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The impact of donor-recipient age difference on graft survival after heart transplant in adults with congenital heart disease

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KEYWORDS:
adult congenital heart disease;
heart transplant;
donor age;
donor selection;
graft survival;
post transplant survival

BACKGROUND: The impact of donor-recipient age difference in adult congenital heart disease (ACHD) patients undergoing heart transplant (HT) is unknown.
METHODS: ACHD patients (≥18 years old) who underwent HT (2000-2020) were identified using the United Network for Organ Sharing database. Graft survival through 10 years based on donor-recipient age difference was evaluated by comparing outcomes of donors > 5 years older than recipients (Older), donors within 5 years of recipient age (Equal Age), and donors > 5 years younger than recipients (Younger, reference group). Cox multivariable analysis was performed to evaluate the effect of donor-recipient age difference on early and late graft survival.
RESULTS: A total of 1,275 ACHD patients underwent HT (60% male, median 35 years old (interquartile range 24-46) with median graft survival of 13.7 years (95% confidence interval [CI] 11.7-16.0). Compared to Younger donors ($n = 306$ [24%]), graft survival was similar with Equal Age donors ($n = 698$ [55%]; log-rank $p = 0.61$), though significantly reduced with Older donors ($n = 271$ [21%]; log-rank $p = 0.03$). In multivariable analysis, late graft survival was similar with Equal Age donors but lower with Older donors (adjusted hazard ratio 1.63, 95% CI 1.16-2.28, $p = 0.005$), with a trend of reduced survival with Older donors in recipients < 30 or ≥40 years old.
CONCLUSIONS: Graft survival in ACHD patients undergoing HT was similar for those with Younger and Equal Age donors. Recipients with Older donors had reduced 10-year survival, possibly related to increased risk in those < 30 and ≥40 years old. These data help inform the optimal donor age for ACHD patients requiring HT.
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Background

Due to advances in surgical technique and medical care, more than 90% of children with congenital heart disease (CHD) live to adulthood, such that there are now more adults than children living with CHD.[1-3] However, long-term survival is reduced for adult congenital heart disease

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(ACHD) patients compared to the general population,[4] and heart failure is a major cause of morbidity and mortality in this population.[5] Heart transplant (HT) is the definitive therapy for patients with end-stage heart failure,[6] though the proportion of ACHD patients who undergo transplant is significantly lower than those who are referred for evaluation.[7,8] Therefore, strategies to increase the probability of successful HT and long-term post-transplant survival for ACHD patients on the HT waitlist are needed.

Donor organ selection is important for both waitlist times as well as post-transplant outcomes, and donor age is one variable known to affect post-transplant outcomes. Contemporary data from the Scientific Registry of Transplant Recipients report increasing donor age as a risk factor for increased late mortality in all recipients as well as the subset of ACHD patients.[9] However, ACHD patients may undergo evaluation and listing for HT at either an adult or pediatric HT program, and there may be differences in donor selection practice between adult and pediatric HT physicians. The adult donor heart selection guidelines from the International Society of Heart and Lung Transplantation (ISHLT) recommend utilizing donor hearts < 45 years old, with the option of using hearts ≥45 years old if the ischemic time is less than 4 hours, there is no significant coronary disease, and taking into consideration estimated survival benefit for the patient.[10] In adolescent HT recipients (ages 11-17 years old), donor age > 25 years has been associated with reduced long-term survival;[11] thus, the ISHLT guidelines for pediatric HT donor selection recommend adolescents not receive a donor heart > 5 years older than their chronological age, especially if the donor heart is > 25 years old.[12] These guidelines may be extrapolated by pediatric HT programs and applied to ACHD patients, which could increase waitlist time.

Given ACHD patients are on average 15 years younger than other adults with heart failure referred for HT,[9,13] assessment of graft survival based on donor-recipient age difference may be a better measure than absolute donor age. Single-center data in non-ACHD patients support similar long-term survival in patients with donors who are older than recipients;[14] however, outcomes of ACHD patients undergoing HT based on donor-recipient age difference have not been previously reported. Therefore, we sought to assess the impact of donor-recipient age difference on graft survival in ACHD patients undergoing HT.

Methods

We studied patients ≥18 years of age who underwent HT in the Organ Procurement Transplant Network/United Network of Organ Sharing (UNOS) registry between January 1, 2000 and December 31, 2020, with follow-up available through December 31, 2021. The local institutional review board assigned exempt status to this study.

Inclusion criteria and patient data accessed

Patients who underwent heart-only transplant with a diagnosis of CHD as their listing diagnosis were included. Patients were also included if there was a diagnosis of hypoplastic left heart syndrome (HLHS) or if 1 of the following words were identified in the thoracic diagnosis text description "transposition," "transposition of the great arteries," "congenital," "CHD," "Ebstein," "Fontan," "tetralogy," "atresia." Recipient information obtained from the database included year of transplant, age, gender, race/ethnicity, weight, height, prior cardiac surgery, listing status, renal function, and presence of mechanical ventilation, ventricular assist device, or extracorporeal membrane oxygenation at the time of transplant. Donor information obtained included age, cause of death, substance use history, medical history (including diabetes and hypertension), serum creatinine, left ventricular ejection fraction, weight, height, and ischemic time.

Outcomes assessed

The primary outcome assessed was graft survival (defined as death or retransplant) through 10 years. Donor-recipient age difference was assessed by comparing recipients with donors > 5 years older (Older) and donors within 5 years (older or younger) of the recipient age (Equal Age) to donors > 5 years younger than recipients (Younger, reference group). Subgroup analysis based on recipient age (< 30 years, 30-39 years, and ≥40 years) was also performed.

Multivariable analysis as described below was performed to evaluate the effect of donor-recipient age difference on early (< 1 year) and late (1-10 years) graft survival over the entire cohort, and by recipient age (< 30 years, 30-39 years, and ≥40 years). Given the recommendation for the use of donor hearts < 45 years of age,[10] the multivariable analysis was repeated excluding patients who received hearts from donors ≥45 years old (Supplemental Material). Given the ISHLT recommendation to avoid donor hearts ≥45 years when potential ischemic time is > 4 hours,[10] the interaction of donor age and ischemic time was evaluated.

Statistical analysis

Baseline characteristics and outcomes are reported and compared for all patients, with further categorization based on donor-recipient age group (Younger, Equal Age, and Older). Categorical data are presented as frequencies and percentages, compared using chi-square. Continuous variables are presented as median (interquartile range [IQR]) with differences assessed using *t*-test (if normally distributed) or Wilcoxon rank-sum test (if non-normally distributed).

Kaplan-Meier survival and Cox-proportional hazard estimates were computed for the overall cohort and stratified by recipient age (< 30 years, 30-39 years, and ≥40 years). Univariate modeling was used to identify patient variables associated with the primary outcome for inclusion in multivariable modeling ($p < 0.10$ was accepted for retention), evaluating year of transplant (era 1; 2000-2012 vs era 2: 2013-2020), transplant center overall, and ACHD-specific HT volume, patient age, sex, race, renal function, listing status (high priority = status 1-3 with current allocation system, status 1A in prior allocation system; low priority = status 4 with current allocation system, status 1B and 2 in prior), ischemic time, donor-recipient sex mismatch, donor characteristics (substance use and medical history, serum creatinine, left ventricular ejection fraction, and cause of death), and ventricular assist device or mechanical ventilation at transplant. To evaluate the interaction between donor-recipient age difference and ischemic time, interaction terms were added to the main model, and −2log likelihoods were compared using chi-square tests with the −2log likelihood of the model without interaction terms.

Results

Baseline characteristics

A total of 1,275 ACHD patients underwent HT (61% male) at a median age of 35 years (IQR 24-46), with 698 (55%) receiving a heart from a Younger donor, 306 (24%) from an Equal Age donor, and 271 (21%) from an Older donor. Most patients (n = 858 [67%]) had known prior cardiac surgery, were non-Hispanic White race (n = 1020 [80%]), and listing status was evenly divided between high (n = 637 [50%]) and low priority (n = 639 [50%]). The median waitlist time was 119 (35-326) days, ischemic time was 3.5 (2.8-4.2) hours, with 128 (10%) recipients supported by ventricular assist devices and 64 (5%) with mechanical ventilation at the time of HT. The proportion of HTs was evenly divided between era 1 (n = 618 [50%]) and era 2 (n = 619 [50%]). The median donor age was 26 (IQR 19-36) years, with the median donor-recipient age difference of −6 years (IQR of 18 years younger than the donors to 2 years older), and most donors (n = 864 [68%]) were the same sex as the recipient. Though the recipients in the Younger donor group were older and had a higher prevalence of renal dysfunction, there were no differences in listing status or mechanical ventilation between the donor age groups (Table 1), and no difference in waitlist time based on recipient age (Supplemental Material) or donor age group (Table 1).

Primary outcome

The estimated median graft survival was 13.7 years (95% confidence interval [CI] 11.7-16.0) for the entire cohort, with 434 deaths and 43 retransplants over 7,363 person-years of follow-up. Compared to those with Younger donors, recipients with Equal Age donors had similar graft survival (log-rank p = 0.61), while those with Older donors had significantly reduced 10-year graft survival (log-rank p = 0.03) (Figure 1). When stratified by recipient age, graft survival was similar across donor age groups for recipients less than 30 years old and those 30 to 39 years old (Figure 2A and B). For recipients more than 40 years of age, survival was similar for those with Equal Age donors compared to those with Younger donors (log-rank p = 0.48), though there was a trend toward reduced survival for those with Older donors (log-rank p = 0.06) (Figure 2C).

Multivariable analysis—early graft survival

In multivariable analysis, early graft survival was similar across all donor age groups (Equal Age: adjusted hazard ratio (aHR) 1.10, 95% CI 0.77-1.61, $p = 0.608$; Older: aHR 1.25, 95% CI 0.82-1.89, $p = 0.300$) (Table 2), including when stratified by recipient age (Figure 3), and when donors ≥45 years of age ($n = 132$) were excluded (Supplemental Table 1). Clinical variables associated with reduced 1-year graft survival are reported in Table 2.

Multivariable analysis—late graft survival

Among 1-year survivors, late graft survival was similar with Equal Age donors (aHR 1.14, 95% CI 0.81-1.61, $p = 0.458$) but lower with Older donors (aHR 1.63, 95% CI 1.16-2.28, $p = 0.005$) (Table 3), which was again not impacted by excluding donors ≥45 years old (Supplemental Table 2). Recipient race was the only additional variable with a significant association with long-term survival (Table 3). When survival was stratified by recipient age, multivariable analysis showed late graft survival was similar for all donor groups, though there was a trend toward reduced survival with Older donors for recipients < 30 years of age (aHR 1.53, 95% CI 0.96-2.43, $p = 0.072$) and ≥40 years of age (aHR 2.24, 95% CI 0.89-5.61, $p = 0.086$) (Figure 3).

Interaction of ischemic time and age

There was no significant interaction between donor-recipient age categories and ischemic time in either the whole cohort (interaction $p = 0.422$) or in the cohort with donors ≥45 excluded (interaction $p = 0.597$) for first post-transplant year.

Discussion

In this large, contemporary analysis of the UNOS HT database, we found 10-year graft survival in ACHD patients undergoing HT was similar if the donor age was within 5 years of recipient age (Equal Age donors), as compared to donors > 5 years younger (Younger donors). However, in recipients who received an HT with a donor > 5 years older (Older donors), there was reduced 10-year survival which was not driven by perioperative or short-term (< 1 year) mortality and did not seem to be related to utilization of donor hearts ≥45 years old. When outcomes were stratified by recipient age in a multivariable analysis, it is possible the reduced survival was driven by recipients < 30 or ≥40 years of age with Older donors; however, this did not reach statistical significance. Overall, these findings suggest utilizing a donor > 5 years older than the recipient in ACHD patients < 30 years old or ≥40 years old may have worse long-term

Table 1 Donor and Recipient Characteristics

	All ACHD HT (n = 1,275)	Younger donor (n = 698)	Equal age (n = 306)	Older donor (n = 271)	p-value
Recipient characteristics					
Year of HT					0.353
2000-2012	647 (51%)	348 (50%)	151 (49%)	148 (55%)	
2013-2020	628 (49%)	350 (50%)	155 (51%)	123 (45%)	
Age at HT (years)	35 (24-46)	43 (34-52)	26 (20-35)	24 (20-31)	< 0.001
Sex					0.418
Male	772 (61%)	412 (59%)	188 (61%)	172 (63%)	
Female	503 (39%)	286 (41%)	118 (39%)	99 (37%)	
Race/ethnicity					0.002
Non-Hispanic White	1,020 (80%)	583 (83%)	240 (78%)	198 (73%)	
Non-Hispanic Black	113 (9%)	48 (7%)	35 (11%)	30 (11%)	
Hispanic	94 (7%)	51 (7%)	17 (6%)	26 (10%)	
Other	48 (4%)	17 (2%)	14 (5%)	17 (6%)	
Support at HT					
Mechanical ventilation	64 (5%)	39 (6%)	15 (5%)	9 (3%)	0.344
VAD	122 (10%)	54 (8%)	35 (11%)	33 (12%)	0.048
ECMO	22 (2%)	8 (1%)	6 (2%)	8 (3%)	0.143
GFR < 60 or dialysis	469 (37%)	294 (42%)	89 (29%)	86 (32%)	< 0.001
Weight at transplant (kg)	69 (58-83)	71 (60-84)	66 (57-80)	67 (56-83)	0.004
Surgical history					0.031
Previous surgery	858 (67%)	490 (70%)	196 (64%)	172 (63%)	
No previous surgery	128 (10%)	74 (11%)	29 (9%)	25 (9%)	
Unknown	289 (23%)	134 (19%)	81 (27%)	74 (27%)	
Listing status					0.155
High priority[a]	637 (50%)	343 (49%)	145 (47%)	149 (55%)	
Low priority[b]	639 (50%)	355 (51%)	161 (53%)	122 (45%)	
Waitlist time (days)	119 (35-326)	116 (37-335)	133 (38-324)	103 (30-296)	0.321
Center characteristics					
Annual HT volume	22 (14-36)	23 (16-36)	19 (9-36)	22 (8-44)	0.002
Total ACHD HTs	21 (9-28)	21 (9-28)	15 (9-29)	22 (8-33)	0.326
Donor/match characteristics					
Donor age	26 (19-36)	22 (18-29)	26 (20-36)	37 (31-45)	< 0.001
Donor-recipient age difference	−6 (−18 to +2)	−16 (−24 to −10)	−1 (−2 to 1)	+10 (7-16)	< 0.001
Donor cause of death					< 0.001
Anoxia	321 (25%)	191 (27%)	65 (21%)	66 (24%)	
Stroke	213 (17%)	81 2 (12%)	53 (17%)	78 (29%)	
Head trauma	703 (55%)	405 (59%)	179 (58%)	119 (44%)	
Other	38 (3%)	20 (3%)	10 (3%)	8 (3%)	
Donor substance history					
Cigarette use	164 (13%)	66 (9%)	38 (12%)	60 (22%)	< 0.001
Cocaine use	185 (15%)	110 (16%)	34 (11%)	41 (15%)	0.345
Donor medical history					
Hypertension	141 (11%)	51 (7%)	40 (13%)	50 (18%)	< 0.001
Diabetes	34 (3%)	17 (2%)	6 (2%)	11 (4%)	0.455
Donor creatinine	1.0 (0.7-1.3)	1.0 (0.7-1.3)	1.0 (0.7-1.3)	0.9 (0.7-1.2)	0.934
Donor ejection fraction	60% (56%-66%)	61% (56%-66%)	60% (55%-65%)	63% (59%-69%)	0.132
Donor-recipient sex					0.014
Same	864 (68%)	477 (68%)	206 (67%)	181 (67%)	
F donor-M recipient	195 (15%)	88 (13%)	53 (17%)	54 (20%)	
M donor-F recipient	216 (17%)	133 (19%)	47 (15%)	36 (13%)	
Donor: recipient weight	1.05 (0.91-1.24)	1.02 (0.88-1.21)	1.08 (0.91-1.29)	1.10 (0.94-1.29)	< 0.001
Donor: recipient height	1.01 (0.97-1.06)	1.01 (0.96-1.06)	1.02 (0.97-1.06)	1.01 (0.97-1.06)	0.176
Ischemic time (hours)	3.5 (2.8-4.2)	3.5 (2.8-4.1)	3.6 (2.9-4.3)	3.6 (2.7-4.3)	0.080

Abbreviations: ACHD, adult congenital heart disease; ECMO, extracorporeal membrane oxygenation; F, female; GFR, glomerular filtration rate; kg, kilogram; HT, heart transplant; M, male; VAD, ventricular assist device.

[a]High priority = status 1 to 3 with current allocation system, status 1A in prior allocation system.

[b]Low priority = status 4 with current allocation system, status 1B and 2 in prior allocation system.

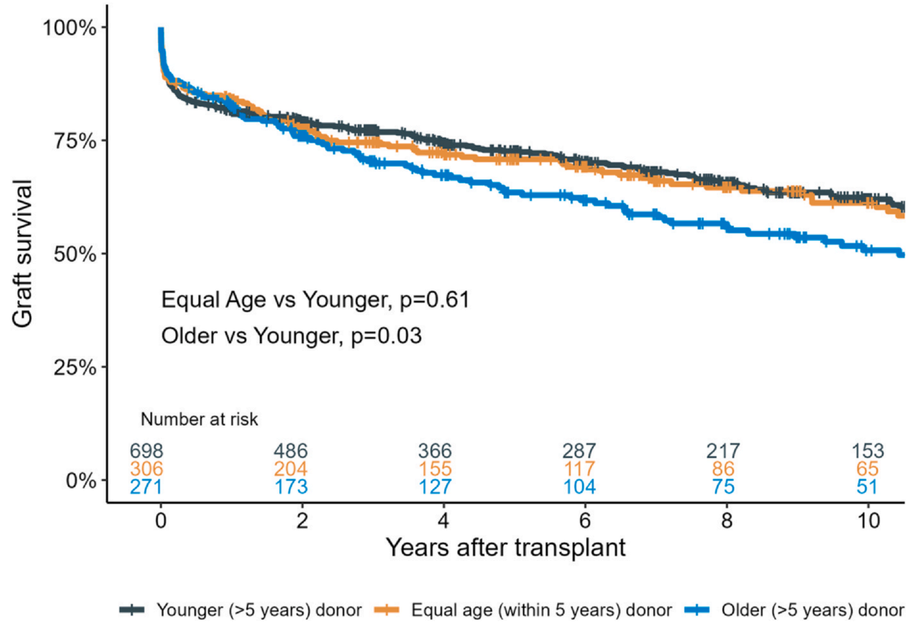

Figure 1 Kaplan-Meier survival curve stratified by donor-recipient age difference.

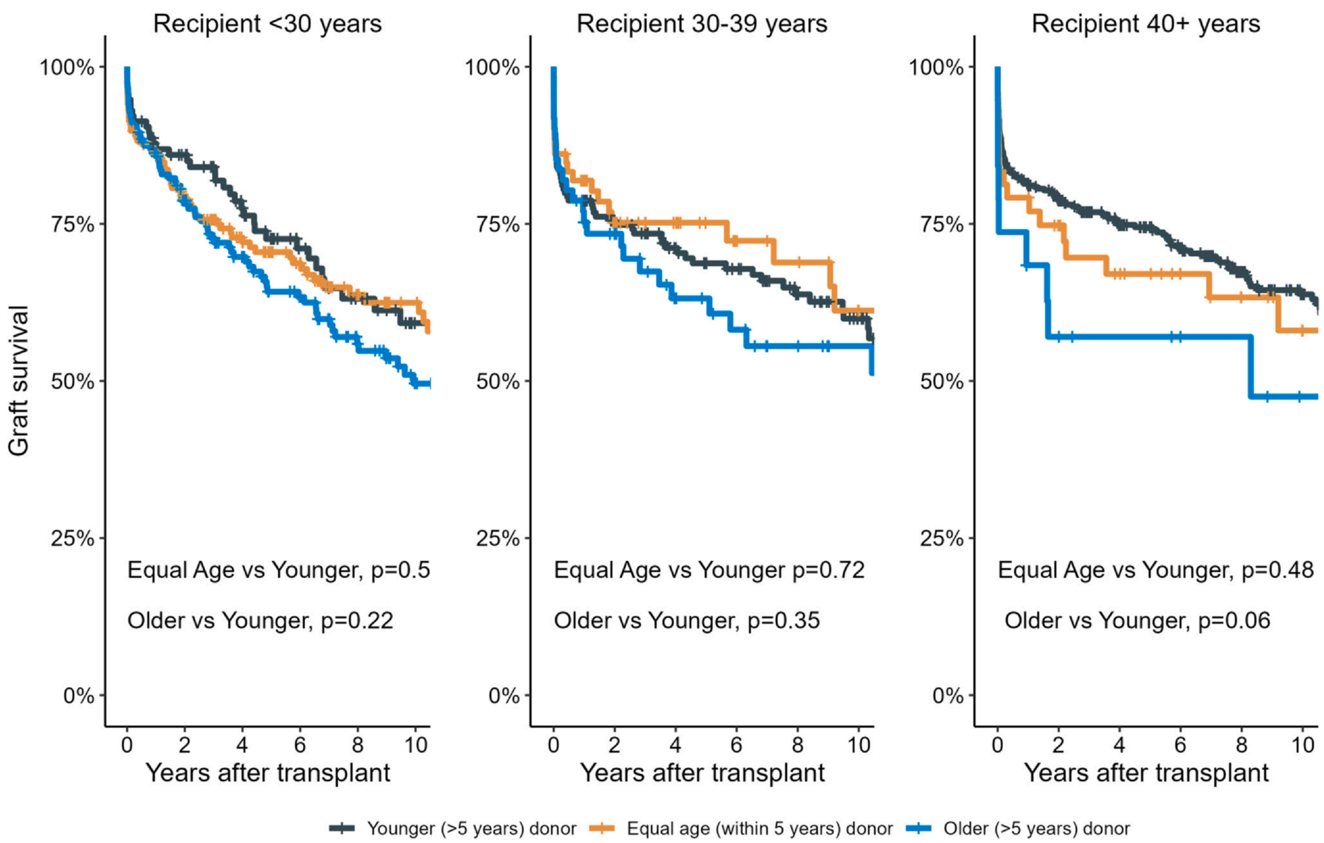

Figure 2 Kaplan-Meier survivals based upon recipient age, stratified by donor-recipient age difference.

survival, and avoiding significant donor-recipient age mismatch in this cohort may be beneficial.

Recent large registry data identify a significant risk of heart failure, including heart failure-related death and need for HT, among all ages in patients with CHD.[15,16] For those patients who require HT, the impact of donor-recipient age on those younger than 18 years of age has helped to identify the optimal donor age for this cohort.[11] However, there is a paucity of data on optimal donor age for adults with CHD undergoing HT. Huntley *et al* identified that donor age was significantly associated with late mortality in patients with ACHD after HT,[9] though applying this data is limited to avoiding older donors, and challenging to use in practice given the wide age range in ACHD patients with heart failure. Ram *et al* found no difference in outcomes based on donor-recipient age difference in non-ACHD patients.[14]

Table 2 Risk Factors for Graft Loss at 1 Year

	Unadjusted		*p*-value	Adjusted		*p*-value
	HR	95% CI		HR	95% CI	
Donor-recipient age difference						
Younger donor	Ref	-	-	Ref	-	-
Similar age	0.88	0.63-1.22	0.427	1.10	0.77-1.61	0.608
Older donor	0.94	0.68-1.32	0.731	1.25	0.82-1.89	0.300
Recipient age	1.01	1.00-1.02	0.009	1.02	1.00-1.03	0.019
Year of transplant						
2000-2012	Ref	-	-			
2013-2020	0.68	0.52-0.89	0.005	0.76	0.57-1.01	0.056
Sex						
Male	Ref		-			
Female	1.08	0.83-1.41	0.564	1.14	0.86-1.51	0.359
Race/ethnicity						
Non-Hispanic White	Ref	-	-	Ref	-	
Non-Hispanic Black	0.91	0.57-1.45	0.681	0.91	0.56-1.49	0.702
Hispanic	0.62	0.34-1.14	0.124	0.74	0.41-1.38	0.344
Other	1.03	0.53-2.00	0.943	1.12	0.57-2.21	0.737
Support at transplant						
Mechanical ventilation	1.72	1.05-2.81	0.033	1.70	1.03-2.82	0.039
VAD	0.91	0.57-1.44	0.685			
GFR < 60 or dialysis	1.63	1.26-2.12	< 0.001	1.43	1.08-1.89	0.013
Listing status						
High priority[a]	0.84	0.65-1.09	0.197			
Low priority[b]	Ref					
Overall HT volume						
< 14/year	1.30	0.95-1.77	0.102			
14-38/year	Ref	-	-			
> 38/year	1.02	0.74-1.42	0.896			
ACHD HT in study period						
< 6	1.22	0.82-1.83	0.333			
6-20	Ref	-	-			
> 20	0.80	0.60-1.07	0.129			
Donor cause of death						
Head trauma	Ref	-	-	Ref	-	-
Anoxia	0.83	0.59-1.16	0.267	0.85	0.60-1.21	0.369
Stroke	1.39	1.00-1.94	0.051	1.21	0.85-1.72	0.298
Other	0.75	0.31-1.84	0.534	0.72	0.29-1.77	0.476
Donor-recipient sex mismatch	1.30	0.99-1.70	0.058	1.24	0.93-1.64	0.141
Donor substance history						
Cigarette use	1.14	0.78-1.65	0.507			
Cocaine use	0.62	0.40-0.97	0.035	0.66	0.42-1.03	0.066
Donor medical history						
Hypertension	0.97	0.63-1.48	0.689			
Diabetes	0.65	0.24-1.74	0.954			
Donor creatinine	0.93	0.82-1.06	0.893			
Donor ejection fraction	1.00	0.98-1.02	0.911			
Donor: recipient weight	0.62	0.37-1.06	0.080	0.66	0.38 – 1.13	0.131
Donor: recipient height	3.13	0.45-21.6	0.247			
Ischemic time > 4 hours	1.60	1.22-2.09	< 0.001	1.68	1.28-2.21	< 0.001

Abbreviations: ACHD, adult congenital heart disease; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; HT, heart transplant; VAD, ventricular assist device.

[a]High priority = status 1 to 3 with current allocation system, status 1A in prior allocation system.

[b]Low priority = status 4 with current allocation system, status 1B and 2 in prior allocation system.

However, donor-recipient age stratification differed in that any donor older than the recipient was considered older, which included 48 total patients.

Our data could inform practice for both adult and pediatric HT programs. The finding that recipients with donors within 10 years of age (5 years younger - 5 years older)

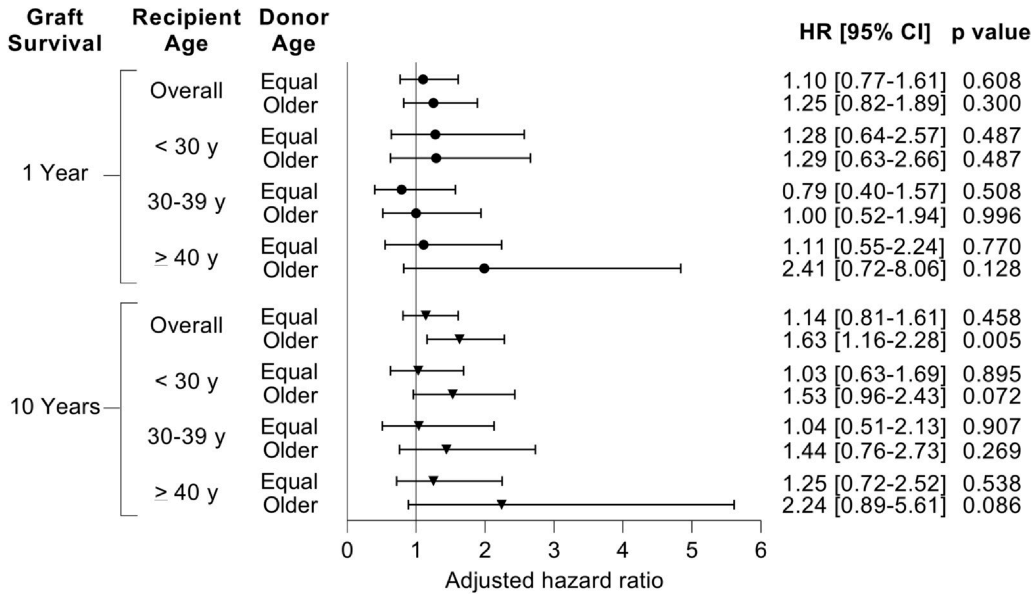

Figure 3 Adjusted hazard ratio for donor-recipient age difference on early and late graft survival. CI, confidence interval; HR, hazard ratio; y, years.

Table 3 Risk Factors for Graft Loss Among 1-Year Survivors

	Unadjusted		*p*-value	Adjusted		*p*-value
	HR	95% CI		HR	95% CI	
Donor-recipient age difference						
> 5 years younger	Ref	-	-	Ref	-	-
Within 5 years	1.27	0.93-1.73	0.127	1.14	0.81-1.61	0.458
> 5 years older	1.79	1.33-2.39	< 0.001	1.63	1.16-2.28	0.005
Recipient age	0.99	0.98-1.00	0.009	0.99	0.98-1.01	0.261
Year of transplant						
2000-2012	Ref	-	-			
2013-2020	1.08	0.78-1.49	0.645			
Sex						
Male	Ref		-			
Female	0.95	0.74-1.23	0.713			
Race/ethnicity						
Non-Hispanic White	Ref	-	-	Ref		-
Non-Hispanic Black	1.94	1.31-2.87	< 0.001	1.97	1.33-2.92	< 0.001
Hispanic	0.57	0.30-1.08	0.083	0.55	0.29-1.03	0.064
Other	1.49	0.76-2.90	0.246	1.28	0.65-2.50	0.477
GFR < 60 or dialysis	0.99	0.77-1.27	0.927			
Donor substance history						
Cigarette use	0.89	0.64-1.26	0.517			
Cocaine use	0.97	0.67-1.41	0.871			
Donor cause of death						
Head trauma	Ref	-	-			
Anoxia	1.04	0.76- 1.44	0.792			
Stroke	0.86	0.61-1.22	0.402			
Other	0.44	0.16-1.17	0.101			
Donor medical history						
Hypertension	0.75	0.49-1.16	0.792			
Diabetes	0.70	0.22-2.18	0.539			
Donor creatinine	1.05	0.96-1.14	0.441			
Donor ejection fraction	1.00	0.98-1.01	0.983			
Ischemic time > 4 hours	1.08	0.83-1.42	0.570			

Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio.

have equivalent short- and long-term survival as younger donors may help pediatric HT programs increase the donor pool. These programs may be less comfortable with donors 40 to 45 years old age range, even for similar-aged recipients, and it is possible the higher waitlist mortality for ACHD patients treated at pediatric centers[17] may be, at least in part, due to longer waitlist times leading to mortality while waiting for a younger donor organ. These data would suggest it would be reasonable to consider an otherwise appropriate donor up to 45 years old for a 40-year-old ACHD patient, which could improve waitlist time and survival.

For an adult institution with an average HT recipient age of 50, the use of 40- to 45-year-old donor hearts may be common. However, although likely limited by sample size such that it did not reach statistical significance when stratified by recipient age, multivariate analysis identified recipients ≥40 years old may be at increased risk for post-HT mortality with Older donors. Though the overall cohort risk was similar when excluding donor hearts ≥45 years old, by definition, there were no recipients ≥40 years old with Older donors in this analysis. Therefore, in recipients ≥40 years old, it is possible that reduced long-term survival may be related to the use of older donor hearts, as prior work has reported mixed outcomes with this population.[18,19] As such, if a 40-year-old ACHD patient is listed as status 4 and stable outside the hospital, awaiting a donor no more than 5 years older may be ideal. However, this needs to be balanced with waitlist mortality. Given patients with ACHD have longer waitlist times and higher waitlist mortality,[20] evaluation of acceptable donors for each patient should be reconsidered depending on their clinical status, as survival with an older donor is better than remaining critically ill in status 1 or 2 and not undergoing transplant.[21]

Multivariate analysis by recipient age also identified that recipients < 30 years old may have reduced survival post-HT with an Older donor, though again this was likely limited by sample size such that results were not statistically significant. While it is possible younger recipients had higher acuity and thus received Older donors, surrogates for acuity, including listing status, waitlist time, and mechanical ventilation, were similar between donor-recipient age groups. Instead, the trend toward reduced survival with Older donors for recipients < 30 years old may be related to the recipient's underlying CHD. Though the UNOS database does not consistently report the type of CHD, it is possible this age group had a significant proportion of patients with Fontan palliation for HLHS. Patients with HLHS typically develop heart failure symptoms at a younger age than other forms of single-ventricle CHD and have worse transplant-free survival.[22] In addition, contemporary data have shown that patients with HLHS who undergo HT have worse short- and long-term survival compared to patients with biventricular CHD and non-HLHS single-ventricle CHD.[23] Thus, in our study, this population may be more similar in age and physiology to recipients with CHD in the study by Westbrook et al, which showed worse outcomes for pediatric recipients who receive an HT from an older donor.[11]

Though prolonged ischemic time did not interact with any donor-recipient age difference category to influence outcomes, ischemic time was a significant independent risk factor for reduced short-term survival in this cohort on multivariable analysis. While there are investigations into extended donor criteria, including prolonged ischemic time,[24] guidelines recommend avoiding donors > 45 years old if the ischemic time > 4 hours.[10] Given this data, it may be better to take an Older donor within close proximity to the recipient to minimize ischemic time, rather than a Younger donor further away with a longer ischemic time.

Limitations

Important limitations of this data include the retrospective analysis, missing data, inaccuracies in reporting, and incomplete follow-up. Cause of death or retransplant is not consistently reported in the data set; thus, we cannot evaluate if coronary vasculopathy was more prevalent with older donors and if this had an impact on outcomes. These registry data do not consistently differentiate the type of CHD in the recipients, and the number and type of prior surgeries are not available. Therefore, patients with simple CHD without prior cardiac surgery as well as complex CHD with 3 prior sternotomies may be categorized into this cohort, though they represent very different surgical risk profiles. Specifically, multiple studies have reported on reduced short-term survival after HT for patients with Fontan circulation,[25-27] especially those with HLHS.[23] In addition, we included only patients who underwent heart-only transplants; thus, excluding outcomes from centers that primarily perform combined heart-liver transplants on patients with Fontan circulation.

Finally, it is important to place this data within the overall context of patients with ACHD with heart failure who are undergoing evaluation for HT. In addition to the risk of clinical worsening and delisting, patients with CHD have significant surgical and nonsurgical risks for transplant, including redo sternotomy, bleeding from collateral vessels, pulmonary hypertension, human leukocyte antigen sensitization from homograft used during prior surgeries, and fewer options for mechanical circulatory support.[28,29] Therefore, there are many challenges in place before there is an opportunity to apply this data on a patient level. As HT allocation may move toward continuous distribution, careful understanding and weighting of ACHD patient clinical status, recipient and donor age, and distance from donor is a necessary next step in maximizing outcomes.

Conclusions

In conclusion, 10-year graft survival in ACHD patients undergoing HT was similar if donor age was within 5 years of recipient age, compared to donors more than 5 years younger. Recipients who received an HT with a donor more than 5 years older had reduced 10-year survival, which may be at least in part driven by recipients < 30 or ≥40 years old.

These data may help inform donor selection, such as pediatric HT programs may be more liberal in accepting donors for ACHD patients of similar age, potentially shortening waitlist times, and adult programs may wait for donors < 5 years old for stable ACHD patients < 30 years old, which may improve long-term post-transplant survival.

Author contributions

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Concept/design: L.W., W.H.M.; Database access: L.W.: Data analysis/interpretation: L.W., W.H.M.; Drafting and writing of article: W.H.M., L.W.; Critical revision and approval of the article: W.H.M., L.W., D.N., C.J.D., and B.L.

Disclosure statement

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhlto.2024.100135.

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