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Outcomes and survival analysis of old-to-old simultaneous pancreas and kidney transplantation

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Summary

Outcomes of old-donor simultaneous pancreas–kidney transplantation (SPKT) have not been thoroughly studied. Scientific Registry of Transplant Recipients data reported for SPKT candidates receiving dialysis wait-listed between 1993 and 2008 (n = 7937) were analyzed for outcomes among those who remained listed (n = 3301) and of SPKT recipients (n = 4636) using multivariable time-dependent regression models. Recipients were stratified by donor/recipient age (cutoff 40 years) into: young-to-young (n = 2099), young-to-old (n = 1873), old-to-young (n = 293), and old-to-old (n = 371). The overall mortality was 12%, 14%, 20%, and 24%, respectively, for those transplanted, and 50% for those remaining on the waiting list. On multivariable analysis, old-donor SPKT was associated with significantly higher overall risks of patient death, death-censored pancreas, and kidney graft failure in both young (73%, 53%, and 63% increased risk, respectively) and old (91%, 124%, and 85% increased risk, respectively) recipients. The adjusted relative mortality risk was similar for recipients of old-donor SPKT compared with wait-listed patients including those who subsequently received young-donor transplants (aHR 0.95; 95% CI 0.78, 1.12) except for candidates in OPOs with waiting times ≥604 days (aHR 0.65, 95% CI 0.45–0.94). Old-donor SPKT results in significantly worse graft survival and patient mortality without any waiting-time benefit as compared to young-donor SPKT, except for candidates with expected long waiting times.

Introduction

Simultaneous pancreas–kidney transplantation (SPKT) is a well-established treatment for patients with insulin-dependent diabetes mellitus and end-stage renal disease [1]. With demand currently exceeding the supply of quality pancreata from deceased donors, there is a strong incentive to maximally utilize the available donor pool [2]. Donor age is a barrier to organ acceptance [3], as it is considered the most important characteristic driving worse outcomes after SPKT transplantation [4–9]. The most commonly reported donor age threshold is >45 years as a result of its association with higher graft failure rates [2,3,10–13] and lower recipient survival in previous studies [1]. However, some have successfully used older donor organs for SPKT with outcomes similar to transplants from younger donors [14–18]. Recently, Salvalaggio *et al.* [2] demonstrated that equivalent life-year expectancies were achieved with old-donor SPKT as with young-donor SPKT after an additional wait of 1.5 years [2]; however, the authors did not assess the survival benefit relative to remaining on the waiting list for a young-donor SPKT.

Recipient age has also been found to be a risk factor for graft and/or patient survival [1,18,19]. Despite these concerns, the number of potential older pancreas transplant recipients added to the wait-list in the US continues to increase [20]. In 1988/1989, the mean recipient age at transplantation was 34.8 years, whereas in 2002/2003 it was 41.1 years [11]. In Europe, the age limit for pancreas transplantation candidates was originally set at 45 years [21]; however, over more than a decade, the maximum age limit has increased and no formal consensus currently exists.

Although age matching has been extensively studied in kidney transplantation, no previous studies have examined the possibility of a combined influence of donor age and recipient age on patient and graft survival after SPKT. This is important as organs from older donors may be more likely to be given to recipients with poorer prognoses (i.e. older candidates) [3]. Additionally, given that graft survival after old-donor SPKT is significantly inferior to that after young-donor SPKT, it is important to determine whether a patient survival benefit exists for recipients of old-donor SPKT. In this study, we evaluate outcomes of old-donor SPKT organs transplanted into old or young recipients and assess whether a patient survival benefit exists for candidates receiving old-donor SPKT rather than waiting on dialysis for a younger SPKT.

Materials and methods

We utilized data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services provide oversight to the activities of the OPTN and SRTR contractors.

Data submitted to the SRTR were accessed to identify all wait-listed candidates for SPKT between January 1, 1993 and December 31, 2008. Candidates were excluded if they were wait-listed for a third organ, had previously received a kidney or pancreas transplant, received an isolated kidney or pancreas transplant after waitlisting, had not begun dialysis prior to December 31, 2008, underwent transplantation prior to the initiation of dialysis, or dialysis status was unknown. The resulting candidate cohort included 7,937 patients. Of these, 4636 underwent SPKT with follow-up until December 31, 2009.

Cox proportional hazards models were fitted to compute covariate-adjusted patient loss, and death-censored pancreas and kidney graft failure. The following donor variables were included in the models: gender, race (African American, other), cause of death (cerebrovascular accident versus other), history of hypertension, body mass index >30 kg/m^2, donation after circulatory death (DCD), terminal serum creatinine (≤ 1.5, >1.5, missing), number of human leukocyte antigen (HLA)-A, B, and DR mismatches with recipient (HLA MM = 6, <6), and cold ischemia time (CIT) (0–6, 7–12, 13–18, >18 h, missing). The following recipient factors were included in the models: gender, race (African American, other), panel-reactive antibody (PRA) level >30%, time from dialysis to waitlisting (<1, 1–3, >3 years); body mass index (>30 kg/m^2, missing), insurance (private, other), location of donor organs [local organ procurement organization (OPO) versus other], history of comorbidity (defined as at least one of the following: peptic ulcer disease, history of cerebrovascular disease, history of peripheral vascular disease, history of drug-treated chronic obstructive pulmonary disease, or history of malignancy), duration of diabetes by tertile (<21, 21–28, >28 years, missing), and year of transplantation (continuous). Transplants were defined as local if the donor and recipient transplant center were in the same OPO. Missing categories were created when a variable result was missing in 3–15% of cases. The proportion of missingness for each variable specifically was as follows: donor hypertension 0.3%, DCD 0.02%, terminal serum creatinine 0.2%, PRA 2.4%, CIT 14.6%, diabetes duration 11.8%, and recipient body mass index 8.2%.

A preliminary Cox model was constructed to determine the cutoff value of donor age which correlates with increasing patient mortality. This model included the variables described above, recipient age (continuous), and donor age (<18, 18–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50 years) (Table 1). The sample sizes of each donor age category were as follows: 946, 1633, 570, 431, 392, 328, 225, and 111 recipients, respectively. The results of this analysis showed that the donor age category beyond which the adjusted hazard of patient mortality is consistently significantly elevated is 40–44; therefore, 40 was chosen as the cutoff value to define the older age groups (Table 1). Donors and recipients were classified as young (age <40 years) or old (age ≥40 years) at the time of transplantation. Donor and recipient ages were combined and categorized into four groups: young-to-young (donor age <40 and recipient age ≥40), young-to-old (donor age <40 and recipient age ≥40), old-to-young (donor age ≥40 and recipient age <40), and old-to-old (donor age ≥40 and recipient age ≥40).

To test the hypothesis that donor age predicts the outcome variable differently dependent upon recipient age, we looked for interactions between these two variables by performing a contrast of parameter estimates using the multivariable models with donor and recipient age tested as categorical and continuous variables.

Time to death was modeled using time-dependent proportional Cox regression models. Candidates entered the study on the date of kidney waiting list registration or the date of first dialysis therapy whichever came later.

Table 1. Multivariable cox model for overall post-transplant mortality.

Parameters (reference group)	Patient mortality Adjusted hazards ratio (95% CI)
Donor age (18–24), years	Reference
<18	0.88 (0.70–1.12)
25–29	0.96 (0.72–1.26)
30–34	1.24 (0.94–1.63)
35–39	0.99 (0.72–1.36)
40–44	1.70 (1.28–2.27)
45–49	1.89 (1.36–2.62)
≥50	2.09 (1.39–3.14)
Recipient age (continuous)	1.02 (1.01–1.03)
Donor gender, female (male)	0.93 (0.78–1.11)
Donor race, African American (other)	1.24 (1.01–1.52)
Donor death from CVA (other)	0.78 (0.49–1.26)
Donor history of hypertension (none)	1.15 (0.86–1.53)
Donor terminal serum creatinine >1.5 mg/dl	1.07 (0.99–1.16)
Donor body mass index >30 (≤30) kg/m^2	1.48 (1.16–1.89)
Donor HLA-mismatches = 6 (<6)	1.20 (1.03–1.40)
Donor, donation after circulatory death	0.70 (0.33–1.47)
Donor, local organ procurement agency	0.92 (0.73–1.16)
Recipient race, African American (other)	1.21 (0.99–1.48)
Recipient gender, female (male)	1.19 (1.01–1.40)
Recipient primary insurance, private (other)	0.79 (0.67–0.94)
Recipient body mass index >30 (≤30) kg/m^2	1.14 (0.91–1.43)
Recipient PRA >30% (≤30)	1.19 (0.84–1.69)
Recipient CIT (<6 h)	
7–12 h	0.80 (0.60–1.06)
13–18 h	0.74 (0.55–0.99)
>18 h	1.04 (0.75–1.45)
Recipient, pretransplant dialysis (<1 year)	
1–3 years	1.17 (0.94–1.44)
>3 years	1.38 (1.08–1.76)
Recipient duration of diabetes (<21 years)	
21–28 years	0.98 (0.79–1.21)
>28 years	1.06 (0.85–1.33)
Recipient year of transplant (continuous)	0.92 (0.88–0.95)
Cormorbidity present (absent)	1.40 (1.14–1.72)

CVA, cerebrovascular accident; HLA, human leukocyte antigen; CIT, cold ischemia time; PRA, panel-reactive antibody.

A preliminary model compared the mortality of recipients that received SPKT from older donors and young donors separately relative to wait-listed candidates (i.e. those not receiving transplants). The main survival benefit model compared the mortality risk associated with old-donor SPK transplants to that of wait-listed candidates plus those who received young-donor SPKs (i.e. standard therapy). Follow-up survival time at risk was censored at the time of waitlisting for another organ or end of study (December 31, 2009). As SPK from young donors may be received by wait-listed candidates, the effect of young-donor SPKT on mortality of wait-listed candidates was accounted for in the calculation of mortality risk in the standard therapy group by not censoring follow-up time-at-risk in the event of young-donor SPKT. In other words, all patients contributed data for time at risk (and death, if it occurred) to the standard therapy group starting at study entry and to the old-donor SPKT group starting at the time of old-donor SPK transplantation. This "switch" constituted the time-dependent old-donor SPKT covariate in the model. Patients who received a young- donor SPKT remained in the standard therapy group. Covariates used for model adjustment included candidate sex, race, PRA, BMI, comorbid conditions, waitlisting year, OPO median waiting time, and median time from first dialysis to waitlisting. As an index of the relative availability of young-donor SPKT, we confounded for the time to SPKT transplantation for each OPO. The tertile of waiting time to transplantation for the OPO of each candidate's registration was assigned as a baseline candidate-level covariate in subgroup analyses.

Multivariable models were fitted with the results from cases that had complete data [196 (2.5%) cases were missing from survival analysis model and 38 (0.8%) cases were missing in transplant outcome models]. No data were imputed. Overall patient survival, death-censored pancreas graft survival, and death-censored kidney graft survival plots were generated from Kaplan–Meier models. Tukey–Kramer adjusted log-rank tests were utilized to compare patient and graft survival between paired age categories. Relevant characteristics of the donor, the recipient, and the graft between patient groups were compared with the chi-square test for categorical variables and the *t*-test for continuous variables. All analyses were performed using SAS software, version 9.2 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was identified by a *P*-value of less than 0.05 and all confidence intervals also used a 95% threshold. This study was approved by the University of Florida Institutional Review Board.

Results

Patient and donor characteristics

Of 7936 candidates listed, 3301 candidates remained on the waiting list and 4636 underwent SPKT. Of SPKT recipients, 3972 received young-donor SPKT (donor age <40) and 664 received and old-donor SPKT (donor age ≥40). The frequency distribution of wait-listed candidates and transplant recipient characteristics is shown in Table 2. Recipients of old-donor SPK were more likely to be older, non-African American, male, obese, privately insured, diagnosed with a comorbidity, and have had less time on dialysis and longer duration of diabetes compared to the recipients of young-donor SPK. Donor characteristics of young-donor and old-donor SPK transplants are shown in Table 3. Donors of the old-donor transplant group were more likely to be non-African American, female, hypertensive, obese, DCD, from

Table 2. Demographics for waiting-list candidates, young-donor SPK recipients, and old-donor recipients, 1993–2008.

Characteristic, *N* (%) or mean ± SD	Waiting-list candidates (*n* = 3301)	Young-donor SPK (*n* = 3972)	Old-donor SPK (*n* = 664)
Recipient age, years	41.0 ± 8.9	39.5 ± 8.3	41.1 ± 8.8
Recipient, African American	697 (21.1)	750 (18.9)	102 (15.4)
Recipient, female	1407 (42.6)	1396 (35.2)	229 (34.5)
Recipient, dialysis			
<1 year	1731 (52.4)	2166 (54.5)	393 (59.2)
1–3 years	1151 (34.9)	1380 (34.7)	215 (32.4)
>3 years	419 (12.7)	426 (10.7)	56 (8.4)
Recipient, BMI >30 kg/m^2	532 (16.1)	483 (12.2)	93 (14.0)
Recipient, PRA >30%	363 (11.6)	184 (4.6)	28 (4.2)
Recipient, private insurance	1287 (39.0)	1782 (44.9)	330 (49.7)
Recipient, duration of diabetes			
<21 years	2002 (60.1)	2742 (69.0)	435 (65.5)
21–28 years	444 (13.5)	478 (12.0)	93 (14.0)
>28 years	377 (11.4)	273 (6.9)	66 (9.9)
Recipient, comorbidity	625 (18.9)	510 (12.8)	95 (14.3)
Recipient, OPO, waiting time			
<368 days	672 (20.4)	1793 (45.1)	301 (45.3)
368–603 days	1043 (31.6)	1270 (32.0)	211 (31.8)
>603 days	1586 (48.1)	909 (22.9)	152 (22.9)

BMI, body mass index; PRA, panel-reactive antibodies; OPO, organ procurement organization; SPK, simultaneous pancreas–kidney. Comorbidity is defined as any one of the following conditions: cerebrovascular accident, peptic ulcer disease, drug-treated chronic obstructive pulmonary disease, peripheral vascular disease, or malignancy.

Table 3. Donor and transplant characteristics for recipients of SPK from young (<40 years) and old (≥40 years) donors, 1993–2009.

Characteristic, *N* (%) or mean ± SD	Young-donor SPK (*n* = 3972)	Old-donor SPK (*n* = 664)
Donor age, years	22.9 ± 7.3	45.3 ± 4.3
Donor race, African American	674 (17.0)	65 (9.8)
Donor sex, female	1104 (27.8)	376 (56.6)
Donor history of hypertension	147 (3.7)	151 (22.9)
Donor, death because of CVA	117 (3.0)	41 (6.2)
Donor, BMI >30 kg/m^2	314 (7.9)	67 (10.1)
Donation after circulatory death	76 (1.9)	21 (3.2)
Donor creatinine >1.5 mg/dl	306 (7.7)	37 (5.6)
Donor OPO, nonlocal	411 (10.4)	106 (16.0)
CIT, h		
<6	356 (9.0)	53 (7.9)
7–12	1579 (39.8)	245 (36.9)
13–18	1047 (26.4)	176 (26.5)
>18	400 (10.1)	103 (15.5)
HLA MM = 6	1758 (44.3)	308 (46.4)

BMI, body mass index; CIT, cold ischemia time; HLA MM, human leukocyte antigen mismatch; DCD, donation after circulatory death; CVA, cerebrovascular accident; SPK, simultaneous pancreas–kidney.

a nonlocal OPO, highly HLA-mismatched, transplanted at longer CIT and to have died of cerebrovascular accident and were less likely to have a terminal serum creatinine >1.5 mg/dl.

Patient survival

The 3-year patient survival of the young-to-young, young-to-old, old-to-young, and old-to-old groups was 92%, 90%, 90%, and 84%, respectively. A graph depicting unadjusted Kaplan–Meier survival curves of the four matched groups is shown in Fig. 1. On multivariable analysis, the adjusted risk of patient death in old-to-old SPKT transplantation was 91% higher (aHR 1.91, 95% CI 1.48–2.46) compared with young-to-old transplants. The adjusted risk of patient death for old-to-young transplants was 73% higher when compared with the young-to-young group (old-to-young aHR 1.73, 95% CI 1.28–2.34). Young-to-old SPKT was associated with a 74% increased risk of mortality compared with young-to-young (aHR 1.74, 95% CI 1.29–2.35).

Testing for an interaction of donor and recipient age for patient survival following SPKT was not significant when variables were tested as categorical (Wald chi-square 0.20, $P = 0.65$) or continuous (Wald chi-square 1.89, $P = 0.17$).

Pancreas and kidney graft survival

Death-censored pancreas graft survival at 3 years of the young-to-young, young-to-old, old-to-young, and old-to-old groups was 79%, 81%, 73%, and 65%, respectively. Kidney death-censored graft survival at 3 years of the young-to-young, young-to-old, old-to-young, and old-to-old groups was 87%, 86%, 79%, and 77%, respectively.

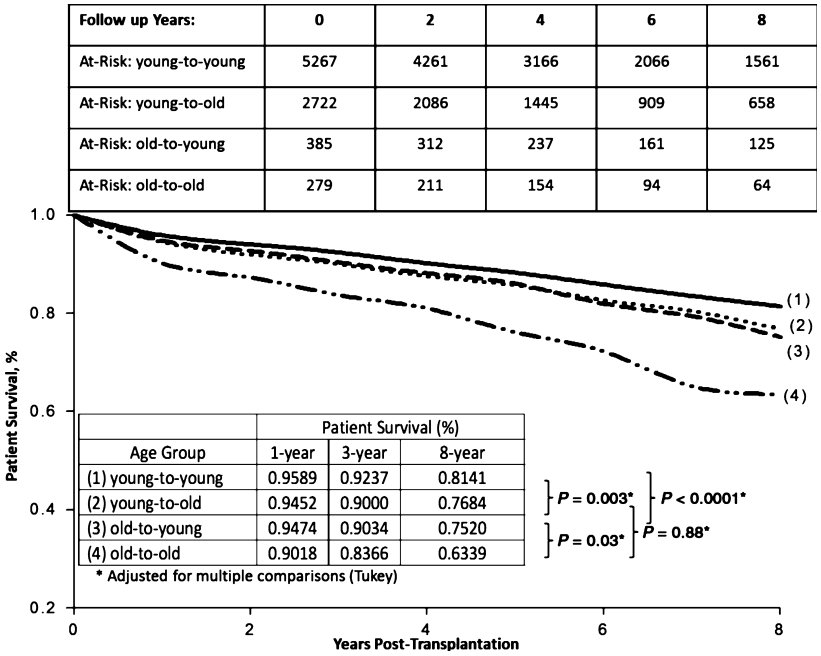

Figure 1 Kaplan–Meier plots of overall patient survival for simultaneous pancreas and kidney transplants by donor and recipient age group.

A graph depicting unadjusted Kaplan–Meier survival curves for each outcome of the four matched groups is shown in Fig. 2. On multivariable analysis, old-to-old SPKT was associated with significantly higher risks of death-censored pancreas graft failure (aHR 2.24, 95% CI 1.74–2.88) and kidney graft failure (aHR 1.85, 95% CI 1.34–2.56) compared with young-to-old transplants. Similarly, old-to-young SPKT conferred significantly higher risks of death-censored pancreas graft failure (aHR 1.53, 95% CI 1.19–1.96) and kidney graft failure (aHR 1.67, 95% CI 1.25–2.23) compared with young-to-young transplants.

A significant interaction between donor and recipient age was noted for death-censored pancreas graft survival when the variables tested were considered as categorized (Wald chi-square 5.02, $P = 0.025$) or as continuous (Wald chi-square 4.99, $P = 0.026$) indicating that the relative hazard of donor age was stronger among older recipients. There was no notable interaction between donor and recipient age with death-censored kidney graft survival when tested as a categorical variable (Wald chi-square 0.26, $P = 0.81$) or as a continuous variable (Wald chi-square 0.02, $P = 0.87$).

Adjusted risk of death for SPKT from old or young donors versus remaining on the waiting list

Among 3301 patients who never received a transplant, 1653 (50%) died before study end. There were 506 (13%) deaths among 3972 recipients of young-donor SPK transplants (donor age <40 years) and 147 (22%) deaths among 664 old-donor SPK transplants (donor age ≥40 years). The adjusted long-term relative mortality risk was 52% lower for old-donor SPKT than for patients on the waiting list (aHR 0.48 95% CI 0.40–0.58). Recipients of young-donor SPKT had a 74% lower long-term mortality risk when compared with wait-listed candidates (aHR 0.26 95% CI 0.22–0.28).

Adjusted risk of death for old-donor SPKT versus standard therapy (waiting list or receiving young-donor SPKT)

There were 371 old-to-old SPKT, 293 old-to-young SPKT, and 7273 who either remained on the waiting list or received young-donor SPKT (standard therapy). The overall mortality in each group was 24%, 20%, and 30%, respectively. The adjusted relative mortality risk was not significantly different for the recipients of old-donor SPKT compared with patients receiving standard therapy, i.e. wait-listed patients including those who subsequently received young-donor transplants (aHR 0.95; 95% CI 0.78, 1.12) (Table 4). Most, but not all, subgroups of old-donor SPKT had no change in mortality risk compared with those receiving standard therapy (Table 4). Only one characteristic was associated with a decreased mortality risk following transplantation with old-donor SPK. Candidates registered in OPOs with waiting times in the longest tertile (≥604 days) had a 35% lower risk of death with an old-donor SPKT compared with standard therapy (aHR 0.65, 95% CI 0.45–0.94). Those wait-listed with OPOs in the middle and lower waiting time tertiles did not have a

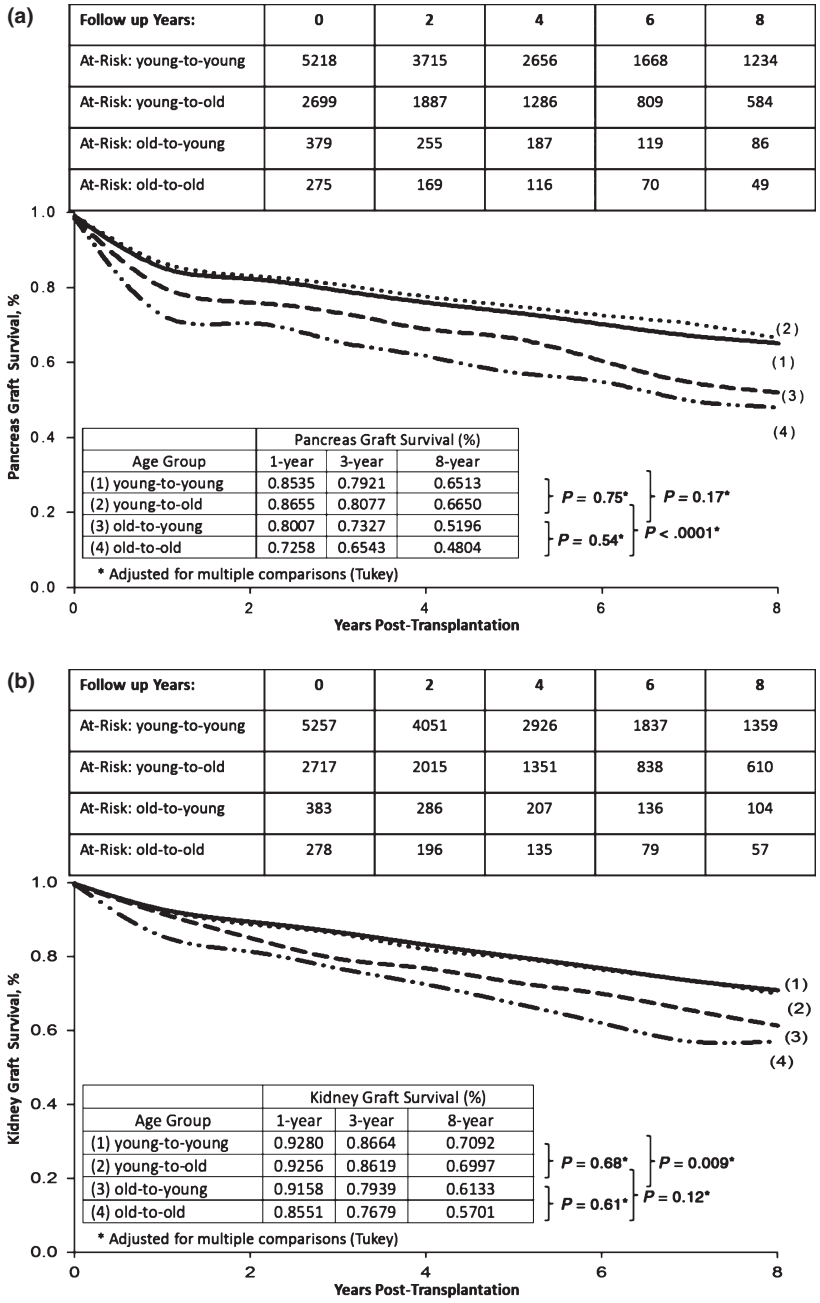

Figure 2 Kaplan–Meier plots of (a) death-censored pancreas graft survival and (b) death-censored kidney graft survival for simultaneous pancreas and kidney transplants by donor and recipient age group.

demonstrable survival benefit from old-donor SPKT (Table 4).

Waiting time of old candidates to receive old versus young SPKT

The mean waiting time of old-to-old SPKT candidates (427 ± 234 days) was similar to that of young-to-old SPKT patients (423 ± 219 days, $P = 0.7458$). Evaluation of mean waiting times within each OPO tertile demonstrates that within the OPOs with the highest median waiting time (≥ 604 days) old patients waited significantly less time to receive old organs than to receive young organs (old-to-old $n = 98$; 374 ± 302 vs. young-to-old $n = 465$, 727 ± 79; $P = 0.0121$); whereas within the middle (368–603 days) OPO tertile of waiting time, the wait for young

Table 4. Relative risk of mortality for old-donor simultaneous pancreas–kidney transplantation (SPKT) versus standard therapy (waiting-list candidates and young-donor simultaneous pancreas–kidney transplantation (SPKT) recipients).

Recipient characteristics (reference)	Adjusted HR (95% confidence interval)	Observations read/used
All	0.95 (0.78–1.12)	7936/7740
Age in years		
<24	4.70 (0.69–1.32)	92/90
25–29	0.82 (0.43–1.56)	724/704
30–39	0.96 (0.71–1.29)	3013/2952
40–49	0.81 (0.60–1.08)	2827/2754
≥50	1.18 (0.85–1.66)	1234/1196
Female	1.06 (0.81–1.38)	3032/2933
Male	0.88 (0.71–1.10)	4905/4763
African American	1.06 (0.69–1.63)	1549/1491
Non-African American	0.93 (0.77–1.12)	6388/6205
Panel-reactive antibody <30%	0.94 (0.79–1.21)	7170/7123
Panel-reactive antibody ≥30%	1.07 (0.56–2.07)	575/573
OPO waiting time <368 days	1.21 (0.93–1.57)	2616/2575
OPO waiting time 368–603 days	0.98 (0.74–1.31)	2674/2627
OPO waiting time ≥604 days	**0.65 (0.45–0.94)**	2647/2494
Pretransplant dialysis <208 days	0.94 (0.70–1.25)	2612/2523
Pretransplant dialysis 208–500 days	0.74 (0.54–1.01)	2703/2623
Pretransplant dialysis >500 days	1.20 (0.91–1.60)	2622/2550
Body mass index <30 kg/m^2	0.95 (0.79–1.15)	6640/6437
Body mass index ≥30 kg/m^2	0.89 (0.55–1.42)	1108/1075
Comorbidity absent	0.90 (0.74–1.09)	6707/6511
Comorbidity present	1.17 (0.82–1.67)	1230/1185

Covariates used for model adjustment included candidate age, sex, race, PRA, OPO median waiting-time tertile, time from first dialysis to wait-listing median time tertile, BMI at time of waitlisting, comorbid conditions present at waitlisting, and wait-listing year (continuous).

organs was only slightly longer than the wait for old SPK organs (old-to-old $n = 119$, 454 ± 63 vs. young-to-old 460 ± 70; $P = 0.3335$). The same lack of significant difference was true for the lowest (<368 days) OPO tertile (old-to-old, $n = 154$, 202 ± 87 vs. $n = 780$, 212 ± 83, $P = 0.1679$).

Center volume effects

To evaluate for center volume effects, we categorized centers by volume tertile 10–51 cases, 51–97 cases, and ≥97 cases during the time period of the study. Fifty-six centers were included and three centers were excluded because of low volume (i.e. total number of transplants performed over the study period <10). We then included the categorized center (by volume tertile) as an additional random effect in the six outcome models indicated in Table 4 for patient survival, and death-censored pancreas and kidney graft survival following transplantation. In all six models, there was an evidence of center-level variation; however, the point estimates and statistical significance of the age-matched groups remained consistent.

Discussion

We found that SPKT of old-donor organs into old or young recipients was associated with significantly increased risks of patient mortality, pancreas failure, and kidney graft failure relative to transplantation of with young-donor organs. There is a clear survival benefit of old patients to undergo any SPKT, either from a young or old donor, relative to waiting on the list and not receiving a transplant. However, there is no survival benefit for candidates to accept old-donor SPKT compared to remaining on the waiting list with the potential to receive a younger organ except for those registered in OPOs with waiting times >605 days.

We found that donor age ≥40 years was a significant risk factor for graft loss (pancreas and/or kidney) in both young and old recipients. A higher risk of technical complications with older grafts has been well documented. Donor age has been found to be a risk factor for graft thrombosis [3,8,22], re-laparotomy [8], anastomotic leakage [3], intra-abdominal infection [3,8], and pancreas-specific complications [23] in various analyses of SPKT only as well as cohorts of SPKT and pancreas alone transplantation. Some have attributed the poor outcome of pancreas grafts from older donors to pre-existing arteriosclerotic lesions in the donor organ [8,12]. It has been hypothesized that decreased arterial inflow secondary to arteriosclerotic lesions may cause attenuated venous outflow or venous stasis leading to venous thrombosis [12].

Whereas in the kidney transplant literature, several studies have suggested that graft survival of isolated kidney transplants from old donors can be significantly better in old recipients [24,25], we found this not to be the case with SPKT. The high kidney graft loss seen with SPKT in our study is not surprising as the outcome of the pancreas often affects the kidney and vice versa. Previous studies have shown that early pancreas loss from technical failure and graft thrombosis predicts worse kidney graft survival following SPKT [26,27]. Additionally, SPKT kidney graft failure may be explained by the presence of the same donor and recipient risk factors (i.e. age) that affect not only the pancreas but also the kidney graft. Lastly, an increased incidence of kidney graft loss from acute rejection may be because of the reduced, tapered, or discontinued immunosuppression that is often necessary in cases of severe, life-threatening intra-abdominal infections and cases of pancreatitis. Recipient age may also be a risk factor for poor outcomes after SPKT and contribute to pancreas or kidney failure. In many studies, recipient age has not been found to be a risk factor for relaparotomy [8,28], technical complications [19,28] or length of stay [28], although two

studies found higher rates of bleeding in patients 50 years of age or older [29,30].

Whereas the aforementioned studies have evaluated donor and recipient risk factors for graft loss separately, ours is the first report to stratify outcomes by age-matched groups and to test for an interaction between donor and recipient age following SPKT. The demonstration of a significant interaction between donor and recipient age specific to pancreas graft loss suggests that the risk of transplanting pancreata from older donors is exacerbated by placement of these organs in recipients of older age. The absence of this interaction relative to patient survival and kidney graft loss suggests that although older recipients and older donor organs may portend worse prognoses independently for these outcomes, there does not appear to be an interactive effect by combining the two.

We have shown that old donor age is not only a risk factor for kidney and pancreas survival but also for patient survival of both young and old recipients. Old-to-old SPKT is a particularly morbid combination with a 91% increased risk of death compared with transplants from young donors. These results highlight the tenuous nature of older recipients who may not be able to survive the higher risks of complications associated with the use of older organs. Previous studies have demonstrated that one of the most influential factors promoting patient survival is a functioning graft [7,11,26,27]. Our results similarly suggest that older recipients do not tolerate well the higher incidence of thrombosis, infection, and other complications that appear to occur with the use of older donor grafts.

Whereas it is clear that old recipients do not tolerate well SPKT of old organs, our data demonstrated excellent overall patient survival when old recipients receive young organs. Some authors have demonstrated satisfactory results of transplantation in old recipients [11,28–30], whereas others have suggested age limitations on potential pancreas transplant recipients, considering age a risk factor for inferior outcomes [1,7,11,19,31]. The favorable results have been attributed, in part, to the utilization of young donors [29] and/or careful selection of transplant candidates [28,30], particularly avoiding candidates with advanced cardiac disease. Pre-existing cardiac problems such as coronary artery disease has been found to significantly correlate with surgical complications [23] and overall patient survival [32] following SPKT. Taken together, these findings suggest that older candidates can be safely transplanted, particularly when given young organs.

It has been previously suggested that high waiting list mortality and long waiting time may justify the increased use of older donor organs for SPKT transplantation [2,14]. Salvalaggio *et al.* [2] observed a 72% reduction in the risk of death with the utilization of old donors compared with long-term waiting; however, a risk-benefit analysis taking into account the additional waiting time to obtain young-donor organs would be necessary to fully address this concept. We found that old-donor SPKT does not confer a survival benefit relative to waiting on the list for a young-donor SPKT except in one subgroup, candidates registered in OPOs with waiting times ≥604 days. In OPOs with shorter median waiting times, the wait for young organs is similar to the wait for old organs. Given that the additional waiting time to obtain young-donor organs is minimal (and actually on average slightly shorter), our finding that the relative mortality risk was not significantly different for recipients of old-donor SPKT compared with patients wait-listed and some receiving young-SPKT is not surprising.

Our results are subject to the limitations inherent in observational data. Because recipients of old organs are often not randomly selected to receive transplants, it is possible that they are in some unmeasured way systemically less (or more) healthy than recipients of young organs. There is the possibility for residual confounding as a result of donor or recipient factors not included in the analysis such as donor anatomy, type of enteric and exocrine drainage, type of preservation fluid, vessel reconstruction, site of implantation, sterilization of the duodenal segment, warm ischemia time, donor pretreatment medications, recipient antimicrobial therapy, degree of immunosuppression, and recipient glycemic control prior to transplantation. Additionally, registry data are somewhat limited toward gaining an understanding of the causes of graft loss; as such it is difficult to assess the direct association of failures that would be more reflective of donor risk factors, recipient characteristics, or the interaction of both. Regarding the survival benefit analysis, selection bias could overstate the benefit of SPKT if candidates in the subgroups were healthier than the average wait-listed candidate. Although we performed statistical adjustments with many potential confounders, unmeasured elements of risk are always present in a cohort study design. Lastly, these data reflect SPKT practices in the US and therefore may not be generalized to other countries with difference allocation policies or practices.

In conclusion, both young and old recipients demonstrate excellent long-term graft and patient survival following SPKT from young donors. Wait-listed candidates do not receive a survival benefit from accepting old-donor SPK organs over remaining on the waiting list for organs from a young donor except those registered in OPOs with long waiting times.

Authorship

LKK: study design, results analysis, writing of the manuscript. XW: designed research/study, statistical analysis. MZ and MC: writing of the manuscript. JS and JM: study design, results analysis.

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