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The Journal of Heart and Lung Transplantation
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Impact of the 18th birthday on waitlist outcomes among young adults listed for heart transplant: A regression discontinuity analysis

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KEYWORDS:
pediatrics;
transplantation;
outcomes;
waitlist;
heart transplantation;
regression discontinuity

BACKGROUND: Patients listed for heart transplant after their 18th birthday purportedly wait longer to receive a donor heart compared with patients listed before their 18th birthday. It is unclear whether there is an actual difference in wait times and whether any difference in wait time is associated with lower likelihood of transplant and/or higher risk of mortality.

METHODS: Organ procurement and transplant network data were used to identify all patients listed for heart transplant between 2006 and 2014 within a 1-year period before and after their 18th birthday. The primary study end-point was the waiting time to receive a donor heart. Secondary end-points included the probability of transplant and waitlist mortality. Regression discontinuity analysis was used to analyze the effect of age on either side of the sharp cut-off value of age 18 years (6,574 days of life), when allocation of donor hearts transitions from the pediatric to adult allocation system.

RESULTS: A total of 360 patients met the study inclusion criteria, including 207 (57.5%) listed during the 12-month period before their 18th birthday under the pediatric allocation system, and 153 (42.5%) listed during the 12 months after their 18th birthday under the adult allocation system. The pediatric cohort was more likely to be listed Status 1A. Otherwise, the 2 groups shared similar baseline characteristics. Overall, patients listed after their 18th birthday waited 8.5 months longer to receive a transplant than adolescents listed before their 18th birthday ($p = 0.01$) and had a 47% lower probability of receiving a transplant ($p = 0.001$), but there was no difference in waitlist mortality ($p = 0.37$).

CONCLUSIONS: Patients listed for heart transplant shortly after their 18th birthday have significantly longer wait-times compared with patients listed shortly before their 18th birthday and a lower probability of transplant, but no significant difference in waitlist mortality. For medically fragile adolescents at high risk of death, birth date may be a relevant factor in the timing of heart transplant listing.

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http://dx.doi.org/10.1016/j.healun.2017.05.018

J Heart Lung Transplant 2017;36:1185–1191

Young adult patients listed for heart transplant (HT) after their 18th birthday purportedly wait longer to receive a donor heart compared with patients listed before their 18th birthday. However, it is unclear whether there is an actual difference in wait-times after adjusting for patient factors and whether any difference in wait-time translates into a lower likelihood of receiving a transplant and/or higher risk of mortality. United Network for Organ Sharing (UNOS) policy dictates that patients listed for HT after their 18th birthday are allocated a donor heart under the adult allocation system, whereas patients listed before their 18th birthday are allocated a donor heart under the pediatric allocation system, where children receive preference for younger donor hearts.[1–3] Thus, to measure the effect of allocation system on waitlist outcomes, the primary aim of this study was to compare wait times for young adults listed for heart transplant immediately before and after their 18th birthday, when patient characteristics are relatively similar. The secondary aims of the study were to compare the probability of reaching transplant and the probability of death while waiting in the 2 study groups.

Methods

Study population and data source

All patients who were listed for orthotopic HT within 1 year of their 18th birthday (ages 17 and 19 years) between January 2006 and March 2014 were identified using Organ Procurement and Transplant Network (OPTN) data. OPTN is an internally audited, mandatory, government-sponsored solid-organ transplant registry that collects information on all solid-organ transplants in the USA. Demographic and clinical information is reported by transplant centers to the OPTN and is supplemented by data from the Social Security Administration. Patients undergoing multiple-organ and heterotopic transplants were excluded. All patients were followed from the time of HT listing until removal (due to transplant, death/deterioration or recovery) or the day of last observation (through June 6, 2014).

Study outcome measures and definitions

The primary study hypothesis was that young adult patients listed for HT immediately after their 18th birthday would have significantly longer wait-times compared with young adults listed before their 18th birthday, after adjusting for patient factors. The secondary hypothesis was that patients listed for HT immediately after their 18th birthday would have a lower probability of receiving a transplant and a higher probability of waitlist mortality than patients listed before their 18th birthday, after adjusting for patient differences. The probabilities of transplant and mortality are defined within 2 years unless otherwise noted. Race/ethnicity data were analyzed as reported by the transplanting center. Glomerular filtration rate (GFR) was estimated using the modified Schwartz formula.[4] Invasive hemodynamic support at transplant was analyzed using previously described categories: oral therapies; inotropes; ventilator; ventricular assist device (VAD); extracorporeal membrane oxygenation (ECMO); or none of the above.[5] None of the subjects had missing data for the variables of age, gender, race, blood type, hemodynamic support, UNOS listing status and the date of waitlist removal (due to transplant, death/deterioration or recovery) during the study period.

Statistical analysis

Summary statistics are presented as median (Quartile 1, Quartile 3) or number (percent). Patients' characteristics were compared across study groups using the chi-square test for categorical variables and the Mann—Whitney *U*-test for continuous variables. Because of instability of the results using Cox regression when age was analyzed as a dichotomous exposure variable using different age windows surrounding the 18th birthday,[6] a regression-discontinuity (RD) analysis was conducted to analyze the treatment effect on waitlist outcomes where treatment is determined by whether the continuous running variable (age) exceeds the cut-off value of age 18 years. The 18th birthday, or day of life 6,574, represents a sharp cut-off value where the allocation system is deterministically assigned solely based on birth date, making it suitable for regression discontinuity analysis. As part of the RD analysis, waitlist time was estimated using ordinary least-squares regression, a parametric regression technique that is a valid method for estimating treatment effects in survival data when the number of right-censored subjects is negligible.[7] The probability of transplant and the probability of mortality were estimated using probit regression, a parametric regression technique like logistic regression where the dependent variable is binary. All estimates were plotted as a function of the initial listing age to determine whether there was a significant discontinuity in the regression line at 18.0 years of age. A non-parametric regression model was used to estimate the effect of age on the 3 outcomes (RD coefficient) at the 18th birthday after adjusting for patient factors. A second age term (linear) was included in the final model to address boundary effects.

Results

Study cohort

Between January 2006 and March 2014, a total of 360 patients 17 to 19 years of age were listed for isolated HT. Of these, 207 (57.5%) were listed before their 18th birthday (the "pediatric cohort") and 153 (42.5%) were listed after their 18th birthday (the "adult cohort"). The baseline characteristics of the study cohort are summarized in Table 1. As expected, the pediatric cohort was younger and more likely to be listed Status 1A. Otherwise, the characteristics of the 2 cohorts were similar.

Table 1 Baseline Characteristics of Study Cohort at Time of Transplant ($N = 360$)

Characteristic	All patients ($N = 360$)	Patients listed before 18th birthday ($N = 207$)	Patients listed after 18th birthday ($N = 153$)	p-value
Age (years)	17.9 (16.9, 18.0)	17.5 (17.3, 17.8)	18.5 (18.3, 18.8)	<0.001
Weight (kg)	64 (54, 79)	63 (54, 76)	65 (55, 83)	0.17
Female	125 (35%)	67 (32%)	58 (38%)	0.28
African American	92 (26%)	56 (27%)	36 (24%)	0.45
Public health insurance	127 (35%)	79 (38%)	48 (32%)	0.23
Cardiomyopathy diagnosis	215 (58%)	121 (59%)	94 (61%)	0.58
Blood type O	181 (50%)	103 (50%)	78 (51%)	0.82
Support at transplant				0.95
Oral	178 (49%)	105 (51%)	73 (48%)	
Inotropes	115 (32%)	63 (30%)	52 (34%)	
Ventilator	8 (2%)	5 (2%)	3 (2%)	
VAD	48 (13%)	28 (14%)	20 (13%)	
ECMO	11 (3%)	6 (3%)	5 (3%)	
GFR at transplant (ml/min/1.73 m^2)[a]	87 (68, 110)	85 (37)	80 (31)	0.33
UNOS status at listing				<0.001
Status 1A	144 (40%)	107 (52%)	37 (24%)	
Status 1B	84 (23%)	27 (13%)	57 (37%)	
Status 2	123 (34%)	70 (34%)	53 (35%)	
Other	9 (3%)	3 (1%)	6 (4%)	

Data presented as median (interquartile range) or number (percent). ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate (modified Schwartz); UNOS, United Network for Organ Sharing; VAD, ventricular assist device.

[a]Data expressed as mean (range or standard deviation).

Overall outcomes

During the median follow-up duration of 73 days, 148 patients (72%) in the pediatric cohort received a transplant, 27 (13%) died or deteriorated, 7 (3%) recovered and 25 (12%) were still listed. In the adult cohort, 103 patients (67%) were transplanted, 17 (11%) died or deteriorated, 4 (3%) recovered and 29 (19%) were still listed. Before adjustment for patient factors, median waitlist time was 60 and 94 days, respectively, for the pediatric and adult cohorts ($p = 0.07$). In unadjusted analyses, there was not a statistically significant difference in probability of transplant and/or waitlist mortality between the 2 cohorts (Figure 1). Using Cox regression to adjust for patient differences, the waitlist time, probability of transplant and waitlist mortality effects varied significantly depending on the model covariates.

Regression discontinuity analysis

Using regression discontinuity analysis, there was a significant discontinuous increase in waitlist time just after the 18th birthday (Figure 2A). Although the trend line for the adult group shows a decrease toward the waitlist time for the pediatric group toward the end of the 19th year, the data need to be interpreted cautiously because the number of observations also decreases toward age 19 years. Moreover, estimates that vary away from the cut-off value (of the 18th birthday) do not affect the primary statistical inference in RD analysis, which focuses on the effect immediately surrounding the cut-off value. There was also a significant discontinuous decrease in the probability of receiving a transplant and a non-significant discontinuous increase in the probability of death immediately after the 18th birthday (Figure 2B and C). By contrast, the control variables and the density of the running variable (age) were essentially continuous around the 18th birthday.

After controlling for baseline characteristics using non-parametric regression to estimate the RD coefficient, the adult cohort waited 8.5 months (263 days) longer than the pediatric cohort ($p = 0.01$; Figure 2A), consistent with the ordinary least-squares model for the 12-month window ($p = 0.05$; Table 2). There was a 47% lower probability of receiving a heart transplant in the older age group by RD analysis ($p = 0.001$; Figure 2B) consistent with the findings of the probit model for the 12-month window ($p = 0.003$). There was no significant difference in waitlist mortality across the 18th birthday threshold by either RD analysis ($p = 0.37$; Figure 2C) or the probit models ($p = 0.11$; Table 2).

In a secondary analysis, we explored the effect of the 18th birthday among the subset of patients initially listed UNOS Status 1A (refer to Table S1 and Figure S1A–C in the Supplementary Material available online at www.jhltonline.org). Among 144 patients (107 in the pediatric cohort and 37 in the adult cohort), there was no difference in waitlist time ($p = 0.84$); however, patients listed as adults had a 36% lower probability of reaching transplant ($p = 0.03$) and a 32% higher probability of mortality ($p = 0.03$) after adjusting for patient factors. The results must be interpreted somewhat cautiously because: (1) there were only 37 patients in the adult group, which limits the statistical power and reduces the stability of the results; and (2) patients were classified according to their initial listing

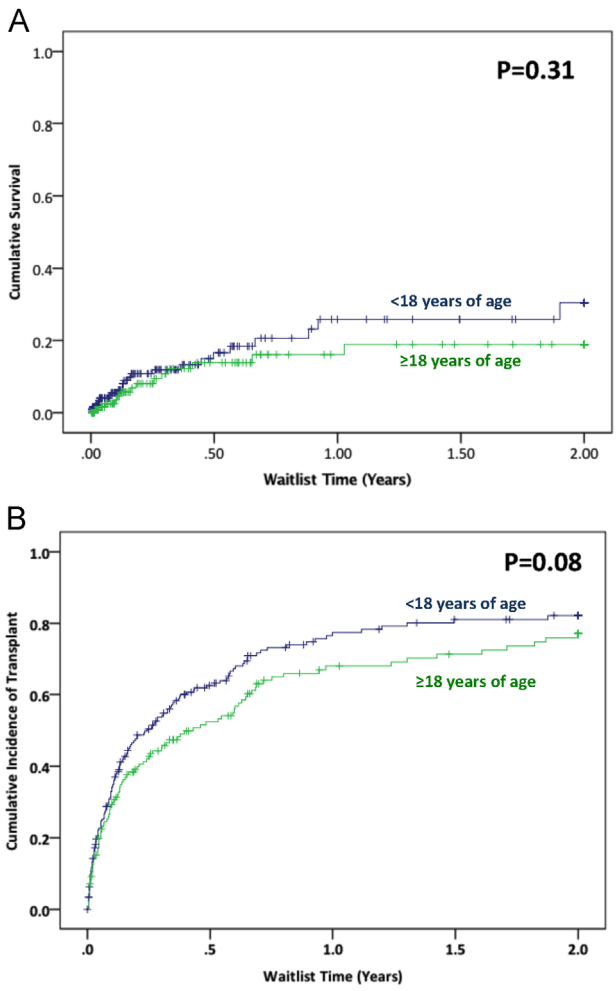

Figure 1 (A) Cumulative waitlist mortality through 24 months based on age group at heart transplant listing relative to the 18th birthday. Patients were censored at the time of transplant or recovery. (B) Cumulative probability of receiving a transplant through 24 months based on age at heart transplant listing relative the 18th birthday. Patients were censored at the time of death or recovery.

status, which can change after initial listing, introducing misclassification effects. However, the direction of the results is consistent with the overall cohort.

Discussion

In this study, we found that young adults listed for HT immediately after their 18th birthday wait longer to receive a donor heart compared with patients listed immediately prior to their 18th birthday. This difference in waitlist time was associated with a lower probability of receiving a donor heart. However, waitlist mortality was no different for young adults listed immediately before or after the 18th birthday. Our findings are consistent with publically available data from UNOS indicating that waitlist times are longer for adults than for children.[1,8] However, these reports analyze patients across larger age group categories and are not risk-adjusted, leaving open the possibility that differences in outcome could be explained by differences in

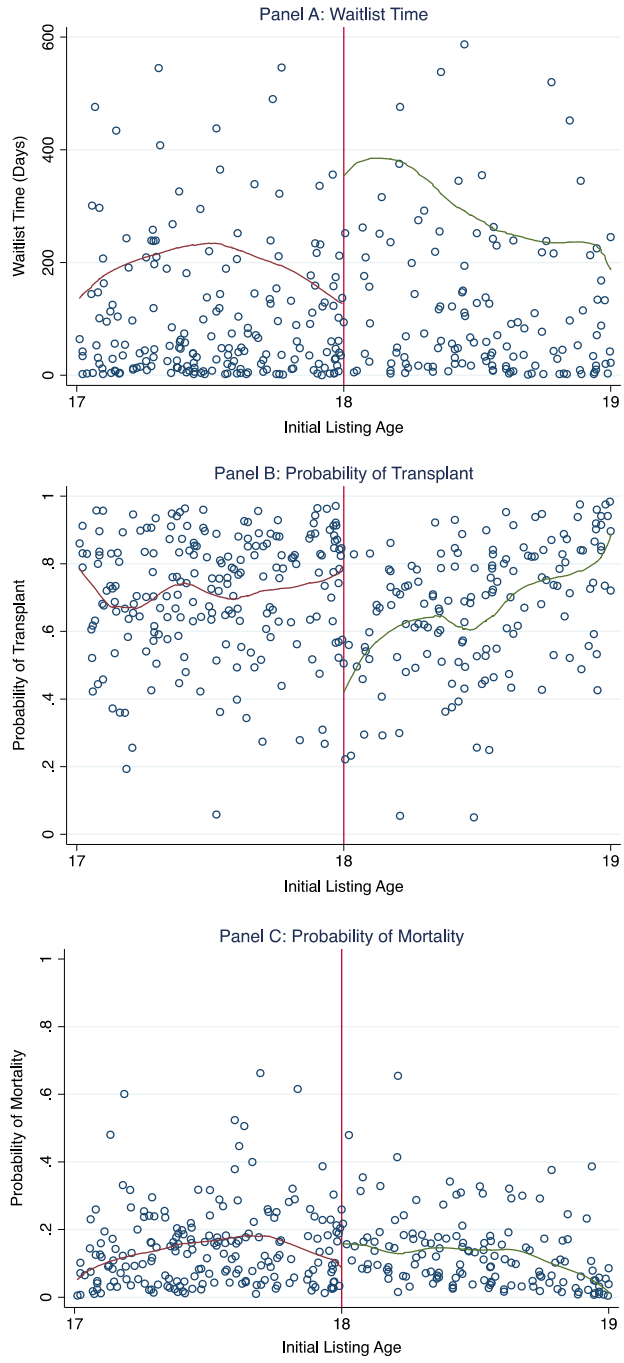

Figure 2 Regression discontinuity graphs demonstrating the effect of age analyzed as a continuous variable on (A) waitlist time, (B) probability of transplant and (C) probability of death within 2 years of transplant listing. (A) Effect of age at listing on waitlist time showing a sharp regression discontinuity at the 18th birthday. After adjusting for patient factors, patients listed immediately after the 18th birthday waited an average of 246 days (8.1 months) longer than patients listed immediately before the 18th birthday ($p = 0.03$). (B) Effect of age at listing on the probability of transplant showing a sharp regression discontinuity at the 18th birthday. After adjusting for patient factors, patients listed immediately before the 18th birthday were 40% more likely to be transplanted than young adults listed immediately after their 18th birthday ($p = 0.01$). (C) Effect of age at listing on the probability of mortality showing a non-significant regression discontinuity at the 18th birthday. After adjusting for patient factors, there was no difference in the probability of death around the 18th birthday ($p = 0.50$).

Table 2 Multivariable Models Examining the Association Between Older Age (Allocation) Group and Heart Transplant Waitlist Time, Probability of Receiving a Transplant and Mortality Within 2 Years of Listing[a]

	Waitlist time (days)		Probability of heart transplant		Probability of mortality	
	Change in days (%)[b]	*p*-value	Change in *Z*-score (%)[b]	*p*-value	Change in *Z*-score (%)[b]	*p*-value
Indicator of age >18 years	183 (76%)	0.05	−0.95 (−28%)[d]	0.003	0.57 (11%)[e]	0.13
Weight at listing	2 (1%)	0.07	0.002 (0.07%)	0.59	−0.01 (−0.1%)	0.21
Blood group O	98 (41%)	0.02	−0.24 (−7%)	0.11	0.15 (3%)	0.41
African American	76 (32%)	0.20	−0.17 (−5%)	0.32	−0.03 (−0.6%)	0.89
Female	−10 (−4%)	0.83	0.10 (3%)	0.53	−0.18 (−3%)	0.38
Renal dysfunction categories[c]						
Normal	—	—	—	—	—	—
Moderate	12 (5%)	0.79	−0.50 (−15%)	0.002	0.83 (16%)	<0.001
Severe	95 (39%)	0.39	−1.70 (−51%)	<0.001	1.86 (36%)	<0.001
Initial UNOS listing status[d]						
Listing Status 2	—	—	—	—	—	—
Listing Status 1B	−204 (−85%)	0.001	0.71 (21%)	<0.001	−0.54 (−10%)	0.05
Listing Status 1A	−219 (−91%)	<0.001	0.54 (16%)	0.002	−0.28 (−5%)	0.21
Others	−186 (−77%)	0.01	−0.35 (−10%)	0.46	−0.11 (−2%)	0.86
Constant	72 (—)	0.55	1.14 (—)	0.01	−0.90 (—)	0.10

[a]Waitlist time was analyzed using an ordinary least-squares model, whereas the probability of transplant and death were analyzed using a probit model.
[b]The change in days is relative to the mean waitlist time for the overall cohort. The change in probability of transplant (and mortality) is reported as the change in the *Z*-score. For example, a change in *Z*-score of 0.95 corresponds to a 28% decrease in the probability of transplant based on the normal distribution.
[c]Renal function categories were defined as follows using GFR as estimated by the modified Schwartz formula. Glomerular filtration rate (GFR) defined as normal ($\geq$90 ml/min/1.73 m^2, GFR category = 3), severely decreased (GFR <30 ml/min/1.73 m^2, GFR category = 1) or moderately decreased for all values in between (GFR category = 2). Normal GFR was the reference group.
[d]United Network for Organ Sharing (UNOS) listing status was defined at the time of initial listing for heart transplant. UNOS Status 2 was the reference group.

patient characteristics or differences in patient management environment unique to adult vs pediatric transplant centers. By contrast, the present study, in which we analyzed the effect of age at the 18th birthday time-point, isolates the effect of age on outcome. To the best of our knowledge, this study is also the first pediatric cardiovascular study to use regression discontinuity as the study's primary statistical methodology.[9,10]

We decided to use regression discontinuity to analyze the effect of age on outcome because: (1) we found model results were unstable using conventional Cox proportional hazards analyses; and (2) the primary scientific question, which focuses on the effect of a sharp, policy-driven age cut-off within the UNOS allocation system, provides a quasi-experimental condition where RD has proven to be helpful in similar situations.[9–14] We speculate that part of the reason the RD results are more stable than Cox analysis is that the conventional multivariable analyses treat the variable of interest, age, as a dichotomous variable rather than a continuous variable, where statistical information (power) may be lost. This variability is consistent with the variable results of the ordinary least-squares and probit models. By contrast, RD focuses the analysis on the instantaneous effect at age 18.

There are several reasons why young adults listed for HT under the pediatric heart allocation system may have shorter waitlist times than under the adult allocation system, and fall into 1 of 2 categories: (1) factors that increase the relative supply of donor hearts to children (e.g., allocation of adult donor hearts to children,[15,16] a higher prevalence of children listed UNOS Status 1A); and (2) factors that decrease the relative demand of donor hearts (e.g., a relatively smaller pool of children listed for transplant, and/or a higher rate of attrition through mortality or recovery[15,16]). Our analysis is limited to examining the net effect of these allocation differences rather than pinpointing which component(s) of the different allocation system is causing the difference. This includes any effect of "gaming" of the system, which is always a possibility, where listing criteria are not strictly objective and human judgment is involved. UNOS data are limited in what they can tell us about the intentions behind center/physician behavior. However, we could find no clear evidence of it here based on the similarity of the baseline characteristics.

Our findings have several implications. First, from a clinical perspective, our findings suggest that, for young adults who are approaching their 18th birthday and are at the highest risk of waitlist mortality, the differential waitlist times may be 1 factor for clinicians to be aware of in the complex medical decision-making relating to the timing of listing. Unfortunately, late heart transplant referrals remain a major problem in pediatrics. Our findings suggest there may be a significant incremental cost to late referrals when it involves a patient in late adolescence.

Second, although waitlist times may be shorter and transplant probability slightly higher under the pediatric allocation system, our findings suggest that the combined effect of the adult and pediatric UNOS heart allocation systems appears to work reasonably well to achieve parity

with respect to waitlist mortality for most patients around their 18th birthday. This finding is consistent with data showing that children have historically faced a far higher hazard of mortality on the waitlist than adults.[8,17] The finding of slightly lower mortality among the subgroup of children listed Status 1A for transplant may be a sign that the mortality curve is beginning to bend for children thanks to greater use of pediatric ventricular assist devices[18] and broader regional sharing of donor organs.[19] Still, because the numbers are small, more data are needed to determine whether this trend is robust.

Last, our findings suggest that RD analysis may be a promising statistical methodology for pediatric research. Indeed, a number of recent publications have suggested RD may be underutilized in medical research.[9,10,20] To date, most studies involving RD have been published in the areas of health policy assessment[12–14] and health economics.[11,12,21] Pediatric clinical research is in dire need of more efficient statistical methodologies to compare treatments because of limited statistical power (Type II statistical error) stemming from the rareness of pediatric diseases and the low event rates. The problem of underpowered pediatric clinical trials has led many researchers to question not only the scientific validity of pediatric studies but have made the point that underpowered trials in pediatrics are unethical[22] by exposing children to investigational drugs without a realistic hope of understanding their comparative efficacy and safety. RD may provide a reasonable alternative analytic strategy for clinicians to draw causal inferences without randomization where Type II error is a major threat to validity, provided the appropriate study conditions exist.

Limitations

Our findings must be interpreted in the context of certain limitations related to the study design. First, it is possible that there was residual confounding around the 18th birthday, leading to an imbalance of the patient characteristics immediately before and after the 18th birthday that could explain the study findings. However, secondary analyses of potential confounders suggest that the characteristics were relatively well balanced. Moreover, alternate models (specifically ordinary least-squares, probit and nonparametric models for estimation of the RD), which adjusted for potential confounders, yielded similar results. Second, because inferences from RD analysis are restricted to subjects at or near the cut-off value, our findings cannot be generalized to subjects further away from the 18th birthday cut-off based on our RD analysis alone. Nevertheless, transplant clinician experience suggests adult candidates across a broader range of ages tend to wait longer, on average, than pediatric candidates, a finding that is supported by publically available unadjusted data from UNOS.[8] Finally, there have been major changes in both the pediatric and adult allocation systems in recent years that could alter the effect estimates in the study. However, because the adult and pediatric allocation systems remain distinct, and the revised allocation systems do not change the fundamental policy that gives preference to children for younger donor hearts, it is unlikely that the effect estimates would change significantly for the comparison groups, even if particular aspects of the allocation policy within each age group have changed.

In conclusion, young adults listed for HT immediately after their 18th birthday wait significantly longer to receive a donor heart compared with young adults listed immediately before their 18th birthday. This difference in waitlist time was found to be associated with a lower probability of receiving a donor heart. However, waitlist mortality was no different for young adults, regardless of when they were listed for HT in relation to their 18th birthday. These findings suggest that the current UNOS allocation policy is achieving equitable waitlist mortality for young adults, regardless of when they are listed in relation to their 18th birthday. Because of the problem of late referrals in pediatric heart transplantation, general cardiologists should be aware of the longer waitlist times for adult candidates, particularly when the patient is medically fragile and may not survive a prolonged waitlist time. Regression discontinuity is a promising statistical methodology that may be underutilized in pediatric cardiovascular research.

Disclosure statement

The authors have no conflicts of interest to disclose.

Appendix A. Supporting materials

Supplementary materials can be found in the online version of this article at www.jhltonline.org/.

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