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Analysis of prognostic factors affecting renal allograft survival

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Abstract. A total of 201 consecutive cadaveric kidney transplantations were performed in 188 patients at the Chinese Great Wall Hospital, Beijing, from October 1977 to May 1990. The overall 1-, 2-, 5-, and 10-year graft survival rates were 75.5%, 64.5%, 37.0%, and 32.9%, respectively. In the last 5 years, these figures have risen to 83.7% at 1 year, 69.5% at 2 years, and 40.8% at 5 years, respectively. The 14 variables correlating to graft survival in the present study were analyzed using the log rank test for univariate analysis and the Cox proportional hazard model for multivariate analysis. The results show that immunosuppressive drug therapy, cold ischemia time, acute tubular necrosis, and infection were significant factors affecting the survival of cadaveric kidney grafts. Triple therapy with low-dose cyclosporin, as compared to conventional immunosuppressive drug therap, significantly increased the 1-year graft survival rate (90.3% vs 31.3%) but did not influence the long-term graft survival rate after 3 years. The incidence of acute tubular necrosis significantly correlated to the cold ischemia time and influenced the 1-year graft survival. Analysis showed that the lymphocytotoxic crossmatch affected graft survival after 3 years and that most late graft losses were due to chronic rejection, suggesting that histocompatibility is the strongest factor affecting long-term graft survival. A beneficial effect of pretransplant blood transfusions on long-term graft survival was seen in patients treated with conventional immunosuppressive drugs but not in cyclosporin-treated patients.

Key words: Kidney transplantation, results – Graft survival, kidney

Renal allograft survival is influenced by many factors, such as recipient age, tissue typing, pretransplant blood transfusions, and immunosuppressive drug regimen. Controversial reports on the impact of the various factors on the survival of kidney transplants have been published in recent years [6, 10, 11]. In this study, we review a series of 201 consecutive cadaveric kidney transplantations performed at the Chinese Great Wall Hospital in order to define the factors that influence graft survival in cadaveric kidney transplantation.

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Materials and methods

The present study included 201 consecutive cadaveric kidney transplantations in 188 patients performed between October 1977 and May 1990 at the Chinese Great Wall Hospital, Beijing. Twelve patients were transplanted twice and one patient received three transplants. There were 145 (77.1%) male and 43 (22.9%) female patients with an age range from 18 to 58 years (mean age 35 years). The primary renal disease was chronic glomerulonephritis in 176 cases (93.6%), chronic pyelonephritis in 6 (3.2%), polycystic nephropathy in 4 (2.1%), and purpuric nephritis in 2 (0.5%). Two different immunosuppressive drug regimens were used in this series: (1) conventional therapy: azathioprine (Aza) + prednisolone (Pred) in 46 cases, transplanted mainly before 1984 and (2) triple therapy: cyclosporin A (CyA) + Aza + Pred in 155 cases grafted after 1985. In both treatment groups, Aza was given orally in a dose of 150–200 mg on the day before operation. Postoperatively, in the conventional therapy group, Aza was given in a dose of 2.5–3.5 mg/kg per day and then gradually reduced to a maintenance dose of 1.5–2.0 mg/kg per day. Pred, in a dose of 100 mg/day, was started orally and tapered by 10 mg/day weekly, until a maintenance dose of 10 mg/day was reached.

In the triple therapy group, oral CyA in a dose of 3–6 mg/kg per day was started when an adequate urine production was established postoperatively and then tapered by 20–50 mg every 3–6 months, withdrawing it at 2 years after transplantation. Aza was administered in a dose of 1.5–2.0 mg/kg per day during the first 3–6 months and was then gradually increased by 12.5–25 mg in parallel with the tapered CyA until a maintenance dose of 2.5–3.0 mg/kg per day was reached. Pred was started in a dose of 0.5 mg/kg per day orally and tapered by 5 mg/day weekly to reach a maintenance dose of 10 mg/day. In this group, there were five cases treated with a new triple therapy: CyA, Pred, and multiglycosides of tripterygium wilfordii (GTW), which is extracted from a Chinese medicinal herb.

Rejection episodes were treated with a high dose of prednisolone or hydroprednisolone or with methylprednisolone given IV for 3–5 consecutive days. Cyclophosphamide (100–200 mg IV) and/or local irradiation of the allograft by a linear accelerator (150 rad, one to three times) was used in any severe rejection episode.

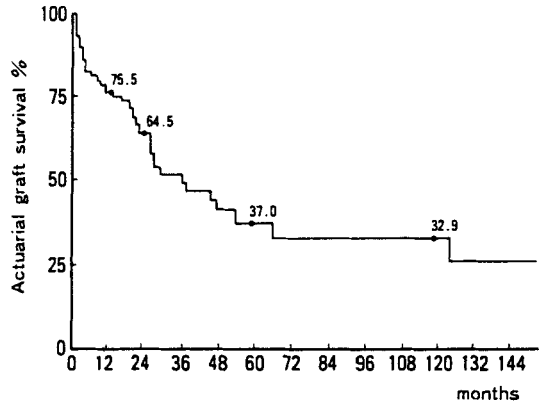

Fig. 1. Actuarial graft survival of 201 cadaveric kidney transplantations between October 1977 and May 1990

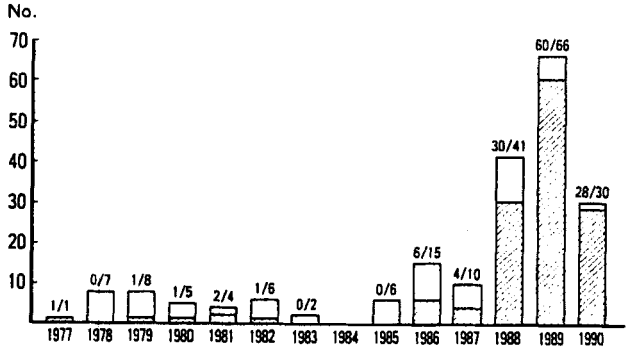

Fig. 2. Annual number of cadaveric kidney transplantations (□) and the number of functioning grafts (▨) at the Chinese Great Wall Hospital between October 1977 and May 1990

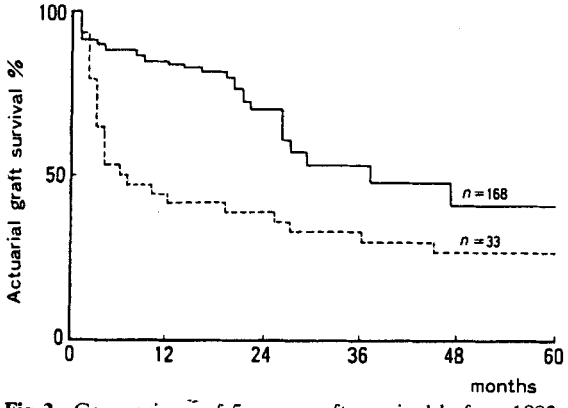

Fig. 3. Comparison of 5-year graft survival before 1983 (----) and after 1985 (——). $P < 0.001$

Actuarial graft survival rates at different points in time after transplantation were assessed by the Kaplan-Meier method according to the principle of the standard life table. The following 14 variables were studied: recipient sex and age, duration of dialysis before transplantation, pretransplant blood transfusions, ABO blood group match, lymphocytotoxic crossmatch, cold ischemia time (CIT), immunosuppressive drug regimen, acute tubular necrosis (ATN), cardiovascular disease, diabetes, infection, hepatic disease, and tuberculosis. The warm ischemia time was not included because it was much the same for all allografts. HLA matching between donor and recipient was performed in only a few cases and was, therefore, not included in the present analysis. Graft loss was defined as either the return to maintenance dialysis, graft nephrectomy, or patient death.

Statistical analysis

Univariate analysis of individual variables was performed using the log rank test. Multivariate analysis for the 14 entry variables listed above was performed using the Cox proportional hazard model. Statistical calculations were carried out using the STATA/2.0 software (Rand, USA) on a Great Wall 0520 C-H computer.

Results

Graft survival

Of the 201 kidney transplantations performed, 134 grafts (66.7%) survived for 1–152 months postoperatively and 67 (33.3%) were lost. The overall 1-, 2-, 5-, and 10-year actuarial graft survival rates were 75.5%, 64.5%, 37.0%, and 32.9%, respectively (Fig. 1). Figure 2 illustrates the number of renal transplantations and the number of functioning grafts per year since 1977. In the last 5 years, the number of transplantations performed, as well as the success rate, have increased significantly. Before 1984, the 1-, 2-, and 5-year graft survival rates were 41.2%, 38.2%, and 26.5%, respectively. After 1985 those figures increased to 83.7% at 1 year, 69.5% at 2 years, and 40.8% at 5 years (Fig. 3). The difference in graft survival rates between these two periods is statistically significant ($P < 0.0001$).

Univariate analysis

Results of univariate analysis (Table 1) show that the duration of dialysis, lymphocytotoxic crossmatch, CIT, immunosuppressive drug regimen, ATN, cardiovascular disease, infection, and hepatic disease were the main factors influencing the 1-year graft survival. The sex and age of the recipient, ABO blood group match, pretransplant blood transfusions, and tuberculosis did not seem to influence early graft survival. Lymphocytotoxic crossmatch and tuberculosis were variables influencing graft survival for more than 3 years.

As to the immunosuppressive drug regimen, Fig. 4 illustrates that triple therapy with low-dose CyA resulted in higher graft survival than conventional therapy. The difference was statistically significant at 1 year (90.3% vs 31.3%, $P < 0.0001$) but not at 3 years.

Pretransplant blood transfusions significantly improved graft survival after 3 years in conventionally treated patients ($P < 0.001$), but no significant difference was seen at any time interval in the CyA-treated patients (Fig. 5).

Multivariate analysis

In the multivariate regression analysis using the Cox proportional hazard model, all 14 variables were justly evaluated for graft survival. In the initial model (Table 2), five factors had a significant influence on graft survival: CIT, immunosuppressive drug regimen, ATN, cardiovascular disease, and infection; these same factors were also determined by the univariate analysis. The final predictor model (Table 3) gave similar results with more com-

Table 1. Univariate analysis of prognostic factors influencing cadaveric kidney allograft survival

	No.[a]	χ^2		P	
		1 year	3 years	1 year	3 year
Sex		0.1034	0.0502	0.7478	0.8227
Male	155				
Female	46				
Age (years)		0.5635	0.8427	0.9047	0.8392
< 30	64				
30–40	81				
40–50	42				
> 50	14				
Duration of dialysis		10.6741	1.2243	0.0048**	0.5422
0	15				
6 months	105				
> 6 months	81				
Pretransplant transfusions		1.2512	2.1908	0.5349	0.3344
0	49				
1000 ml	58				
> 1000 ml	94				
AB0 matching		0.4804	0.0024	0.4882	0.9612
Same	167				
Different	34				
Lymphocytotoxic crossmatch		13.5585	8.3250	0.0011**	0.0156*
Negative	174				
Positive	19				
Cold ischemia time		13.3796	0.8742	0.0012**	0.6459
12 h	122				
24 h	36				
> 24 h	43				
Immunosup pressive regimen		57.5113	0.6943	0.0000 +	0.7067
Aza + Pred	47				
CyA + Aza + Pred	154				
Acute tubular necrosis		17.6807	0.9099	0.0001***	0.6344
Yes	35				
No	158				
Cardiovascular disease		21.9362	1.2402	0.0000****	0.5379
Yes	16				
No	178				
Diabetes		1.2369	3.4831	0.5388	0.1752
Yes	5				
No	190				
Infection		19.2196	1.4229	0.0000****	0.4909
Yes	38				
No	155				
Hepatic disease		11.3192	0.7449	0.0035**	0.6891
Yes	13				
No	179				
Tuberculosis		1.0209	19.6911	0.6002	0.0001***
Yes	4				
No	194				

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$

[a] Some figures were lost in this analysis, with the result that the total number of transplantations does not always equal 201

Table 2. Multivariate analysis of prognostic factors influencing graft survival using the Cox model

	β	SE	P	RR
Sex	0.5196	0.3928	0.188	1.6813
Age	0.0277	0.0185	0.135	1.0281
Duration of dialysis	−0.0173	0.0425	0.684	0.9828
Pretransplant transfusion	−0.0002	0.0001	0.128	0.9998
AB0 matching	−0.1226	0.4096	0.765	0.8846
Lymphocytotoxic crossmatch	−0.7268	0.4453	0.104	0.4834
Cold ischemia time	0.0003	0.0001	0.029*	1.0000
Immunosuppressive regimen	−1.1455	0.3713	0.002**	0.3181
Acute tubular necrosis	1.5363	0.3365	0.000***	4.6473
Cardiovascular disease	1.0708	0.4109	0.010**	2.9176
Diabetes	0.2555	0.8001	0.750	1.2911
Infection	0.7133	0.3061	0.021*	2.0408
Hepatic disease	0.4142	0.4077	0.311	1.5131
Tuberculosis	1.5686	0.9399	0.097	4.8001

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 3. Final analysis result using the Cox model

	β	SE	P	RR
Cold ischemia time	0.0003	0.0001	0.029*	1.0003
Immunosuppressive regimen	−1.3173	0.3019	0.000**	0.2679
Acute tubular necrosis	1.0205	0.2824	0.000**	2.7746
Cardiovascular disease	0.6358	0.3410	0.064	1.8885
Infection	0.6513	0.2728	0.018*	1.9198

* $P < 0.05$, ** $P < 0.001$

Table 4. The relationship between cold ischemia time (CIT) and acute tubular necrosis (ATN)

CIT	No.	ATN	
		Yes (%)	No (%)
< 12 h	115	12 (10.4)	103 (89.6)
12–24 h	36	5 (13.9)	31 (86.1)
> 24 h	42	18 (42.9)	24 (57.1)
Total	193	35 (18.1)	158 (81.9)

$\chi^2 = 22.3208$ $P < 0.0001$

Table 5. Reasons for kidney graft loss in 67 cases

	No.	Time of graft loss post-transplantation (months)						
		0–3	4–6	7–12	13–36	37–60	61–96	97–120
Acute rejection	14	11	2		1			
Kidney rupture	4	4						
Acute tubular necrosis	4	4						
Cardiovascular disease	8	4	1		3			
Infection	10	6		1	1	2		
Hepatic disease	4	2	1	1				
Tuberculosis	1				1			
Chronic rejection	20			7	10	2	1	
Tumor	1							1
Others	1				1			
Total	67	31	4	9	17	4	1	1

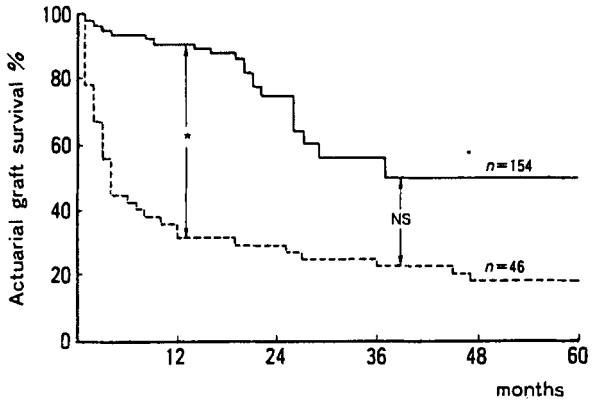

Fig. 4. Actuarial graft survival in CyA-treated (——) and conventionally treated (----) patients. * $P < 0.0001$

parable coefficients (β) and relative risks (RR) but with cardiovascular disease making a smaller contribution ($P = 0.06$) to graft survival.

Table 4 shows the relationship between CIT and ATN. It is obvious that the longer the CIT was, the higher the incidence of ATN became. When the CIT was longer than 24 h, the incidence of ATN increased to 42.9%. There was a very significant difference in ATN incidences between the CIT groups ($P < 0.0001$).

Causes of graft loss

Of the 201 kidney allografts, 67 were lost at different points in time after transplantation (Table 5). The main causes of graft loss were rejection (50.7%), infection (14.9%), cardiovascular disease (11.9%), ATN (5.9%), and hepatic disease (5.9%). Forty-four graft losses (65.2%) occurred within the 1st year after transplantation. Chronic rejection was the main cause for graft loss after more than 3 years post-transplantation.

Discussion

Renal transplantation follows a complex clinical course. Graft survival time after transplantation is influenced by various factors. In this study, overall actuarial graft survival rates at 1, 2, 5, and 10 years were 75.5%, 64.5%, 37.0%, and 32.9%, respectively. Since 1985, the 1-, 2-, and 5-year graft survival rates have increased to 83.7%, 69.5%, and 40.8%, respectively. Results of the log rank test for univariate analysis and the Cox proportional hazard model for multivariate analysis on 14 variables of the survival data in the present study suggest that the type of immunosuppressive regimen, CIT, ATN, and infection correlate significantly with cadaveric renal allograft survival.

Immunosuppressive drug therapy is necessary to prevent allograft rejection. Since the introduction of CyA by Calne et al. [3] in 1978, the 1-year cadaveric kidney allograft survival rate has increased by 10%–30%. However, due to its nephrotoxic side effect, the aim during recent years has been to use lower CyA doses in combination with other immunosuppressive drugs in many transplant centers [2, 7, 9]. The present data show that triple therapy with low doses of CyA not only increased the graft survival rate but also greatly diminished the incidence of nephrotoxicity and facilitated the clinical diagnosis of acute rejection. However, this was only true for the 1-year graft survival rate. For long-term graft survival, there was no significant difference between CyA-treated and non-CyA-treated patient groups, a finding that is in agreement with the conclusion reached by Land [5].

Due to the influence of multitudinous factors, graft loss often occurs in the early postoperative period. In this series, 46.3% of the grafts were lost within the first 3 post-transplant months and 65.7% within the 1st year. Univariate analysis of the data showed that infection, cardiovascular disease, ATN, CIT, hepatic disease, duration of dialysis, and lymphocytotoxic crossmatch were the most important factors influencing early graft survival. It corresponded generally to the analysis of reasons for graft loss. Therefore, adequate dialysis before transplantation, better selection of matched donors, shortening of the CIT, and prevention of complications, such as infections, cardiovascular and hepatic disease, seem to be very important in reducing the number of grafts lost.

For long-term graft survival, our results show that lymphocytotoxic crossmatch influenced graft survival rates at 3 years and that the main cause for graft loss in the late periods was chronic rejection. This suggests that the histocompatibility between donor and recipient is the strongest factor affecting long-term graft survival.

A beneficial effect of pretransplant blood transfusions in both conventionally and CyA-treated patients has been reported by Opelz [8], yet the transfusion effect on graft outcome seemed to diminish during the CyA era. In an analysis of 1039 renal transplantations in Scandinavia, Groth [4] was able to show that graft survival in CyA-treated patients did not correlate with pretransplant blood transfusions. Brynger et al. [1] also reported similar

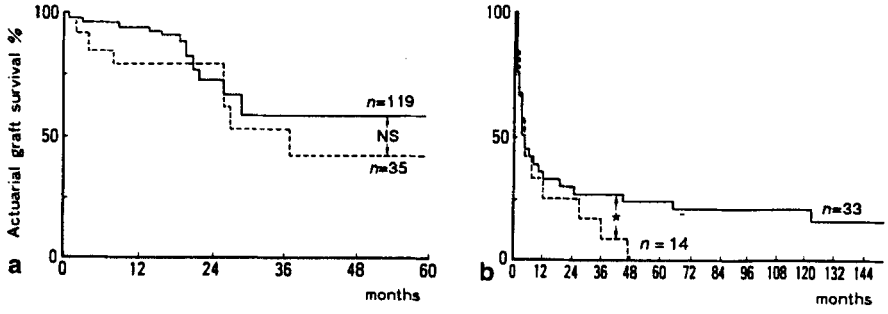

Fig. 5. Effect of pretransplant blood transfusion on graft survival in (**a**) CyA-treated and (**b**) conventionally treated patients. —— Transfusion; ---- no transfusion. * $P < 0.01$

results. In this study, we found a beneficial effect of pretransplant blood transfusions on long-term graft survival in patients treated with conventional immunosuppressive agents but not in patients treated with CyA.

Statistical analysis for the identification of prognostic factors has been a common procedure in assessing renal transplantation programs. In the current update, the prognostic factors of allograft survival determined by the log rank test and the Cox model were in agreement with the clinical observation and the natural course after transplantation. The combination of univariate analysis with multivariate analysis is a powerful tool for studying various covariates and their possible interactions at the same time. The Cox proportional hazard model, in particular, can synthesize and balance the effects of different variables on graft survival, resulting in a high-quality evaluation. The method has also been internationally verified by statistical analysis of survival data.

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