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Multifactorial analysis of the outcome of 6430 cadaver kidney grafts

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Abstract. A total of 6430 cadaver kidney grafts performed within the network of France-Transplant between 1 January 1978 and 1 January 1989 were analyzed. Each case was examined comprehensively in regard to 12 variables. A multifactorial analysis (Cox regression) was used to determine the degree of association between each covariate and the outcome of the graft. The results were evaluated by calculating relative risks of graft failure for each variable. A total of seven covariates appeared to influence graft survival significantly: the period of transplantation ($P = 10^{-8}$), retransplantations ($P = 0.003$), age and sex of the donor ($P = 0.003$ and 0.009 respectively), duration of pretransplant dialysis ($P = 0.03$), pretransplant sensitization to HLA antigens ($P = 0.05$), and matching for HLA-A, -B, and -DR loci ($P = 0.03$). This last parameter has previously been reported as influencing the outcome of the graft in seven out of eight international studies carried out using similar methodology.

Key words: Kidney transplantation, risk factors – Outcome, renal grafts – Multifactorial analysis, kidney transplantation

Many factors influence the outcome of a kidney graft, but their relative importance remains controversial. Several studies have been performed on limited series of patients using monofactorial comparisons, but the series are scarcely large enough to allow a multifactorial analysis. In this study we show the results of the comparison of 12 factors evaluated in a total of 6430 cadaver kidney grafts, an extension of series previously reported on [1, 2].

Materials and methods

A total of 6430 unrelated kidneys grafts performed in the network of France-Transplant between 1 January 1978 and 1 January 1989 were analyzed. Each case has been examined comprehensively in regard to 12 factors. These factors have been chosen according to their use in similar international studies [1–11] and their availability in our database. The 12 variables examined and scores assigned were: recipient and donor sex (1 = male; 2 = female), recipient and donor age (by 5-year categories: 1 = 0–5 years; 2 = 6–10 years; 3 = 11–15 years, and so on) HLA-A, -B, and -DR compatibilities (0 = 0 or 1 shared antigens; 1 = 2 shared antigens; 2 = 3, 4; 3 = 5, 6), date of graft (1 = before 1 January 1979; 2 = after 1 January 1979) and center effect (code number), HLA antibodies before transplantation (0 = negative; 1 = 1–25%; 2 = 26–50%; 3 = 51–75%; 4 = 76–100%), number of graft (1 = first; 2 = second or third), cold ischemia time (h), and duration of pretransplant dialysis (1 = 1–12 months; 2 = 13–60 months; 3 = more than 60 months).

This series was studied using multifactorial analysis. The method developed by Cox for the study of censored data [3] was used to evaluate the effect of each parameter on the outcome of the graft. The results can be expressed as a relative risk (RR), which is the risk

Table 1. Significance (P value) of the influence of the variables investigated on graft survival, evaluated by the Cox model. NS, Lack of significant correlation at the 5% level

	Overall study group ($n = 6430$)	Preimmunized recipients ($n = 2246$)	Non-preimmunized recipients ($n = 4184$)
Donor sex	0.009	0.07	0.05
Donor age	0.003	0.002	NS
Recipient sex	NS	NS	NS
Recipient age	NS	NS	NS
Cold ischemia time	NS	NS	NS
Prexisting HLA antibodies	0.05	–	–
Dialysis duration	0.03	NS	0.02
HLA-A, -B, -DR shared antigens	0.03	0.01	NS
Pretransplant transfusions	NS	NS	NS
Retransplantation	0.003	0.007	NS
Date of graft	10^{-8}	10^{-5}	10^{-5}
Center effect	NS	0.05	NS

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Table 2. Relative risk (RR) of graft failure: overall study group ($n = 6430$)

	Baseline (RR = 1)	Other value of variable	RR
Donor sex	Female	Male	0.88
Donor age	46–50 years	6–10 years	0.81
		26–30 years	0.90
		56–60 years	1.06
		65–70 years	1.11
No. of HLA-A, -B, -DR identities (shared antigens)	0.1	2	0.94
		3.4	0.88
		5.6	0.84
Date of graft	Before 1 January 1979	After 1 January 1979	0.90
Preformed antibodies	Yes	No	0.88
No. of graft	Second	First	0.80
Duration of dialysis	1–12 months	13–60 months	0.91
		> 60 months	0.84

of graft failure for a given value of a variable compared to another value of the same variable chosen as the baseline risk of 1. A value of 2 implies twice the risk and 0.5 half the risk.

We performed statistical analysis of the total series without any exclusions. Additionally, in accordance with the results of previous studies [1, 2], the analysis was carried out separately with the series divided into two groups: recipients with preformed cytotoxic HLA antibodies and unsensitized recipients. The reason for subdividing the study population according to the existence or not of preimmunization is the nodal position of this parameter. The development of cytotoxic antibodies is not an independent event, but a direct consequence of several other parameters (number of pregnancies, transfusion of blood units, and previous grafts), and constitutes an immune state that greatly influences the graft survival rate by increasing the rejection capacity of the recipient.

Comparative analysis with eight already published studies was performed on the basis of the same parameters, with the exception of recipient sex, which was not reported in most series.

Results

When the overall study group is studied, a total of 7 out of 12 covariates appeared to influence graft survival significantly: date of transplantation ($P = 10^{-8}$), number of transplant ($P = 0.003$), age and sex of donor ($P = 0.003$ and 0.009 respectively), pretransplant sensitization to HLA antigens ($P = 0.005$) matching for HLA-A, -B, and -DR ($P = 0.03$), and the duration of pretransplant dialysis ($P = 0.03$; Table 1).

When the study group was subdivided according to pretransplant sensitization status, the matching for HLA ($P = 0.01$) appeared to have a powerful effect on graft survival among the presensitized recipients ($n = 2246$; Table 1). Interestingly, the center effect ($P = 0.05$) appears as a discriminant factor only in this category of presensitized recipients (Table 1). In the category of nonimmunized recipients, only sex of donor, date of transplant ($P = 10^{-5}$), and duration of dialysis emerge as statistically significant factors (Table 1).

The relative risks (RR) of graft failure are shown in Table 2. An example is: male sex of the donor carries an RR of 0.88 and is thus associated with a lower risk of rejection than female sex of the donor, which carries the baseline risk of 1. An RR of 0.84 was found where there are 5 or 6 shared antigens between donor and recipient, compared to the baseline 1 represented by 0 or 1 shared antigen.

Discussion

These results confirm findings we obtained in previous studies of limited series using unifactorial methods, concerning the role of HLA matching in preimmunized recipients [1, 2]. An interesting observation is that three variables (HLA matching, donor age, and retransplantation) significantly influence graft survival in the series as a

Table 3. Comparison of Cox analyses of graft failure in nine international studies of kidney transplants. +, Statistically significant; –, not significant; NT, not tested. This study, 6430 grafts (1978–1988); [4], 3653 first grafts (1978–1983); [5], 303 grafts (1983–1985); [6], 500 grafts (1964–1984); [7], 3811 grafts (1977–1082); [8], 160 grafts (1983–1984); [9], 8394 grafts (1982–1984); [10], 6632 first grafts (1978–1982); [11], 387 grafts (1970–1984)

	This study	Reference							
		[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]
Donor sex	+	–	NT	NT	NT	–	–	–	–
Donor age	+	NT	NT	NT	NT	+	NT	NT	NT
Recipient age	–	+	NT	+	+	–	+	–	+
Prexisting antibodies	+	+	NT	+	+	+	–	+	–
Duration of dialysis	+	+	NT	–	–	NT	NT	NT	–
HLA matching: A, B,	+	+	+	–	+	+	+	+	+
HLA matching: DR	+	NT	+	NT	NT	–	+	+	NT
Pretransplant transfusions	–	NT	NT	–	+	–	+	+	–
Cold ischemia time	–	–	+	–	NT	–	+	NT	–
Retransplantation	+	NT	+	NT	+	NT	+	NT	–
Year of graft	+	–	NT	+	+	NT	NT	NT	–
Center effect	–	NT	NT	NT	+	–	+	+	NT

whole and in the presensitized recipients, but not in the non-immunized patients (Table 1). However, in the case of retransplantations the absence of antibody development is rare, and the analysis should be repeated on further, enlarged series before any definitive statement on the role of regrafting can be made.

In Table 3 we compare our results with those obtained in eight different multifactorial studies of cadaver kidney transplants using comparable statistical and methodological approaches (Cox regression). All these studies, including the present work, have postulated that the effect of matching for HLA-A, -B, and -DR is linear in proportion to the degree of antigen sharing. It must be remembered that these studies [4–11] were carried out over different periods of time and with different protocols for immunosuppressive treatment. Moreover, some series include only first grafts.

There is strong evidence that the role of HLA matching is predominant, since it was observed in all studies with one exception [6]. In the studies shown in Table 3, HLA matching was assessed by comparing mismatched antigens separately locus by locus [4, 5, 8] or together [6, 10, 11]. In three studies, HLA matching was performed by comparing the number of shared antigens [this study, 7, 9]. The other pre-eminent factor influencing graft survival is the preimmunization status, which was found to be significant in the present study and in 5 others [4, 6–8, 10].

It is interesting to notice that of 11 parameters analyzed by the multifactorial method (Cox regression) in nine international studies, covering a total of 30270 renal transplants, HLA matching is the one most often observed to influence the outcome of the graft, at least in preimmunized recipients.

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