ORIGINAL ARTICLE

Are the outcomes of Japanese pancreas transplantation utilizing extended-criteria donors acceptable? A propensity score matching analysis for donors <50 or ≥50 years old

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SUMMARY

In Japan, about 30% of pancreatic transplant donors are ≥50 years old, making them "extended-criteria donors (ECDs)." We analyzed 361 cases of transplantation involving donors from the Japanese pancreas transplantation registry to evaluate the acceptability of ECDs. The patient survival rates at 1, 5, and 10 years after transplantation were 96.6%, 94.9%, and 88.3%, respectively. The survival rates of pancreas and kidney grafts at 1, 5, and 10 years were 85.3%, 74.8%, and 70.6%, and 94.2%, 90.9%, and 80.9%, respectively. Multivariate analysis revealed that no particular donor factors significantly influenced the pancreatic graft survival. Patients were divided into 2 groups: donors ≥50 years old (older group) and those <50 years old (younger group). After propensity score matching, the overall pancreatic graft survival at 1, 5, and 10 years after transplantation in the older group was 82.8%, 71.8%, and 69.5%, respectively, which was almost the same as in the younger group (84.9%, 70.2%, and 67.4%, respectively). No donor factors markedly influenced the pancreatic graft survival, and the outcomes of pancreas transplantation from ECDs ≥50 years old were comparable to those from younger donors.

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Introduction

In Japan, the Revised law of Organ Transplant was enacted in 2010, resulting in a roughly fivefold increase in the number of brain-dead donors [1–3]. Before the law was amended, donors had to express in writing their intention to donate their own organs before brain death to allow donation after brain death (DBD); however, since the amendment, DBD is now possible with only the consent of the family. As a result, around 30–40 cases of pancreas transplantation are now performed annually [2,4]. However, some 200 patients remain on the waiting list, with a mean waiting period of about 3.5 years [4]. The shortage of viable pancreata for transplantation thus remains an issue, despite the revision of the law. Pancreas transplantation, especially simultaneous pancreas–kidney transplant (SPK), is promising for improving not only the quality of life of patients with type 1 diabetes but also their survival prognosis [5]. For this reason, in

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Japan, we now consider pancreas donation from so-called extended-criteria donors (ECDs).

Regarding the donor age, in 194 (34.2%) of the 568 donations from brain-dead patients made by the end of 2018, the donor age was ≥50 years, according to the Japan Organ Transplant Network homepage (https://www.jotnw.or.jp/). In various organ transplant procedures, the donor age and transplantation performance are closely related [6–9]. Regarding pancreas transplantation, Troppmann *et al.* [10,11] revealed that the utilization of pancreata from donors who died of cardiocerebrovascular disease or older donors (especially those ≥45 years old) carried an increased risk of graft thrombosis in a retrospective cohort analysis of 438 cases of pancreas transplantation. Kapur *et al.* [12,13] defined marginal donor criteria as a donor age ≥45 years or hemodynamic instability [requiring high-dose dopamine (>10 μg/kg/min) or ≥2 vasopressors] and revealed no significant difference in the pancreatic graft survival between cases of marginal and non-marginal donors in their prospective study of 137 cases of pancreas transplantation. However, the US data from UNOS showed that the proportion of pancreatic transplant donors ≥45 years old decreased from only 6.3% during 2005–2009 to 3.2% during 2010–2014 [14], while in Japan, more than 40% of pancreatic transplant donors were ≥45 years old, and about 30% of them were ≥50 years old in that same period [4].

These previous reports prompt the following clinical questions for pancreas transplantation: Should donors ≥50 years old really be categorized as ECDs for pancreas transplantation? What donor factors affect the pancreatic graft survival? Are the outcomes of Japanese pancreas transplantation using ECDs, such as those ≥50 years old, acceptable?

We herein report our analysis of the Japanese pancreas transplantation registry to evaluate the outcomes of pancreas transplantation and the acceptability of ECDs for pancreas transplantation using a propensity-matched score analysis.

Methods

Enrolled patients

All recipient candidates were registered with the Japan Organ Transplant Network, and recipient selection was performed based on the following conditions: The blood type must be compatible, and the direct cross-match test must be negative. Recipients on the waiting list were prioritized for selection as follows: (i) The order of the recipients was arranged based on the number of human leukocyte antigen (HLA) mismatches, with priority given to cases involving fewer HLA mismatches; (ii) cases were then prioritized in the order of SPK, pancreas transplantation after kidney transplantation (PAK), and pancreas transplantation alone (PTA); (iii) priority was then given according to the length of the waiting period, with cases involving a longer waiting period prioritized over those with a shorter wait; and (iv) cases were then prioritized in ascending order according to the estimated transport time, with priority given to cases with a shorter estimated transport time.

To evaluate the acceptability of ECDs for pancreas transplantation, the outcomes of the 361 total cases of pancreas transplantation (and their donor information) managed from January 2000 to December 2018 that were registered in the Japan Society for Pancreas and Islet Transplantation were examined. The enrolled cases of pancreas transplantation were performed at 18 centers in Japan.

Study design

The analysis of data of the Japanese pancreas transplantation registry was performed using univariate and multivariate analyses of Cox proportional hazard regression to reveal the impact of risk factors on the pancreatic graft survival. A propensity score-matched analysis was also performed to compare the groups of donors <50 and ≥50 years old. The Kaplan–Meier curves were used to display the patient prognosis and pancreatic and kidney graft survival. Pancreatic graft loss was defined as a C-peptide immunoreactivity (CPR) <0.3 ng/ml and renal graft loss as dialysis reintroduction.

Statistical analyses

All statistical analyses were performed using the EZR software program on R commander version 1.40, which was freely distributed on the homepage of Saitama Medical Center Jichi Medical University [15]. Categorical variables were analyzed with a chi-square test, continuous variables were analyzed using Student's *t*-test, and the log-rank test was used to analyze the graft survival. The propensity score was determined using logistic regression in order to reduce the effect of selection bias with 1:1 paired matching based on each patient's propensity score using a 0.5-caliper width [16]. Donor variables included in the propensity score model were sex, body mass index (BMI), cause of death, episodes of cardiopulmonary arrest, hemodynamic instability [requiring high-dose

Table 1. Donor background characteristics and an analysis of the impact on the pancreatic graft survival using Cox proportional hazard regression.

		Cox proportional hazard regression (univariate analysis)			Cox proportional hazard regression (multivariate analysis)		
	Mean (SD) or *n* (%)	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (years)	40.8 (13.9)	1.012	0.996–1.029	0.141	1.002	0.982–1.023	0.828
Gender (male)							
Male	205 (56.8)	1.391	0.892–2.169	0.145	1.411	0.877–2.270	0.156
Female	156 (43.2)						
BMI (kg/m^2)	21.9 (3.5)	1.007	0.948–1.070	0.816	0.986	0.922–1.054	0.681
Cause of death							
CVA	183 (50.7)	0.724	0.469–1.118	0.145	0.732	0.429–1.250	0.253
Others	178 (49.3)						
Episode of CPA							
Yes	174 (48.2)	0.846	0.549–1.304	0.450	0.832	0.518–1.337	0.447
None	187 (51.8)						
Hemodynamically stability							
Stable	249 (69.0)	0.869	0.544–1.386	0.555	0.889	0.548–1.440	0.631
Unstable	112 (31.0)						
HbA1c (%)	5.4 (0.4)	1.714	1.018–2.886	**0.043**	1.636	0.944–2.835	0.079
Number of mismatch HLA-A							
0	153 (42.4)	1.269	0.939–1.714	0.121			
1	164 (45.4)						
2	44 (12.2)						
Number of mismatch HLA-B							
0	39 (10.8)	1.081	0.773–1.513	0.649			
1	185 (51.2)						
2	137 (38.0)						
Number of mismatch HLA class I							
0	16 (4.4)	1.165	0.940–1.444	0.164			
1	102 (28.3)						
2	147 (40.7)						
3	69 (19.1)						
4	27 (7.5)						
Number of mismatch HLA-DR							
0	135 (37.4)	1.057	0.727–1.536	0.772			
1	205 (56.8)						
2	21 (5.8)						
Total number of mismatch HLA							
0	10 (2.8)	1.136	0.943–1.368	0.181			
1	39 (10.8)						
2	122 (33.8)						
3	109 (30.2)						
4	57 (15.8)						
5	24 (6.6)						
Cold ischemic time (min)	736.6 (170.2)	1.000	0.999–1.001	0.889	1.000	0.999–1.001	0.717
Marginal factor (Kapur's criteria)							
With	219 (60.7)	0.870	0.55–1.366	0.546			
Without	142 (39.3)						
Marginal factor (Troppmann's criteria)							
With	228 (63.2)	0.707	0.443–1.130	0.147			
Without	133 (36.8)						

BMI, body mass index; CPA, cardiopulmonary arrest; CVA, cerebrovascular accident; HLA, human leukocyte antigen. P values <0.05 were considered to indicate the statistical significance and indicated with the bold values.

Transplant International 2020; 33: 1046–1060

dopamine (>10 μg/kg/min) or ≥2 vasopressors], and HbA1c. Recipient background factors were the age, sex, BMI, period of diabetes and hemodialysis, waiting period, and preoperative HbA1c. Operation factors were the type of operation and cold ischemic time (CIT). Immunologic factors were the number of HLA mismatch, induction of T-cell-depleting antibody, and type of calcineurin inhibitor (CNI). *P* values <0.05 were considered to indicate statistical significance.

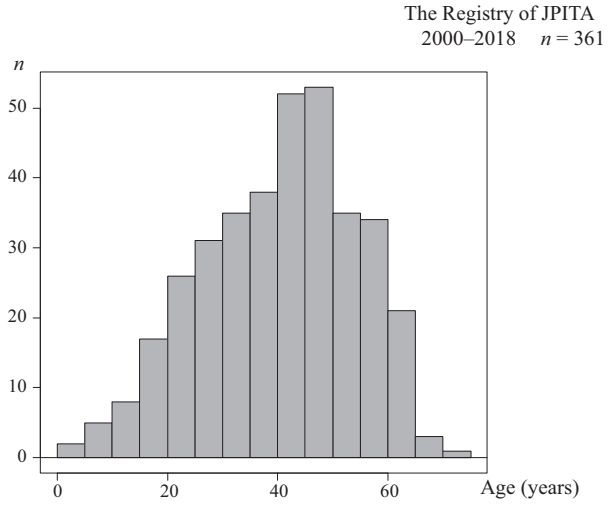


Figure 1 The age distribution of donors in Japan. Among Japanese pancreas transplant donors, 103 (28.5%) were ≥50 years old, and 25 (6.9%) were ≥60 ears old.

Ethical aspects

Before registration, all subjects gave their informed consent to the committee of the Japanese pancreas transplantation registry, and information on the opt-out procedure was published on the Fujita Health University website (https://www.fujita-hu.ac.jp/). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Fujita Health University (HM18-499).

Results

Donors' background characteristics

Table 1 shows the donor background characteristics. The mean donor age was 40.8 ± 13.9 years, with the youngest donor being 5 years old and the oldest 73 years old. As shown in the age distribution of Fig. 1,

Table 2. Recipient background characteristics.

n	Overall 362	SPK 298	PAK 48	PTA 15	*P* value
Age (years)	44.1 (7.8)	44.6 (8.0)	42.5 (5.4)	39.3 (10.0)	0.013
Sex					
Male	136 (37.7)	111 (37.2)	19 (39.6)	6 (40.0)	0.936
Female	225 (62.3)	187 (62.8)	29 (60.4)	9 (60.0)	
BMI (kg/m^2)	20.8 (2.7)	20.9 (2.7)	20.4 (2.9)	22.0 (3.3)	0.124
Preoperative HbA1c (%)	7.64 (1.52)	7.90 (1.67)	7.53 (1.42)	9.11 (2.09)	<0.001
Preoperative period of DM (years)	28.2 (7.9)	28.8 (7.8)	28.0 (6.0)	16.5 (6.4)	<0.001
Preoperative period of HD (days)	2323.8 (2001.8)	2704.7 (1908.5)	684.90 (1513.7)	N/A	<0.001
Waiting period (days)	1289.9 (1159.2)	1348.4 (1166.5)	1124.1 (1154.0)	665.9 (798.9)	0.047
Cold ischemic time (min)	736.64 (170.2)	752.4 (170.2)	650.0 (134.0)	700.1 (195.3)	<0.001
Exocrine drainage method					
Enteric	320 (88.6)	267 (89.6)	38 (79.2)	15 (100.0)	0.039
Bladder	41 (11.4)	31 (10.4)	10 (20.8)	0 (0.0)	
Graft portal vein extension					
None	277 (76.7)	228 (76.5)	38 (79.2)	11 (73.3)	0.876
Yes	84 (23.3)	70 (23.5)	10 (20.8)	4 (26.7)	
Induction of T-cell-depleting antibody					
None	275 (76.2)	242 (81.2)	24 (50.0)	9 (60.0)	<0.001
Yes	86 (23.8)	56 (18.8)	24 (50.0)	6 (40.0)	
Type of CNI					
Tacrolimus	356 (98.6)	295 (99.0)	46 (95.8)	15 (100.0)	0.198
Cyclosporine	5 (1.4)	3 (1.0)	2 (4.2)	0 (0.0)	

BMI, body mass index; CNI, calcineurin inhibitor; DM, diabetes mellitus; HD, hemodialysis; PAK, pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

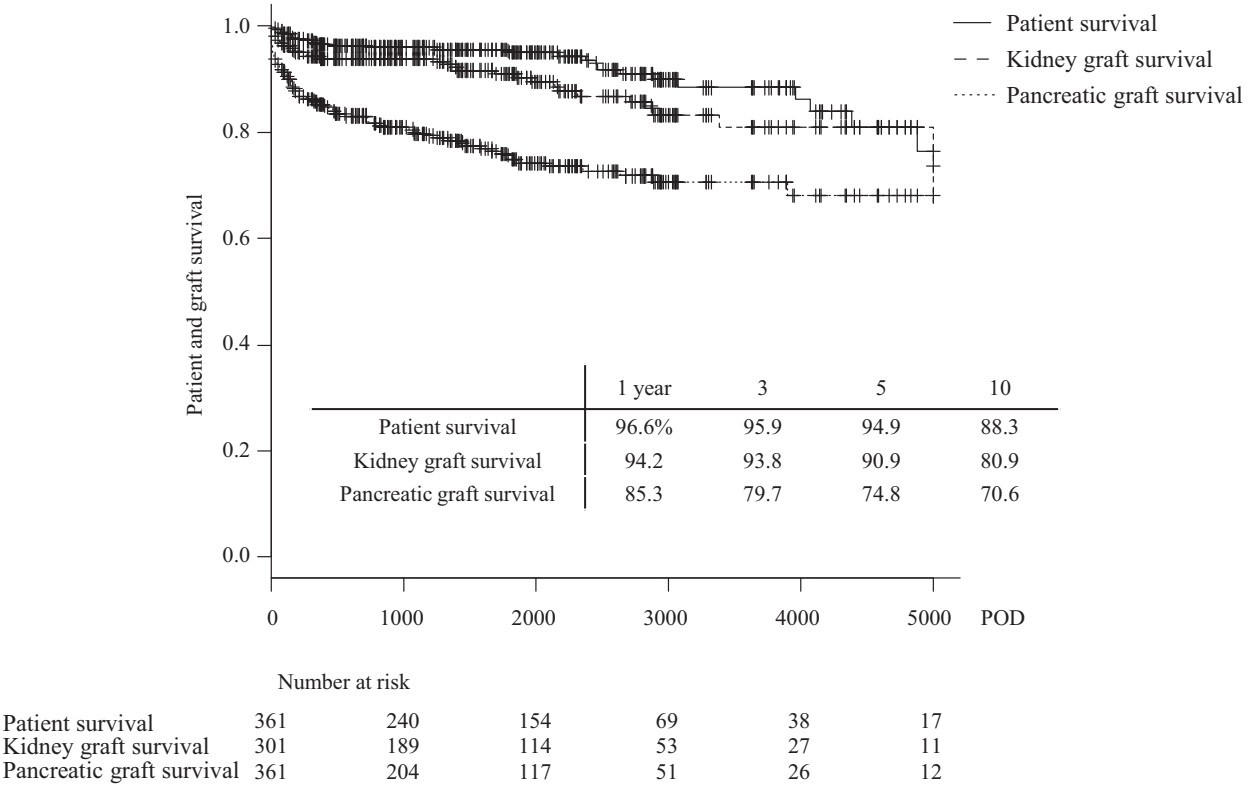


Figure 2 The patient and graft survival after pancreas transplantation in Japan. The patient survival rates at 1, 5, and 10 years after transplantation were 96.6%, 94.9%, and 88.3%, respectively. In addition, the survival rates of pancreas and kidney grafts at 1, 5, and 10 years were 85.3%, 74.8%, and 70.6%, and 94.2%, 90.9%, and 80.9%, respectively.

103 donors (28.5%) were ≥50 years old, and 25 (6.9%) were ≥60 years old. The gender ratio was about 4:3, and the mean BMI was 21.9 ± 3.5 kg/m^2. Among 361 cases, 183 cases (50.7%) of brain death were caused by cerebrovascular accidents, and 174 cases (48.2%) had episodes of cardiopulmonary arrest during the course. A total of 112 cases (30.0%) were hemodynamically unstable at the time of procurement. The mean HbA1c of donors was 5.4% ± 0.4%, with values of ≥7% reported in 1 case and ≥6% in 22 cases (6.1%). The mean total ischemia time was 736.6 ± 170.2 min, with a minimum of 170 min and a maximum of 1383 min. As a result, 219 donors (60.7%) exceeded Kapur's criteria, and 228 (63.2%) exceeded Troppmann's criteria.

Recipients' background characteristics

Recipients' background characteristics are shown in Table 2. The mean age at transplantation was 44.1 years overall, 44.6 years for SPK, 42.5 years for PAK, and 39.3 years for PTA, with the age of patients undergoing PTA, PAK, and SPK decreasing significantly in this order. The mean preoperative period of diabetes was 28.2 years overall, and the mean preoperative dialysis period in SPK patients was 2704.7 days. The mean preoperative period of diabetes undergoing SPK, PAK, and PTA increased significantly in this order. The mean waiting period was 1289.9 days overall and tended to be significantly longer in SPK, PAK, and PTA, sequentially. The mean HbA1c level at transplantation was 7.64% overall and 9.11% in the PTA group, which was much higher than in the SPK and PAK groups.

The patient survival and pancreas and kidney graft survival

The patient survival and pancreatic and renal graft engraftment rates are shown in Fig. 2. The patient survival rates at 1, 5, and 10 years after transplantation were 96.6%, 94.9%, and 88.3%, respectively. In addition, the survival rates of pancreas and kidney grafts at 1, 5, and 10 years were 85.3%, 74.8%, and 70.6%, and 94.2%, 90.9%, and 80.9%, respectively.

To reveal the influence of donor factors on the pancreatic graft survival, a Cox proportional hazard regression model was used (Table 1). A univariate analysis

Table 3. Donor background characteristics and an analysis of the impact on the pancreatic graft survival in SPK using Cox proportional hazard regression.

		Cox proportional hazard regression (univariate analysis)			Cox proportional hazard regression (multivariate analysis)		
	Mean (SD) or *n* (%)	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (years)	40.8 (13.9)	1.014	0.994–1.035	0.177	1.007	0.982–1.032	0.598
Gender (male)							
Male	163 (54.7)	1.329	0.765–2.307	0.313	1.311	0.730–2.354	0.364
Female	135 (45.3)						
BMI (kg/m^2)	22.0 (3.5)	0.999	0.927–1.076	0.978	0.986	0.909–1.070	0.742
Cause of death							
CVA	149 (50.0)	0.651	0.375–1.130	0.127	0.712	0.367–1.383	0.316
Others	149 (50.0)						
Episode of CPA							
Yes	139 (46.6)	0.658	0.375–1.155	0.145	0.742	0.406–1.355	0.331
None	159 (53.4)						
Hemodynamically stability							
Stable	203 (68.1)	1.127	0.642–1.977	0.677	1.078	0.602–1.929	0.801
Unstable	95 (31.9)						
HbA1c (%)	5.43 (0.36)	1.184	0.550–2.549	0.666	1.070	0.485–2.361	0.866
Number of mismatch HLA-A							
0	136 (45.6)	0.933	0.627–1.388	0.732			
1	128 (43.0)						
2	34 (11.4)						
Number of mismatch HLA-B							
0	34 (11.4)	0.933	0.613–1.419	0.745			
1	160 (53.7)						
2	104 (34.9)						
Number of mismatch HLA class I							
0	14 (4.7)	0.935	0.704–1.243	0.645			
1	91 (30.5)						
2	128 (43.0)						
3	43 (14.4)						
4	22 (7.4)						
Number of mismatch HLA-DR							
0	115 (38.6)	0.865	0.512–1.461	0.587			
1	180 (60.4)						
2	3 (1.0)						
Total number of mismatch HLA							
0	9 (3.0)	0.916	0.711–1.181	0.499			
1	33 (11.1)						
2	112 (37.6)						
3	94 (31.5)						
4	39 (13.1)						
5	11 (3.7)						
Cold ischemic time (min)	752.4 (170.2)	1.001	0.999–1.002	0.230	1.001	0.999–1.002	0.301
Marginal factor (Kapur's criteria)							
With	182 (61.1)	0.591	0.320–1.089	0.092			
Without	116 (38.9)						
Marginal factor (Troppmann's criteria)							
With	187 (62.8)	0.649	0.356–1.179	0.556			
Without	111 (37.2)						

BMI, body mass index; CPA, cardiopulmonary arrest; CVA, cerebrovascular accident; HLA, human leukocyte antigen

Table 4. A comparison of the donor background characteristics between donors <50 and ≥50 years old.

	Prematching			Postmatching		
Group	<50 years old	≥50 years old		<50 years old	≥50 years old	
n	258	103		77	77	
	Mean (SD) or *n* (%)		*P* value	Mean (SD) or *n* (%)		*P* value
Donor factors						
Age (years)	34.4 (11.0)	56.7 (4.8)		39.2 (8.5)	56.8 (4.9)	
Gender						
Male	161 (62.4)	44 (42.7)	**0.001**	39 (50.6)	41 (53.2)	0.872
Female	97 (37.6)	59 (57.3)		38 (49.4)	36 (46.8)	
BMI (kg/m^2)	21.9 (3.7)	21.9 (2.9)	0.951	22.3 (3.83)	22.1 (2.8)	0.736
DBD/DCD						
DBD	255 (98.8)	103 (100.0)	0.561	77 (100.0)	77 (100.0)	1.000
DCD	3 (1.2)	0 (0.0)		0 (0.0)	0 (0.0)	
Cause of death						
CVA	105 (40.7)	78 (75.7)	**<0.001**	51 (66.2)	53 (68.8)	0.863
Others	153 (59.3)	25 (24.3)		26 (33.8)	24 (31.2)	
Episode of CPA						
Yes	135 (52.3)	39 (37.9)	**0.014**	40 (51.9)	35 (45.5)	0.519
None	123 (47.7)	64 (62.1)		37 (48.1)	42 (54.5)	
Hemodynamically stability						
Stable	178 (69.0)	71 (68.9)	1.000	53 (68.8)	53 (68.8)	1.000
Unstable	80 (31.0)	32 (31.1)		24 (31.2)	24 (31.2)	
HbA1c (%)	5.37 (0.34)	5.58 (0.44)	**<0.001**	5.53 (0.39)	5.54 (0.46)	0.954
Recipient factors						
Age	44.0 (7.9)	44.5 (7.8)	0.551	43.6 (8.4)	44.2 (7.8)	0.627
Gender						
Male	92 (35.7)	44 (42.7)	0.23	24 (31.2)	30 (39.0)	0.399
Female	166 (64.3)	59 (57.3)		53 (68.8)	47 (61.0)	
BMI (kg/m^2)	20.9 (2.7)	20.7 (2.9)	0.437	20.7 (2.6)	20.8 (3.1)	0.900
Period of DM (years)	28.0 (7.96)	28.7 (7.9)	0.442	29.0 (8.2)	27.8 (7.9)	0.362
Period of HD (days)	2340.6 (1998.3)	2281.5 (2019.7)	0.8	2269.4 (1896.1)	2260.7 (2024.4)	0.978
Waiting period (days)	1312.6 (1182.1)	1232.75 (1103.1)	0.557	1298.4 (1160.8)	1304.6 (1164.7)	0.974
HbA1c (%)	7.61 (1.52)	7.72 (1.53)	0.551	7.67 (1.52)	7.80 (1.60)	0.614
Operation factors						
Type of operation						
SPK	215 (83.3)	83 (80.6)	0.707	66 (85.7)	61 (79.2)	0.340
PAK	32 (12.4)	16 (15.5)		6 (7.8)	12 (15.6)	
PTA	11 (4.3)	4 (3.9)		5 (6.5)	4 (5.2)	
Cold ischemic time (min)	732.6 (162.5)	746.7 (188.7)	0.48	743.1 (164.1)	731.6 (193.0)	0.692
Immunologic factors						
Number of HLA mismatch						
0	9 (3.5)	1 (1.0)	0.214	4 (5.2)	0 (0.0)	0.397
1	26 (10.1)	13 (12.6)		7 (9.1)	9 (11.7)	
2	94 (36.4)	28 (27.2)		26 (33.8)	25 (32.5)	
3	74 (28.7)	35 (34.0)		27 (35.1)	25 (32.5)	
4	36 (14.0)	21 (20.4)		9 (11.7)	14 (18.2)	
5	19 (7.4)	5 (4.9)		4 (5.2)	4 (5.2)	
Induction of T-cell-depleting antibody						
Yes	75 (29.1)	11 (10.7)	**<0.001**	4 (5.2)	9 (11.7)	0.246
None	183 (70.9)	92 (89.3)		73 (94.8)	68 (88.3)	

Transplant International 2020; 33: 1046–1060

Table 4. Continued.

Group	Prematching			Postmatching		
n	<50 years old 258	≥50 years old 103		<50 years old 77	≥50 years old 77	
	Mean (SD) or *n* (%)		*P* value	Mean (SD) or *n* (%)		*P* value
Type of CNI						
Tacrolimus	255 (98.8)	101 (98.1)	0.626	77 (100.0)	76 (98.7)	1.000
Cyclosporine	3 (1.2)	2 (1.9)		0 (0.0)	1 (1.3)	

BMI, body mass index; CNI, calcineurin inhibitor; CPA, cardiopulmonary arrest; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after cardiac death; DM, diabetes mellitus; HD, hemodialysis; HLA, human leukocyte antigen; PAK, pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation. P values <0.05 were considered to indicate the statistical significance and indicated with the bold values.

showed that only the donor's HbA1c significantly influenced the pancreatic survival (hazard ratio = 1.714, $P = 0.04257$). However, a multivariate analysis revealed no factors markedly influenced the pancreatic graft survival. The Cox proportional hazard regression model also showed that neither Kapur's criteria (hazard ratio = 0.8701, $P = 0.5455$) nor Troppmann's criteria (hazard ratio = 0.7074, $P = 0.1472$) affected the Japanese pancreatic graft survival.

A similar analysis was attempted for each surgical procedure. However, PAK and PTA have only a small number of cases, so in the present study, we examined only SPK cases, which accounted for 82.5% of the surgical procedures (Table 3). Both univariate and multivariate analyses using the Cox proportional hazard regression model showed that no donor factors markedly influenced the pancreatic graft survival in cases of SPK.

A propensity score-matched analysis between donors <50 and ≥50 years old

To further examine the factors influencing pancreatic graft engraftment, especially the age, a propensity score-matched analysis was performed. The patients were divided into two groups by donor age: ≥50 years (older group) and <50 years (younger group). On comparing the background characteristics of donors and recipients, and surgery and immunologic factors, a significant difference was noted between the age groups in terms of the donor gender (male:female, younger group = 161:97, older group = 44:59, $P = 0.001$), cause of death [cerebrovascular accident (CVA): others, younger group = 105:153, older group = 78:25, $P < 0.001$], history of cardiopulmonary arrest (CPA; yes: none, younger group = 135:123, older group = 39:64, $P = 0.014$), HbA1c (younger group = 5.37 ± 0.34, older group = 5.58 ± 0.44, $P < 0.001$), and induction of T-cell-depleting antibody (yes: none, younger group = 75:183, older group = 11:92, $P < 0.001$; Table 4). However, after matching, there were no marked differences between the two groups other than in the donor age, although the number of cases in the groups had decreased to 77 each.

The pancreatic graft survival after matching

The overall pancreatic graft survival at 1, 5, and 10 years after transplantation in the older group was 81.3%, 68.4%, and 68.4%, respectively, which was lower than in the younger group (86.9%, 77.5%, and 71.2%, respectively), although there was no significant difference (Fig. 3a). The death-censored pancreatic graft survival at 1, 5, and 10 years after transplantation in the older group (87.0%, 76.5%, and 76.5%, respectively) also tended to be lower than in the younger group (92.3%, 84.9%, and 82.5%, respectively) without a significant difference (Fig. 3b).

After propensity score matching, the overall pancreatic graft survival at 1, 5, and 10 years after transplantation in the older group was 80.4%, 67.8%, and 67.8%, respectively, which was almost the same as in the younger group (82.8%, 67.6%, and 62.1%, respectively) (Fig. 3c). The death-censored pancreatic graft survival showed a similar tendency, with the values at 1, 5, and 10 years after transplantation in the older group being 84.1%, 74.6%, and 74.6%, respectively, compared with those in the younger group being 89.3%, 76.2%, and 72.8%, respectively (Fig. 3d).

Regarding older donors, a further subanalysis to compare the pancreatic graft survival between donors

who were 50–59 and ≥60 years old was performed. The overall pancreatic graft survival of donors who were 50–59 years old at 1, 5, and 10 years after transplantation was 81.8%, 69.9%, and 69.9%, respectively, while those values in donors who were ≥60 years old were 80.0%, 64.5%, and 64.5%, respectively, which tended to be lower but without significant difference (Fig. 3e). The death-censored pancreatic graft survival of donor age ≥60 at 1, 5, and 10 years after transplantation was 87.8%, 70.8%, and 70.8%, respectively, which still showed no significant difference but tended to be lower than that of donor age 50–59 (86.7%, 78.3%, and 78.3%, respectively; Fig. 3f).

One additional subanalysis in terms of the pancreatic graft survival was performed with consideration of age-related interactions. However, even in the analysis using the Cox proportional hazard regression model after dividing cases into younger and older groups, no factors were found to have significantly affected the pancreatic graft survival (Fig. 4).

Discussion

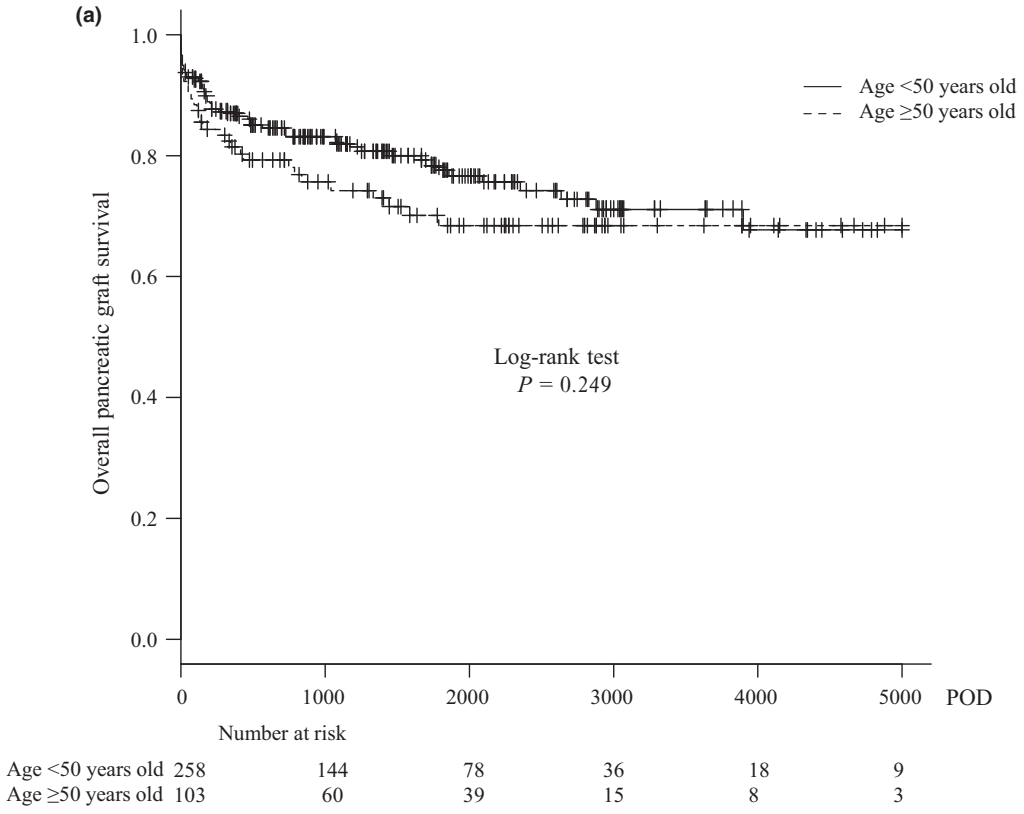
Axelrod *et al.* [17] reported the potential value of the pancreas donor risk index (PDRI) to inform the possibility of organ acceptance and improve the appropriate utilization of higher-risk organs for the pancreas transplantation. However, for Japanese pancreatic transplant, these donors' conditions, such as BMI of ≥30 (6 cases: 1.7%), height of ≥190 cm (0 cases), CIT ≥20 h (four cases: 1.1%), and DCD (three cases: 0.8%), were very rare and all of the donors were Asian ethnicities (all cases were Japanese). Although these conditions greatly influence the PDRI, considering the donor background in Japan, we concluded that extracting ECDs was difficult with PDRI. This was one of the reasons we felt that our study was necessary.

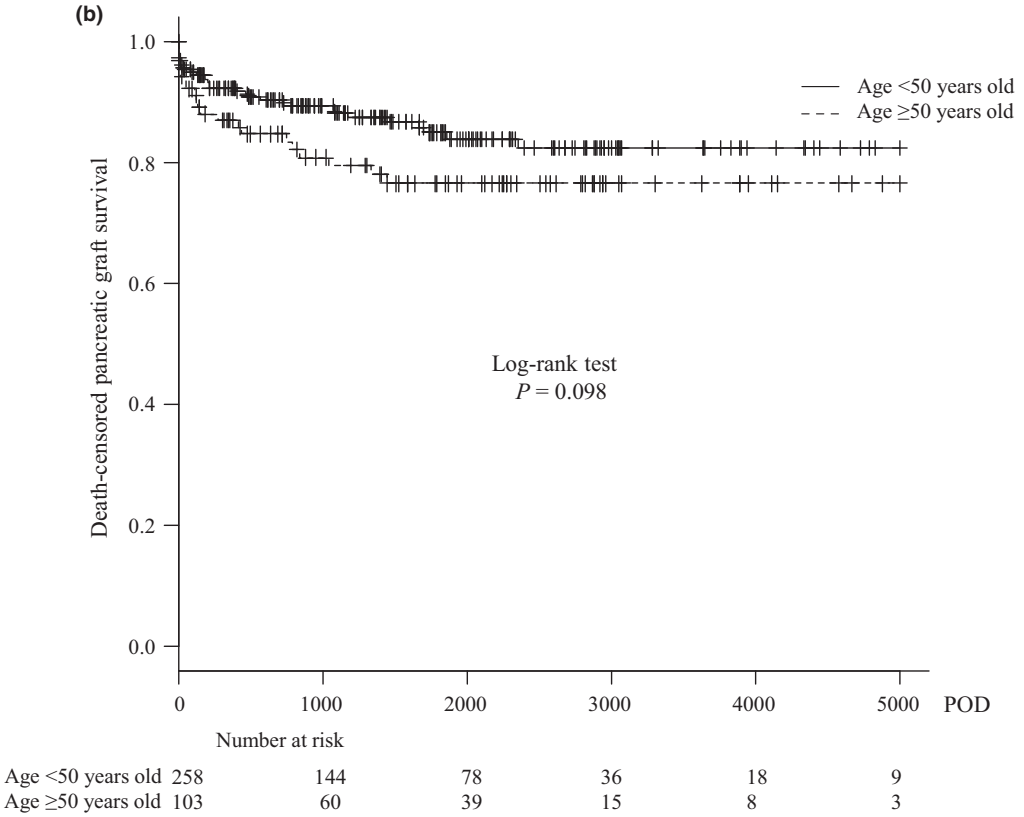
In 2008, before the revision to the organ transplant law in Japan, Ishibashi *et al.* [18] reported on the outcomes of pancreas transplantation in Japan for donations predominantly from marginal donors. Even though donors ≥40 years old comprised 67% of the total donor pool, the pancreas graft survival rates at 1, 3, and 5 years after transplantation were 92%, 80%, and 80%, respectively. Tomimaru *et al.* [19,20] reported that 108 (73.0%) of the 148 total donors were marginal donors as defined by Kapur's criteria, and the pancreas graft survival rates among the marginal donors were 80.9%, 73.2%, and 66.0% at 1, 3, and 5 years after transplantation, respectively; for comparison, these rates were 92.5%, 85.2%, and 77.4%, respectively, in the non-marginal donor group, without significant differences, including cases treated after the revision to the organ transplant law in Japan. However, both of these previous reports involved relatively small pools of donors (36 in Ishibashi's report and 148 in Tomimaru's report). In the present study, the outcomes of a total of 361 cases of pancreas transplantation treated from January 2000 to December 2018 were analyzed for the donor background characteristics and survival rates. The patient survival at 1, 5, and 10 years after transplantation was 96.6%, 94.9%, and 88.3%, respectively, and the pancreatic graft survival at these points was 85.3%, 74.8%, and 70.6%, respectively, which was comparable to the outcomes observed in other countries [14].

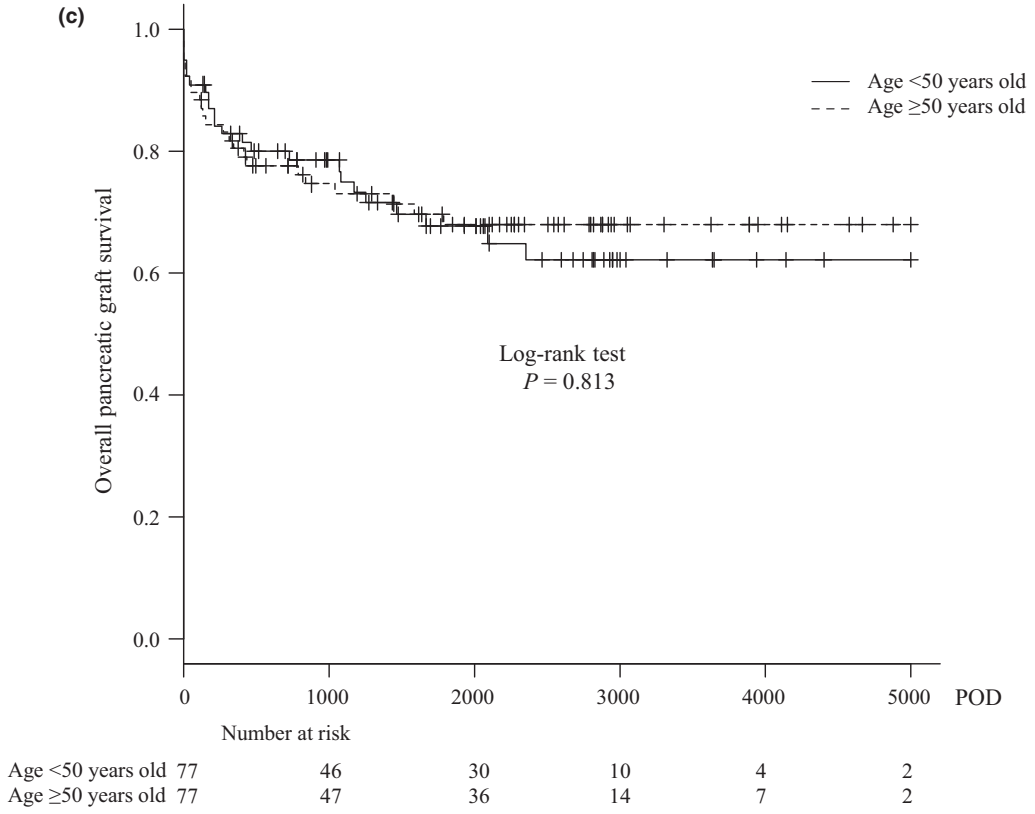
In order to examine the validity of pancreas transplantation from ECDs, such as the elderly, in Japan, a further analysis using propensity score matching and

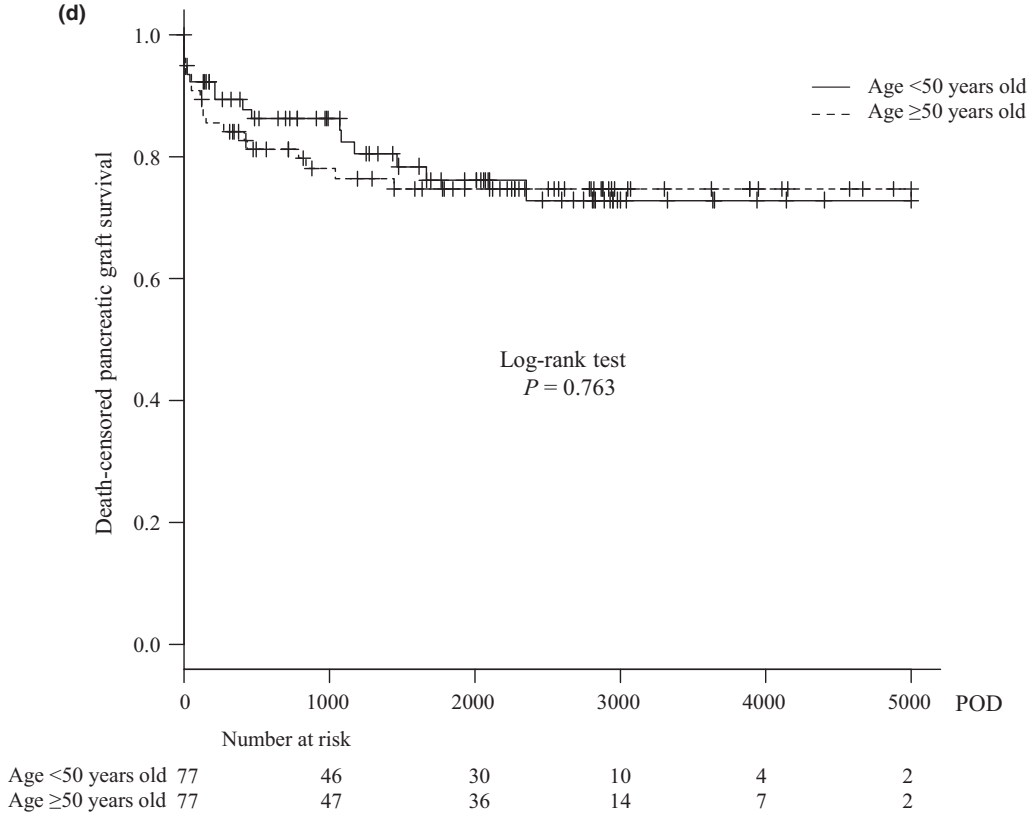
Figure 3 The impact of the donor's age on the graft survival. The comparison of the overall pancreatic graft survival (a) and death-censored pancreatic graft survival (b) before propensity score matching between donors ≥50 years old (older group) and <50 years old (younger group). The overall pancreatic graft survival (c) and death-censored pancreatic graft survival (d) after propensity score matching. The additional subanalysis of the comparison between donors 50–59 and ≥60 years old in the overall pancreatic graft survival (e) and death-censored pancreatic graft survival (f). Prepropensity score matching, the overall pancreatic graft survival (a) at 1, 5, and 10 years after transplantation in the older group was 81.3%, 68.4%, and 68.4%, respectively, which was lower than in the younger group (86.9%, 77.5%, and 71.2%, respectively). The death-censored pancreatic graft survival (b) at 1, 5, and 10 years after transplantation in the older group (87.0%, 76.5%, and 76.5%, respectively) also tended to be lower than in the younger group (92.3%, 84.9%, and 82.5%, respectively) without a significant difference. After propensity score matching, the overall pancreatic graft survival at 1, 5, and 10 years after transplantation in the older group was 80.4%, 67.8%, and 67.8%, respectively, which was almost the same as in the younger group (82.8%, 67.6%, and 62.1%, respectively) (c). The death-censored pancreatic graft survival showed a similar tendency, with values at 1, 5, and 10 years after transplantation in the older group being 84.1%, 74.6%, and 74.6%, respectively, compared with those in the younger group of 89.3%, 76.2%, and 72.8%, respectively (d). The overall pancreatic graft survival of donors 50–59 years old at 1, 5, and 10 years after transplantation was 81.8%, 69.9%, and 69.9%, respectively, while that of donors ≥60 years old was 80.0%, 64.5%, and 64.5%, respectively, which tended to be lower but with no significant difference (e). The death-censored pancreatic graft survival of donors ≥60 years old at 1, 5, and 10 years after transplantation was 87.8%, 70.8%, and 70.8%, respectively, which still showed no significant difference but tended to be lower than that of donors 50–59 years old (86.7%, 78.3%, and 78.3%, respectively) (f).

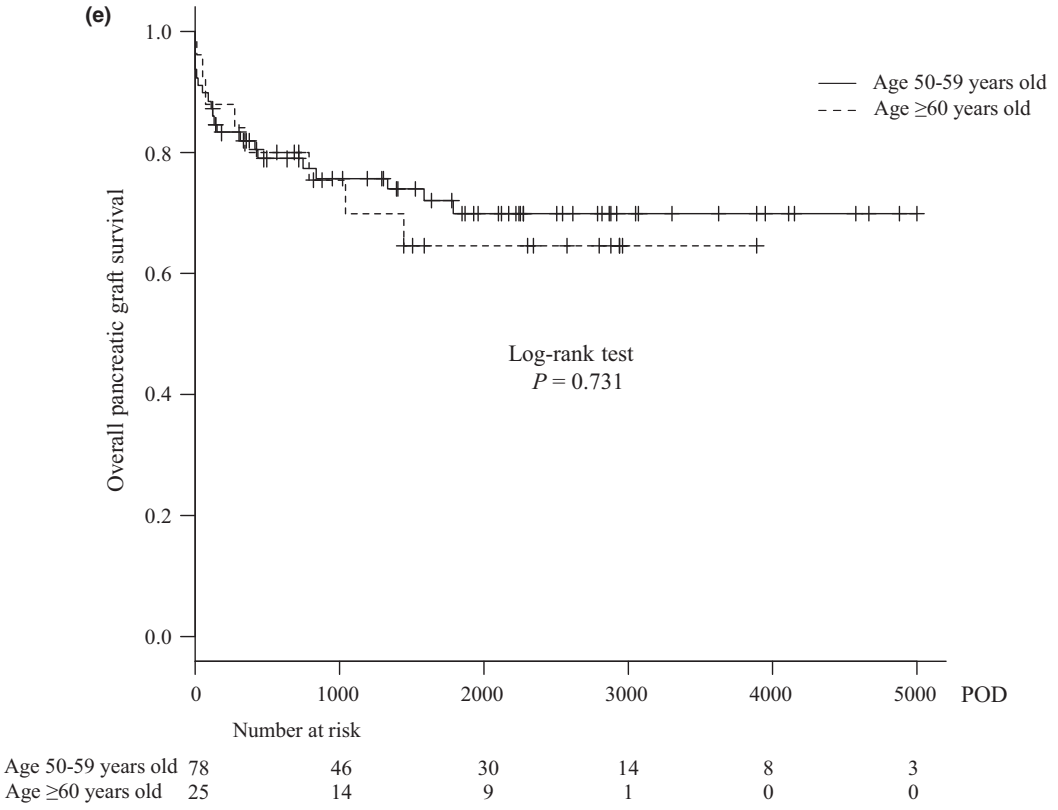
Transplant International 2020; 33: 1046–1060

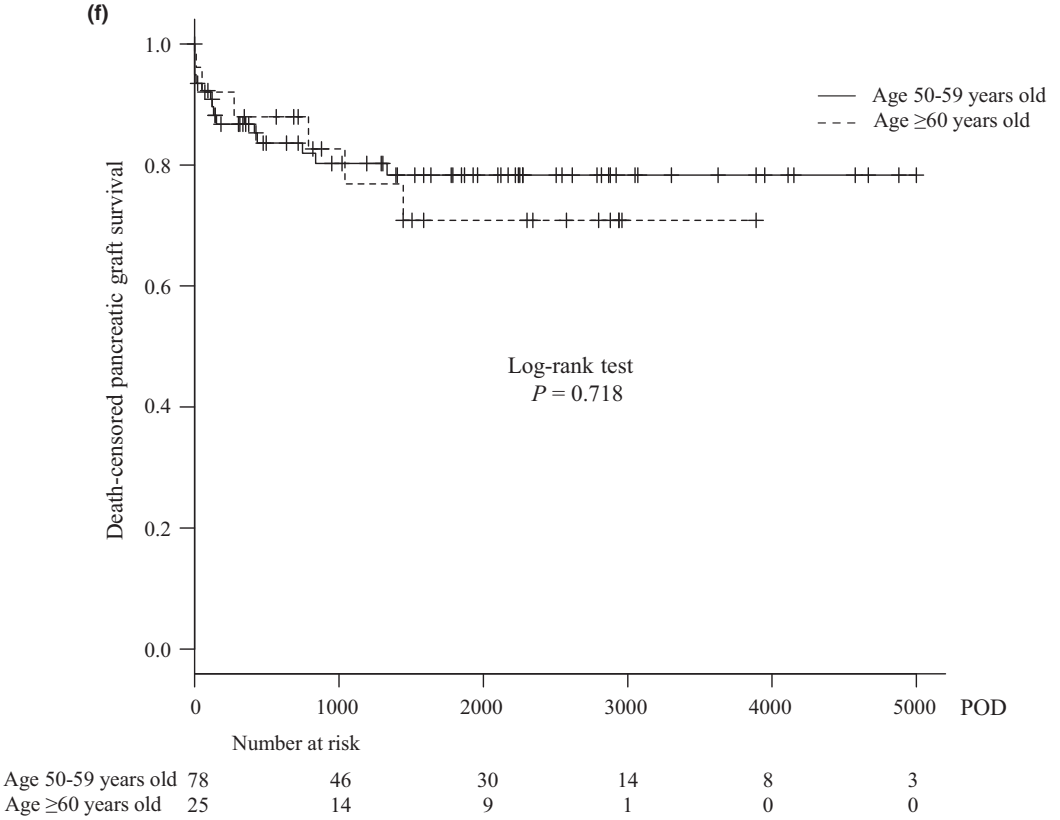












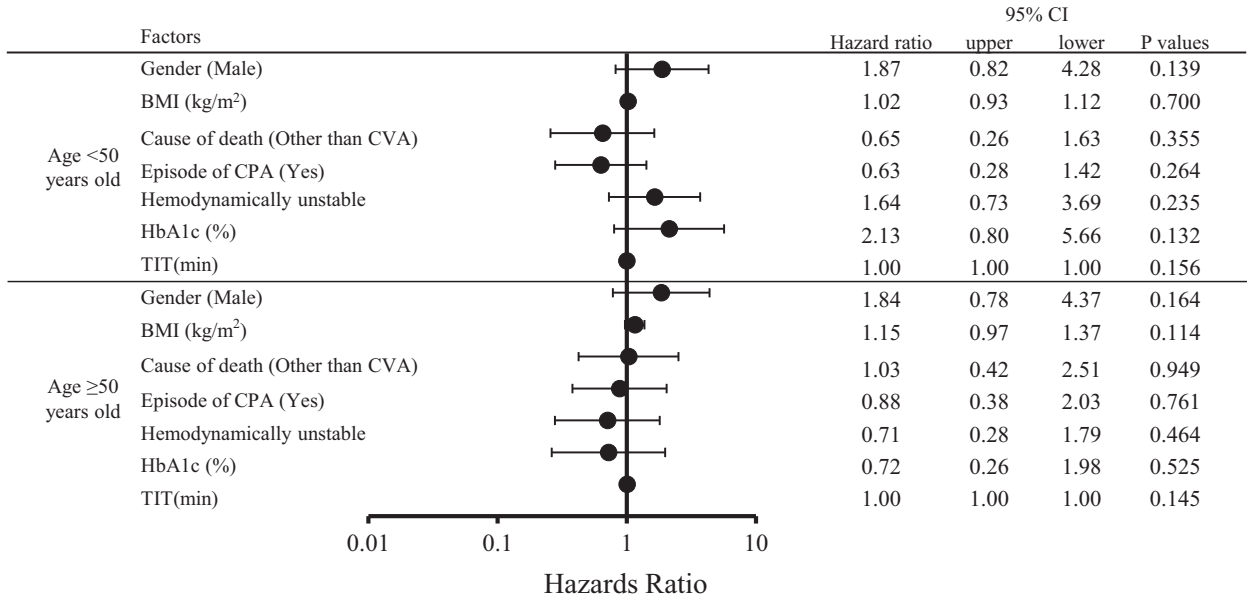


Figure 4 A comparison of the hazard ratios of donor factors influencing the graft survival. The analysis using the Cox proportional hazard regression model after dividing cases into younger and older groups, no factors were found to have significantly affected the pancreatic graft survival.

dividing cases into younger (<50 years) and older groups (≥50 years) based on the donor age was performed. A prematching analysis revealed that there were significant differences between the two groups in the donor gender, cause of death, history of cardiopulmonary arrest, HbA1c value, and induction therapy, while there was no marked difference in any background characteristics between the two groups in the postmatching analysis. There was also no marked difference in the pancreatic graft survival between the two groups after matching, and no factors affecting the pancreatic graft survival were identified in the subsequent subanalysis. Therefore, the pancreas graft survival rate in Japan was also considered comparable to that in other countries, suggesting that the outcomes of pancreas transplantation in Japan using pancreata from ECDs are acceptable.

According to the analysis of the UNOS [21], using pancreata from donors ≥45 years old, brain-dead donors with a history of the cardiocerebrovascular accident, or donors with a prolonged preservation time increased the risk of pancreatic graft failure because of technical failure. In South Korea, a donor age ≥30 years was considered a significant risk factor for a delayed pancreatic graft function, which was associated with a greater risk of overall pancreas graft failure and death-censored graft failure in a study of 135 cases of pancreas transplantations at a single center [22]. However, Salvalaggio *et al*. [23] reported that although the pancreatic and renal graft survival from donors ≥45 years old was indeed inferior to that in younger donors among SPK cases, a substantial survival benefit associated with the use of older donors for SPK transplant was noted compared with remaining on the waiting list.

Of note, several authors reported no correlation between the pancreatic graft survival and the donor age [24,25] or the safe use of pancreata procured from donors ≥45 years old for pancreas transplantation [26,27]. In Germany, a prospective multicenter trial called the EXPAND study was performed to examine whether or not ECDs (donor age, 50–60 years; BMI, 30–34 kg/m^2) were suited for pancreas transplantation [28,29]. In that study, in which 12 German centers performed a total 79 pancreas transplantations, including 18 cases of pancreata from ECDs, the survival rates of both pancreas and kidney grafts from donors ≥50 years old were comparable to those of younger donor. While this finding supports our own results, wherein the outcomes of Japanese transplantation including extended criteria donation were acceptable, there were significant differences in certain donor background characteristics in their study between the ECDs group and the standard care group. In contrast, we adjusted for confounding by propensity score matching to eliminate differences in donor background characteristics between the two groups in our study.

Our study is limited by the number of cases being insufficient for examinations by each surgical procedure. In Japan, the pancreatic graft survival rates of PAK and PTA are markedly poorer than those of SPK [4,30]. Accumulating more cases of pancreas transplantation will enable the investigation of factors affecting the pancreatic graft survival by each surgical procedure in greater detail, which will consequently improve pancreatic transplantation. One more limitation of this study is that the historical background cannot be excluded. The revised law began to be enforced in Japan in 2010, and when comparing the number of cases before and after the revision, only 64 pancreas transplants were performed in the 10 years before the enforcement, while 297 pancreatic transplants were performed in the 9 years since the enforcement of the revised law. However, the pancreatic graft survival rates were not found to differ markedly before and after the revision.

In conclusion, the outcomes of Japanese pancreas transplantation using pancreata from ECDs, such as those ≥50 years old, were comparable to those in other countries, and no donor factors markedly influenced the pancreatic graft survival. Thus, the outcomes of pancreas transplantation and the influence of donor selection in Japan were considered acceptable.

Authorship

TI, TK, NA and KK: participated in research design. TI, TK and NA: participated in the writing of the manuscript. TI, TK and NA: participated in the performance of the research. TK, TA and TI: participated in data collection. TI, TK, NA, TA and TI: participated in data analysis.

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Conflicts of interest

The authors have declared no conflicts of interest.

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