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ORIGINAL ARTICLE

Validation of the Pancreas Donor Risk Index for use in a UK population

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Conflicts of interest
On behalf of all authors, I declare that the authors know of no conflict of interest.

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Summary

Pancreas graft failure rates remain substantial. The PDRI can be used at the time of organ offering, to predict one-year graft survival. This study aimed to validate the PDRI for a UK population. Data for 1021 pancreas transplants were retrieved from a national database for all pancreas transplants. Cases were categorized by PDRI quartile and compared for death-censored graft survival. Significant differences were observed between the UK and US cohorts. The PDRI accurately discriminated graft survival for SPK and was associated with a hazard ratio of 1.52 ($P = 0.009$) in this group. However, in the PTA and PAK groups, no association between PDRI quartile and graft survival was observed. This is the largest study to validate the PDRI in a European cohort and has shown for the first time that the PDRI can be used as a tool to predict graft survival in SPK transplantation, but not PTA or PAK transplantation.

Introduction

Pancreas transplantation offers people with diabetes insulin independence and improvements in both quantity and quality of life. However, graft failure rates are almost 10% at 1 year and 30% at 5 years, and complications such as pancreatitis can be life threatening [1]. As such, pancreas transplantation typically shows the most conservative donor organ acceptance practice and is associated with the lowest conversion rate from donor to transplant [2].

In other abdominal organ transplantation, the use of organs perceived to be from high risk donors is becoming increasingly common in order to optimize organ utilization. However, defining and identifying the marginal pancreas donor has remained a challenge. The preprocurement pancreas suitability score (P-PASS) was developed by Eurotransplant Pancreas Advisory Committee and is a score based on 9 clinical variables that estimate the likelihood that a given donor pancreas will be suitable for transplantation [3]. However, although some small studies have suggested the P-PASS may predict early surgical complications [4], larger studies have not shown the P-PASS to be associated with graft survival [5,6].

Several centres have attempted to identify risk factors and predictors of pancreas graft failure, with some factors such as donor BMI, donor type and donor age appearing to be common amongst studies [7–10]. However, what is not clear from these studies is how to assimilate multiple risk factors in a single donor. Axelrod *et al.* [11] recognized the need for a model that can be used at the time of organ offering, to better assess which pancreases would result in good graft survival. Using data from the Scientific Registry of Transplant Recipients (SRTR) to determine risk factors for pancreas graft failure at 1 year post-transplant, the pancreas donor risk index (PDRI) was constructed, and contained several donor variables and an

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estimate of preservation time. Logistic coefficients for donor factors found to be significantly associated with graft outcome, for a given recipient, were used to form a predictive model. The factors found to confer the greatest risk were increasing donor age, donation after circulatory death (DCD) and Black race. Cause of donor death, serum creatinine, preservation time, donor body mass index (BMI), height and gender were also included. The model was then adjusted, such that the median donor has a PDRI of 1, and a higher PDRI confers a higher risk of graft failure. The PDRI can be used in clinical practice at the time of organ offering to combine donor factors and provide an objective measure of risk, allowing for prediction of one-year graft survival. Knowledge of one-year graft survival may influence decisions on organ allocation and acceptance.

In the UK, organ allocation is nationally co-ordinated with donor organs offered to local centres for a named recipient. Individual clinicians must then interrogate the donor history and status to subjectively determine suitability for their recipient. The UK donor cohort has been noted to show demographic differences to the SRTR cohort, from which the PDRI was derived, necessitating revalidation in this population [12]. If validated for use in a UK population, the PDRI tool may be used to provide an objective measure, potentially standardizing practice and improving organ utilization.

Methods

This was a retrospective registry analysis. Data were retrieved from a nationally maintained database held at NHS Blood and Transplant for all whole organ pancreas transplants performed between April 2004 and July 2011. Data were checked for missing entries. Cases were excluded if pancreas graft outcomes were unknown, or if variables included in Axelrod PDRI calculation were missing. Graft failure was defined by a return to exogenous insulin therapy or explant of organ.

Statistical analyses were performed using SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, NY, USA). The UK data set was described by transplant type (SPK simultaneous pancreas kidney transplant, PTA pancreas transplant alone and PAK pancreas after kidney transplant) and compared to the published US data set for recipient and donor characteristics. Continuous variables were compared using the student's *t*-test, and categorical variables were compared using the chi-squared test.

The PDRI was calculated for all transplanted pancreases using the published formula [11] with appropriate conversion of units as necessary. Cases were categorized according to PDRI quartile and compared for death-censored one-year graft survival by type of transplant using Kaplan–Meier log-rank survival analysis. The association between the PDRI as a continuous variable and death-censored graft survival was determined using Cox Regression analysis.

Results

Demographics

Data for 1265 whole organ pancreas transplants were retrieved. A total of 244 cases were excluded due to missing data. In total, 1021 pancreas transplants were included in the analysis. The demographics of the recipient and donor cohort are displayed in Table 1. The cohort was compared by transplant type, and the PTA group was found to have more female recipients ($P = 0.005$), more donors after circulatory death ($P < 0.001$), shorter cold ischaemia time ($P < 0.001$) and fewer HLA mismatches ($P = 0.018$), reflecting biases in UK allocation procedures and attempts to minimize modifiable risk factors.

The UK cohort was compared to the US cohort utilized in the development of the PDRI formula. Differences between the cohorts, although statistically significant, were numerically and clinically minor in most cases. However, of clinical relevance, the UK donor cohort was older (34.9 vs. 26.3 years, $P < 0.0001$), with a more even gender distribution (49.1% vs. 67.3% male, $P < 0.0001$), largely Caucasian (95.8% vs. 71.8%, $P < 0.0001$) and consisted of a greater proportion of DCD transplants (10.8% vs. 1.4%, $P < 0.0001$).

The calculated PDRI for the UK cohort ranged from 0.49 to 3.40 and was comparable between transplant type (Table 2) and transplant centre (data not shown). The PDRI calculated in the Axelrod cohort had a narrower range compared with the UK cohort, with the UK showing a skew towards greater utilization of higher PDRI donor grafts.

PDRI and graft survival

Comparison of pancreas graft survival by PDRI quartile showed PDRI to accurately discriminate graft survival for SPK with the lowest to highest risk quartiles achieving 1-year survival of 93.1%, 89.1%, 84.6% and 80.5%, respectively (Fig. 1). The lowest risk group (1st quartile) achieved significantly better graft survival compared with the third quartile ($P = 0.018$) and fourth quartile ($P = 0.008$). The greatest discrimination in graft survival was evident in the first 6 months post-transplant, with the survival difference narrowing over time such that the 5-year graft survival was 78.3%, 76.5%, 72.2% and 71.7%, respectively for the corresponding risk quartiles (Fig. 2). In the SPK group, when analysed as a continuous variable, a multivariate Cox regression analysis showed PDRI was associated with graft survival in the SPK group with a hazard ratio of 1.52 ($P = 0.009$).

However, in the PTA and PAK groups, no association between PDRI quartile and graft survival was observed in

Table 1. Cohort characteristics.

	All *N* = 1021	SPK *N* = 842 (82.5%)	PTA *N* = 63 (6.2%)	PAK *N* = 116 (11.4%)
Recipient				
Age (years)	41.64 (8.23)	41.58 (8.21)	41.59 (8.67)	42.10 (8.21)
Gender (%male)	590 (57.8%)	497 (59.0%)	24 (38.1%)	69 (59.5%)
BMI (kg/m2)	25.53 (3.54)	25.54 (3.46)	24.96 (3.23)	25.80 (4.22)
Ethnicity				
Caucasian	948 (92.9%)	777 (92.3%)	62 (98.4%)	109 (94.0%)
Asian	61 (6.0%)	55 (6.5%)	0 (0%)	6 (5.2%)
Black	7 (0.7%)	5 (0.6%)	1 (0.1%)	1 (0.9%)
Chinese	1 (0.1%)	1 (0.1%)	0 (0%)	0 (0%)
Other	4 (0.4%)	4 (0.4%)	0 (0%)	0 (0%)
Waiting time (days)	379.3 (393.5)	379.1 (390.87)	314.7 (83.35)	383.6 (426.382)
Donor				
Age (years)	34.86 (13.19)	35.15 (13.13)	33.33 (14.10)	33.57 (13.11)
Gender (%male)	501 (49.1%)	409 (48.6%)	27 (42.9%)	65 (56.0%)
BMI (kg/m2)	23.63 (3.56)	23.64 (3.53)	23.23 (4.08)	23.72 (3.52)
Ethnicity				
Caucasian	978 (95.8%)	805 (95.6%)	61 (96.8%)	112 (96.6%)
Asian	26 (2.5%)	22 (2.6%)	1 (1.6%)	3 (2.6%)
Black	6 (0.6%)	6 (0.7%)	0 (0%)	0 (0%)
Chinese	1 (0.1%)	1 (0.1)	0 (0%)	0 (0%)
Mixed	8 (0.8%)	7 (0.8%)	0 (0%)	1 (0.9%)
Other	2 (0.2%)	1 (0.1%)	1 (1.6%)	0 (0%)
DCD	110 (10.8%)	77 (9.1%)	18 (28.6%)	15 (12.9%)
Serum				
Sodium (mmol/l)	148.4 (8.52)	148.51 (8.54)	147.10 (8.58)	148.58 (8.35)
Creatinine (μmol/l)	80.05 (39.05)	78.62 (36.18)	84.38 (56.71)	88.01 (46.16)
Amylase (IU/l)	115.38 (203.4)	119.17 (218.14)	147.10 (8.58)	99.84 (116.91)
ALT (IU/l)	72.02 (233.89)	70.73 (207.61)	57.35 (71.92)	88.95 (403.79)
GGT (IU/l)	72.1 (81.69)	72.69 (84.52)	62.30 (44.96)	73.39 (76.63)
PMH				
Hypertension	75 (7.3%)	62 (7.5%)	6 (9.7%)	7 (6.1%)
Smoking	500 (49%)	419 (50.6%)	23 (37.1%)	58 (50.9%)
Alcohol	74 (7.2%)	61 (7.4%)	4 (6.5%)	9 (7.9%)
Drugs	85 (8.3%)	73 (9.0%)	4 (6.6%)	8 (7.0%)
Transplant				
No				
1	984 (91.4%)	837 (99.4%	60 (95.2%)	87 (75.0%)
2	35 (3.4%)	5 (0.6%)	3 (4.8%)	27 (23.3%)
3	2 (0.2%)	0 (0%)	0 (0%)	2 (1.7%)
CIT (mins)	779.6 (217.7)	772.0 (215.27)	726.03 (161.53)	863.61 (241.12)
HLA mismatch				
0–2	132 (12.9%)	99 (11.7%)	15 (23.8%)	22 (19.0%)
3–4	540 (52.9%)	450 (53.4%)	25 (39.7%)	61 (52.6%)
5–6	349 (34.2%)	293 (34.8%)	23 (36.5%)	33 (28.4%)
Transplant year				
2004	40	37	0	3
2005	92	80	0	12
2006	133	113	2	18
2007	178	145	9	24
2008	160	123	15	22
2009	172	137	16	19
2010	160	135	11	14

Data are presented as mean (SD) or n (%). SPK, simultaneous pancreas kidney transplant; PTA, pancreas transplant alone; PAK, pancreas after kidney; BMI, body mass index; DCD, donor after circulatory death; ALT, alanine transaminase, GGT, gamma-glutamyl transferase; PMH, past medical history; CIT, cold ischaemia time; HLA, human leucocyte antigen.

Table 2. Distribution of PDRI in UK cohort.

Centile	All *N* = 1021	SPK *N* = 842 (82.5%)	PTA *N* = 63 (6.2%)	PAK *N* = 116 (11.4%)	Axelrod *N* = 3375
0	0.49	0.49	0.58	0.64	0.64
25	0.92	0.90	0.97	0.92	0.84
50	1.29	1.30	1.24	1.21	1.00
75	1.77	1.78	1.69	1.77	1.30
100	3.40	3.12	2.64	3.40	2.86

SPK, simultaneous pancreas kidney transplant; PTA, pancreas transplant alone; PAK, pancreas after kidney.

Kaplan–Meier analysis (Fig. 1). Multivariate Cox regression analysis with PDRI as a continuous variable also showed that PDRI was not be significantly associated with graft outcome in these groups (PTA: HR 1.98, $P = 0.19$; PAK: HR 0.95, $P = 0.86$).

Discussion

The PDRI was designed using SRTR data to provide a model to be used pretransplant to inform risk and guide organ utilization. This is the first study to validate the PDRI for use in a large European cohort. We have highlighted the significant demographic differences in the UK cohorts, with the UK using older, DCD donors and representing a more Caucasian population. Although the incidence of risk factors varies between the two cohorts, the PDRI is similar implying that clinicians in both countries are combining risk factors effectively with no difference in risk aversion.

We have shown the PDRI to be significantly associated with early graft survival in SPK transplants. However, the

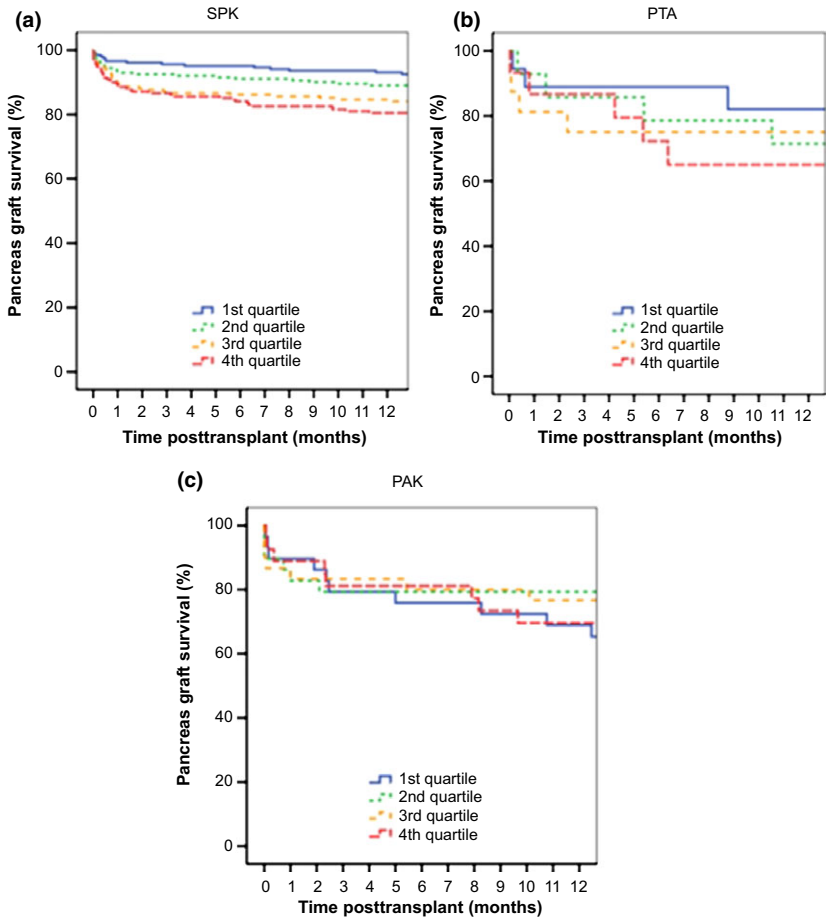

Figure 1 Kaplan–Meier survival according to PDRI quartile: (a) SPK, (b) PTA, (c) PAK. SPK, simultaneous pancreas kidney transplant; PTA, pancreas transplant alone; PAK, pancreas after kidney.

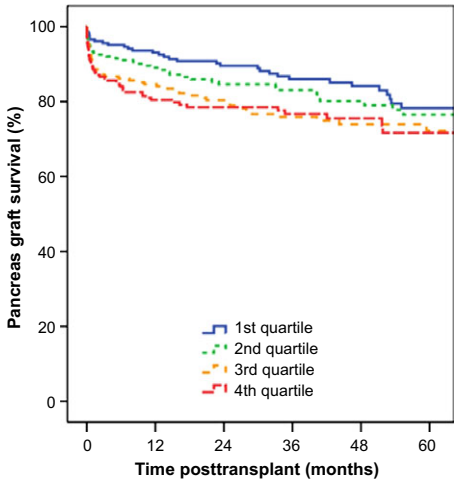

Figure 2 5-year survival for SPK transplants by PDRI quartile. SPK, simultaneous pancreas kidney transplant; PTA, pancreas transplant alone; PAK, pancreas after kidney.

difference between the highest and lowest risk group was reduced to less than 7% at 5 years. Although the PDRI is a useful to tool to estimate graft survival, good outcomes were achieved throughout the PDRI range, and so the impact on graft utilization may be minimal. Certainly, graft survival in the lowest risk group remained 78% at 5 years, indicating other factors are impacting on survival and that additional research in donor and recipient management is necessary to improve outcomes further.

We have also shown that the PDRI was not able to discriminate graft survival in the PTA and PAK groups, although this may be due to small numbers in this group. We did observe, however, that the universally reported poorer outcomes in PTA and PAK transplantation were not related to donor risk. Like Axelrod, we observed poorer survival even for a given donor risk. The superior outcomes observed in SPK transplants have been considered in part attributable to surrogate postoperative monitoring of rejection episode via the transplanted kidney [13]. Our findings corroborate the assumption that poor outcomes correlate with a lack of reliable monitoring in the PTA group.

Inevitably, as this was a retrospective registry analysis, some cases had to be excluded due to missing data; nevertheless, there is no evidence to suggest this has a negative effect on interpretation, and this study remains the largest to date. We have been able to show statistical validity of the PDRI for use in SPK transplant, but not in PTA or PAK transplant and this may be due to small numbers in the latter group. Graft failure has been defined as a return to exogenous insulin and further analysis into causes of graft failure, or insulin dosing analyses was not feasible in this study.

This is the only study to validate the PDRI in a European cohort and confirms that the PDRI is equally valid in a European as in a North American population for SPK transplantation. However, it suffers from the same limitation that the survival difference between the lowest and highest risk groups is small, and as such may have limited clinical utility. Donor risk factors in PTA and PAK are similar to SPK and do not therefore explain the poor outcomes in this group. Better analysis of which donors are associated with superior outcomes may contribute; however, identification of post-transplant markers will be a key for improving graft survival after pancreas transplantation.

Authorship

All authors participated in research design, performance of the research and writing of the paper. SM: performed the data analysis.

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References

1. Mittal S, Gough SC. Pancreas transplantation: a treatment option for people with diabetes. *Diabetic Med* 2014; **31**: 512.
2. http://www.organdonation.nhs.uk/statistics/transplant_activity_report/current_activity_reports/ukt/national_organ_retrieval_service.pdf
3. Vinkers MT, Rahmel AO, Slot MC, Smits JM, Schareck WD. Influence of a donor quality score on pancreas transplant survival in the eurotransplant area. *Transpl Proc* 2008; **40**: 3606.
4. Ziaja J, Krol R, Pawlicki J, *et al.* Donor-dependent risk factors for early surgical complications after simultaneous pancreas-kidney transplantation. *Transpl Proc* 2011; **43**: 3092.
5. Woeste G, Moench C, Hauser IA, Geiger H, Scheuermann E, Bechstein WO. Can the preprocurement pancreas suitability score predict ischemia-reperfusion injury and graft survival after pancreas transplantation? *Transpl Proc* 2010; **42**: 4202.
6. Schenker P, Vonend O, Ertas N, Wunsch A, Viebahn R. Preprocurement pancreas allocation suitability score does not correlate with long-term pancreas graft survival. *Transpl Proc* 2010; **42**: 178.
7. Gruessner RW, Troppmann C, Barrou B, *et al.* Assessment of donor and recipient risk factors on pancreas transplant outcome. *Transpl Proc* 1994; **26**: 437.
8. Humar A, Ramcharan T, Kandaswamy R, Gruessner RW, Gruessner AG, Sutherland DE. The impact of donor obesity on outcomes after cadaver pancreas transplants. *Am J Transplant* 2004; **4**: 605.

9. Sousa MG, Linhares MM, Salzedas-Netto AA, *et al.* Risk factors of pancreatic graft loss and death of receptor after simultaneous pancreas/kidney transplantation. *Transpl Proc* 2014; **46**: 1827.
10. Salvalaggio PR, Schnitzler MA, Abbott KC, *et al.* Patient and graft survival implications of simultaneous pancreas kidney transplantation from old donors. *Am J Transplant* 2007; **7**: 1561.
11. Axelrod DA, Sung RS, Meyer KH, Wolfe RA, Kaufman DB. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant* 2010; **10**: 837.
12. Mittal S, Sharples E, Lee F, *et al.* App to reality: snapshot validation of the US Pancreas Donor Risk Index in a UK center. *J Surg Res* 2013; **183**: 841.
13. Margreiter C, Pratschke J, Margreiter R. Immunological monitoring after pancreas transplantation. *Curr Opinion Organ Transplant* 2013; **18**: 71.