

Use of Donors at Age Extremes for Simultaneous Pancreas-Kidney Transplant

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Abstract

Introduction: There is a shortage of optimal pancreatic donors for simultaneous pancreas and kidney transplant (SPKT), as such there is interest in utilizing donors at extremes of age to expand the donor pool. We sought to evaluate outcomes in SPKT from pediatric donors (PDs) to older donors (ODs). **Patients and Methods:** We identified patients who underwent simultaneous pancreas and kidney transplant at a single, high-volume institution from 1988–2013. We evaluated for differences in transplant organ function (estimated glomerular filtration rate [GFR], serum glucose, and urine amylase), early (technical) graft loss, and patient and graft survival. **Results:** A total of 729 SPKT were performed during the study, with 32 PDs, 652 standard donors (SDs), and 45 ODs. Renal function was slightly worse in OD. Otherwise, graft function was similar between all three groups at up to 5 years. There was no difference in censored survival analyses for both kidney and pancreas allografts. There was comparable short-term and long-term patient survival among all groups. **Conclusions:** Overall, the use of pancreas from pediatric and ODs for SPKT has comparable outcome to SDs. Kidneys from donors above 50 may have lower GFR, but otherwise, have comparable long-term patient and graft survival.

Keywords: End-stage renal disease, graft survival, kidney transplantation, older donor, pancreas transplantation, pediatric donor, survival analysis, type 1 diabetes mellitus

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a major cause of morbidity and mortality in the United States and accounts for about 245 billion annual health-care costs.^[1-4] There are 1.25 million Americans are living with T1DM, 85% of who are adults, with 40, 000 new diagnoses each year, and an estimated 5 million people with T1DM in the U. S. by 2050.^[3-7] Simultaneous pancreas-kidney transplant (SPKT) is a well-established treatment for patients with T1DM complicated by end-stage renal disease.^[8-13] Despite an increase in the number of deceased donor pancreata recovered over the last decade, the overall number of pancreas transplants has continued to decline.^[14,15] This is, in part, due to historically poor outcomes from pancreas transplant. The recent implementation of a new pancreas allocation system, along with the proposal for a consistent definition of pancreas graft failure, as well as improving outcomes (graft and patient survival), is expected to improve the overall rates of SPKT being performed.^[16,17] Unfortunately, the number of diabetic patients on the pancreas transplant waiting list continues to rise and exceeds the number

of available donor organs.^[16,18] This mandates different options to expand the donor pool while maintaining excellent outcome.

Conventionally, pediatric donors (PDs) have been underutilized for SPKT. This was mostly driven by the lack of standard criteria for an acceptable pancreas graft.^[19,20] PDs are considered by most centers to be marginal grafts due to perceived lower islet mass, higher technical demand, and potential complications.^[21-23] Older donors (ODs) are equally also underutilized due to a perceived shorter graft survival and less optimal function.^[16,24] However, there is growing evidence from single-center studies that these organs may provide comparable outcomes to standard age donors.^[19,23,25-29] Nevertheless, there remains a paucity of the literature to encourage the use of these donors, and as such, many centers

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remain reluctant to use these organs in the absence of stronger evidence to support their use. Our study aims to evaluate the outcome of SPKT in donors at extremes of age using our over 20-year institutional database.

METHODS

Settings

We performed a retrospective review of a prospectively collected database registry for all SPKTs performed between 1988 and 2013. During that period, we performed 32 SPKT using PDs, 652 using standard (control) donors, and 45 using ODs. Those cases were reviewed and compared based on 1-, 3-, 5-, and 10-year patient and graft survival, transplanted organs function (estimated glomerular filtration rate [eGFR], serum glucose, and urine amylase), and incidence of early graft loss. The study was approved by the Institutional Review Board.

Treatment protocol

The surgical management of T1DM evolved over the period of data collection but consisted of either simultaneous pancreas-kidney (SPK), pancreas-after-kidney, pancreas-transplant-alone, or more recently pancreatic islet cell transplantation. The operative technique for SPK transplantation has equally changed over the years and remains a subject of great debate. Our preferred approach, including changes in our immunosuppression protocols, has been previously published elsewhere.^[30-34] All organ procurements were done by standard techniques and preserved in the University of Wisconsin solution.

Data collection and statistics

A prospectively maintained database of all transplant patients (total 729) was utilized for demographic data and patient outcome, survival, and graft failure. In this study, pediatric kidney and pancreas deceased donors (PDs) were defined as being between the age of 0–13 years ($n = 32$; 4.4%), and more than 20 kg body weight. We considered standard (control) donors (SDs) to be between the age of 13–50 years ($N = 652$; 89.4%) and ODs to be older than 50 years ($n = 45$; 6.2%). Chi-square tests and Fisher's exact tests were used to analyze categorical variables, and Student *t*-test and ANOVA were used to compare continuous variables. Univariate analyses were performed to characterize transplanted organ-specific outcomes over time including creatinine, average glucose levels, hemoglobin A1c (HgA1c), average urinary amylase, and average GFR. The Kaplan–Meier product limit methods were used to estimate overall patient and graft death-censored survival, and log-rank tests were used to compare the overall long-term patient and graft survival between age groups. IBM Corp. Data analysis was performed in SPSS (IBM SPSS Statistics for Windows, Version 24.0, IBM Corp., Armonk, NY, USA).

RESULTS

Organs from younger donors tended to be transplanted into younger recipients ($P = 0.018$). There was a significantly higher

proportion of male recipients in the SD group, compared to the pediatric and OD groups, which had a higher proportion of female recipients. A high proportion of the PDs suffered from a cerebrovascular accident. There were no statistically significant differences in other baseline characteristics including race and pretransplant diagnosis between the three groups [Tables 1 and 2]. A small percentage of patients underwent transplantation due to end-stage renal disease not directly related to their diabetes, and an even smaller percentage underwent SPKT due to Type 2 diabetes. Technical graft loss, described as graft loss within 30 days of transplant, was equivalent between PD and control groups. The same was true for ODs.

There was no significant difference in average HgA1c between groups at up to 5-year post-transplantation [Table 2 and Figure 1]. Similarly, the average urine amylase was similar across all three groups at up to 5-year postkidney transplant [Table 3 and Figure 1]. Due to the paucity of data available, c-peptides were not analyzed. With regard to kidney function, there was no difference in the average GFR between the PD group and SD group. However, there was a significantly lower GFR in the OD group, and this persisted for 5-year post-transplantation [Table 3 and Figure 1].

In multivariate analyses, there was a trend toward early pancreas graft survival advantage in the PD group, although no significant difference was seen in the long. Furthermore, there was a trend toward between early and long-term

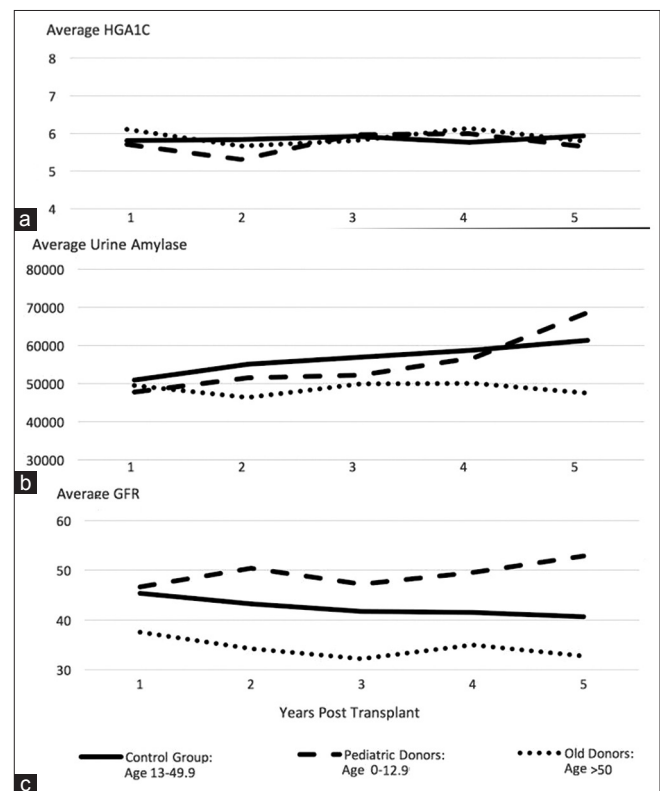


Figure 1: Trends of hemoglobin A1c (a), urine amylase trends (b) and glomerular filtration rate (c) post-transplant (up to five years).

Table 1: Comparison of baseline characteristics of pediatric donor group to control donor group (n, percentage, or mean, standard deviation)

| Characteristics | Control group: Donors between ages 13.0-49.9 (n=652) | Young donors: Donors between ages 0-12.9 (n=32) | P* |
|--|--|---|-------|
| Recipient age at transplant† | 39 (8) | 36 (7) | 0.018 |
| Donor age (years)† | 29 (10) | 9 (2) | 0.000 |
| Donor weight (kg)† | 74.7 (16) | 39.4 (11) | 0.000 |
| Gender, n (%) | | | |
| Males | 417 (64) | 15 (47) | 0.050 |
| Females | 235 (36) | 17 (53) | |
| Race, n (%) | | | |
| African American/black | 51 (8) | 3 (9) | 0.889 |
| White | 590 (91) | 29 (91) | |
| Other | 5 (1) | 0 | |
| Pretransplant diagnosis, n (%) | | | |
| Type 1 Diabetes | 379 (58) | 17 (53.1) | 0.895 |
| Type 2 Diabetes | 3 (0.5) | 0 | |
| Diabetes unknown type | 207 (32) | 11 (34.4) | |
| End-stage renal disease, other causes | 8 (1) | 0 | |
| Retransplant/graft failure | 3 (0.5) | 0 | |
| Unknown | 52 (8.0) | 4 (12.5) | |
| Cause of death, n (%) | | | |
| Anoxia | 62 (10) | 6 (20) | 0.183 |
| CVA/stroke | 154 (25) | 3 (10) | |
| Head trauma | 364 (58) | 20 (67) | |
| CNS tumor | 3 (1) | 0 | |
| Other | 39 (6) | 1 (3) | |
| Pancreas graft loss in <30 days, n (%) | 38 (11) | 1 (6) | 0.553 |
| Kidney graft loss in <30 days, n (%) | 19 (3) | 0 | 0.327 |

*P value by t-test for continuous variables and Chi-square test for categorical variable, †Mean and SD. CVA: Cerebrovascular accident, CNS: Central nervous system, SD: Standard deviation

kidney survival advantage in the PD group compared to SD group and OD group, although this did not reach statistical significance [Figures 2 and 3]. Overall, there was no short-term or long-term patient survival difference between all three groups [Figure 4].

DISCUSSION

Despite the overall improving outcomes in SPK transplant, fewer SPK transplants are performed nationally. This trend is probably multifactorial. Better medical management for diabetic patients has resulted in delayed diabetic complications and is reflected by fewer patient or delay in referrals and listing for SPK transplant. In addition, less optimal donor quality may be limiting perceived donor options. In 2014, there were 954 pancreas transplants were performed, while there were 1233 patients waiting for a pancreas transplant.^[16] Hence, although great progress has been made in minimally invasive techniques for pancreatic endocrine replacement therapy, SPK transplant remains the treatment of choice for diabetic patients with the end-stage renal disease.^[35] SPK achieves normoglycemia, improves the quality of life, prolongs patient survival, and prevents of the progression of most of the diabetic complications. Unfortunately, these results cannot be

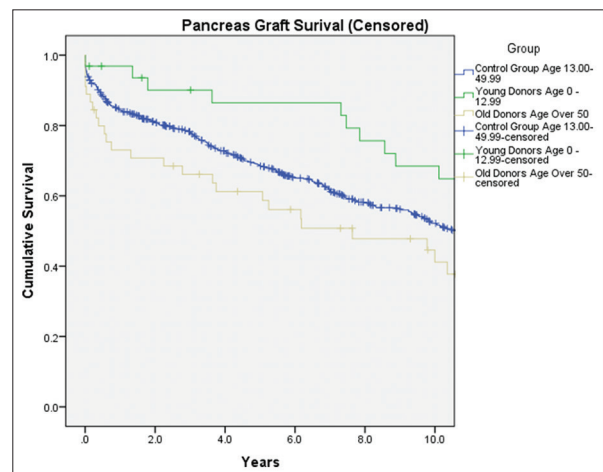


Figure 2: Kaplan–Meier curves of mortality-censored pancreas graft survival

Test of equality of survival distributions for the different levels of group

| | χ^2 | P |
|---|----------|-------|
| Log rank (mantel-cox) (late/long-term) | 3.723 | 0.155 |
| Tarone-ware (middle/mid-term) | 6.349 | 0.042 |
| Breslow (generalized Wilcoxon) (early/short-term) | 7.576 | 0.023 |

Table 2: Comparison of baseline characteristics of older donor group to control donor group (n, %, or mean, standard deviation)

| Characteristics | Control group: Donors between ages 13.0-49.9 (n=652) | Young donors: Donors between ages 0-12.9 (n=32) | P* |
|--|--|---|-------|
| Recipient age at transplant† | 39 (8) | 41 (7) | 0.095 |
| Donor age (years)† | 29 (10) | 53 (3) | 0.000 |
| Donor weight (kg)† | 74.7 (16) | 74.0 (11) | 0.832 |
| Donor BMI† | 30.2 (28) | 29.8 (24.4) | 0.933 |
| Gender, n (%) | | | |
| Males | 417 (64) | 21 (47) | 0.020 |
| Females | 235 (36) | 24 (53) | |
| Race, n (%) | | | |
| African American/black | 51 (8) | 5 (11) | 0.555 |
| White | 590 (91) | 39 (87) | |
| Other | 5 (1) | 1 (2) | |
| Pretransplant diagnosis, n (%) | | | |
| Type 1 Diabetes | 379 (58) | 27 (60) | 0.211 |
| Type 2 Diabetes | 3 (0.5) | 1 (2) | |
| Diabetes of unknown type | 207 (32) | 17 (38) | |
| End-stage renal disease, other causes | 8 (1) | 0 | |
| Retransplant/graft failure | 3 (0.5) | 0 | |
| Unknown | 52 (8.0) | 0 | |
| Cause of death, n (%) | | | |
| Anoxia | 62 (10) | 2 (5) | 0.000 |
| CVA/stroke | 154 (25) | 29 (67) | |
| Head trauma | 364 (58) | 10 (23) | |
| CNS tumor | 3 (1) | 0 | |
| Other | 39 (6) | 2 (5) | |
| Pancreas graft loss in <30 days, n (%) | 30 (11) | 5 (18) | 0.235 |
| Kidney graft loss in <30 days, n (%) | 19 (3) | 2 (4) | 0.561 |

*P value by t-test for continuous variables and Chi-square test for categorical variables, †Mean and SD. BMI: Body mass index, CVA: Cerebrovascular accident, CNS: Central nervous system, SD: Standard deviation

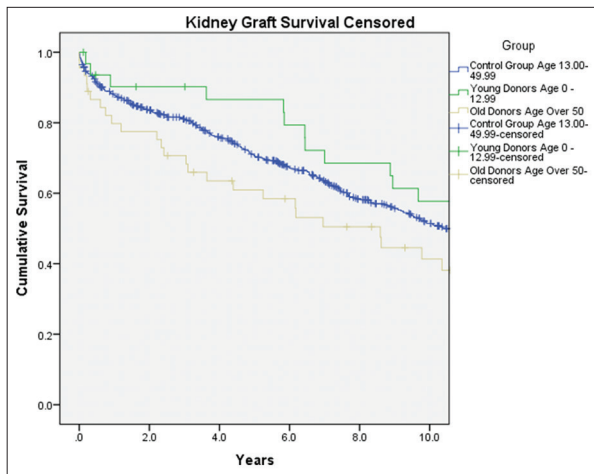


Figure 3: Kaplan–Meier curves of mortality-censored kidney graft survival

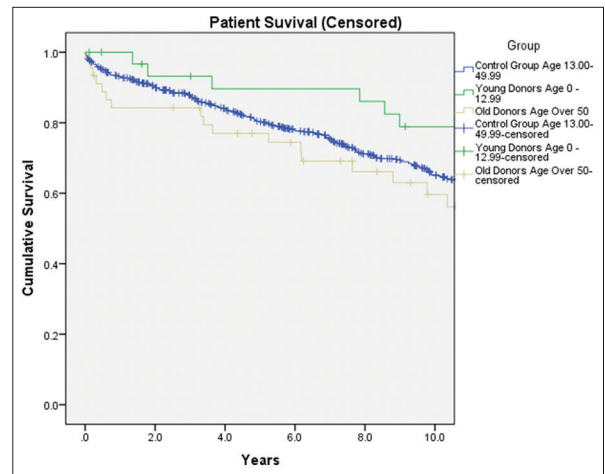


Figure 4: Kaplan–Meier curves of mortality-censored overall patient survival

| Test of equality of survival distributions for the different levels of group | χ^2 | P |
|--|----------|-------|
| Log rank (mantel-cox) (late/long-term) | 5.180 | 0.075 |
| Tarone-ware (middle/mid-term) | 4.983 | 0.083 |
| Breslow (generalized Wilcoxon) (early/short-term) | 5.145 | 0.076 |

| Test of equality of survival distributions for the different levels of group | χ^2 | P |
|--|----------|-------|
| Log rank (mantel-cox) (late/long-term) | 2.411 | 0.300 |
| Breslow (generalized Wilcoxon) (early/short-term) | 3.871 | 0.144 |
| Tarone-ware (middle/mid-term) | 3.312 | 0.191 |

Table 3: Hemoglobin A1c values. Urine amylase and Glomerular filtration rate measurements averaged over time.

| Time post transplant | 1 week | 3 months | 6 months | 9 months | 1 year | 2 years | 3 years | 4 years | 5 years |
|----------------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
| HgA1C (%) | | | | | | | | | |
| Control group (SD) | 7.34 (1.6) | 5.41 (1.3) | 5.56 (1.3) | 5.80 (1.3) | 5.81 (1.4) | 5.84 (1.3) | 5.92 (1.6) | 5.76 (1.2) | 5.94 (1.4) |
| Pediatric donors (SD; <i>P</i>) | 7.25 (1.6; 0.951) | 5.13 (0.56; 0.614) | 5.25 (0.79; 0.541) | 5.48 (0.66; 0.598) | 5.71 (1.2; 0.854) | 5.31 (1.7; 0.343) | 5.97 (1.3; 0.955) | 5.99 (1.3; 0.644) | 5.65 (1.3; 0.605) |
| Old donors (SD; <i>P</i>) | 8.10 (N/A; 0.643) | 5.63 (0.63; 0.697) | 5.78 (0.55; 0.683) | 6.50 (3.1; 0.639) | 6.11 (0.90; 0.630) | 5.66 (0.96; 0.546) | 5.81 (0.82; 0.684) | 6.13 (1.5; 0.360) | 5.79 (0.79; 0.767) |
| Urine amylase | | | | | | | | | |
| Control group (SD) | 29,584 (23,959) | 54,097 (39,161) | 54,688 (52,859) | 559,153 (122,660) | 50,882 (45,745) | 55,009 (54,130) | 56,938 (68,098) | 58,614 (55,215) | 61,293 (66,418) |
| Pediatric donors (SD; <i>P</i>) | 25,634 (17,765; 0.366) | 47,532 (32,892; 0.377) | 50,391 (34,475; 0.671) | 52,011 (42,786; 0.670) | 47,792 (28,633; 0.738) | 51,561 (30,119; 0.767) | 52,193 (41,850; 0.764) | 56,829 (40,165; 0.896) | 68,596 (83,992; 0.675) |
| Old donors (SD; <i>P</i>) | 21,489 (18,773; 0.643) | 46,583 (54,688; 0.697) | 44,261 (36,506; 0.683) | 49,956 (43,506; 0.639) | 50,974 (52,546; 0.630) | 47,902 (42,031; 0.546) | 51,776 (42,592; 0.684) | 50,078 (29,956; 0.360) | 47,461 (26,979; 0.767) |
| GFR | | | | | | | | | |
| Control group (SD) | 53.7 (23.6) | 49.2 (19.7) | 47.4 (16.6) | 46.4 (16.8) | 45.4 (16.4) | 43.2 (17.0) | 41.7 (17.4) | 41.5 (18.0) | 40.7 (17.4) |
| Pediatric donors (SD; <i>P</i>) | 47.5 (18.5; 0.154) | 42.8 (15.0; 0.080) | 45.3 (16.7; 0.503) | 46.3 (19.3; 0.975) | 46.7 (21.0; 0.682) | 50.5 (24.4; 0.154) | 47.2 (20.4; 0.140) | 49.8 (21.0; 0.040) | 52.9 (34.0; 0.119) |
| Old donors (SD; <i>P</i>) | 39.8 (20.6; 0.000) | 40.6 (13.4; 0.007) | 39.0 (11.9; 0.002) | 36.2 (10.9; 0.004) | 36.9 (10.8; 0.003) | 33.2 (11.0; 0.001) | 31.7 (11.1; 0.002) | 34.2 (15.0; 0.041) | 32.4 (11.2; 0.028) |

All values indicate an average HgA1C values, urinary amylase and eGFR over indicated time period (mean and SD). Results are compared to the control group and *P* values indicated in parentheses. **P*<0.05 indicates statistically significant difference compared to the control group. HgA1C: Hemoglobin A1c, SD: Standard deviation, N/A: Not available. Mean, SD, and *P* values in parenthesis for hypothesis testing comparing control to pediatric donor group and control to the old donor group [Audit1, 3 and 5 respectively].

realized for all patients as most transplant centers shy away from using pancreata from donors at extreme of age due to fear of technical complications and concerns about transplant organ function. Our study demonstrates that these organs can be used safely and effectively. Although kidneys from ODs may have a lower GFR, initially, there is no difference in long-term patient and graft survival related to this finding. Per Organ Procurement and Transplantation Network data, between 2010 and 2014, an average of 434/year donors between the ages of 6–10 years underwent organ recovery. However, only 5% of pancreata from those donors were transplanted. Furthermore, an average of 8175/year donors between the ages of 50–65 years underwent organ recovery, and only 1% of pancreata from those donors were transplanted.^[36]

One of the most feared complications of pancreatic transplantation is arterial thrombosis, as this often results in graft loss. Humar *et al.* showed reported the highest graft failure rates in SPK, with a majority of graft failures resulting from graft thrombosis.^[22,37] The technical challenges associated with transplantation of smaller grafts have resulted in an added fear of using PDs for transplantation. Although previous large center trials^[25,28,38] have demonstrated similar findings of equal outcomes from PDs, use of PDs is not yet widely accepted. We found no difference in technical complications or early graft loss between the pediatric and donor groups. At this center, the cutoff for PDs was 20 kg, which might eliminate some of the technical concerns alluded to above. Although some studies have the use of smaller weight patients, these were limited to a few centers, and more data are needed to encourage its use.

The use of ODs for SPK transplant in our results was not associated with inferior patient and graft survival. When compared to patients on the waitlist and those not transplanted, the OD age group had a better patient survival. Our study showed a 5-year patient survival of more than 70%, which is higher than a previous report by White *et al.* who reported a 46% 4-year patient survival.^[35] Previous studies have raised concerns about the pancreas allograft from ODs. These grafts are thought to have a lower islet cell mass and function,^[21,24] raising concerns of early graft failure. In addition, grafts from ODs have been associated with increased graft thrombosis and graft failure.^[39,40] Our results show similar long-term outcomes in this patient group with respect to graft and patient survival. Although baseline GFR was lower in this group, this did not translate to the worse long-term outcome.

Our study is limited by its retrospective nature, and although the different cohorts are evenly matched except for age, the absence of randomization could introduce bias in the data. Transplant centers make an effort to size match the donors to the recipients, which can introduce bias in the observed outcomes. This, likely, explains the higher proportion of female recipients in the PD group. Pediatric donations tend to be transplanted in other younger patients or women, who have similar body surface area, and thus vessel size. In addition, all pancreas transplants in the study were done by bladder

drainage, which in some studies have been shown to have a favorable outcome in SPK.^[22,39] Finally, the database did not capture immediate reoperation rates, rejection episodes, length of hospital stay, or rehospitalizations, all of which could potentially impact postoperative morbidity and quality of life.

CONCLUSIONS

Using PDs for SPKT have comparable outcomes to using SDs, and associated with similar long-term survival without increased risk of technical complications. Compared to other age groups, ODs are associated with significantly lower eGFR but otherwise comparable pancreas function, patient, and graft survival. The decreasing number of ideal pancreas donors mandates exploring other options to care for patients waiting for needed life-saving organs. Donors at extremes of age should be considered for donation as they provide excellent and comparable short- and long-term recipient outcomes. Their use can increase donor pool and decrease waiting time on the transplant list.

Authors' contribution

All authors contributed to the conception, planning, conduct of the study, drafting, and revising of the manuscript, and approval of its last version.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

This work has been approved by the Institutional Review Board of The Ohio State University (IRB #: 2015H0402).

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