

## ORIGINAL ARTICLE

# Recipient age and outcome after pancreas transplantation: a retrospective dual-center analysis

Franka Messner<sup>1</sup> , Marjolein Leemkuil<sup>2</sup> , Yifan Yu<sup>3</sup>, Allan B. Massie<sup>3,4</sup>, Felix J. Krendl<sup>1</sup>, Stan Benjamins<sup>2</sup> , Claudia Bösmüller<sup>1</sup>, Annemarie Weissenbacher<sup>1</sup>, Stefan Schneeberger<sup>1</sup> , Robert A. Pol<sup>2</sup> & Christian Margreiter<sup>1</sup>

1 Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Innsbruck, Austria

2 Department of Surgery, University Medical Center Groningen, Groningen, The Netherlands

3 Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD, USA

4 Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

## Correspondence

Franka Messner, MD, Department of Visceral, Transplant and Thoracic Surgery, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria.

Tel.: 0043-50-504-22601;

fax: 0043-50-504-22602;

e-mail: franka.messner@i-med.ac.at

**Local ethics committee:** No. 1069/2019

## ABSTRACT

With a later onset of diabetes complications and thus increasing age of transplant candidates, many centers have extended upper age limits for pancreas transplantation. This study investigates the effect of recipient and donor age on outcomes after pancreas transplantation. We retrospectively analyzed 565 pancreas transplants performed at two Eurotransplant centers. The cohort was split at a recipient and donor age of 50 and 40 years, respectively. Median recipient age in old patients ( $\geq 50$  years; 27.2%) was 54 years and 40 years in young patients ( $< 50$  years). Compared to young recipients, old recipients had an inferior patient survival rate ( $\geq 50$ : 5yr, 82.8%; 10yr, 65.6%;  $< 50$ : 5yr, 93.3%; 10yr, 82.0%;  $P < 0.0001$ ). Old recipients demonstrated comparable death-censored pancreas ( $\geq 50$ : 1yr, 80.6%; 5yr, 70.2%;  $< 50$ : 1yr, 87.3%; 5yr, 77.8%;  $P = 0.35$ ) and kidney graft survival ( $\geq 50$ : 1yr, 97.4%; 5yr, 90.6%;  $< 50$ : 1yr, 97.8%; 5yr, 90.2%;  $P = 0.53$ ) compared to young recipients. Besides a lower rate of kidney rejection, similar relative risks for postoperative complications were detected in old and young patients. This study shows that despite an increased mortality in old recipients, excellent graft survival can be achieved similar to that of young patients. Age alone should not exclude patients from receiving a pancreas transplant.

*Transplant International* 2021; 34: 657–668

## Key words

donor age, postoperative complications, recipient age, simultaneous pancreas kidney transplantation, survival

Received: 15 July 2020; Revision requested: 24 August 2020; Accepted: 8 February 2021;

Published online: 1 March 2021

## Introduction

Simultaneous pancreas kidney transplantation (SPK) is an established treatment for patients with type 1 diabetes mellitus (T1DM) and end-stage renal disease. In diabetic kidney transplant recipients, it is associated with a significant survival benefit compared with deceased donor kidney transplantation alone [1–4]

In the past, recipient age greater than 50 was considered a relative contraindication for performing a pancreas transplantation at many centers [5]. In the last two decades, however, a higher rate of older transplant candidates was seen that was mainly because of advances in diabetes management and consecutively later onset of secondary diabetic complications. Together with better pretransplant evaluation, the refinement of the surgical

technique, perioperative management, and the introduction of modern immunosuppressive protocols, many centers have become more liberal regarding age limits for their pancreas transplant candidates.

However, not only considerations regarding recipient age restrictions have changed but also the attitude toward accepting grafts from older donors. With the growing gap between organ availability and demand, reconsiderations of age limits are necessary to ensure an acceptable waiting time and waitlist mortality [6,7] This is especially crucial in light of an aging population and concurrently older donor pool [8] In 2018, 27% of deceased donors reported in Eurotransplant (ET) were over the age of 65 [8] While the median donor age for any organ increased by 10 years from 45 to 55 years over the last two decades in the ET region, only the median age of deceased donor pancreata remained unchanged (between 30 and 40 years) [8] This might be because of the fact that donor age is considered to be an important factor determining post-transplant outcome in pancreas transplantation [9–11] Despite reports from donor organs  $\geq 45$  years with good five-year death-censored kidney (77.8%) and pancreas graft survival (71.3%) [12] higher donor age ( $> 40$  years) results in significantly worse graft survival and higher patient mortality when compared to young donors in recipients of similar age groups after receiving an SPK [13].

Thus far, only one ET center reported their long-term results of pancreas transplantation in recipients older than 50 years [14] In contrast to other large registry studies from the United States, they did, however, not detect differences in patient and graft survival and postoperative complication rates including second-look operations, pancreas graft thrombosis, and one-year rejection rates [13,15].

The aim of this study is to evaluate the impact of recipient and donor age on the short- and long-term outcome after pancreas transplantation in two ET centers.

## Patients and methods

### Study population

The study was approved by the local ethics committee (No. 1069/2019). We retrospectively analyzed all consecutively performed pancreas transplants at the Medical University of Innsbruck ( $n = 474$ ) and the University Medical Centre Groningen ( $n = 91$ ) between January 1996 and December 2018. Donor characteristics were obtained from the ET donor registration platform. Perioperative data, recipient characteristics, and follow-up

data were retrospectively collected from medical records (electronic patient file, archived discharge, and follow-up letters). Organ allocation was performed according to the Eurotransplant Pancreas Allocation system (EPAS) [16].

### Surgical procedure

Simultaneous pancreas kidney (SPK), pancreas after kidney (PAK), or pancreas transplant alone (PTA) transplantations were carried out according to standard techniques as published before [17–20] Full-size pancreas grafts were procured in a no-touch technique after perfusion with University of Wisconsin (UW) or histidine-tryptophan-ketoglutarate (HTK) solution. Briefly, the renal artery and vein were anastomosed to the left external iliac vessels; the pancreas graft was transplanted intraperitoneally into the right middle to lower quadrant. In routine cases, the portal vein was anastomosed to the inferior vena cava and the common iliac artery of the Y-graft, after reconstruction with the donor iliac bifurcation (donor external iliac artery to graft superior mesenteric artery and donor internal iliac artery to graft splenic artery), to the right common iliac artery of the recipient. In most cases, a duodenojejunostomy was performed to the upper jejunum (40 cm distally to the ligament of Treitz) for exocrine drainage; however, in approximately 10% of cases, a bladder drainage was performed. At the Medical University of Innsbruck (MUI), all patients received induction therapy with antithymocyte globulin (ATG; 4mg/kg; standard agent) or alemtuzumab (30 mg; as part of prospective study;  $n = 14$ ) [21] and methylprednisolone (500 mg) intraoperatively. At the University Medical Centre Groningen (UMCG), standard induction therapy consisted of alemtuzumab (1996), ATG or basiliximab (1997–2009), basiliximab (2009–2017) or alemtuzumab (2017–2018), and methylprednisolone (500 mg) intraoperatively. Standard maintenance immunosuppression consisted of tacrolimus (trough level: initial 10–15 ng/ml, 8 ng/ml at 9 months, and 4–6 ng/ml after 12 months), or cyclosporine A (only MUI; trough level: initial 180–200 ng/ml, 100–130 ng/ml at 9 months, 80–100 ng/ml at 12 months), prednisone (postoperatively tapered to 5 mg/d), and mycophenolic acid (2000 mg/d). Perioperative antibiotics, antifungal, and antiviral treatment consisted of piperacillin/tazobactam, ciprofloxacin, and fluconazole at the MUI, cefazoline/cefuroxime, fluconazole, metronidazole at the UMCG, and trimethoprim-sulfamethoxazole, and ganciclovir or valganciclovir. Postoperatively, all patients received initially intravenous (PTT goal: 45–50 seconds) and later subcutaneous

heparin (body-weight adapted). Long-term anticoagulation consisted of daily acetyl salicylic acid (50 or 100 mg/d) in most patients related to pre-existing conditions such as coronary artery and/or peripheral vascular disease. At the ICU and later at the general ward, blood glucose levels were treated with insulin if they exceeded 150 and 180 mg/dl, respectively.

## Definitions

According to the literature [13,14,22,23] and our own center experience with age limitations, we divided our recipient cohort in young (< 50 years) and old ( $\geq 50$  years) recipients. For donor age, the cohort was split at 40 years (young:  $\leq 40$  years, old:  $> 40$  years). Follow-up time was calculated from date of transplantation until date of last known clinical status or death. Rejection of the kidney and pancreas graft was defined as clinically suspected or histologically proven and treated rejection episodes during the first postoperative month. Postoperative complications were classified according to the Clavien–Dindo criteria [24,25] Delayed pancreas graft function (DPGF) was defined as the transient need for exogenous insulin in the first two weeks after transplantation, and delayed kidney graft function (DKGF) was defined as the need for  $\geq$  two hemodialysis sessions after SPK during the first week after transplantation [26,27] The pancreas donor risk index (PDRI) was calculated according to Axelrod et al. [28] Postoperative hemorrhage was defined as a drop in hemoglobin levels that required blood transfusion and/or intervention (endoscopic or surgical).

## Outcomes

Primary outcome parameters were patient survival (censored for retransplantation) and all-cause and death-censored pancreas and kidney (in case of SPK) graft survival. All-cause (including graft loss as a result of patient death; acPGF) and death-censored pancreas graft failure (excluding graft loss as a result of patient death; dcPGF) was defined according to OPTN/SRTR [29] For kidney grafts, all-cause (including graft loss as a result of patient death; acKGF) and death-censored (excluding graft loss as a result of patient death; dcKGF) graft failure was defined as return to dialysis.

Secondary outcome parameters included the occurrence of kidney and/or pancreas graft rejection, postoperative hemorrhage, wound infection, and postoperative complications Clavien–Dindo  $\geq 3a$ , delayed pancreas

and kidney graft function, and relative length of hospital stay.

## Statistical analysis

We used the chi-square tests or Fisher's exact test (categorical variables) and rank-sum tests (continuous variables) to compare donor and recipient characteristics. Patient, all-cause, and death-censored pancreas and kidney graft survival rates were estimated by the Kaplan–Meier method and compared by log-rank test. Patient and graft survival between recipients  $< 50$  years and  $\geq 50$  years were compared by Cox proportional hazard regression adjusted for type of pancreas transplant, recipient BMI, recipient CMV status, endocrine drainage, recipient sex, donor amylase, retransplantation, and year of transplantation. The relative risk (RR) of secondary outcomes between the two groups was estimated by log-binomial regression and adjusted for the same parameters as defined for the Cox regression analysis. An interaction analysis of recipient age and donor age was performed using unadjusted and adjusted Cox proportional hazard models. All tests were two-sided, and a *P*-value of 0.05 was considered statistically significant. Confidence intervals are reported as per the method of Louis and Zeger [30] All analyses were performed using IBM SPSS Statistics 26 (Armonk, New York) and Stata 15 for Linux (College Station, Texas).

## Results

### Study population

Of the 565 patients, 154 (27.2%) were equal to or older than 50 years (“old recipients”) and 411 (72.8%) were younger than 50 years (“young recipients”) (Table 1). Compared to young recipients, old recipients had similar donor age (median 30 [20–41] vs. 31 [IQR 21–40]; *P* = 0.80), donor BMI (median 23 [IQR: 21–25] vs. 23 [IQR: 22–25]; *P* = 0.93), donor sex (male 63.0% vs. 61.8%; *P* = 0.80), PDRI (median 1.06 [IQR: 0.84–1.41] vs. 1.11 [IQR: 0.87–1.38]; *P* = 0.47), donor creatinine levels (median 0.80 [IQR: 0.63–1.00] vs. 0.80 [IQR: 0.63–1.03]; *P* = 0.60), and donor type (DBD 96.1% vs. 97.8%; *P* = 0.26). However, they had significantly lower donor serum amylase levels prior to organ procurement (median 62 [IQR: 33–120] vs. 79 U/l [IQR: 41–150]; *P* = 0.005).

The median overall age of the cohort was 44 (IQR: 37–51) years. Old recipients had a higher BMI (median 24 [IQR: 22–27] vs. 23 [IQR: 21–25]; *P* = 0.001), more

**Table 1.** Donor and recipient demographics.

Recipient age	Total	< 50 years	≥ 50 years	P-value
Number (%)	465 (100)	411 (72.8)	154 (27.2)	
Donor age, median (IQR)	30 (21, 40)	31 (21, 40)	30 (20, 41)	0.80
Donor BMI, median (IQR)	23 (22, 25)	23 (22, 25)	23 (21, 25)	0.93
Donor male (%)	351 (62.1)	254 (61.8)	97 (63.0)	0.80
Donor creatinine (mg/dl), median (IQR)	0.80 (0.63, 1.00)	0.80 (0.63, 1.00)	0.80 (0.63, 1.03)	0.60
Donor amylase level (U/l), median (IQR)	72 (38, 135)	79 (41, 150)	62 (33, 120)	0.005
PDRI, median (IQR)	1.10 (0.85, 1.39)	1.11 (0.87, 1.38)	1.06 (0.84, 1.41)	0.47
Donor CMV+ (%)	283 (52.6)	200 (51.4)	83 (55.7)	0.37
Donor blood type (%)				0.81
A	224 (39.6)	165 (40.2)	59 (38.3)	
AB	16 (2.8)	10 (2.4)	6 (3.9)	
B	69 (12.2)	50 (12.2)	19 (12.3)	
O	256 (45.3)	186 (45.3)	70 (45.5)	
Donor type (%)				0.26
DBD	550 (97.3)	402 (97.8)	148 (96.1)	
DCD	15 (2.7)	9 (2.2)	6 (3.9)	
Recipient age (years), median (IQR)	44 (37, 51)	40 (35,45)	54 (52,58)	<0.001
50–55			86 (15.2%)	
56–60			52 (9.2%)	
>60			16 (2.8%)	
Recipient BMI, median (IQR)	23 (21, 25)	23 (21, 25)	24 (22, 27)	0.001
Recipient CMV+ (%)	291 (54.3)	194 (49.9)	97 (66.0)	<0.001
Endocrine drainage (%)				0.019
Systemic	529 (94.3)	379 (92.9)	150 (98.0)	
Portal	32 (5.7)	29 (7.1)	3 (2.0)	
Exocrine Drainage (%)				0.79
Enteric	504 (89.5)	367 (89.7)	137 (89.0)	
Vesical	59 (10.4)	42 (10.3)	17 (11.0)	
Type of Pancreas Transplantation (%)				0.022
SPK	491 (86.9)	367 (89.3)	124 (80.5)	
PAK	51 (9.0)	30 (7.3)	21 (13.6)	
PTA	23 (4.1)	14 (3.4)	9 (5.8)	
PRA (%)				0.10
≤20%	345(92.7)	258 (91.5)	87 (96.7)	
>20%	27 (7.3)	24 (8.5)	3 (3.3)	
Recipient male (%)	358 (63.4)	251 (61.1)	107 (69.5)	0.065
Recipient blood type (%)				0.94
A	230 (40.7)	167 (40.6)	63 (40.9)	
AB	28 (5.0)	19 (4.6)	9 (5.8)	
B	76 (13.5)	56 (13.6)	20 (13.0)	
O	231 (40.9)	169 (41.1)	62 (40.3)	
Recipients wait time (months), median (IQR)	7 (3, 12)	6 (3, 12)	8 (3, 17)	0.094
Recipient creatinine level at discharge, median (IQR)	1.20 (0.91, 1.5)	1.20 (0.96, 1.50)	1.20 (0.90, 1.48)	0.34
Transplant year, median (IQR)	2005 (2001, 2011)	2005 (2000, 2010)	2007 (2002, 2012)	0.004
Retransplantation (%)	75 (16.1)	43 (10.5)	32 (20.8)	0.001
Recipient cause of death (%)				0.024
Cardiac	31 (22.9)	23 (26.7)	8 (16.3)	
Infection	37 (27.4)	20 (23.3)	17 (34.7)	
Malignancy	15 (11.1)	8 (9.3)	7 (14.3)	
Cerebrovascular	10 (7.4)	6 (7.0)	4 (8.2)	
Hemorrhage	9 (6.7)	6 (7.0)	3 (6.1)	
Other	33 (24.4)	23 (26.7)	10 (20.4)	

IQR, interquartile range; PDRI, pancreas donor risk index; CMV, cytomegaly virus; DBD, donation after brain death; DCD, donation after cardiac death; BMI, body mass index; SPK, simultaneous pancreas kidney transplantation, PAK, pancreas after kidney transplantation; PTA, pancreas transplant alone; PRA, panel reactive antibodies.

were CMV IgG+ (66.0% vs. 49.9%;  $P < 0.001$ ) and their endocrine drainage was more frequently performed systemically (98.0% vs. 92.9%;  $P = 0.019$ ) compared to young recipients. In contrast to young recipients, old recipients received significantly less frequent an SPK (80.5% vs. 89.3%;  $P = 0.022$ ) were transplanted in a more recent year (median 2007 [IQR: 2002–2012] vs. 2005 [IQR: 2000–2010];  $P = 0.004$ ) and received significantly more often a retransplantation (20.8% vs. 10.5%;  $P = 0.001$ ) (Table 1).

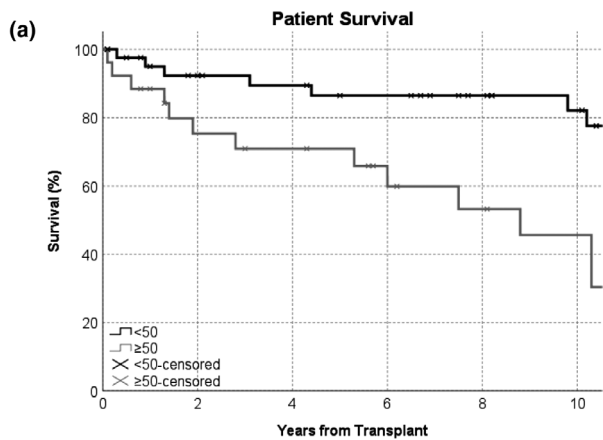
**Patient survival**

Ninety-day-, one-, five-, and ten-year patient survival was 98.5%, 95.4%, 82.8%, and 65.6% in old recipients compared to 99.7%, 98.4%, 93.3%, and 82.0% (log rank  $P < 0.0001$ ) in young recipients (Fig. 1a, Table 2). After adjustment for group differences, patient survival was, with a 2.68-fold increased risk of death, still significantly inferior in old recipients (aHR 2.68 [95%CI 1.73–4.15];  $P < 0.001$ ) (Table 3). A 7% increase in hazard of death was detected per advancing year of recipient age (aHR 1.07 [95%CI 1.04–1.09];  $P < 0.001$ ) (Fig. 1b). Significant

differences in causes of death in old and young patients were recorded ( $P = 0.024$ ) (Table 1). In old recipients, infections (34.7% vs. 23.3%) and malignancy (14.3% vs. 9.3%) were more, and cardiac events (16.3% vs. 26.7%) were less frequent causes of death compared to young recipients. Compared to 50–55-year-old recipients, >55-year-old recipients had a significantly inferior patient survival (log rank  $P = 0.031$ ) (Figure S1).

**All-cause and death-censored pancreas and kidney graft survival**

Old recipients experienced a significantly inferior all-cause pancreas graft survival (acPGS) at ninety days, and one, five, and ten years with 85.6%, 77.2%, 60.3%, and 44.8% survival compared to 90.9%, 86.1%, 73.7%, and 54.1% in young recipients (log rank  $P = 0.011$ ) (Fig. 2a, Table 2). Death-censored pancreas graft survival (dcPGS) was similar between both groups, with 85.6%, 80.6%, 70.2%, and 62.9% survival at ninety days, one, five, and ten years in the old group and 91.1%, 87.3%, 77.8%, and 63.7% survival in the young group (log rank  $P = 0.35$ ) (Fig. 2b, Table 2). Ninety-day, and one-, five-, and ten-year all-cause kidney graft survival (acKGS) survival tended to be inferior in old recipients with 96.7%, 91.5%, 76.3%, and 61.5% compared to 98.9%, 96.4%, 85.4%, and 67.5% in young recipients (log rank  $P = 0.052$ ) (Fig. 2c, Table 2). Similar death-censored kidney graft survival (dcKGS) in old and young recipients was observed at ninety days, one, five, and ten years after transplant with 98.4%, 97.4%, 90.6%, and 83.7%, and 98.9%, 97.8%, 90.2%, and 79.3%, respectively (log rank  $P = 0.53$ ) (Fig. 2d, Table 2). After adjustment for group differences (Table 3), death-censored pancreas and kidney graft survival remained similar between both groups (dcPGS: aHR 1.02 [95%CI 0.68–1.48],  $P > 0.9$ ; dcKGS: aHR 1.11 [95%CI 0.63–1.97],  $P = 0.71$ ), and comparable all-cause pancreas graft survival was seen (acPGS: aHR 1.24 [95%CI 0.91–1.70],  $P = 0.18$ ). All-cause kidney graft survival remained significantly inferior in old recipients (acKGS: aHR 1.70 [95%CI 1.16–2.50],  $P = 0.006$ ).



Number at risk						
	0	2	4	6	8	10
<50	42	33	31	28	23	19
≥50	25	17	15	10	8	6

(b)

	aHR*	95%CI	p-value
Patient			
death	8.63	2.09-35.63	0.003

\* Model adjusted for type of pancreas transplant, recipient BMI, recipient CMV status, endocrine drainage, recipient sex, donor amylase, retransplantation, and transplant year

**Figure 1** (a) Patient survival comparing pancreas recipients < 50 years and ≥ 50 years. A significantly better patient survival was seen in younger (< 50 years) recipients (log rank  $P < 0.0001$ ). (b) Adjusted hazard ratio for death per advanced year of recipient age.

**Postoperative complications**

For most complications, comparable rates were recorded after transplantation in old and young recipients (Table 4). Both groups had a similar rate of bleeding (21.2% vs. 21.0%; aRR 0.91 [95%CI 0.61–1.37];  $P = 0.66$ ), wound infection (10.5% vs. 11.0%; aRR 1.05 [95%CI 0.57–1.95];  $P = 0.87$ ), Clavien–Dindo ≥ 3 complications (47.1% vs. 44.7%; aRR 1.12 [95%CI

**Table 2.** Patient, death-censored, and all-cause pancreas and kidney graft survival comparing recipients < 50 years and recipients ≥ 50 years transplanted between 1996 and 2018 at the Medical University of Innsbruck (Austria) and at the University Hospital Center Groningen (The Netherlands).

Recipient age	< 50 years	≥ 50 years	P-value
Patient survival (%)			<i>P</i> < 0.0001
90 day	99.7	98.5	
1 year	98.4	95.4	
5 year	93.3	82.8	
10 year	82.0	65.6	
Pancreas all-cause graft survival (%)			<i>P</i> = 0.011
90 day	90.9	85.6	
1 year	86.1	77.2	
5 year	73.7	60.3	
10 year	54.1	44.8	
Pancreas death-censored graft survival (%)			<i>P</i> = 0.35
90 day	91.1	85.6	
1 year	87.3	80.6	
5 year	77.8	70.2	
10 year	63.7	62.9	
Kidney all-cause graft survival (%)			<i>P</i> = 0.052
90 day	98.9	96.7	
1 year	96.4	91.5	
5 year	85.4	76.3	
10 year	67.5	61.5	
Kidney death-censored graft survival (%)			<i>P</i> = 0.53
90 day	98.9	98.4	
1 year	97.8	97.4	
5 year	90.2	90.6	
10 year	79.3	83.7	

**Table 3.** Adjusted hazard ratio for patient, death-censored, and all-cause pancreas and kidney graft survival comparing recipients younger and equal to or older than 50 years.

	aHR*	aHR*	95% CI	P-value
Recipient age	≥ 50 years	< 50 years		
Pancreas				
DCGF	Ref.	1.02	0.68–1.48	>0.9
ACGF	Ref.	1.24	0.91–1.70	0.18
Kidney				
DCGF	Ref.	1.11	0.63–1.97	0.71
ACGF	Ref.	1.70	1.16–2.50	0.006
Patient				
Death	Ref.	2.68	1.73–4.15	<0.001

aHR, adjusted hazard ratio; CI, confidence interval; DCGF, death-censored graft failure; ACGF, all-cause graft failure.

\*Model adjusted for type of pancreas transplant, recipient BMI, recipient CMV status, endocrine drainage, recipient sex, donor amylase, retransplantation, and transplant year.

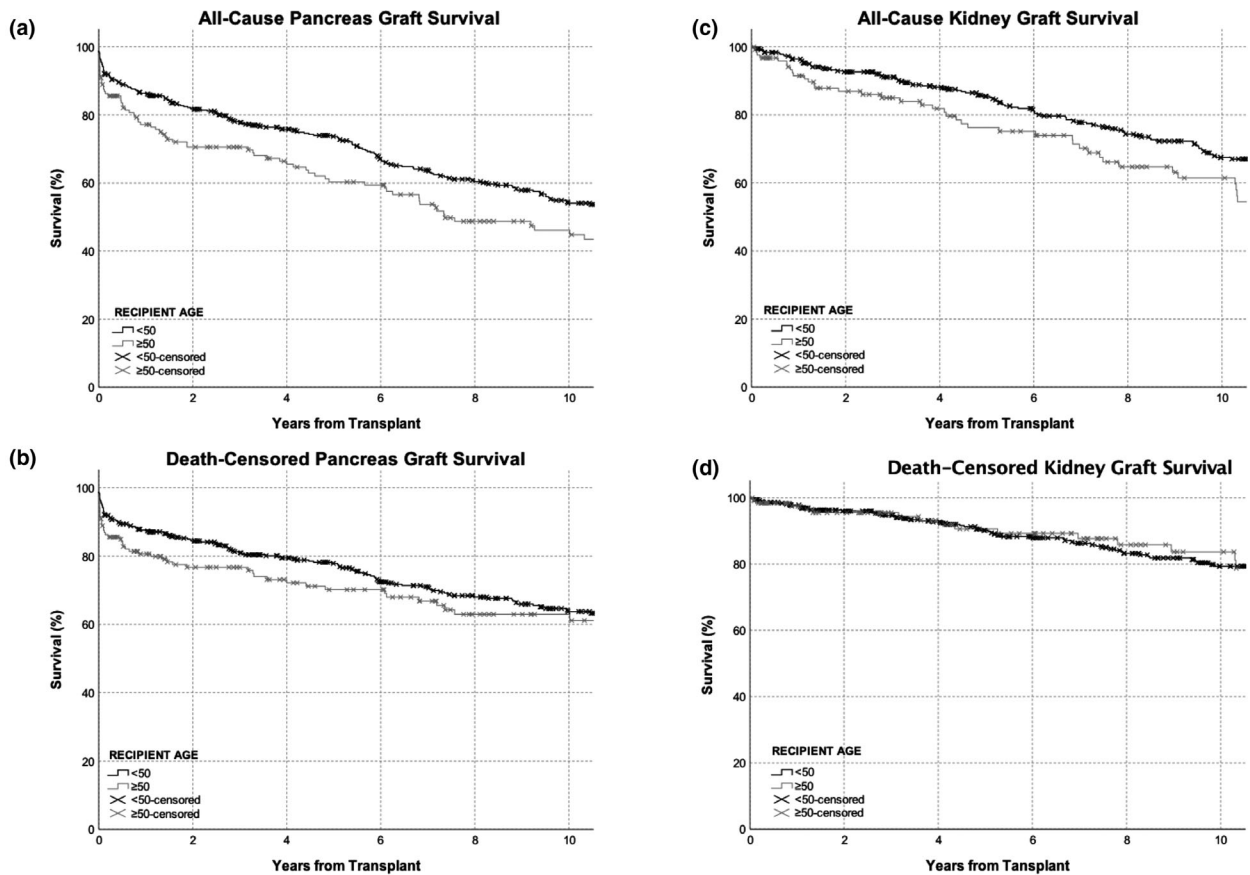
0.85–1.47]; *P* = 0.41), pancreas delayed graft function (50.7% vs. 46.8%; aRR 1.11 [95%CI 0.90–1.37]; *P* = 0.33), kidney delayed graft function (31.0% vs.

26.9%; aRR 0.96 [95%CI 0.68–1.36]; *P* = 0.83), and relative length of stay (median 26 days [IQR: 16–35] vs. 25 days [IQR 18–32]; aRR 0.1 [95%CI –0.001–0.19]; *P* = 0.053). While a similar rate of pancreas graft rejections was seen in both groups (16.5% vs. 14.9%; aRR 0.81 [95%CI 0.49–1.36]; *P* = 0.43), kidney graft rejections were significantly less frequent in old recipients (4.8% vs. 13.7%; aRR 0.41 [95%CI 0.19–0.90]; *P* = 0.026).

### Donor age and patient and graft survival

Patient survival was similar between recipients who received grafts from donors aged ≤ 40 and > 40 years (log rank *P* = 0.64; Fig. 3a). Per year of advancing donor age, a 1.4% increased risk of patient death was detected (aHR 1.014 [95%CI 0.99–1.03], *P* = 0.16) (Fig. 3b). No interaction between recipient and donor age was seen in an unadjusted (*P* = 0.070) and adjusted (*P* = 0.058) cox regression analysis (Table S1). All-cause as well as death-censored pancreas and kidney graft survival were significantly inferior in recipients of old donor grafts compared to young ones (acPGS: log rank





Number at risk							Number at risk						
<50	406	308	255	208	174	137	<50	367	311	266	222	187	149
≥50	153	94	77	66	44	35	≥50	124	93	75	64	45	36

**Figure 2** (a) All-cause and (b) death-censored pancreas graft survival. Death-censored pancreas graft survival was similar between < 50 and ≥ 50-year-old pancreas graft recipients (log rank  $P = 0.35$ ). All-cause pancreas graft survival was significantly better in younger recipients (log rank  $P = 0.011$ ). (c) All-cause and (d) death-censored kidney graft survival. Kidneys from < 50-year-old recipients had similar death-censored kidney graft survival to those from ≥ 50-year-old recipients (log rank  $P = 0.53$ ). All-cause kidney graft survival was significantly superior in recipients < 50 years (log rank  $P = 0.052$ ).

**Table 4.** Relative risk of postoperative complications, delayed graft function, and length of hospital stay in old (≥ 50 years) recipients compared to young (<50 years) recipients.

	aRR*	95%CI	P-value
Rejection pancreas	0.81	0.49–1.36	0.43
Rejection kidney	0.41	0.19–0.90	0.026
Bleeding	0.91	0.61–1.37	0.66
Wound infection	1.05	0.57–1.95	0.87
Clavien Dindo ≥ 3	1.12	0.85–1.47	0.41
Pancreas delayed graft function	1.11	0.9–1.37	0.33
Kidney delayed graft function	0.96	0.68–1.36	0.83
Relative length of stay	0.1	–0.001–0.19	0.053

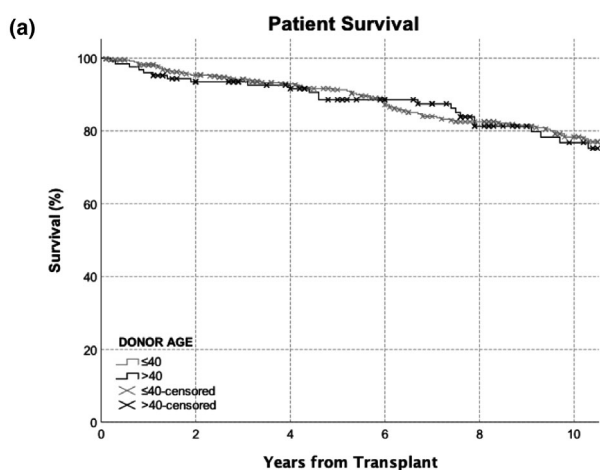
aHR, adjusted hazard ratio; CI, confidence interval.

\*Model adjusted for type of pancreas transplant, recipient BMI, recipient CMV status, endocrine drainage, recipient sex, donor amylase, retransplantation, and transplant year.

$P = 0.038$ , dcPGS: log rank  $P = 0.012$ , acKGS: log rank  $P = 0.007$ , dcKGS: log rank  $P = 0.018$ , Fig. 4a–d).

### Pancreas Graft failure within the first year

Patient survival of recipients that experienced pancreas graft failure within one year post-transplant (PGF < 1yr) was significantly inferior in old recipients (log rank  $P = 0.002$ ) with a one-, five-, and ten-year survival rate of 88.5%, 70.9%, and 45.6%, compared to 95.0%, 86.5%, and 82.2% in young recipients (Fig. 5a). After adjustment for group differences, hazard of death was 8.6-fold increased for old recipients with PGF < 1yr compared to young recipients with PGF < 1yr (aHR 8.63 [96%CI 2.09–35.63],  $P = 0.003$ ; Fig. 5b). Old patients with PGF < 1yr had a similar risk of death compared to old patients without PGF < 1yr (aHR of 2.00 [95%CI 0.88–4.53]  $P = 0.10$ ). Most frequent causes of PGF < 1yr were thrombosis (41.9% vs. 36.0%), infection (32.0% vs. 16.3%), rejection (8% vs. 30.4%), and bleeding (12.0% vs. 9.3%) in old and young recipients with PGF < 1yr, respectively. Pancreas retransplantation did not influence the occurrence of PGF < 1yr ( $P = 0.32$ ).



Number at risk						
≤40	385	333	290	249	218	178
>40	125	106	94	80	62	50

	aHR*	95%CI	p-value
Donor age (per year)			
death	1.014	0.99-1.03	0.16

\* Model adjusted for type of pancreas transplant, recipient BMI, recipient CMV status, endocrine drainage, recipient sex, donor amylase, retransplantation, and transplant year

**Figure 3** (a) Patient survival comparing recipients of donor grafts ≤ 40 and > 40 years. A comparable patient survival was seen in young and old donor grafts (log rank  $P = 0.642$ ). (b) Adjusted hazard ratio for death per advanced year of donor age.

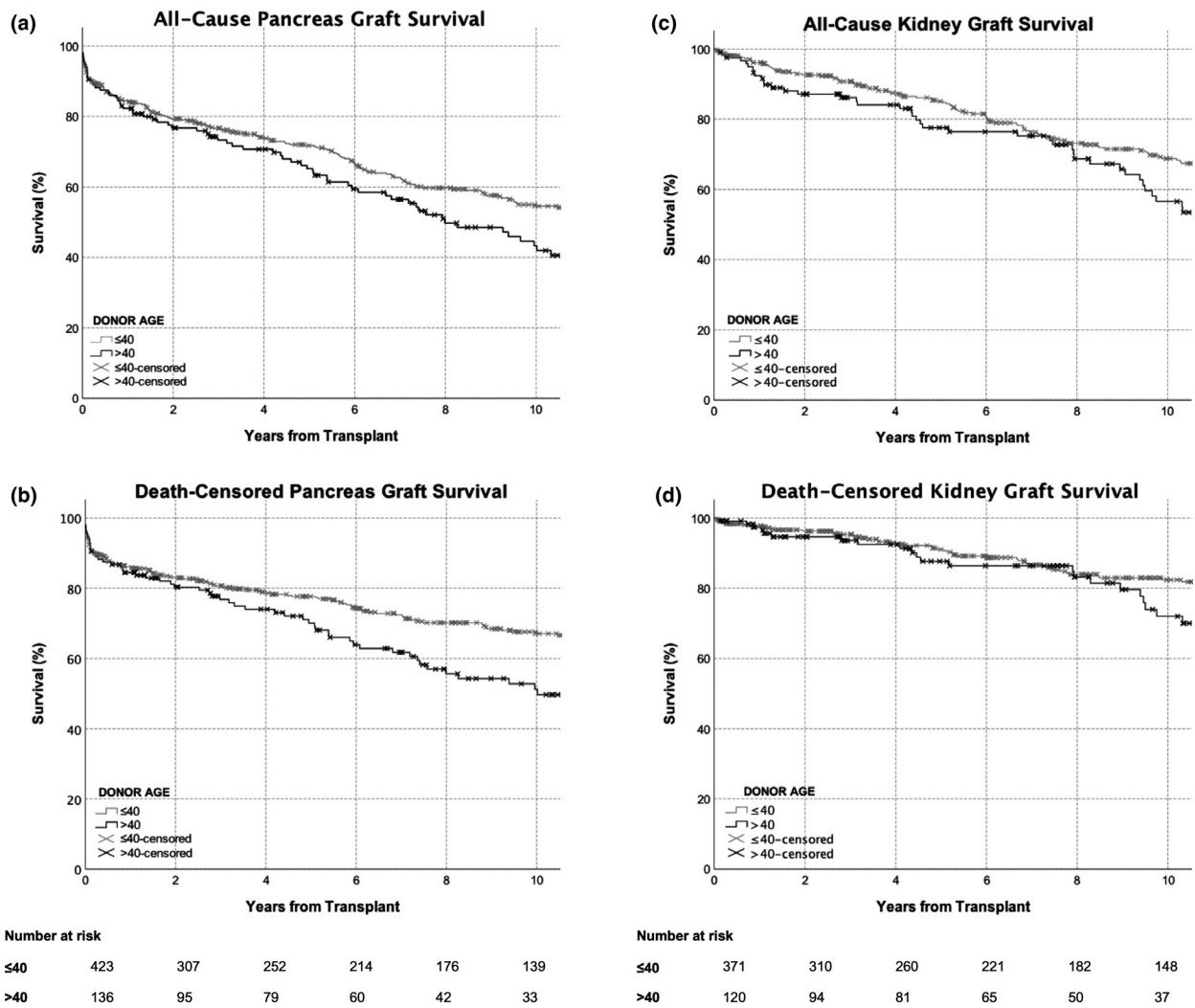
### Discussion

This retrospective two-center study showed that old recipients had a significantly inferior patient survival compared to young recipients. Old recipients in our cohort died more frequently from infection and malignancies but less frequently from cardiovascular events. These results are in line with other published studies [31,32] and might be attributed to our strict pretransplant cardiovascular assessment of pancreas transplant candidates with a low threshold for invasive cardiac evaluation, especially in older patients with a long history of diabetes in order to reduce the incidence of post-transplant cardiac events [33]. Despite significantly increased mortality, old recipients exhibited excellent pancreas and kidney graft survival rates that were equivalent to those of young recipients. Donor age, in our cohort, was not associated with increased risk of patient death. Pancreas graft failure within the first year was, in line with the literature [34] most frequently attributed to graft thrombosis and resulted in an increased hazard of death in old recipients with PGF < 1yr compared to young recipients with PGF < 1yr.

Recipient age and its influence on outcome has already been studied; however, widely diverging results regarding post-transplant outcome were reported. To date, only one German study investigated long-term outcomes in pancreas transplant recipients older than 50 years in the Eurotransplant region. Schenker et al. performed a single-center study [14] and included a total of 398 patients of which 69 (17%) were ≥ 50 years. These authors reported comparable patient, pancreas, and kidney graft survival rates. In line with our report, similar rates of post-transplant complications such as second-look operations (34% vs. 33%), pancreas graft thrombosis (14% vs. 11%), and one-year pancreas rejection rates (35% vs. 31%) were seen. In addition, six single-center studies also reported comparable patient and graft survival in old recipients [2,22,32,35–37].

In contrast, three published studies demonstrated a correlation between recipient age and patient and/or graft survival: A recent single-center study by the Oxford Transplant Centre [31] compared 83 transplants in patients aged 55 to 67 to 444 aged 23 to 54. While no difference in death-censored kidney and pancreas graft survival was detected, the group reported, equivalent to our results, an inferior patient survival in old recipients (5 yrs., 89% vs 77%, 10 yrs. 78% vs 36%;  $P < 0.001$ ). Additionally, their data demonstrated a correlation between graft function at one-year post-transplant and patient survival in SPK recipients; kidney



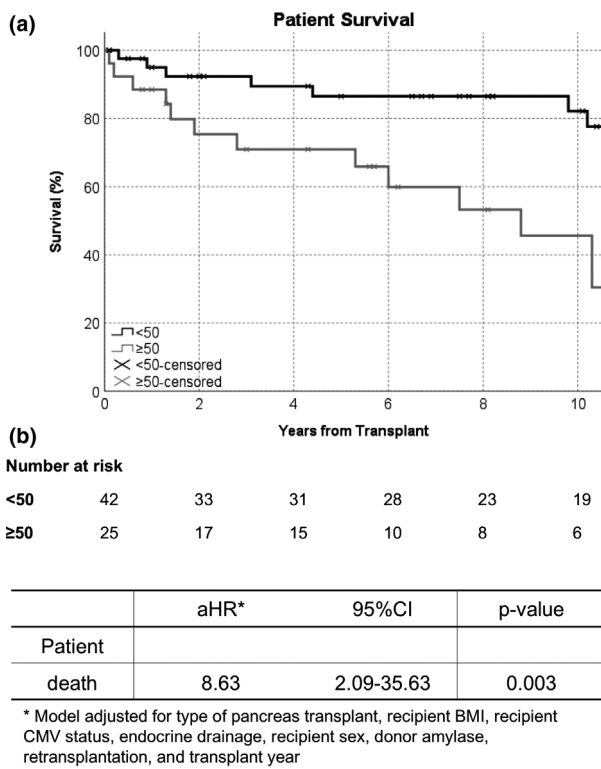


**Figure 4** (a) All-cause and (b) death-censored pancreas as well as (c) all-cause and (d) death-censored kidney graft survival between recipients of ≤ 40- and > 40-year-old donor grafts. Graft survival was significantly superior in recipients of ≤ 40-year-old donor organs compared to > 40-year-old donor grafts (acPGS: log rank  $P = 0.038$ ; dcPGS: log rank  $P = 0.012$ ; acKGS: log rank  $P = 0.007$ ; dcKGS: log rank  $P = 0.018$ ). acPGS, all-cause pancreas graft survival; dcPGS, death-censored pancreas graft survival; acKGS, all-cause kidney graft survival; dcKGS, death-censored kidney graft survival.

graft failure, or failure of both organs were significantly associated with increased mortality compared to pancreas graft failure alone or dual graft function. In our cohort, one-year pancreas graft failure in old recipients was associated with increased post-transplant mortality compared to graft failure in young patients. Most common cause of death in patients with PGF < 1yr was cardiac events and infectious complications. Freise et al. [38] compared ten SPK recipients ≥ 49 years to 114 < 49 years of age and found not only an inferior pancreas (92% vs. 50%) and kidney (92% vs. 70%) graft survival at one year, but moreover, a markedly increased mortality rate of 30% in old compared to 5.3% in young recipients. One of the largest studies on this topic was reported by Siskind et al. [15] This

registry study included data of 20,854 patients captured in the UNOS database between 1996 and 2012 and divided patients into groups based on age categories with a total of 3440 recipients ≥ 50 years and 280 ≥ 60 years of age. Interestingly, graft survival was lowest in 18 to 29 year olds and only long-term (≥ 10 years) graft survival was worse in ≥ 60-year-old recipients. Patient survival, in contrast, significantly dropped with increasing age.

While some reports [39,40] demonstrate equivalent outcome of extended and standard criteria donor pancreas grafts, other studies show an increased hazard of patient death, as well as death-censored pancreas and kidney graft failure, when old (>40 years) grafts were used. Donor age in our cohort did not negatively impact



**Figure 5** (a) Patient survival after pancreas graft loss within one year from transplant in old and young recipients (log rank  $P = 0.002$ ) and (b) corresponding adjusted hazard ratio.

patient survival, but recipients of older donor organs had a significantly impaired graft survival compared to recipients of younger organs. Kayler et al. demonstrated that recipients of old donor organs had a similar adjusted relative mortality risk as patients who remained on the waitlist and subsequently got a SPK of a young donor if transplanted within 604 days waiting time [13] Arenas-Bonilla et al. [23] divided their cohort of 115 SPK recipients into four age categories based on recipient and donor age (cut-off 40 years) and did not find any differences in patient, pancreas or kidney graft survival. Yet, because young to old tended to have a superior survival compared to old-to-old, they concluded that old recipients benefit from younger donor organs.

The current study has several limitations. First, this study is of retrospective nature. Despite being a large cohort from the Eurotransplant region on this topic, the relatively low patient numbers might introduce either type 1 or type 2 bias. As our study includes transplants performed over a wide span of time, differences in patient care, immunosuppression, and operative technique may also skew final results. Based on the split demographics, several confounding variables including donor amylase levels, recipient BMI, recipient CMV

status, type of transplantation, and transplant year were identified that also may have biased reported long-term outcomes. We also included patients after retransplantation and PAK/PTA transplants in this study; however, sensitivity analysis (Table S2) revealed similar results compared to SPK recipients undergoing a first transplantation. Lastly, this study is not corrected for age-related variation in mortality which could bias observed differences.

### Conclusion

Under the current donor selection criteria, an extension of donor age limits seems to be justifiable without compromising graft survival. Old recipients demonstrate an increased mortality that most likely correlates with a generally higher frailty because of advanced secondary diabetic complications. Despite inferior survival compared to young recipients, old recipients should be considered for pancreas transplantation as excellent graft survival can be expected that is known to lead to more favorable outcome in these patients [2,32] Finally, the association between PGF < 1yr and increased mortality in old compared to young recipients underlines the beneficial effect of glycemic control in this more fragile population.

### Authorship

FM: performed data collection, performed statistical analysis, conceptualized, wrote and revised the manuscript. ML: performed data collection and revised the manuscript. YY and ABM: performed statistical analysis and wrote the manuscript. FJK, SB and CB: performed data collection, wrote and revised the manuscript. AW, SS, RAP and CM: conceptualized and revised the manuscript.

### Conflict of interest

The authors declare no conflicts of interest.

### Funding

None.

### Acknowledgments

The authors thank Prof. Hanno Ulmer from the Department of Medical Statistics, Informatics and Health Economics at the Medical University of Innsbruck, Austria, for his advice on interaction analyses.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1** Patient survival of recipients aged < 50, 50-55, and > 55 years.

**Table S1** Interaction analysis of recipient and donor age.

**Table S2** Sensitivity analysis.

## REFERENCES

- Reddy KS, Stablein D, Taranto S, *et al.* Long-term survival following simultaneous kidney-pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. *Am J Kidney Dis* 2003; **41**: 464.
- Scalea JR, Redfield RR, Arpali E, *et al.* Pancreas transplantation in older patients is safe, but patient selection is paramount. *Transpl Int* 2016; **29**: 810.
- Mohan P, Safi K, Little DM, *et al.* Improved patient survival in recipients of simultaneous pancreas-kidney transplant compared with kidney transplant alone in patients with type 1 diabetes mellitus and end-stage renal disease. *Br J Surg* 2003; **90**: 1137.
- Esmeijer K, Hoogeveen EK, Van Den Boog PJM, *et al.* Superior long-term survival for simultaneous pancreas-kidney transplantation as renal replacement therapy: 30-year follow-up of a nationwide cohort. *Diabetes Care* 2020; **43**: 321.
- 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 Transpl* 2014; **28**: 990.
- Giwa S, Lewis JK, Alvarez L, *et al.* The promise of organ and tissue preservation to transform medicine HHS Public Access Author manuscript. *Nat Biotechnol* 2017; **35**: 530.
- Ward A, Klassen DK, Franz KM, Giwa S, Lewis JK. Social, economic, and policy implications of organ preservation advances. *Curr Opin Organ Transplant* 2018; **23**: 336.
- Annual Reports | Eurotransplant. Available from: [https://www.eurotransplant.org/cms/index.php?page=annual\\_reports](https://www.eurotransplant.org/cms/index.php?page=annual_reports).
- Boggi U, Del Chiaro M, Vistoli F, *et al.* Pancreas transplantation from marginal donors. *Transplant Proc* 2004; **36**: 566.
- Troppmann C, Gruessner AC, Dunn DL, Sutherland DER, Gruessner RWG. Surgical Complications Requiring Early Relaparotomy After Pancreas Transplantation. *Ann Surg* 1998; **227**: 255.
- Humar A, Ramcharan T, Kandaswamy R, Gruessner RWG, Gruessner AC, Sutherland DER. Technical failures after pancreas transplants: why grafts fail and the risk factors—a multivariate analysis. *Transplantation* 2004; **78**: 1188.
- Salvalaggio PR, Schnitzler MA, Abbott KC, *et al.* Patient and Graft Survival Implications of Simultaneous Pancreas Kidney Transplantation From Old Donors. *Am J Transplant* 2007; **7**: 1561.
- Kayler LK, Wen X, Zachariah M, Casey M, Schold J, Magliocca J. Outcomes and survival analysis of old-to-old simultaneous pancreas and kidney transplantation. *Transpl Int* 2013; **26**: 963.
- Schenker P, Vonend O, Krüger B, *et al.* Long-term results of pancreas transplantation in patients older than 50 years. *Transpl Int* 2011; **24**: 136.
- 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.
- Chapter 7 ET Pancreas Allocation System (EPAS). Available from: <https://www.eurotransplant.org/wp-content/uploads/2020/01/H7-EPAS.pdf>.
- Bösmüller C, Messner F, Margreiter C, *et al.* Outcome in Pancreas Grafts After BK Virus Viremia in Simultaneous Pancreas-Kidney Transplants. *Transplant Direct* 2017; **3**: e154.
- Messner F, Bösmüller C, Oberhuber R, *et al.* Late recurrent bleeding episodes from duodenojejunostomy after pancreas transplantation. *Clin Transplant* 2018; **32**: e13350.
- Messner F, Etra JW, Haugen CE, *et al.* Sex matching does not impact the outcome after simultaneous pancreas-kidney transplantation. *Clin Transplant* 2019; **33**: e13717.
- Gasteiger S, Cardini B, Göbel G, *et al.* Outcomes of pancreas retransplantation in patients with pancreas graft failure. *Br J Surg* 2018; **105**: 1816.
- Bösmüller C, Sieb M, Öllinger R, *et al.* Tacrolimus monotherapy following alemtuzumab induction in combined kidney-pancreas transplantation: Results of a prospective randomized trial. *Ann Transplant* 2012; **17**: 45.
- 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.
- Arenas-Bonilla AJ, Campos-Hernández JP, Carrasco-Valiente J, *et al.* Influence of Donor and Recipient Ages in Survival of Simultaneous Pancreas-Kidney Transplantation. *Transplant Proc* 2016; **48**: 3033.
- Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. *Ann Surg* 2004; **240**: 205.
- Clavien PA, Barkun J, de Oliveira ML, *et al.* The Clavien-Dindo Classification of Surgical Complications. *Ann Surg* 2009; **250**: 187.
- Mallon DH, Summers DM, Bradley JA, Pettigrew GJ. Defining Delayed Graft Function after Renal Transplantation. *Transplantation* 2013; **96**: 885.
- Koning O, van Bockel J, van der Woude F, Persijn G, Hermans J, Ploeg R. Risk factors for delayed graft function in University of Wisconsin solution preserved kidneys from multiorgan donors. European Multi-center Study Group on Organ Preservation. *Transpl Proc* 1995; **27**: 752.
- Axelrod DA, Sung RS, Meyer KH, Axelrod DA. Systematic Evaluation of Pancreas Allograft Quality, Outcomes and Geographic Variation in Utilization. *Am J Transplant* 2010; **10**: 837.
- Kandaswamy R, Stock PG, Gustafson SK, *et al.* OPTN/SRTR. Annual Data Report. *Pancreas* 2018; **2018**: 1.
- Louis TA, Zeger SL. Effective communication of standard errors and confidence intervals. *Biostatistics* 2008; **10**: 1.
- Mittal S, Smilevska R, Franklin R, *et al.* An analysis of the association

- between older recipient age and outcomes after whole-organ pancreas transplantation – a single-centre, retrospective study. *Transpl Int* 2020; **33**(5): 529–535.
32. Montagud-Marrahi E, Molina-Andújar A, Pané A, *et al.* Outcomes of pancreas transplantation in older diabetic patients. *BMJ Open Diabetes Res Care* 2020; **8**: 10.
  33. Eschertzhuber S, Hohlrieder M, Boesmueller C, *et al.* Incidence of coronary heart disease and cardiac events in patients undergoing kidney and pancreatic transplantation. In: *Transplantation Proceedings*. Elsevier USA; 2005. p. 1297–300.
  34. Finger EB, Radosevich DM, Dunn TB, *et al.* A Composite Risk Model for Predicting Technical Failure in Pancreas Transplantation. *Am J Transplant* 2013; **13**: 1840.
  35. Laurence JM, Marquez MA, Seal JB, *et al.* The Effect of Recipient Age on Outcome After Pancreas Transplantation. *Transplantation* 2015; **99**: e13.
  36. Afaneh C, Rich BS, Aull MJ, Hartono C, Leaser DB, Kapur S. Pancreas Transplantation: Does Age Increase Morbidity? *J Transplant* 2011; **2011**: 1.
  37. Shah AP, Mangus RS, Powelson JA, *et al.* Impact of recipient age on whole organ pancreas transplantation. *Clin Transplant* 2013; **27**: E49.
  38. Freise CE, Stock PG, Melzer JS. Increased Morbidity and Mortality of Simultaneous Pancreas-Renal Transplantation in Patients Over 49 Years of Age. *Transplant Proc* 1998; **30**: 292.
  39. Proneth A, Schnitzbauer AA, Schenker P, *et al.* Extended Pancreas Donor Program - The EXPAND Study: A Prospective Multicenter Trial Testing the Use of Pancreas Donors Older Than 50 Years. *Transplantation* 2018; **102**: 1330.
  40. Ito T, Kenmochi T, Nishikawa T, *et al.* A Novel Screening Test for Detecting Graft Thrombosis After Pancreatic Transplantation Using Contrast-enhanced Ultrasonography With Sonazoid. *Transplant Proc* 2014; **46**: 1917.