Delayed graft function in renal transplantation

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CHAPTER 2

DELAYED GRAFT FUNCTION INFLUENCES RENAL FUNCTION, BUT NOT SURVIVAL

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Background In renal transplantation, the impact of delayed graft function (DGF) on prognosis is controversial. We analyzed the risk factors of DGF and its impact on graft function and prognosis.
Methods 734 cadaveric renal transplants performed between 1983 and 1997 were analyzed. DGF was diagnosed when serum creatinine levels increased, remained unchanged or decreased less than 10 % per day in three consecutive days, in the first week after transplantation. Creatinine clearances of more or less than 50 ml/min or 30 ml/min at 1 year were used as cut-off points for optimal and suboptimal graft function, respectively. The logistic regression model was used to identify independent risk factor related to DGF and renal function 1 year after transplantation. The Cox regression model was used to examine the influence of DGF on long-term graft survival.
Results Multivariate analysis revealed the following risk factors for DGF (Odds Ratio, 95% Confident Interval): recipient pre-transplantation mean arterial blood pressure of less than 100 mmHg: 2.08 (1.43 –3.03), female donor to male recipient combination: 1.55, 1.02 – 2.35, donor age of more than 50 years: 2.21, 1.49 – 3.26, cold ischemia time of more than 28 hours: 1.78, 1.19 –2.63 and peak panel reactive antibodies of more than 50 %: 1.7, 1.15 - 2.55. The incidence of DGF was one of the independent risk factors for suboptimal graft function at 1 year: 1.68, 1.14 – 2.48 together with donor age of more than 50 years: 2.39, 1.61 – 3.57, female donor gender: 1.99, 1.42 –2.78, the occurrence of acute rejection episodes 2.66, 1.87 – 3.78, peak panel reactive antibodies of more than 50 %: 1.67, 1.15 –2.47 and sharing of 1-3 vs. 4-8 CREGs 1.65, 1.09 –2.49. Moreover, DGF was one of the two independent risk factors for acute rejection episodes, but it had no independent effect on graft survival.
Conclusion Several risk factors for DGF were identified of which a low recipient pre-transplant mean arterial blood pressure, the transplantation of kidneys from female donors to male recipients and a prolonged cold ischemia time are potentially avoidable. Although DGF is one of the several risk factors of acute rejection and suboptimal function at 1 year, it is not independently associated with an increased rate of graft loss.

INTRODUCTION

In renal transplantation there is controversy regarding the impact of delayed graft function (DGF) on long-term outcome. This may relate to different criteria used to define DGF or to differences in data analysis. Most authors use the need for dialysis within the first week as the diagnostic inclusion criterion but this does not differentiate the various causes of DGF such as ischemia- reperfusion injury or early acute rejection episodes. In addition, the degree of renal damage is often not taken into consideration. In the UNOS registry, DGF defined as the need for dialysis in the first week after transplantation had a significant and independent impact on graft half-life. This effect was distinct from cold ischemia time, occurrence of acute rejection episodes, donor age and serum creatinine levels (1,2). Others found a detrimental effect of DGF, also defined as the need for dialysis in the first week, on graft survival only when it was complicated by one or more acute rejection episodes (3,4). Using the time required to reach a Cockroft renal clearance of more than 10 ml/min, DGF lasting for more than 6 days had a deleterious effect on graft survival whereas DGF of shorter duration did not influence graft survival (5). In the present paper, we analyzed the risk factors of DGF defined by stringent criteria, independent from the need of dialysis. Moreover, as graft function at 1 year is a strong surrogate marker of late graft outcome (6,7), we also studied the impact of DGF on 1-year graft function, graft loss and long-term prognosis.

MATERIALS EN METHODS

Patients

All patients who received a cadaveric renal transplant in our center between April of 1983 and December of 1996 were included in the study. Kidneys were allocated according to the matching and allocation criteria of Eurotransplant. We aimed to accept kidneys with no more than two HLA-mismatches with a priority for HLA-DR matching.

Immunosuppressive regimen

The standard immunosuppressive regimen consisted of prednisone and Cyclosporine-A [Sandimmune (CsA)]. Sixty-two patients (8,4%) did not receive CsA and were initially treated with azathioprine (Aza) in a dosage of 2 mg/kg/day. Two hundred and seven (28%) patients initially treated with CsA were randomly or on clinical grounds converted to Aza within the first six post-transplant months. CsA was administered intravenously in a dose of 3 mg/kg /day for the first 48 hours, starting at the onset of surgery. The initial oral dose of CsA was 10 mg/kg/day from day 2 onward, divided in three daily doses and subsequently tapered. Doses were adjusted according to CsA trough levels. After 6 weeks, the total dose was given as a once daily dose. In the first three months, the target 24-hour CsA trough level was between 250 and 500 μg/l. We targeted to a 24-hour trough level range after 3 months between 50 and 150 μg/l. All patients received 20 mg of prednisone starting on day one;

this dose was reduced by 2.5 mg every fortnight until a daily maintenance dose of 10 mg was reached. Rejection episodes were treated with 1 gram of methylprednisolone intravenously for 3 days or rabbit anti-thymocyte globulin for 10 days, as previously described (8).

Definitions

To exclude patients who were dialyzed for reasons other than impaired graft function, we diagnosed delayed graft function (DGF) retrospectively if the serum creatinine level increased, remained unchanged or decreased by less than 10% per day immediately after surgery during three consecutive days for more than 1 week. If a graft biopsy taken within the first post-transplant week showed rejection, it was assumed that the graft did not have DGF and it was categorized as primary function. Primary Non-Function (PNF) was defined as the absence of a decrease in the serum creatinine level that ultimately resulted in graft nephrectomy. Primary Function (PF) was defined as a decrease of the serum creatinine level of more than 10% per day over three consecutive days within the first week after surgery.
Graft loss was defined as resumption of dialysis treatments. Early graft loss was defined as graft loss within the first year after transplantation. Graft survival was censored for patient death with functioning graft. Renal Function at one year was calculated using the Cockroft-Gault Formula (9):

$$\text{Creatinine clearance} = ((140\text{-age}) \times \text{weight (kg)} \times A) / (\text{Serum creatinine } (\mu\text{mol/l}) \times 0,8)$$

In which A = 1 in males and A = 0,85 in females.

Study Design

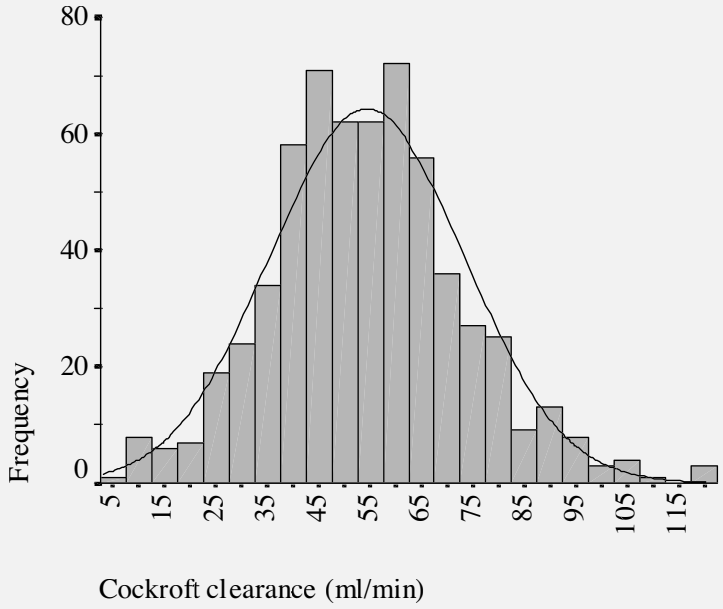
Risk factors of DGF and the impact of DGF on renal function within the first year were analyzed and compared with grafts experiencing PF. Moreover, a broad spectrum of donor-, recipient- and transplantation related variables were studied (Table 1). Acute rejection episodes were diagnosed on clinical grounds and confirmed by biopsy, unless a biopsy could not be obtained. Rejections were classified as predominantly interstitial or vascular, although most vascular rejections had variable degrees of interstitial inflammation. Mean arterial blood pressure (MAP) was calculated, using the following formula:

$$\text{MAP} = (\text{Diastolic Blood Pressure} \times 2 + \text{Systolic Blood Pressure})/ 3$$

Cross-Reactive Groups (GREG) are defined as the HLA public epitopes of the class-I MHC-antigens, based on the amino acid residue system as proposed for UNOS allocation (10). Not only the degree of mismatching, but also the effect of sharing between donor and recipient of HLA antigens was studied. The term "mismatch" was used for the number of HLA antigens that donor and recipient did not have in common, whereas the term "shares" was used for the number of corresponding HLA antigens between donor and recipient.
In our study population, the mean endogenous creatinine clearance at 1 year is approximately 50 ml/min (fig.1). Arithmetical graft half-life is 70 years for grafts with a creatinine clearance of more than 50 ml/min and 18,5 years for grafts with a 1-year creatinine clearance of less than 50 ml/min. Therefore, patients having a creatinine clearance of more or

less than 50 ml/min were categorized as optimal or suboptimal function respectively. We furthermore analyzed the data using a graft function of more or less than 30 ml/min as the dependent variable. This cut-off point represents the mean minus one standard deviation and is a more stringent outcome parameter. Arithmetical graft half-life is 53 years for grafts with a creatinine clearance of more than 30 ml/min and 7 years for grafts with a 1-year creatinine clearance of less than 30 ml/min. To predict outcome at 1 year, patients experiencing graft-loss within this year, were categorized as having suboptimal function at 1 year. To study the additional impact of DGF on outcome after the first year, we analyzed its effect in different strata of renal function after 1 year.

Fig. 1 Frequency-distribution curve of the Cockroft clearances at 1 year in 604 transplant patients.



Statistical analysis

The logistic regression model was used to determine the factors significantly related to DGF, early graft loss, acute rejection and renal function at one year in an uni-variate way. The significant predictors of each parameter of renal function were next fitted in a multivariate model. Step forward selection techniques were used to determine significant risk factors. The risk is expressed as Odds Ratio (OR) + 95% Confidence Interval (95% CI). The impact of a suboptimal Cockroft clearance at 1 year on late graft loss was studied using the Cox regression model. By using this model we were able to correct for the time of follow up to graft loss. The risk is expressed as a Relative Risk (RR) + 95% Confidence Interval (95% CI). We used the Kaplan Meier survival analysis (Log-rank test) to compare graft failure in the different strata of Cockroft clearance at 1 year. We used the SPSS software package (9.0) for all analyses.

RESULTS

Seven hundred and ninety patients were included in the study; 24 (3.0%) were not analyzed because of primary non-function and 32 (4.1%) because of missing data on DGF. Demographic data are shown in Table 1. DGF was diagnosed if the serum creatinine level increased, remained unchanged or decreased less than 10% per day immediately after surgery during three consecutive days for more than 1 week. Twenty eight (11.8%) of the patients experiencing renal dysfunction in the first week, making dialysis treatment necessary, had a biopsy proven acute rejection episode and were classified as PF.

Table 1: Characteristics at time of transplantation.

Risk Factor	**Total** (N=734)	**PF** N=551 (75.1%)	**DGF** N=183 (24.9%)
Recipient			
Age (years)	46 (13)	46 (12)	47 (14)
Gender (% female)	38	38	39
Peak panel reactive antibodies (PRAH) (%)	31 (32)	29 (31)	36 (35)
Current panel reactive antibodies (PRAC) (%)	12 (23)	11 (22)	14 (26)
MAP before transplantation (mmHg)	109 (16)	110 (17)	106 (16)
Donor			
Age (yrs.)	37 (14)	36 (14)	42 (14)
Gender (% female)	41.7	44.9	40.5
Cause of death:			
Trauma / Cardio-vascular (%)	47.5 / 52.5	49.5 / 50.5	41.8 / 58.2
Transplantation related			
Gender Mismatch			
No mismatch (%)	54	56	46
Donor male-Recipient female (%)	21	20	24
Donor female-Recipient male (%)	25	23	30
Transplant status			
First transplant (%)	83	76	79
>1 transplant (%)	17	24	21
Cold Ischemia Time (hours)	29 (7)	28 (7)	30 (7)
Warm Ischemia Time (min.)	28 (9)	28 (9)	28 (9)
Immuno-suppression at transplantation			
Aza/pred. (%)	8	9	6
Immuno-suppression at 6 months			
Aza/pred. (%)	28.1	29.6	23.5
HLA			
Mismatch	1.9 (1.1)	1.9 (1.1)	1.9 (1.2)
Shares	3.7 (1.0)	3.6 (1.0)	3.6 (1.1)

GREG			
Mismatch	1.2 (1.1)	1.2 (1.1)	1.1 (1.0)
Shares	4.5 (1.2)	4.5 (1.2)	4.5 (1.1)
Number of rejection episodes < 1 year			
1 (%)	23	23	24
2 (%)	23	20	30
>2 (%)	11	10	13
Type of rejection < 1 year			
Interstitial (%)	36	34	41
Vascular (%)	14	12	21
Clinical (%)	8	8	7
Graft Loss within 1 year (%)	13	11	19
Clearance at 1 year (ml/min)	53 (20)	55 (20)	47 (21)

Data are expressed as mean ± SD unless otherwise stated

Risk Factors for Delayed Graft Function

In an univariate analysis, donor age of more than 50 years, mean arterial blood pressure (MAP) of less than 100 mmHg, cold ischemia time (CIT) of over 28 hours, transplantation of a kidney from a female donor to a male recipient and peak panel reactive antibodies of over 50 % were associated with DGF. All these factors were subsequently entered in a multivariate analysis and remained significant (table 2).

Risk factors for sub-optimal graft function after one year

To analyze the impact of DGF and other factors on graft function after 1 year we used the creatinine clearance of more or less than 50 ml/min as the dependent variable. The univariate analysis revealed DGF as a risk factor for a sub-optimal graft function after 1 year. Other risk factors for suboptimal function included donor age of more than 50 years, female donor gender, donor cause of death (cardio-vascular versus trauma), total warm ischemia time, peak panel reactive antibodies of more than 50%, current panel reactive antibodies, sharing of less than 3 cross reactive antigens groups (CREG) and the number of acute rejection episodes within the first year. All these factors were entered in a multivariate analysis and as shown in table 3, remained significant with the exception of donor cause of death and the warm ischemia time.
As a creatinine clearance of 30 ml/min is a more stringent outcome variable for graft function, we also analyzed 30 ml/min at 1 year as the dependent variable. In the uni-variate analysis, DGF remained a significant risk factor, as were donor age of more than 50 years, female donor gender and sharing of 3 or less CREGs. The use of an initial Aza-based immunosuppressive regimen, the occurrence of acute rejection episodes and vascular rejection, were all associated with suboptimal outcome. Table 4 shows the results of the multivariate analysis. The incidence of DGF (OR 1.81; 95% CI 1.17 – 2.81), the use of kidneys from donors older than 50 years (OR 2.11; 95% CI 1.35 – 3.29), the initial use of an Aza-based immunosuppressive regimen (OR 2.53; 95% CI 1.32 – 4.83), the sharing of 3 or less CREGs (OR 2.53; 95% CI 1,30

– 3,35) and the incidence of acute rejection episodes (OR 4.00; 95% CI 2.41 – 5.65) remained significantly and independently related to a graft function of less than 30ml/min after 1 year. We were not able to analyze recipient's age, weight and gender as risk factors, because these variables were used in the Cockroft-Gault method to estimate graft function.

Table 2: Risk factors for Delayed Graft Function [a]

Variable	Odds Ratio	95% CI [b]
Donor age		
>50 years	2.21	1.49 – 3.26
Recipient MAP before transplantation		
<100 mmHg	2.08	1.43 – 3.03
Cold Ischemia Time		
>28 hours	1.78	1.19 – 2.63
Gender Mismatch		
No mismatch	1	
Donor male- Recipient female	1.09	0.69 – 1.73
Donor female- Recipient male	1.55	1.02 – 2.35
Peak Panel Reactive Antibodies		
> 50%	1.7	1.15 – 2.55

[a] Multivariate analysis [b] 95% CI: 95% Confidence Interval

Table 3: Risk factors for suboptimal function (creatinine clearance < 50-ml/min) at 1 year after transplantation, including graft-loss in the first year [a]

Variable	Odds Ratio	95% CI [b]
Delayed graft function	1.68	1.14 – 2.48
Donor age		
> 50 years	2.39	1.61 – 3.57
CREG-sharing		
1-3 shares vs. 4-8 shares	1.65	1.09 – 2.49
Number of acute rejection episodes		
>1	2.66	1.87 - 3.78
Donor Gender		
Female vs. male	1.99	1.42 – 2.78
Peak panel reactive antibodies		
>50%	1.67	1.15 – 2.47

[a] Multivariate analysis; [b] 95% CI: 95% Confidence Interval

Table 4: Risk Factors for a1-year creatinine clearance <30 ml/min including graft-loss within 1 year [a]

Variable	Odds Ratio	95% CI [b]
Delayed graft function	1.81	1.17 – 2.81
Donor Age		
> 50 years	2.11	1.35 – 3.29
Immuno-suppressive regimen at time of transplantation		
Aza/Pred. Vs. CsA/Pred.	2.53	1.32 – 4.83
CREG- sharing		
1-3 vs. 4-8 shares	2.53	1.30 – 3.35
Number of acute rejection episodes		
>1	4.00	2.41 – 5.65

[a] Multivariate analysis; [b] 95% CI: 95% Confidence Interval

Occurrence of acute rejection episodes within one year after transplantation.

DGF was associated with an increasing likelihood of acute rejection episodes in an univariate analysis as were female donor gender, HLA-DR mismatch, peak panel reactive antibodies of more than 50% and retransplant status of the recipient. HLA-sharing correlates inversely with the incidence of acute rejection episodes. Table 5 shows the independent risk factors for acute rejection in the first year, in the multi-variate analysis. The incidence of acute rejection episodes was independently associated with DGF (OR 1.61; 95% CI 1.11–2.33), an increase of HLA-DR mismatch (OR 2.36; 95% CI 1.68– 3.31) and peak panel reactive antibodies of more than 50 % (OR 1.60; 95% CI 1.12 – 2.30).

Table 5: Riskfactors for the occurrence of acute rejection episodes within 1 year [a]

Variable	Odds Ratio	95% CI [b]
Delayed Graft Function	1.61	1.11 – 2.33
Mismatch HLA DR		
>=1	2.36	1.68– 3.31
Peak Panel Reactive Antibodies		
> 50%	1.60	1.12 – 2.30

[a] Multivariate analysis; [b] 95% CI: 95% Confidence Interval

Influence of DGF on graft loss

Fig.2 shows the univariate Kaplan Meier graft survival estimates, of patients with primary function and patients with delayed graft function. There is a significantly decreased graft-survival in patients with DGF, with an arithmetical graft half-life of 12.8 years, compared to 21.7 years for patients not experiencing DGF. The main effect of DGF on graft loss seems to take place in the first year, whereas after the first year, especially after 6 years there is no dif-

ference in outcome (data not shown). The short-and long-term graft losses were analyzed separately.

In an univariate analysis, DGF was correlated with graft loss within the first year, as were female donor gender, an Aza-based immunosuppressive regimen, CIT of more than 24 hours and the number and type of rejection episodes. Sharing of HLA Class-1 antigens correlated inversely with graft loss. However, when the data were entered in a multivariate analysis neither DGF (OR 1.52; 95% CI 0.92 –2.53) nor cold ischemic time (OR 1.17; 95% CI 0.72 –1.88) remained a risk factor for graft-loss within the first year. Acute rejection episodes, especially vascular rejection (OR 9.32; 95% CI 4.77 – 18.2), female donor gender (OR 1.70; 95% CI 1.07 – 2.68), and an Aza-based immunosuppressive regimen (OR 2.07; 95% CI 1.05 – 4.09) remained independently associated with graft loss within the first year (Table 6).

Graft loss after the first year was associated in a univariate analysis with recipient age of less than 50 years and donor age of more than 50 years, the occurrence of acute rejection episodes in the first year and a cold ischemia time of more than 34 hours. Increased sharing of HLA antigens, sharing of 4-8 vs. 3 or less CREGs and higher creatinine clearance at 1 year correlated inversely with graft loss. DGF was not an independent risk factor for graft loss after the first year (OR 1.58; 95% CI 0.98 – 2.54). Table 7 shows the results of the multivariate analysis. The occurrence of acute rejection episodes (OR 1.38; 95% CI 1.11 – 1.71), recipient age of less than 50 years (OR 1.70; 95% CI 1.00 – 2.86) and a cold ischemia time of more than 34 hours (OR 1.90; 95% CI 1.20 – 3.05) were all independent risk factors for late graft loss. As soon as the Cockroft clearance after 1 year was fitted in the model as a continuous parameter, CIT and recipient age were no risk factors anymore. Therefore, graft function at 1 year was a strong predictor of late graft outcome (RR 0.96; 95% CI 0.95-0.97 per ml/min). When graft function after 1 year was divided in 4 strata of clearance of > 50 ml/min, clearance of 40-50 ml/min, clearance of 30-40 ml/min and clearance of < 30 ml/min, DGF had no additional effect on graft survival in any stratum (fig.3).

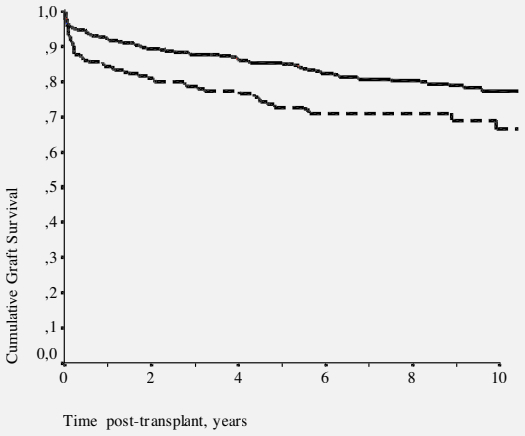


Fig. 2 Graft survival according to the incidence of DGF.

Kaplan-Meier estimates for transplants experiencing PF (solid rule; N=550); half-life: 21.7 years and experiencing DGF (dashed rule; N= 183); arithmetical half-life: 12.8 years. Log-rank test P = 0,0005.

Table 6: Risk factors for graft loss within 1 year [a]

Variable	Odds Ratio	95% CI [b]
Donor Related		
Gender of donor	1	
Female vs. Male	1.70	1.07 – 2.68
Transplantation related		
Immunosuppressive Regimen		
Aza / Pred. vs. CsA / Pred.	2.07	1.05 – 4.09
Type of rejection < 1 year		
No	1	
Interstitial	2.64	1.33 – 5.22
Vascular	9.32	4.77 – 18.2
Clinical (no biopsy)	3.61	1.45 – 8.99

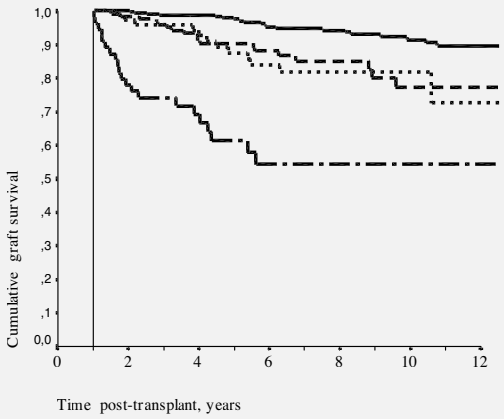
[a] Multivariate analysis; [b] 95% CI: 95% Confidence Interval

Table 7: Riskfactors of graft loss after 1 year [a]

Variable	Relative Risk	95% CI [b]
Recipient age		
<50 years	1.70	1.00– 2.86
Cold Ischemia Time		
> 34 hours	1.91	1.20 – 3.05
Occurrence of acute rejection episodes	1,38	1.11 – 1.71

[a] Multivariate analysis; [b] 95% CI: 95% Confidence Interval

Fig. 3 Graft survival according to graft function 1 year after transplantation.



Kaplan-Meier estimates for transplants experiencing a 1-year creatinine clearance of >50 ml/min (solid rule; N= 339); arithmetical half-life: 70 years; 40-50 ml/min (short dashed rule N= 135); arithmetical half-life: 30 years; 30-40 ml/min (long dashed rule; N= 79) arithmetical half-life: 25 years and < 30 ml/min. (long, short, long dashed rule; N= 56), half-life: 7 years.

DISCUSSION

In this retrospective study we examined the risk factors and prognostic significance of DGF in renal transplantation. In contrast to most other studies that examined this, we used a more stringent definition of DGF and analyzed the effect of DGF on graft function and survival independently. When DGF was diagnosed if the serum creatinine level increased, remained unchanged or decreased less than 10% per day immediately after surgery during three consecutive days for more than 1 week, 183 (23.2%) patients experienced DGF and 551 (69.7%) had primary graft function. If we defined DGF as the need of dialysis in the first week, 244 (33.9%) of the patients would have been classified as having DGF. This means that 26 % of patients that were dialyzed post-operatively required dialysis treatment for other reasons than DGF and that 10% of the patients experiencing DGF did not need dialysis treatment.

Studies on transplant outcomes have traditionally focused on patient- and graft survival as end-points without consideration of graft function. Although graft loss is the worst type of graft dysfunction, grafts with an impaired function require the most intense follow-up and therapeutic management and are economically most costly (11). For this reason graft function as a parameter in studies on outcome of kidney transplantation, should be considered.

One of the possible mechanisms of the decreased GFR in DGF seems related to tubular damage resulting from ischemia/reperfusion injury. Tubular epithelial cell degeneration, tubular cell exfoliation, interstitial edema and interstitial cellular infiltration are usually observed in biopsies in DGF (12). In the early phase, tubular obstruction by exfoliated tubular cells results in a low net. filtration pressure (13). Later, decreased sodium reabsorption results in afferent vasoconstriction and diminished glomerular filtration pressures through the tubulo-glomerular feedback mechanism (14). Another factor related to DGF is brain

death (15), but all the patients studied received a cadaveric transplant.
In the present study we found that DGF was significantly associated with the use of kidneys from older donors, particularly donors of more than 50 years of age, with the use of female donor kidneys transplanted into male recipients, a cold ischemia time of more than 28 hours, historic panel reactive antibodies of more than 50% and a recipient's pretransplant MAP of less than 100 mmHg. Other authors have also reported an increased incidence of DGF in grafts from older donors (1,16-18). In human adults, total metabolism and renal function in terms of glomerular filtration rate and renal blood flow, decrease with age. This is associated with a decrease in the number of glomeruli, a decrease in the mean glomerular volume (19) and interstitial fibrosis (20, 21). It is conceivable that such kidneys are more susceptible to additional insults such as brain death and the transplantation procedure.
The higher incidence of DGF in female donor to male recipient combinations could be explained by the absence of estrogens in the male environment. In-vitro studies have shown that the administration of estrogens leads to dilation of aortic rings (22) as has been described in-vivo in human coronary arteries (23). It is therefore conceivable that female kidneys when transplanted into a male environment experience more vasoconstriction and thus are more prone to DGF. An interesting observation is the finding that a low pretransplant blood pressure level in the recipient confers a significant risk to DGF (Table 2). A stable hemodynamic condition and possibly some degree of extra-cellular volume expansion are associated with good perfusion of the graft immediately after recirculation (24,25). Moreover, invasive hemodynamic studies have shown that a high pulmonary artery (26) or central venous pressures (27) before, during and after the transplantation surgery correlates inversely with the incidence of DGF. As ischemia-reperfusion injury results in the loss of auto-regulation (28), the beneficial effect of hypervolemia may result in an increased glomerular perfusion flow and pressure. It is unknown, whether the reduced incidence of DGF in patients treated with peritoneal dialysis, as found by some authors (29,30,30), is also based on an increased total extracellular fluid volume. A CIT of longer than 28 hours was also independently associated with an increased risk of DGF, as found by others (31-34). This is probably also the result of increased vasoconstriction (35) and renal damage as a result of ischemic injury. Peak panel reactive antibodies constitute another independent risk factors for DGF, as was noted by others (5). In studies in which DGF was defined as the need of dialysis within the first week after transplantation, DGF could theoretically have included acute rejection episodes. Although we corrected for acute rejection episodes, peak panel reactive antibodies remained independently correlated with DGF. It is thus conceivable that we missed some very early rejection episodes, as we did not biopsy every graft experiencing DGF, within 1 week. In contrast to another study (5), we found no effect of the initial immunosuppressive regimen on early graft function.
The transplanted nephron mass and subsequent graft damage determine renal function and many of the riskfactors for graft loss operate very likely through these factors (36,37). We found that the number of acute rejection episodes, donor age, donor gender, DGF and decreased sharing of CREGs are correlated independently with graft function at 1 year. Using either 50 or 30 ml/min as the cut-off point, DGF remained a risk factor for poor graft function at 1 year. Although DGF is a strong risk factor for acute rejection episodes (OR 1.63 95% CI 1.11 – 2.33), the effect of DGF on graft function was independent from the number of rejection episodes. Long term follow-up studies of native kidneys that have experienced

ATN suggested a decrease in renal function in most cases, albeit it was not associated with chronic failure (38,39). However, experimental studies in rats have shown that ischemia added to ongoing injury results in more severe tissue damage (40). Some authors found an effect of DGF on graft survival only in combination with acute rejection episodes (3,4,41). In our model, DGF had no influence on graft loss at 1 year or after the first year. Renal function at 1 year is probably a more important determinant for late graft loss, as suggested in the Collaborative Transplant Study (42). To further study the effect of DGF on late outcome, we stratified renal function after 1 year in 4 strata (fig. 3) and demonstrated that renal function at 1 year is a risk factor of late graft-loss. When the contribution of DGF on late graft loss was analyzed in these strata, there was no additional effect of DGF on outcome.

In this retrospective study we found that DGF, defined as the absence of a decline in serum creatinine of 10% or more in three consecutive days for more than 1 week after transplantation has an independent effect on graft function at one year as well as on the incidence of acute rejection episodes, but it does not seem to influence early or late graft loss. Graft survival after 1 year is mainly determined by the creatinine clearance at 1 year, which suggests that the influence of DGF on graft survival is through graft function at 1 year. We also found that the incidence of DGF is related to pretransplantation MAP, probably as a marker for the effective circulating volume. Furthermore, the use of kidneys from older donors or from female donors transplanted into male recipients increases the risk for DGF. It remains to be seen whether changing these risk factors improves the rate of DGF as well as long term function.

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