ORIGINAL ARTICLE

An analysis of the association between older recipient age and outcomes after whole-organ pancreas transplantation – a single-centre, retrospective study

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SUMMARY

Older people are increasingly being referred for consideration for pancreas transplantation (PT). We investigated the outcomes after PT in our older recipient cohort. A prospectively maintained database was interrogated. The cohort was analysed for associations between outcome and older recipient age. A total of 444 transplants were performed in patients aged 23–54 years and 83 transplants in patients aged 55–67 years. There was no difference in death-censored pancreas or kidney graft survival between the groups. Patient death was associated with older recipient age (HR 1.63 per 10-year increase). In multivariate Cox regression, risk of mortality was also associated with post-transplant myocardial infarction (HR 7.25, $P = 0.006$), pancreas failure (HR 1.91, $P = 0.003$) and kidney failure (HR 3.55, $P < 0.001$). About 40% of recipients who died in the first year post-transplant suffered early graft loss. Those alive at a year post-transplant had inferior survival if they had lost their kidney graft ($P < 0.001$). Mortality is higher in older patients and is strongly associated with pancreas and kidney graft failure. This suggests that pancreas transplantation is feasible in older recipients, and careful selection of donor organs is important to optimize survival.

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Introduction

Pancreas transplantation offers insulin independence and improved quality of life for those suitable for the procedure [1]. Improvements in medical care have resulted in an older population of people with type 1 diabetes and, alongside widening of indication criteria to include people with insulin-dependent type 2 diabetes and developments in pre-assessment techniques, this has resulted in an increase in the number of older people being referred as potential recipients for pancreas transplantation. Many transplant centres include an upper age limit as part of their referral criteria, often relatively arbitrarily selected.

Diabetes is associated with significant comorbidity, particularly cardiovascular disease which accounts for the leading cause of death in this cohort [2]. Additionally, pancreas transplantation is a rather complex

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surgical procedure, associated with significant risk of requiring transfusion, return to theatre for complications and the sequelae of graft pancreatitis. With an expanding population of patients with diabetes and its complications, pancreas transplantation in older recipients is now an increasingly relevant consideration.

We aimed to describe the outcomes and investigate risk factors for outcomes after pancreas transplantation in older recipients at our centre.

Materials and methods

Patient cohort

This is a single-centre, retrospective clinical study. Data were retrieved from a research database for all pancreas transplants performed between 2002 and 2016 in recipients aged over 55 years old. Simultaneous pancreas kidney transplants (SPK) and isolated pancreas transplants (IP) were included. The IP group included both pancreas after kidney (PAK) and pancreas transplant alone (PTA) recipients. Previous analyses and national data have shown graft and patient survival after PAK and PTA to be equivalent, and therefore, owing to small numbers these two patient groups were analysed together [3]. Data relating to donor and recipient variables, post-transplant cardiac events, graft survival and patient survival were recorded and compared to a cohort of contemporaneous pancreas transplant recipients aged <55 years at the time of transplant.

All patients were managed according to a standard clinical protocol. Patients referred for consideration of pancreas transplantation were assessed by a consultant surgeon in an assessment clinic and checked against unit listing criteria. Metabolic work-up was performed and consisted of eliciting diabetic history, the presence and extent of diabetic complications and medication history, examination including body mass index (BMI) as well as blood tests including serum c-peptide levels, HbA1c and autoantibody levels. Potential recipients with type 2 diabetes were offered pancreas transplantation providing BMI was within acceptable range (<30 kg/m^2), and insulin doses were less than 1 unit/kg/day. Amputation, blindness and gastroparesis were not considered contraindications to transplant. A clinical examination of the peripheral vasculature was made, and further investigation requested only in very selected cases where imaging would benefit implantation planning. A plan for perioperative feeding jejunostomy was made for selected patients with severe gastroparesis.

Our unit does not have a predefined upper age limit for consideration for pancreas transplantation, and no specific frailty assessment was performed. Potential recipients were appropriately counselled and underwent investigations including standard blood tests, histocompatibility profiling and cardiac assessment. All patients were discussed in a multi-disciplinary listing meeting to determine the likelihood that pancreas transplantation would offer clinical benefit. Potential recipients were considered to gain additional benefit from, and be fit enough to tolerate, the additional stress of the pancreas transplant above a kidney transplant alone. Where a potential recipient was on dialysis and/or had a long predicted waiting time and had a potential living donor, living donor kidney transplantation followed by PAK was considered. These decisions were made on a case-by-case basis.

Myocardial perfusion scanning was undertaken where possible, with stress echocardiography accepted as an alternative. If myocardial perfusion scanning was abnormal, potential recipients were referred for angiography and/or cardiac intervention. All cases where there was abnormality in the cardiac screening were discussed in a Cardiology Multi-disciplinary meeting comprising cardiologists, anaesthetists and surgeons prior to listing.

All potential recipients underwent routine pretransplant immunogenetic analysis comprising ABO grouping, HLA genotyping and alloantibody detection. These data were used to inform potential waiting times to transplantation and were used to enable national allocation of deceased donor organs. Deceased donor organs were allocated to potential recipients via a centrally managed national organ allocation process. All transplants were performed with systemic venous drainage. Enteric ductal drainage was used in all except ten recipients, who received IP transplants with bladder drainage because of a change in centre protocol. All recipients received alemtuzumab induction (Campath 30 mg, day 1 and day 2) immunosuppression. Maintenance immunosuppression therapy consisted of tacrolimus, initially at 0.5 mg/kg bd, and titrated to maintain trough levels between 8 and 10 ng/ml throughout the follow-up and mycophenolate mofetil, at 750 mg bd, with dose adjustments as clinically indicated. Intraoperative intravenous heparin was utilized for anticoagulation, with postoperative dextran infusion and prophylactic subcutaneous heparin. All recipients received prophylaxis against pneumocystis pneumonia and fungal infection, with additional cytomegalovirus and tuberculosis prophylaxis as indicated. Postoperative steroids were not used routinely. No modifications were

Transplant International 2020; 33: 529–535

made to the immunosuppression regimen based on recipient age.

Post-transplant recipients were regularly reviewed in centre outpatients clinics and referred back to their referring units after six months post-transplant, with annual review at our centre. As such, detailed data regarding the frequency of infections and readmissions were not collected as much of this care was undertaken at the recipient's local centres. Graft failure was defined as a return to insulin dependence. Values for serum c-peptide or exogenous insulin doses were not collected at the time of failure. Graft failure that occurred within 90 days of transplant was considered early graft failure secondary to technical failure, thrombosis and/or graft pancreatitis. Graft failure that occurred after 90 days post-transplant was considered chronic pancreas graft failure secondary to rejection or recurrence of diabetes. Pancreas biopsies are not performed at our centre, and as such, defining a precise cause of graft loss was not possible. Rejection was assumed based on the clinical context. Data were entered into an anonymized database and analysed as below.

Statistical analysis

Quantitative parametric data were compared between groups using Student's *t*-test or the Mann–Whitney *U* test in the case of nonparametric distribution. Cross-tabulated data were analysed by the chi-squared test or by Fisher's exact test when the expected count was <5. Patient and death-censored graft survival and recipient age at time of transplant were assessed using Kaplan–Meier curves and compared with the log-rank test. The Cox proportional hazard regression model was utilized to estimate the impact of recipient age and co-variables known to impact on pancreas graft survival. Variables with a significance level of $P < 0.15$ on univariate analysis were selected for inclusion in the multivariate model. Values of $P < 0.05$ were considered statistically significant. Statistical calculations were made using SPSS for Windows software (IBM SPSS Statistics version 22; Chicago, IL, USA).

Results

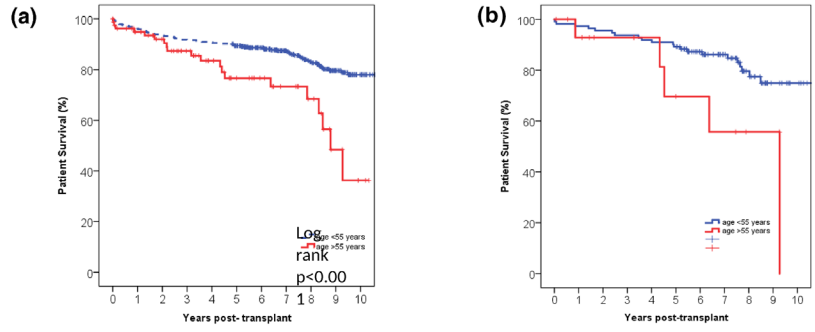
A total of 527 transplant recipients were included in the analysis. A total of 444 transplants (84.2%) were performed in patients aged 23–54 years. A total of 83 transplants were performed in patients aged 55–67 years. The cohort included 59 (11.2%) recipients aged 55–59 years, 19 (3.6%) recipients aged 60–64 years and 5 (1.5%) recipients aged 65–67 years. Older recipients (aged over 55 years) had slightly higher BMI (26.3 vs. 25.3 kg/m^2, $P = 0.025$) and were more likely to have type 2 diabetes (10% vs. 2.7%, $P = 0.003$) and a longer duration of diabetes (32.2 vs. 27.4 years, $P = 0.025$); Table 1.

Six of 83 recipients (7.2%) in the older recipient group had abnormal pretransplant cardiac investigations requiring intervention. Three went on to percutaneous cardiac intervention, and three underwent coronary artery bypass grafting. In the younger group, three of 444 (0.7%) recipients had abnormal cardiac investigations resulting in intervention to be considered. Two went on to percutaneous cardiac intervention, and one was managed with optimization of medical management.

Owing to the National matching algorithm, older recipients were more likely to receive pancreases from older donors (40.5 vs. 35.8 years, $P = 0.004$) but there were no other statistically significant differences in donor- and transplant-related factors, including donor BMI, DCD status, cold ischaemia time or transplant type (SPK versus IP) as shown in Table 1.

Table 1. Cohort demographics relating to recipient and donor variables.

	Young recipients (23–54 year)	Older recipients (55+ year)	*P*-value
N	444	83	
Recipient BMI (kg/m^2)	25.3 ± 6.6	26.3 ± 3.4	0.025
Recipient gender (% female)	176 (39.6%)	31 (37.3%)	0.758
Diabetes type (% type 2)	12 (2.7%)	8 (10.0%)	0.003
Diabetes duration (years)	27.4 ± 8.4	32.2 ± 13.6	0.025
Donor age (years)	35.8 ± 13.1	40.5 ± 14.8	0.004
Donor BMI (kg/m^2)	24.0 ± 4.3	23.3 ± 4.7	0.310
Donor type (% DCD)	56 (12.7%)	12 (16.4%)	0.328
CIT (min)	685 ± 169	690 ± 150	0.813
Transplant (% SPK)	333 (75%)	67 (80.7%)	0.358



	0	1	3	5	10
<55	333	319	304	288	53
>55	67	56	40	23	2

0	1	3	5	10
111	108	104	99	10
16	13	10	5	0

Figure 1 Patient survival after pancreas transplantation, stratified by age, in (a) simultaneous pancreas kidney and (b) isolated pancreas.

Post-transplant rates of cardiac events and interventions were low in both groups with no statistically significant differences between the groups (CVA 3.8% vs. 2.3%, MI 1.3% vs. 0.7% and PCI 1.3% vs. 0.5%).

In unadjusted Kaplan–Meier analysis, patient survival was inferior in the older age group; however, early patient survival was equivalent with divergence evident only beyond 2 years post-transplant (1 year 96% vs. 95%, 3 year 92% vs. 87%, 5 year 89% vs. 77% and 10 year 78% vs. 36%; $P < 0.001$; Fig. 1). In the older group, the cause of death was recorded as cardiac failure or sudden cardiac death (4/20, 20%), respiratory failure (3/20, 15%), malignancy (3/20, 15%), cerebrovascular accident (1/20, 0.5%), trauma (1/20, 0.5%), haemorrhage (1/20, 0.5%) or unknown (7/20, 35%).

In an adjusted multivariate Cox regression model, risk of mortality was not independently associated with recipient BMI, donor organ characteristics (age, BMI, DCD status and CIT) or type of transplant (SPK versus IP). However, when considered as a continuous variable, increasing recipient age (HR 1.05, CI 1.02–1.07; $P < 0.001$), or HR 1.63 per 10-year age increase, was independently associated with death. Post-transplant MI (HR 7.25, CI 1.75–30.1; $P = 0.006$), pancreas graft failure (HR 1.91, CI 1.24–2.96; $P = 0.003$) and kidney graft failure (HR 3.55, CI 2.14–5.89; $P < 0.001$) were also all independently associated with mortality.

In the multivariate analysis, no recipient-, donor- or transplant-related factors could be identified to predict post-transplant MI or kidney graft failure. Pancreas graft failure was associated with IP transplant (HR 2.47, CI 1.65–3.69; $P < 0.001$), donor age (HR 1.02, CI 1.00–1.03; $P = 0.48$) and recipient male gender (HR 1.61, CI 1.08–2.40; $P = 0.02$) but was not predicted by recipient age group, BMI, duration of diabetes, donor BMI, DCD status or cold ischaemia time.

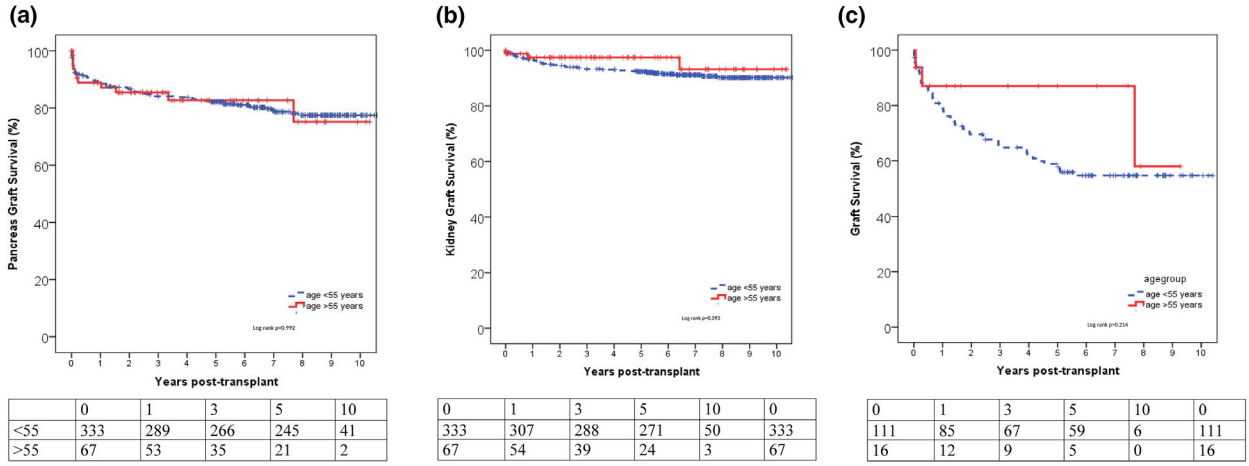
Comparing recipients aged over 55 years to those <55 years, in Kaplan–Meier analysis, there was no difference between the older and younger groups in death-censored pancreas graft survival or kidney graft survival; Fig. 2.

Twenty recipients died within the first year post-transplant, of which 12 died with both organs functioning, seven suffered pancreas graft failure within the first 60 days post-transplant, and one recipient lost both grafts in the first 60 days. Further Kaplan–Meier analysis comparing surviving recipient groups by status at 1 year post–transplant, both pancreas and kidney function ($n = 99$ IP, $n = 341$ SPK), pancreas failed ($n = 25$ IP, $n = 27$ SPK), kidney failed ($n = 8$ SPK) or both organs failed ($n = 7$ SPK), found there was no significant difference in patient survival between the groups in the case of IP transplant; however, failure of the kidney ($P = 0.002$) or both organs ($P < 0.001$) was significantly associated with higher mortality compared to pancreas failure or dual stable function. Those with dual function achieved a five-year survival of 91.3% for IP and 93.9% for SPK (Fig. 3).

Discussion

In this study, we describe the outcomes of a large cohort of pancreas transplants in older recipients at a single large-volume pancreas programme in the modern era, including a number of recipients aged over 60 years old. We found death-censored pancreas and kidney graft survival to be equivalent to outcomes in younger recipients. In other solid organ transplantation, death-censored graft survival has been noted to be equivalent in older recipients [4], whereas in pancreas transplantation a previous UNOS database analysis suggested that optimal graft survival is seen in those aged 40–49 years with poorer graft

Transplant International 2020; 33: 529–535



	0	1	3	5	10
<55	333	289	266	245	41
>55	67	53	35	21	2

0	1	3	5	10	0
333	307	288	271	50	333
67	54	39	24	3	67

0	1	3	5	10	0
111	85	67	59	6	111
16	12	9	5	0	16

Figure 2 Graft survival stratified by age. Pancreas (a) and kidney (b) graft survival in simultaneous pancreas kidney transplants; pancreas graft survival (c) in isolated pancreas transplant.

survival in older age groups [5]. However, single-centre studies have not demonstrated any difference in graft outcomes between older and younger recipients.

Laurence *et al.* compared 30 recipients aged over 55 years to 352 younger recipients and found no difference in rates of postoperative complications, graft or patient survival. However, they note a lower rate of rejection in the older group (13% vs. 33%, although details of how this was diagnosed are not presented) [6]. Scalea *et al.* [7] analysed 720 recipients of whom 28 were over 55 years and found that older recipients receiving SPK had better survival than those receiving kidney alone. While there may be some evidence that the excellent glycaemic control achieved in SPK transplantation may have some survival benefit, it must be recognized that in this analysis, the recipients selected for SPK and those selected for kidney alone had different comorbidity profiles resulting in selection bias and therefore making the groups incomparable. Equivalent graft and patient survival rates have also been reported by other single-centre analyses, including patients aged over 50 years and over 60 years old at the time of transplant [7,8], that support the findings of this study.

At the same time, we have demonstrated an association between recipient age and increased mortality over time in both Kaplan–Meier and multivariate analyses, although divergence in survival rates was only evident after two years post-transplant in Kaplan–Meier analysis. This refutes the concept that perioperative mortality risk should preclude consideration of older recipients

(a)

	0	1	3	5	10
Dual function	340	334	311	282	49
Pancreas loss	27	26	25	23	6
Kidney loss	8	8	5	4	0
Both lost	7	3	2	0	0

(b)

0	1	3	5	10
99	96	90	82	8
25	24	23	21	2

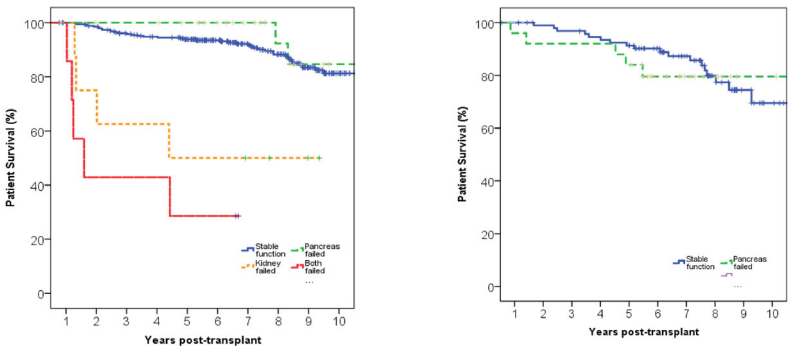


Figure 3 Patient survival in pancreas transplant recipients alive at 1 year post-transplant stratified by organ function for (a) simultaneous pancreas kidney and (b) isolated pancreas.

for pancreas transplant. Indeed, rates of cerebrovascular and cardiovascular events were low in both groups, suggesting pancreas transplantation is feasible carefully selected in older recipients with the use of robust cardiac pre-assessment and optimization. Other studies have reported higher pre-operative cardiac intervention rates to that observed in our study, with Laurence et al describing cardiac intervention in the older recipient group at a rate of 46% vs. 13%, despite the recipient groups showing equivalent duration of diabetes pretransplant [6]. Scalea also demonstrated that recipients over 55 years of age are more likely to have a pretransplant cardiac intervention, but not more likely to have post-transplant cardiac events than recipients aged 45 and over [7].

Protocols for pretransplant assessment and cardiac optimization vary between transplant centres. Historically, angiocardiography was recommended for cardiac assessment; however, with the emergence of more sophisticated radiological cardiac imaging modalities, there has been a trend away from this invasive investigation. Stress echocardiography has also been used for cardiac stratification [9], while in our unit the mainstay of pretransplant assessment is myocardial perfusion scanning, as it offers the advantage of sensitive and detailed functional assessment in these high-risk patients.

Further to any analysis that has been presented previously, we have performed multivariate assessment of factors associated with patient survival and demonstrated that postoperative MI, kidney failure and pancreas graft failure are independently associated with a higher risk of mortality. While there were no factors identified to predict risk of MI or kidney graft loss, donor age was identified as a potentially useful risk factor for pancreas graft loss. Donor age has been established in many single-centre [10] and national database analyses to be associated with poor pancreas graft survival and forms the most significant predictor in the Pancreas Donor Risk Index [11].

Life expectancy for patients with end-stage renal failure secondary to type 1 diabetes is low with a median survival of five years after initiation of renal replacement therapy, reduced to 3.5 years for patients over 55 years of age [8]. Previous analyses have shown that the use of older donors for pancreas transplantation is acceptable and offers survival benefit over remaining on the waiting list [12]. However, in an analysis of SRTR data, Kayler *et al.* [13]reported that older recipients (>40 years) can achieve graft and patient survival rates equivalent or superior to younger recipients when allocated a pancreas from a younger donor (<40 years). While there was a survival benefit for older recipients to undergo transplantation rather than remaining on the waiting list, older donors were associated with higher graft failure and mortality rates when allocated to both younger and older recipients, with outcomes poorest in the older recipient group. Similar conclusions had been drawn in other published analyses [14]. Our analysis found 40% of recipients who died within the first year post-transplant and had suffered the insult of early pancreas or kidney graft failure. About 96% of patients survived beyond one year post-transplant and enjoyed a five-year survival of 91.3% for IP and 93.9% for SPK in the context of stable pancreas and kidney function. Although the use of young donor organs for transplantation into recipients at the upper limit of acceptable age criteria may be controversial, it is important to balance risk factors in organ selection at time of offering for this cohort of patients in order to optimize graft and patient survival.

In conclusion, this analysis has demonstrated equivalent graft outcomes in recipients over and below 55 years of age at the time of transplant. Age alone should not be an exclusion criterion for pancreas transplantation. While recipient age is predictive of patient mortality, excellent patient survival can be achieved in the context of stable graft function. Pancreas and kidney graft failure are both highly predictive of mortality, and therefore, careful selection of donor organs is recommended in this cohort.

Authorship

SM, RS, RF and CH: participated in collection of data, analysis and preparation of manuscript. SK, GV, IQ, SR, JG, RP, PF and SS: participated in preparation of the manuscript.

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Conflicts of interest

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