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Delayed graft function of more than six days strongly decreases long-term survival of transplanted kidneys

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Background. We reviewed 843 first cadaver kidney transplants carried out consecutively at our center to examine the effect on long-term graft survival of the duration of delayed graft function (DGF), defined as the time taken for the kidney to attain the threshold of a Cockcroft calculated creatinine clearance (cC_{Cr}) $\geq$ 10 ml/min.

Methods. Using a multivariate Cox survival analysis we evaluated the consequences of DGF on allograft survival, and then by regression analysis identified the factors contributing to the occurrence of DGF. Finally, using a Kaplan Meier analysis we compared the profiles of graft failure according to the duration of DGF.

Results. Defining DGF in terms of cC_{Cr} rather than necessity for dialysis after transplantation allowed better prediction of long-term graft loss. Indeed, patients with a Cockcroft-based DGF $>$ six days who did not require dialysis (12%) had a significantly poorer long-term graft outcome than those with a DGF $\leq$ six days. Furthermore, we showed that a DGF of six days could be taken as a cut-off point that marked a significant difference in the long-term graft survival rate ($P < 0.0001$). Surprisingly, further extension of the duration of DGF $>$ six days was not associated with further worsening of graft survival (except in DGF $>$ 30 days).

Conclusion. Our results suggest a threshold effect in the lesions that ultimately results in long-term functional deficiency. In addition, we show that the need for dialysis is not an adequate criterium for DGF in terms of long-term outcome prediction.

Delayed graft function (DGF) is the most common complication affecting kidney allografts in the immediate post-transplant period. Defined as the necessity for dialysis in the first week after surgery, delayed graft function occurs in 20% to 50% of patients receiving a first cadaver graft [1, 2]. DGF is usually the result of ischemic damage to the graft before or during harvesting, and is further aggravated by the reperfusion syndrome, a multifactorial event in which polymorphonuclear (PMN) cells play a major role [reviewed in 3]. DGF, or its experimental counterpart, can indeed be significantly attenuated by agents that inhibit PMN/endothelial cell interactions, such as anti-ICAM or anti-LFA1 monoclonal antibodies, in animals [4] and perhaps in humans, as we have recently suggested [5]. The role of DGF in graft survival is controversial. Troppman et al have suggested that DGF without rejection may have no impact on long-term graft survival [6]. However, other reports have shown that DGF and acute rejection episodes influence graft outcome independently and have additive adverse effects [7]. To review the impact of DGF on long-term graft survival and the risk factors for its occurrence, we analyzed the case histories of a large adult population (843 patients) of first cadaver kidney graft recipients, all transplanted in our department since 1986. Particular attention was paid to the clinical assessment of the magnitude of early graft dysfunction. We report here that defining DGF in terms of the Cockcroft calculated creatinine clearance (cC_{Cr}), rather than in terms of necessity for dialysis after surgery, allowed a better prediction of long-term graft survival. DGF lasting less than six days was associated with a highly significant increase ($P < 10^{-4}$) in long-term graft survival compared to that following a DGF lasting more than six days.

Key words: transplantation, graft survival, dialysis, mortality prediction.

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METHODS

We studied a population of 843 adult patients who had consecutively received a first cadaver kidney graft at our center between January 1986 and December 1995. This time interval was chosen because 1986 was the first year during which prospective data were recorded and the various parameters tested below were validated.

Patients

Table 1 shows the demographic characteristics of recipients and donors. All data concerning recipients and donors

Table 1. Demographic characteristics of the population of the 843 first kidney cadaver grafts consecutively performed between January 1986 and 1995

Mean recipient age ± SD (range)	45.7 ± 13.2 (18–73)
Mean donor age ± SD (range)	34.9 ± 14.5 (1–69)
Recipient sex	62.2% male
Donor sex	74.2% male
Mean HLA-A-B-DR mismatches ± SD	3.3 ± 1.3
Mean HLA-DR mismatches ± SD	1.0 ± 0.7
PRA (mean of historical maximum) ± SD	11.2% ± 24.2
Mean cold ischemia time ± SD (range) *hours*	34 ± 9.8 (5–60)
Mean DGF ± SD *days* (range)	7.7 ± 7.3 (1–58)
Mean number of post-graft dialyses ± SD (range)	1.4 ± 2.2 (0–16)

Table 2. Distribution of induction regimens administered immediately after transplantation; Repartition of patients according to the DGF groups

Induction regimen	Total of patients	DGF ≤ 6 days	DGF > 6 days
ATG	597 (70.8%)	332 (75.1%)	265 (66%)
MoAb (α IL2-R, α CD4, α LFA1)	147 (17.5%)	81 (18.3%)	66 (16.4%)
CsA + CS + Aza/MMF	50 (6%)	19 (4.3%)	31 (7.7%)
HLA derived peptide	25 (3.2%)	7 (1.6%)	18 (4.4%)
Others	21 (2.5%)	3 (0.7%)	4 (1%)

were stored in real time in a computerized database and were double checked by a clinical research assistant. Data were then considered valid and were included in the analysis. Fifty-three patients (6%) were not analyzed for DGF as a result of (*1*) immediate vascular thrombosis of the kidney (24 patients), (*2*) immediate recurrence of focal segmental glomerulosclerosis (2 patients) or (*3*) death (5 patients), during the first week after surgery, or of (*4*) missing data (9 patients) and (*5*) never-functioning kidney (13 patients, 1.4%).

Definitions of delayed graft function and acute rejection episodes

DGF is usually defined as the necessity for dialysis during the first week after transplantation [6, 8]. However, some patients had to be dialyzed after surgery despite an immediately functioning graft, because of water and electrolyte imbalances for instance. More frequently, in some recipients who did have DGF it was possible to avoid dialysis, because clinical and laboratory parameters remained stable after surgery despite very low graft function. For these reasons, DGF for the purposes of this study was defined as the time required for the kidney to reach a Cockcroft calculated creatinine clearance (cC_{Cr}) ≥ 10 ml/min, a level determined empirically as being the threshold for minimal graft function. The Cockcroft clearance was obtained according to the following formula:

$$[(140 - \text{age}) \times \text{weight (kg)} \times F]/[0.814 \times \text{blood creatinine (mmol/liter)}]$$

where F = 1.23 for male and 1.04 for female subjects [9, 10]. Therefore a patient who would have reached (that is, ≥) 10 ml/min of cC_{Cr} at any date after transplantation (of course, independently from dialysis day values) would be classified as not having a DGF after this date whatever the subsequent evolution of his or her graft function.

Acute rejection episodes (AR) were diagnosed on the grounds of clinical symptoms and confirmed by kidney biopsy in all cases unless technically impossible. In the latter event, rejection episodes with intention-to-treat and response to the treatment were taken into account. acute rejection episode treatment consisted of intravenous steroid boluses for five days, followed by antithymocyte globulins (ATG) in the event of steroid resistance (that is, stable or increased blood creatinine after the last bolus and absence of histological improvement).

Immunosuppressive therapy

During the study period, several protocols for the induction of immunosuppression were used. Seventy one percent (70.8%) of patients were treated from day one (D1) after surgery with a sequential therapy combining azathioprine (Aza) at 2 mg/kg/day, steroids at 1 mg/kg/day and either monoclonal antibodies (anti-CD4 [11], anti-interleukin-2 receptor [12], or anti-LFA1 [5]) or polyclonal antithymocyte globulins (ATG) as induction therapy, followed by cyclosporine A (CsA) starting at a dose of 8 mg/kg/day for maintenance therapy. Steroids were tapered off by 10 mg every five days down to a dose of 10 mg/day, and generally stopped after three months of follow-up. CsA dosage was adjusted to yield blood levels of 150 to 250 ng/ml as measured by monoclonal radioimmunoassay. Aza was monitored by assessment of white blood cell counts. Only a minority of patients (9.2%) received the triple regimen of CsA, steroids and Aza or mycophenolate mofetyl (Cellcept®) from D0 after grafting. Finally, 3.2% of patients received an HLA B2702 derived peptide [13] during the first 10 days combined with triple therapy (Table 2).

Study variables

The effect on DGF of the following pre- and post-transplantation parameters were studied: recipient and donor age and sex, HLA incompatibilities, highest "historical" level of anti-T panel reactive antibodies (PRA), cold ischemia time (CIT), requirement of post-transplantation dialysis, induction therapy with or without CsA from day 1 after surgery and number of acute rejection episodes.

Statistical methods

The Cox semiparametric model was used to evaluate the influence of pre- and post-transplantation parameters on graft survival. The logistic regression model was used to determine the prognostic factors significantly related to

Table 3. DGF as an independent risk factor for long-term graft survival: results of the Cox model analysis

Variables	Exp(coefficient) (RR)	*P* value
Number of AR episodes	1.762	0.0001
DGF	1.033	0.0001
Recipient age	1.017	0.005
Recipient sex	0.635	0.002
Cold ischemia time	1.000	0.03

Table 4. Description of the variables independently linked to DGF using logistic regression analysis

Variables	*P* (Chi^2)	Odds ratio
Donor age	0.0001	0.978
Cold ischemia time	0.0001	0.999
CsA from day 0	0.0005	0.459
Anti-T PRA	0.01	0.992

DGF using stepwise selection. For this analysis, a binary variable was created for DGF, considering the classes DGF $\leq$ six days and DGF $>$ six days. The two groups of patients obtained according to these DFG classes were then compared using a multivariate analysis of variance, considering all the prognostic factors globally. On the basis of the significant overall result, a more detailed analysis was performed using: (*1*) a Kaplan-Meier survival analysis (log-rank test) to compare the profiles of graft failure after transplantation, (*2*) Student's *t*-test for quantitative parameters (taking correction for non-homogeneous variances into account where necessary), (*3*) the Wilcoxon non-parametric test to compare ordinal parameters, and (*4*) the Chi-squared test for category parameters. *P* values less than 0.05 were assumed to indicate a statistically significant difference. Patients who died during the study were considered transplant failures.

RESULTS

General incidence of DGF

The mean duration of DGF defined as Cockcroft calculated clearance threshold of $\leq$ 10 ml/min was 7.7 $\pm$ 7.3 (range 1 to 58) days. A total of 47.5% of patients had DGF longer than one week after surgery, 14.3% longer than two weeks and only 1.7% longer than one month. The mean number of dialyses was 1 $\pm$ 2 (range 0 to 16) and 47% of patients were dialyzed at least once after transplantation. The differences resulting from the two methods of assessing DGF are set out below.

Influence of pre- and post-transplantation parameters on long-term graft survival

Based on the Cockcroft calculated clearance, the results of the Cox model analysis show that among the parameters studied, graft loss was strongly associated with DGF (RR = 1.03, P $<$ 0.0001), recipient age (RR = 1.017, $P < 0.005$), cold ischemia time duration (RR = 1, $P < 0.03$), recipient sex (RR = 0.63, $P < 0.002$) and with the occurrence of one or more acute rejection episodes (RR = 1.7, $P < 0.0001$; Table 3). Because DGF was identified by the Cox model analysis as a strong prognostic factor for long-term graft survival, we then built a logistic regression to determine which variables had independently influenced the occurrence of DGF.

Role of pre- and post-transplantation parameters on the occurrence of DGF

Age ($P < 0.0001$), cold ischemia time ($P < 0.0001$), use of CsA from day 1 after surgery ($P < 0.0005$) and highest level of anti-T PRA ($P < 0.01$) were significantly and independently correlated to DGF (Table 4).

Impact of short-time DGF on long-term graft function

We then studied the impact of the duration of DGF on graft survival. A DGF of six days was clearly identified as a significant threshold by the Kaplan Meier survival analysis (Fig. 1). DGFs lasting 1, 2, 3, 4, 5 or 6 days resulted in similar long-term survival rate (Figs. 2 and 3). In addition, there was no significant difference in graft survival between DGFs longer than six days, excepted for 10 recipients with a DGF $>$ 30 days. Patients with a DGF $\leq$ six days (group 1, $N = 442$) had 78% graft survival at 10 years as compared to 67% when DGF duration was above six days (group 2, $N = 401$; log rank test, $P < 0.0001$).

Comparison of risk factors according to duration of DGF

The two groups of patients (DGF $\leq$ or $>$ six days) were then compared using a multivariate analysis of variance, globally considering all the parameters studied. As shown in Table 5, the two populations significantly differed in terms of donor age, anti-T PRA level, cold ischemia time, number of acute rejection episodes, and use of CsA from day 0 after surgery, thus confirming the results obtained in the logistic regression analysis.

Analysis of DGF according to its definition: cC_{Cr} or requirement of dialysis after surgery

The requirement of at least a dialysis was itself a prognostic factor of graft survival (log rank test, $P < 0.01$; Fig. 4). However, 48 patients (10%) in group 1 (DGF $\leq$ six days) were found to have been dialyzed (for hyperkalemia and/or for water excess) immediately after surgery, showing that the two definitions overlap in this group of immediately functioning grafts. However, their 10 years graft survival was not different with those patients with DGF $\leq$ six days who were not dialyzed (log rank test, $P < 0.9$). Indeed, in group 2 (DGF $>$ six days), 12.5% of patients were not dialyzed despite having a Cockcroft DGF longer than six days. Interestingly, even though the duration of

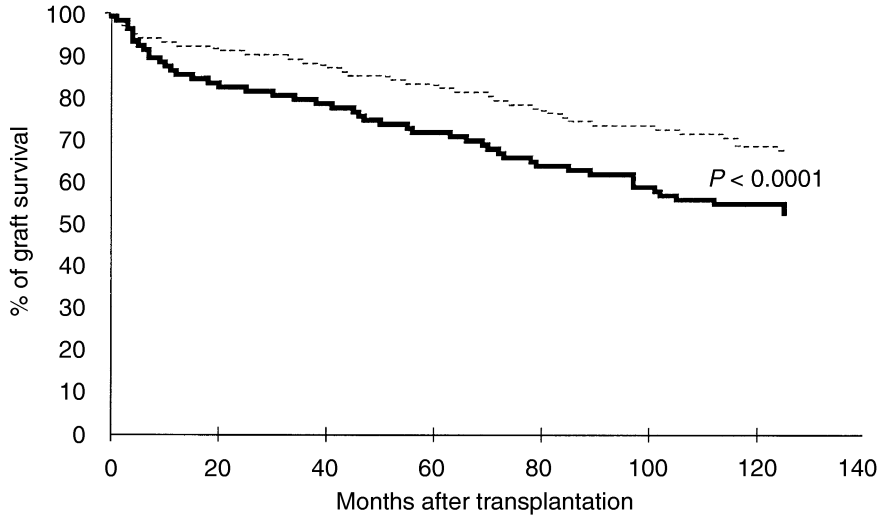

Fig. 1. Kaplan Meier analysis of graft survival according to duration of DGF when the cut-off was at six days: (- - -; $N = 442$) group 1 ≤ six days; (—; $N = 401$) group 2 > six days. The difference is highly significant ($P < 10^{-4}$).

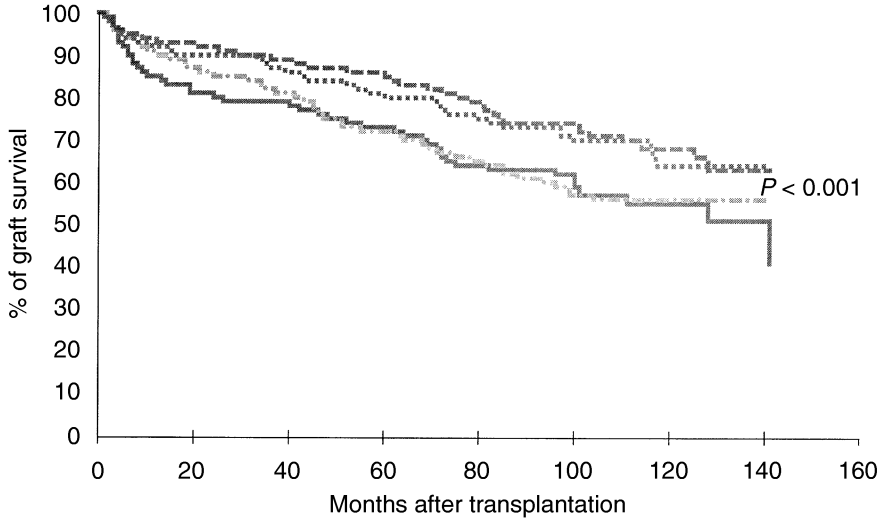

Fig. 2. Kaplan Meier analysis of graft survival according to duration of DGF: (. . . . . ; $N = 221$) DGFs lasting one day, or (– – – –; $N = 221$) 2, 3, 4, 5 and 6 days, resulted in similar long-term survival rates. There was no significant different graft survival for DGFs between 7 to 10 days (–·–·–; $N = 157$) and longer than 10 days (—; $N = 244$). However, DGF ≥ 30 days were associated with very poor outcome (not shown).

DGF (defined in terms of the cC_{Cr} threshold of 10 ml/min) in group 2 was significantly longer ($P < 10^{-5}$) in patients who required at least one dialysis (14 ± 6.5, range 7 to 58 days), than in those who needed no dialysis (10 ± 6, range 7–40 days), there was no significant difference between these two subsets of patients in graft survival rate. Moreover, even in the subset of group 2 patients not requiring dialysis, graft survival remained significantly lower than in group 1 patients ($P < 0.001$). These results suggest, therefore, that the requirement of dialyses is inadequate as a criterion by which to define DGF if the latter is to be seen in terms of its impact on long-term graft survival. Indeed, fully 12.5% of patients with DGF > six days (according to our definition) were not dialyzed, despite being at high risk of long-term graft loss (Fig. 5). Taken together, that is, DGF > six days without dialysis requirement and DGF ≤ six days with dialysis, 22.5% of the entire population did not correspond to a unique definition of DGF.

DISCUSSION

DGF is high on the list of immediate postoperative complications of kidney transplantation. Among its clinical consequences are increased morbidity and cost in the immediate post-transplantation period, with prolonged hospital stay and the necessity for substitute dialysis [14]. Furthermore, Hirata, Cecka and Terasaki showed that patients requiring dialysis because graft function was not immediate were at a significantly higher risk of death than patients with immediate graft function [15]. In our population of first cadaver graft recipients, multivariate Cox proportional hazard analysis of graft survival showed that DGF was an independent risk factor for graft loss, as were other parameters such as recipient age, one year graft function and occurrence of acute rejection episodes during follow-up. DGF itself, as shown by logistic regression, was independently linked to cold ischemia time, donor and

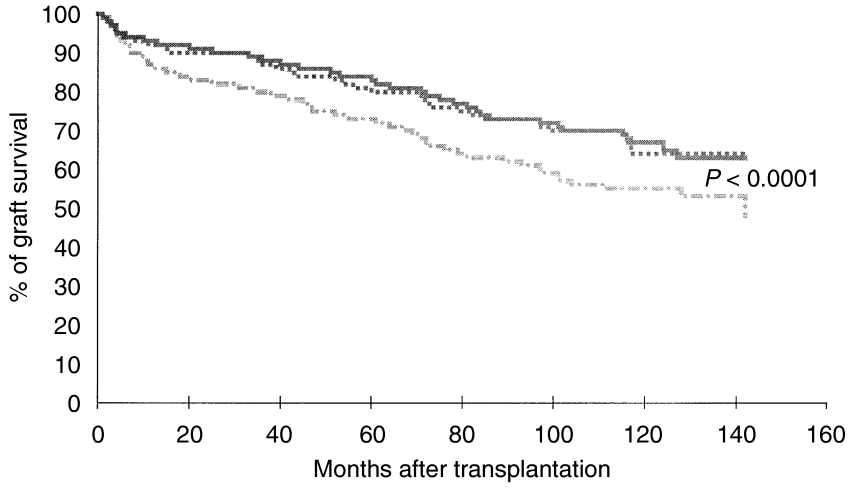

Fig. 3. Kaplan Meier analysis of graft survival comparing patients with (. . . .) an immediate graft function (that is, ≤ one day; $N = 221$) and with (– – – –; $N = 442$) DGF ≤ six days; (▬; $N = 401$): DGF > six days. There was no difference between immediate graft function and DGF ≤ six days in terms of long-term graft survival.

Table 5. Comparison of variables in group 1 (DGF ≤ 6 days) and group 2 (DGF > 6 days)

Variables	DGF ≤ 6 days ($N = 442$)	DGF > 3 days ($N = 401$)	*P* value
Donor age *years*	mean: 32 ± 14	37 ± 14	0.0001
Recipient age	mean: 45 ± 13.7	46.3 ± 13	NS
Recipient sex	62.2% male	66% male	NS
Donor sex	74.2% male	71% male	NS
% of Anti-T PRA	8% ± 21%	13% ± 26%	0.002
% of HLA-A-B-DR mismatches			
≤2	25.3%	23.2%	NS
3/4	56%	57%	NS
≥5	18.7%	19.8%	NS
% of HLA-DR mismatches			
0	22%	22.4%	NS
1	56%	55%	NS
2	22%	22.6%	NS
Cold ischemia time	mean: 31.5 ± 10 hr	36.6 ± 9 hr	0.0001
Induction with CsA from D0	10%	17.2%	0.002
Number of AR > = 1	29%	37.4%	0.01

recipient age, use of CsA from day 0 and highest level of anti-T PRA. Some studies have suggested that graft survival in patients with or without DGF is the same if no acute rejection episode occurs, but is lower in patients with both DGF and acute rejection episode when compared to patients with DGF alone [1, 16, 17]. However, these results are still controversial, other studies having reported that acute rejection episode and DGF were independent risk factors for allograft survival [2, 8, 18–20]. Our analysis shows that DGF and acute rejection episode are indeed independent risk factors for graft outcome. Nevertheless, the incidence of AR episodes was significantly higher in group 1 with prolonged DGF (≥ six days). As other authors have already pointed out [17], it is possible that the assessment of DGF and AR could be biased by the increased number of biopsies performed when DGF is prolonged, leading to overestimation of the incidence of AR based on histological changes only. The long term effect of DGF on graft survival could ultimately be explained by the subsequent reduction of the nephron mass leading to hyperfiltration, glomerular hypertension, nephrosclerosis and chronic decline of graft function [3, 21, 22]. It is thus not surprising that donor renal vascular disease (and related or pre-existing atheromatosis of the arteries) are independent variables also influencing the occurrence of DGF by indirectly adding to ischemia/reperfusion injury and contributing to the reduction in nephron mass. CsA treatment has been also shown to be associated with a reduction in glomerular filtration rate (GFR) that may result in early renal dysfunction [23]. Interestingly, although CsA administered immediately after surgery was indeed linked to an increased frequency of DGF, it did not affect long-term graft survival. However, it has been suggested that in some specific conditions such as the early (induction) CsA/OKT3 simultaneous administration, the presence of CsA could be associated with a decrease in long-term graft survival, which is an effect that could be related more to an immunological mechanism than to DGF [24]. The most surprising point that our study brought to light was the importance of the criteria used to define DGF.

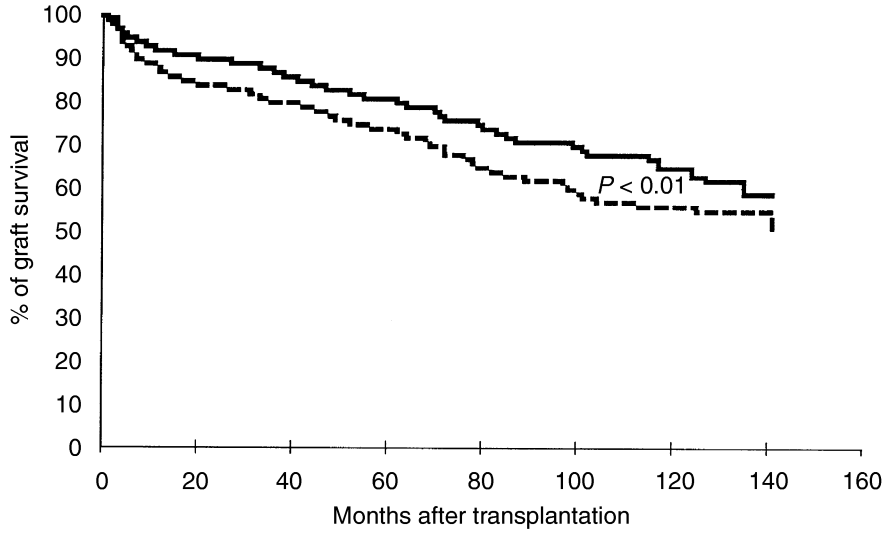

Fig. 4. Kaplan Meier graft survival analysis according to the requirement of at least one dialysis after graft: (▬; $N = 440$) dialysis = 0; (– – – –; $N = 403$) dialysis ≥ 1. Patients needed at least one dialysis after graft had a significantly lower graft survival than patients who did not require post-graft dialysis.

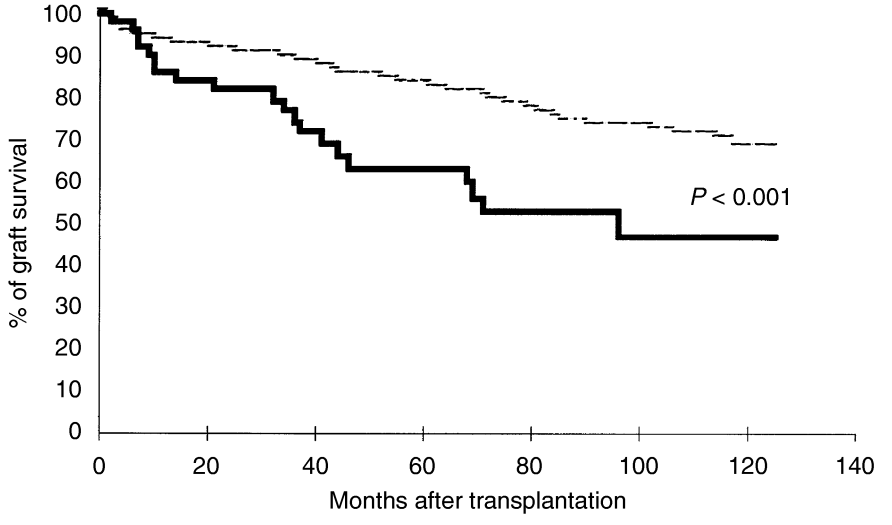

Fig. 5. Kaplan Meier graft survival analysis in patients of group 1 (DGF ≤ six days) as compared to patients of group 2 (DGF > six days) without post-graft dialysis (- - - DGF ≤ six days, $N = 442$; —— DGF > six days without post-graft dialysis, $N = 50$). The outcome of patients with low function (Cockcroft < 10 ml/min) but without dialysis is similar to that of patients who needed dialysis.

Indeed, based on a *quantitative* assessment of DGF using the Cockcroft calculated creatinine clearance, we were able to determine a cut-off point (shorter or longer than six days) by which to distinguish the population actually "at high risk" of long term graft dysfunction. In addition, we found that a significant number of patients with low function (Cockcroft < 10 ml/min) but who were not dialyzed was at the same risk as the dialyzed ones, indicating that the need for dialysis is not adequate to predict the long term effect of DGF. This also suggests that there is a threshold effect in the extent of the lesions resulting from DGF of more than six days and, whatever the duration of DGF after the first six days, no further significant consequences on graft survival ensued in the analyzed cohort except for patients with an exceptionally long DGF (>30 days). It therefore seems that DGF of less than six days is associated with reversible lesions that can undergo complete repair. Additional immunologic or toxic aggression (PRA, AR, CsA) and other factors that may further increase the effect of reperfusion injury (cold ischemia time, donor and recipient age) may lead to more pronounced graft damage with further loss of nephron mass and exhaustion of functional reserves, resulting ultimately in premature graft loss.

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REFERENCES

1. Troppmann CGK, Benedetti E, Almond S, Gruessner RWG, Najarian JS, Matas AJ: Delayed graft function, acute rejection, and outcome after cadaver reanal transplantation. *Transplantation* 59:962–968, 1995
2. Feldman HIGR, Berlin A, Roth DA, Sibolobovsky R, Kushner S, Brayman KL, Eilen Burns J, Kobrin SM, Friedman AL, Grossman A: Delayed function reduces renal allograft survival independent of acute rejection. *Nephrol Dial Transplant* 11:1306–1313, 1996
3. Land W, Messmer K: The impact of ischemia/reperfusion injury on specific and non-specific early and late chronic events after organ transplantation. *Transplant Rev* 10:108–127, 1996
4. Kelly KJ, Williams WW, Colvin RB, Bonventre JV: Antibodies to InterCellular adhesion molecule I protects the kidney against ischemic injury. *PNAS* 91:812–816, 1994
5. Hourmant M, Bedrossian J, Durand D, Lebranchu Y, Renoult E, Caudrelier P, Buffet R, Soulillou JP: A randomized multicenter trial comparing LFA1 monoclonal antibody with rabbit antithymocyte globulin as induction treatment in first kidney transplantation. *Transplantation* 62:1565–1570, 1996
6. Troppman C GK, Gillingham KJ, Gruessnerr WG, Dunn DL, Payne WD, Nayarian JS, Matas AJ: Delayed graft function in the absence of rejection has no long-term impact. *Transplantation* 61: 1331–1337, 1996
7. Ojo AO WR, Held PJ, Port FK, Schmouder RL: Delayed graft function: Risk factors and implications for renal allograft survival. *Transplantation* 633:968–974, 1997
8. Pirsch JDPR, Gange S, D'Alessandro AM, Knechtle SJ, Sollinger HW, Kalayoglu M, Belzer OF: Determinant of graft survival after renal transplantation. *Transplantation* 61:1581–1586, 1996
9. Robertshaw M, Lai NK, Swaminathan R: Restriction of creatinine clearance from plasma creatinine: Comparison of five formulae. *Br J Clin Pharmac* 28:275–280, 1989
10. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31–41, 1976
11. Dantal J, Ninin E, Hourmant M, Boeffard F, Cantarovich D, Giral M, Wijdenes J, Soulillou JP, Le Mauff B: Anti-CD4 MoAb therapy in kidney transplantation. A pilot study in early prophylaxis of rejection. *Transplantation* 62:1502–1506, 1996
12. Soulillou JP, Cantarovich D, Le Mauff B, Giral M, Hourmant M, Hirn M, Jacques Y: Randomized trial of an anti-interleukin 2 receptor monoclonal antibody (33B3.1) versus rabbit antithymocyte globulin (ATG) in prophylaxis of early rejection in human renal transplantation. *N Engl J Med* 322:1175–1182, 1990
13. Giral M, Cuturi MC, Nguyen JM, Josien R, Dantal J, Floc'h R, Buelow R, Pouletty P, Soulillou JP: Decreased cytotoxic activity of natural killer cells in kidney allograft recipients treated with human HLA-derived peptide. *Transplantation* 63:1004–1011, 1997
14. Rosenthal JT, Wilkinson A, Ettenger RB: The high cost of delayed graft function in cadaveric renal transplantation. *Transplantation* 51:1115–1117, 1991
15. Hirata CY, Cecka JM, Terasaki P: Patients death after renal transplantation–An analysis of its role in graft outcome. *Transplantation* 61:1479–1483, 1996
16. Halloran PAM, Farewell V, Ludwin D, Smith EK, Tsai SY, Bear RA, Cole EH, Fenton SS, Cattran DC: Early function as the principal correlate of graft survival. *Transplantation* 46:223–228, 1988
17. Halloran PAM, Farewell V: Factors influencing early renal fuction in cadaver kidney transplants. *Transplantation* 45:122–127, 1988
18. Nicholson MLWT, Horsburgh T, Edwards CM, Veitch PS, Bell PRF: The relative influence of delayed graft function and acute rejection on renal transplant survival. *Transplant Int* 9:415–419, 1996
19. Najarian JS, Gillingham KJ, Sutherland DER, Reinsmoen NL, Payne WD, Matas AJ: The impact of the quality of initial graft function on cadaver kidney transplants. *Transplantation* 57:812–816, 1994
20. Humar A, Johnson EM, Payne WD, Wrenshall L, Sutherland DE, Najarian JS, Gillingham KJ, Matas AJ: Effect of initial graft function on renal allograft rejection and survival. *Clin Transplant* 11:623–627, 1997
21. Brenner BM: Nephron underdosing: A programmed cause of chronic allograft failure. *Am J Kidney Dis* 21:66–72, 1993
22. Sanfilippo F, Vaughn WK, Spees EK, Lucas BA: The detrimental effects of delayed graft function in cadavre donor renal transplantation. *Transplantation* 38:643–648, 1984
23. De Mattos AM, Andoh TF, Bennett WM: Cyclosporine nephropathy: Clinical histological and functional aspects. *Transplant Rev* 10:225–235, 1996
24. Opelz G, Collaborative Transplant Study: Efficacy of rejection prophylaxis with OKT3 in renal transplantation. *Transplantation* 60: 1220–1224, 1995