Risk factors and outcome in clinical pancreas transplantation

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Colophon
Risk factors and outcome in clinical pancreas transplantation
Thesis, Leiden University, 2019, The Netherlands
Wouter H. Kopp, 2019, The Netherlands

ISBN: 978-94-6361-287-6
Layout and printing by: Optima Grafische Communicatie (www.ogc.nl)

Financial support received by Nederlandse Transplantatie Vereniging, Dutch Kidney Foundation, Leiden University Medical Center, Haaglanden Medisch Centrum, Chipsoft B.V. for the printing of this thesis is gratefully acknowledged.

Cover design by Manon Zuurmond, medical illustrator LUMC

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Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op donderdag 19 september 2019
klokke 15:00 uur

door

Wouter Harry Kopp

geboren te Leiderdorp
in 1988

Promotor
Prof. dr. J.F. Hamming

Copromotor
Dr. A.E. Braat

Leden promotiecommissie
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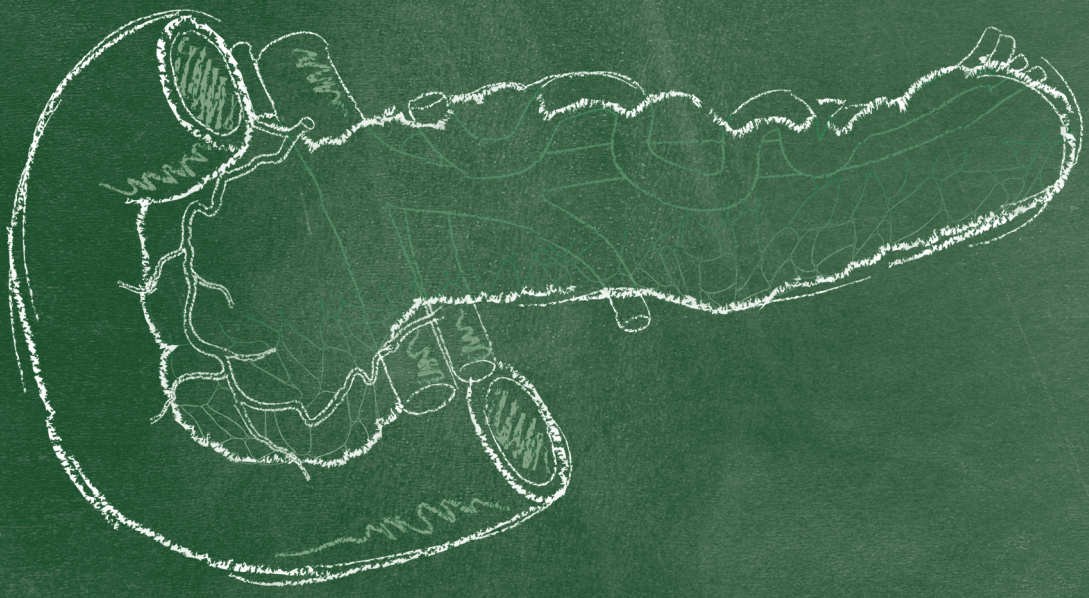

1 General introduction

GENERAL INTRODUCTION

Pancreas transplantation is to date the only definitive treatment option for patients with type 1 diabetes mellitus (T1DM). For patients with metabolic dysregulation-induced end stage renal disease (ESRD) a simultaneous kidney and pancreas transplantation is an option, whereas for non-uremic patients suffering from hypoglycemic unawareness solitary pancreas transplantation is a feasible option.

In December 1966, at the University of Minnesota Hospital, Kelly and Lillehei, performed the first pancreas transplantation, combined with a kidney transplantation, to treat a uremic, type I diabetic patient. The results of their series were published by another pancreas transplantation pioneer, David Sutherland, in a hallmark paper on pancreas transplantation in 2001.[1] More recently, other larger single center studies that were published came from Wisconsin, USA[2] and the first large European series was from Innsbruck.[3] Multiple other large pancreas transplantation centers and (inter)national registries have published results as well and all show excellent outcomes in terms of survival.[4-8] Table 1 represents an overview of their results.

Since the first transplantation, over 50.000 pancreas transplantations have been performed worldwide.[9] Most of these transplantations were performed as a simultaneous pancreas kidney (SPK) transplantation, which is still the most commonly performed type of pancreas transplantation. The first pancreas transplantation in the Netherlands was performed at the Academic Hospital Leiden (currently Leiden University Medical Center) in 1984.[10]

Both the increased experience in dedicated pancreas transplantation centers and ongoing success have paved the way and pancreas transplantation became an accepted treatment for a broader range of suitable recipients. This phenomenon has frequently been described as 'the transplant paradox'[11]: that by increasing the numbers of transplantation and thus increasing experience and awareness, the indications and recipient selection become increasingly more liberal. This leads to waiting lists increasing even more, and without a similar increase in organs leads to organ shortage and increased waiting time. On the other hand, it appears that for many healthcare professionals pancreas transplantation is still a black box and many still think of it as an experimental procedure. Through increasing awareness, the number of suitable candidates and transplantations may increase. This may have partially been the aim of Smets *et al.* in a study in which all Dutch type 1 diabetic patients that started renal replacement therapy (RRT) in The Netherlands were included.[12] Furthermore, this study was the first randomized trials that showed that, for patients suffering from (imminent) renal failure secondary to type 1 diabetes, a 50% reduction in long term mortality may be achieved by simultaneous pancreas kidney transplantation, as compared to kidney transplantation alone. This was a vital addition to previous reports that predominantly focused on prolonged kidney graft survival and increased quality of life after simultaneous pancreas

kidney transplantation and even contradicted each other on the benefit of addition pancreas transplantation.[13,14]

A large part of this thesis was made possible by Eurotransplant. Eurotransplant manages the above mentioned waiting list; acts as a mediator between the donor and the recipient and plays a key role in the distribution of organs in 8 European countries (The Netherlands, Belgium, Luxembourg, Germany, Austria, Slovenia, Croatia, Hungary).[15] In order to be able to perform this key task of allocation, Eurotransplant collects data on donors and recipients. In addition to allocation, Eurotransplant is continuously trying to improve allocation algorithms based on the latest medical, ethical and legal principles. In order to do so, Eurotransplant also collects data on outcome following transplantation. In this thesis, these Eurotransplant data, along with data derived from Leiden University Medical Center, will be analyzed.

Patients suffering from ESRD due to T1DM that are eligible for kidney transplantation are the prime candidates for SPK. In patients with ESRD, the benefits of a simultaneous pancreas kidney transplantation outweigh the burden of life-long immunosuppression and the surgical risks of the operation. The goal of pancreas transplantation, in the context of simultaneous pancreas transplantation is to achieve exogenous insulin independence. By achieving insulin independence, the benefits are rendering patients free from intensive blood glucose self-monitoring and insulin administration, protection of the kidney transplant, as well as counteracting, stabilizing, and perhaps even reversing, the progression of other secondary complications such retinopathy and neuropathy.[16,17] Patients with ESRD that already received a kidney transplant might be candidates for pancreas after kidney (PAK) transplantation, then also gaining the benefits SPK recipients have. In case of life-threatening hypoglycemic unawareness, patients not suffering from ESRD might still be considered as candidates for pancreas transplantation alone (PTA) in case of brittle diabetes or failure to achieve euglycemia on intensive exogenous therapy.[14,18] SPK may also be a suitable option for patients not yet suffering from ESRD, but who are expected to become RRT dependent in the nearby future: a so-called pre-emptive transplantation.[6] To date, the selection of patients with type 2 diabetes mellitus for pancreas transplantation is controversial and, although pancreas transplantation is performed for T2DM, this constitutes only a very small minority and is therefore, beyond the scope of this thesis.[19] Some patients with maturity onset diabetes of the young (MODY) may, on the other hand, be suitable candidates for transplantation.[20]

In selected cases, islet of Langerhans transplantation is a feasible option, which may be performed to render the recipient insulin independent.[21,22] However, in most cases, islet transplantation is performed to protect the recipient and the graft from the secondary complications of the underlying disease. Due to inferior graft survival rates (in terms of insulin independence) of islet transplantation, as compared to vascularized pancreas, vascularized transplantation is still the preferred first step in beta-cell replacement therapy in

our hospital. Furthermore, the islet yield from one single donor is frequently not enough to render the recipient off exogenous insulin and islets of two or more donors are combined to get an adequate islet yield for one recipient. Islet after kidney transplantation may be a less surgically invasive and thus suitable option for patients that may not be fit for surgery or following multiple previously failed vascularized pancreas transplants to protect the kidney graft against secondary complications associated with diabetes, without rendering the patient insulin independent.[23]

Outcome following pancreas transplantation is excellent, with death censored graft survival rates around 80% after 5 years and patient survival rates around 90% after 5 years (table 1). While improvements in immunosuppressive regimes have improved mid- to long term outcome by protecting the recipient and his/her graft from rejection, short term outcome is still limited by a high incidence of surgical complications. This early graft failure is usually well-defined, since most patients require immediate graft explantation and exogenous insulin therapy. Defining longer term graft failure on the other hand is more difficult. Different definitions are being used around the world.

Table 1. Overview of results of large single center or national registry studies

			Patient survival		Pancreas graft survival		Definition of pancreas graft failure
Authors	Center/Country	Year	1 year	5 years	1 year	5 years	
Sutherland et al.	Minneapolis, Minnesota, USA	2001	92%	88%	79%	73%	Non-death censored insulin independence
Thai et al.	Pittsburgh, USA	2004	100%		94%		Not-stated
Sollinger et al.	Madison, Wisconsin, USA	2009	97%	89%	88%	76%	Not-stated
Ollinger at al.	Innsbruck, Austria	2011	98%	94%	88%	82%	Insulin independence
Muthusamy et al	United Kingdom	2012	95-96%		87-88%		Death censored insulin independence
Walter et al.	Bochum, Germany	2014	96%	91%	80%	73%	Not-stated
Kopp et al.	Leiden, The Netherlands	2015	96%	87%	84%	76%	OPTN defined
Kopp et al.	Eurotransplant region	2016	94%	91%*	84%	79%*	Death censored, center reported

* 3-year survival

Failure may be defined as return to exogenous insulin therapy. Failure may also be defined as poor glycemic control (for example based on ADA definition of T1DM) or even absent c-peptide. Clearly, using one definition would be preferable, as different definitions yield different results and different different suggestions for the best definition have been proposed.[24,25]

The most feared complication is graft thrombosis. Because its etiology is still not fully understood, there is still no consensus on how to deal with this 'Achilles heel' of pancreas transplantation.[26] Not only the change from high blood flow in the donor to low blood flow in the recipient, ischemia reperfusion injury and procurement related tissue damage with subsequent leakage of lytic enzymes[27], but also the change from uremic to non-uremic recipients are thought to play a role. Center specific protocols concerning surgical technique, immunosuppression, inotropic support may also play a role. Several strategies have been undertaken to deal with this complication, including tailor made high dose anticoagulants using thromboelastography (TEG)[28], strict radiological follow up[29,30] and different operating techniques.[4,31] In case of complete thrombosis, donor pancreatectomy is usually required. Some studies report on graft salvage, either by endovascular or surgical interventions.[32,34] In case of partial thrombosis, which is considered to be 'normal' due to the changes in vascularization (especially by ligation of the splenic vein) by some physicians, grafts may be preserved by treating the patients with intravenous heparin and oral anticoagulants.[35]

In general, outcome following transplantation depends on several factors and might best be described as the following equation: donor + procurement + recipient + center and experience = outcome. Next to those 4 factors, yet unknown or unidentified factors, play a role. This thesis contains data that might further fill in the equation, by elaborating on most individual factors and measuring their association with outcome.

Outline of this thesis

Chapter 2 of this thesis provides an overview of 30 years of pancreas transplantation at the LUMC. Pancreas graft survival is defined by multiple factors in this chapter.

Currently, there is a worldwide debate on how pancreas graft failure should be defined. Whether death censored or uncensored and whether this should be reinstitution of exogenous insulin therapy, the use of oral anti hyperglycemic agents, absent c-peptide, return of diabetes mellitus, yet remains unclear and without consensus. In general, graft failure in this thesis was defined as death censored and return to exogenous insulin therapy, unless defined otherwise in specific chapters.

Next to valid definition of outcome, valid measures to evaluate which factors enter the equation are just as important. **Chapters 3 and 4** of this thesis elaborate on tools to measure pancreas donor quality, which are an important factor in the equation. In 2008, a Eurotransplant derived tool, called the Preprocurement Pancreas Allocation Suitability Score (P-PASS) was introduced.[36] This was the first tool to describe pancreas donor quality in an evidence-based model. In 2010, Axelrod introduced the Pancreas Donor Risk Index (PDRI).[37] In **chapter 3**, we aimed to validate the UNOS based PDRI in our center, since in liver transplantation had previously shown that differences in populations exist. This would be the first step in the possible implementation of the PDRI. **Chapter 4** elaborates on the use of different risk indices in organ allocation policies. After investigating risk indices in

our own center (chapter 3), we evaluated both existing risk indices (P-PASS and PDRI) in a large Eurotransplant donor database for their ability to predict allocation outcome. In this study, factors unknown at time of allocation, were set to reference.

In **chapter 5**, using a similar Eurotransplant database, supplemented with outcome data, the center effect is investigated as a part of the equation. Using a large Eurotransplant database, the relationship between center volume and outcome was demonstrated.

Chapter 6 elaborates on one of the major concerns following pancreas transplantation: pancreas graft thrombosis.[38] This feared complication has frequently been described as the 'Achilles heel' of pancreas transplantation. In this chapter, we aimed to investigate a less frequently reported problem: partial graft thrombosis and its clinical implications. In **chapter 7**, another risk factor is investigated. In order to keep up with organ shortage, transplant professionals are increasingly forced to accept grafts from extended criteria donors, such as grafts from donation after circulatory death (DCD) donors. In this chapter, the Leiden University Medical Center experience with DCD pancreas transplantation is described.

Chapter 8 summarizes and discusses all results and conclusions described in this thesis. **Chapter 9** is a general discussion and **chapter 10** contains future perspectives in the field of pancreas transplantation and in particular the clinical research field. **Chapter 11** is the Dutch summary of this thesis and contains explanations for people less experienced in the medical field.

Since the first pancreas transplantation in 1966, the procedure has gone from an experimental surgical treatment to the, to date, single definitive treatment for T1DM. Multiple factors have to be considered when determining and interpreting outcome following pancreas transplantation, amongst them the factors studied in this thesis. Even though the experience around the world is steadily increasing, the way to fully understand all physiological, pathophysiological and clinical aspects of this highly complex procedure is still long and the equation remains yet to be completed.

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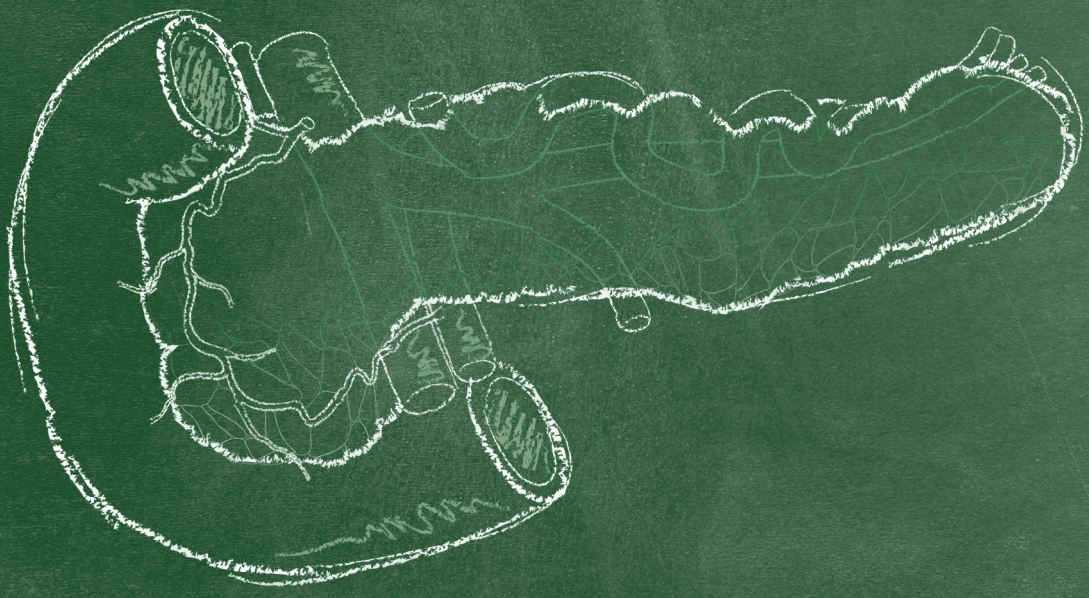

2

Thirty Years of Pancreas Transplantation at Leiden University Medical Center: Long-Term Follow-Up in a Large Eurotransplant Center

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Transplantation. 2015 Sep; 99 (9)

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ABSTRACT

Introduction: An overview of 30 years of pancreas transplantation at a high-volume center. Analysis of patient survival– and graft survival–associated risk factors.

Methods: All pancreas transplantations performed in our center from January 1, 1984, till December 31, 2012, were evaluated. Covariates influencing pancreas graft survival were analyzed using both univariate and multivariate analysis and Kaplan-Meier analysis.

Results: In the study period, 349 pancreas transplantations were performed. With the introduction of modern induction therapy in 1999, 5-year patient survival improved to 92.0% ($p = 0.003$). Five-year pancreas graft survival improved to 80.3% ($p = 0.026$). Pancreas graft survival was influenced by left or right donor kidney, transplant type, local origin of procurement team, pancreas cold ischemia time, recipient cerebrovascular disease. Pancreas donor risk index increased to 1.39 over the years and pancreas donor risk index 1.24 or higher is a risk factor for graft survival ($p = 0.007$).

Conclusions: This study has shown excellent results in patient and pancreas graft survival after 30 years of pancreas transplantation in a high-volume center. Different donor, transplant, and recipient related risk factors influence pancreas graft survival. Even with higher risk pancreas donors, good results can be achieved.

Simultaneous pancreas and kidney (SPK) transplantation is currently the first choice of treatment for patients with type 1 diabetes mellitus (T1DM) and related end-stage renal disease. Pancreas transplant alone (PTA) transplantation can be performed in case of T1DM with preserved kidney function in case of hypoglycemic unawareness.[1] The first pancreas transplantation in the Netherlands was performed at the Leiden University Medical Center (LUMC) in 1984.[2] Over the past 30 years, LUMC has become one of the largest pancreas transplantation centers within the Eurotransplant region.[3]

In the current literature, there are several publications reporting on long-term results after pancreas transplantation. The first large series were described by Sutherland et al[4] in 2001. More recently, Sollinger et al[5] also reported on 22 years of follow-up of 1000 pancreas transplantations in Wisconsin, followed by more recent reports describing risk factors and long-term experiences.[6-9] The largest European series is from Innsbruck, Austria, reporting on results of 509 consecutive pancreas transplantations with long-term follow-up.[10] However, when comparing results from different trans- plant centers, it appears that no standard definition of pancreas graft survival is being used, making adequate comparison difficult. In 2008, the Pancreas Transplant Committee (PTC) of the Organ Procurement Transplantation Network (OPTN) pled for 1 definition of pancreas graft function and failure, pointing out the importance of a unified definition, which should be used worldwide.[11] In most studies, several donor-, transplant-, and recipient- related risk factors are believed to influence outcome after transplantation. The pancreas donor risk index (PDRI) was constructed by Axelrod and allowed for structural assessment of donor quality and prediction of 1-year graft survival after pancreas transplantation.[8]

Furthermore, center volume may also play a role in the outcome. In 2004, Mandal has shown that low volume pancreas transplantation centers (<10 transplantation/year) have poorer outcome in graft survival compared to medium (10–20 transplantations/year) or high (>21 transplantations/ year) volume centers.[12]

The objective of this study is to describe the results, measured in patient and pancreas graft survivals, of 30 years of pancreas transplantation in recipients with T1DM and possible related complications at the LUMC and to analyze donor-, transplant-, and recipient-related risk factors influencing pancreas graft survival. Also, we hope to show that with relatively lower quality donors, indicated by high PDRI, we are able to achieve good outcome in our high-volume center.

METHODS

This study is a retrospective database analysis of all consecutive pancreas transplantations performed at the LUMC, from the first pancreas transplantation on May 14, 1984, till December 31, 2012. For all 349 transplantations, follow-up was collected until October 31, 2013.

Data Collection

All donor, transplant (Table 1), and recipient (Table 2) characteristics were systematically registered. Follow-up data were recorded to analyze outcome after pancreas transplantation, including; Hba1c levels, insulin use, c-peptide, fasting plasma glucose, patient death date and cause, failure date, failure cause, number of treated rejection episodes, date of transplantectomy, date last patient contact.

Table 1. Donor and transplant factors and their influence in univariate analyses on pancreas graft survival

Donor factor	**N (%)**	***P*[a]**	**X^2**
Age category		0.006	12.391
<30[b]	134 (38)		
30-39	78 (22)		
40-50	128 (37)		
>50	9 (3)		
Sex		0.48	0.507
Male	171 (49)		
Female	178 (51)		
Cause of death		0.37	3.143
Trauma	129 (37)		
CVA	199 (57)		
Anoxia	9 (3)		
Other	12 (3)		
Diabetes Mellitus	0 (0)	n/a	
Hypertension (yes)	26 (7)	0.11	2.559
Malignancy (yes)	1 (0.3)	0.589	0.292
Drug use (yes)	8 (2)	0.51	0.426
Alcohol use (yes)	7 (2)	0.08	2.984
HCVAb pos	0 (0)	n/a	
HBcAb pos	2 (1)	0.342	2.143
CMV IgM/IgG pos	130 (37)	0.76	0.092
Cardiac arrest (yes)[b]	40 (12)	0.019	5.508
Hypotensive period (yes)[c]	123 (35)	0.56	0.342
Use of vasopressors (yes)	277 (79)	0.52	0.405
DCDD (yes)	6 (2)	0.86	0.031
	Median (range)	***P*[d]**	
Age, y	36 (10-57)	0.006	
BMI	23 (14-35)	0.81	
Serum sodium (mmol/L)	144 (123-175)	0.58	
Serum creatinine (umol/L)	70 (25-190)	0.3	
Serum lipase (U/L)	20 (7-332)	0.61	
ICU stay (days)	2 (1-33)	0.058	
Serum amylase (U/L)	80 (7-1756)	0.029	
ICU stay (days)	2 (1-33)	0.058	

Table 1. (continued)

Transplant factor	N (%)	P^a	X^2
Allocation		0.66	0.837
Local	48 (14)		
Regional	234 (67)		
Extra-regional	67 (19)		
Procurement team		<0.001	17.441
Local [b]	60 (17)		
Non-local	240 (69)		
Unknown	49 (14)		
Transplantation type		<0.001	15.355
SPK [b]	325 (93)		
PAK	21 (6)		
PTA	3 (1)		
Donor kidney		<0.001	32.951
No kidney	24 (7)		
Left [b]	276 (79)		
Right	49 (14)		
Perfusion fluid		<0.001	27.999
UW [b]	312 (89)		
HTK	25 (7)		
Other	12 (3)		
	Median (range)	P^d	
Cold ischemia time (h)	12 (3-20)	0.005	
PDRI	1.24 (0.68-2.31)	0.25	
P-PASS	16 (9-22)	0.74	

[a] Univariate Kaplan-Meier analysis (Log Rank Mantel-Cox)

[b] Favorable factor in univariate analysis

[c] Defined as: systolic pressure < 80 mmHg, for at least 10 minutes.

[d] Univariate Cox-regression analysis

n/a not applicable; HTK, histidine-tryptophan-ketoglutarate; ICU, intensive care unit; IgG, immunoglobulin G; IgM, immunoglobulin M.

Postoperative Care

From March 1999, patients received any form of modern induction therapy, either interleukin (IL)-II receptor antagonist or antithymocyte globulin (ATG). Currently, first started in December 2007, induction therapy consists of administration of anti-CD52 monoclonal antibody (alemtuzumab). Before 1999, patients received either anti-CD3 antibody (OKT3) or no induction therapy. As maintenance therapy, recipients are currently administered combination therapy, consisting of tacrolimus and mycophenolate mofetil. Until 1996, recipients received cyclosporine, azathioprine, and prednisone. From that time, until 2002, when cyclosporine was replaced with tacrolimus, patients received mycophenolate mofetil

Table 2. Recipient factors and their influence in univariate analyses on pancreas graft survival

Recipient factor	N (%)	*P*[a]	X^2
Age category		0.59	1.915
<40	156 (45)		
40-49	142 (41)		
50-59	49 (14)		
≥60	2 (0.6)		
Sex		0.42	0.652
Male	210 (60)		
Female	139 (40)		
Type of dialysis		0.835	0.361
No dialysis (pre-emptive transplant)	144 (41)		
Haemodialysis	93 (27)		
Peritoneal dialysis	112 (32)		
Repeated transplantation		0.4	0.715
First transplant	330 (95)		
Re-transplant	19 (5)		
Thrombo-embolic event	4 (1)	0.253	1.307
Cerebrovascular disease	21 (6)	0.011	6.418
Coronary artery disease	54 (16)	0.591	0.289
CABG	11 (3)	0.557	0.345
PTCA	23 (7)	0.382	0.763
CMV mismatch		0.121	2.41
No mismatch (D-/R-)	269 (77)		
D+/R-	72 (21)		
Unknown	8 (2)		
Modern induction therapy		0.026	4.939
Yes[b]	237 (68)		
No	112 (32)		
Primary drainage		0.55	0.367
Bowel	91 (26)		
Bladder	256 (73)		
Unknown	2 (1)		
	Median (range)	*P*[c]	
Age	42 (23-64)	0.99	
BMI	24 (17-33)	0.2	
Time on waiting list	1.1 (0-10)	0.32	
Time since DM I (years)	27 (12-48)	0.51	
Time since first dialysis treatment (years)	0.69 (0-8)	0.3	
Total HLA mismatches	4 (0-6)	0.86	

[a] Univariate Kaplan-Meier analysis (Log Rank Mantel-Cox)

[b] Favorable factor in univariate analysis

[c] Univariate Cox-regression analysis

instead of azathioprine. Starting in 2008, routine administration of prednisone was ceased. Patients currently receive low dose (2850 IE) low molecular weight heparin in a twice-daily regime as graft thrombosis prophylaxis. This regime was started in 2008. Before that, regular antithrombotic therapy consisted of the same dose, administered once daily. On discovery of partial graft thrombosis, patients are prescribed vitamin K antagonists for a duration of at least 3 months. Routine computed tomography imaging is per- formed between the 4th and 7th day after transplantation, depending on renal (graft) function.

Analysis

Outcome was characterized by patient survival and graft survival. Patient death with a functioning graft was not considered as graft failure (death-censored graft survival). Endocrine pancreatic function was subdivided in grades A to E, using HbA1c and use of insulin as markers for pancreatic graft function. In this study and in particular, when performing univariate analysis, the OPTN definition of graft failure was used as a guideline, in which allograft function classified as grade A and B were considered as functioning grafts, and grafts with grades C, D, and E were considered as failed allografts. According to this definition, persistent HbA1c greater than 6.3% and/or insulin was classified as grade C (insulin use less than 50% of pretransplant dose) or grade D (insulin use more than 50% of pretransplant dose), and persistent HbA1c 7.0% or higher was classified as grade E. Standard OGTT was not performed in analyzing graft function, for this was not required for classification of graft failure using the OPTN PTC definition. Graft thrombosis was defined as the presence of intravascular thrombus, proven after removal of the pancreas graft in case of complete thrombosis and, in case of partial thrombosis, presence of partial intravascular thrombus. Technical failure (TF) consists of pancreas graft thrombosis, infections, graft pancreatitis, leakage, and bleeding.[13] Early graft failure was defined as graft failure within 90 days after transplantation.[7] To compare groups based on outcome, we used the start of modern immunosuppressive induction therapy (ATG/IL-II receptor antagonist/ alemtuzumab) in March 1999 as a dividing point in the analysis of graft survival. The start of immunosuppressive therapy as induction therapy was a landmark in transplantation medicine, with marked improvement of long-term results in pancreas transplantation.

Statistical Analysis

For statistical survival analysis, Kaplan-Meier and Cox regression models were performed using SPSS version 20.0. Significant factors in univariate analysis will be entered into a multivariate model. Other factors will be added to the model using stepwise forward selection. A p-value less than 0.05 was considered significant for factors in both univariate and multivariate analyses.

RESULTS

Donor and transplant characteristics are shown in Table 1. In the study period, a total of 349 consecutive pancreas transplantations were performed at the LUMC, of which 325 (93.1%) were simultaneous pancreas kidney, 21 (6.0%) were pancreas after kidney, and 3 (0.9%) were PTA. Mean follow-up was 8.0 years (0–24.2 years). Recipient characteristics are shown in Table 2. Primary indication for transplantation was T1DM (99.7%) with (96.8%) or without (2.9%) renal complications. In total, 19 retransplantations (5.4%) were performed, all were included in the analysis.

In univariate analysis, death-censored pancreas graft survival was influenced by the following donor- and transplantation-related risk factors: donor age ($p = 0.006$), donor alcohol use ($p = 0.08$), serum amylase ($p = 0.029$), origin of procurement team ($p < 0.001$), transplantation type ($p < 0.001$), donor kidney side ($p < 0.001$), perfusion fluid ($p < 0.001$), and cold ischemia time ($p = 0.005$). Donor cardiac arrest had a protective effect on pancreas graft survival ($p = 0.019$), not on kidney graft survival ($p = 0.823$). Retransplantation was found not to be a significant covariate for pancreas graft survival in univariate analysis ($p = 0.40$). Recipient-related risk factors influencing pancreas graft survival were: cerebrovascular disease ($p = 0.011$) and induction therapy ($p = 0.026$). Results of the univariate analyses of death-censored OPTN-defined graft survival of all donor, transplant, and recipient factors are also reported in Tables 1 and 2.

In 256 (73%) patients, bladder drainage was initial drainage method. Of these patients, 171 (66.7%) were converted to enteric drainage. Median (25th–75th percentile) interval between transplantation and conversion was 339 (173–772) days. Recipients who were bladder drained and not converted to bowel drainage had significantly worse pancreas graft survival ($p < 0.001$)

Overall patient survival at 1, 5, and 10 years was 95.7%, 86.9%, and 74.6%, respectively. One-, 5-, and 10-year overall pancreas graft survival was: 83.6%, 76.4%, and 70.8%, respectively, using the OPTN definition. Death-censored pancreas graft survival was 85.1%, 78.2%, and 72.8% at 1, 5 and 10 years in the SPK subgroup. For pancreas after kidney, this was 66.0% and 55.0%, longest follow-up before pancreas graft failure was 8.9 years. Longest death-censored graft survival was 3.2 years for PTA grafts, with 1-year graft survival at 33.0%.

When pancreas graft failure occurred (n = 99), in the majority of cases, this was caused by graft thrombosis (35.4%) or rejection (20.2%). Other causes of graft failure were atrophy or exhaustion of the graft (6.1%), infection (5.1%), and bleeding (4.0%). Early pancreas graft failure due to TF occurred in 33 cases, 29 of which were due to graft thrombosis. From January 1, 2001, 43 cases of partial graft thrombosis occurred in 213 patients (20.2%). From January 1, 2008, the incidence of graft failure due to complete thrombosis was 9.3%.

Kidney graft survival at 1, 5, and 10 years was 91.6%, 87.9%, and 81.6%. Kidney graft survival was significantly better when left kidney was donated, compared to when right kidney was donated: 94.4% versus 75.7% at 1-year follow-up ($p < 0.001$). Main reasons for right kidney graft loss were rejection (33.3%) or patient death (33.3%). Right kidney graft loss due to thrombosis occurred in 1 case.

Clinical Outcome in Different Periods of Induction Therapy

Long-term results of the transplantations performed in the LUMC are shown in Figure 1, divided by transplant period (using the start of modern induction therapy in March 1999 as a dividing point). Two hundred thirty-seven (67.9%) recipients received modern induction therapy. Recipients in the induction therapy group were older ($p < 0.001$), had higher body mass index ($p = 0.004$), had been on the waiting list longer ($p < 0.001$), and had longer duration of diabetes mellitus ($p < 0.001$). They received pancreas grafts from higher body mass index donors ($p = 0.025$) and higher Pancreas Preprocurement Allocation Suitability Score donors ($p < 0.001$). Donors also had higher creatinine levels ($p = 0.013$), had had less hypotensive periods ($p = 0.003$), but had had more cardiac arrests ($p = 0.001$). They received more regionally allocated grafts ($p = 0.001$), but less local and extraregional allocated grafts ($p = 0.001$) Also, they received more grafts procured by the local team ($p < 0.001$). In the modern era, more pancreas grafts were transplanted without kidney, but less with right kidney ($p < 0.001$). Additionally, 20 (8.4%) were PAK in the modern era versus 1 (0.9%) in the historic group ($p = 0.022$). All recipients in the historic group were bladder drained, whereas 91 (38.4%) in the modern group were primarily enteric drained ($p < 0.001$).

Patient survival (Figure 1a) at 1-year, 5-year, and 10-year follow-up was, respectively, 93.8%, 78.4%, and 65.7% for the historic group and 96.6%, 92.0%, and 80.9% for modern induction therapy group and was significantly better in the more recent period ($p = 0.003$). Death-censored pancreas graft survival (Figure 1b) at 1, 5, and 10 years was 73.0%, 68.2%, and 65.0%, respectively, in the historic group, and 88.5%, 80.3%, and 72.3%, respectively, in the modern induction therapy group. These results were also significantly better in the modern era ($p = 0.026$).

Different regimes of induction therapy led to following 1-year, 5-year, and 10-year pancreas graft survival rates: 75.6, 69.5%, and 66.8% without induction therapy; 68.0%, 64.0%, and 64.0% for OKT3; 89.1%, 83.5%, and 77.4% for IL-II receptor antagonists; 85.1%, 78.2%, and 67.1% for ATG; and 91.2% for alemtuzumab. Long-term follow-up (5 years and 10 years) of alemtuzumab induction therapy is not yet available.

In the first 6 months after transplantation, kidney biopsy-proven acute rejection in SPK transplantation recipients occurred in 85.9% of recipients without induction therapy (n = 91), 82.6% with OKT3 (n = 25), 52.8% with IL-II receptor antagonists (n = 37), 42.6% with ATG (n = 108), and 11.4% with alemtuzumab (n = 81) ($p < 0.001$). Data on induction therapy were missing for 6 patients; 1 patient received both IL-II receptor antagonist and ATG.

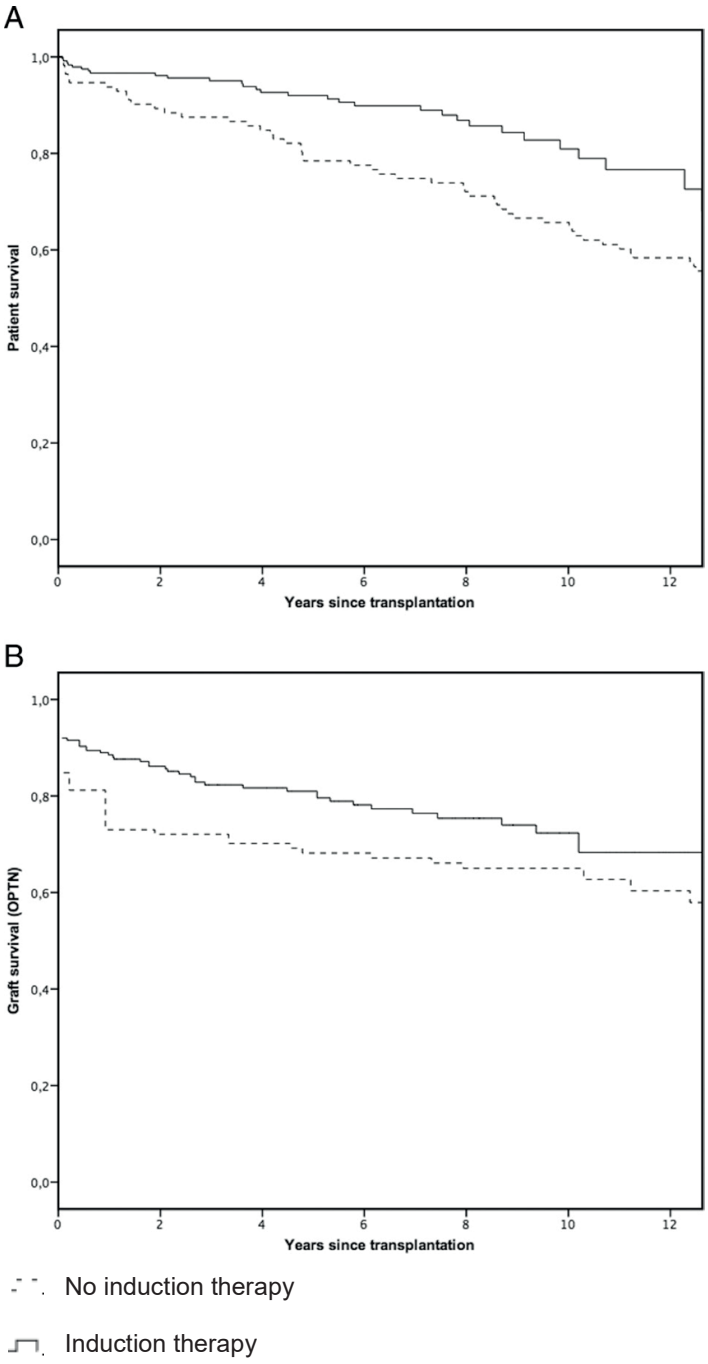

Figure 1a. Kaplan Meier survival curves of patient survival divided by use of induction therapy (p=0,003)
Figure 1b. Kaplan Meier survival curves of OPTN defined death censored graft survival divided by use of induction therapy (p=0,026)

Multivariate Analysis

Stratified by induction therapy, in a multivariate Cox-regression analysis, significant factors from univariate analysis were entered. Other factors were entered, and the model was fitted using forward selection. Significant factors of this multivariate analysis were: donor left versus right kidney: hazards ratio (HR), 3.18 (95% confidence interval [95% CI], 1.49–6.76, $p = 0.003$); SPK versus PAK/PTA: HR, 3.68 (95% CI, 1.65–8.19; $p = 0.001$); local origin of procurement center: HR, 2.72 (95% CI, 1.11–6.68, $p = 0.029$); pancreas cold ischemia time: HR, 0.9 (95% CI, 0.81–0.99; $p = 0.033$); recipient cerebrovascular disease: HR, 3.52 (1.41–8.78, $p = 0.002$) for OPTN-defined death-censored pancreas graft survival (Table 3). Primary enteric or bladder drainage was borderline associated with pancreas graft survival in favor of bladder drainage: HR, 3.81 ($p = 0.051$).

Table 3. Multivariate analysis[a] of risk factors influencing pancreas graft survival

Factor	HR	95% CI	*P*
Donor kidney side			
Left kidney	ref.		
Right kidney	3.18	1.49 – 6.76	0.003
No kidney[b]	n/a		n/a
Transplant type			
SPK	ref.		
PTA/PAK	3.68	1.65 - 8.19	0.001
Procurement center			
Local	ref.		
Non-local	2.72	1.11 - 6.68	0.029
Pancreas cold ischemia time	0.90	0.81 – 0.99	0.033
Recipient cerebrovascular disease			
No	ref.		
Yes	3.52	1.41 - 8.78	0.007

[a] Forward selection stepwise multivariate analysis using OPTN definition for graft survival

[b] Unable to calculate HR due to stratum effect

Donor Quality and Graft Survival

Median PDRI was 1.24. Quality of donors decreased since the start of the transplant program, indicated by an increase of median PDRI. The PDRI was calculated for each period: 1984 to 1991: PDRI, 1.14 (0.68–2.20); 1992 to 1998: PDRI, 1.20 (0.73–2.01); 1999 to 2005: PDRI, 1.25 (0.72–2.31); 2006 to 2012: PDRI, 1.39 (0.70–2.21). The PDRI of 5 recipients could not be calculated. The PDRI was not associated with pancreas graft survival in univariate analysis, when analyzed as a continuous variable ($p = 0.25$). However, PRDI 1.24 or higher donor grafts had significant poorer outcome compared to PDRI less than 1.24: 71.2% versus 83.8% graft survival at 5 years follow-up ($p = 0.007$). Starting in 2011, so far, 6

recipients were transplanted using grafts from donation after circulatory determination of death (DCDD) donors.[14] With these numbers, DCDD did not influence graft survival (p= 0.86).

DISCUSSION

This article is an overview of 30 years of pancreas transplantation at our center.

Results, measured in patient and pancreas graft survival as defined by the OPTN, have improved over the last decade. As shown in this study, survival, especially 1-year graft survival, has significantly improved since the introduction of modern regimes of pre-transplantation induction therapy. Improvement in surgical technique and maintenance immunosuppression therapy, however, may also have contributed to improved outcome. Furthermore, clinical experience with pancreas transplantation has improved throughout the center over the course of these 30 years. Incidence of kidney biopsy-proven acute rejection has also declined with introduction of modern induction therapy.

Several limitations apply to the study. It concerns single-center results, albeit from one of the larger pancreas transplantation centers in Europe. Because of the retrospective nature of our study, some selected data are incomplete. Because routine follow-up in our center does not include measurement of plasma C-peptide, values were only used for the determination of graft failure when present.

We have shown satisfying results in concordance with other large transplant centers and databases: Ollinger et al[10] report a 94.3% patient survival and 81.5% pancreas graft survival (exogenous insulin dependent) at 5-year follow up in the last decade in Innsbruck, Austria. The largest series of pancreas transplantations described, is from Minnesota and reports 1-year patient survival rates between 93.8% and 96.2% and 1-year death censored pancreas graft survival between 78.6% and 80.7% for local or imported allografts between 1998 and 2008 ($p > 0.05$).[6] Vinkers reported 1-year graft survival of 82% for recipients of P-PASS less than 17 donor allografts and 64% for recipients of P-PASS of 17 or higher donor allografts in a Eurotransplant cohort. Muthusamy et al[15] compared DBD donors to DCDD donors in the United Kingdom and reported 88% versus 87% ($p = 0.9$) 1-year pancreas graft survival, defined as insulin administration dependency. Discussion still remains about the value of predictive models. We have shown that median PDRI is not associated with pancreas graft survival in this series. The authors believe that the increase of PDRI over time, together with simultaneous increase of pancreas graft survival over time, is responsible for this absent relationship. The continuous increase in PDRI over the years has not led to inferior outcome. On the contrary, outcome is still improving, whereas, from 2006 till 2012, median donor PDRI was 1.39, equally to a United Network for Organ Sharing donation after cardiac determination of death donor.[8]

In 2012, Leiden University Medical Center was the second largest whole organ pancreas transplantation center in the Eurotransplant region.[16] Combining both findings might implicate that high-volume transplant centers might be able to compensate for inferior donor quality and that, currently, PDRI might not yet be reliable enough to predict outcome in the European cohort. As we have shown earlier, liver donor quality, measured in DRI, is inferior in the European region, as compared to the United States.[17] Additional studies from own center show a relationship between pancreas graft survival and PDRI, when using median PDRI (1.24) as a cutoff value in multivariate analysis (unpublished data).

Multivariate analyses revealed left or right donor kidney, transplant type, local origin of procurement center, pancreas cold ischemia time, and recipient cerebrovascular disease as individual determents of OPTN-defined death-censored pancreas graft survival. Interestingly, primary bladder drainage was borderline favorable for graft survival after multivariate analysis, even with nonconverted patients, which have inferior outcome, included in this group. This result is similar to results found by Finger et al[7] when composing a risk model for predicting TF. The authors feel that the 2-step approach, initial bladder drainage followed by conversion to enteric drainage, is a suitable and feasible drainage method for high-risk recipients, for example, with repeated peritonitis or high-risk donors or grafts.[18,19] However, risks of repeated surgery will have to be measured against graft survival benefit, as was stated earlier by Sollinger et al[5] who reported no difference in outcome for both techniques. Even though the use of UW as perfusion fluid was a protective factor in univariate analysis, this effect did not remain significant after multivariate analysis. It has previously been shown that the use of histidine-tryptophan-ketoglutarate bears an increased risk of graft failure in pancreas transplantation.[20] The lack of relationship in this series might be due to the large amount of transplantations that were conducted using UW solution as perfusate. The use of DCDD pancreas did not influence graft survival in this series, and is, as we have shown earlier, a feasible option to expand the donor pool.[14] After multivariate analysis, donor cardiac arrest was no longer a protective factor for pancreas graft survival. Also, donor cardiac arrest did not influence kidney graft survival. The authors believe that, in this study, the effect could be explained by small sample size, even though reports are published where ischemic preconditioning might have a beneficial effect on outcome.[21] Pancreas graft thrombosis is still an important complication after pancreas transplantation, even with modern regimes of anticoagulation therapy.

All pancreas transplantations (SPK, PTA, and PAK) were analyzed together. It was previously shown that pooled results provide useful data for reporting on program-specific outcome.[22] Results might even be better in patient and graft survivals if only SPK transplantations were analyzed because it is known that both other categories are associated with poorer outcome.[10]

In our opinion, preemptive SPK transplantation is a feasible option in recipients suffering from preterminal renal disease. This is indicated by the high number of preemptive

transplantations that was carried out at our center. Even though it did not influence graft survival, preventing recipients from becoming dialysis-dependent, provides improved quality of life in the pretransplantation phase. Interestingly, next to studies demonstrating superior outcome in kidney graft survival, depending on donation of left or right kidney,[23] this study demonstrates that a donated left or right kidney significantly influences pancreas graft survival. This could be explained, however, by the large difference in 1-year kidney graft survival of left and right donated kidneys. Early kidney graft loss results in a pancreas-alone state, probably with comparable results as initial PTA transplantations. Right renal vein length and possible fragility might bear an increased thrombosis risk; however, in this study, this does not appear to be the reason for inferior kidney graft survival of the right kidney. The authors do not have an explanation for high rejection rates with donated right kidneys.

Pancreas graft survival in this study was death censored and measured using the OPTN PTC definition as guideline, where death with functioning graft was not considered graft failure. Using this definition allows for objective measurement of graft failure, using HbA1c, fasting plasma glucose, and casual plasma glucose, rather than measuring graft failure using restart of insulin therapy definition, for this, is, in our opinion, a more subjective way and also, predominantly, physician dependent.

When using the restart of any exogenous insulin after the directly postoperative period as a measure for pancreas graft survival or graft failure, results are different. Insulin-defined graft survival is different than OPTN-defined graft survival, with a difference of almost 6% at 10-year follow-up. Comparing both definitions of graft survival and (re)initiating, the discussion on the definition of graft survival will be subject of further studies. Without a general consensus on the definition of graft survival, future studies comparing graft survival in different cohorts would be difficult. Future studies will also have to be evaluated for their definitions of pancreas graft survival.

Even though center size was not investigated in this study per se, this study still shows that in a large center, a good result can be achieved without the use of perfect donor grafts. It is our opinion that future studies will have to point out the value of center size on the outcome after transplantation, not only in the field of pancreas transplantation. This opinion was recently shared by Nijboer et al.[24] Also, this study has shown better result with grafts procured by the local team. This might be because our center performs pancreas transplantation itself, and this may lead to higher quality of the transplanted graft and thus improved graft survival.[25] In this perspective, the authors believe that early graft failure should be included in graft survival analysis, especially in pancreas transplantation because surgical complications are still an important risk factor in pancreas transplantation.

In conclusion, long-term patient and pancreas graft survival in this cohort was excellent and at least equal to results in other large centers. However, the exact nature and interpretation of the findings are highly dependent on which definition for pancreas graft success or

failure is used. Higher volume transplant centers might be able to achieve the same outcome in graft survival with higher-risk donors.

ACKNOWLEDGMENTS

The authors thank Marko Mallat, Marije Nijenhuis (Department of Nephrology, LUMC) and Erwin de Vries (Eurotransplant data manager) for their contribution in the data collection process.

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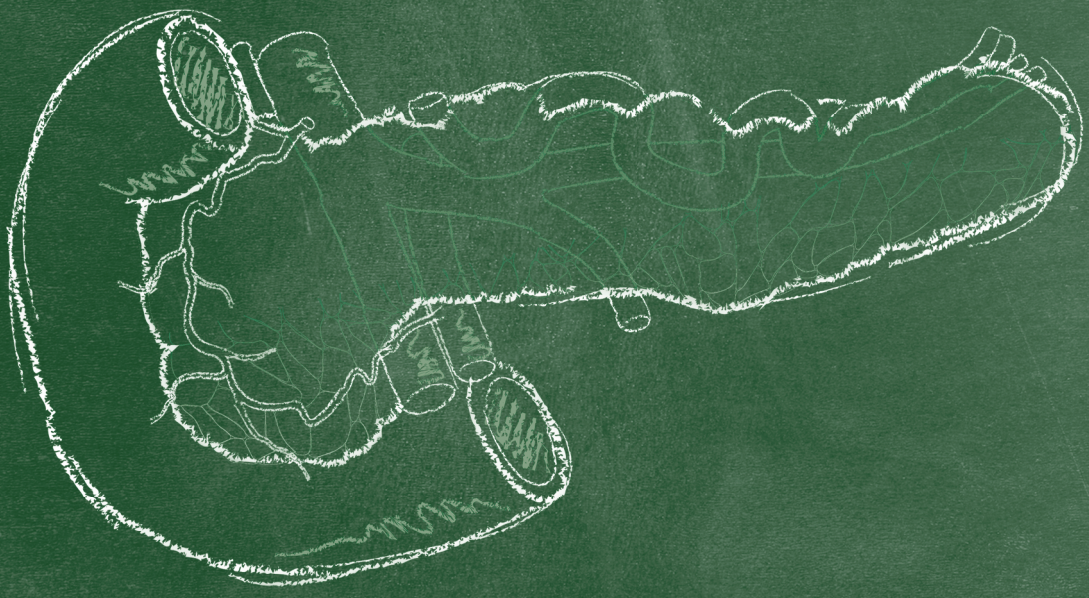

3

The Value of PDRI and P-PASS as Predictors of Outcome After Pancreas Transplantation in a Large European Pancreas Transplantation Center

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Pancreas. 2016 Mar; 45 (3)

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Introduction: In 2008, the preprocurement pancreas suitability score (P-PASS) was introduced within Eurotransplant to predict suitability of pancreas donors. A P-PASS of 17 or higher would have lower graft survival compared with pancreatic grafts from donors with a P-PASS lower than 17. In 2010, a continuous model, the pancreas donor risk index (PDRI), was designed. Before using this model in the European donor population, it has to be validated in the European setting.

Methods: In this study, P-PASS and PDRI were validated using the results of all pancreas transplants performed at our center. The P-PASS and PDRI were compared as both continuous and dichotomous values. The original cutoff point of 17 divided P-PASS groups. Median PDRI (1.24) divided PDRI groups.

Results: In total, 349 pancreas transplantations were performed. The P-PASS of 17 or higher was not associated with graft survival ($p = 0.448$). The PDRI of 1.24 or higher was associated with reduced graft survival in univariate analysis ($p = 0.007$) and multivariate analysis ($p = 0.002$). The PDRI concordance index was 0.69.

Conclusions: The P-PASS has no predictive value for pancreas graft survival and should not be used in clinical decision making. The PDRI is a significant predictor of pancreas graft survival but should be used carefully, because good results can be achieved with grafts from high-PDRI donors.

INTRODUCTION

The well-known scarcity of suitable organ allografts available for transplantation and the increasing number of patients on the waiting list[1] has stimulated the use of extended criteria donors. The difficulty with these extended criteria donors is the lack of a good definition. Several factors for pancreas donors are named as extended, such as high donor age, high body mass index (BMI), and pancreas allografts from donation after circulatory determination of death (DCDD) donors.[2] However, there is no clear consensus on the extended criteria of pancreas donor and the question remains whether extended donor criteria donors should be used for pancreas donation at all.[3]

The preprocurement pancreas suitability score (P-PASS) was introduced within Eurotransplant in 2008.[4] This score, consisting of solely donor factors (age, BMI, intensive care unit [ICU] stay, asystole, sodium, amylase, lipase, and inotropic therapy), is primarily intended to identify a suitable pancreas donor, using a cutoff point of 17. The P-PASS is even believed to predict graft survival, where a pancreas from a donor with a P-PASS of 17 or higher would have a lower graft survival as compared with a pancreas from a donor with a P-PASS lower than 17.[5] Even though this is a continuous model, the disadvantage of this donor score is the fact that its current use is a black-and-white model approach and several single-center studies already demonstrated the lack of relation between P-PASS and (long-term) graft survival.[6,7]

In 2010, a risk index for predicting graft survival after pancreas transplantation was designed using data from the Organ Procurement and Transplantation Network (OPTN): the pancreas donor risk index (PDRI). This continuous model consists of 8 donor factors (age, sex, race, height, BMI, serum creatinine, cause of death [COD], and DCDD) and 2 transplant factors (cold ischemia time [CIT] and type of transplant, meaning simultaneous pancreas kidney [SPK], pancreas after kidney [PAK], or pancreas transplant alone [PTA] transplantation).[8]

Because no valid predictive model currently exists for pancreas transplantation in the European setting, it would be of additional value to investigate these 2 pancreatic graft donor models. Organ donors in the United Network for Organ Sharing and the Eurotransplant region are quite different,[9] so the PDRI should ideally first be validated in a European setting. Regarding the P-PASS, because it was designed more than 5 years ago and the donor population changed a lot since then, the question rises if this model is still up-to-date.

The objective of this single-center study was to compare P-PASS and PDRI in our own center in their ability to predict graft survival after pancreas transplantation, using univariate and multivariate analysis.

MATERIALS AND METHODS

Data

This study is a retrospective database analysis of all pancreas transplantations performed in our center from the first pancreas transplantation in 1984 until January 1, 2013. Donor, transplant, and recipient characteristics are displayed in Tables 1 to 4.

Table 1. Donor and transplant demographics in both P-PASS groups

	Pass < 17	**Pass ≥ 17**	
Donor factor	**N (%)**	**N (%)**	***P*[a]**
Age category			<0.001
<30	107 (56)	12 (9.5)	
30-39	40 (20.9)	30 (23.8)	
40-50	42 (22)	80 (63.5)	
>50	2 (1)	4 (3.2)	
Sex			
Male	98 (51.3)	58 (46)	0.358
Cause of death			<0.001
Trauma	87 (45.5)	29 (23)	
CVA	91 (47.6)	89 (70.6)	
Anoxia	6 (3.1)	3 (2.4)	
Other	7 (3.7)	5 (4)	
Diabetes Mellitus	0 (n/a)	0 (n/a)	n/a
Hypertension	11 (5.8)	11 (8.7)	0.308
Malignancy	0 (n/a)	1 (0.8)	0.397
Drug use	7 (3.7)	1 (0.8)	0.152
Alcohol use	2 (1)	5 (4)	0.119
HCVAb pos	0 (n/a)	0 (n/a)	n/a
HBcAb pos	1 (0.8)	1 (0.8)	1
HIVAb pos	0 (n/a)	0 (n/a)	n/a
Cardiac arrest	20 (10.5)	20 (15.9)	0.156
Hypotensive period	68 (35.6)	40 (31.7)	0.478
Use of vasopressors	137 (71.7)	115 (91.3)	<0.001
DCDD (yes)	5 (2.6)	1 (0.8)	0.408
	Median (range)	**Median (range)**	***P*[b]**
Age, y	27 (10-52)	43 (16-54)	<0.001
Height, cm	175 (130-196)	175 (155-200)	0.704
Weight, kg	65 (27-100)	77 (45-105)	<0.001
BMI	22 (14-33)	25 (18-35)	<0.001
Serum sodium, mmol/L	144 (123-175)	144 (128-167)	0.875

Table 1. Donor and transplant demographics in both P-PASS groups (continued)

	Pass < 17	Pass ≥ 17	
Donor factor	**Median (range)**	**Median (range)**	***P*[a]**
Serum creatinine, umol/L	70 (8-1756)	68 (28-190)	0.762
Serum lipase, U/L	21 (9-332)	20 (7-169)	0.524
Serum amylase, U/L	77 (8-1756)	92 (7-1057)	0.726
ICU stay, d	2 (1-33)	2 (1-24)	0.001
Transplant factor	**N (%)**	**N (%)**	***P*[a]**
Allocation			0.725
Local	23 (12)	17 (13.5)	
Regional	128 (67)	87 (69)	
Extra-regional	40 (20.9)	22 (17.5)	
Procurement team			0.219
Local	32 (16.8)	27 (21.4)	
Non-local	135 (70.7)	90 (71.4)	
Unknown	24 (12.6)	9 (7.1)	
Transplantation type			0.131
SPK	181 (94.8)	114 (90.5)	
PAK	10 (5.2)	10 (7.9)	
PTA	0 (n/a)	2 (1.6)	
Donor kidney			0.144
No kidney	10 (5.2)	12 (9.5)	
Left	154 (80.6)	103 (81.7)	
Right	27 (14.1)	11 (8.7)	
Perfusion fluid			0.564
UW	176 (92.1)	113 (89.7)	
HTK	14 (7.3)	11 (8.7)	
Other	1 (0.5)	2 (1.6)	
	Median (range)	**Median (range)**	***P*[b]**
Cold ischemia time, h	12 (5-20)	11 (4-19)	0.397
PDRI	1.03 (0.68-2.21)	1.61 (0.76-2.31)	<0.001
P-PASS	15 (9-16)	18 (17-22)	<0.001

[a] Pearson X^2

[b] Independent Samples Median Test

Analysis

To compare both predictive models, pancreatic graft survival was used as endpoint. Graft survival was defined using uniform definition of graft function/failure for whole pancreas and islet transplant by the Pancreas Transplantation Committee as a guideline.[10] Endocrine pancreatic function was subdivided in grades A to E using HbA1c and the use of exogenous insulin as markers for pancreatic graft function. Allografts classified as grades A and B were

considered functioning grafts and grafts with grades C to E were considered failed allografts. According to this definition, persistent HbA1c more than 6.3% and/or exogenous insulin use was classified as grade C (insulin use <50% of pretransplant dose) or grade D (insulin use >50% of pretransplant dose) and persistent HbA1c of 7.0% or higher was classified as grade E. A full breakdown of categories A to E at different follow-up points is shown online (SDC Figure 1, http://links.lww.com/MPA/A417).

Table 2. Recipient demographics in both P-PASS groups

	Pass < 17	**Pass ≥ 17**	
Recipient factor	**N (%)**	**N (%)**	***P*[a]**
Age category			0.182
<40	85 (44.5)	49 (38.9)	
40-49	82 (42.9)	53 (42.1)	
50-59	24 (12.6)	22 (17.5)	
≥60	0 (n/a)	2 (1.6)	
Sex			0.444
Male	110 (57.6)	78 (61.9)	
Type of dialysis			0.988
No dialysis (pre-emptive transplant)	82 (42.9)	53 (42.1)	
Hemodialysis	51 (26.7)	34 (27)	
Peritoneal dialysis	58 (30.4)	39 (31)	
Repeated transplantation	9 (4.7)	9 (7.1)	0.36
CMV mismatch	40 (21.1)	29 (23.2)	0.652
Modern induction therapy	65 (34)	107 (84.9)	<0.001
Primary drainage			0.02
Bowel	45 (23.6)	45 (35.7)	
Bladder	145 (75.9)	81 (64.3)	
Coronary artery disease	31 (16.2)	17 (13.5)	0.499
Cerebrovascular disease	12 (6.3)	8 (6.3)	0.986
Thromboembolic event	3 (1.6)	1 (0.8)	1.000
	Median (range)	**Median (range)**	***P*[b]**
Age, y	42 (23-57)	43 (25-64)	0.136
BMI	23 (17-33)	24 (18-33)	0.081
Time on waiting list, y	1 (0-6)	1 (0-10)	0.047
Time since DM I, y	27 (14-48)	29 (12-45)	0.177
Time since first dialysis treatment, y	0.7 (0-6.8)	0.6 (0-8.3)	0.945
Total HLA mismatches	4 (0-6)	4 (1-6)	0.845

[a] Pearson X^2

[b] Independent Samples Median Test

Table 3. Donor and transplant demographics in both PDRI groups

	PDRI < 1.24	PDRI ≥ 1.24	
Donor factor	**N (%)**	**N (%)**	***P*[a]**
Age category			<0.001
<30	130 (76.9)	2 (1.1)	
30-39	35 (20.7)	43 (24.6)	
40-50	4 (2.4)	123 (70.3)	
>50	0 (n/a)	7 (4)	
Sex			
Male	106 (62.7)	64 (36.6)	<0.001
Cause of death			<0.001
Trauma	105 (62.1)	21 (12)	
CVA	47 (27.8)	150 (85.7)	
Anoxia	8 (4.7)	1 (0.6)	
Other	9 (5.3)	3 (1.7)	
Diabetes Mellitus	0 (n/a)	0 (n/a)	n/a
Hypertension	0 (n/a)	25 (14.3)	<0.001
Malignancy	1 (0.6)	0 (n/a)	0.308
Drug use	4 (2.4)	4 (2.3)	0.96
Alcohol use	2 (1.2)	5 (2.9)	0.272
HCVAb pos	0 (n/a)	0 (n/a)	n/a
HBcAb pos	2 (1.2)	0 (n/a)	0.149
HIVAb pos	0 (n/a)	0 (n/a)	n/a
Cardiac arrest	29 (17.2)	11 (6.3)	0.002
Hypotensive period	68 (40.2)	54 (30.9)	0.069
Use of vasopressors	133 (78.7)	141 (80.6)	0.666
DCDD (yes)	5 (3)	1 (0.6)	0.091
	Median (range)	**Median (range)**	***P*[b]**
Age, y	21 (10-42)	44 (24-54)	<0.001
Height, cm	178 (130-197)	170 (155-200)	<0.001
Weight, kg	70 (27-105)	70 (45-100)	0.77
BMI	23 (14-33)	23 (18-35)	0.031
Serum sodium, mmol/L	145 (128-175)	144 (123-167)	0.487
Serum creatinine, umol/L	71 (31-138)	64 (25-190)	0.052
Serum lipase, U/L	29 (7-332)	19 (9-140)	0.188
Serum amylase, U/L	97 (7-1756)	62 (11-846)	0.001
ICU stay, d	2 (1-33)	2 (1-24)	0.36

Table 3. Donor and transplant demographics in both PDRI groups (continued)

	PDRI < 1.24	PDRI ≥ 1.24	
Transplant factor	**N (%)**	**N (%)**	***P*[a]**
Allocation			0.058
Local	23 (13.6)	24 (13.7)	
Regional	105 (62.1)	126 (72)	
Extra-regional	41 (24.3)	25 (14.3)	
Procurement team			0.572
Local	26 (15.4)	34 (19.4)	
Non-local	121 (71.6)	117 (66.9)	
Unknown	22 (13)	24 (13.7)	
Transplantation type			0.108
SPK	153 (90.5)	168 (96)	
PAK	15 (8.9)	6 (3.4)	
PTA	1 (0.6)	1 (0.6)	
Donor kidney			0.125
No kidney	16 (9.5)	7 (4)	
Left	130 (76.9)	144 (82.3)	
Right	23 (13.6)	24 (13.7)	
Perfusion fluid			0.313
UW	150 (88.8)	161 (92)	
HTK	13 (7.7)	12 (6.9)	
Other	6 (3.6)	2 (1.1)	
	Median (range)	**Median (range)**	***P*[b]**
Cold ischemia time, h	12 (4-20)	12 (4-19)	0.829
PDRI	0.91 (0.68-1.23)	1.65 (1.24-2.31)	<0.001
P-PASS	14 (9-20)	17 (13-22)	<0.001

[a] Pearson X^2

[b] Independent Samples Median Test

Graft survival was death censored and patient death with functioning graft was not considered graft failure. Graft survival was defined as time from the date of transplantation until the date of graft failure.

For the statistical survival analysis, Kaplan-Meier method for categorical variables and Cox proportional hazards regression model for continuous variables were used, with SPSS Version 22.0. Because the P-PASS was originally constructed using a cutoff of 17, this cutoff point separated groups. The P-PASS was also analyzed as a continuous model. Because the PDRI was developed as a continuous risk model, it was analyzed accordingly. In addition, the median PDRI was used as a cutoff point, to compare groups on the basis of low or high PDRI. Donor race was not included in the analysis, because this is not registered in the Eu-

Table 4. Recipient demographics in both DPRI groups

	PDRI < 1.24	PDRI ≥ 1.24	
Recipient factor	**N (%)**	**N (%)**	***P*[a]**
Age category			0.149
<40	85 (50.3)	67 (38.3)	
40-49	60 (35.5)	81 (46.3)	
50-59	23 (13.6)	26 (14.9)	
≥60	1 (0.6)	1 (0.6)	
Sex			0.477
Male	110 (57.9)	78 (61.9)	
Type of dialysis			0.654
No dialysis (pre-emptive transplant)	73 (43.2)	68 (38.9)	
Hemodialysis	42 (24.9)	50 (28.6)	
Peritoneal dialysis	54 (32)	57 (32.6)	
Repeated transplantation	9 (4.7)	9 (7.1)	0.366
CMV mismatch	27 (16.4)	45 (26)	0.030
Modern induction therapy	109 (64.5)	128 (73.1)	0.083
Primary drainage			0.701
Bowel	43 (25.6)	48 (27.4)	
Bladder	125 (74.4)	127 (72.6)	
Coronary artery disease	31 (16.5)	17 (13.6)	0.487
Cerebrovascular disease	12 (6.4)	8 (6.4)	0.995
Thromboembolic event	3 (1.6)	1 (0.8)	0.539
	Median (range)	**Median (range)**	***P*[b]**
Age, y	40 (23-64)	43 (23-64)	0.009
BMI	23 (17-33)	24 (18-33)	0.156
Time on waiting list, y	1 (0-10)	1 (0-6)	0.783
Time since DM I, y	26 (14-44)	29 (12-48)	0.030
Time since first dialysis treatment, y	0.7 (0-8)	0.7 (0-7)	1.000
Total HLA mismatches	4 (1-6)	4 (0-6)	0.254

[a] Pearson Chi-Square

[b] Independent Samples Median Test

rotransplant database. All donors were set to reference (caucasian). For group analysis (both P-PASS and PDRI), risk factors were considered in a forward selection-based model, if a factor is unequally distributed across both groups (χ^2 $p < 0.1$) and that factor is considered to influence graft survival in univariate or multivariate graft survival analysis ($p < 0.1$).[11] In multivariate analysis, $_{log}$PDRI was used. For both univariate and multivariate analyses, a p-value of less than 0.05 was considered significant.

RESULTS

A total of 349 pancreas transplantations were performed at the Leiden University Medical Center from January 1, 1984 to January 1, 2013. For all 349 transplantations, follow-up was conducted until October 31, 2013.

Analysis of P-PASS

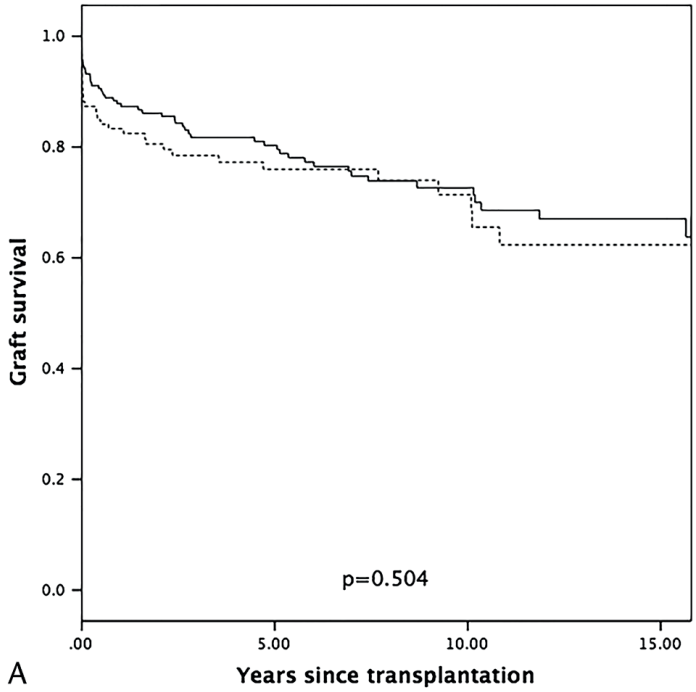
The cohort was divided into 2 groups, using the original cut-off point of P-PASS lower than 17 (n = 191) and P-PASS of 17 or higher (n = 126). From 32 donors, the P-PASS could not be calculated. Demographic donor, recipient, and transplantation factors of both P-PASS lower than 17 and P-PASS of 17 or higher related transplantations are shown in Tables 1 and 2. Groups were different on the following P-PASS–associated risk factors: donor age ($p < 0.001$), use of vasopressors ($p < 0.001$), BMI ($p < 0.001$), and duration of ICU stay ($p< 0.001$). Mean duration of ICU stay was 2.7 days in P-PASS lower than 17 and 3.7 days in P-PASS of 17 or higher ($p = 0.01$). Other factors that were also significantly different among groups were weight ($p < 0.001$), COD ($p < 0.001$), PDRI ($p < 0.001$), modern induction therapy ($p < 0.001$), and primary enteric or bladder drainage ($p = 0.02$). Induction therapy and primary enteric or bladder drainage had little influence on graft survival ($p < 0.1$).

The P-PASS with the cutoff point of P-PASS lower than 17 was not associated with graft survival ($p = 0.504$). Graft survival at 1-year, 5-year, and 10-year follow-up for P-PASS lower than 17 was 87.8%, 81%, and 72.7% and for P-PASS of 17 or higher was 83.3%, 76.0%, and 71.4%, respectively (Fig. 1A). After changing the cutoff to P-PASS lower than 20 (n = 299) and P-PASS of 20 or higher (n = 18), we still did not find a relation with outcome after transplantation ($p = 0.402$). Graft survival at 1-year follow-up for these 2 groups was 86% and 83%, respectively (Fig. 1B). These groups were different on the following graft survival predictors: local or nonlocal origin of procurement center and induction therapy ($p < 0.1$).

As a continuous model, P-PASS was not associated with graft survival ($p = 0.738$). When analyzing the P-PASS in a multivariate analysis using the original cutoff of 17, there was no significant relation with outcome: hazard ratio (HR), 1.19 (0.76–1.85, $p = 0.448$). When the cutoff P-PASS of 20 or higher was used in the multivariate analysis, the association was stronger, however, still not significant: HR, 2.21 (0.95–5.16, $p = 0.067$). With P-PASS evaluated as a continuous model, multivariate analysis still revealed no relation with outcome: HR, 1.03 (0.93–1.14, $p = 0.574$).

Analysis of PDRI

The median PDRI was 1.24. The PDRI was analyzed both as a continuous model and using a cutoff of PDRI of 1.24. The 2 groups were PDRI lower than 1.24 (n = 169) and PDRI of 1.24 or higher (n = 175). The PDRI of 5 donors could not be calculated. Demographics of donor, recipient, and transplantation factors of both PDRI lower than 1.24 and PDRI



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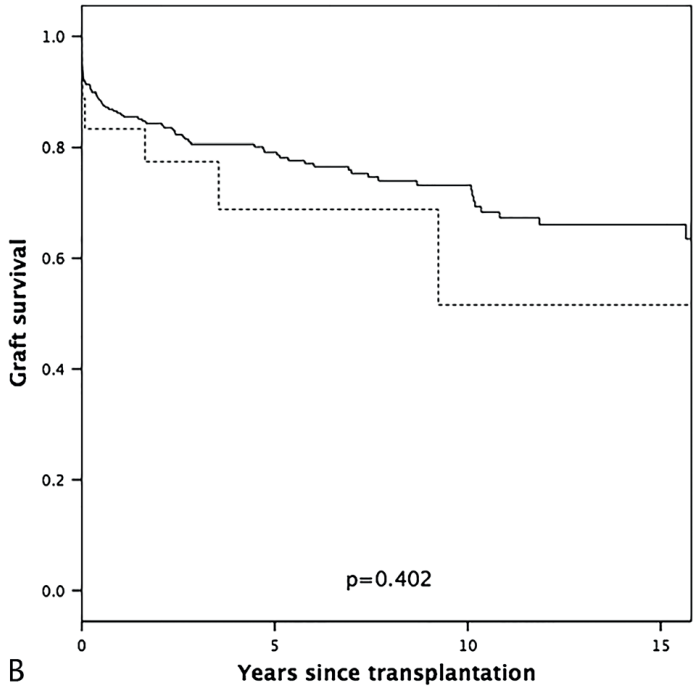

B

Figure 1. A Comparison of P-PASS categories: P-PASS < 17 versus P-PASS ≥ 17.
B Comparison of P-PASS categories: P-PASS < 20 versus P-PASS ≥ 20.

of 1.24 or higher related transplantations are shown in Tables 3 and 4. The groups were different on the following PDRI-associated risk factors: donor age ($p < 0.001$), donor sex ($p < 0.001$), donor height ($p < 0.001$), donor BMI ($p = 0.031$), and COD ($p < 0.001$). Factors not included in PDRI that were different among groups were donor hypertension ($p < 0.001$), donor cardiac arrest ($p = 0.002$), serum amylase ($p = 0.001$), P-PASS ($p < 0.001$), recipient age ($p = 0.009$), donor-recipient cytomegalovirus mismatch ($p = 0.03$), and time since onset of DM1 ($p = 0.03$). Donor cardiac arrest, serum amylase, and induction therapy had little influence on graft survival ($p < 0.1$).

Graft survival at 1-year, 5-year, and 10-year follow-up was 90.4%, 83.8%, and 77% in the low-PDRI group and 78.3%, 71.2%, and 66.7% in the high-PDRI group, respectively. In the univariate analysis, PDRI was significantly associated with graft survival using the cutoff point of PRDI of 1.24 ($p = 0.007$, Fig. 2). As a continuous model, PDRI did not influence graft survival ($p = 0.254$).

In the multivariate analysis, PDRI higher than 1.24 was associated with decreased graft survival: HR, 2.02 (1.29–3.16, $p = 0.002$). As a continuous model, PDRI was associated with graft survival, however, not significantly: HR, 1.85 (0.87–3.91, $p = 0.110$). The concordance index (c-index) for the PDRI was 0.69 (standard error, 0.045).

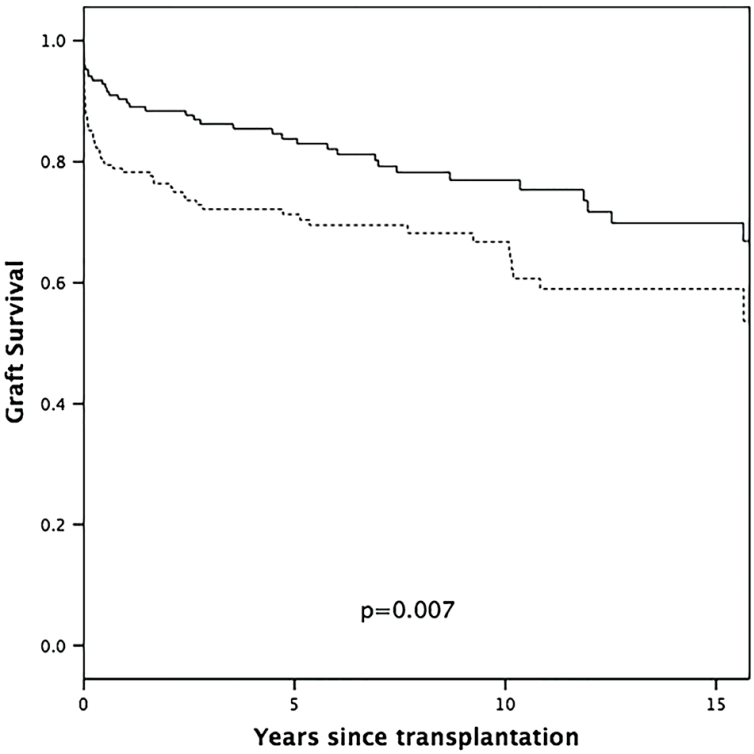

Figure 2. Comparison of PDRI categories: low PDRI < 1.24 versus high PDRI ≥ 1.24.

DISCUSSION

This study evaluates the following 2 current models for graft failure risk calculation of pancreas allograft donors: the PDRI and P-PASS. At first, the P-PASS was re-evaluated for its ability to predict outcome after pancreas transplantation. The P-PASS is currently used by Eurotransplant and pancreas transplant centers as categorical variable to identify a suitable pancreas donor, which is why it was analyzed as a categorical variable. Second, the PDRI was evaluated in our center (one of the larger European pancreas transplantation centers). To our knowledge, this is the first and largest study to evaluate the PDRI in the European region. A small study was conducted by Mittal et al[12] investigating the relationship between 1-year graft survival and PDRI for both SPK and PTA transplantations using the PDRI smartphone application. They confirm the relationship between graft survival and PDRI, however, only for SPK transplantations. In our study, the median PDRI was 1.24, which indicates the difference in donor quality between our center and the OPTN region, where median donor quality was in concordance with PDRI of 1.0. This is in line with other data used for validation of the DRI and construction of the Eurotransplant donor risk index in liver transplantation, showing higher risk donors in the European (Eurotransplant) region.[9]

For the analyses of both models (PDRI/P-PASS), we defined graft survival using the OPTN definition as a guideline. The authors feel that this is a uniform definition of graft survival and graft survival was analyzed accordingly. The main reason for this definition was its objectivity with regard to graft failure, because the moment of restart of exogenous insulin therapy as the moment of graft failure is a subjective way of defining graft failure. Worldwide, not all physicians are evenly aggressive in treating hyperglycemia and the restart of insulin therapy might differ between transplant centers.

The absent relationship between the P-PASS and outcome after pancreas transplantation has been demonstrated previously. Two studies from different Eurotransplant pancreas transplantation centers showed that there was no correlation between long-term pancreas graft survival and the P-PASS.[6,7] Furthermore, it was concluded that pancreas allografts should not be rejected purely on the basis of high P-PASS values. The results of our study are in concordance with these previous studies. Regardless of the P-PASS, no significant difference was found between pancreas allograft survival with a P-PASS lower than 17 or 17 or higher. Even after altering the cutoff point to a P-PASS of 20, there was no significant difference in outcome. The choice to select a P-PASS of 20 as another cutoff point was arbitrary; however, the absent relationship, even with this higher cutoff, confirms that the P-PASS should not be used to decline pancreas allografts beforehand nor predict pancreas graft failure and it even raises the question whether it should be used to identify a suitable pancreas before allocation to any recipient, for which it was initially developed. In this study, it was not possible to examine the influence of P-PASS on graft acceptance practice, because

only accepted and actually transplanted organs were included in the analysis. In the original P-PASS study, a relationship between this model and organ acceptance was demonstrated.[5]

The PDRI was significantly associated with graft survival in univariate and multivariate analysis when using a cutoff of a PDRI of 1.24. It was not possible to establish a relationship between graft survival and the groups originally formulated by Axelrod et al.[8] The authors believe that this is mainly due to the smaller numbers per group when breaking up in more groups. As a continuous model, the PDRI was not associated with graft survival, which might also be explained by too low numbers in the analysis. However, the association was stronger in the multivariate analyses. On the other hand, the index of concordance (c-index) indicates that PDRI might be a valid predictor of graft survival and demonstrates the potential for clinical decision making in the future. The PDRI could potentially be used for risk stratification and also to compare studies and give an indication of the pancreas graft quality used within a center/region. The c-index was in accordance with the one reported in the original study by Axelrod et al.[8] It might be interesting to adjust the PDRI to the European donor population and validate the model in a multicentered European cohort, before implementing the model in clinical practice, as was done for the DRI and Eurotransplant donor risk index in liver transplantation,[13] because this might lead to a more optimal model with adjusted weighing of risk factors or additional factors. Even with PDRI of 1.24 or higher, long-term graft survival was relatively good (67% vs 77% at 10 years), indicating that pancreas allografts should not be declined only on the basis of a higher PDRI. The good results with high-PDRI donor grafts could (partially) be explained by the long experience in pancreas transplantation in our center and proper recipient selection. Furthermore, the scarcity of optimal pancreas donors has pushed us to be more liberal in accepting grafts.

The difference in significance between both models might be explained by the fact that P-PASS was originally designed as a suitable donor identifier based on a "soft" criterium as expert opinion, whereas the PDRI was initially intended to predict graft survival in transplanted grafts. To have a good, describing donor risk model in pancreas transplantation would be of great additional value. Within the field of pancreas transplantation, there are currently a lot of different opinions with regard to organ donor quality, as was recently described by Loss et al in a survey among German pancreas transplant surgeons.[14] Obviously, there are certain risk factors that are commonly accepted (e.g. age, ICU stay, macroscopy of the organ), but it would be of additional value to get a clear risk indication at the moment of an organ offer. The PDRI would be ideal for this, even though it was not analyzed for its ability to predict graft acceptance in this study. The authors feel that unknown factors at time of organ offering (CIT and transplant type) could be estimated or imputed on the basis of historical data.

One of the potential limitations of our study was the fact that we only analyzed pancreas allografts that were actually transplanted and the fact that this was conducted in a single-center database. At our center, the Leiden University Medical Center, we have 30 years of

experience in pancreas transplantation and currently we are one of the largest pancreas transplantation centers in the Eurotransplant region.[11] Another limitation was the absence of donor parameters, such as serum lipase, serum amylase, and admission at ICU, because these were not available in the Eurotransplant database. Therefore, it was not possible to calculate the P-PASS in 32 cases. On account of missing values for donor height, BMI, and serum creatinine, we were not able to calculate the PDRI in 5 cases. We are aware that the evaluation period is almost 30 years, with major changes concerning immunosuppression, donor and recipient management, and clinical experience. These factors might all have contributed to outcome; however, the aim of this study was only to analyze both donor quality models in their ability to predict graft survival. In multivariate analyses of both prediction models, introduction of modern induction therapy (1999) was used as a surrogate marker to correct for major improvement in outcome in terms of graft survival. The validation of a donor risk index is the first step toward donor to recipient matching in pancreas transplantation, in which both donors as well as recipient risk indices are to be incorporated. However, in The Netherlands allocation is currently purely based on waiting time.

CONCLUSIONS

The P-PASS has no prognostic value for outcome after pancreas transplantation and the use of this model as a criterion for the evaluation of pancreas donors and prediction of graft survival is highly questionable. The PDRI is the more favorable model, because this study shows its ability to predict graft survival and it could therefore be helpful for clinical decision making. Although high-PDRI donors have a strong association with decreased graft survival, they should never be declined solely on the basis of their score, because these high risk grafts (PDRI $\geq$ 1.24) still have a good outcome. Further development of a European PDRI is warranted and should be performed in a multicenter collaboration.

ACKNOWLEDGMENT

The authors thank Erwin de Vries, Eurotransplant, Marko Mallat, and Marije Nijenhuis, from the Department of Nephrology, for their assistance in the data collection process.

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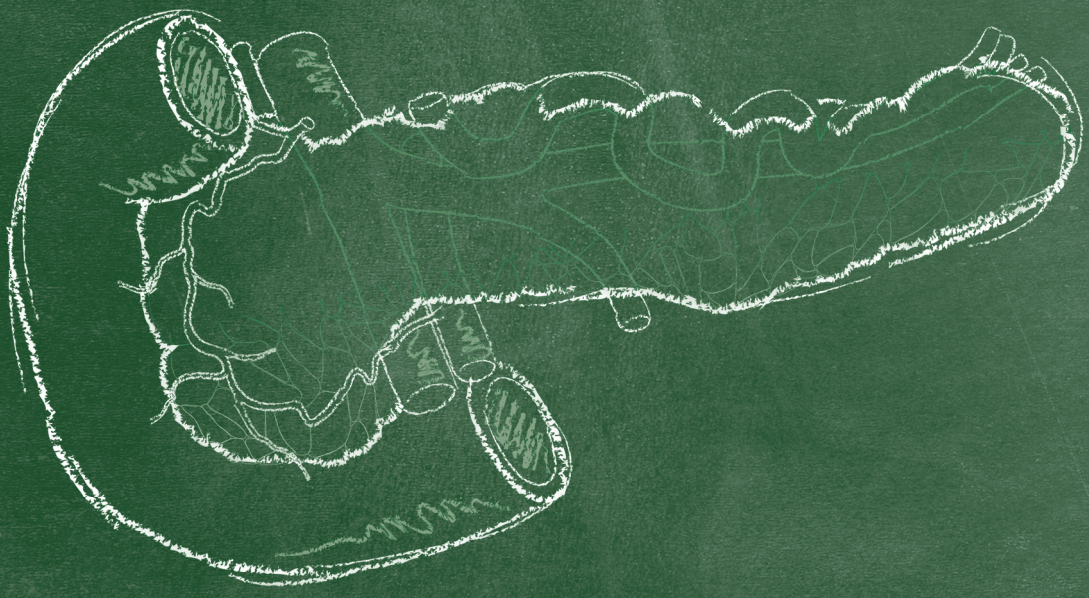

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Donor risk indices in pancreas allocation in the Eurotransplant region

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Transplant International. 2016; 29: 921-929

Introduction: Pancreas donor selection and recognition are important to cope with increasing organ shortage. We aim to show that the PDRI is more useful than the P-PASS to predict acceptance and should thus be preferred over P-PASS.

Methods: Eurotransplant donors from 2004 until 2014 were included in this study. PDRI logistical factors were set to reference to purely reflect donor quality (PDRI donor). PDRI and P-PASS association with allocation outcome was studied using area under the receiver operating characteristic curve (AUROC). Regional differences in donor quality were also investigated.

Results: Of the 10 444 pancreata that were reported, 6090 (58.3%) were accepted and 2947 (28.2%) were transplanted. We found that P-PASS was inferior to $PDRI_{donor}$ in its ability to predict organ reporting, acceptance, and transplantation: AUC 0.63, 0.67 and 0.73 for P-PASS vs. 0.78, 0.79 and 0.84 for $PDRI_{donor}$, respectively. Furthermore, there were significant differences in donor quality among different Eurotransplant countries, both in reported donors and in transplanted organs.

Conclusions: PDRI is a powerful predictor of allocation outcome and should be preferred over P-PASS. Proper donor selection and recognition, and possibly a more liberal approach toward inferior quality donors, may increase donation and transplant rates.

INTRODUCTION

Pancreas (and combined kidney) transplantation is the definitive treatment for patients with type 1 diabetes mellitus and end-stage renal disease.[1-4] With increasing scarcity of suitable organ donors, the Eurotransplant Pancreas Advisory Committee is continuously working to improve pancreas transplantation outcomes, in part by improving the organ allocation process. Especially in pancreas transplantation, where discard rates are among the highest of all organs, proper donor recognition and selection is paramount.[5,6]

In 2008, the Eurotransplant International Foundation introduced the preprocurement pancreas allocation suitability score (P-PASS) was introduced.[7] This donor scoring system, which was one of the first quantitative donor scoring systems, consists solely of donor factors (age, body mass index (BMI), duration of intensive care unit (ICU) stay, duration of asystole, sodium, amylase, lipase and inotropic therapy). The system identifies a suitable pancreas donor, using a cut-off value of 17 (range 9–27). Its intention was to educate and inform transplant professionals, such as ICU clinicians referring potential donors, as well as transplant coordinators reporting donors to Eurotransplant. Side by side with this education, the donation rates were thought to increase, which appeared to be the case since 2009.[8]

The disadvantage of the P-PASS is that it was initially developed based on acceptance rate, without data on patient and graft survival. While the same authors went on to identify a relationship with graft survival in a later study[9], studies by other researchers could not find any correlation between P-PASS and graft survival.[10-12]

Seven years after its introduction, the original P-PASS thresholds have shifted along with increasing donor age and numbers of donation after circulatory death (DCD) pancreas transplantations.[13,14] Some factors are less relevant than previously believed or caused by other mechanisms, for example brain dead donors with high serum amylase due to mandibular trauma. This elevated amylase does not affect the outcome following pancreas transplantation.[15] Eurotransplant professionals still use the P-PASS to make decisions about the allocation process (e.g. whether to continue with whole-organ allocation, to proceed to islet allocation or to evaluate changes in guidelines), despite the above-mentioned shortcomings. Also, data on lipase and amylase might not always be available, which makes calculation of the P-PASS impossible in the current Eurotransplant algorithm. Therefore, a more recent and precise tool is needed.

In 2010, a risk index for predicting graft survival after pancreas transplantation was designed using data from the Organ Procurement and Transplantation Network (OPTN): the pancreas donor risk index (PDRI).[16] This model consists of eight donor factors (age, sex, race, height, BMI, serum creatinine, cause of death (COD), and DCD) along with two transplant/logistical factors (cold ischemia time (CIT) and type of transplant (simultaneous pancreas–kidney transplantation (SPK), pancreas after kidney transplantation (PAK) or pancreas transplant-alone (PTA) transplantation)). The advantage of this PDRI is that it was

derived from a large data set. This evidence-based approach provided an index (indicating that the standard donor has a score of 1.0), which allows for direct comparison of a potential donor with this standard donor. This risk index was recently validated as means for predicting graft survival in the UK population[17] and in The Netherlands.[12] The concept of a donor risk index allows risk estimation prior to transplantation and might aid in decision-making whether to accept the offer as well as, perhaps even more important, comparison of results post-transplantation.

While CIT and type of transplant are unknown factors of the PDRI at the time of organ reporting, these factors could be estimated or imputed based on historical data. In this study, these factors were set to reference, so that the PDRI calculations would purely reflect donor quality ($PDRI_{donor}$) and the concept would be the same as that from the P-PASS.

The objective of this study was to compare the association of the P-PASS and $PDRI_{donor}$ with organ acceptance and pancreas transplantation and to investigate whether the PDRI is a more useful tool for donor characterization. If PDRI is more useful tool at the time of organ reporting or offering, it might replace P-PASS. Also, we reported PDRI for transplanted organs to provide insight regarding regional differences in donor quality.

MATERIALS AND METHODS

Donor selection

All donors of whom one or more abdominal organs were reported to Eurotransplant from January 2004 until December 2014 were included in the study. The data that were collected are shown in Table 1.

Data that were stored incorrectly in the Eurotransplant database (wrong unit, wrong entry) were corrected as following: for creatinine data, any 0.5% lower and 0.5% upper outliers were cross-checked and corrected when necessary. All data were converted to mg/dl. For BMI data, any values >60 and <10 were checked for feasibility and corrected when appropriate and possible. Anything below 17 was considered a low P-PASS value, whereas P-PASS equal to or above 17 was considered a high P-PASS value, as was originally defined by the P-PASS authors. Eurotransplant currently recommends considering pancreas donation in cases of a low P-PASS[18] values.

Pancreas donor risk index (PDRI)

PDRI was calculated according to Axelrod et al.[16] Race is not recorded in the Eurotransplant database and was excluded from PDRI calculations (i.e. all donors were considered as the PDRI reference Caucasian donor). For all transplanted whole pancreas, pancreas donor risk index (PDRI) was calculated. Pancreas after kidney (PAK) was coded only when solitary kidney transplantation was followed by solitary pancreas transplantation. Solitary pancreas

retransplantation after SPK was considered pancreas transplant alone (PTA). Cold ischemia time (CIT) was coded in hours and, when missing, was imputed using 20 multiple imputation rounds in SPSS. CIT was the single factor that was imputed. Donor center, donor age, donor gender, weight, height, BMI, cause of death, donor type (DBD versus DCD), liver donor (Y/N), transplant center, transplant type, and CIT were set as predictors for multiple imputation. Donor quality in different Eurotransplant countries was assessed using PDRI. Mean and standard deviations were displayed, and P-values were calculated using one-way analysis of variance methods.

Pancreas donor risk index ($PDRI_{donor}$)

$PDRI_{donor}$ was calculated for all reported pancreas donors, where CIT was set to 12 h and transplant type was set to SPK, as these were the reference values in the original equation. This $PDRI_{donor}$ enabled the use of the PDRI at time of organ reporting and was analyzed for its association with pancreas acceptance and transplantation.

Statistical methods

Statistical analyses were performed in SPSS version 22. P-value <0.05 was considered significant for all analyses. $PDRI_{donor}$ and P-PASS were evaluated as continuous variables for their ability to predict allocation outcome (reported, accepted, procured, transplanted) using area under the receiver operating curve (AUROC) analysis. Odds ratios for high and low P-PASS were calculated for allocation outcome. Also, P-PASS was evaluated for its correlation with $PDRI_{donor}$ using Spearman's rank correlation coefficients. Pancreas discard was defined as an organ being procured, but not transplanted.

Results

In the study period (January 2004–December 2014), 23 851 abdominal organ donors were reported to Eurotransplant. Of these organ donors, 10 444 (43.8%) reported pancreas; 21 063 (88.3%) reported liver; and 22 336 and 22 379 (93.6% and 93.8%) reported left and right kidney, respectively. More than half of the donors (53.8%) were reported from Germany. Other baseline demographics are shown in Table 1.

Allocation outcome

Of the 10 444 pancreas donors, 10 092 (96.6%) pancreases were offered. Offered pancreases were accepted from 6090 (58.3%) donors. Procurement of the pancreas took place in 4731 (45.3%) procedures. In 2947 cases (28.2%), the pancreas donation procedure led to transplantation. An overview of allocation outcome is shown in Fig. 1. Pancreas was discarded in 1784 cases (56.8%).

The majority of transplants were primary simultaneous pancreas and kidney (SPK) transplants (70.5%), followed by islet transplantations (14.1%). Retransplantations were

Table 1. Demographics of reported donors (minimum 1 abdominal organ) to Eurotransplant (January 2004 – December 2014)

	n (%)
Donors	23851 (100)
Sex [a/b]	
Male	13079 (54.8)
Female	10772 (45.2)
Bloodtype	
A	10198 (42.8)
B	1317 (5.5)
AB	2687 (11.3)
O	9649 (40.5)
Cause of death [a]	
Stroke	14820 (62.1)
Trauma	5456 (22.9)
Circulatory	1264 (5.3)
Anoxia	1604 (6.7)
CNS tumor	147 (0.6)
Other	560 (2.3)
Donor type [a]	
DBD	21639 (90.7)
DCD	2212 (9.3)
Reported organs	
Liver	21063 (88.3)
Pancreas	10444 (43.8)
Left kidney	22336 (93.6)
Right kidney	22379 (93.8)
Inotropic support (Y)[b]	19139 (80.2)
Cardiac arrest [b]	
Yes	3207 (13.4)
No	9888 (41.5)
Unknown	10756 (45.1)
Donor country	
Austria	2263 (9.5)
Belgium	3319 (13.9)
Croatia	945 (4.0)
Germany	12811 (53.7)
Hungary	345 (1.4)
Luxembourg	48 (0.2)
Netherlands	3048 (12.8)
Slovenia	416 (1.7)
Outside ET	656 (2.8)

Table 1. Demographics of reported donors (minimum 1 abdominal organ) to Eurotransplant (January 2004 – December 2014) (continued)

	n	Missing (%)	Median (25^{th} – 75^{th} pct)
Age, y [a/b]	23851	0	53 (41 - 64)
Weight, kg	23849	<0.1	75 (68 - 85)
Height, cm [a]	23851	0	172 (165 - 180)
BMI, kg/m^2 [a/b]	23849	<0.1	25.2 (23.1 - 27.8)
Sodium, mmol/l [b]	23648	0.9	147 (142 - 152)
Creatinine, mg/dl [a]	23851	0	0.86 (0.64 – 1.17)
Amylase, U/l [b]	16378	31.3	73 (39 - 145)
Lipase, U/l [b]	16582	30.5	29 (17 - 68)
PPASS	19767	17.1	19 (17 - 20)

[a] PDRI factor
[b] P-PASS factor

performed in 206 patients (7.0%), and these were pancreas after SPK (5.0%) or SPK after SPK (2.0%) (Table 2).

P-PASS evaluation

P-PASS could be calculated in 19 767 cases (82.9% of all 23 851 organ donors). P-PASS could not be calculated in 4084 cases (17.1% of all 23 851 donors). This was mainly due to missing amylase and lipase values (n = 3253) or unknown ICU stay (n = 739). Median (25th–75th percentile) P-PASS was 19 (17–20). From all 10 444 pancreas donors, P-PASS could be calculated in 9795 cases (93.7%). Of these donors, 3497 (35.7% of these 9795 donors) yielded a low P-PASS value. In 2516 cases (71.9% of those 3497 cases), the responsible transplant coordinator adhered to the Eurotransplant recommendation and reported the pancreas to Eurotransplant. In 745 cases (28.1%), despite a low P-PASS value, the pancreas was not reported to Eurotransplant due to other (unspecified) medical reasons. Of the 16 270 high P-PASS-value- donors, 7279 of 16 270 (44.7%) pancreases were reported to Eurotransplant. Odds ratio of a pancreas being accepted with low versus high P-PASS was 2.21 (95% CI 2.13–2.31) (Table 2). Pancreas reported, accepted, procured and transplanted versus not reported, not accepted, not procured and not transplanted, respectively, yielded the following AUROC's (95% CI of AUROC): 0.63 (0.62–0.63), 0.67 (0.67–0.68), 0.68 (0.67–0.69) and 0.73 (0.72–0.74), respectively (Figure S1 a–d). AUROC's (95% CI of AUROC): 0.78 (0.77–0.78), 0.79 (0.78–0.80), 0.76 (0.75–0.77), and 0.84 (0.83–0.84), respectively (Figure S2 a–d).

$PDRI_{donor}$ evaluation

After correction of the raw data, $PDRI_{donor}$ was calculated (Table 1 for individual factors). There was a significant correlation between P-PASS and $PDRI_{donor}$ for all donors (Spearman's

Table 2. Pancreas allocation outcome and transplant types

	N (%)	Odds ratio (95% CI) P-PASS<17 vs. P-PASS≥17
Reported to Eurotransplant	10444 (100)	1.61 (1.57 – 1.65)
Accepted by transplant center	6090 (58.3)	2.21 (2.13 – 2.31)
Pancreas procured	4731 (45.3)	2.31 (2.21 – 2.43)
Pancreas transplanted	2947 (28.2)	3.43 (3.21 – 3.66)

Pancreas transplanted	2947 (100)
Primary transplantation	
Simultaneous pancreas kidney (SPK)	2077 (70.5)
Pancreas transplant alone (PTA)	96 (3.3)
Pancreas after kidney (PAK)	29 (1)
Multi organ transplantation	62 (2.1)
Islets	417 (14.1)
Simultaneous islet kidney (SIK)	6 (0.2)
Islets after kidney (IAK)	35 (1.2)
Secondary transplantation	
Pancreas after SPK	147 (5.0)
SPK after SPK	59 (2.0)
Islets after SPK	19 (0.6)

r = 0.343, p < 0.001). Correlations were stronger for different outcomes: reported (r = 0.479), accepted (r = 0.557), procured (r = 0.569), and transplanted (r = 0.615) (p < 0.001 for all). Pancreas reported, accepted, procured and transplanted versus not reported, not accepted, not procured and not transplanted, respectively, yielded the following AUROC's (95% CI of AUROC): 0.78 (0.77–0.78), 0.79 (0.78–0.80), 0.76 (0.75–0.77), and 0.84 (0.83–0.84), respectively (Figure S2 a–d). Pooled sample $PDRI_{donor}$ was 1.27 (0.42). Dutch donor centers reported the highest $PDRI_{donor}$ values from donors, with a mean $PDRI_{donor}$ value of 2.50 (SD 1.08). Most pancreata (48.6%) were reported in German donor centers (mean $PDRI_{donor}$ 1.69, SD 0.66).

Pancreas donor risk index for transplanted organs

From 2408 transplanted pancreata, cold ischemia time was missing in 756 (31.3%) cases. Prior to imputation rounds, mean (SD) cold ischemia time was 10.7 (3.1) hours. Cold ischemia time could not be imputed in 67 cases due to missing predictors; this resulted in known cold ischemia time for 2341 transplanted grafts. Pooled sample mean CIT was 10.7 h after 20 imputation rounds. Pancreas donor risk index (PDRI) was calculated for all transplanted pancreas grafts with known cold ischemia time. The pooled sample mean

(SD) PDRI was 1.24 (0.41). PDRI was significantly lower than $PDRI_{donor}$: 0.027 (95% CI of difference 0.023–0.030, $p < 0.001$). Slovenia transplanted the highest PDRI organs, although only 8 PDRI could be calculated due to many missing values, with a pooled sample mean of 1.64 (SD 0.30). Dutch transplant centers transplanted the 2nd highest PDRI organs, with a pooled sample mean of 1.35 (SD 0.43). All other data are shown in Tables 3 and 4.

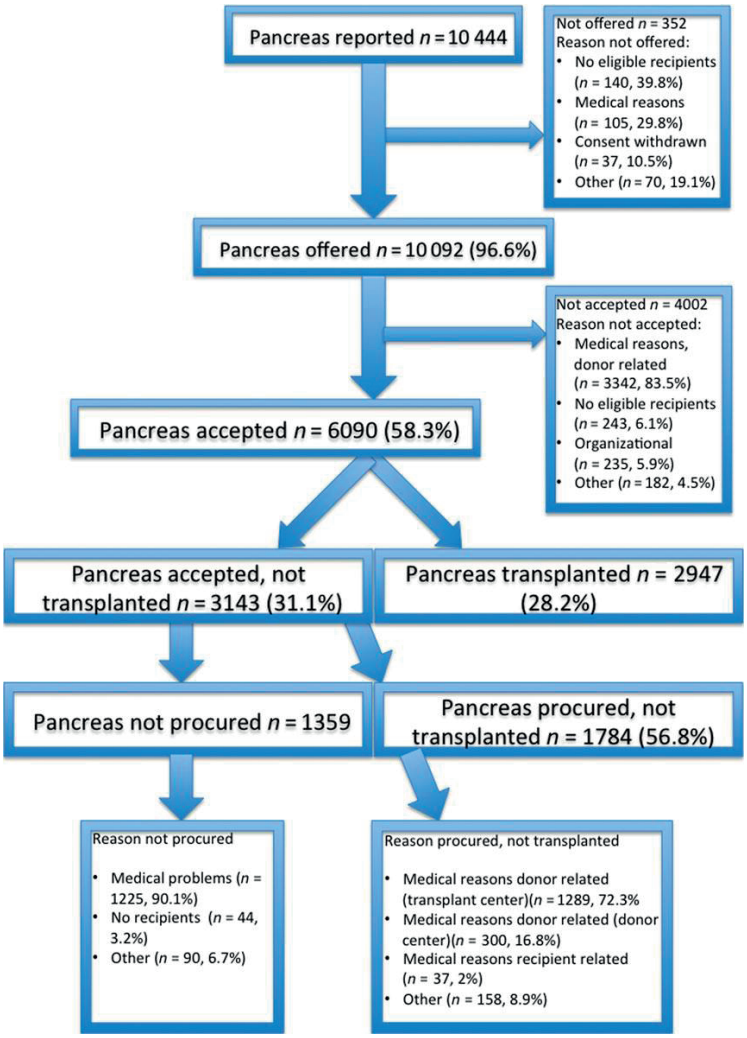

Figure 1. Allocation outcome

Table 3. Donor risk index per Eurotransplant country by allocation outcome for whole organ

	Pancreas reported [a]		Accepted		Transplanted whole organ		Transplanted whole organ	
		$PDRI_{donor}$		$PDRI_{donor}$		$PDRI_{donor}$		PDRI
	N	Mean (SD)	**N**	Mean (SD)	**N**	Mean (SD)	**N**	Mean (SD [c])
Austria	634	1.44 (0.57)	421	1.24 (0.42)	303	1.23 (0.42)	298	1.19 (0.40)
Belgium	2090	2.07 (1.03)	258	1.21 (0.38)	197	1.18 (0.36)	181	1.14 (0.36)
Croatia	261	1.48 (0.59)	85	1.05 (0.29)	68	1.04 (0.30)	68	1.00 (0.28)
Germany	5027	1.69 (0.66)	2766	1.39 (0.48)	1626	1.28 (0.42)	1588	1.24 (0.41)
Hungary	59	1.43 (0.47)	43	1.33 (0.39)	23	1.16 (0.34)	23	1.12 (0.33)
Luxembourg	29	1.67 (0.91)	0		0		0	
Netherlands	2028	2.50 (1.08)	345	1.43 (0.49)	245	1.39 (0.45)	242	1.35 (0.43)
Slovenia	211	1.67 (0.63)	23	1.45 (0.43)	8	1.64 (0.42)	8	1.64 (0.30)
Total	10339	1.90 (0.90)	3941	1.36 (0.47)	2470	1.27 (0.42)	2408	1.24 (0.41)
p [b]		p<0.001		p<0.001		p<0.001		p<0.001

[a] By donorcountry, all others displayed by accepting/transplant country
[b] One way analysis of variance (ANOVA)
[c] Pseudo-SD for imputed data

Table 4. Donor risk index per Eurotransplant country by allocation outcome for islets

	Pancreas reported [a]		Accepted		Transplanted islets	
	N	$PDRI_{donor}$	**N**	$PDRI_{donor}$	**N**	$PDRI_{donor}$
Austria	634	1.44 (0.57)	37	2.07 (0.53)	5	1.94 (0.37)
Belgium	2090	2.07 (1.03)	1509	2.25 (0.93)	392	2.27 (0.87)
Croatia	261	1.48 (0.59)	0		0	
Germany	5027	1.69 (0.66)	134	2.19 (0.61)	25	2.22 (0.56)
Hungary	59	1.43 (0.47)	0		0	
Luxembourg	29	1.67 (0.91)	0		0	
Netherlands	2028	2.50 (1.08)	469	2.55 (0.91)	55	2.24 (0.81)
Slovenia	211	1.67 (0.63)	0		0	
Total	10339	1.90 (0.90)	2149	2.31 (0.91)	477	2.26 (0.85)
p [b]		p<0.001		p<0.001		p=0.846

[a] By donorcountry, all others displayed by accepting/transplant country
[b] Mean (SD). One-way ANOVA

DISCUSSION

This study is an overview of the pancreas quality of donors in the Eurotransplant area. Currently available donor risk indices, both Preprocurement Pancreas Allocation Suitability Score (P-PASS) and the Pancreas Donor Risk Index (PDRI), were evaluated for their ability to predict allocation outcome in the study cohort. It has become clear from this study that

many potential donors are not being utilized and discard rates are high. This study also shows that in pancreas transplantation there is not so much an absolute shortage of organs, but merely a shortage of organs that are presumed suitable. Therefore, proper donor selection within a broad cohort of potential pancreas donors is important. We therefore selected the widest possible range of donors, without limiting age or BMI. Currently, guidelines in The Netherlands consider whole-organ DBD pancreas donation up to 60 years appropriate, and up to 50 years for DCD donation. In the UK, the upper age limit is even higher.[19] Despite this wide range, 75% of the donor population in our study was below 64 years and might therefore possibly be considered for pancreas transplantation.

The P-PASS is a scoring tool that was developed at Eurotransplant in 2008. It is well known that increasing organ shortage has pushed transplant professionals to accepting more extended criteria donor organs. Therefore, we aimed to analyze whether the P-PASS in its current form still has any value in the allocation process, whether it is still of aid to transplant professionals, and whether it can and should be used in the future. Compared to the data provided by the original authors, who analyzed a cohort from 2002 until 2005[7], the median potential donor quality, as measured by P-PASS, has declined to a median of 19. This finding questions the applicability of the P-PASS in current allocation practices, considering the recommendation that is given by Eurotransplant that any donor with a P-PASS below 17 should be considered as a potential donor. It is remarkable that the P-PASS could not be calculated in 17% of the cases. The fact that 28% of the potential donors were not reported due to medical reasons, despite a low P-PASS, questions the value of the current cut-off. Furthermore, some P-PASS factors have become more common today, so the question is whether the P-PASS scoring system is still up to date. Especially in countries with relatively high numbers of DCD donors, such as The Netherlands and, to a lesser extent, Belgium, P-PASS does not fully apply, as the factor DCD is not taken into account (although it is a known risk factor[16]). Also, in our cohort, median donor age was 53 years, which does not compare to the earlier reported median age of 34 years, for accepted donor grafts, nor to the median age of 40 years, for grafts that were not accepted. The odds ratio of pancreas acceptance with low versus high P-PASS was lower than reported by the original authors, which also indicates its decreased predictive value.[7]

The Pancreas Donor Risk Index, which was developed using OPTN data in 2010, was recently validated in a European setting to predict graft survival.[12,17] Again, as the $PDRI_{donor}$ only contains donor factors, similar to the P-PASS, it would be applicable at the time of organ allocation. We deliberately chose not to modify the intrinsic regression coefficients of the model, but decided to use the model with the logistical factors set to their reference values. In this model, cold ischemia time was set to 12h, race set to Caucasian, and transplant type set to SPK. With this approach, we were able to establish excellent discriminatory properties of the model. The additional value of the full PDRI is that it has already been proven to be associated with graft survival.

Even though the correlation between P-PASS and $PDRI_{donor}$ was statistically significant, the correlation coefficient indicates that the actual correlation was not perfect. Both indices share risk factors and have different factors, which explains this partial correlation. For example, age and BMI are included in both indices. Both factors influence the final P-PASS score, as well as the PDRI and have also been identified as risk factors in other studies.[20,21] One of the strongest risk factors of the PDRI, DCD donation, is not included in the P-PASS. DCD pancreas transplantation has become a more accepted option in recent years.[14,22,23] With traumatic brain injuries, elevated amylase, as one of the P-PASS factors, does not have to be related to pancreas injury, but increases the P-PASS score.[15] Duration of ICU stay and vasopressor use, P-PASS but not PDRI factors, are associated with pancreas being declined for transplantation.[6,24] Because these donors are declined for transplantation, there is little evidence to support that finding. A small trial found no association with donor vasopressor use and short-term outcome.[25] Electrolytes, such as the P-PASS factor sodium and the PDRI factor creatinine, do not necessarily influence pancreas graft survival, but they do provide insight in donor kidney function and general donor condition. Especially creatinine, the main indicator of kidney function, may reflect kidney damage (but also other organ damage) in an early stage. When taking those factors into account, it is obvious that the role of P-PASS in organ allocation should be reconsidered. Furthermore, from this study it becomes clear that the $PDRI_{donor}$ is a more powerful tool to predict allocation outcome. All supplemental AUROC curves show that the PDRI is superior over the P-PASS. This implies that the $PDRI_{donor}$ and PDRI are more valuable tools in donor selection and donor population comparison and should be used instead of the P-PASS for aforementioned applications.

The difference in pancreas donor quality in different Eurotransplant countries is a remarkable finding. Donation after cardiac death is believed to play a major role in the high $PDRI_{donor}$ values in The Netherlands and Belgium. Even with these high-risk donors, good outcomes can be achieved, so organs and potential donors should never be turned down solely based on high PDRI; a high PDRI value should not be used as a single argument to turn down an organ offer. PDRI is merely a valid tool to estimate outcome. The authors think that this assessment is useful for physician-to-patient communication as well as retrospective reporting purposes. Other factors, such as recipient selection and center experience, should also be taken into account. Furthermore, countries with a lower mean $PDRI_{donor}$ that also have increasing waiting lists and increased waiting time until transplantation[26,27] might utilize a more aggressive approach by accepting higher risk donors. Therefore, to answer the question on the usefulness of these donor risk indices raised by Berney and Kandaswamy in a recent commentary in Transplant International, a donor risk index, such as the PDRI, can be helpful in proper donor selection, but also in describing a certain donor population to compare center or country specific outcome.[28]

The most important limitation of our study is that our data do not contain any outcome after transplantation. Eurotransplant depends on the willingness of its related transplant

centers for data entry and data on survival is not complete. The authors therefore chose to select allocation outcome as a surrogate marker for donor quality. The authors presume that once an organ is transplanted, outcome among centers is comparable, taking the differences in donor and recipient populations into account. Multiple studies from large Eurotransplant centers have shown excellent results in terms of graft and patient survival.[1, 4, 29, 30] Ideally, we would have validated the PDRI for graft survival in the Eurotransplant region in this study. Unfortunately, due to above-mentioned reasons, this was not possible and requires further study.

CONCLUSION

As the pancreas donor risk index (PDRI) has been shown to be associated with outcome in other studies and this study shows that the $PDRI_{donor}$ has a stronger association with allocation outcome, the pancreas donor risk index (in both forms) should be used instead of the P-PASS in organ allocation practices, as well as to describe overall pancreas donor quality in a population. Adequate donor recognition in different Eurotransplant regions might lead to increased numbers of successful pancreas donation procedures. The authors believe that better tools to identify donors will eventually increase donation rates. The PDRI is such a tool.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge all Eurotransplant Pancreas Advisory Committee Members that approved the study: Ms. C. Jansen, Dr. H. Arbogast, Prof. Dr. F.H.J. Claas, Prof. Dr. P. Gillard, Prof. Dr. P. Hengster, Dr. S. Jadrijevic, Dr. A. Kahl, Dr. Kalmar Nagy, Dr. P. Schenker, Dr. J. Ringers and Dr. A. Tomazic. Emilie is gratefully acknowledged for her editorial comments.

SUPPLEMENTAL DATA

Supplemental figure 1. P-PASS AUROC for reported pancreas grafts (a), accepted pancreas grafts (b), procured pancreas grafts (c) and transplanted pancreas grafts (d).

Fig. 1a

Fig. 1b

Fig. 1c

Fig. 1d

Supplemental figure 2. $PDRI_{donor}$ AUROC for reported pancreas grafts (a), accepted pancreas grafts (b), procured pancreas grafts (c) and transplanted pancreas grafts (d).

Fig. 2a

Fig. 2b

Fig. 2c

Fig. 2d

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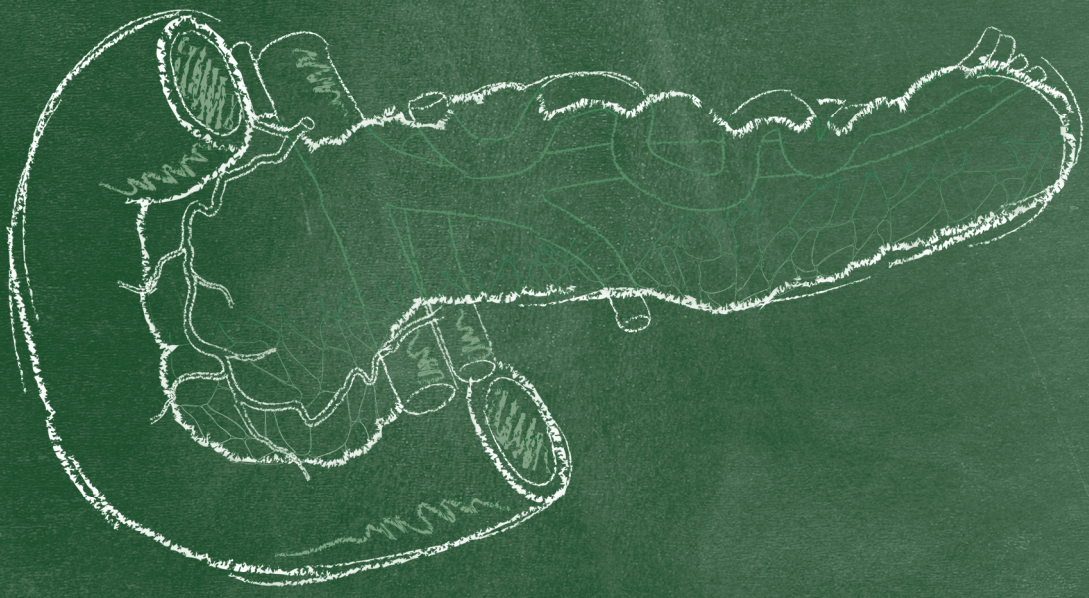

5

Center Volume Is Associated With Outcome After Pancreas Transplantation Within the Eurotransplant Region

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Transplantation. 2017 Jun; 101(6); 1247 - 1253

Introduction: Outcome after surgery depends on several factors, among these, the annual volume-outcome relationship. This might also be the case in a highly complex field as pancreas transplantation. No study has investigated this relationship in a European setting.

Methods: All consecutive pancreas transplantations from January 2008 until December 2013 were included. Donor-, recipient-, and transplant-related factors were analyzed for their association with patient and graft survivals. Centers were classified in equally sized groups as being low volume (<5 transplantations on average each year in the 5 preceding years), medium volume (5-13/year), or high volume (≥13/year).

Results: In the study period, 1276 pancreas transplantations were included. Unadjusted 1-year patient survival was associated with center volume and was best in high volume centers, compared with medium and low volume: 96.5%, 94% and 92.3%, respectively (p = 0.017). Pancreas donor risk index (PDRI) was highest in high volume centers: 1.38 versus 1.21 in medium and 1.25 in low volume centers ($p < 0.001$). Pancreas graft survival at 1 year did not differ significantly between volume categories: 86%, 83.2%, and 81.6%, respectively (p = 0.114). After multivariate Cox-regression analysis, higher PDRI (hazard ratio [HR], 1.60; $p < 0.001$), retransplantation (HR, 1.91; p = 0.002) and higher recipient body mass index (HR, 1.04; p = 0.024) were risk factors for pancreas graft failure. High center volume was protective for graft failure (HR, 0.70; p = 0.037) compared with low center volume.

Conclusions: Patient and graft survival after pancreas transplantation are superior in higher volume centers. High volume centers have good results, even though they transplant organs with the highest PDRI.

INTRODUCTION

Pancreas transplantation is the only definitive treatment for patients with type 1 diabetes mellitus. This can be as a simultaneous pancreas kidney transplantation (SPK) in case of end-stage renal disease (ESRD) or as a solitary pancreas transplant (pancreas after kidney [PAK], pancreas transplant alone [PTA]) in case of life-threatening hypoglycemic unawareness.[1-3] Even though the number of patients on the waiting list is relatively stable since 2009, optimal usage of scarce number of potential pancreas allografts is still highly important.[4] Apart from donor, recipient and transplant factors influencing outcome after transplantation,[5,6] center factors may also play a significant role.

The Dutch Institute for Clinical Auditing has been working on valid outcome measures in 18 domains of health care, most of them in oncological surgery. Eurotransplant is a non-profit organization that facilitates patient-oriented allocation and cross-border exchange of deceased donor organs. Active for transplant centers and their associated tissue typing laboratories and donor hospitals in 8 countries, Eurotransplant ensures an optimal use of donor organs. To be able to develop allocation policies based on state-of-the-art medical knowledge, Eurotransplant collects donor, recipient, and center data, as well as outcome data after transplantation. Information on center-related outcome, provided that they represent valid and useful outcome measures, should be publicly available: to centers, to improve their results; to patients, to make a well-founded decision on a preferred center; and to politicians, to design legitimate healthcare policies. This information can be derived from organizations, such as the Dutch Institute for Clinical Auditing or Eurotransplant or from single-center reports.

With this information, efforts are being put into concentrating "high complex, low volume" care in The Netherlands.[7] Especially oncology care is subject of this ongoing change. Transplantation has been the subject of concentration of care by the government longer and especially pancreas transplantation, with currently only 2 of 8 transplant centers with an active pancreas transplantation program. The question rises whether this concentration is justified and if the volume outcome relationship also exists in the field of pancreas transplantation, as has been stated before.[8,9] Recently, a German study advocated for an extensive analysis of volume-outcome after transplantation.[10] In 2014, within Eurotransplant there were 37 centers with an active pancreas transplant program, performing a total of 199 vascularized pancreas transplants, thus averaging an annual number of pancreas transplantations of a little over 5 each year.[4]

The aim of this study is to investigate the effect of center volume on outcome after pancreas transplantation in the Eurotransplant region.

Design

All consecutive vascularized pancreas transplantations that were performed in Eurotransplant centers from January 1, 2008, until December 31, 2013, were analyzed. Donor, procurement, recipient, and transplant data that were derived from the standard Eurotransplant database are shown in Table 1. Follow-up data were collected through the Eurotransplant registry. The Eurotransplant registry data were extracted at October 6, 2015. Graft survival was death censored. A frequently used definition of graft failure is that graft failure has occurred, when the recipient had returned to exogenous insulin therapy. This was the definition that the authors applied to all patients that were transplanted at the Leiden University Medical Center. For all other centers, it was unknown which definition was used, so the definition of pancreas graft failure was left up to the discretion of the transplant centers. When graft failure and death occurred at the same day or a graft had not been reported as failed before recipient death, this was not considered graft failure, and these cases were censored. The procurement surgeon determined organ quality (good, acceptable, poor) based on macroscopic evaluation; however, exact criteria were unknown.

Center volume for each year was defined as the total transplant volume of the 5 preceding years, based on standard Eurotransplant data reports (i.e., factor center volume for 2008 was based on average volume from 2003 to 2007, for 2009 based on 2004 to 2008, and so on).[11] Volume calculations were not performed for centers before their entry in the Eurotransplant collaboration. Croatia entered Eurotransplant in 2007, therefore, only transplants in 2013 (volume based on 2008-2012) were included in the center volume-survival analysis. Hungary entered in 2013, so was excluded from the center volume-survival analysis. Three equally sized groups were determined (low, medium, and high volume), based on the total volume in the 5 preceding years. Multiorgan transplants were only used to compute the total volume and were excluded from further analysis. Data in all 3 categories were pooled in order not to compromise recipient privacy and in order to not be able to identify individual centers.

Statistical Analysis

Differences between different volume categories were displayed using pooled sample mean and SE. P-values were calculated using 1-way analysis of variance. Missing values were imputed using 20 imputation rounds. Missing survival data were not imputed. Survival analysis for categorical variables was done using Kaplan-Meier estimates and groups were compared using Log-rank tests. Continuous variables were analyzed using Cox proportional hazard models after testing of the proportional hazards assumption.[12] P-values less than 0.05 were considered statistically significant. All significant factors from univariate survival analysis, as well as factors that were different among volume groups were entered in multivariate Cox proportional hazards model. To account for clustering of the data, robust sandwich estimates of the standard errors were used in multivariate analysis.[13] Only complete cases after multiple imputations were analyzed.

Table 1. Demographics, univariate analysis of association with pancreas graft survival [a]

	N (%)	P	X^2
Donors	1276 (100)		
Sex [b] (male)		0.150	2.070
Male	678 (53.1)		
Female	598 (46.9)		
Cause of death [b]		0.076	8.460
Cerebrovascular accident	624 (48.9)		
Trauma	497 (38.9)		
Circulational/Anoxia	115 (9.0)		
CNS tumor	7 (0.5)		
Other	33 (2.6)		
Donor type [b]		0.387	0.749
DBD	1268 (99.4)		
DCD	8 (0.6)		
	Mean (SD)	**P**	**HR**
Age, y [b]	32 (12)	0.006	1.014
Weight, kg	71 (14)	0.218	1.006
Height, cm [b]	173 (12)	0.884	1.001
BMI, kg/m^2 [b]	23 (3)	0.036	1.045
Sodium, mmol/l	147 (9)	0.611	1.004
Creatinine, mg/dl [b]	0.87 (0.58)	0.358	1.089
Amylase, U/l	125 (281)	0.114	1.000
PDRI	1.27 [c]	0.006	1.466
	N (%)	**P**	**X^2**
Transplant			
Perfusion solution		0.036	6.658
UW [d]	339 (26.6)		
HTK	906 (71)		
Other	13 (1.0)		
Unknown	18 (1.4)		
Transplant type [b]		<0.001	61.191
SPK [d]	1148 (90.0)		
PAK	84 (6.6)		
PTA	44 (3.4)		
Retransplantation (yes)	118 (9.2)	<0.001	13.036

Table 1. Demographics, univariate analysis of association with pancreas graft survival [a] (continued)

Transplant year		0.691	3.060
2008	199 (16.4)		
2009	172 (14.2)		
2010	228 (18.8)		
2011	220 (18.1)		
2012	211 (17.4)		
2013	184 (15.2)		
	Mean	**P**	**HR**
Pancreas cold ischemia, h [b]	10.4**	0.610	1.012
	N (%)	**P**	**X^2**
Recipient			
Gender		0.577	0.312
Male	785 (61.5)		
Female	491 (38.5)		
End stage renal disease			
No end stage renal disease (PAK/PTA)	128 (10.0)		
End stage renal disease (SPK)		0.140	0.140
Pre-emptive	218 (19.0)		
Hemodialysis	736 (64.1)		
Peritoneal dialysis	194 (16.9)		
	Mean (SD)	**P**	**HR**
Age, y	44 (9)	0.487	0.995
BMI, kg/m^2	24 [c]	0.025	1.038
Waiting time, y	1.15 (1.3)	0.970	0.998

[a] Kaplan-Meier estimates (Log rank Mantel-Cox) for categorical variables. Cox proportional hazards for continuous variables.
[b] PDRI factor
[c] based on imputed data
[d] favorable factor

Missing Data Imputation

Recipient weight (6.2%), recipient height (6.2%), and pancreas cold ischemia (25.4%) had missing values. Variables that were included in the imputation model were: donor age, sex, weight, height, body mass index (BMI), cause of death, creatinine, DBD versus DCD, pancreas donor risk index (PDRI), and donor country; recipient age, sex, weight, height, dialysis type, waiting time; pancreas cold ischemia time in minutes and hours, total pancreas cold ischemia time (hours), transplant type (SPK, PAK, PTA), center volume, warm ischemic period, transplant center, transplant year, organ quality, perfusion solution. Warm ischemic time, PDRI, creatinine, amylase, lipase, sodium, transplant center, donor country, perfusion solution, and organ quality were used as indicators only. Imputation method

was automatically selected by SPSS (SPSS version 22, IBM, North Castle, NY) based on patterns of missing value analysis. To reduce sampling variability from the imputations, 20 imputation rounds were performed.[14] Results of multiple imputations are shown in Table 2. Recipient BMI and PDRI were calculated based on the imputed values.

Table 2. Imputation of missing data

	Original data			Imputed data [a]		
	n	% missing	Mean (SEM)	n	% missing	Mean (SEM)
Recipient height (cm)	1198	6.2	172 (0.26)	1276	0	172 (0.26)
Recipient weight (kg)	1198	6.2	72 (0.39)	1276	0	72 (0.40)
Pancreas CIT (hr)	952	25.4	10.4 (0.09)	1276	0	10.4 (0.08)

[a] 20 rounds of multiple imputations

RESULTS

In the study period (January 2008 to December 2013), 1276 pancreas transplantations were included in the study. There were 1148 (90%) SPK transplantations, 84 (6.6%) PAK transplantation, and 44 (3.4%) PTA transplantations. During the study and follow-up period, 122 (9.6%) patients were reported deceased and 256 (20.1%) grafts were reported as failed (death-censored). Mean duration of follow-up was 3.2 years. Mean pancreas donor risk index was 1.27. Demographics are shown in Table 1.

Patient and Pancreas Graft Survival

Overall patient survival at 180 days, 1 year, and 3 years was 95.4%, 94.1%, and 91.2%, respectively. Patient death was associated with higher recipient age (hazard ratio [HR], 1.03; $p = 0.006$). Pancreas graft survival (death-censored) at 180 days, 1 year, and 3 years was 85.3%, 83.7%, and 78.8%, respectively. Pancreas graft failure was associated with higher donor age ($p = 0.006$), higher donor BMI ($p = 0.036$), higher PDRI ($p = 0.007$), and high recipient BMI ($p = 0.027$), retransplantation ($p < 0.001$) and the use of histidine tryptophan ketoglutarate (HTK) as perfusion solution ($p = 0.036$). Simultaneous pancreas kidney transplantation ($p < 0.001$) was protective in univariate analysis. Results of univariate analysis on factors associated with pancreas graft failure are shown in Table 1. Year of transplant was not associated with pancreas graft survival ($p = 0.69$).

In a separate subgroup analysis of recipients with ESRD (SPK recipients), the influence of dialysis modality (either pre-emptive transplantation, peritoneal dialysis or hemodialysis) was analyzed for the association with patient and graft survival. In this analysis, patient ($p = 0.235$) and graft survivals ($p = 0.140$) were not associated with dialysis technique.

Analysis of Center Volume on Outcome

For 1214 (95.1%) transplantations, center volume was calculated. Nine transplantations (0.7%) were from Hungary and 53 (4.2%) from Croatia, and these were excluded, because they had too few preceding years in Eurotransplant. Low volume centers (<25 transplantations/5 preceding years) performed 396 (32.6%) transplantations, 425 (35%) were performed in medium volume (25-64 transplantations/5 years) centers and 393 (32.4%) in high volume (≥65 transplantations/5 years) centers. An overview of number of transplantations in each year by center category is shown in Table S1 (SDC, http://links.lww. com/TP/B303). Center demographics are shown in Table 3. The pooled sample mean PDRI of donors transplanted in different categories differed significantly: 1.25 in low volume centers, 1.21 in medium volume centers, and 1.38 in high volume centers ($p < 0.001$). Post hoc testing (Bonferroni corrections) showed that PDRI only differed between high versus low ($p < 0.001$) and high versus medium ($p < 0.001$), not low versus medium ($p = 0.316$). High volume centers transplanted patients with ESRD more frequently in a preemptive setting, compared with low and medium volume ($p < 0.001$). Mean time from waiting list registration to transplantation

Table 3. Demographics in center categories

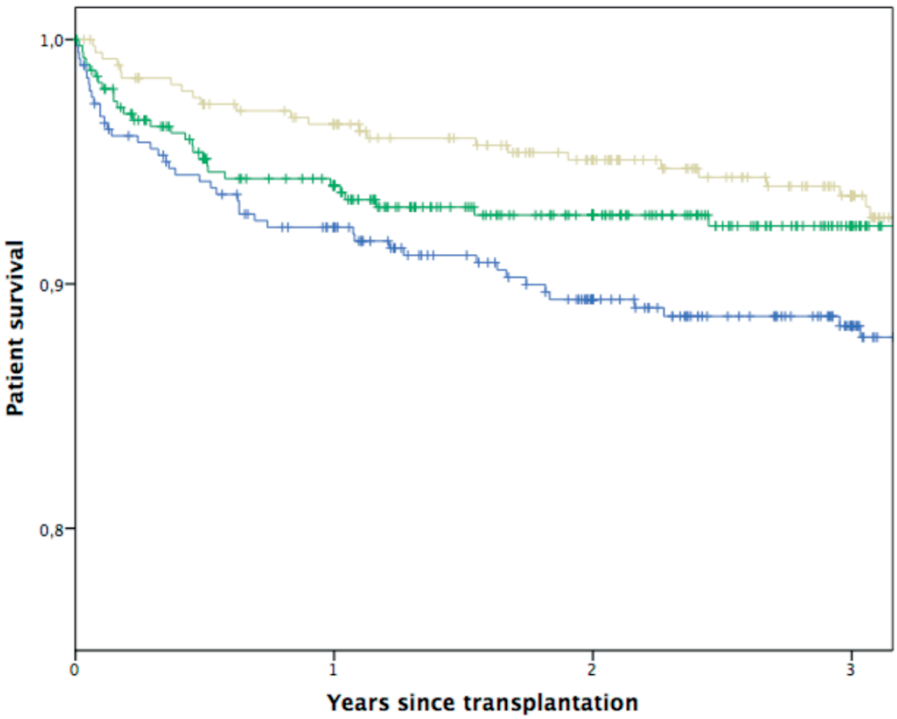
	Low volume [b]	Medium volume [b]	High volume [b]	p [a]
n	396 (32.6%)	425 (35%)	393 (32.4%)	
PDRI	1.25 (0.41)	1.21 (0.41)	1.38 (0.46)	<0.001
PDRI factors				
Donor age, y	33 (11)	30 (12)	35 (13)	<0.001
Donor BMI, kg/m^2	23.6 (2.8)	22.9 (3.2)	23.3 (2.9)	0.005
Pancreas CIT, hr	9.7 (2.6)	10.4 (3.1)	11.2 (2.6)	<0.001
SPK transplantation	361 (91.2%)	375 (88.2%)	353 (89.8%)	0.019
Cause of death (stroke)	196 (49.5%)	194 (45.6%)	210 (53.4%)	0.252
DCD	0 (0%)	0 (0%)	8 (2%)	<0.001
Recipient age, y	44 (8.7)	44 (8.6)	44 (8.7)	0.660
Recipient BMI, kg/m^2	24.2 (4.2)	24.1 (3.8)	24.2 (3.8)	0.593
Sensitized				0.177
6 – 80 % PRA	15 (4%)	28 (6.9%)	21 (5.5%)	
>80% PRA	3 (0.8%)	0 (0%)	3 (0.8%)	
Waiting time, d	586 (434)	649 (497)	583 (532)	0.087
Retransplantations	32 (8.1%)	46 (10.8%)	40 (10.2%)	0.387
End stage renal disease (SPK)				<0.001
Pre-emptive	61 (16.9%)	54 (14.4%)	101 (28.6%)	
Hemodialysis	243 (67.3%)	262 (69.9%)	192 (54.4%)	
Peritoneal dialysis	57 (15.8%)	59 (15.7%)	60 (17.0%)	

[a] One-way ANOVA for continuous variables (mean, SD), X^2 for categorical variables (n, %)

[b] Low volume (<5 transplantations/year), medium volume (5-13/year) or high volume (≥ 13/year).

was not significantly different in 3 volume categories (Table 3). The proportional hazards assumption was not violated (p = 0.350).

Patients transplanted in high volume centers had longest patient survival (p = 0.017) (Figure 1A). Other than age and center volume, no factors were significantly associated with patient survival in univariate analysis. After correcting for recipient age (HR, 1.04; 95% confidence interval [95% CI], 1.02-1.06; p = 0.001) in a multivariate Cox regression analysis, high volume (HR, 0.51; 95% CI, 0.32-0.81, p = 0.004) but not medium volume (HR, 0.65; 95% CI, 0.42-1.00; p = 0.052) was protective compared with low volume. One

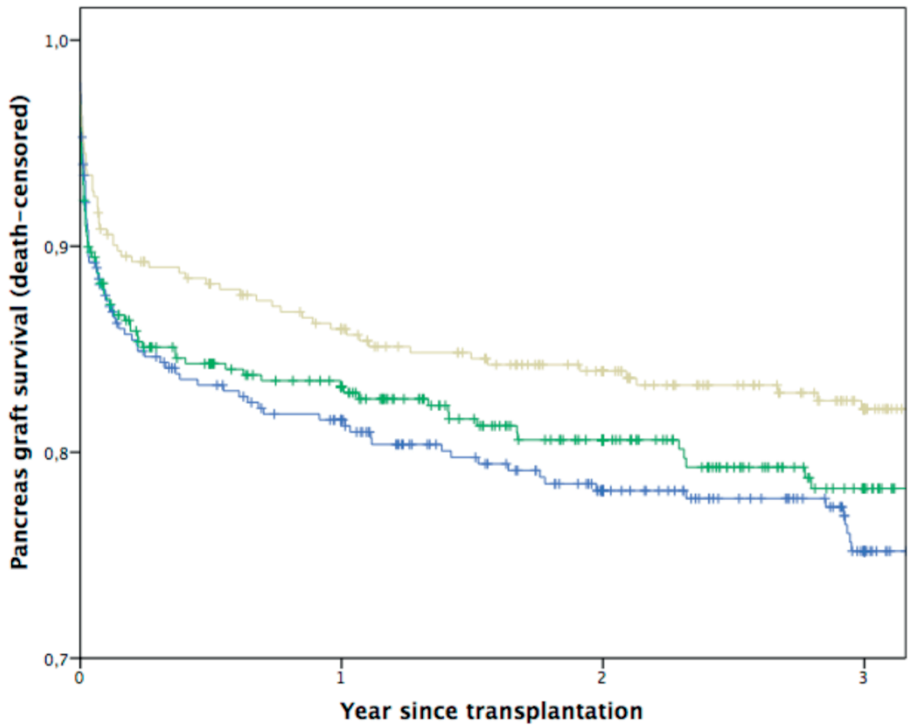


	0 days	180 days	1 year	3 years
Low volume				
N at risk	382	353	332	216
Patient survival	100%	94.2%	92.3%	88.3%
Medium volume				
N at risk	399	353	329	170
Patient survival	100%	95.1%	94.0%	92.4%
High volume				
N at risk	382	360	346	236
Patient survival	100%	97.4%	96.5%	93.6%

Figure 1a Kaplan-Meier estimates for patient survival in different volume categories (p=0.017)

hundred twelve cases (8.8%) were excluded due to missing follow-up data or because they were performed in the first years of Croatian or Hungarian membership of Eurotransplant.

In univariate analysis, graft survival was not significantly different among the 3 categories (p = 0.11) (Figure 1B). Higher PDRI (HR, 1.60; p<0.001), retransplantation (HR, 1.91; p = 0.002), and higher recipient BMI (HR, 1.04; p = 0.024) were independent risk factors for pancreas graft failure after multivariate Cox regression analysis. Perfusion with University of Wisconsin (UW) solution was not protective after multivariate analysis, compared with



	0 days	180 days	1 year	3 years
Low volume				
N at risk	382	300	280	170
Graft survival	100%	83.3%	81.6%	75.2%
Medium volume				
N at risk	399	310	284	139
Graft survival	100%	84.3%	83.2%	78.2%
High volume				
N at risk	382	324	307	203
Graft survival	100%	88.2%	86.0%	82.1%

Figure 1b Kaplan-Meier estimates for pancreas graft survival in different volume categories (p=0.114)

HTK (p = 0.111) or other solutions (p = 0.739). Higher center volume was associated with a lower risk of pancreas graft failure. This effect was statistically significant for low versus high volume (HR, 0.70; p = 0.037), but not for low versus medium volume (HR, 0.89; p = 0.562). Results of multivariate analyses are shown in Table 4a. One hundred thirty (10.2%) cases were excluded from multivariate analysis due to missing follow-up data or because they were performed in the first years of Croatian or Hungarian membership of Eurotransplant.

In a separate subgroup analysis (Table 4b) with only SPK transplants included, PDRI, volume category, and perfusion solution (significant factors from univariate analysis),

Table 4.1. Multivariate analysis of association of risk factors with pancreas graft survival (all transplantations)

	HR (95% CI)	**P**
PDRI	1.60 (1.23 - 2.07)	<0.001
Perfusion solution		
UW	reference	
HTK	1.28 (0.95 - 1.72)	0.111
Other	0.71 (0.09 – 5.40)	0.739
Retransplantation	1.91 (1.26 - 2.91)	0.002
Recipient BMI	1.04 (1.00 - 1.07)	0.024
Center volume		
Low volume	reference	
Medium volume	0.89 (0.59 - 1.33)	0.562
High volume	0.70 (0.50 - 0.98)	0.037

Table 4.2. Multivariate analysis of association of risk factors with pancreas graft survival (SPK transplantations)

	HR (95% CI)	**P**
PDRI	1.94 (1.45 – 2.60)	<0.001
Perfusion solution		
UW	reference	
HTK	1.56 (1.07 – 2.28)	0.021
Other	1.02 (0.13 – 7.93)	0.984
Retransplantation	1.33 (0.84 – 2.13)	0.227
End stage renal disease		
Pre-emptive	reference	
Hemodialysis	0.97 (0.67 – 1.39)	0.85
Peritoneal dialysis	1.47 (0.96 – 2.24)	0.07
Recipient BMI	1.04 (1.00 – 1.07)	0.047
Center volume		
Low volume	reference	
Medium volume	0.91 (0.58 – 1.44)	0.696
High volume	0.69 (0.49 – 0.97)	0.032

recipient BMI, and dialysis category were included in multivariate analysis. In this multivariate analysis, high PDRI was associated with graft failure (HR, 1.94; $p < 0.001$). High volume, as compared to low volume, was protective for graft failure (HR, 0.69; $p = 0.032$), whereas medium volume was not (HR, 0.91; $p = 0.696$). The use of HTK was associated with a higher risk of graft failure compared with UW (HR, 1.56, $p = 0.021$). Whether a recipient was transplanted preemptively or while on dialysis was not associated with pancreas graft survival. Of all 1148 SPK transplantations, 119 (10.4%) were excluded from multivariate analysis due to missing follow-up data or because they were performed in the first years of Croatian or Hungarian membership of Eurotransplant.

DISCUSSION

This study investigates the association of center volume with outcome after pancreas transplantation. We have shown that there is a significant relationship between center volume (defined as volume in 5 preceding years) and outcome, measured both in patient survival years as in pancreas graft survival years.

In this study, center volume was calculated based on the total number of pancreas transplantations in the previous 5 years. The authors have the opinion that 5 years is a reasonable timeframe to maintain an experienced program for pancreas transplantations. The calculations of volume were deliberately performed on data from preceding years, in order not to violate assumptions in analysis of longitudinal data.[11] This allowed us to analyze the influence of volume on outcome, and we excluded the possibility that lower or higher volume was influenced by previous results. This is the preferred method to investigate volume-outcome in any specialty; however, results might have been clouded by the fact that centers were allowed to migrate between the categories. It could thus have been that a center was defined as medium volume in the first year, but was analyzed as being low volume in the following year. This might be considered as a limitation, but the authors consider this as a strength of the study, because this method allowed us to establish the existence of the volume-outcome relationship, without considering the individual center effect. We acknowledge the fact that center volume is a surrogate marker, because true quality depends on multiple factors, such as surgical experience, adequate recipient selection and screening, postoperative care, and long-term follow-up protocols.

Patient survival after transplantation was associated with recipient age, as well as center volume. Higher recipient age was a risk factor for patient death, whereas high center volume was a protective factor. The better patient survival might be explained by a more rigorous pretransplant screening, especially regarding cardiovascular status of the intended recipients, and more optimal posttransplant management of cardiovascular complications in higher volume centers. A recent study from Scalea et al[15] demonstrated comparable

patient survival in older recipients in a high volume center with very strict pretransplant cardiovascular workup.

In univariate analysis, we could not find a significant difference in graft survival and center volume. However, when correcting for relevant donor and recipient characteristics in multivariate analysis, the association with graft failure and center volume became clear. High volume centers have better results compared with low volume centers, even though they are more aggressive in their acceptance policy, indicated by higher PDRI. Furthermore, from our available recipient data, we did not establish a significant difference in transplant recipient demographics (age, BMI, waiting time, retransplantation) that could have explained these results.

Even though it is not the aim of our study, next to the volume-outcome relationship, several other factors that were significantly associated with pancreas graft survival were identified. The first is the pancreas donor risk index (PDRI), which was found to be associated with graft failure. This is in line with results from previous studies.[16,17] Next to donor risk, 2 recipient factors were also found to be risk factors for inferior graft survival. Higher recipient BMI is considered a risk factor in many types of surgery, being associated with higher complication rate, and this relationship has recently been confirmed in 2 studies on pancreas transplantation.[18,19] The results of our study confirm this increased risk for recipients with higher BMI. Also, retransplantation was a risk factor for graft failure (in fact, the strongest). The authors believe that this is independent of the transplant type, because we corrected for transplant type using the PDRI. Our results are in line with previously published results from a large registry analysis from the United States.[20] For the subgroup of SPK transplantations, retransplantation was not a significant risk factor. This may be because of small numbers, because most retransplantations are performed in a PAK/PTA setting.

The protective effect of UW as perfusion solution in univariate analysis disappeared after multivariate analysis of all transplantations. Possible explanations could be that HTK was used in higher risk donors, retransplantations or that HTK was used more frequently in low volume centers. On the other hand, HTK was identified as an independent risk factor for graft failure in the subgroup analysis of SPK transplantations. The authors think that this study provides more evidence regarding the optimal cold storage solution for pancreata.[21] To identify an association was not within the scope of this study and to adequately investigate the relationship between outcome and perfusion solution a randomized controlled trial would be preferred. No association with transplant year and graft survival was found in this study, indicating that in this cohort, the era effect was of minor importance. The relatively modern cohort (without major changes in surgical techniques, preservation methods and immunosuppression) may be the reason for this absent association.

This study had some limitations. Most important one is the definition of graft failure. Because there appears to be no consensus on the definition of pancreas graft failure, graft

failure was left up to the discretion of the centers. There may be significant differences in reported survival rates, depending on the definitions. Furthermore, data on reported survival and exact numbers lost to follow-up may not be complete; this may have influenced the results. Also, Eurotransplant depends on data filled in by the donor and transplant centers. Some data were missing, however, multiple imputation has been shown to provide valid results and is an accepted technique to handle missing data.[22,23] We believe that using this technique did not influence the results in any way and has provided valid estimations of the missing data. The authors realize that the volume cutoffs that were chosen are debatable, however, still feasible, when looking at centers privacy and current group sizes. It could be that, next to recipient age, patient survival was associated with factors, such as preexistent peripheral artery disease, coronary or cerebrovascular disease; however, these data were not available in this study.

In conclusion, it is a remarkable finding that almost one third of all pancreas transplantations in the Eurotransplant region are being performed in centers that had performed less than on average 5 transplantations each year in the 5 preceding years. Given the fact that the highest risk organs are transplanted in the high volume centers with good outcome, it is an interesting thought that improving experience in the pancreas transplant centers may facilitate acceptance and allow transplantation of higher risk organs and increase transplant numbers.

ACKNOWLEDGMENT

The authors would like to gratefully acknowledge Erwin de Vries (Eurotransplant data manager) for his efforts in collecting the data. Eurotransplant transplant centers are also gratefully acknowledged for submitting the data to Eurotransplant.

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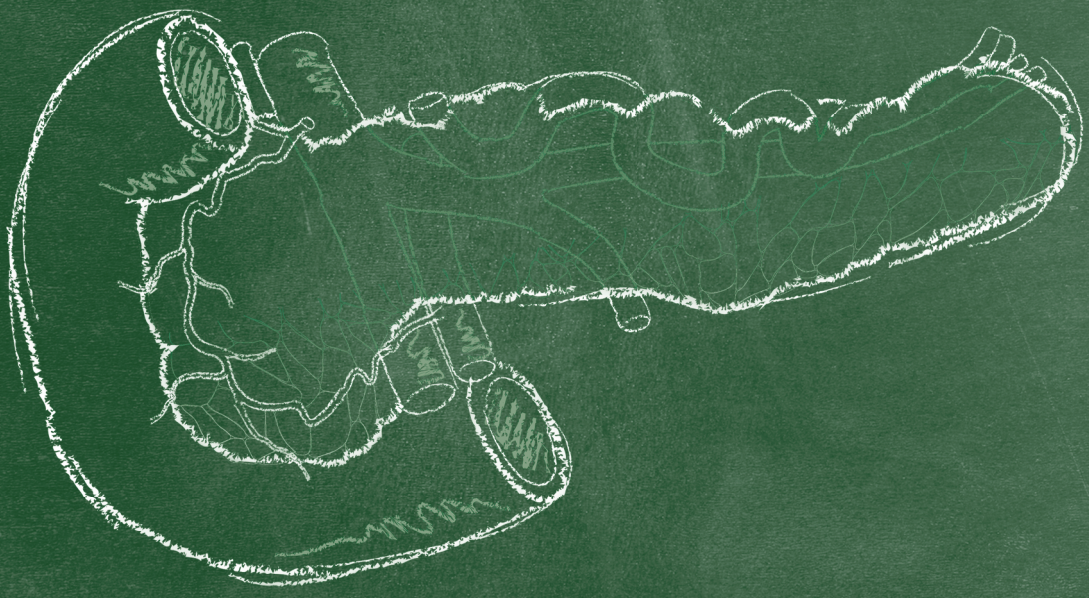

6

Retrospective study on detection, treatment, and clinical outcome of graft thrombosis following pancreas transplantation

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Transplant International 2019 Apr;32(4):410-417.

Introduction: Complete graft thrombosis is the leading cause of early graft loss following pancreas transplantation. Partial thrombosis is usually subclinical and discovered on routine imaging. Treatment options may vary in such cases. We describe the incidence and relevance of partial graft thrombosis in a large transplant center.

Methods: All consecutive pancreas transplantation at our center (2004–2015) were included in this study. Radiological follow-up, type and quantity of thrombosis prophylaxis, complications and graft and patient survival were collected. Partial thrombosis and follow-up were also studied.

Results: All 230 pancreas transplantations were included in the analysis. Computed tomography was performed in most cases (89.1%). Early graft failure occurred in 23 patients (13/23 due to graft thrombosis, 3/23 bleeding, 1/23 anastomotic leakage, 6/23 secondary to antibody mediated rejection). There was evidence of partial thrombosis in 59 cases (26%), of which, the majority was treated with heparin and a vitamin K antagonist with graft preservation in 57/59 patients (97%).

Conclusions: Thrombosis is the leading cause of early graft loss following pancreas transplantation. Computed tomography allows for early detection of partial thrombosis, which is usually subclinical. Partial graft thrombosis occurs in about 25% of all cases. In this series, treatment with anticoagulant therapy (heparin and vitamin K antagonist) resulted in graft preservation in almost all cases.

INTRODUCTION

Graft thrombosis is still considered the Achilles' heel of pancreas transplantation. Great successes have been achieved with this procedure in terms of curing patients from type 1 diabetes mellitus over the last 40 years, but thrombosis remains a challenging problem with a reported incidence of 3–10%.[1,2] Several risk factors are associated with complete graft thrombosis which usually leads to graft loss. A review on risk factors showed that donor age, cerebrovascular death, procurement related problems, type of preservation solution, and graft pancreatitis are risk factors.[1] The Pancreas Donor Risk Index (PDRI), which was developed using data on 1 year graft survival, clearly shows that a higher donor risk leads to a higher risk of graft failure.[3]

Complete graft thrombosis, in most cases accompanied by marked hyperglycemia and/or graft tenderness, is the most common cause of early pancreas graft loss.[2,4] Little is known about the clinical significance of partial graft thrombosis. By some, this is believed to be a 'physiological' phenomenon caused by ligation of the mesenteric and splenic veins and their side branches.[5] Especially in pancreas transplantation, this ligating of smaller vessels contributes to Virchow's triad (hypercoagulable state, venous stasis, and endothelial injury), which may be one of the contributors to the relatively high incidence of thrombosis in pancreas transplantation, as compared to other organs.[6] However, sometimes partial thrombosis extends from the ligated venous ends to larger and more centrally located veins. Partial graft thrombosis is usually subclinical (i.e. without hyperglycaemia) and discovered on routine ultrasound or computed tomography (CT) imaging in the early postoperative phase.[7] It is unclear whether this form of thrombosis should be considered a precursor for complete thrombosis. If this were so, it would be necessary to detect its presence as early as possible, so antithrombotic treatment may salvage the graft. One recent study, where only donors younger than 40 years of age without other risk factors for graft thrombosis, showed a partial thrombosis incidence of 27%. All of these partial thrombosis were safely managed with unfractionated intravenous heparin, without any negative consequences.[8] Another recent study proposed a CT-based grading scheme for graft thrombosis, stating that not all graft thrombosis requires treatment.[9] It is our aim to evaluate these findings by describing our experience regarding partial thrombosis. We evaluated the clinical relevance of this partial thrombosis, the incidence, clinical outcome, and treatment.

Study population and design

A retrospective analysis in which all consecutive pancreas transplantations [simultaneous pancreas kidney (SPK), pancreas after kidney (PAK), pancreas transplant alone (PTA)] from January 1st 2004 until December 31st 2015 performed at the Leiden University Medical Center were included. A minimum of 90 days follow-up was registered.

Recipient surgical technique

Standard SPK transplantations were performed using a midline incision, where the kidney was first transplanted in the left iliac fossa without direct ureteric anastomosis, allowing for hemodynamic stability and reduction of edema, followed by the pancreas on the right, anastomosed on the common iliac artery and caval vein. Only then is the ureteric anastomosis completed. Since 2011, exocrine drainage is usually performed by duodeno-enterostomy. Prior to 2011, duodeno-cystostomy with secondary enteric conversion to duodeno-enterostomy after 12 months was performed in most cases. For recipients with PRA≤6%, the transplantation commenced directly after blood type confirmation and crossmatch was performed retrospectively as soon as possible.[10] Recipients received routine postoperative intravenous contrast enhanced CT imaging within the first week after transplantation to rule out any postoperative complications. This was performed sooner when indicated (e.g. two consecutive blood glucose levels above 10 mM) or later when impaired kidney function hindered early CT imaging. Indications for imaging (including per protocol imaging) and their respective outcome (whether thrombosis was diagnosed or not) are shown in Table 2. In most cases of complete thrombosis, our intention is to surgically salvage or remove the graft. In case of partial or peripheral thrombosis, patients are initially treated with therapeutic intravenous heparin, followed by conversion to vitamin K antagonists (VKA) for at least 3 months. At that moment follow-up CT imaging was performed. In our center, no routine screening for thrombophilia is performed.

Post-transplant medical therapy

Since 2008, recipient immunosuppressive therapy consists of alemtuzumab induction (15 mg subcutaneous, 1st dose preoperative, 2nd dose postoperative day 1), rapidly tapered steroids (3 days, 500–250–125 mg intravenous), followed by tacrolimus (trough levels 8–12 g/l) and mycophenolate mofetil maintenance immunosuppressive therapy. Previous protocols (regarding induction and maintenance) were described elsewhere.[4] Standard anticoagulation therapy consisted of a twice daily, low dose low molecular weight heparin (LMWH), based on the recipients weight: nadroparin 2 dd 5700 IE for patients weighing over 100 kg and nadroparin 2dd 2850 IE for patients below 100 kg. This was a once daily regime prior to 2007, as is our standard protocol to prevent deep venous thrombosis and pulmonary embolism in all surgical patients. The first dose is administered at the recovery room and no other anticoagulants, especially platelet inhibitors, are prescribed. The clinical protocol was changed after the data collection and currently states that patients are prescribed once daily 5700 IE LWMH, and adjusted in case of impaired kidney function. In all cases, LMWH was prescribed for duration of the hospital admission. No new anti-platelet therapy was prescribed in the postoperative period.

Data collection

Donor, recipient, and transplant related risk factors are shown in Table 1. Follow-up data include HbA1c levels, surgical interventions, imaging studies including the reason for imaging, as well as anticoagulation therapy during the first postoperative admission, date last seen, date of restart of exogenous insulin therapy. When thrombosis, either partial or complete, occurred, clinical outcomes were registered. Only graft thrombosis within the first 90 days (early graft loss) was analyzed. Very peripheral thrombosis in ligated ends of veins, was not considered graft thrombosis, this is considered grade 1 pancreas graft thrombosis according to the recent study from Cambridge.[9] When thrombus was found in the parenchymal part of either superior mesenteric or splenic vein but there was still passage of contrast and perfusion of the graft, this was considered partial thrombosis. Absence of contrast due to thrombus was considered complete thrombosis. The actual involved vessel was not recorded in the database. Antibody mediated rejection (AMR) was defined as positive C4d staining and signs of rejection on histological examination of the graft following explantation and the presence of donor specific antibodies (DSA). Suspected AMR was defined as the presence of either positive C4d or the presence of DSA.[11] Graft thrombosis was considered to be secondary to AMR when AMR was suspected. Consequently, graft thrombosis was only considered primarily when rejection was not suspected and data were reported separately.

Statistical analysis

Risk factors associated with thrombosis were analyzed using Chi-square analyses for categorical variables and Analysis of Variance (ANOVA) tests for continuous variables. Whether partial thrombosis was associated with graft survival was analyzed using Cox-regression analysis.

RESULTS

Overall results

In the study period a total of 230 consecutive pancreas transplantations were performed, of which 203 (88%) were SPK, 25 (11%) were PAK, and two (0.9%) were PTA. Fifteen of 230 (6.5%) were retransplantations. Donation after circulatory death (DCD) pancreata were used in 21 (9.1%) transplantations. Median cold ischemia time for pancreata was 10.7 h, for kidneys 10 h. Donor and recipient characteristics are shown in Table 1. Mean hospital stay after transplantation was 26 days (SD 16 days). Median follow-up was 4.5 years (0–12 years). Mean PDRI was 1.36 (SD 0.44). Early graft failure occurred in 23 (10%) cases (90 days graft survival 90.0%). Eighteen of these grafts were lost due to thrombosis (7.8%), three due to bleeding, one due to anastomotic leakage, and one due to T-cell mediated rejection.[11] One

Table 1a. Demographics of donors

		No thrombosis	Partial thrombosis	Complete thrombosis	
	n (%)	n (%)	n (%)	n (%)	p [a]
Gender					0.29
Male	100 (44)	69 (45)	26 (44)	5 (26)	
Female	130 (56)	83 (55)	33 (56)	14 (74)	
Cause of death					0.49
Stroke	131 (57)	84 (55)	32 (54)	15 (79)	
Trauma	76 (33)	53 (35)	19 (32)	4 (21)	
Anoxia	15 (6.5)	10 (7)	5 (9)	0 (0)	
Other	8 (3.5)	5 (3)	3 (5)	0 (0)	
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age, y	35 (13)	34 (13)	36 (13)	40 (11)	0.07
BMI, kg/m^2	23 (3)	23 (3)	23 (2)	25 (3)	**0.02**
PDRI	1.36 (0.44)	1.34 (0.43)	1.40 (0.47)	1.48 (0.40)	0.32

Table 1b. Demographics of recipients

	n (%)	n (%)	n (%)	n (%)	
Gender					0.05
Male	133 (58)	92 (61)	35 (59)	6 (32)	
Female	97 (42)	60 (39)	24 (41)	13 (68)	
Previous graft thrombosis	13 (6)	8 (5)	4 (7)	1 (5)	0.91
Sensitized (PRA>5%) [b]	19 (12)	14 (14)	3 (8)	2 (13)	0.66
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age, y	43 (8)	43 (7)	43 (9)	43 (5)	0.95
BMI, kg/m^2	25 (4)	25 (4)	25 (3)	25 (3)	0.84

year graft survival was 87%, longer term results of our series have been published elsewhere recently.[12] Follow-up was complete until June 2016.

Postoperative imaging

In 205 (89%) patients, computed tomography was the first postoperative radiological study. In 21 cases (9.1%) this was ultrasound. In one case MRI was used and in three cases no imaging was performed. Median interval from transplantation until the first (sequential CT imaging was performed during follow-up, but is not reported in this study) radiological investigation was 6 days (IQR 3–9 days). The reasons for imaging were as follows: majority per protocol (without (acute) clinical indication), 122/227 (54%), because of sudden progressive hyperglycemia in 52 cases (23%), because of persistent fever in 19 cases (8.4%) and because of abdominal tenderness in 12 cases (5.3%). Other indications included increase

Table 1c. Demographics of transplantations

	n (%)	n (%)	n (%)	n (%)	
Transplant type					0.18
SPK	203 (88)	137 (90)	51 (86)	15 (79)	
PAK	25 (11)	14 (9)	8 (14)	3 (16)	
PTA	2 (1)	1 (1)	0 (0)	1 (5)	
Donation after circulatory death	21 (9)	14 (9)	7 (12)	0 (0)	0.30
Retransplant	15 (6.5)	9 (6)	4 (7)	2 (11)	0.74
Perfusion solution					0.43
UW	208 (90)	139 (91)	51 (86)	18 (95)	
HTK/Other	22 (10)	13 (9)	8 (14)	1 (5)	
Exocrine drainage					0.91
Duodenocystostomy	86 (37)	56 (37)	22 (37)	8 (42)	
Duodeno-enterostomy	144 (63)	96 (63)	37 (63)	11 (58)	
Anticoagulant therapy					0.87
Nadroparin 2850IE	71 (31)	43 (30)	21 (36)	7 (37)	
Nadroparin 5700IE (2dd2850IE)	143 (62)	97 (66)	35 (60)	11 (58)	
Nadroparin 11400IE (2dd5700IE) [c]	9 (4)	6 (4)	2 (2)	1 (5)	

[a] Chi-square for categorical variables, ANOVA for continuous variables
[b] PRA known 160/230
[c] Therapeutic dosage LMWH or iv heparin

Table 2. Indications for postoperative imaging associated with diagnosis of thrombosis

	n	Thrombosis		
		Yes	No	Uncertain
Imaging reason		n (%)	n (%)	n (%)
Protocol	122	30 (25)	80 (66)	12 (10)
Hyperglycemia	52	20 (39)	25 (48)	7 (14)
Fever	19	3 (16)	13 (68)	3 (16)
Abdominal tenderness	12	2 (17)	8 (67)	2 (17)
Other	20	6 (30)	11 (55)	3 (15)

Pearson X^2 *p=0.48*

in serum amylase, hematuria in a bladder drained patient, or decreased hemoglobin levels. There was no statistical significant association between reason for imaging and whether thrombosis was diagnosed (p = 0.48) (Table 2). In 25% of the per protocol scans (in the absence of clinical symptoms), thrombosis was diagnosed. In 10–17% of the performed CT scans the radiologist did or could not diagnose or exclude thrombosis.

Postoperative thrombosis

In 78/230 cases (34%) CT imaging showed signs of graft thrombosis (either complete occlusive graft thrombosis or non-occlusive peripheral thrombosis requiring treatment) within 90 days (Fig. 1). Higher recipient BMI was associated with a higher risk of complete thrombosis (p = 0.019). Although our center does not routinely screen for hypercoagulable states (e.g. protein S or C deficiency) there were two recipients (one protein C deficiency and protein S deficiency) with hypercoagulable syndromes, both did not develop thrombosis. Also, previous graft thrombosis was not associated with renewed graft thrombosis in this series. In 19/230 cases (8.2%) complete venous thrombosis was found. In 2/19 there also was arterial thrombosis. This arterial thrombosis was considered to be secondary to venous thrombosis, since, during transplantectomy of the pancreas, arterial anastomoses were patent. Thrombosis was secondary to confirmed AMR in 2/19 cases and to suspected AMR in 4/19 cases.[11] In 17/19 cases the graft had to be removed. In one case with both splenic and superior mesenteric venous occlusion, the patient was put on therapeutic anticoagulation therapy with intravenous heparin and later switched to VKA resulting in preserved graft function. This strategy was chosen because blood glucose levels remained normal and contrast CT showed normal parenchymal perfusion of the graft. In one case partial thrombosis had progressed to complete venous thrombosis at the 3-month follow-up CT scan. This patient was insulin independent and kept on anticoagulation. In 11/17 after transplantectomy, patients were relisted on the waiting list: two for islet transplantation and nine for PAK transplantation.

In 59/230 (25.6%) there was evidence of partial thrombosis on CT imaging (Fig. 1). Follow-up data were available in 47 of 59 patients. All 59 patients were treated with intravenous heparin, followed by VKA (one patient received acetylsalicylic acid (ASA) instead of VKA, the reason was unknown). In 36/47, there was no evidence of remaining thrombus on follow-up CT scan after a median of 94 days (4–284 days), VKA were ceased and patients were switched to ASA. Median duration of oral anticoagulant use was 122 days (6–1902 days). In seven patients, thrombus was still present at the end of follow-up and patients were kept on OAC. In four cases, thrombus had progressed, with persistent functioning in two cases and graft failure in the other two. Figure S1 represents and an overview of patients and different forms/stages of thrombosis. Median duration of follow-up after discovery of partial thrombosis was 125 days (range 4–804 days). When complete graft thrombosis was not the cause of graft failure, early graft failure occurred in 3/59 (5%) following partial thrombosis versus 3/149 (2%) when there was no evidence of thrombosis at all (p = 0.35). Adjusting for PDRI, using Cox-regression analysis, partial thrombosis was not associated with pancreas graft survival (HR 0.89, 95% CI 0.36–2.24, p = 0.81), compared to no thrombosis.

Median interval between transplantation and diagnosis of complete graft thrombosis was 3 days, 84% occurred within the first week. Complete thrombosis that was believed to have occurred secondary to AMR was diagnosed after a median of 2 days. All transplantations

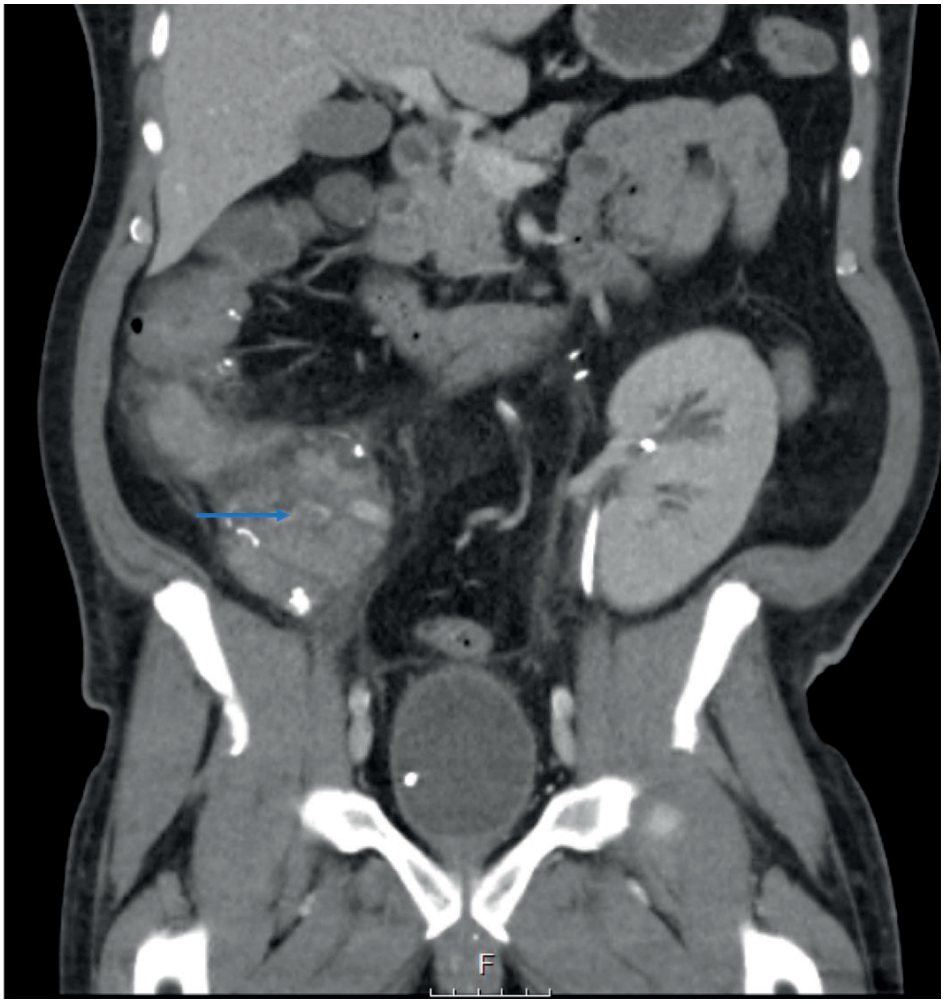

Figure 1. Computed tomography image of partial thrombosis in head of the pancreas (arrow).

Table 3. Indications for relaparotomy following transplantation

	n (%)
Thrombosis	19 (8.3)
Bleeding	22 (9.6)
Infection	13 (5.7)
Bowel anastomosis leakage	3 (1.3)
Other	3 (1.3)

were performed with negative retrospective crossmatch and only 1/6 patients had PRA>6% (in this case 12% at time of transplantation, 55% highest). Donor specific antibodies were positive in 2/6. Median interval between transplantation and diagnosis of partial thrombosis was 6 days. The rate of thrombosis did not increase over the years (p = 0.77). Total reoperation rate was 26% (59/ 230). In 22/230 cases (9.6%), surgical intervention was required for a bleeding complication (Table 3).

For seven recipients, the postoperative anticoagulation regime could not be identified from the patient records. Standard postoperative anticoagulation with LMWH in single dose (which was per protocol prior to 2007) was administered to 71 patients (31%) and 143 patients (62%) received double dose from the 1st post-operative day until discharge. Nine patients (3.9%) were on therapeutic anticoagulation (intravenous heparin or high dose LMWH), since they required anticoagulation prior to the transplantation due to cardiac arrhythmias or peripheral vascular disease. Seventeen patients received platelet aggregation inhibition after transplantation, all because this was prescribed to them prior to transplantation. Different anticoagulation is prescribed throughout the field (Table 4). Standard anticoagulation protocol with single or double dose LMWH was not significantly associated with complete thrombosis risk, 7/71 (9.9%) vs. 11/143 (7.7%) (p = 0.59) or partial thrombosis risk, 21/71 (30%) vs. 35/143 (25%) (p = 0.42).

Table 4. Overview of reported anticoagulation (<1 week postoperative)

Leiden University Medical Center	LMWH (nadroparin) 2850IE, twice daily
Madison, Wisconsin	ASA
Oxford	ASA, subcutaneous heparin. Tailor-made based on TEG
Bochum	Unfractionated heparin iv
Pisa	LMWH (nadoparin) 5700IE, once daily for SPK; unfractionated heparin iv for PTA/PAK
Minnesota	Unfractionated heparin iv
Oslo, Norway	LMWH (dalteparin) 5000IE, once daily. PO day 0+1, Dextran 500ml + ASA
San Fransisco	Aspirin, dipyridamole and unfractionated heparin iv in non-uremic
Cambridge	Epoprostenol, ASA

DISCUSSION

This study is an overview of diagnosis and treatment of thrombosis following pancreas transplantation. As shown in previous literature, graft thrombosis is the leading cause of early graft failure.[1,2] Our findings corroborate with those results. We also evaluated partial venous thrombosis, a complication following pancreas transplantation of which little is known.[5,8]

Standard radiological follow-up in our center consists of contrast enhanced CT. This could be considered quite aggressive, especially since kidney function may still be impaired in the early postoperative phase. In our series, data on kidney DGF (hemodialysis within the first week) have been published elsewhere, and DGF is mostly related to DCD pancreas transplantation.[12] In the case of DGF, CT imaging was usually postponed until kidney function was restored. Unfortunately, no data on acute kidney injury (25% increase in eGFR or 44 uM increase in serum creatinine) were available in our database. However, CT imaging allows for early detection of sub-clinical partial thrombosis, which may be amenable for treatment.[7,9] This is supported by the finding that in 25% of the CT scans that were performed per protocol, some form of thrombosis was discovered. Furthermore, especially fever and abdominal tenderness appear to be aspecific clinical features accompanying thrombosis. Obviously, these may indicate other complications, which may be the indication for imaging. Some centers may prefer the use of ultrasound.[13,14] A disadvantage of ultrasound may be that not all vessels are visualized properly by overlying bowel gas and that an experienced radiologist has to be available, making results observer dependent. The proposed grading system of thrombosis by the Cambridge group is supported. Unfortunately, due to the retrospective nature of our study, the grading system was not incorporated in our database.[9] Even though CT imaging in this study was inconclusive in 10–17% with regard to graft thrombosis, we do, however, believe that CT imaging should be part of routine follow-up, following pancreas transplantation. It has to be noted however, that in our study, we did not consider very peripheral thrombosis (grade 1) amongst the cases of thrombosis. These forms of thrombosis were considered not to be clinically relevant. Further studies will focus on quantifying the grade of thrombosis in our center and which forms are clinically relevant and require treatment.

Complete thrombosis leading to graft loss occurred in 17 patients. In all cases, this was with venous thrombosis. The two cases of arterial thrombosis are believed to be secondary to the venous thrombosis. The percentage of graft thrombosis in our series is similar to that reported in literature although some centers report even lower thrombosis rates.[15] The thrombosis rate, however, is likely related to intrinsic risks of the pancreatic graft, reflecting, for example, in the PDRI. As published before, due to scarcity of donors, the pancreata reported and accepted in our country have a relatively higher PDRI as compared to other countries.[16] Also, as is shown in this study, thrombosis may be secondary to (antibody mediated) rejection, and thus, the incidence of 'true' thrombosis was lower (in fact 13/230, 5.7%). It is not always clear from previously published reports whether thrombosis was secondary to rejection. In this study, the relationship of peripancreatic infection or pancreatitis was not studied, however, one of our previous reports did not show an association between pancreatitis and thrombosis (2/30).[12]

In 59 patients (26%), there was evidence of partial thrombosis. This is in line with recent results published by Harbell.[8] Most patients were treated with heparin and VKA. During

follow-up, the majority of thrombus resolved with this treatment and most recipients remained insulin independent. In fact, only four progressed to complete thrombosis, of which only two required exogenous insulin. This data show that our current treatment of this partial thrombosis is effective and sufficient in preventing graft loss. However, we cannot predict outcome if no anticoagulants would have been given. Patients with partial thrombosis were treated with VKA after intravenous heparinization. Novel oral anticoagulants or directly acting oral anticoagulants (NOAC/DOAC) may also be used, however the experience with graft thrombosis is limited to our knowledge. Because of the risk of partial thrombosis, we suggest to include CT imaging in routine follow-up, to evaluate the presence (or absence) of thrombus. In our series, VKA were ceased only after CT imaging had confirmed resolution of thrombus, which was substantially longer than 3 months in some cases.

We currently prescribe once daily LWMH (5700 IE) to most of our patients as thrombosis prophylaxis. Whether this is the optimal treatment remains up for debate. Clearly, there are as many possibilities as there are pancreas transplant centers: intravenous heparin, LWMH, acetylsalicylic acid, and a combination of either of them.[2,8,15,17-20] We did not find an association between single or double dose LMWH prescription and thrombosis. It could however be that changes over time, especially in donor quality, may have masked such an association. It may be that the double dose LWMH masked an increased thrombosis risk with the increased willingness to accept higher risk donor grafts in more recent years. As was shown in this study, the change in protocol to a double dose of LMWH did come at the cost of a slightly higher bleeding risk, which on the other hand, may also have been caused by higher donor risk. Being even more aggressive in terms of anticoagulation, either by prescribing higher dosage of LMWH or prescribing intravenous heparin to each patient, does not seem justified in our series and may only be necessary in case of certain risk factors in a setting of tailor-made anticoagulation, for example when using intra-operative thromboelastograms (TEG).[6,17] Since adequate modification into Virchow's triad is difficult in the setting of pancreas transplantation, optimal monitoring of the cascade of coagulation is paramount. A combination of intra-operative TEG and postoperative CT imaging, may lead to the most optimal protocol in preventing both complete, as well as partial thrombosis. Furthermore, almost 75% of the patients in our current series (those that did not develop any form of thrombosis) would be 'over-treated' and thus be exposed to a potential higher bleeding risk.

Several limitations apply to our study. Due to the retrospective design, it was not possible to retrieve all the data. Also, protocol adjustments, in particular from once to twice daily LMWH as thrombosis prophylaxis, may have obscured results. As was stated prior in the discussion, it remains unclear which form of partial thrombosis is clinically significant. Whether these patients require anticoagulation, possibly associated with higher bleeding risk, would optimally be investigated in a randomized trial, where patients with grade 2 would be randomized to receive a particular dose of anticoagulation, or even none. The incorporation of CT imaging into clinical practice can't be supported by data from this

study, but its usefulness has been studied and published in Transplant International 25 years ago, and has been part of our clinical protocol since then.[21]

CONCLUSION

This study summarizes the single center outcome with regard to graft thrombosis following pancreas transplantation. We have shown that our current protocol to prevent graft thrombosis with once or twice daily low dose LMWH results in a low thrombosis incidence of 5.7%, similar to that reported in literature. Partial thrombosis is frequently discovered on routine CT imaging following transplantation. It is usually without clinical symptoms and may be adequately treated with heparin and VKA, with preservation of adequate graft function. Both postoperative CT imaging, as well as treatment with VKA for partial thrombosis, remain standard treatment at our transplant center.

SUPPORTING INFORMATION

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

SUPPLEMENTAL DATA

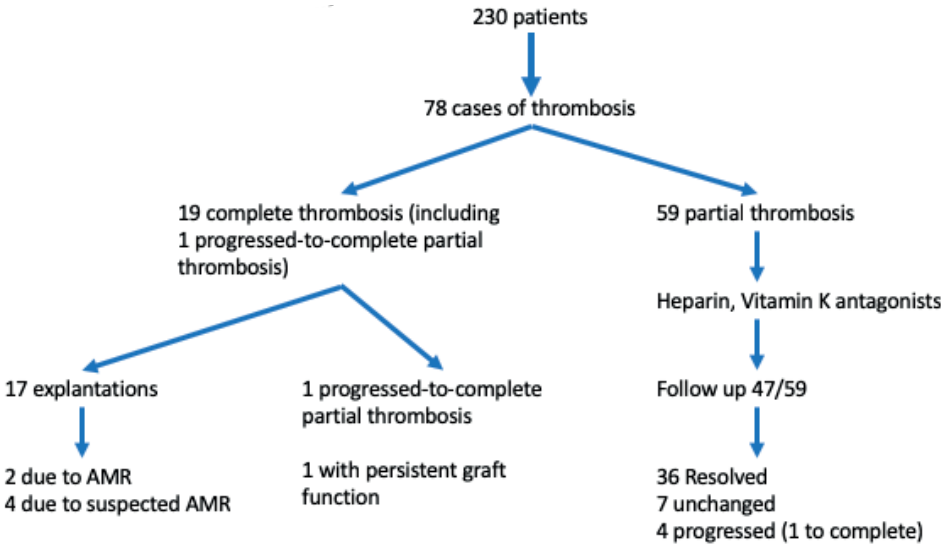

Figure S1. Flowchart of patients and stages of thrombosis through follow-up.

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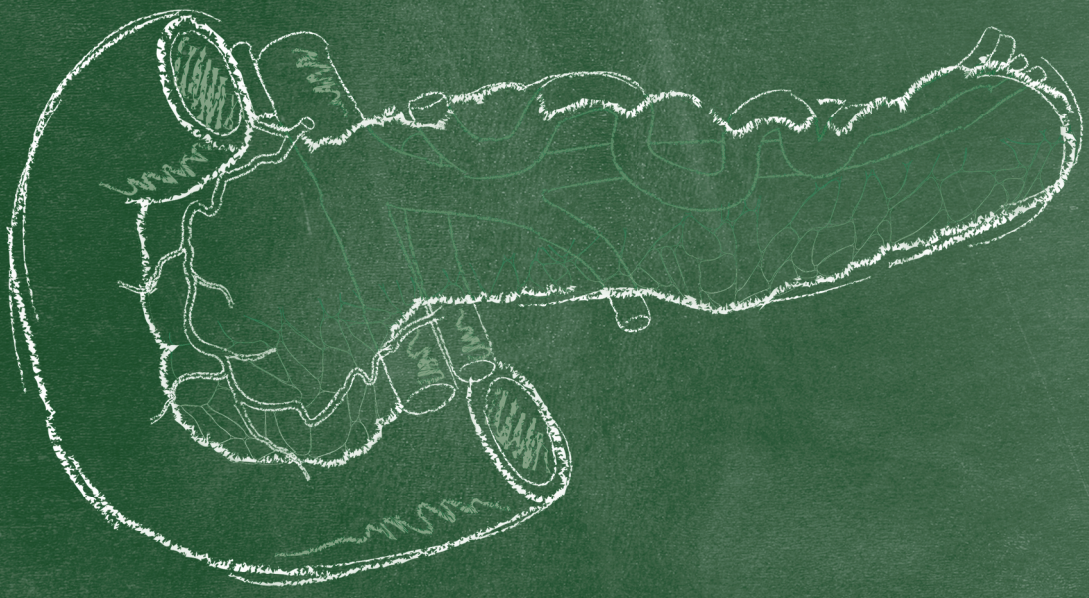

7

Pancreas transplantation with grafts from donors deceased after circulatory death (DCD): 5 years single center experience

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Transplantation 2018 Feb;102(2):333-3

Introduction: Donation after circulatory death (DCD) pancreas transplantation has been shown to be an additional way to deal with donor organ shortages. The results of 5-year DCD pancreas transplantation are presented.

Methods: A retrospective, single center analysis (2011 – 2015) was performed to compare the results of donation after brain death (DBD) to DCD pancreas transplantation.

Results: During the study period, 104 pancreas transplantations (83 from DBD and 21 from DCD) were performed. Median pancreas donor risk index (PDRI) was 1.47, (DBD 1.61 vs. DCD 1.35 ($p=0.144$)). Without the factor DCD, PDRI from DCD donors was significantly lower (DBD 1.61 vs DCD 0.97 ($p<0.001$). Donor age was the only donor related risk factor associated with pancreas graft survival (HR 1.06, $p=0.037$). Postoperative bleeding and kidney DGF occurred more frequently in recipients from DCD ($p=0.006$). However, DCD pancreata had a lower incidence of thrombosis. Kidney and pancreas graft survival were equally good in both groups.

Conclusions: Pancreas transplantation from DCD donors yields comparable results to DBD donors when PDRI of DCD are relatively low. Most DCD donors are younger donors with trauma as cause of death. These DCD pancreas grafts may be a better option to cope with increasing organ shortages than exploring the limits with older (and higher PDRI) DBD donors.

INTRODUCTION

Pancreas transplantation from donation after brain death (DBD) has been steadily improving over the last decades with good long-term outcome in terms of patient and graft survival.[1-3] Simultaneously, the number of patients and time on the waiting list increased in the Eurotransplant area.[4,5] Unfortunately, suitable DBD organs matching this need remained stagnant.[5] Pancreatic grafts from donation after circulatory death (DCD) have been shown to be suitable for transplantation and may provide an additional organ source.[6-11]

The first DCD pancreas transplantation in our center was performed in 2011.[8] In 2015, 52% of all donor procedures in The Netherlands were DCD, and 9/20 (45%) of pancreas transplantations at our institute were from DCD procedures.[12]

The warm ischemic period during graft procurement is generally believed to inflict more ischemia reperfusion injury and subsequently postreperfusion graft pancreatitis and thrombosis. This makes transplant professionals reluctant to accept DCD grafts for transplantation. In general, peripancreatic infections occur in approximately 35% of all pancreas transplantations, but the question is whether these are all clinically significant.[13,14] However, with careful DCD donor selection, the detrimental effects of warm ischemia on the allograft may be limited.

This study investigates whether the use of DCD pancreas donors is feasible when careful donor selection, indicated by the Pancreas Donor Risk Index (PDRI), is performed. More specifically, short term outcome (90 days patient and graft survival and complications, specifically post reperfusion graft pancreatitis, peripancreatic infection, bleeding, graft thrombosis) were investigated.

MATERIALS AND METHODS

All consecutive primary pancreas transplantations performed at Leiden University Medical Center from January 2011 until December 2015 were included in this study. Follow up was collected until May 1st 2016. Standard SPK transplantations were performed using a midline incision. The kidney was first transplanted in the left iliac fossa, followed by the pancreas on the right anastomosed on the iliac artery and caval vein. Exocrine drainage was performed by duodeno-enterostomy. All patients received alemtuzumab induction therapy (15 mg subcutaneous on both the day of the transplantation and first postoperative day). Standard maintenance immunosuppression consisted of tacrolimus (Prograft) (twice daily 5mg based on trough levels 8-12 ug/l until 6 weeks, from then trough levels 5-10 ug/l) or cyclosporine (trough levels 150-200 ug/l until 6 weeks, from then trough levels 100-150 ug/l) combined with mycophenolate mofetil (twice daily 500mg when tacrolimus was prescribed and twice daily 1000mg when cyclosporine was prescribed), with or without addition of steroids.

Standard anticoagulant therapy after pancreas transplantation consisted of subcutaneous low molecular weight heparin (nadroparin) 2850IE twice daily. If indicated prior to transplantation, therapeutic doses were prescribed (eg, in case of atrial fibrillation or previous deep venous thrombosis or pulmonary embolisms).

Data collection

Donor, recipient and transplant related risk factors are shown in Tables 1-3. Follow up data included: peak serum amylase and drain fluid amylase levels during the first 3 postoperative days, surgical and percutaneous reinterventions, patient and pancreas and kidney graft survival (including causes of graft failure). Pancreas graft failure was death censored and defined as return to exogenous insulin therapy. Minimal follow up was 90 days, to allow for analysis of early pancreas graft failure (EGF).[15] Kidney graft failure (death censored) was defined as need for renal replacement therapy or relisting on the kidney transplant waiting list.

Table 1. Demographics of donors after brain death and donors after circulatory death.

		DBD		DCD		
		n	%	n	%	p-value
Gender						**0.037**
Male		27	32%	12	57%	
Female		56	68%	9	43%	
Cause of death						**<0.001**
Stroke		54	65%	5	24%	
Trauma		22	26%	7	33%	
Anoxia		3	4%	7	33%	
Other		4	5%	2	10%	
	Median	Min - max		Median	Min - max	
Age	43	10 - 60		27	11 - 47	**0.003**
BMI	23	17 - 29		22	18 - 29	0.329
ICU days	2	0 - 13		3	0 - 7	**0.009**
Creatinine (mg/dL)	0.64	0.35 - 4.65		0.67	0.43 - 1.13	0.523
PDRI	1.61	0.68 - 2.48		1.35	1.03 - 2.44	0.143
PDRI (donortype excluded)	1.61	0.68 - 2.48		0.97	0.74 - 1.75	**<0.001**

* Difference measured using Chi square for categorical and Mann-Whitney for continuous variables

Analysis

Donor warm ischemia time was calculated from the time of withdrawal of ventilatory support (WVS) until the start of organ cold perfusion. Functional warm ischemia time was considered to start when systolic blood pressure < 50 mmHg, in line with Eurotransplant and British Transplantation Society guidelines.[16,17] Post reperfusion graft pancreatitis

Table 2. Demographics of recipients of DBD or DCD organs.

	DBD		DCD		
	n	%	n	%	p-value
Gender					0.526
Male	45	46%	13	62%	
Female	38	54%	8	38%	
Coronary artery disease	11	13%	3	14%	>0.999
Cerebrovascular disease	10	13%	1	5%	0.455
Peripheral vascular disease	29	35%	8	38%	0.816
Sensitized (PRA>5%)	17	21%	5	24%	0.771
End stage renal disease (SPK recipients)					0.609
Preemptive	36	47%	7	35%	
Hemodialysis	24	32%	8	40%	
Peritoneal dialysis	16	21%	5	25%	
	Median	Min - max	Median	Min - max	
Age	43	25 - 64	43	28 - 55	>0.999
BMI	25	17 - 35	26	17 - 34	0.625

* Difference measured using Chi square for categorical and Mann-Whitney for continuous variables

was defined as an increased serum amylase levels (> 250U/L) in combination with drain fluid amylase levels (>3000U/L), not requiring additional interventions.[18] Peripancreatic infection was defined as any peripancreatic infection, including abscess, infected fluid collection or hematoma, requiring surgical intervention or radiological, percutaneous drainage (Clavien-Dindo grade IIIa/b).[14,18] All other surgical complications, such as bleeding, anastomotic leakage, graft thrombosis, graft loss, and Clavien-Dindo grade III or higher were analysed. Other complications, such as pneumonia, postoperative wound infection and urinary tract infection were not included in the database. Delayed kidney graft function (DGF) was defined as the need for renal replacement therapy within the first week after transplantation. Patient and graft survival were estimated using the Kaplan-Meier method.

Organ procurement

Standard DCD organ procurement in The Netherlands starts with withdrawal of ventilatory support at the ICU. No ante-mortem interventions (heparin administration or femoral artery cannulation) are legally allowed in The Netherlands. Following cardiac arrest, a 5-minute 'no touch'-period is mandatory and when auto resuscitation does not occur within this period, the declaration of death is issued. Upon arrival in the operating room, a rapid laparotomy is carried out. The aorta is cannulated, the inferior caval vein vented and pressurized infusion of ice-cold preservation solution is started. This marks the end of the first warm ischemic period WIT. The remaining procedure, as well as DBD organ procurement, is performed as described in the ESOT MOD learning course.[19] Of note, in

Table 3. Demographics of transplantations of DBD or DCD organs.

	DBD		DCD		
	n	%	n	%	p-value
Transplant type					>0.999
SPK	76	92%	20	95%	
PAK	7	8%	1	5%	
PTA	0	0%	0	0%	
Perfusion solution					0.075
UW	74	89%	15	71%	
HTK/Other	9	11%	6	29%	
Anticoagulant therapy					0.180
Nadroparin 2850IE	8	9%	0	0%	
Nadroparin 5700IE	71	86%	21	100%	
Nadroparin 11400IE**	4	5%	0	0%	
Immunosuppression					0.073
Cyclosporin + Mycophenolate	1	1%	0	0%	
Cyclosporin + Mycophenolate + Prednisone	2	2%	3	14%	
Tacrolimus + Mycophenolate	74	89%	18	86%	
Tacrolimus + Mycophenolate + Prednisone	6	7%	0	0%	
	Median	Min - max	Median	Min - max	
Pancreas CIT (hr)	10	4 - 14	11	7 - 15	0.143
Pancreas donor functional WIT (min) ***			27	12 – 42	n/a
Pancreas donor WIT (min)****			31	15 - 45	n/a
Pancreas recipient WIT (min)	26	14 - 64	25	10 - 41	0.613

* Difference measured using Chi square for categorical and Mann-Whitney for continuous variables
** These patients were on anticoagulation prior to transplantation
*** Withdrawal of ventilatory support - systolic blood pressure < 50 mmHg
**** Withdrawal of ventilatory support - organ cold perfusion

both DCD and DBD procedures mobilization of the pancreas was performed only after cold perfusion. Procurements were carried out by independent procurement teams, sometimes consisting of a local team, as was described elsewhere.[20] All organs were cold stored on ice in University of Wisconsin (UW) solution or histidine-tryptophan-ketoglutarate (HTK) solution.

RESULTS

In the 5-year study period (2011 –2015), 83 DBD (76 SPK, 7 PAK) and 21 DCD (20 SPK, 1 PAK) primary pancreas transplantations were performed. All DCD donors were Maastricht category III. From the 83 DBD grafts, 3 were from another country and all other grafts, including all 21 DCD grafts, were from The Netherlands. Our local team procured 31/104 (30%). Of 21 DCD grafts, 8 (38%) were procured locally, compared to 23/83 (28%) DBD grafts (p=0.353). Four pancreatic grafts were initially bladder drained with conversion to enteric drainage in a second operation in 2 cases, as described before.(21) All other grafts were anastomosed to the terminal ileum. Donor, recipient and transplant demographics are shown in Table 1-3. There was no significant difference in steroid-free immunosuppression between both groups (90% in DBD vs. 86% in DCD, p=0.073). Mean duration of follow up was 2.6 years for DBD organ recipients and 2.2 years for DCD organ recipients (p=0.2).

Median PDRI of all pancreata was 1.47 (0.68 – 2.48). No statistical significant difference in PDRI of DBD grafts compared to DCD grafts (1.61 vs. 1.35, p=0.143) was observed. However, if donor type was excluded from the PDRI calculation, the difference between DBD and DCD was significant (1.61 vs 0.97 respectively, p<0.001). DCD donors were significantly younger than DBD donors:27 (11 – 47) years vs 43 (10 – 60) years (median (range), p=0.001). Stroke was the leading cause of death in DBD (65%), whereas DCD donors died from trauma or anoxia in 66% of the cases (p=0.001). Median donor WIT of DCD grafts was 31 (15 – 45) minutes, median functional WIT was 27 (12 – 42) minutes. (Table 3)

Graft pancreatitis and peripancreatic infection

Postreperfusion graft pancreatitis occurred in 47 patients (45%), of which 27 resolved spontaneously without interventions. The remaining 20 recipients developed (infected) fluid collections that required intervention (either percutaneous or surgical drainage). Peri-

Table 4. Early (<90 days) postoperative complications after DBD and DCD transplantation.

	DBD		DCD		p value
	n	%	n	%	
Thrombosis					0.282
Complete	8	10%	0	0%	
Partial	24	29%	7	33%	
Bleeding	9	11%	8	38%	**0.006**
Post reperfusion graft pancreatitis	40	48%	7	33%	0.222
Peripancreatic infection	25	30%	5	24%	0.568
Pancreas graft loss	9	11%	0	0%	0.198
Kidney delayed graft function	10	13%	7	35%	**0.041**
Patient death	1	1%	0	0%	>0.999

pancreatic infection that was not preceded by postreperfusion graft pancreatitis occurred in 10 patients (Table 4). There was no statistical difference in the incidence of graft pancreatitis between DBD and DCD graft recipients. Logistical regression analysis did not show an association between donor WIT with post reperfusion pancreatitis and peripancreatic infection. From 30 patients that suffered from peripancreatic infection, 2 lost their graft within 90 days due to thrombosis.

Other Early Postoperative Outcome

Relaparotomy was required in 32/104 patients (31%). In 17 patients, a reoperation was required due to postoperative bleeding. This occurred significantly more frequent in recipient of DCD organs (11% vs. 38%, p=0.005). DBD organ recipients lost 9 grafts (7 due to thrombosis, 1 due to bleeding and 1 due to anastomotic leakage), versus none of the DCD organ recipients (p=0.198). Of all 96 SPK recipients, 17 (16%) suffered from kidney delayed graft function (DGF). Kidney DGF occurred significantly more frequently with kidneys from DCD donors (13% vs. 35%, p=0.043). There was a statistically significant association with kidney DGF and reinterventions for bleeding (6/17), compared to recipients with immediate kidney function who required fewer reinterventions (10/80, p=0.032). Prescription of steroids as part of initial immunosuppression was not associated with thrombosis (p=0.314) One recipient with a DBD SPK died during the initial hospital stay due to systemic inflammatory response syndrome following 2 exploratory laparotomies for anastomotic leakages.

Long Term Outcome

Mean duration of follow up was 2.5 years (SD 1.3 years). Kaplan- Meier estimated patient survival after 90 days, 1 year and 2 years was 98.8%, 97.5% and 94.5% for DBD recipients versus 100% for DCD recipients after 2 years (p=0.268) (Figure 1). Kaplan-Meier estimated pancreas graft survival after 90 days, 1 year and 2 years was 89.2%, 85.5% and 85.5% for DBD organs and 100%, 100% and 93.3%, respectively, for DCD organs (p=0.428) (Figure 2). For recipients with functioning grafts (insulin independence) at 3 months (n=95), data on HbA1c levels were available in 81/95 (85%). Mean HbA1c was 33 mmol/mol (SD 4mmol/mol) in the DBD group and 32 mmol/mol (SD 5 mmol/mol) in the DCD group (p=0.45). Kaplan Meier estimated kidney graft survival after 90 days, 1 year and 2 years was 98.7%, 96.0% and 94.1% for DBD kidneys and 100%, 93.8% and 93.8% for DCD kidneys (p=0.342) (Figure 3).

In univariate survival analysis, analyzing the complete cohort, donor age was a significant risk factor for pancreas graft failure (HR 1.06, 95% CI 1.00 – 1.11, p=0.037). Also, PAK was a significant risk factor for pancreas graft failure compared to SPK (Chi^2 11.80, p=0.001). DCD, as stated above, and donor cause of death (Chi^2 3.51, p=0.320) were not associated with pancreas graft survival. Using a previously described PDRI cut-off of 1.24[22], high PDRI was identified as a risk factor for pancreas graft failure (Chi^2 4.61, p=0.032). Numbers

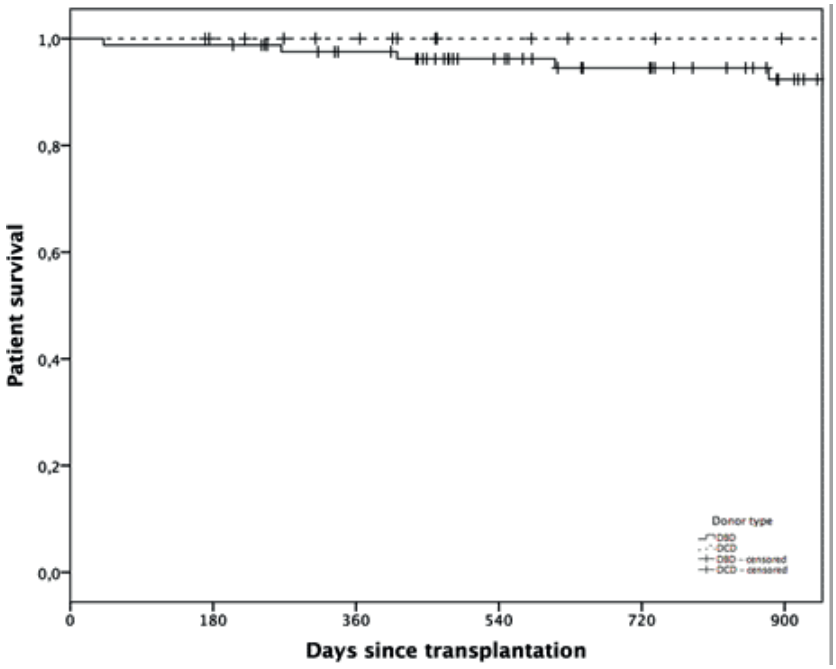

Figure 1. Kaplan-Meier estimated patient survival at 90 days, 1 year, and 2 years for DBD pancreas recipients versus DCD pancreas recipients.

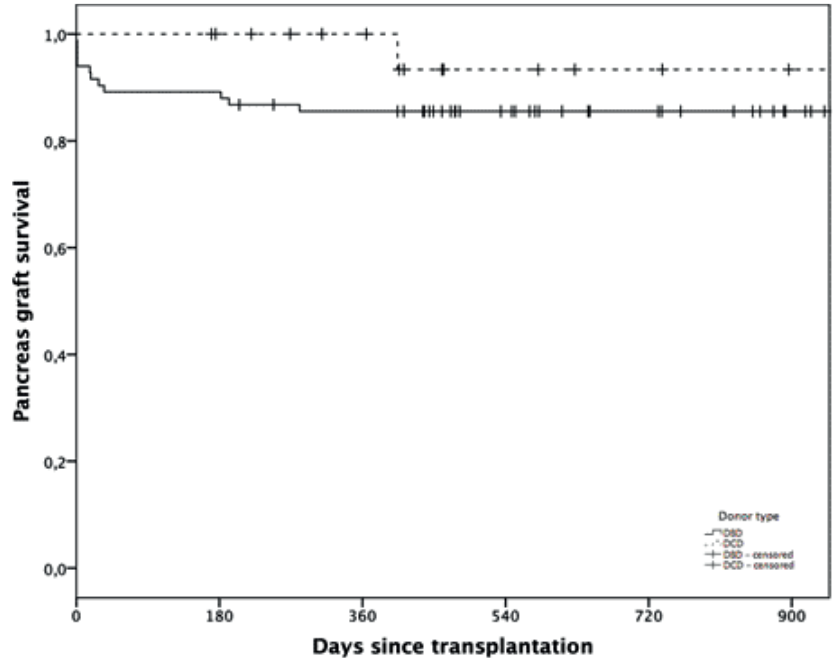

Figure 2. Kaplan-Meier estimated pancreas graft survival at 90 days, 1 year, and 2 years for DBD pancreas grafts versus DCD pancreas grafts.

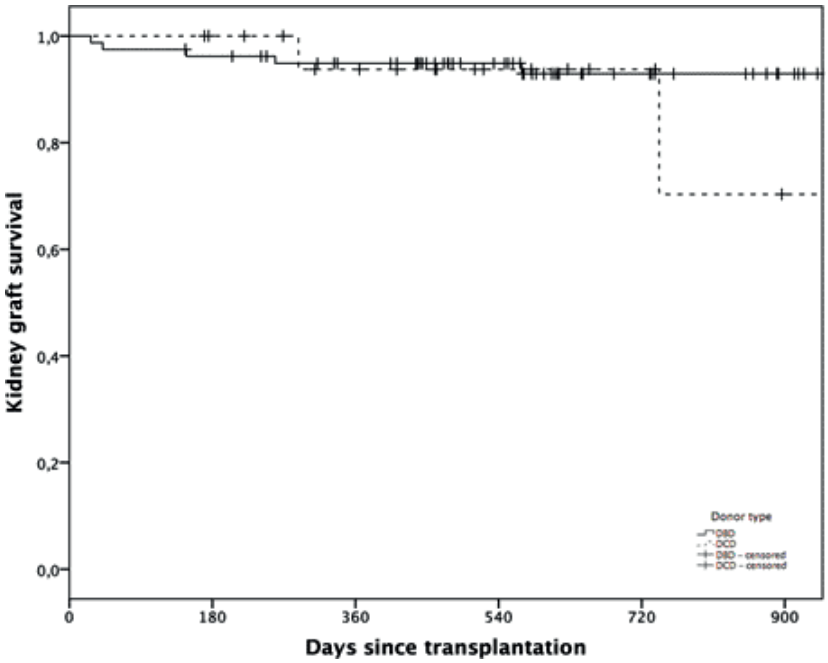

Figure 3. Kaplan-Meier estimated kidney graft survival at 90 days, 1 year and 2 years for DBD kidney grafts versus DCD kidney grafts.

were too small to analyse PDRI as a continuous variable and to perform multivariate Cox-regression analysis.

DISCUSSION

This study compares the outcome of DCD pancreas transplantation to DBD pancreas transplantation in a recent cohort. This study shows that pancreas transplantation from young (mainly low PDRI) donors, either DCD or DBD, yields good results. Consequently, DCD grafts with low PDRI should certainly be considered for transplantation.

Multiple reports, as well as multiple recent meta-analyses, have shown that it is feasible to utilize DCD pancreata for vascularized pancreas transplantation.[6,9-11,23] Our results corroborate with these results. Even more, this study demonstrates that with careful donor selection, especially in terms of donor age, but also transplant type (SPK vs. PAK), results from DCD pancreas transplantation are comparable to those of DBD pancreas transplantation. DBD donors had other risk factors and were on average from older donors and had more frequently stroke as a cause of death. All DCD grafts were from The Netherlands, mostly from the western region (17/21), to keep CIT as short as possible. Therefore, PDRI was not

significantly different between DBD and DCD donors. But when the factor 'donor type' (DBD or DCD) was eliminated from the equation, the differences in PDRI were remarkable and showed that DCD donors with otherwise near-to-perfect characteristics were selected. These data indicate that DCD donors can be used for pancreas transplantation, especially with relatively low PDRI (in our study mean PDRI 1.35). The number of reinterventions (30.8%) is comparable to the number reported in most studies, which may be as high as 35% in pancreas transplantation.[24] In our opinion, and in accordance with the risk analysis in this study, DCD donors can be used in addition to DBD donors with more unfavorable donor characteristics.

Elaborating on individual risk factors such as age, this may be explained by the fact that young donors tend to have leaner pancreas grafts, with smooth intravascular lining. The absence of excessive peripancreatic fat may facilitate easier back table procedure (with construction of the Y-graft and trimming of excess fat). We hypothesize that these factors may prevent early fatty necrosis with subsequent peripancreatic infection and thrombosis. In terms of PDRI, a 28- year-old DCD donor bears a similar risk as a 41-year-old DBD donor.[7,25]

The donor WIT we report is like that described in the large study from the UK[5], but longer than the 15 – 20 minutes that have previously been mentioned in studies from the United States.[6,23,26] Again, the current study shows that, even with prolonged donor WITs, even up to 45 minutes (withdrawal of ventilatory support to cold perfusion) and, which may even be more important, prolonged periods of relative hypoperfusion (functional warm ischemia time up to 42 minutes) good results can be achieved. This has also been shown by another single center report in 2012, which reported donor WITs up to 110 minutes, albeit with very long agonal phase in at least 1 case.[9] Nevertheless, WIT should still be considered an important risk factor associated with postoperative complications such as kidney DGF.

An interesting observation was the higher risk of bleeding in DCD. It could be that the higher bleeding percentage in DCD recipients may be related to the higher percentage of kidney DGF in this group and subsequently antifactor Xa accumulation or uremia associated thrombopathy. In this study, no anti-factor Xa was determined as a measure of nadroparin accumulation, nor were blood urea levels post transplantation registered. Therefore, it was not possible to proof these interactions. The clinical data show a higher percentage of bleeding in the kidney DGF group. The same mechanism may explain the difference in graft thrombosis, although this difference was not statistically significant. In those cases, following DCD pancreas transplantation, delayed or slower kidney graft function may have caused factor Xa accumulation and subsequently, may have played a role in the prevention of pancreas graft thrombosis. We realize that the 10% risk of complete pancreas graft thrombosis in the DBD group seems rather high. However, 1 of cases with thrombosis did not lead to graft loss and was preserved with function with anticoagulant treatment. Another explanation might be the relative high risk pancreas grafts that are be-

ing used in The Netherlands (medium PDRI 1.61 in this study).[27] We do not believe that procurement, back table preparation or transplantation caused the difference, since all are done the same for DBD and DCD.

The percentage of postreperfusion graft pancreatitis in this study is 45%. In a review by Nadalin et al, postreperfusion graft pancreatitis is thought to occur in up to 100% of pancreas transplantation and is usually self-limiting.[13] However, this difference could be explained by the definition. We arbitrarily defined postreperfusion graft pancreatitis as elevated drain amylase levels in combination with elevated serum amylase. Neither DCD nor the duration of donor WIT were found to be a risk factor for postreperfusion pancreatitis or peripancreatic infection. In our series, of 48 patients that suffered from post reperfusion graft pancreatitis, only 20 (42%) also suffered from peripancreatic infection. This is 19% of our total population, which is like data reported in 2013.[14] Furthermore, 10/30 peripancreatic infections weren't preceded by any biochemical abnormalities. The clinical relevance of postreperfusion graft pancreatitis is not entirely clear.[13,18] Interestingly, there were slightly more peripancreatic infections in DBD. Possibly, this is caused by the higher donor age in DBD.

Mid to long-term kidney, pancreas and patient survival were generally good. Although DCD organ recipients suffered from more postoperative bleeding and endured more kidney delayed graft function, this did not reflect in inferior long term outcome. All patients with functioning pancreas grafts at 90 days had good glycemic control and kidney function. Pancreas graft survival (insulin independence) was excellent, especially for the DCD recipients, even up to 2 years after transplantation. Kidney graft survival was also good in both groups.

Several limitations apply to this study. This is a retrospective database analysis with possible drawbacks that are characteristic of such studies. In addition, the data concern a single center and there was a relatively small number of patients in the study. This limited our ability to perform a multivariate risk factor analysis. Nevertheless, this is still 1 of largest single center reports on DCD pancreas transplantation that included all consecutive DCD pancreas transplantations in our center.[23] There is an ongoing discussion in the pancreas transplant community concerning the definition of pancreas graft failure. In this study, failure was defined as insulin independence (death censored). We appreciate that this is a subjective definition, which makes comparison difficult. However, this definition reflects the clinical situation of this patient, which is evaluated by a clinician. HbA1c levels, both at any time during follow and at start of exogenous insulin levels, facilitate comparison between different reports. We did not report HbA1c at the start of exogenous insulin therapy, since almost all had failed within 90 days (and HbA1c would thus reflect glycemic control from prior to the transplantation). Unpublished data from our center indicates that graft survival depends partially on the definition of failure. The protocol of immunosuppression changed over the course of the study. We now aim to transplant our patients in a steroid free regime,

with only tacrolimus and mycophenolate mofetil. There is no evidence that this change in protocol influenced our results with regards to graft survival.

We did not experience a high rate of complications leading to graft loss in the DCD donors. These data indicate that that DCD donors can be considered for pancreas donation with all parameters and possible risk factors taken into account. A pancreas graft from a young, lean, DCD donor after trauma, with short cold ischemia time may in fact yield better results than pancreas grafts from older DBD donors. All those parameters combined, that are reflected in a low PDRI, may be a better predictor than just DBD or DCD. In our opinion, such low PDRI DCD donors should not be precluded from vascularized pancreas donation beforehand.

CONCLUSION

Pancreas transplantation from carefully chosen DCD donors yields good results. Other factors than merely DCD are important in predicting outcome. We advocate that DCD pancreata, especially those with lower PDRI (younger donors and trauma as cause of death) should be considered for transplantation. This study shows that, although DCD recipients have more postoperative bleeding and kidney DGF, pancreas and kidney graft survival are at least equal to that of DBD recipients. Hopefully, these results will convince other transplant centers to utilize pancreata from DCD donors.

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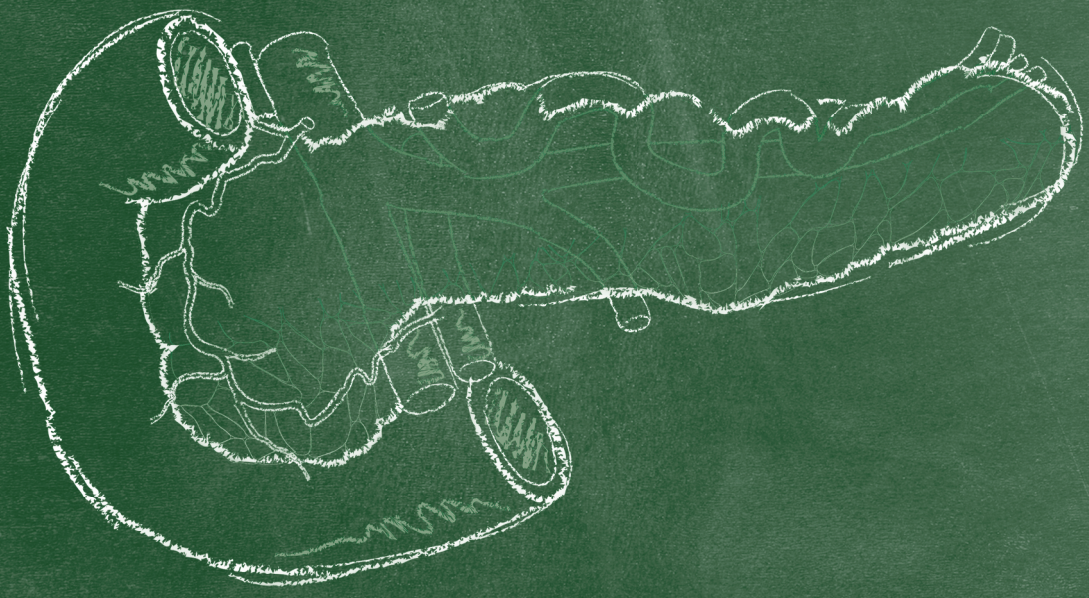


8

Summary of chapters

SUMMARY OF CHAPTERS

The aim of this thesis was to evaluate and investigate factors that are associated with the outcome following clinical pancreas transplantation. Although still considered an experimental procedure by some, over the past 50 years pancreas transplantation has proven to be a lifesaving treatment for patients with diabetes mellitus and in fact the only curative option. The procedure itself comes at certain risks, which as this thesis argues, may lead to loss of a valuable graft and, even more dramatically, loss of life. Therefore donor, recipient and treatment selections are to be optimized. This thesis answers questions and addresses problems and challenges associated with pancreas transplantation. It is a product of the close collaboration of the transplantation division of the Leiden University Medical Center and the Eurotransplant International Foundation.

Chapter 2 provides an overview of the first 30 years of pancreas transplantation at Leiden University Medical Center. In those 30 years and through the effort of dedicated professionals, LUMC has become one of the largest pancreas transplant centers in Europe. The chapter describes a single-center study and is one of the few studies to evaluate long-term outcome following pancreas transplantation in the era of modern induction therapies.

Comparing the results from chapter 2 to results published in literature, it became clear that outcome, amongst other factors, largely depends on donor related risk factors and that adequate prediction models would be needed to compare outcome data. Those prediction models are frequently used in organ transplantation.[1-7] In pancreas transplantation specifically, two prediction models exist: Preprocurement Pancreas Allocation Suitability Score (P-PASS)[5] and Pancreas Donor Risk Index (PDRI).[4] In chapter 3, outcome data from LUMC were analyzed to validate both models in a single center. It showed that P-PASS was inferior to PDRI and the recommendation was that P-PASS should not be used in clinical decision making.

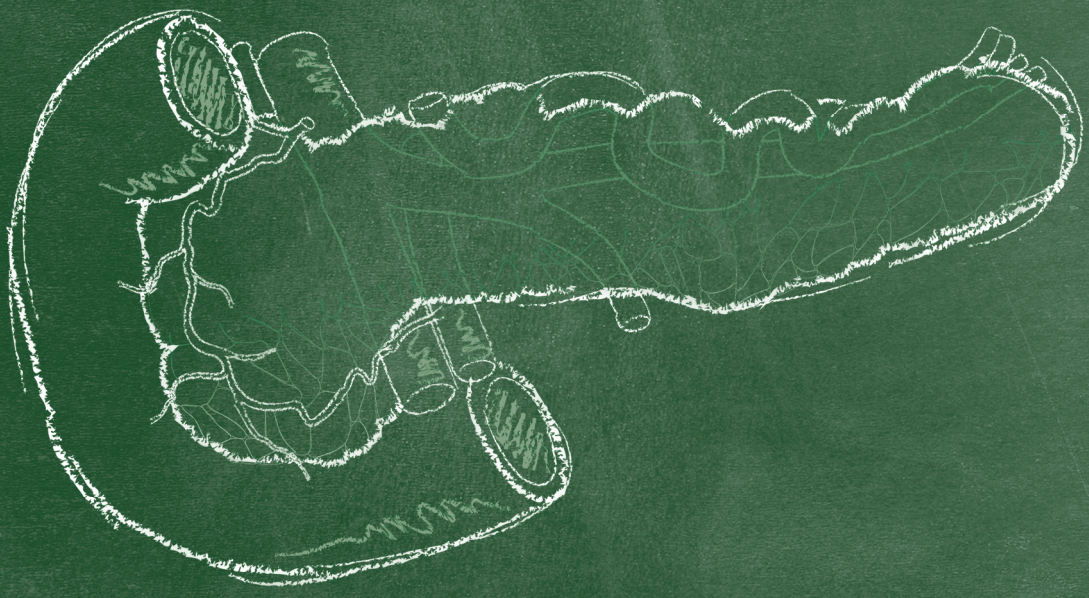
Chapter 4 evaluates the predictive capacity of both models in the Eurotransplant database. Similar to the original P-PASS article, allocation outcome was used as primary endpoint instead of transplantation outcome as used in the original PDRI article. Interestingly, even in this study, PDRI outperformed P-PASS. Another interesting finding was that large differences in donor quality and donor acceptance policies exist, even within the Eurotransplant region.

Chapter 5 describes outcome data of almost 1300 pancreas transplantations within the Eurotransplant region. This study was the first to show that pancreas transplantation outcome is associated with center volume. Even though the higher volume centers accepted higher risk donor graft, outcome in terms of graft and patient survival were superior compared to low volume centers. This study advocates centralization of this highly complex procedure.

In chapter 6, pancreas graft thrombosis was studied. This feared complication and leading cause of graft failure is still a very challenging problem. Many strategies have been under-

taken to detect and prevent thrombosis.[8-14] In this chapter, in particular, detection using CT imaging and treatment of (usually subclinical) partial graft thrombosis was analyzed. Using the current protocol, with heparin and vitamin K antagonists, partial graft thrombosis rarely progressed to full, occlusive thrombosis and graft function was preserved. However, it remains unclear whether such anticoagulation therapy is warranted for all kinds of partial thrombosis.

Chapter 7, describes another risk factor related to the pancreas donor. Donation after determination of circulatory death (DCD) remains a controversial topic in pancreas transplantation. This study showed that, with strict donor selection, excellent results can be achieved with DCD pancreas donors and that these results are similar to those of donation after determination of brain death (DBD) pancreas donors.



9

General discussion

GENERAL DISCUSSION

Pancreas transplantation is to date the only definitive treatment for patients with type 1 diabetes mellitus. Other types of diabetes, such as type 2 diabetes mellitus or mature-onset-diabetes of the young (MODY) in different forms may also be treated with transplantation. The former being an accepted treatment, the latter is not being performed as often and was not studied in this thesis. For patients with concomitant end stage renal disease, pancreas transplantation combined with kidney transplantation (either in a simultaneous or by consecutive procedures) does not only improve quality of life by rendering the patient off exogenous insulin and dialysis, but also by reversing secondary diabetic complications and protecting the kidney graft.[15-17] With this in mind, a successful procedure may be considered life-saving, even though the absence of endogenous insulin may not be life-threatening per se.[18,19] In the case of absence of endogenous insulin and when life-threatening hypoglycemic unawareness occurs, solitary or pancreas transplant alone (PTA) may be a feasible and life-saving option.[20,21]

This thesis focusses on a variety of risk factors that may play an important role in the outcome following pancreas transplantation. As was stated in the introduction, the equation predicting outcome contains the following factors: donor risk factors, recipient risk factors, center related factors and procurement related factors. Some of those factors were studied in this thesis, others were also studied, but are not a part of this thesis and will only be mentioned briefly in this discussion.

Prior to discussing outcome related data that was studied in this thesis, one important remark has to be made: pancreas transplantation research is lacking one uniform definition of pancreas graft failure. This makes comparison of outcome in different studies and centers difficult. Also, organ transplant registries, such as the Eurotransplant registry, encounter problems with the lack of adequate definitions. Sub-analyses on the definition of graft survival were performed using the data described in the first chapter.[22] This was the first study to evaluate the difference. It showed that the difference especially becomes relevant at a longer time after transplant, up to 28% after ten years, when exogenous insulin therapy use was used as definition (76% graft survival) compared to when the definition of DM, as defined by the American Diabetes Association (ADA) was used (48% graft survival).[23] The need for a uniform definition of graft failure does not necessarily apply to early graft failure. Graft failure early after transplantation is generally caused by surgical complications (such as thrombosis, bleeding or pancreatitis) which usually warrants direct organ removal and subsequent return to exogenous insulin therapy.[24] The definition of early graft failure (EGF) is clear and insulin has to be administered to keep the patient alive and euglycemic. In such cases, measuring HbA1c values, which may be of interest for long-term graft failure, will partly represent pre-transplantation values and would thus be futile. On the mid- and longer term, the difference in reported graft survival increases with the duration of follow up.[22]

Although one perfect definition of pancreas graft failure does not exist, there are definitions that have advantages over others. A definition that is based on regularly available data, should form the basis of a uniform definition. This allows for easy implementation in databases and registries. During the development of this thesis, it became clear that definitions that are constructed of multiple endpoints, such as the OPTN definition in chapter 1, are difficult to use for research purposes, since many clinical parameters (HbA1c, C- peptide, exogenous insulin use) would have to be entered in the database. Also, using a definition that is based on lab values only, is a snapshot analysis and does not allow individual assessment of the patient, which can only be done by a physician. For example: a definition states that a graft had failed in case of HbA1c > 48 mmol/mol and low c-peptide.

Given patient A, who has low c-peptide, has low bodyweight and is not-dependent on exogenous insulin, but suffers from in infection or rejection and has high HbA1c at time of measurement. This graft should be considered a failed graft based on the definition, even though, when evaluated by both physician and patient, the transplant might still be functioning. Furthermore, not every clinic does routine c-peptide measurements on their patients. Despite the limitations that are mentioned above, a workgroup consisting of members of both European Pancreas and Islet Transplantation Association (EPITA) and International Pancreas and Islet Transplantation Association (IPITA) elaborately evaluated all pros and cons and reached consensus on the definition of B-cell replacement therapy success and failure; the Igls definition of functional and clinical outcomes for ß-cell replacement therapy or 'Igls criteria' on pancreas graft failure (Table 1).[25] In this definition, which is based on lab values (HbA1c, C-peptide) and medical records (hypoglycemia due to exogenous insulin overdose, exogenous insulin requirement), ß -cell replacement is considered successful with good to optimal ß -cell graft function and considered failed with marginal or failed ß -cell graft function. This is the definition that is recommended when reporting pancreas transplantation results.

ß-cell graft functional status	HbA1c, % (mmol/mol)	Severe hypoglycemia, events per yr	Insulin requirements, U/kg/day	C-peptide	Treatment success
Optimal	≤ 6.5(48)	None	None	>Baseline	Yes
Good	< 7.0 (53)	None	<50% baseline	>Baseline	Yes
Marginal	Baseline	< Baseline	≥50% baseline	>Baseline	No
Failure	Baseline	Baseline	Baseline	Baseline	No

Table 1. Igls definition of functional and clinical outcomes for ß-cell replacement therapy (25)

Prediction models have become increasingly more important in transplantation. Such models, and in particular donor risk indices (DRI), were initially developed to predict outcome following transplantation.[1-4] This was thought to be helpful in clinical decision making, as well as physician-to-patient communication. In pancreas transplantation, the

first prediction model was described by Vinkers *et al*.[5] Using routine data on organ acceptance, the preprocurement pancreas allocation suitability score (P-PASS) was developed. This score was implemented in Eurotransplant in 2010, assisting transplant coordinators and other professionals to estimate whether it would be suitable to report the pancreas for transplantation. Also, it has been validated to predict survival.[26] It has been widely used since then and is still being used in some countries. Data in this thesis, amongst other reports, have repeatedly shown the limited value of P-PASS.[27,28] One recent study from Poland reported that PDRI was not related to outcome, however even with low risk donors (PDRI < 1.0), 1 year death-uncensored graft survival was only 66% and therefore their results seem incomparable to other reports.[29] Even more, 8 years after its introduction, the PDRI is considered superior, as is shown in this thesis.[30,31] More recently, another study from Germany also reported that PDRI but not P-PASS is associated with pancreas graft survival.[32]

The first step was to validate the newly constructed PDRI by Axelrod in the contemporary database that was described in chapter 2[33] Also, the P-PASS was evaluated in this cohort to predict graft survival. This was the first time that the PDRI would be validated in another cohort. The results are described in chapter 3. Following the first study on DRI, our aim was to re-evaluate and basically re- do the study that was performed by Vinkers.[5] In close collaboration with Eurotransplant a similar, but larger database was constructed to repeat the experiment Vinkers carried out. This database contained 10 444 pancreas donors. The P-PASS that was constructed by Vinkers was compared to the PDRI constructed by Axelrod, but modified to contain only donor factors.

The modified PDRI, contained only donor factors and was, in that regard, in line with the concept of Vinkers' P-PASS. This study clearly revealed the limitations of the P-PASS. The P-PASS does not include all factors that are believed relevant in pancreas transplantation, because it was designed based on a historic database with strict age and BMI limits. Another important factor here is DCD, which nowadays contributes to a large proportion of all donors in the Netherlands. Only donors below 50 years old were included, with a mean of 35 years old. This study shows, that this in no way represents the current donor population and recently the German EXPAND trial advocated that older and higher BMI donors should be used for pancreas transplantation.[34] When comparing both models side by side in their ability to predict allocation outcome (that is, the organ being accepted), it appeared that the PDRI was superior over the P-PASS. Unfortunately, this database did not include the most clinically relevant endpoint, namely pancreas graft survival, since outcome after transplantation is not routinely recorded in the Eurotransplant database. Nevertheless, since the PDRI had been validated to graft survival in the above mentioned study by Axelrod[4], the study advised to use PDRI for donor selection instead of P-PASS. Unfortunately, the P-PASS is still a tool that is used in the Eurotransplant community, despite its limitations.

In general, there is a lot of discussion about the clinical usefulness of prediction models, such as the PDRI. Advocates of these models claim that they might be used in clinical deci-

sion making, for example to accept or decline a graft that is offered for transplantation. It is stated that, by using the PDRI, a structured and evidence based decision can be achieved. Opponents on the other hand, claim that the data included in a model is too scarce to draw any solid conclusions and that there are many more factors that need to be taken into account when making this decision. Based on the data in this thesis, especially in chapter 3 and 4, arguments for both statements can be found. Clearly, the PDRI performs better than the P-PASS in predicting outcome. The poor performers should not be used in a clinical setting.

Furthermore, only a small percentage of the variation in graft survival is explained by DRIs, even when correcting for other factors that may play a role (recipient factors, center factors). In conclusion, using DRIs for clinical decision making has to be done with great caution. The greatest advantage of the PDRI, or any validated risk index for that matter, is that it allows comparison of large groups of donors in a standardized way. Chapter 3 and 4 of this thesis provide such examples. By providing these insights, we may be able to better communicate with each other about how to improve the transplantation community and thereby improving transplantation numbers and outcome.

Chapter 5 shows that there is a clear relationship with the annual number of transplantations performed in a center and outcome. Striking is the fact that not only is the procedure more successful in higher volume centers, but also that patients survive longer after transplantation when they are transplanted in a high volume center. This study shows that higher volume centers are more willing to accept higher risk organs for transplantation and still have better results as compared to low volume centers. This is a vicious circle that will be even more pronounced in the future since centers will be forced to accept higher risk donors due to organ shortage. Therefore smaller centers are less likely to accept organs for transplantation and subsequently will become smaller and smaller. This will lead to a loss of expertise and even more reluctance to accept higher risk organs. This is the first study to actually show such a relationship, one which obviously was thought to exist by many professionals, because such relationships had been published for other fields of organ transplantation.[35,36] Similar studies on both pancreas, but also liver transplantation have been published afterwards and have shown similar results.[37,38] Because of the perceived relationship with volume and outcome, collecting data for such a study is problematic, because lower volume centers may feel reluctant to provide data. Unfortunately, in Europe, or in the Eurotransplant area, there are no mandatory registries.

Another problem in transplantation and especially in pancreas transplantation is procurement related injury. A study has shown that procurement related pancreas injury may occur in up to 50% of the cases, and this is often the most important reason of the organ being declined for transplantation.[39] At Leiden University, in close collaboration with the 'Nederlandse Transplantatie Stichting' (Dutch Transplantation Foundation, NTS), a novel method was developed to assess procurement related injury and it was used to analyze

procurement quality in a prospective nationwide study.[40] Quality forms had to be completed by both the procurement and the accepting surgeon (which is usually not the same surgeon because in The Netherlands separate teams perform the donor procedure). In this study, a new method to describe similarities and discrepancies between both forms was introduced. It appeared that in 23% of the cases there was a discrepancy between both surgeons. It could be that accepting surgeons are either more critical in their appraisal of an organ, that they are more experienced in evaluating this particular organ or that circumstances to evaluate are simply more optimal (better lighting, back table procedure). Regardless, this system allows evaluation of the procurement quality in The Netherlands in a prospective study. Especially in pancreas procurement, there was an association between procurement related injury and the number of organs procured, where lower procurement volume was a risk factor for injury.

These data are in line with the data that was used in chapter 5, which show a similar relationship in outcome after pancreas transplantation and clearly both studies provide arguments for (further) centralization of pancreas transplantation and procurement.

Whether centralization will lead to higher outcome remains to be seen, however high volume centers might be more willing to accept donors with certain risk factors. Risk factors that are related to poor outcome, are usually attributed to the donor. Factors such as donor age, BMI, cause of death and impaired kidney function are related to early graft failure due to technical failure, caused by graft thrombosis, bleeding or pancreatitis.[24] It is acknowledged that still, after many years of pancreas transplantation, graft thrombosis remains the Achilles' Heel of pancreas transplantation. Usually, complete graft thrombosis occurs within the first 2 weeks after transplantation and may be secondary to rejection or surgical complications. The Virchow triad of endothelial injury, venous stasis and hypercoagulability is believed to also play a role in the development of thrombosis.[10,41] Venous stasis is caused by changes in splanchnic blood flow (from high flow in de the donor to low flow in the recipient due to exclusion of splenic and intestinal blood flow). Hemodynamic instability in the peri-operative period, sudden changes in extent of uremia following kidney transplantation or calcineurin inhibitor use may also be associated with thrombosis. Complete thrombosis is extensively studied and multiple strategies have been proposed to prevent and treat this complication. For example, the positioning of the graft and type of enteric drainage of the pancreas graft, may be associated with graft thrombosis.[42,43] Currently, in most centers, the pancreas is anastomosed 'head up' to either part of the small intestine from duodenum to terminal ileum, to prevent the graft from kinking due to gravitational forces or to allow duodeno-duodenal anastomosis *(expert opinion)*. Complete thrombosis usually leads to immediate graft failure, although endovascular or surgical salvage procedures and even conservative treatment have been reported with varying rates of success.[44-46] These studies state that salvage procedures in case of complete thrombosis should be considered. Partial graft thrombosis remains a far less studied entity. Questions still remain whether

this entity requires treatment, for example whether patients with partial graft thrombosis require anticoagulation with heparin. LUMC results, as presented in chapter 6 clearly show that using heparin and vitamin K antagonists leads to excellent outcome, however, it is not known what the outcome would have been if patients would not have been treated. Perhaps, outcome would have been similar. Using, by some considered as controversial, CT imaging allows visualization of partial thrombosis that may be amenable to treatment. Using color enhanced doppler ultrasound may also be an option to investigate thrombosis, but can only be used in experienced hands.[47] This requires either training of transplant surgeons in the use of doppler or intensive collaboration with radiologists. The former may be preferable, because ultrasound analysis may then be done daily and/or instantly upon indication. Also, another advantage lies in the omission of intravenous contrast, which may damage the newly transplanted kidney. Evaluating recent data, contrast induced acute kidney injury (CI-AKI) due to iodine based contrast media occurs in about 2.5% of patients with chronic kidney disease undergoing contrast based CT, although kidney transplant recipients are excluded from those studies.[48]

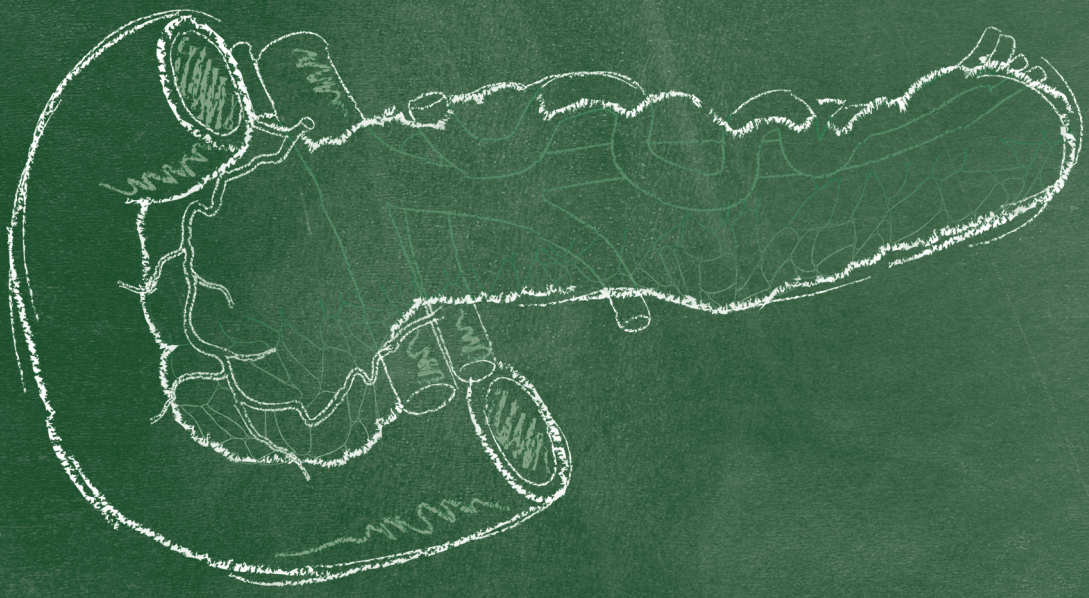
Future studies should focus on identifying and investigating factors that may be associated with thrombosis. Also, intra-operative measurements may be investigated. For example, ROTEM or thromboelastrography[11,49] analysis during and after transplantation may provide more insight. Also maintaining hemodynamic stability throughout the transplantation may influence the risk of thrombosis. Whether this is achieved by transplanting the kidney first, as is done in our center, or whether the use of catecholamines should be limited or used liberally, remains unclear.

In the 7th chapter, another recent cohort of pancreas transplantations in our center was analyzed. The main goal of the study was to compare the results of DCD pancreas transplantation, which is generally considered to be a high risk pancreas transplantation, to standard DBD pancreas transplantation. By analyzing the specific outcome of DBD to DCD pancreas transplantation and showing good results for the DCD group, we aimed to increase the potential donor pool. It became clear from this study that results following DCD pancreas transplantation were at least equal to those of DBD pancreas transplantation. This however, has to be interpreted with caution due to multiple issues raised in the study. The first issue is donor selection: DCD donors were generally younger and had considerably fewer risk factors. This reflected in a relatively low PDRI in the DCD group and when DCD was not taken into account, these donors could otherwise be considered low risk. The relatively higher risk of graft loss could be largely attributed to the numbers of early graft loss in the DBD group, mainly due to thrombosis. Simultaneously, the risk of bleeding was lower in the DBD group. Obviously, this suggests some form of yin and yang analogy. The suggestion of factor Xa accumulation was raised in the study. This would be caused by impaired kidney function following DCD transplantation, due to the higher incidence of DGF. In this retrospective study, factor Xa was not measured, therefore the relationship could not

be proven. In any case, the study shows that simply declining DCD donors for vascularized pancreas transplantation seems unjustified and not based on data. Especially, with younger and donors with less other risk factors, excellent results can be achieved following DCD pancreas transplantation.

CONCLUSION

Beta-cell replacement therapy, and in particular pancreas transplantation is the only curative treatment for patients with complicated type 1 diabetes mellitus. Due to organ shortage, transplantation professionals are forced to accept higher risk organ donors to meet the increasing demand. This thesis investigates these risks and shows that it is justified to accept a certain risk, for example by transplanting grafts from DCD donors. Graft thrombosis is still the main cause of early graft failure, but in the light of long term outcome, the risk is acceptable and the majority can be treated with good outcome. Preferably performed in high volume centers with good outcomes, pancreas transplantation is life-saving for patients with type 1 diabetes mellitus, especially when combined with kidney transplantation in case of concomitant end stage renal disease.



10 Future perspectives

FUTURE PERSPECTIVES

In the nearby future, pancreas transplantation will remain the only definitive option for patients with type 1 diabetes mellitus. Although promising, pre-clinical results on the treatment of diabetes mellitus, have, so far, not been translated into clinical practice. Islet transplantation currently exists complementary to vascularized pancreas transplantation and results are improving, however, rendering patients of exogenous insulin in the long term, is still difficult.[50,51] In the future, using stem-cell based cells or even xenotransplantation, diabetes may be treated or cured, however, current progress is still on the experimental, laboratory and pre-clinical level.[52,53]

Multinational collaborations in organ sharing

Implementation of new evidence into the allocation algorithms in a multi-national collaboration such as Eurotransplant will remain a challenge in the future. Understandably, national legislation, as well as nationalistic feelings, may delay implementation of science-based organ allocation. Efforts to maintain multinational collaborations are paramount, especially for those highly vulnerable recipients that benefit most from larger donor populations, such as highly immunized recipients and small children. Another advantage of large collaborations is the availability of large amounts of data. The Eurotransplant database contains donor, recipient and transplant data. The Eurotransplant Registry is a voluntary registry where centers can enter their outcome data. High levels of data completeness, as is achieved in UK Transplant Registry, is lacking in the Eurotransplant registry. Currently, Eurotransplant depends on both synchronization with national registries, as well as the willingness of the centers to deliver outcome data, mostly encouraged by the hard work of the registry coworkers. A (semi-)mandatory Eurotransplant, or even European registry would allow for multinational studies in the field of organ transplantation.

Legislation to increase the donor pool

Increasing the donor pool may be done in several ways. First, and this is beyond the scope of this thesis, legislation may be used to increase the number of potential donors. In a presumed consent or opt-out system, where all adults are considered to be an organ donor unless they object, the number of donors per million inhabitants will very likely increase, as is the case in Belgium, Spain and Croatia. Fortunately, such a bill was recently accepted in The Netherlands and will be written into law soon. Despite its good intentions, the law caused an increase in people registering 'decline' in the national registry. So, whether this law will lead to higher donation rates remains to be seen, but it will encourage people to consider their decision and discuss it with their peers. By raising awareness for organ donation, which is partially done by this law, organ donation following brain death or controlled DCD may become standard practice and the public may become more liberal and hopefully

more accepting towards the subject. Although this law attempts to solve organ shortage, this will probably be insufficient and therefore, extending donor criteria and novel preservation techniques are required.

Centralization

As was stated earlier in this discussion, centers should strive to centralize and concentrate their programs, perhaps even across borders (e.g. The Netherlands and Belgium), although national or regional centralization would be a big step forward. This will inevitably lead to loss of transplant programs in some centers and increase in numbers in others. This is in line with regular healthcare reforms, at least in The Netherlands, where high complex – low volume care has been centralized for a long time.[54] Communicating the reason for those reforms is crucial in physician to patient communication. The data in this thesis, together with other recently published studies, may support those reforms. Also, improving pancreas procurement quality, by centralizing procurement teams, preferably using procurement surgeons that are based in pancreas centers. This is largely done in The Netherlands already with independent procurement teams (so-called "Zelfstandig Uitname Teams"), but a similar system has to be extended to other countries. By centralizing both procurement and transplantation, procurement injuries can be minimized and even the highest risk organs, which will be become the standard in the future, may yield higher numbers of transplantation, with excellent results. Unfortunately, despite centralization and certification, procurement related injury is still a problem, especially in pancreas procurement.[39,40,55] Centralization is not a decision that is made by clinicians, but by politicians and other policymakers, also because, as stated above, some centers may lose their transplant program.

Machine perfusion

Novel preservation methods are being studied all around the world, with a special interest towards machine perfusion.[56] This may be done intracorporal in the donor or extracorporal after procurement and may also be combined with the traditional static cold storage. It may be done using special preservation solutions or blood and using different temperatures, ranging from ice-cold to near physiological. Especially normothermic machine perfusion may be promising due to the possibility to provide near-physiological circulation providing oxygen and nutrients, elimination of waste products and toxins, endothelial protection and viability assessment.[57] To date, machine perfusion for vascularized pancreas transplantation has been tested in pre-clinical studies and appears to be difficult due to the delicate structure of the organ. Promising results may be translated into clinical practice in the nearby future.[57-59] Machine perfusion of pancreata for clinical islet transplantation appears to be feasible and might improve islet viability.[60-61] The only clinical application of machine based perfusion of pancreata is being performed using normothermic regional perfusion (NRP) in a controlled DCD setting. In these cases following circulatory arrest, organs are preserved

in-situ at physiologic temperatures, allowing for reversal of deleterious ischemia related to the DCD procedure, as well as in-situ graft viability assessment. This may lead to the acceptance and transplantation of grafts that may have otherwise been discarded.[62,63]

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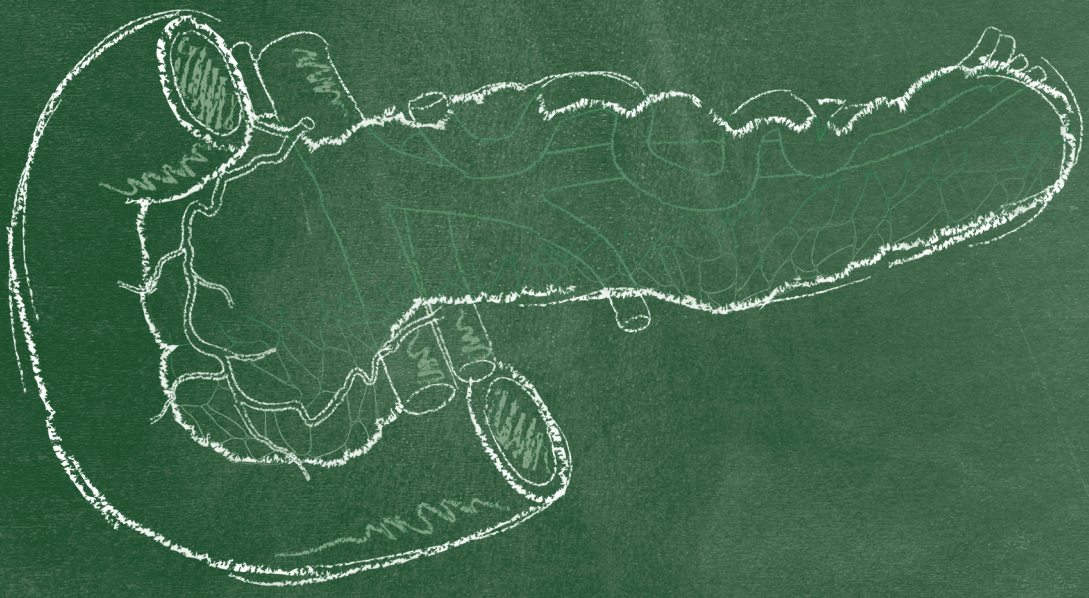


11 Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Dit proefschrift gaat over de gevolgen en een mogelijke behandeling voor suikerziekte, met name de vorm die op jonge leeftijd voorkomt: type 1 diabetes mellitus. Deze vorm van suikerziekte wordt gekenmerkt door een tekort aan insuline, een stof die een belangrijke rol speelt in de energiehuishouding en glucosebalans van het menselijk lichaam. Insuline wordt geproduceerd door de alvleesklier, ook het pancreas genoemd. Het pancreas is een orgaan dat in de buik bij de twaalfvingerige darm ligt en is onderdeel van ons spijsverteringsstelsel. Het geeft naast insuline aan het bloed, ook nog spijsverteringsenzymen aan de darm af. Type 1 diabetes wordt veroorzaakt doordat het eigen afweersysteem van de patiënt de insuline producerende cellen in de alvleesklier afbreekt, een auto-immuunziekte. Er bestaat ook nog een andere vorm van suikerziekte, type 2 diabetes. Deze vorm komt vaker op latere leeftijd voor en heeft met name te maken met leefstijl.

Bij type 1 diabetes is een patiënt altijd afhankelijk van insuline injecties of insulinepompen. Soms zijn deze methoden niet voldoende en zorgt een continue disbalans in glucose en insuline voor schade aan bloedvaten en zenuwen, waardoor patiënten problemen krijgen met onder andere hun nieren en ogen. In enkele gevallen is de schade zelfs zo groot dat patiënten afhankelijk worden van nierdialyse. Omdat de levensverwachting van patiënten die afhankelijk zijn van dialyse slecht is, is dit het moment dat patiënten in aanmerking komen voor een niertransplantatie. Om te voorkomen dat de suikerziekte ook de getransplanteerde nier aantast, kan simultaan een alvleesklier worden getransplanteerd: een gecombineerde nier-pancreastransplantatie. Een pancreastransplantatie alleen is ook mogelijk. Deze pancreata voor transplantatie zijn afkomstig van overleden donoren. Het overgrote deel wordt gedoneerd door hersendode patiënten. Hierbij klopt het hart nog, is de bloedcirculatie van een patiënt op de intensive care nog intact en wordt de patiënt kunstmatig beademd. De hersenen zijn zodanig beschadigd dat bewustzijn, pijngevoel of reflexen afwezig zijn en dat herstel onmogelijk is.

In dit proefschrift worden de risico's onderzocht en resultaten beschreven van deze gecombineerde nier-pancreastransplantatie, maar ook van pancreastransplantatie alleen. Het laat zien dat er risico's zijn en dat het daarom niet voor iedere patiënt de beste optie is, maar dat bij goede uitkomsten de procedure levensreddend is.

In dit proefschrift zijn risicofactoren onderzocht en hun relatie met de uitkomsten van klinische gevasculariseerde pancreastransplantatie. De eerste pancreastransplantatie werd door Kelly en Lillehei uitgevoerd in University of Minnesota Hospital in 1966. Sindsdien zijn wereldwijd meer dan 50.000 pancreastransplantaties uitgevoerd. De meest gebruikelijke procedure is een gecombineerde nier-pancreastransplantatie. Echter een solitaire pancreastransplantatie is ook een optie, eventueel voor of na een niertransplantatie. Het orgaan is meestal afkomstig van een hersendode donor met intacte circulatie: heartbeating donatie

(HB) of donation after brain death (DBD). Donatie na gecontroleerde circulatiestilstand op een intensive care, genaamd non-heartbeating donatie (NHB) of donation after circulatory death (DCD), is ook mogelijk. De eerste pancreastransplantatie in Nederland werd in 1984 in het Academisch Ziekenhuis in Leiden uitgevoerd, zoals te lezen in hoofdstuk twee.

Achtergrond

Pancreastransplantatie is tot op heden de enige curatieve behandeling voor patiënten met diabetes mellitus type 1. Bij type 2 diabetes of MODY (maturity onset diabetes of the young), kan pancreastransplantatie een optie zijn, dit is echter minder gebruikelijk. Met name patiënten met diabetes gerelateerd nierfalen komen in aanmerking voor een (gecombineerd) nier-pancreastransplantaat. Dit kan zowel gebeuren in één procedure of als opeenvolgende procedures waarbij eerst een nier wordt getransplanteerd (van een levende of overleden donor) en daarna een pancreas (pancreas after kidney, PAK) of andersom (pancreas transplant alone, PTA). PTA kan ook gedaan worden bij patiënten met niet in te stellen diabetes met levensbedreigende hypoglycemieen, zonder nierfalen.

Door een gecombineerde transplantatie, wordt niet alleen de kwaliteit van leven verbeterd (de patiënt is immers vrij van insuline toedieningen), maar ook wordt het niertransplantaat beschermd tegen nieuwe schade door diabetes, waardoor de patiënt niet meer afhankelijk is van dialyse. Dit in ogenschouw nemende, kan worden gesteld dat een succesvolle behandeling levensreddend is. De uitkomsten na pancreas transplantatie worden meestal beschreven aan de hand van insuline onafhankelijkheid na transplantatie en patiënt overleving.

Niet iedere patiënt met type 1 diabetes komt in aanmerking voor een pancreastransplantatie. De lasten van levenslange immunosuppressiva en de risico's van een grote operatie wegen niet op tegen de baten, indien de patiënt adequaat is ingesteld op insuline therapie en nog geen secundaire complicaties heeft. Pancreastransplantatie voor maligniteiten wordt in Nederland niet gedaan.

Naast gevascullariseerde pancreastransplantatie is het ook mogelijk om insuline producerende β-cellen te isoleren uit de eilandjes van Langerhans. Preparaten van enkele donoren worden meestal gecombineerd tot één preparaat en getransplanteerd. Hoewel het voor patiënten, die slecht in te stellen zijn op insuline, in de meeste gevallen nog niet goed mogelijk is om hiermee insuline onafhankelijk te worden, is het wel goed mogelijk om de ziekte en secundaire complicaties te stabiliseren. Op deze manier kan dus ook een eventueel niertransplantaat beter beschermd worden. Eilandjestransplantatie wordt in dit proefschrift buiten beschouwing gelaten.

Pancreastransplantatie is al jaren geen experimentele behandeling meer. Door groeiende ervaring en sterk verbeterde resultaten is men in toenemende mate bereid om meer patiënten te transplanteren. Dit leidt tot een stijging van het aantal patiënten op de wachtlijst. Dit fenomeen wordt frequent beschreven als de transplantatie paradox: door een meer liberale selectie van ontvangers, stijgt de vraag harder dan het aanbod van donororganen, waardoor

de wachtlijst exponentieel groeit. Om de vraag bij te benen, zijn behandelaars genoodzaakt om risico's te accepteren als het gaat om donorkarakteristieken. Dit proefschrift beschrijft enkele van deze risico's en de resultaten wanneer deze risico's worden geaccepteerd.

Door deze groeiende expertise en ervaring zijn de uitkomsten van pancreastransplantatie anno 2019 uitstekend. Gemiddeld heeft 80% van de ontvangers vijf jaar na transplantatie nog een werkend transplantaat en is dus niet afhankelijk van insuline. 90% van de mensen zijn vijf jaar na de transplantatie nog in leven. Helaas gaat nog altijd een aantal van de getransplanteerde organen verloren. Het grootste risico op transplantaatverlies is in de vroege postoperatieve fase, met name door transplantaat trombose. Dit proefschrift richt zich dan ook met name op uitkomsten in deze vroege fase.

Donor-risicofactoren en predictiemodellen in pancreastransplantatie

Aangezien het ontbrak aan objectieve maten om deze risicofactoren te kwantificeren zijn in 2008 en 2010 twee modellen ontwikkeld om deze factoren uit te drukken in maat en getal, respectievelijk de Preprocurement Pancreas Allocation Suitability Score (P-PASS) en de Pancreas Donor Risk Index (PDRI). Beide modellen incorporeren verschillende donor gerelateerde risicofactoren, zoals leeftijd, body mass index (BMI), intensive care opname, nierfunctie, ischemie tijd en trachten op basis van historische data een gewogen inschatting te maken van hun invloed op de uitkomst.

Om te beginnen, zijn beide modellen gevalideerd op onze eigen dataset. In deze dataset blijkt de P-PASS geen goede voorspeller te zijn van uitkomst na transplantatie. Uit hoofdstuk drie blijkt dat de PDRI in onze dataset een significante voorspeller is van de uitkomst na transplantatie en dus valide instrument om de uitkomst na transplantatie te voorspellen. Desondanks blijft er veel (terechte) kritiek op deze modellen: ze zouden onvoldoende rekening houden met overige factoren en de klinische blik van de professional zal toch altijd prevaleren boven een statistisch model. Het belangrijkste voordeel van deze gevalideerde modellen is wel, dat het ons in staat stelt om donorpopulaties op een objectieve manier te vergelijken, zoals duidelijk wordt in hoofdstukken vier en vijf.

In hoofdstuk vier is onderzocht of de bestaande predictiemodellen gebruikt zouden kunnen worden in het proces van orgaan allocatie. De eerdergenoemde P-PASS was oorspronkelijk ontwikkeld om een voorspelling te doen over de geschiktheid van een pancreas voor donatie. In de ontwikkeling van de P-PASS zijn geen data over uitkomsten na transplantatie verwerkt. Daarentegen is de PDRI juist gebaseerd op data na transplantatie. De data in hoofdstuk drie laten zien dat de PDRI, zoals verwacht, beter in staat is om de uitkomst na transplantatie te voorspellen in vergelijking met de P-PASS. Uit hoofdstuk vier blijkt bovendien dat de PDRI een betere voorspeller is van de uitkomst van allocatie en dus in beide gevallen superieur is aan de P-PASS.

Daarnaast is een opvallende uitkomst in dit hoofdstuk dat grote verschillen bestaan in geaccepteerde donorrisico's ondanks de nauwe samenwerking binnen Eurotransplant.

Goede uitkomsten met relatief hoge donorrisico's (zoals in Nederland), zouden andere landen (zoals België) kunnen stimuleren liberaler te zijn in hun aannamebeleid, en organen met een verhoogd risico op falen te transplanteren of buiten de eigen regio aan te bieden. Uiteindelijk wordt het voordeel van een transplantatie bepaald door het verschil tussen uitkomst zonder transplantatie en de risico's van transplantatie van dat specifieke orgaan. Dat betekent dat in een regio met een laag aantal orgaandonoren, een orgaan met een verhoogd risicoprofiel eerder geaccepteerd zou moeten worden voor transplantatie. Deze resultaten zouden dus een stimulans kunnen zijn om een nog intensievere internationale uitwisseling van organen te bewerkstelligen, waardoor kostbare organen niet verloren gaan.

Hoofdstuk vijf gaat nader in op het centrum effect bij pancreas transplantatie. Het centrum effect beschrijft de relatie tussen de uitkomsten na transplantatie en het aantal procedures dat jaarlijks wordt uitgevoerd. Binnen de Eurotransplant regio (Nederland, België, Luxemburg, Duitsland, Oostenrijk, Slovenië, Kroatië en Hongarije) zijn meerdere centra die minder dan vijf transplantaties per jaar uitvoeren. Deze studie laat duidelijk zien dat bij vier of minder transplantaties per jaar het risico op overlijden van de ontvanger of falen van het transplantaat aanzienlijk en significant stijgt ten opzichte van centra waar 13 of meer transplantaties worden uitgevoerd. Daarnaast blijkt dat de hoog volume centra (13 of meer) bereid zijn om een hoger donor risico te accepteren en te transplanteren, zonder dat dit de resultaten negatief beïnvloed. Vergelijkbare verschillen, weliswaar kleiner, zijn ook te zien bij de centra die tussen vijf en 13 transplantaties per jaar uitvoeren met respectievelijk de kleinere groep van vier of minder transplantaties en met de grootste groep van 13 transplantaties of meer.

De Achilles hiel

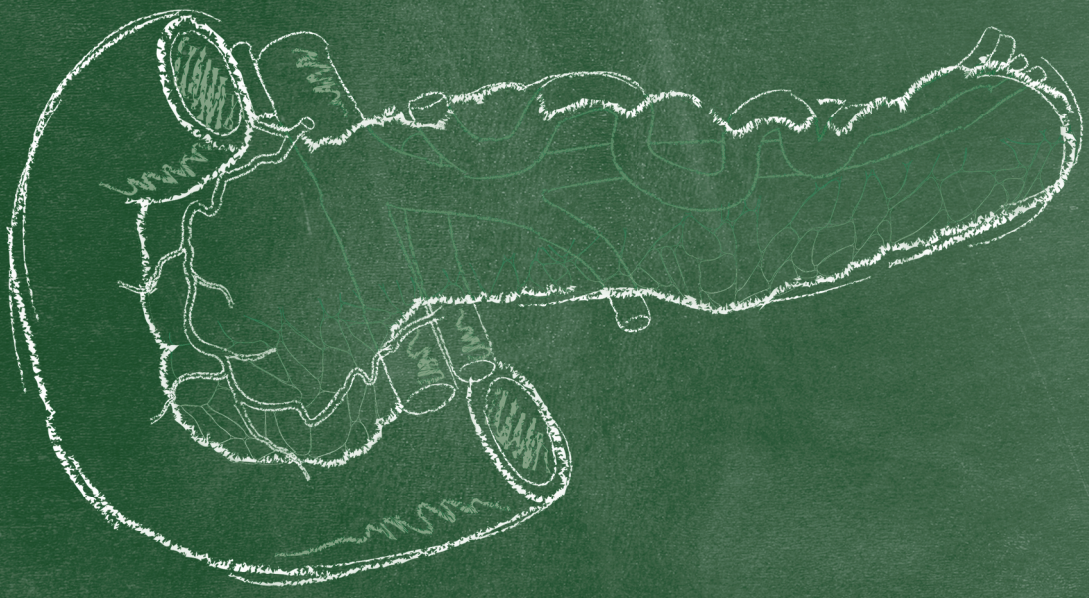
Zoals eerder beschreven in deze samenvatting en te lezen in hoofdstuk zes, is de belangrijkste oorzaak van transplantaat falen na pancreas transplantatie, de vorming van bloedstolsels in het transplantaat: transplantaat trombose. Ondanks alle vooruitgang in medicatie, monitoring en chirurgische techniek, blijft transplantaat trombose de Achilles hiel van de gehele procedure. De reden is niet compleet duidelijk en waarschijnlijk is sprake van een combinatie van afstoting, orgaanschade tijdens de uitname, back-table procedure of transplantatie en ischemie. Daarnaast is het zeker dat er sprake is van meerdere risicofactoren voor trombose, ook wel beschreven in de trias van Virchow: verandering van doorbloeding (door het verwijderen van de milt), schade aan bloedvaten (door de chirurgische procedure zelf), verhoogde bloedstollingsneiging (doordat stollingsremmende eiwitten (ureum) door de nieuwe getransplanteerde nier worden uitgescheiden). Verscheidene behandelingen en strategieën ter voorkoming en behandeling van transplantaat trombose zijn voorgesteld, allen met verschillende mate van succes. Complete trombose van het getransplanteerde orgaan leidt vrijwel altijd tot orgaanverlies, terwijl gedeeltelijke trombose in de meeste gevallen goed behandeld kan worden met bloedverdunners.

Donatie na circulatiestilstand

Donatie van organen, in dit specifieke geval pancreata, na een gecontroleerde circulatiestilstand op een intensive care (non-heartbeating of donation after circulatory death) wordt in toenemende mate gedaan omdat het aanbod heartbeating donoren niet toereikend is. Ondanks het mogelijk schadelijke effect van zuurstoftekort (ischemie) tijdens de hartstilstand blijkt toch dat ook met deze groep donoren goede resultaten bereikt kunnen worden. De resultaten in hoofdstuk zeven laten zien dat bij de meeste DCD donoren de overige karakteristieken (met name leeftijd en doodsoorzaak) gunstiger zijn dan van DBD donoren en dat de uitkomsten tenminste vergelijkbaar zijn met die van DBD transplantatie. DCD pancreas transplantatie is dus een goede manier om een deel van schaarste aan donoren op te vullen.

Conclusie

Pancreas transplantatie is in meer dan 50 jaar uitgegroeid van een experimentele naar een levensreddende procedure voor een geselecteerde groep patiënten met type 1 diabetes mellitus. Door een tekort aan geschikte donororganen worden behandelaars gedwongen om meer risico's te nemen in het accepteren van organen. Het blijkt dat hoog-volume centra goede resultaten behalen met betrekking tot insuline onafhankelijkheid en patiënt overleving, juist ook met deze hogere donorrisico's. Dit proefschrift onderzoekt deze risico's en laat zien dat sommige risico's, zoals het transplanteren van DCD organen, acceptabel zijn met goede uitkomsten.



Appendices

Abbreviations and definition

List of publications

Acknowledgement (Dankwoord)

ABBREVIATIONS

ADA	American Diabetes Association
AMR	Antibody mediated rejection
ANOVA	Analysis of variance
ASA	Acetylsalicylic acid
ATG	Antithymocyte globulin
BMI	Body mass index
CIT	Cold ischemia time
COD	Cause of death
CT	Computed tomography
DBD	Donation after brain death
DCD	Donation after circulatory death
DCDD	Donation after circulatory determination of death
DGF	Delayed graft function
DOAC	Directly acting oral anticoagulants
DRI	Donor risk index
DSA	Donor specific antibodies
EGF	Early graft failure
EPAC	Eurotransplant pancreas advisory committee
EPITA	European pancreas and islet transplantation association
ESOT	European society for organ transplantation
ESRD	End stage renal disease
HR	Hazard ratio
HTK	Histidine tryptophan ketoglutarate
ICU	Intensive care unit
IL	Interleukin
IPITA	International pancreas and islet transplantation association
LMWH	Low molecular weight heparin
LUMC	Leiden University Medical Center
MOD	Multi organ donation
MODY	Maturity onset diabetes of the young
MRI	Magnetic resonance imaging
NOAC	Novel oral anticoagulants
NRP	Normothermic regional perfusion
NTS	Nederlands transplantatie stichting
OAC	Oral anticoagulation
OGTT	Oral glucose tolerance test
OPTN	Organ procurement transplantation network

PAK	Pancreas after kidney
PDRI	Pancreas donor risk index
P-PASS	Preprocurement pancreas allocation suitability score
PRA	Panel reactive antibodies
PTA	Pancreas transplantation alone
PTC	Pancreas transplant committee
RRT	Renal replacement therapy
SD	Standard deviation
SE	Standard exception
SPK	Simultaneous pancreas kidney
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TEG	Thromboelastography
TF	Technical failure
UNOS	United network for organ sharing
UW	University of Wisconsin
VKA	Vitamin K antagonist
WIT	Warm ischemia time
WVS	Withdrawal of ventilatory support

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CURRICULUM VITAE

Wouter Harry Kopp was born April 27th 1988 in Leiderdorp. He is the eldest of three brothers. He attended gymnasium at Visser 't Hooft Lyceum in Leiden and graduated in 2006. In the same year he started his medical studies at the Leiden University Medical Center.

As an active member of LSV Minerva he participated in multiple committees. Also, during this period, he worked as a student allocation officer at Eurotransplant International Foundation. This is where he first came into close contact with organ transplantation. Already during the final months of his medical study in December 2013, he started as a student researcher at the department of surgery, under the supervision of dr. A.E. Braat. During these months, the foundation was laid for the first chapter of this thesis.

After graduating from medical school, he was appointed a combined position as PhD researcher at the Department of Surgery at Leiden University Medical Center and as a medical staff member at Eurotransplant. Data and findings reported in this thesis, as well as on the specific subject of organ allocation were presented at different international meetings. During this period, he lived in The Hague.

Since July 2016 he is working at the Haaglanden Medical Center as a resident of surgery. He started his formal training residency in General Surgery in July 2017 under supervision of dr. H.J. Smeets.

Wouter will be moving to Utrecht with his girlfriend Liz this fall.

DANKWOORD

Dat het schrijven van een proefschrift een werk van de lange adem is, ondervindt men pas als het ook echt gedaan is. Het was voor mij onmogelijk geweest dit te bereiken zonder de hulpen van velen.

Geachte Prof. dr. Hamming, Beste Jaap, ondanks dat je niet vanaf het begin bij dit proefschrift betrokken was, ben je voor mij op exact het juiste moment ingestapt. Na een onrustige tijd maakte jij direct duidelijk dat ik me alleen nog maar diende bezig te houden met het schrijven van een proefschrift en de randzaken moest laten varen. Hartelijk dank.

Beste Dries, onze niet aflatende discussies en momenten van tegenstrijdige inzichten vormen de basis van dit proefschrift. Jouw persoonlijke en eigenzinnige manier van begeleiding is zeer stimulerend en dat blijkt uit de aanwas van nieuwe onderzoekers. Dat ik ook de veranderingen in jouw privéleven van dichtbij mocht meemaken, beschouw ik als een bonus.

Alle mensen bij Eurotransplant, jullie hebben ervoor gezorgd dat bijna tweeëneenhalf jaar voorbij vlogen. De medische staf en in het bijzonder Axel, Undine en Serge, die de kans zagen om een vruchtbare samenwerking tussen het LUMC en Eurotransplant op te bouwen en deze op een zeer goede manier in te vullen. Joris, in jouw voetsporen treden was niet makkelijk, maar de trein reed op volle snelheid. Erwin, zonder jouw databases, zou mijn werk niet mogelijk zijn geweest. Je zult voor altijd gemist worden.

Alle chirurgen van de maatschap Haagse Chirurgen en alle assistenten van het HMC. Terugkomen in de kliniek voelde dankzij jullie als een warm bad. Dat ik nu opgeleid mag worden tot chirurg op deze plek is ook één van de redenen dat dit boekje er nu is.

Sandro, Andre, Jeroen, Volkert en Jan en alle transplantatiechirurgen van het LUMC. Zonder jullie energie en betrokkenheid was het nooit mogelijk geweest zo'n programma op te bouwen. Caroline, Marije, Josephine, bedankt dat jullie 2 jaar lang iedere dinsdag tegen mij aan wilden kijken.

Max en Arty, dankzij jullie ideeën en contacten en waanzinnige gastvrijheid, inmiddels 10 jaar geleden is het onderzoekers vlammetje gaan branden. Dank voor de mooie tijd bij jullie in Arlington. Arty, hartelijk dank voor het lezen van het proefschrift.

Mannen van de Papengracht, Skander, Danny, Hilten, Erik, Tis en de rest waarmee ik heb gewoond, dank dat jullie ook voor een deel aan mijn 'opvoeding' hebben bijgedragen.

Clubgenoten, dank dat jullie iedere keer naar al ons geneeskundig gezever willen luisteren. Ik ga er van uit dat dit nog vele jaren zal doorgaan, zeker nu het academisch gehalte steeds verder omhoog gaat.

Maarten, Maarten en Bas, ik zal de officiële namen die ons binden op deze plek niet noemen. Wat mij betreft een vriendschap gesmeed voor het leven. Dat jullie mij alleen in Den Haag achterlieten, vergeef ik jullie.

Kees, avonden bij jou thuis, met een inmiddels goed rokend groen eitje, waren vaak een welkome afleiding. Dat het allemaal gelukt is, is ook aan jou te danken.

Bou en Ro, van 'vijanden' vroeger naar beste maten nu. Ik ben ongelofelijk trots op jullie en vind het waanzinnig om te zien hoe jullie je eigen leven opbouwen.

Pap en mam, zonder jullie was ik nooit gekomen op de plek waar ik nu sta. Jullie nooit-aflatende support hebben mij hier gebracht. Jullie trots en onvoorwaardelijke liefde vervult me altijd met een groot gevoel van dank. Ik hoop dat jullie samen nog vele jaren in goede gezondheid van deze nieuwe periode in jullie leven mogen genieten.

Lieve Liz, ondanks dat je me nooit als fulltime onderzoeker hebt meegemaakt, mag jij niet ontbreken in dit dankwoord. Je zorgt ervoor dat ik een betere versie van mezelf word. Daarom ben ik intens gelukkig dat ik jou heb weten over te halen jouw leven met mij te delen, ook al duurde dat bijna net zo lang als het voltooien van dit proefschrift.