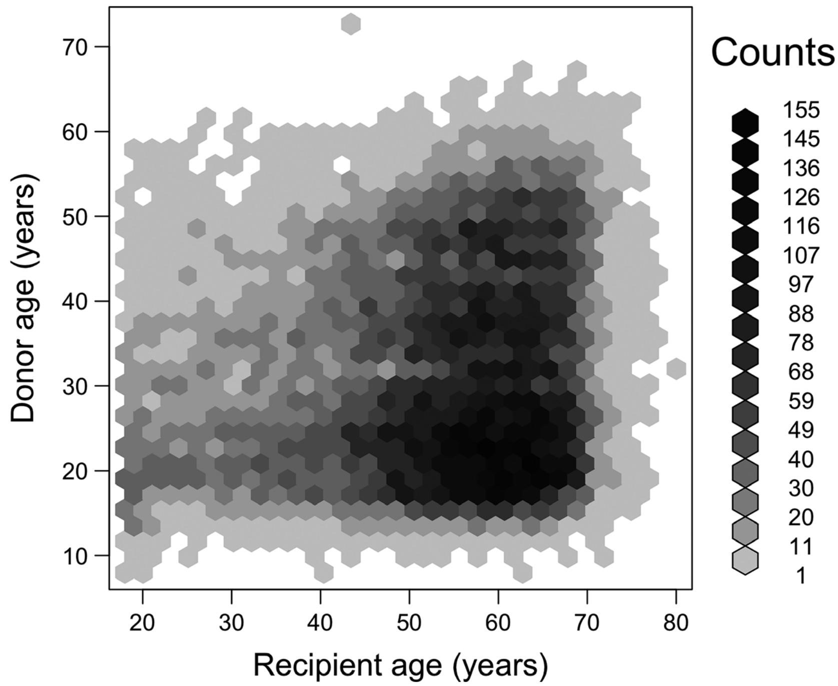

Figure 1 Hexagonal bin plot illustrating bivariate distribution of donor and recipient age

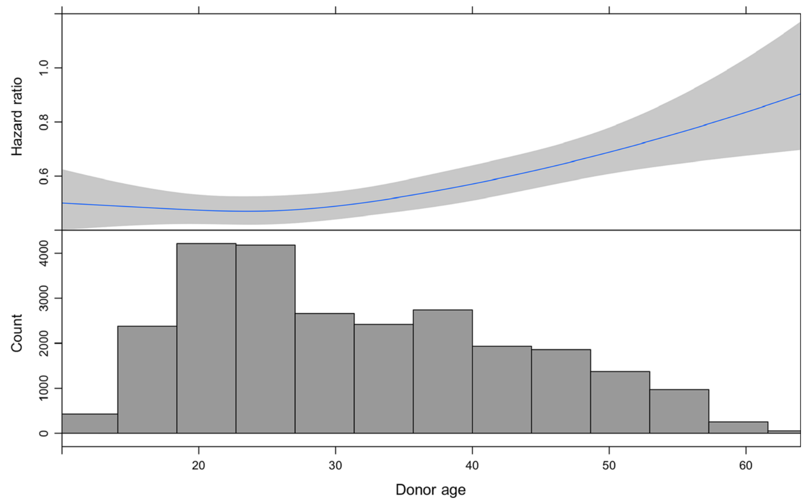

Figure 2 Unadjusted Cox proportional hazards model using restricted cubic splines illustrating relationship between donor age and recipient survival (top). Distribution of donor age (bottom).

analysis (Fig. 4), older donors were associated with worse survival in both younger and older recipients. The impact of older donors on recipient survival was similar for both younger and older recipients (6.2% decreased median survival for younger recipients compared to 7.4% decreased median survival for older recipients).

Discussion

In this retrospective analysis of the 2005–2018 UNOS heart transplant database, we analyzed the association between donor and recipient age on post-transplant recipient survival. While increasing donor age was associated with worsening survival in a near-linear fashion, increasing recipient age correlated with improved survival until approximately age 47–50, after which increasing age predicted decreased survival. We also found that the relationship between donor and recipient age did not significantly affect survival following heart transplant, suggesting that age-based donor–recipient matching for organ allocation would not improve survival in heart transplantation. In addition, we analyzed the association between age and survival in a rigorous fashion using restricted cubic splines, modeling age as both a continuous and binary categorical variable. This is in

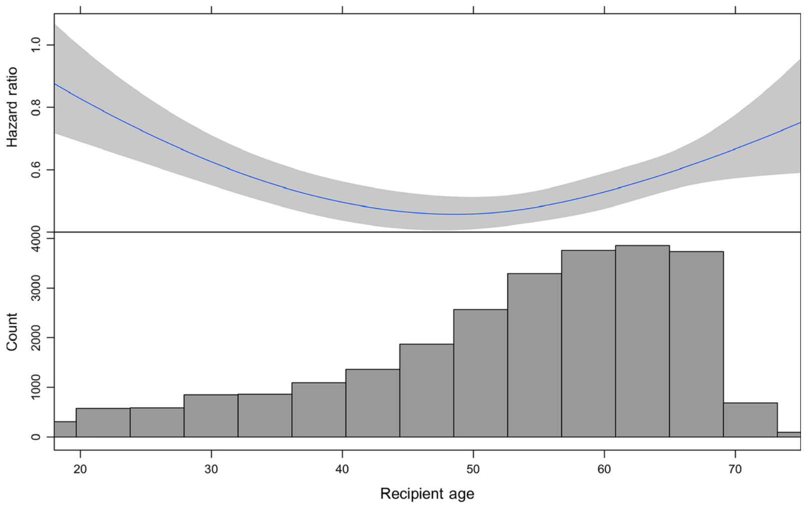

Figure 3 Unadjusted Cox proportional hazards model using restricted cubic splines illustrating relationship between recipient age and survival (top). Distribution of recipient age (bottom).

contrast to the vast majority of published literature, which have largely utilized arbitrarily defined age cohorts with unclear clinical significance.

An important finding of this study, namely the lack of a relationship or interaction between donor and recipient age with regard to survival, suggests that the "cost" of an older donor in heart transplantation is unchanged by recipient age and is not mitigated by using a younger recipient. Similarly, the adverse effect of an older recipient is not modified by the age of the donor. This finding is comparable to that of a 2014 single-center retrospective analysis of 1190 heart transplants over a 27-year period by Eskandary and colleagues from Austria [8]. Interestingly, multiple large retrospective analyses have reached opposite conclusions in kidney transplantation, suggesting that organ-dependent rather than systemic factors may predominantly mediate the effect of age on survival in solid organ transplantation [5,9].

While there have been several published single-center retrospective reports finding no association between heart transplant donor age and recipient post-transplant survival, the majority of large multicenter retrospective studies, like the present analysis, have found an inverse relationship between increasing donor age and recipient survival. In their 2015 analyses, both Roig and Prieto found no differences in early, mid, or late survival among recipients receiving allografts from younger or older donors [2,10]. In addition to having relatively small sample sizes, both studies utilized arbitrarily defined donor age cohorts in their respective analyses. These findings are in contrast to a 1999 single-center study by Del Rizzo, as well as 1991 and 2014 national registry analyses by Alexander and Weber, respectively, which demonstrated lower survival associated with increased donor age [1,11,12]. Similarly, a recent UNOS analysis of heart transplants between 2004 and 2013 by Daniel and colleagues also demonstrated decreasing survival associated with increasing donor age, especially among donors greater than age 50 [13]. Additionally, Bergenfeldt and colleagues found increasing donor and recipient age was associated with higher mortality in their retrospective analysis of the 1988–2013 ISHLT Registry [14]. These findings are especially relevant for European transplant centers, which have observed a steady increase in average donor age since the 1980s, while there has only been a moderate increase in North America [15]. Prior studies, however, have demonstrated improved survival among status 1A recipients following transplantation with older donor hearts as compared with medical therapy alone, suggesting that organ allocation should continue to be maximized even in the older donor pool [1].

The mechanism of increasing donor age correlating with lower survival is likely multifactorial and has yet to be fully elucidated. In a 2007 retrospective review of the UNOS heart transplant database, Russo and colleagues found that grafts from younger donors tended to better tolerate increased ischemia times, a finding consistent with a subgroup analysis from the Del Rizzo study [11,16]. In addition to being increasingly sensitive to ischemia, multiple studies have found an association between older donor hearts and the incidence of allograft vasculopathy [2]. In the present study's subgroup analysis of recipients who survived at least 90 days post-transplant, increasing donor age remained an independent predictor of worsened survival. These findings suggest that the mechanism of donor age impacting recipient survival goes beyond its impact on primary graft dysfunction.

Table 3. Cox proportional hazards model of post-transplant survival

Predictor	Hazard ratio	95% Confidence interval Lower	95% Confidence interval Upper	*P*-value
Age				
Donor age [years, reference: 30 (median)]				<0.001
22 (25th percentile)	0.95	0.87	1.03	
41 (75th percentile)	1.18	1.09	1.28	
Recipient age [years, reference: 56 (median)]				<0.001
46 (25th percentile)	0.93	0.86	1.01	
63 (75th percentile)	1.17	1.08	1.26	
Donor age:recipient age interaction*				0.281
Donor/graft characteristics				
Ethnicity (reference: white)				0.006
Black	1.11	1.02	1.21	
Hispanic	1.05	0.97	1.14	
Others	1.20	1.02	1.42	
Ejection fraction (EF, reference: 60 [median])				0.177
55 (25th percentile)	1.01	0.93	1.08	
65 (75th percentile)	0.96	0.90	1.01	
Ischemic time (hours, reference: 3.2 [median])				<0.001
2.4 (25th percentile)	0.97	0.89	1.05	
3.8 (75th percentile)	1.07	1.00	1.15	
Recipient characteristics				
Male gender (reference: female)	0.93	0.86	1.00	0.050
Gender mismatch (reference: no mismatch)				0.121
Female donor/male recipient	1.07	0.99	1.17	
Male donor/female recipient	1.03	0.92	1.16	
Donor/recipient BMI ratio (reference: 0.98 [median])				0.002
0.85 (25th percentile)	1.03	0.96	1.11	
1.15 (75th percentile)	1.00	0.94	1.07	
Ethnicity (reference: white)				<0.001
Black	1.33	1.24	1.43	
Hispanic	1.07	0.96	1.20	
Others	0.95	0.81	1.11	
Diabetes	1.23	1.15	1.31	<0.001
Heart failure etiology (reference: ischemic cardiomyopathy)				<0.001
Nonischemic dilated cardiomyopathy	0.79	0.74	0.84	
Others	0.93	0.85	1.01	
VAD at transplant	1.16	1.07	1.26	<0.001
IV inotropes at transplant	0.96	0.90	1.02	0.176
IV antibiotics in two weeks before transplant	1.25	1.15	1.35	<0.001
Creatinine (mg/dL, reference: 1.2 [median])				<0.001
0.9 (25th percentile)	0.95	0.89	1.02	
1.5 (75th percentile)	1.19	1.13	1.25	
Total bilirubin (mg/dL, reference: 0.8 [median])				<0.001
0.5 (25th percentile)	0.96	0.90	1.02	
1.2 (75th percentile)	1.06	1.02	1.10	
Transplant 2012 or later (reference: pre-2012)	0.90	0.84	0.97	0.842
Pretransplant recipient status (reference: ICU)				0.007
Hospitalized (non-ICU)	0.96	0.86	1.06	
Not hospitalized	0.88	0.82	0.96	

BMI, body mass index; ICU, intensive care unit; VAD, ventricular assist device.

Continuous variables modeled using restricted cubic splines with 5 knots (locations based on distribution). *P*-value for continuous variables corresponds to global Wald test.

*Insignificant interaction term between donor and recipient age, removed from final model. Transplant center ID entered as cluster variable.

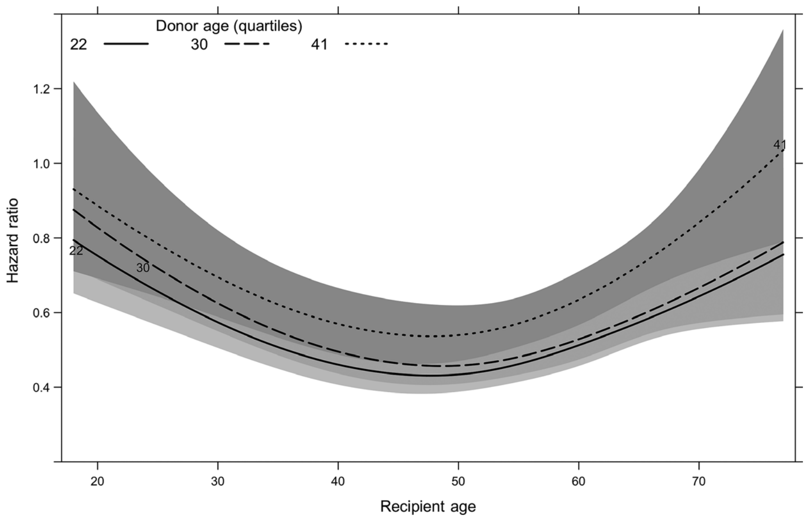

Figure 4 Multivariable-adjusted Cox proportional hazards model using restricted cubic splines illustrating relationship between recipient age and post-transplant survival. Donor age quartiles plotted, demonstrating no significant interaction between donor and recipient age.

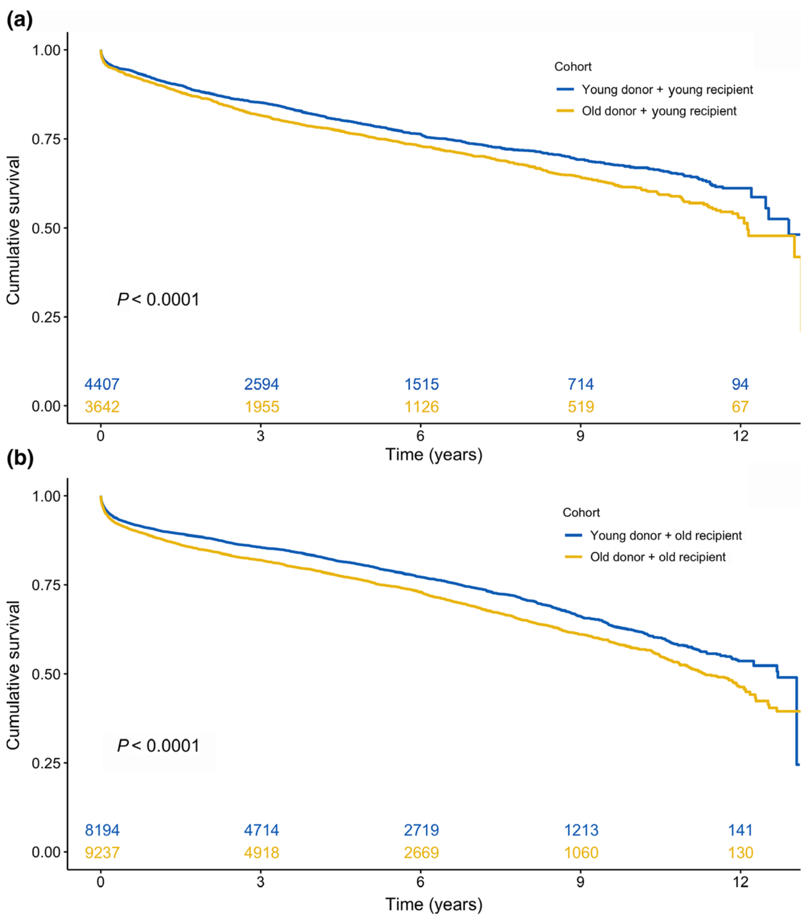

Figure 5 Unadjusted Kaplan–Meier analysis illustrating post-transplant survival of younger (panel a) and older (panel b) recipients stratified by donor age. Younger and older donors defined as those below and above age 30, respectively. Younger and older recipients defined as those below and above age 50, respectively.

The majority of studies, similar to the present study, have found that recipients at the extremes of age experience worse survival. Large multicenter retrospective analyses from 1993 and 1994 by Bourge and Young [3,17], respectively, correlated younger and older recipients with poorer survival. Similarly, in a 2017 retrospective analysis of the International Society of Heart and Lung Transplantation database, Wever-Pinzon *et al.* [18] demonstrated an association between increasing recipient age and risk of death. Furthermore, they concluded that younger recipients were more likely to die of acute rejection, vasculopathy, and graft failure while mortality among older recipients tended to be driven to a greater extent by infection, malignancy, and renal failure. Similar findings were also cited in the ISHLT 2013 heart transplant report, which focused on donor and recipient age [19]. There are a number of possible mediators of the relationship between increasing recipient age and post-transplant mortality proposed in the literature. Several studies have suggested that older recipients are subject to an age-related depletion in innate, humoral, and cell-mediated immune response via functional alterations in B- and T-cell populations, which may account for the higher incidence of acute rejection among younger recipients [20]. The resulting immunosenescence may also contribute to higher rates of infection and malignancy as recipient cause of death among older patients [21,22].

There are several limitations to this study. As a retrospective review of a large national registry, we are limited by the quantity and quality of available predictor variables, which weakens our ability to control for potential confounders. For instance, prior studies have suggested that increased mortality among young recipients may be in part driven by immunosuppression non-compliance, which we were unable to examine [19]. Specific high-volume centers may also be more experienced with older recipients, which may confound the analysis. We did, however, control for center clustering in our multivariable models. There is also a significant potential for bias, as the clinical severity of transplant candidates likely influences the quality of donor allografts deemed acceptable for transplant. In addition, we were unable to analyze the impact of donor and recipient age matching on long-term survival, given the modern cohort utilized. Perhaps most importantly, the studied population of donors and recipients represents a highly selected group and this study does not evaluate ages of donors and recipients who were not utilized or offered transplant. Ultimately, a randomized clinical trial would be the most robust way to study this important research question. Given that a randomized trial would be quite infeasible in this population, however, the UNOS/OPTN Registry is an ideal data source for this analysis as it captures 100% of transplants performed in the United States, thereby mitigating selection biases associated with single-institution analyses.

Conclusion

Increasing donor age and both younger and older recipient age are independently associated with worsened post-transplant recipient survival. Further, the relationship between donor and recipient age does not impact post-transplant survival, suggesting that age-based donor–recipient matching for organ allocation would not improve survival following heart transplantation.

Authorship

OKJ and VR: designed the study, performed the analysis, and wrote the manuscript. JK, MH, CP, and CM: contributed to the design of the study and writing as well as reviewing of the manuscript.

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Conflict of interest

The authors have declared no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Cohort size and associated survival estimates pertaining to young and old donor and recipient sensitivity analysis.

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