Transplant International

ORIGINAL ARTICLE

Pancreas transplantation in older patients is safe, but patient selection is paramount

Joseph R. Scalea, Robert R. Redfield III, Emre Arpali, Glen Leverson, Hans W. Sollinger, Dixon B. Kaufman & Jon S. Odorico

Division of Transplantation, Department of Surgery, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI, USA

Correspondence
Joseph R. Scalea MD, 600 Highland Avenue, H4/780 Division of Transplantation, University of Wisconsin Hospital and Clinics, Madison, WI 53792, USA.
Tel.: 410-905-4053;
fax: 608-262-6280;
e-mail: scalea@surgery.wisc.edu

Presentation
This paper was presented as a poster at the American Transplant Congress in Philadelphia, Pennsylvania in the spring of 2015.

SUMMARY

Pancreas transplant outcomes have progressively improved. Despite this, some centers have continued to employ historical age limits for pancreas transplant candidates. We sought to determine the importance of chronological age in determining patient and graft survival rates after pancreas transplantation. A single-center, retrospective study of adult, deceased donor simultaneous pancreas and kidney (SPK) and solitary pancreas transplants (SP, including pancreas transplant alone and pancreas after kidney transplants) in recipients ≥ 55 years (55 +), occurring between July 1, 1999, and June 30, 2012, was performed. Seven-hundred and forty patients underwent pancreas transplantation, of which 28 patients were 55 + . Patient survival was comparable for younger and older pancreas transplant recipients. Both non-death-censored and death-censored pancreatic graft survival rates were similar in younger and in older patients. Patients aged 45–54 and those aged 55 + had more frequent cardiovascular events than younger pancreas transplant recipients. There was no difference in renal graft survival for SPK patients when compared with diabetic kidney transplant alone recipients aged 55 years and older. Older pancreas transplant recipients had acceptable long-term patient and graft survival rates, although complications may occur. Chronological age alone should not exclude a patient for pancreas transplant candidacy.

Transplant International 2016; 29: 810–818

Key words
age, cardiac disease, outcome, pancreas clinical, transplantation in the elderly

Received: 6 October 2015; Revision requested: 3 November 2015; Accepted: 29 January 2016

Introduction

Surgeons have generally been wary of performing pancreas transplants in older patients. This is due in large part to the complexity and risks of the procedure, and potential for unrecognized cardiac and vascular pathology, which can negatively impact patient and graft outcomes [1–3]. However, this exclusionary practice has been based on limited data. Some authors have described acceptable outcomes in older patients, whereas others have remained more cautious [1,3–6]. However, the risk versus benefit ratio for procedures such as pancreas transplantation can change dramatically over time as outcomes improve and as risk factors, both modifiable and nonmodifiable, become better appreciated [7]. Indeed, with improvements in technical aspects of pancreas transplantation, post-transplant care, and immunosuppression, pancreas transplant outcomes have continually improved [7]. However, a counterpoint to improving outcomes is the fact that patients are being referred for transplantation at an older age and later in their course of diabetes. For example, the

doi:10.1111/tri.12754

percentage of patients aged 50–64 listed for pancreas transplantation in UNOS doubled from 1998 to 2010 [7–9]. Accordingly, the number of pancreas transplant recipients aged 50 + has increased over the last decade, while the number of pancreas recipients aged 18–34 and 35–49 has decreased [7]. In 2009, UNOS reported 22.6% of all pancreas transplant recipients were 50 + years of age (PTA: 28.4%, SPK: 21.4%, PAK: 23.7%). Older patients on the waiting list and those transplanted in recent years may reflect delayed progression to end-stage nephropathy and better diabetes care, education and advanced insulin delivery technologies [10,11]. Consequently, patients arriving to transplant centers for transplantation are older. As the diabetic population being referred for transplantation ages, determination of the acceptability of age restrictions is more important than ever [8].

Given the limited and conflicting data available to inform patient candidacy in the context of changing recipient demographics and improving graft outcomes, our primary objective was to describe in a recent cohort the patient and graft outcomes of those who received pancreas transplants aged 55 years and older. These results show that pancreas transplantation in older patients is safe, but that patient selection and rigorous preoperative work-up are imperative.

Methods

Study population

After obtaining institutional review board approval, we conducted a retrospective, single-center study of adult pancreas transplant procedures performed during the time period between July 1, 1999, and June 30, 2013. We included all pancreas transplants alone, simultaneous pancreas and kidney transplants, and pancreas after kidney transplants having a minimum of 1-year follow-up. Patient demographics were considered, as well as patient and non-death-censored graft survival and death-censored graft survival.

Our primary study group was patients with pancreas transplants who were aged 55 years or older. Our comparison groups were as follows: group 1 ($n = 28$), aged 55 and older; group 2 ($n = 229$), aged 45-54; group 3 ($n = 316$), aged 35-44; and group 4 ($n = 167$), aged 25-34. A fifth group ($n = 260$) of diabetic, deceased donor renal transplant recipients aged 55 and older was included as an additional comparator. Pancreas transplantation as well as immunosuppressive protocols used at the University of Wisconsin has been described previously [12–14]. Our surgical approach for the time period studied here included only enteric drainage of exocrine secretions, and systemic drainage for the venous outflow. Immunosuppression regimens generally included induction with a steroid taper (typically 100 mg of intravenous dexamethasone tapered to 10 mg of oral prednisone twice daily over a period of approximately 10 days). Thymoglobulin was the primary T-cell depletion agent for SP as well as SPK patients with increased immunologic risk. IL-2 receptor blockade was used for selected patients undergoing SPK who had lower immunologic risk. Advanced age is used as a consideration for immunosuppression reduction in the maintenance stage, as an outpatient.

With regard to patient evaluation, patients with both type I and type II diabetes are considered candidates for pancreas transplantation. In the case of type II diabetes, c-peptide-positive patients are required to have a body mass index lower than 30. Based on that stress tests in the diabetic population are less sensitive for coronary disease, the cardiac evaluation at our center is rigorous. Generally, a history of diabetes greater than 5 years at the time of evaluation prompts a preoperative cardiac catheterization. Anecdotally, older patients are scrutinized to a more significant degree with regard to preoperative evaluation, and compounded risk from medical comorbidities is considered heavily in the decision to proceed with pancreas transplantation.

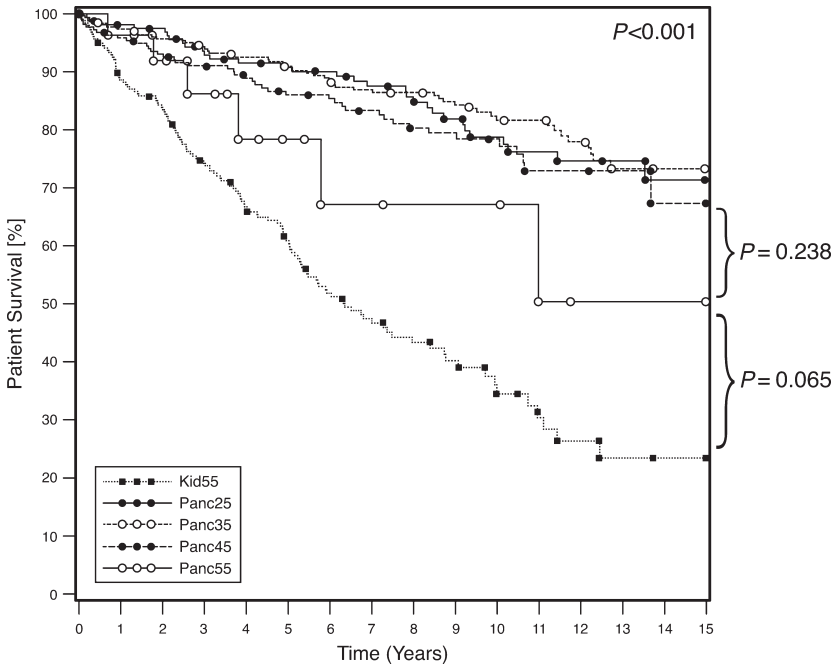
Outcomes

Kidney graft failure was defined as initiation of dialysis, and pancreas graft failure was defined as re-initiation of an exogenous insulin requirement. Cardiovascular events and rejection were determined by from the medical record. Cardiovascular complications included myocardial demand, myocardial infarction, or need for cardiac stenting and/or coronary artery bypass grafting; these criteria were used so as to identify as many patients as possible who experienced a cardiac event. Rejection events included biopsy-proven acute cellular, antibody-mediated, mixed, and chronic rejection of the pancreas. For details regarding the standard pretransplantation cardiac work-up at the University of Wisconsin, please see the discussion section.

Statistical analyses

We determined actuarial patient and graft survival rates, death-censored graft survival rates, and the cumulative incidence of biopsy-proven acute rejection episodes.

(a)



(b)

Patient Survival		Panc55+	45–54	35–44	25–34	Kid55+
		Group 1	Group 2	Group 3	Group 4	Group 5
Panc55+	Group 1	--	--	--	--	--
45–54	Group 2	0.238	--	--	--	--
35–44	Group 3	0.037	0.173	--	--	--
25–34	Group 4	0.071	0.444	0.689	--	--
Kid55+	Group 5	0.065	0.001	0.001	0.001	--

Figure 1 Patient survival after transplantation (Figure 1a). Among pancreas transplant recipients, survival was only lower for group 1 when compared with group 3. Diabetic kidney transplant recipients had worse patient survival than all pancreas transplant groups with the exception of group 1 ($P = 0.065$). *P*-values for pairwise comparison of each curve are presented in Figure 1b. Panc55 = group 1; Panc45 = group 2; Panc35 = group 3; Panc25 = group 4; Kid55 = group 5.

Actuarial patient and graft survival rates were calculated beginning at the time of transplantation. Kidney graft failure was defined as removal, or loss of function requiring return to dialysis. Pancreas graft failure was defined as removal, or loss of function requiring return to insulin therapy. Actuarial survival estimates were calculated using Kaplan–Meier life table analysis [15], and the series was followed through July 1, 2014. The Cox–Mantel test was used to compare differences in rejection rates. All statistical tests were two-tailed; $P < 0.05$ was considered significant. In each figs. (1-4), *P*-values are shown in the upper right-hand corner of each Kaplan–Meier curve. These *P*-values relate to pairwise comparison of all represented curves. Individual comparisons are presented in the text, legends, and the figures themselves.

Results

A total of 740 pancreas transplants were performed during the study period. Twenty-eight pancreas transplant recipients were aged 55 years or older (Table 1). There were 584 (78.9%) primary pancreas transplants, 129 (17.4%) were second transplants, 22 (3.0%) third transplants, and 5 (0.7%) were quaternary transplants. In the cohort of recipients aged 55 years or older, 18 (64.3%) were primary, 8 (28.6%) were secondary, and 2 (7.1%) were tertiary pancreas transplants. The vast majority of patients who underwent pancreas transplantation carried a diagnosis of type I diabetes mellitus (Table 2). In contrast, only 42 of 260 older patients (16.2%) who received kidney transplants alone (group 5) had type I diabetes. Older patients were far less likely to undergo combined kidney pancreas transplantation (39%), versus pancreas transplantation alone (61.0%; $P < 0.001$). All recipients of kidney transplants alone (group 5) were diabetic. Of these patients, 238 (91.5) were primary transplants, 21 (8.1%) were secondary, and 1 (0.4%) was a tertiary kidney transplant.

Our primary objective was to determine whether there were any statistically significant differences in

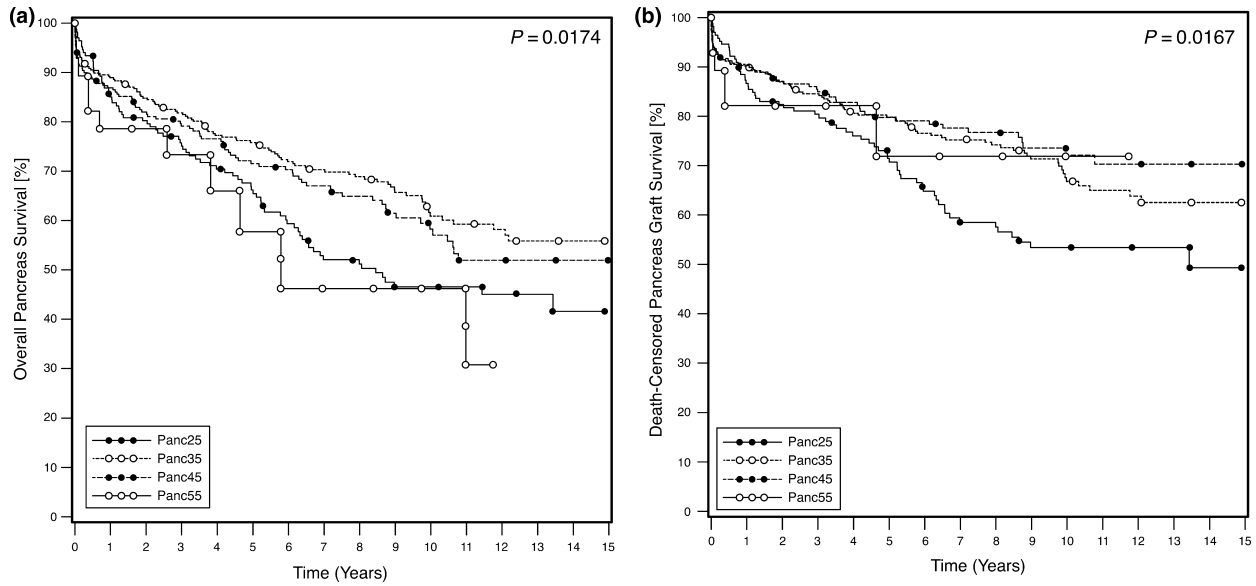


Figure 2 Age-stratified pancreas graft survival. Non-death-censored (Figure 2a) and death-censored (Figure 2b) pancreas graft survival between group 1 and groups 2, 3, or 4. Data include pancreas graft survival from PTA, PAK, and SPK procedures. DC, death censored; GS, graft survival; PTA, pancreas transplant alone; PAK, pancreas after kidney transplant; SPK, simultaneous pancreas and kidney transplant. Statistics based on test of equality across strata using log rank. Presented *P*-values relate to comparison of all four curves. Panc55 = group 1; Panc45 = group 2; Panc35 = group 3; Panc25 = group 4.

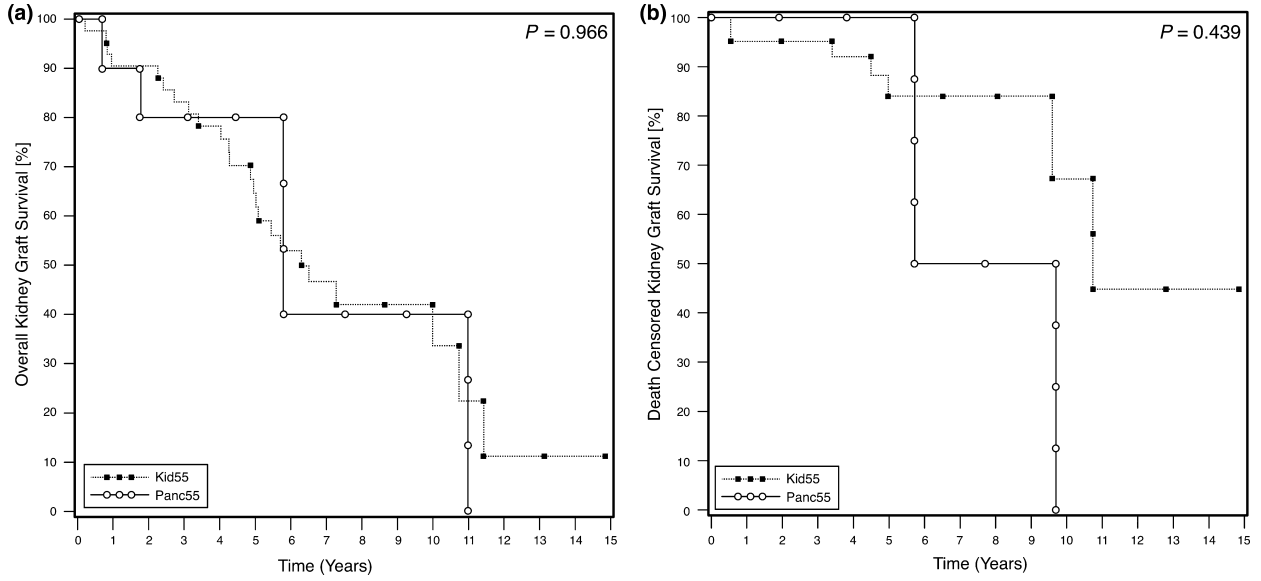


Figure 3 Kidney graft survival in patients aged 55 and older. There was no difference in non-death-censored kidney graft survival (Figure 3a) when SPK kidney grafts were compared with kidneys alone in patients aged 55 and older ($P = 0.65$). Death-censored graft survival (Figure 3b) was also not different ($P = 0.944$). DC and non-DC kidney graft survival in patients aged 55 years or older following: 1) kidney transplants alone and 2) SPK and PAK procedures. DC, death censored; GS, graft survival, SPK, simultaneous pancreas and kidney transplant; PAK, pancreas after kidney transplant. There were 11 SPK patients aged 55 and older from whom a comparison of renal graft survival could be compared to group 5 ($n = 260$). Statistics based on test of equality across strata using log rank. Panc55 = group 1; Kid55 = group 5.

patient and graft survival rates between the different cohorts of pancreas transplant recipients stratified by age. Our secondary objective was to analyze a recipient cohort similar in age who received pancreas or kidney transplants, respectively, and to determine any differences in outcomes.

Regarding our primary objective, pairwise comparisons of pancreas patient and graft survival between

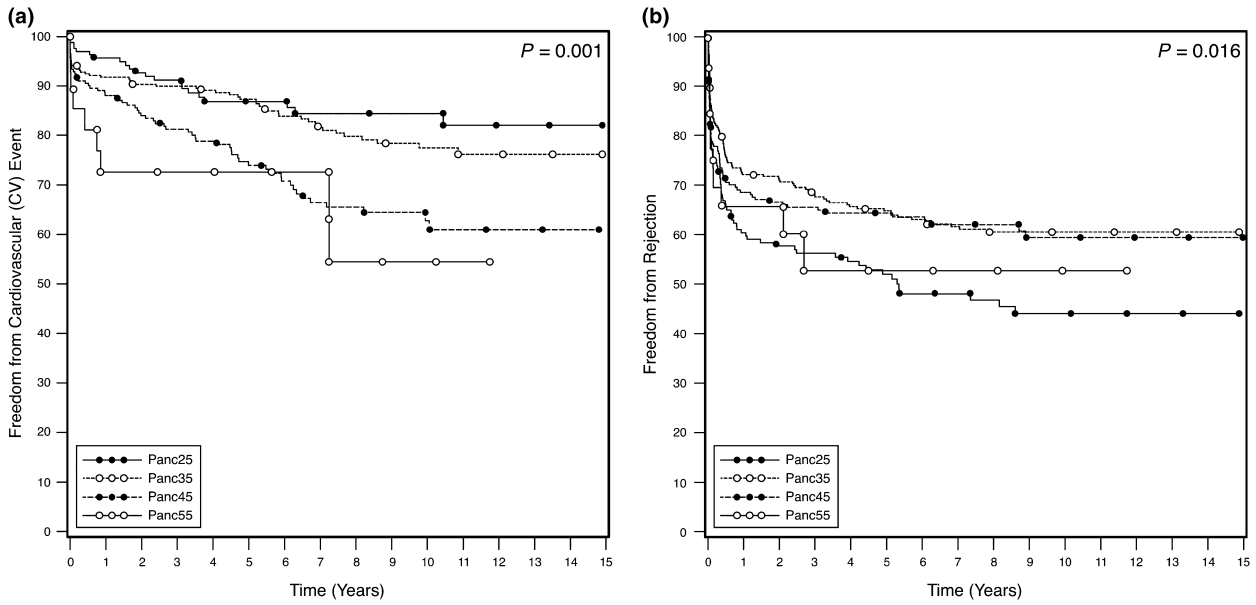


Figure 4 Freedom from cardiovascular events (Figure 4a). Pairwise comparison of group 1 vs. 2, P = NS; group 3 vs. 4, P = NS; group 1 vs. 3 and 4, $P < 0.05$; group 2 vs. 3 and 4, $P < 0.05$. Freedom from pancreas graft rejection (Fig. 4b) in patients receiving pancreatic transplants. Younger patients were more likely to experience rejection. CV, cardiovascular. Presented P-values relate to comparison of all four curves. Panc55 = group 1; Panc45 = group 2; Panc35 = group 3; Panc25 = group 4.

Table 1. Demographics for patient groups 1–5.

	Pancreas (n = 740)				Kidney (n = 260)	
	55 + Group 1	45-54 Group 2	35-44 Group 3	25-34 Group 4	55 + Group 5	P-VALUE
Number (n (%))*	28 (2.8)	229 (22.9)	316 (31.6)	167 (16.7)	260 (26.0)	<0.01
Mean Age (years)	57.0	48.7	40.0	31.4	62.2	<0.01
Gender (male; n (%))†	22 (78.6)	131 (57.2)	206 (65.2)	79 (47.3)	181 (69.6)	<0.01
Race						<0.01
Caucasian [n (%)]†	27 (96.4)	220 (96.1)	292 (92.4)	151 (90.4)	214 (82.3)	NS
African American [n (%)]†	1 (3.6)	6 (2.6)	17 (5.4)	14 (8.4)	21 (8.1)	NS
Other [n (%)]†	0 (0)	3 (1.3)	7 (2.2)	2 (1.1)	25 (8.1)	NS
Type of Pancreas Transplant						
SPK (n = 552; n (%))†	11 (39.3)	164 (71.6)	241 (76.3)	136 (81.4)	NA	<0.01
SP [n = 188; n (%)]†	17 (60.7)	65 (28.4)	75 (23.7)	31 (18.6)	NA	<0.01

SPK, simultaneous pancreas and kidney transplant; SP, solitary pancreas and kidney transplant (includes pancreas transplant alone and pancreas after kidney); NS, not significant; NA, not applicable.

*percent calculated from all patients (pancreas plus kidney, total n = 1000.

†percent calculated from all patients in each age strata (i.e., kidney 55 + , pancreas 55 + , etc.).

groups were made (Figure 1). There was a trend toward worse patient survival in group 1 (55 +) patients, but the worst patient survival outcomes were found in those diabetic uremic patients receiving kidney transplants alone. Actuarial non-death-censored and death-censored pancreas graft survival rates were analyzed. Neither non-death-censored nor death-censored pancreas graft survival rates between group 1 and groups 2, 3, or 4 were statistically significantly different from one another (Figure 2a and 2b). We did observe a significant difference in non-death-censored pancreas graft survival between groups 3 and 4 (P = 0.039). There was no difference in non-death-censored and death-censored kidney graft survival rates in SPK patients aged 55 and

Table 2. Diagnosis of diabetes type in pancreas transplant recipients.

Diabetes diagnosis	SP	SPK	Kidney alone
Type 1 Diabetes	186	548	42*
Type 2 Diabetes	2	4	218*
Total	188	552	260

DM1, diabetes mellitus type I; DM2, diabetes mellitus type II; SP, solitary pancreas transplant (pancreas transplant alone and pancreas after kidney); SPK, simultaneous pancreas and kidney transplant.

*Difference between frequency of DMI and II in kidney alone and pancreas transplant groups was statistically significant at $P < 0.01$.

Table 3. Pretransplantation cardiac catheterization incidence, as stratified by age in pancreas transplantation candidates.

*Pretransplantation catheterization and intervention			
	Diagnostic Catheterization	Catheterization and Angioplasty	Catheterization and Stent
Group 1	64.3	3.6	35.7
Group 2	58.1	3.5	12.7
Group 3	43.4	2.9	7.0
Group 4	32.3	1.2	2.4
P-Value	0.001	0.55	0.001

*Rows 1–4 presented as percentages, *P*-value represents chi-squared analysis.

older compared with younger SPK patients (Figure 3a and 3b). With regard to kidney graft survival in patients aged 55 years and older, when we controlled for the type of diabetes ($n = 42$ type 1 diabetic kidney transplant recipients vs. $n = 10$ type 1 diabetic SPK recipients), we again found no difference in graft survival ($P = 0.439$).

We observed higher rates of cardiovascular events in older patients (Figure 4a). Patients in groups 1 and 2 were more likely to experience a cardiovascular event than those in groups 3 and 4 ($P < 0.001$). There was no difference in cardiovascular event incidence when comparing group 3 with 4, or group 1 with group 2. Analysis of freedom from pancreas graft rejection in pancreas transplant recipients revealed that the youngest patients (group 4) were at significantly higher risk of rejection than those in group 3 or in group 2. There was no difference in risk of rejection between group 1 and group 4 (Figure 4b). We next evaluated the need for pretransplantation cardiac catheterization in each group. The incidence of pretransplantation catheterization increased incrementally, for each age-stratified group. That is, those aged 25-34 years had an incidence of 32%, 43% in those aged 35-44 years, and 58% in those aged 45-54, and for patients aged 55 years and older, the incidence of pretransplantation catheterization was 64% ($P < 0.001$). These interventions led to a stent more frequently in older patients as well (Table 3). Notably, the incidence of catheterization, angioplasty, and stenting in older kidney transplant patients was not different when compared with the oldest pancreas transplant recipients ($P = 0.36$, $P = 0.43$, and $0 = 0.06$, respectively).

Regarding our secondary objective, we observed that diabetic recipients of kidney transplants alone aged 55 + (group 5) years had statistically significantly lower patient survivals when compared with every other group (Figure 1), with the exception of pancreas transplant recipients aged 55 + years ($P = 0.065$). We observed statistically significantly lower patient survival in patients aged 55 years and older, only when compared with group 3 ($P = 0.037$). In contrast, there was no difference in patient survival when group 1 was compared with group 2 or with group 4, suggesting patients aged 55 + years have a nearly equal likelihood of surviving long-term post-transplant as patients between 45–54 and younger than 35 in our cohort.

Discussion

There has been an evolution of our understanding of age limits for transplantation of the pancreas over the last 20 years. In 1998, Freise *et al.* [1] showed that increased age (50 years and older, $n = 10$) was a risk factor for early graft loss and mortality. They observed that when grafts were lost, they were lost within the first year, and that graft losses were not due to cardiac events. In 2008, Ablorsu *et al.* [3] published their results with 31 pancreas transplants (SP and SPK) from 2001 to 2007 where the recipients were over the age of 50. The authors showed no difference in patient or graft survival when compared with younger recipients. Notably, there was also no observed difference in technical complication rate. The investigators did observe a higher rate of respiratory infection in the old cohort, however.

In 2011, Schenker *et al.* [16] reported on 69 pancreas transplant recipients (SP and SPK) older than 50 years of age who were transplanted between 1994 and 2009. Older patients had similar rates of re-laparotomy, rejection, and patient and graft survival. In this study, there were differences in the older and younger groups, such as enteric

drainage rates; this difference likely reflected trends in surgical technique over the course of the study. In addition, older patients were transplanted later in the data set.

In 2013, Shah *et al.* [4] published their experience with 405 pancreas transplants. Patients were stratified by age; among these, 85 patients were aged 50–59 years and 18 patients were 60 years or older. Graft survival at 5 years was statistically worse for recipients who were younger than 30 years of age at the time of transplantation. Importantly, patient and graft survival rates were not statistically different between the older (50–59 and >60 years) cohorts and the middle age (31–49 years) cohorts. This single-center study demonstrated that excellent outcomes can be achieved in pancreas transplant recipients of advanced age.

Most recently, in 2014, Siskind *et al.* [6] published an analysis of more than 20 000 pancreas transplant recipients reported to UNOS. Of these, 3440 patients were over the age of 50. In contrast to the single-center study results reported by Shah *et al.*, the authors observed worse patient and graft survival, when compared with younger age cohorts. While this study carries an impressive number of patients, there were some limitations insofar as granularity.

Our data demonstrate acceptable patient and graft survival rates after pancreas transplantation in recipients aged 55 + years, when compared with younger patients. These data need to be qualified by the knowledge that many of the oldest pancreas transplant recipients were transplanted in the last several years. As such, there is a potential era bias in the comparison of these patients with those who were transplanted years ago. In addition, there is a potential patient selection bias inherent in the retrospective nature of this study. Nevertheless, our findings of acceptable patient and graft survival rates after pancreas transplantation in patients older than 55 years of age are relevant to consider in light of the hesitancy of many transplant centers to offer pancreas transplantation to these candidates.

Diabetic kidney transplant patients (group 5) were included as a comparator. These patients were included to investigate the outcomes of older patients undergoing a less complex transplant operation. Notably, the incidence of type I diabetes was far less frequent in the kidney transplant alone group. We believe this is due to our aggressive policy to offer SPK transplantation as the primary option for type 1 diabetic uremic patients and the fact that only a subset of type 2 diabetic uremic patients are typically eligible for SPK transplantation due to accumulation of other comorbidities. This dissimilarity may have affected our data because uremic type I and type II diabetes may differ with regard to (i) duration of disease, (ii) presence of metabolic syndrome, and (iii) associated obesity and other recipient risk factors. Nonetheless, we found that diabetic kidney transplant patients have worse kidney graft survival than do those patients who underwent pancreas transplantation. This underscores the severity of renal failure in the aging diabetic population and the importance of pretransplantation patient selection and optimization. As such, the patient survival in older patients with diabetes requiring a renal transplant is quite poor. Accordingly, many older patients with type 1 diabetes were considered noncandidates for pancreas transplantation ($n = 42$, group 5). On the other hand, these data show that even in the oldest population, a pancreas transplant in addition to the kidney transplant procedure did not confer increased risk of death or graft failure, despite ostensible increases in patients' quality of life.

We observed a higher rate of cardiovascular events in the two older cohorts of pancreas transplant recipients compared with the younger recipient cohorts. In 2000, La Rocca *et al.* [17] compared the incidence of cardiovascular events in SPK patients, diabetic kidney transplant alone patients, and patients with diabetes on dialysis. Authors found a higher rate of cardiovascular complication in those who underwent kidney transplant versus those who underwent pancreas transplantation. Interpretation of these data is difficult because their results were not age-stratified. Additionally, and much like the present study, patients with diabetes who receive a kidney transplant alone were perhaps not pancreas transplant candidates because they were deemed too ill. In a more recent study, Medina-Polo *et al.* [18] showed that in patients with functioning SPKs, 5 of 89 patients (5.6%) experienced a cardiovascular event at a mean follow-up of almost 3 years. Notably, of these 5 events, 4 (80%) were perioperative. Again, these data were not age-stratified. In the present report, our observed incidence of cardiovascular events increased (statistically) with increasing age (i.e., comparing group 3 to group 2). That is, there were significantly more cardiovascular events following pancreas transplantation in recipients aged 45 years and older. Our data set represents one of the few designed to evaluate age-stratified cardiac risk after pancreas transplantation. Taken together, these data reinforce the importance of preoperative cardiac optimization for pancreatic transplant candidates.

The finding of increased frequency of cardiovascular complications in the older pancreas transplant recipient is perhaps not surprising. Based on the high prevalence of coronary artery atherosclerosis in patients with

diabetes, its asymptomatic presentation, and the high false-negative rates of cardiac stress tests, it is our practice for over 10 years to rigorously scrutinize the cardiovascular health of all pancreas transplantation candidates, typically with a cardiac stress test as well as coronary angiography prior to listing. Despite this rigorous and comprehensive evaluation, we observed more frequent CV events post-transplantation in the 45–55 group and in the 55 + group, whereas we observed only few CV events in those younger than 45 years. In older pancreas recipients, it is not uncommon to have been exposed to the deleterious effects of diabetes for 40–50 years prior to undergoing transplantation. Thus, patient selection and medical optimization of the pancreas transplant candidate is critical to the success of the post-transplant patient.

We also evaluated rates of acute rejection stratified by recipient age. Other authors have shown lower rates of rejection in older patients [19,20]. In the present study, we found that rejection is more common in younger patients and less common in older recipients. The reason for lower rates of rejection in older patients observed in our study and others[19] is not clear. One explanation for this finding is the phenomenon of immunosenescence [21–23]. Mechanisms underlying this difference in rejection rate have been suggested. Some investigators have hypothesized that as T cells age, small dysregulations (signaling, etc.) become magnified and lead, over time, to T-cell dysfunction. Inhibited B-cell development and a decrement in B-cell affinity maturation have been observed in older individuals [21,22,24]. Multiple pathways of innate immunity also appear to be compromised in the elderly [23,25,26]. Taken together, these subtle defects in immune function that can develop with age may explain a blunted alloreactive response and ultimately lower overall rates of rejection.

Shortcomings of our study include its retrospective nature and the small number of patients in our oldest age group. However, because the oldest patients from our study are uncommonly transplanted, it is our interpretation that this granular, single-center experience with pancreas transplantation represents proof of principle that these procedures can be safely performed in this population. While our data provide support for pancreas transplantation in the oldest patient group, it is possible that as a result of the limited number of patients in this group, we have encountered a type II statistical error. Accordingly, larger multicenter studies will be required.

In conclusion, we have observed acceptable patient and graft outcomes in pancreas transplant recipients aged 55 years and older. Although lower rates of immunologic rejection in older pancreas transplant recipients is a potential advantage, the adverse consequences of advanced and unrecognized cardiovascular disease is a major clinical concern in this population. Given the long-term exposure to the deleterious effects of diabetes mellitus, patient selection and a rigorous preoperative evaluation are of paramount importance in achieving long-term success after pancreas transplantation.

Author contributions

JRS designed the study, analyzed the data, and wrote and edited the manuscript. RRR and EA assisted with study design, analyzed the data, and edited the manuscript. GL acquired and analyzed the data. HWS and DBK analyzed the data and edited the manuscript. JSO designed the study, analyzed the data, assisted with writing the manuscript, and edited the manuscript.

Funding

The authors have declared no funding.

Conflict of interest

The authors have no financial disclosures.

Acknowledgements

The authors would like to thank Ms. Karen Williams, a senior editor in the department of surgery, at the University of Wisconsin for her expert assistance with the development of our study figures.

REFERENCES

1. Freise CE, Stock PG, Melzer JS. Increased morbidity and mortality of simultaneous pancreas-renal transplantation in patients over 49 years of age. *Transpl Proc* 1998; **30**: 292.
2. Freise CE, Narumi S, Stock PG, Melzer JS. Simultaneous pancreas-kidney transplantation: an overview of indications, complications, and outcomes. *West J Med* 1999; **170**: 11.
3. Ablorsu E, Ghazanfar A, Mehra S, *et al.* Outcome of pancreas transplantation in recipients older than 50 years: a single-centre experience. *Transplantation* 2008; **86**: 1511.

4. Shah AP, Mangus RS, Powelson JA, *et al.* Impact of recipient age on whole organ pancreas transplantation. *Clin Transplant* 2013; **27**: E49.
5. Redfield RR, Scalea JR, Odorico JS. Simultaneous pancreas and kidney transplantation: current trends and future directions. *Curr Opin Organ Transplant* 2015; **20**: 94.
6. Siskind E, Maloney C, Akerman M, *et al.* An analysis of pancreas transplantation outcomes based on age groupings–an update of the UNOS database. *Clin Transplant* 2014; **28**: 990.
7. Israni AK, Skeans MA, Gustafson SK, *et al.* OPTN/SRTR 2012 Annual Data Report: pancreas. *Am J Transplant* 2014; **14**(Suppl. 1): 45.
8. Matas AJ, Smith JM, Skeans MA, *et al.* OPTN/SRTR 2011 Annual Data Report: kidney. *Am J Transplant* 2013; **13**(Suppl. 1): 11.
9. Kandaswamy R, Stock PG, Skeans MA, *et al.* OPTN/SRTR 2011 Annual Data Report: pancreas. *Am J Transplant* 2013; **13**(Suppl. 1): 47.
10. Chandie Shaw PK, Vandenbroucke JP, Tjandra YI, *et al.* Increased end-stage diabetic nephropathy in Indo-Asian immigrants living in the Netherlands. *Diabetologia* 2002; **45**: 337.
11. Chandie Shaw PK, Van Es LA, Paul LC, Rosendaal FR, Souverijn JH, Vandenbroucke JP. Renal disease in relatives of Indo-Asian Type 2 diabetic patients with end-stage diabetic nephropathy. *Diabetologia* 2003; **46**: 618.
12. Sollinger HW, Odorico JS, Becker YT, D'Alessandro AM, Pirsch JD. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. *Ann Surg* 2009; **250**: 618.
13. Niederhaus SV, Leverson GE, Lorentzen DF, *et al.* Acute cellular and antibody-mediated rejection of the pancreas allograft: incidence, risk factors and outcomes. *Am J Transplant* 2013; **13**: 2945.
14. Niederhaus SV, Kaufman DB, Odorico JS. Induction therapy in pancreas transplantation. *Transpl Int* 2013; **26**: 704.
15. Lee ET, Go OT. Survival analysis in public health research. *Annu Rev Public Health* 1997; **18**: 105.
16. Schenker P, Vonend O, Kruger B, *et al.* Long-term results of pancreas transplantation in patients older than 50 years. *Transpl Int* 2011; **24**: 136.
17. La Rocca E, Fiorina P, Astorri E, *et al.* Patient survival and cardiovascular events after kidney-pancreas transplantation: comparison with kidney transplantation alone in uremic IDDM patients. *Cell Transplant* 2000; **9**: 929.
18. Medina-Polo J, Dominguez-Esteban M, Morales JM, *et al.* Cardiovascular events after simultaneous pancreas-kidney transplantation. *Transpl Proc* 2010; **42**: 2981.
19. Knoll GA. Kidney transplantation in the older adult. *Am J Kidney Dis* 2013; **61**: 790.
20. Dempster NJ, Ceresa CD, Aitken E, Kingsmore D. Outcomes following renal transplantation in older people: a retrospective cohort study. *BMC Geriatr* 2013; **13**: 79.
21. Nikolich-Zugich J. Aging of the T cell compartment in mice and humans: from no naive expectations to foggy memories. *J Immunol* 2014; **193**: 2622.
22. Nusser A, Nuber N, Wirz OF, Rolink H, Andersson J, Rolink A. The development of autoimmune features in aging mice is closely associated with alterations of the peripheral CD4(+) T-cell compartment. *Eur J Immunol* 2014; **44**: 2893.
23. Oh J, Lee YD, Wagers AJ. Stem cell aging: mechanisms, regulators and therapeutic opportunities. *Nat Med* 2014; **20**: 870.
24. Riley RL. Impaired B lymphopoiesis in old age: a role for inflammatory B cells? *Immunol Res* 2013; **57**: 361.
25. McAuley JL, Tate MD, MacKenzie-Kludas CJ, *et al.* Activation of the NLRP3 inflammasome by IAV virulence protein PB1-F2 contributes to severe pathophysiology and disease. *PLoS Pathog* 2013; **9**: e1003392.
26. Salminen A, Ojala J, Kaarniranta K, Kauppinen A. Mitochondrial dysfunction and oxidative stress activate inflammasomes: impact on the aging process and age-related diseases. *Cell Mol Life Sci* 2012; **69**: 2999.