



Original article

Patient and graft survival in pancreas transplant recipients: The EFISPAN study

Pedro Ventura-Aguiar^{a,*}, Mercedes Cabello^b, Isabel Beneyto^c, Dolores Navarro Cabello^d, Guadalupe Tabernero^e, Angel Alonso^f, Juan Carlos Ruiz^g, Santiago Llorente^h, on behalf of the EFISPAN group

^a Department of Nephrology and Kidney Transplantation, Hospital Clinic, Barcelona, Spain

^b Department of Nephrology, Hospital Regional Universitario de Málaga, Málaga, Spain

^c Department of Nephrology, Hospital La Fe, Valencia, Spain

^d Department of Nephrology, Hospital Reina Sofía, Córdoba, Spain

^e Department of Nephrology, Hospital Universitario de Salamanca, Salamanca, Spain

^f Department of Nephrology, Hospital Universitario de A Coruña, A Coruña, Spain

^g Department of Nephrology, Hospital Marqués de Valdecilla, University of Cantabria, IDIVAL, Santander, Spain

^h Department of Nephrology, Hospital Virgen de la Arrixaca, Murcia, Spain

ARTICLE INFO

Article history:

Received 8 March 2021

Accepted 15 September 2021

Available online 26 November 2021

Keywords:

Cardiovascular disease

Diabetes

Graft survival

Kidney disease

Kidney transplant

Pancreas transplant

ABSTRACT

Introduction and objectives: Graft outcomes in pancreas transplantation have improved in recent decades, but data are mainly derived from registries or prospective single-centre studies. This large epidemiological study was undertaken to investigate the impact of clinical and demographic factors on graft and patient survival in pancreas transplant recipients in Spain, and to provide robust, country-wide, practice-based data to complement registry findings.

Patients and methods: We conducted a retrospective, longitudinal, epidemiological study to assess risk factors impacting patient and graft survival in pancreas transplant recipients in eight centres in Spain. All patients transplanted between 1 January 2008 and 31 December 2012 were included; data were collected until 31 December 2015. The Kaplan–Meier method was used for all time-to-event analyses, including patient survival, graft survival, acute rejection, and BPAR. For graft survival analysis, in cases of death with functioning graft, patients were censored without any event on the date of death. For acute rejection and BPAR, patients were censored without any event on the date of death or graft loss. Univariable and multivariable analyses (Cox proportional hazards model) were conducted to assess the association between baseline clinical and demographic characteristics and patient/graft survival.

Abbreviations: BMI, body mass index; BPAR, biopsy-proven acute rejection; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IPTR, International Pancreas Transplant Registry; IQR, interquartile range; IRODaT, International Registry in Organ Donation and Transplantation; MDRD-4, Modification of Diet in Renal Disease-4; MMF, mycophenolate mofetil; MPA, mycophenolic acid; OPTN, US Organ Procurement and Transplantation Network; PAK, pancreas-after-kidney transplantation; PTA, pancreas transplantation alone; SBP, systolic blood pressure; SD, standard deviation; SPK, simultaneous pancreas and kidney transplantation; UNOS, United Network for Organ Sharing.

* Corresponding author.

E-mail address: pventura@clinic.cat (P. Ventura-Aguiar).

<https://doi.org/10.1016/j.nefro.2021.09.016>

0211-6995/© 2021 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Results: Data were included for 241 (80.1%) simultaneous pancreas-kidney transplants, 56 (18.6%) pancreas-after-kidney transplants and 4 (1.3%) pancreas transplants alone. Mean \pm standard deviation time from diagnosis until transplantation was 26.1 ± 7.5 years. Nineteen patients died, mainly due to infections ($n = 10$); the remaining 282 patients (93.7%) survived from transplantation until the end of the study. Among 55 patients (18.3%) with pancreas graft loss, the main reasons were vascular thrombosis ($n = 19$), chronic rejection ($n = 10$), acute rejection ($n = 6$) and death with a functioning graft ($n = 5$). The overall rate of vascular-related death was 1.3% at 5 years post transplant. Univariable analysis showed that patient age and weight, donor age, previous kidney transplantation, previous cardiovascular events and need for insulin more than 48 h post transplantation were significantly associated with pancreas graft survival. Of these, in multivariable analyses pancreas graft survival was inferior in patients who had received a previous kidney transplant prior to pancreas transplantation (log-rank test, $p = 0.0002$). Glucose metabolism, renal function and cardiovascular risk factors were generally stable following transplantation.

Conclusions: The results of this multicentre study highlight the excellent patient and graft outcomes following pancreas transplantation, with a notably low incidence of cardiovascular events.

© 2021 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Supervivencia del paciente y del injerto en receptores de trasplante de páncreas: estudio EFISPAN

R E S U M E N

Palabras clave:

Enfermedad cardiovascular
Diabetes
Supervivencia del injerto
Enfermedad renal
Trasplante de riñón
Trasplante de páncreas

Introducción y objetivos: Los resultados del injerto en el trasplante de páncreas han mejorado en las últimas décadas, pero los datos provienen principalmente de registros o estudios prospectivos unicéntricos. Este estudio epidemiológico se llevó a cabo para investigar el impacto de los factores clínicos y demográficos en la supervivencia del injerto y del paciente en receptores de trasplante de páncreas en España, y proporcionar datos sólidos, basados en la práctica a nivel nacional, para complementar los hallazgos de los registros.

Pacientes y métodos: Realizamos un estudio epidemiológico longitudinal, retrospectivo, para evaluar los factores de riesgo que influyen en la supervivencia del paciente y del injerto en receptores de trasplante de páncreas en 8 centros de España. Se incluyeron todos los pacientes trasplantados entre el 1 de enero de 2008 y el 31 de diciembre de 2012; los datos se recogieron hasta el 31 de diciembre de 2015. Se utilizó el método de Kaplan-Meier para todos los análisis del tiempo transcurrido hasta el evento, incluida la supervivencia del paciente, la supervivencia del injerto, el rechazo agudo y el BPAR. Para el análisis de la supervivencia del injerto, en los casos de muerte con injerto funcional, los pacientes fueron censurados sin ningún evento en la fecha de la muerte. Para el rechazo agudo y BPAR, los pacientes fueron censurados sin ningún evento en la fecha de la muerte o pérdida del injerto. Se realizaron análisis univariados y multivariados (modelo de riesgos proporcionales de Cox) para evaluar la asociación entre las características clínicas y demográficas basales y la supervivencia del paciente/injerto.

Resultados: Se incluyeron datos de 241 (80,1%) trasplantes de páncreas-riñón simultáneos, 56 (18,6%) trasplantes de páncreas después de riñón y 4 (1,3%) trasplantes de páncreas aislados. El tiempo medio \pm desviación estándar desde el diagnóstico hasta el trasplante fue de $26,1 \pm 7,5$ años. Diecinueve pacientes fallecieron, principalmente por infecciones ($n = 10$); los 282 pacientes restantes (93,7%) sobrevivieron desde el trasplante hasta el final del estudio. De los 55 pacientes (18,3%) con pérdida del injerto de páncreas, las principales razones fueron trombosis vascular ($n = 19$), rechazo crónico ($n = 10$), rechazo agudo ($n = 6$) y muerte con un injerto funcional ($n = 5$). La tasa global de muerte relacionada con eventos vasculares fue del 1,3% a los 5 años del trasplante. El análisis univariable mostró que la edad y el peso del paciente, la edad del donante, el trasplante renal previo, los eventos cardiovasculares previos y la necesidad de insulina durante más de 48 h después del trasplante se asociaron significativamente con la supervivencia del injerto de páncreas. De estos, en los análisis multivariados, la supervivencia del injerto de páncreas fue inferior en los pacientes

que habían recibido un trasplante de riñón previo al trasplante de páncreas (prueba de rango logarítmico, $p = 0,0002$). El metabolismo de la glucosa, la función renal y los factores de riesgo cardiovasculares se mantuvieron en general estables después del trasplante.

Conclusiones: Los datos obtenidos de este estudio multicéntrico destacan los excelentes resultados del paciente y del injerto después del trasplante de páncreas, con una incidencia notablemente baja de eventos cardiovasculares.

© 2021 Sociedad Española de Nefrología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Pancreas (with or without kidney) transplantation is an established treatment option for patients with type 1 diabetes and end-stage renal disease, as well as for selected patients with type 2 or type 1 diabetes with labile glucose control.^{1,2} Simultaneous pancreas and kidney transplantation (SPK) is the most frequently performed procedure (80%)³; alternative approaches include pancreas-after-kidney transplantation (PAK) and pancreas transplantation alone (PTA), although PTA remains a minority procedure (<5%).³

While there have been considerable improvements in pancreas transplantation medicine in recent years, particularly in SPK,^{2,4} data have generally derived from single-centre studies^{5,6} and registries (e.g. United Network for Organ Sharing [UNOS], International Registry in Organ Donation and Transplantation [IRODaT], and the International Pancreas Transplant Registry [IPTR]).^{2,4,7} As a consequence, there are still gaps in knowledge in terms of efficacy, risks and long-term benefits of pancreas transplantation.⁴ The paucity of these data, together with the increasing prevalence of diabetes mellitus in Europe and worldwide,⁸ highlights a pressing need to identify factors that influence recipient and graft survival, as well as the metabolic control obtained after pancreas transplantation.

The number of pancreas transplants in Europe has increased over the last 12 years from 4069 in 2005–2009, to 4433 in 2010–2014.² In Spain, 5249 solid organ transplants were performed in 2017, including 70 pancreas transplants at 12 pancreas transplant centres.⁷ As the number of pancreas transplants increases, evidence regarding factors that may influence mortality and comorbidity is emerging. We therefore undertook this large epidemiological study to investigate the impact of clinical and demographic factors on graft and patient survival in pancreas transplant recipients, and to provide robust, country-wide, practice-based data to complement the registry findings.

Patients and methods

Study design and patients

This was a retrospective, longitudinal, 5-year epidemiological study to evaluate clinical and demographic variables impacting survival in pancreas transplant recipients at eight pancreas transplantation centres in Spain. Although all

12 Spanish centres that perform pancreas transplantation were invited to participate, four centres declined to participate for administrative or other internal reasons. All patients transplanted between 1 January 2008 and 31 December 2012 were included; data were collected until 31 December 2015. Due to protracted development of the clinical study report and manuscript, the data were not available for publication until 2020.

The study was conducted in accordance with the Declaration of Helsinki, the International Council of Harmonisation Good Clinical Practice guidelines for observational studies, and local ethical committee regulations in all participating centres. Each patient provided informed consent for inclusion in this study. Retrospective data were collected and anonymized by investigators, preserving confidentiality according to local regulation. Data collection was performed from medical records if the patient met one of the following inclusion criteria: SPK transplantation performed in patients with diabetes mellitus and end-stage renal disease; PAK performed in patients with diabetes mellitus and a functioning kidney graft from a living-related or deceased donor; or PTA performed in patients with labile diabetes mellitus and preserved renal function. In patients undergoing PAK who had received more than one kidney transplant, the last kidney transplant was the reference for data collection.

Endpoints

The co-primary endpoints were patient survival and pancreas graft survival. Patient survival was calculated from the time of pancreas transplantation until either the date of death or study end. Pancreas graft survival was calculated based on the time from transplantation until pancreas graft loss, patient death with functioning pancreas graft, or study end. Pancreas graft failure was defined as C-peptide <1 ng/mL and exogenous insulin requirements >0.5 IU/kg/day.

Secondary endpoints included: kidney graft survival (defined as time from kidney transplantation until return to dialysis or kidney graft loss), acute pancreatic rejection and biopsy-proven acute rejection (BPAR), acute kidney rejection and BPAR, renal function, glucose metabolism, lipid levels and blood pressure. With the exception of kidney transplant outcomes (i.e. kidney graft survival, and acute kidney rejection and BPAR), secondary endpoints were assessed in all patients irrespective of transplant type.

Patient and donor parameters were assessed to determine possible associations with patient survival and pancreas

graft survival. These included the recipient variables: age, sex, weight, body mass index (BMI), type of transplant (SPK, PAK, PTA) and cardiovascular events; and the donor variables: age, sex and pancreas ischaemic time. Safety events occurring during follow-up were also recorded.

Statistical analyses

Continuous variables were summarized as mean \pm standard deviation (SD) or median [interquartile range (IQR)], as appropriate. Categorical variables were summarized as incidence counts or rates. The Kaplan–Meier method was used for all time-to-event analyses, including patient survival, graft survival, acute rejection, and BPAR. For graft survival analysis, in cases of death with functioning graft, patients were censored without any event on the date of death. For acute rejection and BPAR, patients were censored without any event on the date of death or graft loss. Univariable and multivariable analyses (Cox proportional hazards model) were conducted to assess the association between baseline clinical and demographic characteristics and patient/graft survival. Factors found to be associated with patient/graft survival in univariable analyses were included in the multivariable analysis and backward elimination applied to identify the variables that significantly affected patient survival. There were no imputations for missing data. All analyses were performed using SAS[®] Version 9.3, and $p \leq 0.05$ was considered statistically significant.

Results

Patient characteristics

Of 304 patients recruited into the study, three were excluded from the analysis because no post-transplant data were available. Of the 301 patients included in the analysis, there were 241 (80.1%) SPKs, 56 (18.6%) PAKs and four (1.3%) PTAs. Nineteen patients died during the study period. The majority of patients (65.4%) were followed for 3 years after pancreatic transplantation, and 87 (28.9%) were followed for 5 years (Supplementary Fig. 1). The median follow-up period from pancreas transplantation was 3.2 years (maximum 5.6 years).

Patient demographics and baseline characteristics for all transplant recipients are presented in Table 1. The mean \pm SD age of patients at pancreas transplantation was 40.3 \pm 7.5 years; 67.1% were male and 94.4% were Caucasian. The majority of transplant recipients had diabetes mellitus type I (96.7%) and were receiving dialysis (82.3%). The mean \pm SD time from diagnosis of diabetes (including type I, type II and maturity onset diabetes of the young) until transplantation was 26.1 \pm 7.5 years. For the 56 transplant recipients in the PAK group, the median (range) time from kidney transplantation to pancreas transplantation was 2.7 (0.6–14.1) years.

Pancreas donors had a mean \pm SD age of 32.6 \pm 10.6 years (range, 5–54 years), and the majority (57.6%) were male, with a mean \pm SD BMI of 23.6 \pm 2.6 kg/m². Most pancreas donors died as a result of traumatic brain injury (43.3%) or from cerebrovascular causes (42.0%) (Table 2).

Table 1 – Demographics and baseline characteristics for all transplant recipients (SPK, PAK, PTA).

Characteristics	Transplant recipients (N = 301)
Age (years), mean \pm SD	40.3 \pm 7.5
Male/female, n (%)	202 (67.1)/99 (32.9)
Caucasian/Arab/Hispanic, n (%)	284 (94.4)/11 (3.7)/6 (2.0)
BMI (kg/m ²), mean \pm SD [n = 283]	23.8 \pm 3.7
Diabetes mellitus, n (%)	301 (100)
Type I	291 (96.7)
Type II	5 (1.7)
Other	5 (1.7)
Viral serology (positive), n (%)	
CMV [n = 296]	204 (68.9)
EBV [n = 277]	242 (87.4)
HBV [n = 300]	4 (1.3)
HCV [n = 300]	8 (2.7)
HIV [n = 300]	1 (0.3)
Type of dialysis, n (%) [n = 299]	
Haemodialysis	172 (57.5)
Peritoneal dialysis	57 (19.1)
Haemodialysis and peritoneal dialysis	17 (5.7)
No dialysis	53 (17.7)
Time with diabetes until transplantation (years), mean \pm SD [n = 298]	26.1 \pm 7.5
Transplant type/graft location/surgical technique, n (%)	
Pancreas graft location [n = 297]	
Right iliac fossa/left iliac fossa	285 (96.0)/12 (4.0)
Pancreas surgical technique: venous drainage	301 (100.0) ^a /0 (0)
Systemic/portal	287 (95.3)/14 (4.7)
Immunosuppression (transplantation day), n (%)	301 (100.0)
Tacrolimus	
Immediate-release tacrolimus [n = 251]	216 (86.1)
Prolonged-release tacrolimus [n = 251]	35 (13.9)
MMF/MPA	301 (100.0)
Prednisone	301 (100.0)
Induction immunosuppression, n (%)	299 (99.3)
Anti-IL-2	161 (53.5)
Thymoglobulin	138 (45.8)

^a A duodenoenterostomy enteric drainage procedure was performed in most pancreas transplant recipients (99.3% [298/300 patients]).

BMI, body mass index; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL-2, interleukin-2; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SD, standard deviation; SPK, simultaneous pancreas and kidney transplantation

Immunosuppressive regimens

Of the 301 patients, all except two received induction therapy with either anti-interleukin-2 (IL-2) receptor ($n = 161$; 53.5%) or thymoglobulin ($n = 138$; 45.8%). All 301 patients received prednisone at baseline; by the end of the study, of 87 patients with available data at 5 years, 65 (74.7%) were receiving prednisone (Supplementary Table 1). All patients were treated with tacrolimus; at baseline, of the 251 patients with available formulation data, 216 (86.1%) received immediate-release tacrolimus. By the end of the study, of the 85 patients with

Table 2 – Pancreas donor transplantation data.

Characteristics	Transplant recipients (N = 301)
Donor	
Age (years), mean ± SD [n = 294]	32.6 ± 10.6
Male/female, n (%) [n = 290]	167 (57.6)/123 (42.4)
Weight, kg, mean ± SD [n = 248]	69.1 ± 10.6
BMI (kg/m ²), mean ± SD [n = 210]	23.6 ± 2.6
Cause of death, n (%) [n = 293]	
Traumatic brain injury	127 (43.3)
Cerebrocardiovascular	123 (42.0)
Other	43 (14.7)
Ischaemic time (h) [n = 293]	10.1 ± 3.1
Viral serology (positive), n (%)	
CMV	161 (53.5)
EBV	37 (12.3)
HBV	1 (0.3)
HCV	0 (0.0)
HIV	0 (0.0)

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SD, standard deviation.

available formulation data at 5 years, 57 (67.1%) were receiving prolonged-release tacrolimus (Supplementary Table 1). The dose of tacrolimus decreased over the 5 years of the study. All 301 patients received concomitant immunosuppression with mycophenolate at baseline [193 (64.1%) received mycophenolate mofetil (MMF) and 108 (35.9%) received mycophenolic acid (MPA)]. Of 85 patients with available data at the end of the study at 5 years, 80 (94.1%) were taking these therapies (Supplementary Table 1).

Patient survival

A total of 282 recipients (93.7%) survived from the date of transplantation until the study end, with estimated 12-month, 3-year and 5-year survival rates of 98.7%, 96.1% and 94.4%, respectively (Fig. 1). A total of 19 (6.3%) recipients died dur-

ing the study period, due to infection (n = 10, 52.6%), vascular disease (n = 4, 21.1%), sudden death (n = 2, 10.5%), gastrointestinal haemorrhage (n = 2, 10.5%) and road traffic accident (n = 1, 5.3%). The overall rate of vascular-related death was 1.3% at 5 years post-transplant.

Pancreas graft survival

A total of 246 (81.7%) pancreas grafts survived from transplantation date to study end, with estimated 12-month, 3-year and 5-year pancreas graft survival rates of 87.8%, 84.9% and 83.0%, respectively (Fig. 2). Fifty-five (18.3%) patients experienced pancreas graft loss during the study. In these patients, primary non-function occurred in 22 transplants (40.0%), due to vascular thrombosis (n = 19, 34.5%), poor graft perfusion (n = 2, 3.6%) and bile leak (n = 1, 1.8%). The remaining causes of graft loss were acute (n = 6, 10.9%) and chronic rejection (n = 10, 18.2%), infection (n = 2, 3.6%), 10 (18.2%) due to other reasons, and death with a functioning graft (n = 5, 9.1%).

Kidney graft survival

Of the 297 recipients who received either SPK or PAK transplants, 271 kidney grafts (91.2%) survived from transplantation date until the end of the observation period (Fig. 3). For the 26 recipients (8.8%) who developed graft loss during the observation period, the reasons for graft loss included: death with a functioning graft (n = 7, 26.9%), chronic humoral rejection (n = 4, 15.4%), thrombosis (n = 4, 15.4%), cellular rejection (n = 3, 11.5%), acute humoral rejection (n = 1, 3.8%), glomerular disease (recurrent or de novo) (each n = 1, 3.8%), and other reasons (n = 6, 23.1%).

Acute pancreatic rejection

Of 77 episodes of acute pancreatic rejection in 55 recipients (18.3%), 29 were BPAR (37.7%). The estimated proportion of patients who had not experienced acute rejection was 83.2% at 12 months post-transplant, and 81.7% at 5 years (Fig. 4). At the end of the study, 91.7% of patients had not experienced a BPAR event.

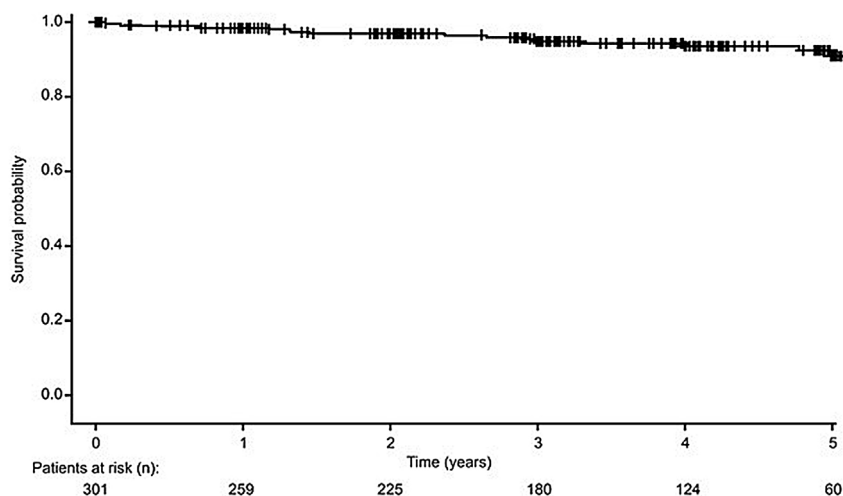


Fig. 1 – Kaplan–Meier curve of overall patient survival.

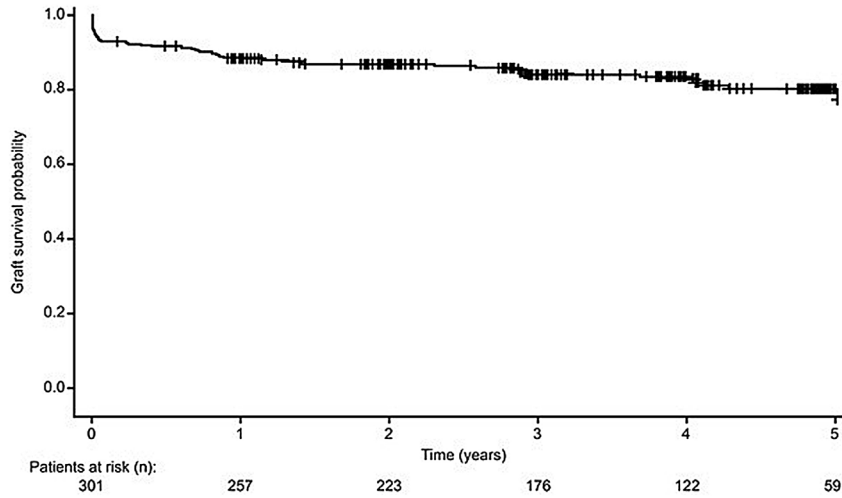


Fig. 2 – Kaplan–Meier curve of pancreas graft survival.

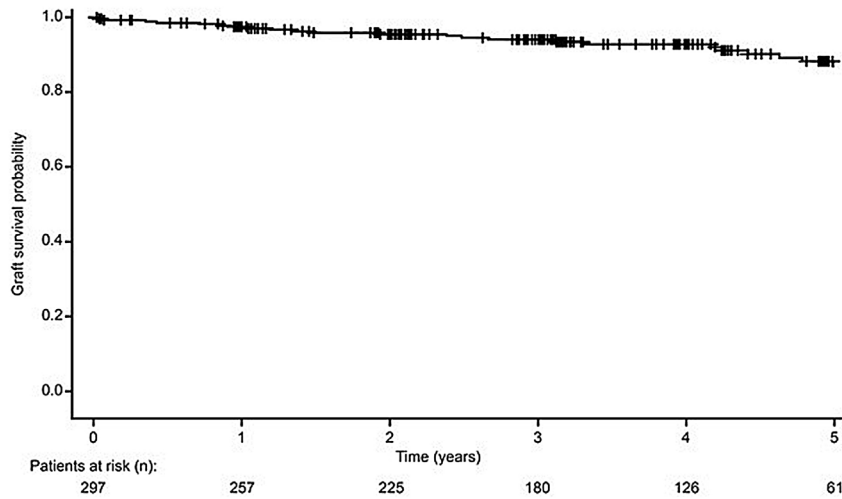


Fig. 3 – Kaplan–Meier curve of kidney graft survival.

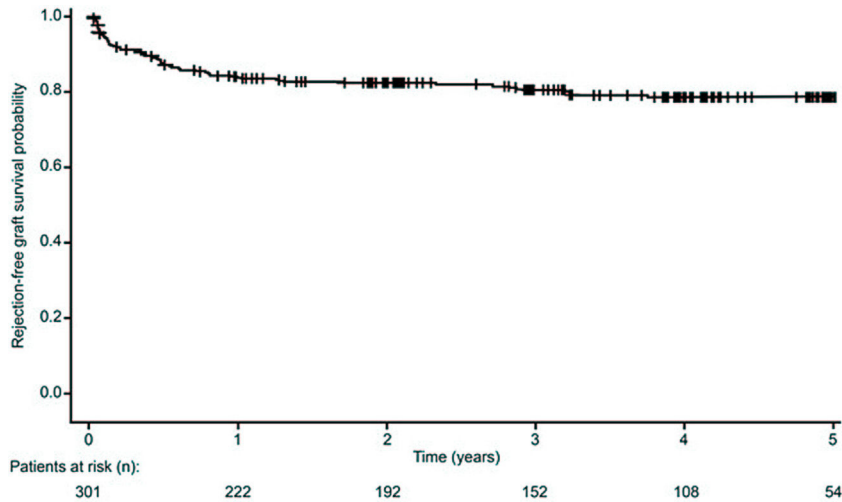


Fig. 4 – Kaplan–Meier curve of pancreas acute rejection-free survival.

Table 3 – Renal function and glucose metabolism from day of pancreas transplant to study end.

	Time post-transplant							
	1 month	3 months	6 months	12 months	2 years	3 years	4 years	5 years
Renal function								
<i>Serum creatinine</i>								
n	284	283	277	269	241	197	142	87
Mean ± SD, mg/dL	1.8 ± 5.3	2.0 ± 12.1	1.4 ± 0.5	1.3 ± 0.6	1.3 ± 0.8	1.3 ± 1.0	1.3 ± 1.0	1.3 ± 0.5
<i>eGFR (MDRD-4)</i>								
n	281	281	275	267	241	196	142	87
Mean ± SD, mL/min/1.73 m ²	61.8 ± 23.7	65.0 ± 21.3	63.6 ± 20.6	65.4 ± 19.3	66.6 ± 20.9	67.7 ± 21.2	68.8 ± 21.0	70.2 ± 23.0
<i>Proteinuria</i>								
n	238	242	245	241	206	166	124	79
Median (IQR), mg/24 h	251.0 (156, 400)	208.0 (141, 342)	203.0 (123, 312)	200.0 (120, 300)	198.0 (116, 300)	191.0 (101, 300)	174.0 (100, 294)	170.0 (100, 310)
<i>UPCR</i>								
n	139	147	143	137	118	94	72	39
Median (IQR)	123.0 (0.6, 218)	105.0 (0.5, 182)	94.0 (0.5, 165)	91.0 (0.4, 154)	94.5 (0.3, 139)	83.5 (0.2, 133)	78.5 (0.2, 142.9)	50.0 (0.2, 105)
Glucose metabolism								
<i>C-peptide (ng/mL)</i>								
n	186	187	190	199	183	157	123	75
Mean ± SD (ng/mL)	5.4 ± 9.5	3.4 ± 1.6	3.1 ± 1.7	3.0 ± 3.0	2.8 ± 1.7	2.6 ± 2.4	2.2 ± 1.9	1.8 ± 1.1
<i>Glycemia</i>								
n	280	282	274	264	238	186	138	83
Mean ± SD, mg/dL	95.8 ± 36.7	89.0 ± 31.7	90.6 ± 20.5	92.0 ± 31.0	135.1 ± 691.0	91.6 ± 29.3	92.7 ± 27.2	92.6 ± 19.7
<i>Amylases</i>								
n	248	251	238	236	212	167	125	66
Mean ± SD, U/L	93.4 ± 48.3	77.6 ± 42.0	83.4 ± 68.0	76.4 ± 38.0	77.4 ± 31.6	76.7 ± 30.4	72.3 ± 28.4	75.8 ± 30.0
<i>Lipase</i>								
n	169	174	168	163	146	119	83	44
Mean ± SD, U/L	57.9 ± 47.5	47.6 ± 39.7	70.8 ± 150.0	43.1 ± 34.8	43.2 ± 35.1	38.9 ± 23.6	37.9 ± 36.6	50.6 ± 48.5
<i>HbA1c</i>								
n	242	264	261	258	225	185	135	84
Mean ± SD, %	5.7 ± 0.9	5.4 ± 1.1	5.4 ± 3.1	5.4 ± 0.8	5.4 ± 0.7	5.5 ± 0.8	5.5 ± 0.8	5.5 ± 0.8
<i>Anti-GAD</i>								
n	28	61	59	56	68	63	46	22
Mean ± SD, U/mL	9.7 ± 19.8	4.1 ± 10.2	2.3 ± 4.2	4.3 ± 10.6	2.7 ± 5.7	5.7 ± 12.8	3.5 ± 6.0	2.9 ± 4.5

eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; GAD, glutamic acid decarboxylase; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; SD, standard deviation; UPCR, urine protein-to-creatinine ratio

Acute kidney rejection

Of 67 episodes of acute kidney rejection in 49 recipients (16.5%; based on clinical criteria and/or laboratory analyses), 49 were episodes of BPAR in 39 patients (13.1%). At the end of the study, 83.5% and 86.9% of patients had not experienced acute kidney rejection or BPAR, respectively.

Renal function and glucose metabolism

Renal function improved from the day of pancreas transplantation up to Month 6 and remained generally stable thereafter. At 5 years, mean ± SD serum creatinine concentration was 1.3 ± 0.5 mg/dL and mean ± SD estimated glomerular filtration rate (eGFR; Modification of Diet in Renal Disease-4 [MDRD-4]) was 70.2 ± 23.0 mL/min/1.73 m² (Table 3). Proteinuria remained stable throughout the study period, with a median (IQR) of 170.0 (100, 310) mg/24 h at 5 years.

Median urine protein-to-creatinine ratio decreased gradually throughout the study period. Glucose metabolism parameters generally remained stable over the 5 years of follow-up (Table 3), with the exception of C-peptide which decreased throughout the study period from 5.4 ± 9.5 ng/mL at Month 1 to 1.8 ± 1.1 ng/mL at 5 years.

Cardiovascular risk factors

BMI increased from Month 1 post-transplant to the end of the study (22.9 ± 3.5 to 25.0 ± 4.4 kg/m²). Lipid profiles remained stable from the day of transplantation to the end of the study: total cholesterol (167.9 ± 42.2–165.2 ± 31.9 mg/dL), high density lipoprotein cholesterol (47.5 ± 16.2–54.3 ± 12.3 mg/dL), low density lipoprotein cholesterol (90.0 ± 27.2–92.6 ± 23.1 mg/dL); triglycerides decreased from 135.4 ± 71.3 on the day of transplantation to 103.1 ± 108.2 mg/dL at 5 years. A similar

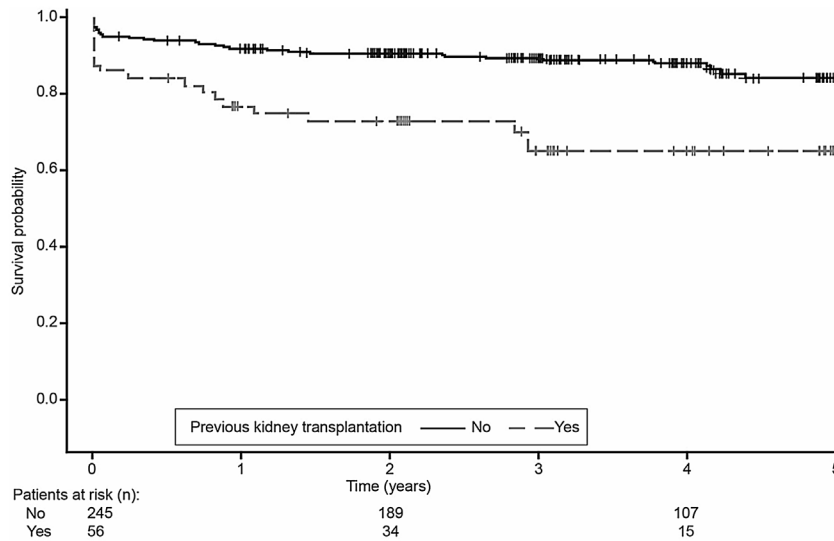


Fig. 5 – Kaplan–Meier curve of pancreas graft survival according to previous kidney transplant (No, SPK or PTA; Yes, PAK).

proportion of recipients were being treated with statins at transplant (51.2%) and at study end (51.7%).

Systolic and diastolic blood pressure (SBP and DBP) remained stable from Month 1 post-transplant to the end of the study (SBP: 127.5 ± 18.4–128.2 ± 16.6 mmHg; DBP: 74.2 ± 12.6–74.9 ± 11.0 mmHg). The proportion of patients with hypertension was 22.2% on the day of transplantation, which decreased and remained stable post-transplant (range, 5.3–8.4%). Post-transplant, the most commonly used hypertension treatments were beta blockers (range, 20.4–24.9%) and calcium antagonists (range, 18.4–25.4%) (Supplementary Table 2). Compared with 1 month post-transplant, the proportion of patients receiving an ACEi or ARB numerically increased by 5 years, while the proportion of patients receiving calcium antagonists decreased.

Association of risk factors with patient and graft survival

Given the high patient survival rate, data for the association of risk factors with patient survival are not reported.

Univariable analysis showed that patient age and weight, donor age, previous kidney transplantation, previous cardiovascular events and need for insulin more than 48 h post-transplantation were significantly associated with pancreas graft survival. Using a Cox proportional hazards model that included these variables, with backward elimination, previous kidney transplant was the only significant risk factor for graft failure (HR = 3.3, 95% CI: 1.8, 5.9; *p* < 0.0001). Kaplan–Meier analysis confirmed that pancreas graft survival was inferior in patients who had received a kidney transplant prior to pancreas transplantation compared with those who had not received a kidney transplant prior to pancreas transplantation (log-rank test, *p* = 0.0002) (Fig. 5).

Safety observations

Table 4 shows the reports of post-transplant surgical intervention, cardiovascular events, infections and tumours occurring

Table 4 – Adverse events during the observation period (transplant day to 5 years post-transplant).

Adverse events during the observation period	Transplant recipients (N = 301)
Surgeries, n procedures/n patients (%)	143/104 (34.6)
Graft thrombosis	12/12 (4.0)
Intestinal fistula	5/5 (1.7)
Bleeding	22/20 (6.6)
Abscess	17/15 (5.0)
Other	87/74 (24.6)
No surgery, n patients (%)	197 (65.4)
CV events, n events/n patients (%)	25/21 (7.0)
Cerebrovascular accident	7/7 (2.3)
Coronary disease	3/3 (1.0)
Amputations	15/12 (4.0)
No CV events, n patients (%)	280 (93.0)
Infections, n infections/n patients (%)	246/150 (49.8)
Bacterial	199/124 (41.2)
Viral	47/42 (14.0)
Fungal	7/7 (2.3)
No infections, n patients (%)	151 (50.2)
Tumours, n (% of total patients)	11 (3.7)
Skin	5 (1.7)
Solid organ	2 (0.7)
Lymphoproliferative	2 (0.7)
Other	2 (0.7)
No tumours, n patients (%)	290 (96.3)

CV, cardiovascular.

during the study. A total of 143 surgical procedures were required in 104 patients (34.6%); 25% of these patients required a surgical procedure during the first 6 months post-transplant. There were 25 cardiovascular events in 21 patients (7.0%), including cerebrovascular accident, coronary disease and amputations. There were 246 infections in 150 patients (49.8%), the majority of which were recorded as 'bacterial' in origin (*n* = 199), occurring in 124 patients (41.2%). The median time from pancreas transplantation until the first infection

was 2.3 years. Only eleven patients (3.7%) developed tumours during the study.

Discussion

This study provides comprehensive, real-world data from a national patient series of routinely-monitored pancreas transplant recipients in Spain. Data from 301 pancreas transplant recipients were included, with the majority undergoing SPK transplantation, the most frequently performed pancreas transplant procedure.³ The Kaplan–Meier estimated 5-year patient survival rate (94.4%) was high and consistent with current 5-year survival rates in the US⁴ and also another European cohort.⁶ A total of 19 recipients died during the 5-year period; the main cause of death was infection, predominantly bacterial in origin. Complications due to bacterial infections continue to be a primary cause of morbidity and mortality in pancreas transplant recipients.⁹ In another study of 410 Spanish patients who received pancreas transplants, most of which were SPK, the most common complication was infection following surgery (experienced by 12% of patients), while the second most common complication was abdominal abscess (7.3% of patients).¹⁰

The pancreas graft survival rate at the end of this study (81.7%) was higher than the current rates reported in the US (SPK, 73%; PAK, 65%; PTA, 53%),⁴ but similar to that observed in two other Spanish studies (84.5% [SPK only] and 79.1% [SPK, PAK and PTA] at 5 years, respectively),^{11,12} and also the rate reported in the Netherlands (SPK, PAK, PTA, multivisceral and retransplant, 80.3%, following the introduction of modern induction therapy in 1999).⁶ The rate was lower than the rate of 95% reported by Gutiérrez et al. for a group of 20 Spanish patients who received SPK¹³; however, it should be noted that the follow-up period for those patients was 6 months, which is shorter than the 5-year observation period in the current study.

Our data show that pancreas graft survival was inferior in patients who had received a kidney transplant prior to pancreas transplantation compared with those who had not received a kidney transplant prior to pancreas transplantation. The higher rate of pancreas graft survival in SPK versus PAK during the first 3 years after pancreas transplant has been reported to be mainly due to an increased rate of immunologic graft loss in PAK.^{2,14} Nevertheless, it should be noted that PAK remains an appropriate option for some patients; for example, those on the SPK waitlist for whom a kidney becomes available. Results of a recent retrospective analysis of data from the US Organ Procurement and Transplantation Network (OPTN) show that PAK transplant recipients have an overall survival advantage compared with uraemic diabetic patients on the SPK waitlist who did not receive a transplant.¹⁵ PAK was also shown to be associated with increased kidney graft survival compared with that seen in patients with type 1 diabetes who received only a kidney transplant.¹⁵

Acute rejection as a cause of pancreas graft loss generally occurs 7–12 months post-transplant.¹⁶ As well as immunologic rejection, pancreatic allograft thrombosis is a major non-immunologic cause of pancreas graft loss, with a reported incidence of 23%,¹⁷ and accounting for a reported 29% of grafts

lost during the first 6 months after pancreas transplant.¹⁸ Over this 5 year study, 55 patients (18.3%) experienced pancreas graft loss, mainly due to vascular thrombosis (34.5%) followed by chronic rejection (18.2%). These findings are consistent with a cumulative rate of graft loss of 14.0% at 5 years in a retrospective, single-centre US study conducted in 227 consecutive SPK, PAK and PTA patients, in which 57 recipients experienced 79 acute rejection episodes.¹⁹

Maintenance protocols after pancreas transplantation generally comprise tacrolimus and MMF with early or delayed corticosteroid withdrawal.^{20–22} The majority of recipients in this study received induction immunosuppression with immediate-release tacrolimus (86.1%), MMF (64.1%) and MPA (35.9%), and all patients received induction immunosuppression with prednisone. Overall, 25% of patients achieved corticosteroid withdrawal (prednisone) by the end of the study, with 94.1% of patients still receiving MMF or MPA, and 74.7% receiving prednisone.

Glucose metabolism and renal function were also maintained following transplantation. Although the urine protein-to-creatinine ratio dipped at 2 years and then increased at 5 years, this was not clinically significant given that proteinuria levels were low until 4 years and then increased, probably due to the increased chance of chronic histologic lesions at 5 years.

Limitations

While this study included a large number of pancreas transplant recipients, there was a considerable difference in the number and types of transplantations performed at the different centres, and four national transplant centres did not participate. Despite this, the setting reflects national clinical practice in Spain for this patient population. The broad inclusion criteria were necessary to ensure all three pancreas transplantation types were considered during the study. Given the high patient survival rate, data for the association of risk factors with patient survival were not reported. Additionally, kidney graft survival was not analyzed according to pancreas transplant type. Additionally, the proportion of patients with missing data increased over time, either due to a lack of follow-up assessments or to omission of results from the medical records. The data relating to renal function and glucose metabolism should therefore be interpreted with caution.

Conclusion

This real-world, retrospective study showed high patient and graft survival rates after PTA, SPK and PAK transplantation performed in Spain. Glucose metabolism, renal function and cardiovascular risk factors were generally stable following transplantation, and the rate of death was 6.3% at 5 years post-transplant. Risk factors were not assessed for patient survival due to the high patient survival rate; however, pancreas graft survival was higher in patients without a previous kidney transplant.

Data statement

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>

Funding

This study was sponsored by Astellas Pharma, S.A.

Authors' contribution

All authors made substantial contributions to the conception and design of the study, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; and provided final approval for submission.

Conflict of interest

All authors report non-financial support from Astellas Pharma Inc during the conduct of the study.

Acknowledgments

The authors would like to thank Professor Maria José Ricart for their wisdom, friendship, and leadership in the development of pancreas transplantation as an established treatment in Spain. Anisha Mehra, PhD, CMPP™ and Rachel Parratt, Ph.D. assisted in drafting the manuscript under the direction of the authors, and provided editorial support throughout its development for Cello Health MedErgy. Editorial support was funded by Astellas Pharma Inc.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.nefro.2021.09.016](https://doi.org/10.1016/j.nefro.2021.09.016).

REFERENCES

- Jamil AKS. Pancreas and beta islet cell transplantation – evidence base and outcomes. *J Diabetes Metab.* 2016;7:680, <http://dx.doi.org/10.4172/2155-6156.1000680>.
- Gruessner AC, Gruessner RWG. Pancreas transplantation of US and non-US cases from 2005 to 2014 as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). *Rev Diabetic Stud.* 2016;13:35–58, <http://dx.doi.org/10.1900/RDS.2016.13.35>.
- Clatworthy M, Watson C, Allison M, Dark J. *Transplantation at a glance*. Hoboken, NJ: John Wiley & Sons, Ltd.; 2012.
- Dean PG, Kukla A, Stegall MD, Kudva YC. Pancreas transplantation. *BMJ.* 2017;357:j1321, <http://dx.doi.org/10.1136/bmj.j1321>.
- Rogers J, Farney AC, Orlando G, Iskandar SS, Doares W, Gautreaux MD, et al. Pancreas transplantation: the Wake Forest experience in the new millennium. *World J Diabetes.* 2014;5:951–61, <http://dx.doi.org/10.4239/wjd.v5.i6.951>.
- Kopp WH, Verhagen MJJ, Blok JJ, Huurman VAL, de Fijter JW, de Koning EJ, et al. Thirty years of pancreas transplantation at Leiden University Medical Center: long-term follow-up in a large Eurotransplant Center. *Transplantation.* 2015;99:e145–51, <http://dx.doi.org/10.1097/TP.0000000000000604>.
- International Registry on Organ Donation and Transplantation (IRODat). Spain deceased organ donor evolution [Internet]. Available from: <http://www.irodat.org/?p=databas&c=ES> [cited 12 Dec 2019].
- World Health Organization. Global report on diabetes [Internet]; 2016. Available from: <https://www.who.int/diabetes/global-report/en/> [cited 12 December 2019].
- Meirelles RF Jr, Salvaggio P, Pacheco-Silva A. Pancreas transplantation: review. *Einstein (Sao Paulo).* 2015;13:305–9, <http://dx.doi.org/10.1590/S1679-45082015RW3163>.
- Moya-Herraiz A, Muñoz-Bellvis L, Ferrer-Fàbrega J, Manrique Municio A, Pérez-Daga JA, Muñoz-Casares C, et al. Estudio cooperativo del Grupo Español de Trasplante de Páncreas (GETP): complicaciones quirúrgicas. *Cir Esp (English Ed).* 2015;93:300–6, <http://dx.doi.org/10.1016/j.cireng.2014.12.019>.
- Campos Hernández JP, Gómez Gómez E, Carrasco Valiente J, Márquez López FJ, Ruiz García J, Anglada Curado FJ, et al. Influence of surgical complications on kidney graft survival in recipients of simultaneous pancreas kidney transplantation. *Transplant Proc.* 2015;47:112–6, <http://dx.doi.org/10.1016/j.transproceed.2014.12.010>.
- Ferrer-Fàbrega J, Cano-Vargas B, Ventura-Aguilar P, Cárdenas G, García-Criado Á, López-Boado MA, et al. Early intestinal complications following pancreas transplantation: lessons learned from over 300 cases – a retrospective single-center study. *Transpl Int.* 2021;34:139–52, <http://dx.doi.org/10.1111/tri.13775>.
- Gutiérrez P, Marrero D, Hernández D, Vivancos S, Pérez-Tamajón L, Rodríguez de Vera JM, et al. Surgical complications and renal function after kidney alone or simultaneous pancreas-kidney transplantation: a matched comparative study. *Nephrol Dial Transplant.* 2007;22:1451–5, <http://dx.doi.org/10.1093/ndt/gfl771>.
- Ventura-Aguilar P, Ferrer J, Revuelta I, Paredes D, de Sousa-Amorim E, Rovira J, et al. Pancreas outcomes between living and deceased kidney donor in pancreas after kidney transplantation patients. *Nephrol Dial Transplant.* 2018;33:2052–9, <http://dx.doi.org/10.1093/ndt/gfy133>.
- Fridell JA, Niederhaus S, Curry M, Urban R, Fox A, Odorico J. The survival advantage of pancreas after kidney transplant. *Am J Transplant.* 2019;19:823–30, <http://dx.doi.org/10.1111/ajt.15106>.
- Patil DT, Yerian LM. Pancreas transplant: recent advances and spectrum of features in pancreas allograft pathology. *Adv Anat Pathol.* 2010;17:202–8, <http://dx.doi.org/10.1097/PAP.0b013e3181d97635>.
- Hakeem A, Chen J, Iype S, Clatworthy MR, Watson CJE, Godfrey EM, et al. Pancreatic allograft thrombosis: suggestion for a CT grading system and management algorithm. *Am J Transplant.* 2018;18:163–79, <http://dx.doi.org/10.1111/ajt.14433>.
- Muthusamy ASR, Giangrande PLF, Friend PJ. Pancreas allograft thrombosis. *Transplantation.* 2010;90:705–7, <http://dx.doi.org/10.1097/TP.0b013e3181eb2ea0>.

19. Dong M, Parsaik AK, Kremers W, Sun A, Dean P, Prieto M, et al. Acute pancreas allograft rejection is associated with increased risk of graft failure in pancreas transplantation. *Am J Transplant*. 2013;13:1019-25, <http://dx.doi.org/10.1111/ajt.12167>.
20. Kandaswamy R, Stock PG, Gustafson SK, Skeans MA, Curry MA, Prentice MA, et al. OPTN/SRTR 2015 annual data report: pancreas. *Am J Transplant*. 2017;17:117-73, <http://dx.doi.org/10.1111/ajt.14125>.
21. Kimelman M, Brandacher G. Trends in immunosuppression after pancreas transplantation: what is in the pipeline? *Curr Opin Organ Transpl*. 2013;18:76-82, <http://dx.doi.org/10.1097/MOT.0b013e32835c6eda>.
22. Montero N, Webster AC, Royuela A, Zamora J, Crespo Barrio M, Pascual J. Steroid avoidance or withdrawal for pancreas and pancreas with kidney transplant recipients. *Cochrane Database Syst Rev*. 2014:CD007669, <http://dx.doi.org/10.1002/14651858.CD007669.pub2>.