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Prognostic risk factors for graft failure following pancreas transplantation: results of multivariate analysis of data from the International Pancreas Transplant Registry

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Abstract. A multivariate analysis of prognostic factors for graft failure was performed on patients in the International Pancreas Transplant Registry. The analysis was restricted to the period January 1978 to June 1987 and included 764 patients. All patients had at least 1 year of follow-up. The following variables were studied: transplant year, continent (N. America, Europe, others), type of donor (cadaver, living related mismatched, living related HLA-identical), donor mismatch at the HLA A, B loci, donor mismatch at the DR loci, preservation time, kidney association (pancreas transplant alone, simultaneous pancreas and kidney transplant, pancreas after kidney transplant), whole versus segmental pancreatic transplant, graft duct management technique (polymer injection, enteric drainage, stomach drainage, bladder drainage), and immunosuppression. By stepwise, logistic regression analysis, we found that the following factors were predictive for 1-year graft function: donor mismatch at the DR loci ($P = 0.0003$), kidney association ($P < 0.0001$), type of donor ($P = 0.04$), and immunosuppression ($P = 0.0002$). For donor mismatch at the DR loci, we found an odds ratio for success of 2.2 for 0 versus 2 mismatches. The odds for success were 2.9 for simultaneous pancreas and kidney transplant versus pancreas transplant alone. The best results – 79% 1-year graft survival – were obtained for the combination of 0 mismatches at the DR loci, pancreas after kidney transplant, living related HLA-identical donor, and the immunosuppressive regimen consisting of cyclosporin, azathioprine, and prednisone. Patients receiving a pancreas transplant alone with 0 mismatches at the DR loci, living related HLA-identical donor, and triple immunosuppressive regimen had a predicted 1-year graft survival of 71%.

Key words: Pancreas transplantation, risk factors – Pancreas, registry – Risk factors, graft failure, in pancreas transplantation

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The rationale for pancreas transplantation is that even without blood glucose monitoring, a successful transplant will assure completely normal regulation of glucose metabolism. Refinements in surgical technique, combined with better immunosuppression, have provided improved results and have stimulated a widespread performance of pancreas transplantation [2, 3, 5, 6, 12, 14, 17]. Recently, more than 300 new cases yearly have been reported to the International Pancreas Transplant Registry, located in Minneapolis [14]. The pancreas graft function rate has steadily improved and, in recipients of simultaneous kidney transplants, is now approaching that of other solid organs [12].

Although the results are improving, the factors that influence the prognosis have not been precisely defined. The purpose of this study was to determine which factors were the most important for pancreas graft survival by using a multivariate statistical technique to analyze a large patient sample in the pancreas transplant registry data base. By defining such factors, treatment regimens could be changed in order to further improve the results.

Patients and methods

The International Pancreas Transplant Registry has prospectively collected information on all pancreas transplant cases in the world since 1980 [2] and has information from all cases before 1980, courtesy of the old American College of Surgeons/National Institute of Health Organ Transplant Registry and the surgeons pioneering pancreas transplantation. Between 17 December 1966 and 30 June 1988, 1549 pancreas transplants in 1440 diabetic patients were reported to the Registries. For the period 1966–1977, 64 cases were reported, but as these, in many ways, should be considered experimental, they were excluded from this analysis. In order to have at least 1 year of follow-up, cases transplanted after 30 June 1987 were also excluded, leaving 1237 transplants for further study.

Because there were too few cases in certain categories, recipients with the following variable codes were excluded from the analysis: simultaneous pancreas and kidney transplant in nonuremic patients ($n = 5$), open duct intraperitoneal drainage technique ($n = 21$), duct ligation ($n = 13$), and ureteric drainage ($n = 8$). Four hundred twenty-six recipients were excluded because information for one or more variables was missing. The group that was finally included in the multivariate analysis consisted of 764 patients.

Table 1. Patient characteristics and frequency distribution for 764 patients having a pancreas transplant. Aza, Azathioprine; CyA, cyclosporin A; Pred, prednisone

Variable	Category	Number of patients	(%)
Donor type	Cadaver	711	(93)
	Living related mismatched	25	(3)
	Living related HLA-identical	28	(4)
Preservation time	< 6 hours	575	(75)
	7–12 hours	143	(19)
	> 12 hours	46	(6)
Pancreas with/ without kidney	Pancreas alone	152	(19)
	Pancreas and kidney simultaneously	474	(62)
	Pancreas after kidney	138	(18)
Donor mismatch (AB)	0 mismatches	40	(5)
	1 mismatch	75	(10)
	2 mismatches	194	(25)
	3 mismatches	264	(35)
	4 mismatches	191	(25)
Donor mismatch (DR)	0 mismatches	114	(15)
	1 mismatch	352	(46)
	2 mismatches	297	(39)
Whole/segmental graft	Whole pancreas	206	(27)
	Pancreas and duodenum	75	(10)
	Segmental pancreas	483	(63)
Duct management technique	Duct injection	238	(31)
	Enteric drainage	259	(34)
	Stomach drainage	24	(3)
	Bladder drainage	243	(33)
Immuno-suppression	CyA + Pred	230	(30)
	CyA + Aza + Pred	471	(62)
	Aza + Pred	63	(8)
ALG	Yes	236	(31)
	No	528	(69)

The patient sample was studied with 1-year graft survival as the dependent variable. A graft was considered as functioning for as long as the patient was normoglycemic and insulin-independent. Patients who died with a functioning graft were also recorded as failures.

The following variables were chosen as independent variables: transplant year (1978–1983, 1984–1985, 1986–1987); continent (North America, Europe, other); type of donor (cadaver, living related HLA-mismatched, living related HLA-identical); number of donor antigens mismatched at the HLA-A, B loci; number of donor antigens mismatched at the DR loci; preservation time; kidney transplant association (pancreas transplant alone, simultaneous pancreas and kidney transplant, pancreas after kidney transplant); whole versus segmental pancreas transplant; graft duct management technique (polymer injection, stomach drainage, enteric drainage, bladder drainage), and prophylactic immunosuppression [azathioprine without cyclosporin, cyclosporin without azathioprine, cyclosporin and azathioprine combined; with or without antilymphocyte globulin (ALG); with or without OKT3]. The variables age at transplant and sex were not included in the analysis because a large number of values were missing for each variable.

The logistic regression analysis was also performed for a recipient sample limited to technically successful cases (grafts failing from thrombosis, local infection, bleeding, or other such problems were excluded). This reduced the number of transplants to 551, and the only causes of graft failure in this cohort were rejection or death with a functioning graft.

The logistic regression analysis was performed backward with all independent variables included in the model at the start. Variables were then eliminated, one at a time, starting with the one of least significance. The stopping criterion chosen for the stepping process was a P value of 0.05. By then, the applied model fit the data well, with a Hosmer goodness of fit P value of 0.73. Odds ratios, confidence intervals, and estimated 1-year graft survival were calculated for each category of the remaining variables in the model [8].

All computations were performed with BMDP statistical software [4], using the CLINFO Computer System (VAX 11/750, VMS operating system, Digital Equipment Corporation), in the Clinical Research Center at the University of Minnesota.

Results

The variables analyzed and their frequencies are listed in Table 1. Table 2 gives a univariate crosstabulation between the dependent 1-year graft function and all independent variables. We found no relation between 1-year graft survival and preservation time, cadaveric versus living related donor, donor mismatch at the HLA A, B loci, whole versus segmental graft, pancreatic duct treatment technique, ALG, or OKT3. A significant relation was revealed between 1-year graft survival and pancreas transplant with versus without a kidney graft, donor mismatch at the DR locus, type of immunosuppression, transplant period, and continent. Pancreas transplant alone had a 1-year graft function of 28% versus 46% for simultaneous pancreas and kidney transplant. Although the 1-year graft survival for pancreas alone transplants was improved when technically successful cases only were considered, pancreas and kidney transplantation simultaneously fared considerably better. For technically successful cases, pancreatic duct treatment technique was also an important factor, with the best results for stomach drainage (69%) and for enteric drainage (60%). As for immunosuppression, the best results were achieved when cyclosporin, azathioprine, and prednisone were given together; ALG and OKT3 did not seem to add any benefit to the immunosuppression.

The stepwise, logistic regression analysis revealed that the variables pancreas with/without a kidney transplant, donor mismatch at the DR locus, type of donor, and immunosuppression should be in the model predicting 1-year graft survival (Table 3). When the odds for success for pancreas transplants alone was set to 1, the odds ratio for simultaneous pancreas and kidney transplants versus pancreas transplants alone was 2.9 and for pancreas after kidney transplants 1.5.

Donor mismatch at the DR loci was also found to be important in predicting 1-year graft function, with an odds ratio for success of 2.2 for 2 mismatches versus 0 mismatches, and this was highly significant.

As for type of donor, living related HLA-identical donors gave the best results, with an odds ratio of 3.3 versus cadaveric donors. Mismatched living related donors, however, had the same 1-year graft survival as cadaveric donors.

For immunosuppression, the best results were found when cyclosporin, azathioprine, and prednisone were given simultaneously. The odds for success increased from 1 to 3.6 when compared to azathioprine and prednisone.

For the technically successful group, the same four factors were found to be of importance in predicting 1-year

Table 2. One-year graft survival following pancreas transplants for all patients and for technically successful cases. Aza, Azathioprine; CyA, cyclosporin A; Pred, prednisone

Variable	Category	All transplants		Technically successful cases	
		P	(%)	*P*	(%)
Donor type	Cadaver	= 0.23	39.6	= 0.40	54.0
	Living related mismatched		29.2		50.0
	Living related HLA-identical		51.6		68.2
Preservation time	< 6 hours	= 0.65	41.4	= 0.88	55.0
	7–12 hours		37.3		57.7
	> 13 hours		38.8		56.3
Pancreas with/without kidney	Pancreas alone	< 0.0001	27.6	< 0.0001	39.6
	Pancreas and kidney simultaneously		45.8		61.3
	Pancreas after kidney		32.3		44.6
Donor mismatch (AB)	0 mismatches	= 0.15	53.5	= 0.25	66.7
	1 mismatch		44.9		58.6
	2 mismatches		38.6		53.1
	3 mismatches		35.7		49.5
	4 mismatches		42.0		58.4
Donor mismatch (DR)	0 mismatches	= 0.004	53.2	= 0.01	68.1
	1 mismatch		37.2		51.9
	2 mismatches		37.4		51.8
Whole/segmental graft	Whole pancreas	= 0.41	36.2	= 0.15	48.2
	Pancreas and duodenum		42.7		59.6
	Segmental pancreas		40.9		56.4
Ductal treatment technique	Ductal injection	= 0.51	38.2	= 0.05	49.7
	Enteric drainage		41.6		59.8
	Stomach drainage		36.0		69.2
	Bladder drainage		41.1		55.2
Immunosuppression	CyA + Pred	= 0.0006	36.7	= 0.0002	48.6
	CyA + Aza + Pred		44.7		61.1
	Aza + Pred		23.1		34.6
ALG	Yes	= 0.43	37.8	= 0.70	53.2
	No		40.7		54.9
OKT3	Yes	= 0.37	30.0	= 0.07	33.3
	No		40.0		55.1
Transplant year	1978–1983	= 0.001	28.2	= 0.0001	38.2
	1984–1985		41.4		57.6
	1986–1987		44.4		60.2
Continent	North America	= 0.05	37.3	= 0.04	51.4
	Europe		43.0		58.2
	Other		11.1		16.7

graft survival, but then with OKT3 also included in the model. Patients who were not treated with OKT3 had a graft-survival benefit of 3.3:1 versus those given this treatment.

The variables transplant year, continent, cadaveric versus living related donor, preservation time, donor mismatch at the HLA A, B loci, whole versus segmental graft, duct management technique, and with/without antilymphocyte globulin were not significant in predicting graft survival.

The best estimated 1-year graft survival – 79% – was found for the combination pancreas after kidney transplant, 0 donor mismatches at the DR loci, living related HLA-identical donor, and the immunosuppressive regimen consisting of cyclosporin, azathioprine, and prednisone. Patients receiving a pancreas transplant alone, with 0 mismatches at the DR loci, living related HLA-identical donor, and triple immunosuppressive regimen had a predicted 1-year graft survival of 71%. Some of the combinations of variables for predicted graft survival are depicted in Table 4.

Discussion

Due to the small number of transplants performed at each institution, the short follow-up, and continuous changes in transplant protocols, it is difficult to determine which factors are favorable and which unfavorable for pancreas graft function. To overcome some of these problems, this analysis focused on a large patient sample from the International Pancreas Transplant Registry, using the multivariate, stepwise, logistic regression technique.

The benefit of applying multivariate analyses is demonstrated in Tables 2 and 3. By using univariate two-by-

Table 3. Predictive factors for 1-year graft survival in pancreatic transplants (multivariate analysis). Aza, Azathioprine; CyA, cyclosporin A; Pred, prednisone

Variable	All patients			Technically successful		
	P	Odds ratio	Confidence interval	*P*	Odds ratio	Confidence internal
Pancreas with/without kidney	< 0.0001			< 0.0001		
Pancreas alone		1			1	
Pancreas/kidney simultaneously		2.9	(1.8–4.6)		3.8	(2.3–6.3)
Pancreas after kidney		1.5	(0.9–2.6)		1.8	(1.0–3.4)
Donor mismatch (DR)	= 0.005			= 0.007		
2 mismatches		1			1	
1 mismatch		1.0	(0.7–1.5)		1.1	(0.7–1.6)
0 mismatches		2.2	(1.3–3.7)		2.6	(1.4–5.0)
Immunosuppression	= 0.0001			< 0.0001		
Aza + Pred		1			1	
CyA + Pred		2.5	(1.3–4.8)		2.6	(1.2–5.7)
CyA + Aza + Pred		3.6	(1.9–6.9)		4.8	(2.2–10.4)
Donor relation	= 0.04			= 0.03		
Cadaver		1			1	
Mismatched related		1.2	(0.5–3.2)		1.7	(0.6–5.3)
HLA-identical related		3.3	(1.3–8.4)		4.8	(1.4–17.1)
OKT3				= 0.02		
Yes					1	
No					3.3	(1.2–9.5)

two tables, the variables transplant year and continent appeared to be of importance in predicting graft survival. However, these variables were not found to be significant in the logistic regression model, probably due to interaction with other factors. On the other hand, the variable type of donor was not found to be significant by univariate analysis, but was in the multivariate model.

In univariate analysis from a single institution [14], it was found that a pancreas transplanted simultaneously with a kidney fared better than a pancreas transplanted alone, and this difference was confirmed in the analysis from the Registry. One possible explanation is that the uremic state is, in itself, immunosuppressive [7] and, therefore, that simultaneous pancreas and kidney transplant recipients are less likely to reject. This suggests that the indication for pancreas transplantation is an important factor for the outcome. There is no evidence, however, that adding a kidney to a pancreas transplant in nonuremic recipients would improve the results.

Even though the pancreas graft survival rate is high in uremic recipients of simultaneous kidney transplants, pancreas transplants alone have a role in selected nonuremic, nonkidney recipients, since a major goal of pancreas transplantation is to prevent or halt the progression of diabetic complications [16]. Although controversial [11, 15], guidelines for pancreas transplants for such patients have been developed [18]. Based on the knowledge available, it is important to perform the transplant at a relatively early stage, before diabetic nephropathy is too far advanced [13].

Table 4. Predicted 1-year graft survival (%) for patients having a cadaveric pancreas transplant and on a triple immunosuppressive regimen

DR mismatches	0	1	2
Pancreas transplant alone	43	26	26
Simultaneous pancreas and kidney transplant	69	50	50
Pancreas after kidney transplant	54	35	34

The introduction of cyclosporin has been cited as a factor in the improved results following pancreas transplantation [1]. The value of combining cyclosporin, azathioprine, and prednisone was confirmed in this study, as patients treated with this combination had a higher 1-year graft survival than any other combination. Whether or not antilymphocyte agents improve the results is uncertain. The patients treated with OKT3 fared worse than those not given this treatment. The reason for this is uncertain; the OKT3 was putatively given prophylactically, but if actually given as a rejection episode treatment, this result would be expected.

As found in univariate analysis, donor HLA mismatches are of importance in predicting graft survival. The dominant factor was donor mismatch at the DR loci, and the odds for success were 2.2 times higher for a 0 mismatch than for a 2 mismatch. This effect was further increased by the variable type of donor, as a living related HLA-identical donor fared 3.3 times better than a cadaveric donor. A mismatched living related donor, however, had the same graft survival as a cadaveric donor.

Improved results have been reported from some institutions using the bladder drainage technique for duct management [10, 12, 19]. The bladder drainage technique has the advantage of allowing for the direct monitoring of graft exocrine function by measurement of urine amylase activity, thereby leading to early diagnosis and treatment of rejection episodes [2, 3, 9, 12]. However, in this analysis,

the graft management technique was not found to be of importance in predicting graft survival.

In sum, logistic regression analysis of data from the International Pancreas Transplant Registry shows that pancreas transplant recipients with a 0 DR mismatched donor, recipients of a simultaneous kidney transplant or of a pancreas from a living related HLA-identical donor after a previous kidney transplant, receiving triple immunosuppressive therapy have the best chance of maintaining graft function for 1 or more years post-transplantation. Institutions could theoretically achieve the best survival rates by selecting only uremic patients who would undergo a simultaneous kidney transplant. However, by simply minimizing DR mismatches, acceptable results in recipients of pancreas transplants alone can also be achieved.

References

1. Calne RY, White DJG (1982) The use of cyclosporine in clinical organ grafting. Ann Surg 196: 453–462
2. Corry RJ, Nghiem DD, Schulak JA (1986) Surgical treatment of diabetic nephropathy with simultaneous pancreaticoduodenal and renal transplantation. Surg Gynecol Obstet 162: 547–555
3. Cosimi AB, Auchincloss H, Delmonica FL, Fang L, Nathan DM, Tolkoff-Rubin N, Rubin RH, Yang HC, Russell PS (1988) Combined kidney and pancreas transplantation in diabetics. Arch Surg 123: 621–625
4. Dixon WJ (1983) BMDP statistical software. University of California Press, Berkeley
5. Dubernard JM, La Rocca E, Gelet A, Faure JL, Long D, Martin X, Lefrancois N, Blanc N, Monti L, Touraine JL, Træger J (1987) Simultaneous pancreas and kidney transplantation: long-term results and comparison of two surgical techniques. Transplant Proc 19: 2285–2287
6. Illner WD, Schleibner S, Abendroth D, Landgraf R, Land W (1987) Recent improvement in clinical pancreas transplantation. Transplant Proc 19: 3870–3871
7. Lawrence HS (1965) Uremia: nature's immunosuppressive device. Ann Intern Med 1: 166–168
8. Lemeshow S, Hosmer DW (1984) Estimating odds ratios with categorically scaled covariates in multiple logistic regression analysis. J Epidemiol 119: 147–151
9. Prieto M, Sutherland DER, Fernández-Cruz L, Heil J, Najarian JS (1987) Experimental and clinical experience with urinary amylase monitoring for early diagnosis of rejection in pancreas transplantation. Transplantation 43: 71–79
10. Prieto M, Sutherland DER, Goetz FC, Rosenberg ME, Najarian JS (1987) Pancreas transplant results according to the technique of duct management: bladder versus enteric drainage. Surgery 102: 680–691
11. Pyke D (1988) Role of pancreas transplantation. Lancet I: 9
12. Sollinger HW, Stratta RJ, Kalayoglu M, Pirsch JD, Belzer FO (1987) Pancreas transplantation with pancreaticocystostomy and quadruple immunosuppression. Surgery 102: 672–676
13. Sutherland DER (1988) Who should get a pancreas transplant? Diabetes Care 11: 681–685
14. Sutherland DER, Goetz FC, Moudry KC, Najarian JS (1988) Pancreatic transplantation – a single institutions experience. Diab Nutr Metab 1: 57–64
15. Sutherland DER, Goetz FC, Najarian JS (1988) Pancreas transplantation for diabetes. Lancet I: 1100–1101
16. Sutherland DER, Kendall DM, Moudry KC, Navarro X, Kennedy WR, Ramsay RC, Steffes MW, Mauer SM, Goetz FC, Najarian JS (1988) Pancreas transplantation in nonuremic, Type I diabetic recipients. Surgery 104: 453–462
17. Tydén G, Brattström G, Lundgren G, Östman J, Gunnarsson R, Groth CG (1987) Improved results of pancreatic transplantation by avoiding nonimmunological graft failures. Transplantation 43: 674–676
18. University of Michigan criteria for pancreas transplants alone (1988) Diabetes Care 11: 669–678
19. Wright FH, Smith JL, Ames SA, Schanbacher B, Corry RJ (1989) Function of pancreas allografts more than 1 year following transplantation. Arch Surg 124: 796–800