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Renal transplantation outcomes: has delayed graft function any impact?

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ABSTRACT

Background: Delayed graft function (DGF) is defined as the need for dialysis during the first post-transplantation week. Its frequency ranges from 5 to 50% in deceased-donor kidney transplants. Several studies have demonstrated an association of DGF with reduced graft survival, but other authors have not observed this relationship.

Aim: The aim of this study was to analyse risk factors for DGF after deceased-donor kidney transplantation and compare clinical outcomes of no DGF *vs.* DGF recipients.

Patients and Methods: We retrospectively reviewed the clinical data of 471 patients who received a kidney transplant from a cadaveric heart-beating donor in our unit between January 2006 and September 2009. We classified the recipients into two groups: Group 1 (without DGF) and Group 2 (with DGF).

Results: Of the 471 recipients, 117 (24.8%) had DGF. On univariate analysis, recipient age (p=0.250) and gender (p=0.665), donor gender (p=0.908), donor cause of brain death – traumatic *versus* non-traumatic – (p=0.308), prior renal transplant (p=0.076) and panel-reactive antibody levels (p=0.357) were not statistically different between the two groups. A multivariate analysis of risk factors for DGF showed donor age ≥50 years (OR: 1.67; p=0.020), recipient time on dialysis (OR:1.01; p=0.016), donor serum creatinine ≥1.5 mg/dL (OR:2.93; p=0.001), cold ischaemia time ≥20 hours – 70% *vs.* 45% (OR:1.43; p=0.024) and number of HLA haplotypes matches ≤3 (OR:1.78; p=0.002), to be the most significant risk factors. After 1-year follow up, the DGF group showed worse graft function (serum creatinine 1.66±0.7 *vs.* 1.32±0.4 mg/dL; p<0.001).

DGF was associated with a 35% relative increase in the risk of acute rejection (OR: 1.35; 95% CI 1.43-3.88), at the end of the first year.

Initial graft function significantly influenced graft survival: the 3-year death-censored graft survival rate was 97.3% for recipients without DGF and 77.5% for those with DGF (p<0.001). The 3-year patient survival between groups 1 and 2 were 94.6% and 84.5%, respectively (p=0.106).

Conclusion: Older donor age, higher donor serum creatinine level, longer time on dialysis, prolonged cold ischaemia time and inferior number of HLA haplotypes matches were associated with a greater incidence of DGF, leading to increased risk for an acute rejection episode, and reduced graft survival after 3 years. DFG was associated with multiple risk factors and contributed to worse graft outcomes. It is an independent risk factor for graft loss and an important marker of other factors that affect decisively the outcome of renal transplantation.

Key-Words:
Delayed graft function; graft survival; outcomes; renal transplantation; risk factors.

INTRODUCTION

Delayed graft function (DGF) is a well-known complication affecting the kidney allograft in the immediate posttransplantation period. It is defined as the need for dialysis during the first posttransplantation week[1,2].

The frequency of DGF ranges from 5 to 50% in deceased-donor kidney transplants[1,3]. DGF is usually the result of predominant ischaemic injury to the graft before and during procurement and is further aggravated by the reperfusion syndrome, a multifactorial event in which immunologic factors also play a role[2]. DGF has multiple causes, such as cold ischemia time, donor haemodynamics, recipient factors and transplantation procedures that produce severe ischaemia reperfusion lesion. Donor ages ‹10 and ›60 years old show negative impacts on graft function, namely, a two-fold increase in the risk for DGF[3,4]. Other donor-associated risks include predonation dehydration, oliguria, low blood pressure, and/or a medical history of classic systemic hypertension, diabetes, vascular disease, atherosclerosis and obesity[3]. The most frequent risk factor is total ischaemia time, which may be increased with prolonged vascular anastomosis in the presence of disproportion of donor/recipient vessels or donor vascular atheromatosis[5].

The typical histological finding of DGF is acute tubular necrosis (ATN) after associated with interstitial or endothelial injury. This process increases the risk for acute rejection episodes and epithelial mesenchymal transdifferentiation, increasing the risk of chronic allograft dysfunction[5,6].

If the ischaemia-reperfusion injury in DGF leads to incomplete recovery due to inability of the kidney cells to regenerate completely, then the functioning graft will have reduced survival due to reduced nephron mass[6]. Furthermore, alloimmune responses that are known to be accentuated during DGF can contribute either to acute rejection or to accelerated interstitial nephritis and tubular atrophy (IF/TA), reducing graft survival[1,2]. On the other hand, if DGF is completely reversible, then there should be no effect of DGF on longer term graft survival[7].

DGF generally leads to a more complex postoperative course for the patient. In addition, DGF is associated with prolonged hospital stay, higher transplantation costs and adverse effects on the rehabilitation of transplant recipients[8]. The deleterious effects of DGF in the immediate posttransplant period are well known. However, the long term impact of DGF is more controversial and has not been studied systematically.

In the literature, researchers disagree on the impact of DGF on long-term outcomes. Several studies have demonstrated an association of DGF with reduced graft survival rates, while others have found no such relationship[6,9-11]. Either finding may seem plausible.

The universal organ donor shortage and lengthening kidney transplant waiting lists compel us to use kidneys from expanded criteria donors (ECD). Thus, it is vital that we understand the long-term consequences of DGF and determine whether the premature graft loss that occurs in these kidneys with high risk of DGF may negate the benefits obtained from expanding the donor pool[2].

The purpose of our study was to analyse independent risk factors for DGF and its influence on graft and patient survival.

PATIENTS AND METHODS

We analysed the medical records of 471 patients who received a kidney transplant from a deceased donor between January 2006 and September 2009 in our unit. We excluded recipients of kidneys from living donors as well as patients who experienced graft loss or death during the first week posttransplantation.

We collected data on the recipient – age, gender, race, time on dialysis, aetiology of ESRD, panel reactive antibody (PRA) titre, number of HLA haplotypes matches, prior renal transplant, total hospital stay time – and on the donor – age, gender, cause of brain death, serum creatinine (SCr) and cold ischaemia time (CIT).

In posttransplantation period we classified the recipients into two groups: Group 1, without DGF and Group 2, with DGF. DFG was defined, in accordance with other studies, as the need for dialysis during the first posttransplantation week.

Posttransplantation follow-up included graft and recipient survival, episodes of acute rejection (AR) in the first year after transplantation, SCr at 1, 3, 6

and 12 months after transplantation and cause of death or graft loss, when applicable.

The diagnosis of acute rejection was based on histological criteria from graft biopsy.

The primary measure outcome was graft survival. Secondary outcomes were patient survival, occurrence of AR episodes and kidney function.

All data was computed using the SPSS software program for Windows™ (version 17.0, SPSS, Chicago, IL, USA). Numerical variables are shown as mean±standard deviation. Univariate analysis was performed using the chi-square test for categorical variables and Student *T* test for continuous ones. Logistic regression analysis was employed to indentify independent risk factors for DGF. Repeat measures method was used to analyse changes in SCr levels between the two groups. The Kaplan-Meier method was used to analyse graft and patient survival; for the differences in survival, a log-rank test was used. A *p* value less than 0.05 was considered statistically significant.

RESULTS

In our study, 117 (24.8%) of 471 renal transplant recipients displayed DGF.

Table I shows baseline characteristics of the two groups: Group 1, without DGF; Group 2, with DGF. In this cohort, mean follow-up time was 28.6±14.4 months.

We found no statistically significant differences between the two groups in terms of recipient age, gender, prior renal transplant and aetiology of ESRD. However, group comparisons showed that the DGF group include recipients with longer time on dialysis (63.7±48 *vs.* 80.7±59.7 months; *p*=0.016). DGF was associated with prolonged hospital stay (28±15 *vs.* 14±8 days; *p*=0.02).

Table I

Baseline characteristics of the transplant recipients

Recipient	No DGF (Group 1)	DGF (Group 2)	p value
Number of patients (N/%)	354 (75.2%)	117 (24.8%)	
Male Gender	219 (61.9%)	75 (64.1%)	0.665
Age (years)	48.4±13.1 (range 11-74)	54.2±18.1 (range 18-75)	0.250
Time on Dialysis (months)	**63.7±48**	**80.7±59.7**	**0.016**
Prior Renal Transplant	36 (10.2%)	19 (16.2%)	0.076
Caucasian Race (%)	95.8%	96.6%	0.06
Aetiology of ESRD			
Diabetes	23.3%	30.2%	0.768
Chronic pyelonephritis	11.3%	6.1%	0.08
ADPKD	10.2%	5.9%	0.901
Chronic glomerulonephritis	21.9%	17%	0.06
Other/Undetermined	33.3%	40.8%	0.055
Donor			
Age (Years)	46.5±16.9	51.4±19.8	0.062
Male Gender	226 (63.8%)	74 (63.2%)	0.908
Cause of Brain Death			
(Traumatic vs. Nontraumatic	42.1% / 57.9%	36.8% / 63.2%	0.308
SCr (mg/dL)	0.94±0.33	1.14±0.65	0.421
CIT (hours)	18.8±5.8	19.4±5.4	0.07
HLA matches			
A	0.60±0.58	0.51±0.62	0.47
B	0.48±0.55	0.49±0.42	0.32
DR	1.17±0.72	1.01±0.79	0.08
Total	2.37±1.25	2.01±1.06	0.904
PRA ≥ 50% (n/%)	14 / 4%	7 / 6%	0.08
Hospital stay time (days)	**14±5**	**28±15**	**0.02**

Data from 471 transplant recipients are presented as mean ± SD. DGF (Delayed Graft Function); ESRD (End-Stage Renal Disease); ADPKD (Autosomal Dominant Polycystic Kidney Disease); SCr (Serum Creatinine); CIT (Cold Ischaemia Time). The significance level is 0.05.

Regarding deceased-donor characteristics, comparison between recipients in group 1 and 2 showed no statistically significant differences for age, gender, causes of brain death and donor SCr. Considering HLA matches and the number of hypersensitised patients (defined as PRA titre higher than 50%), there were no statistically significant differences between the two groups. Differences in CIT were also not statistically significant.

Risk factors

The results of our multivariate analysis of risk factors for DGF are shown in Table II. In this cohort, the most significant risk factors for DGF were donor age ≥50 years (OR:1.76; p=0.020); recipient time on dialysis (OR:1.01; p=0.016), donor SCr ≥1.5 mg/dL (OR:2.93; p=0.001), CIT ≥20 hours (OR:1.43; p=0.024) and number of HLA haplotypes matches ≤3 (OR:1.78; p=0.002).

Table II

Risk factors for DGF; multivariate analysis

Risk Factor	95% CI for OR	p value
Donor age (years) ≥ 50 (vs.< 50)	1.67	0.020
Donor Scr (mg/dL) ≥1.5 (vs.< 1.5)	2.93	0.001
CIT (hours) ≥ 20 (vs.< 20)	1.43	0.024
Recipient time on dialysis	1.01	0.016
HLA matching ≤ 3 (vs.> 3)	1.78	0.002

Statistical method by multiple logistic regressions. CI (confidence interval); OR (Odds Ratio), SCr (Serum Creatinine), CIT (Cold Ischaemia Time). The significance level is 0.05.

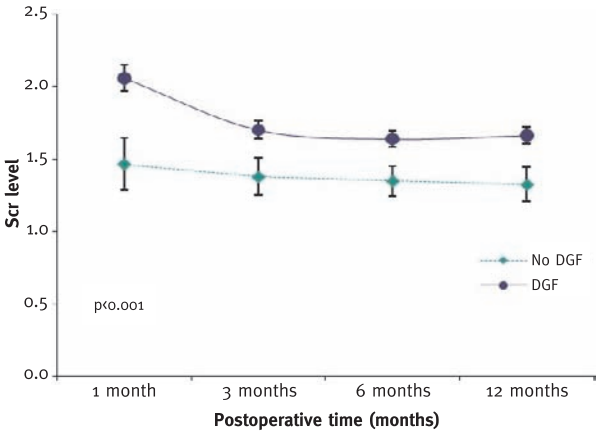

Figure 1

Comparison of mean serum creatinine level at 1, 3, 6 and 12 months post-transplantation between group 1 and group 2. DGF (Delayed Graft Function). Statistical significance between two groups was p <0.001.

Graft function

For recipients with functioning grafts, kidney function (as measured by mean SCr at 1, 3, 6 and 12 months posttransplantation) was significantly worse if DGF occurred; at 1 year past transplant SCr was 1.32 mg/dL in group 1 *vs.* 1.66 mg/dL in group 2 (p<0.001) Fig.1.

Acute rejection rate

Initial graft function influenced subsequent risk for AR. DGF was associated with a 35% relative increase in the risk of acute rejection (OR: 1.35; 95% CI 1.43-3.88), at the end of the first year. By 1 year posttransplant, AR was seen in 25% of those with DGF and in 12% of those without DGF (p=0.002).

Graft and Patient survival

Death-censored graft survival rates for the two groups are shown in Fig. 2. In our study, the 3-year death-censored graft survival rate was 97.3% and 77.5%, for groups 1 and 2 respectively. Again, we noted a statistically significant difference in graft survival between

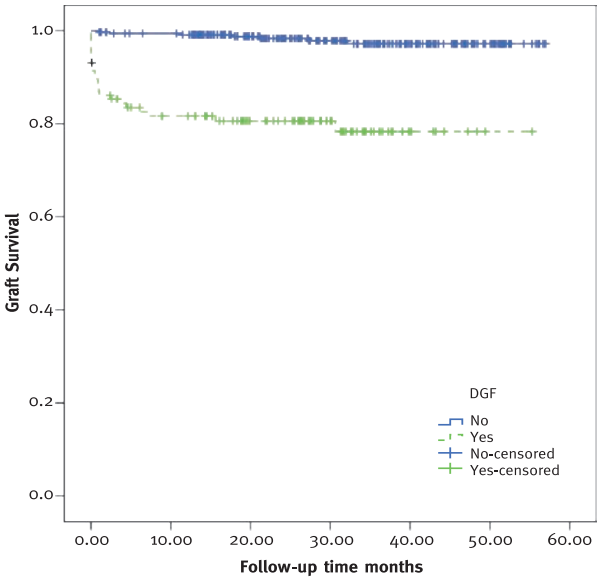

Figure 2

Graft survival in both groups; comparison of the Kaplan-Meier curves showed significant differences using log-rank test (p <0.001)

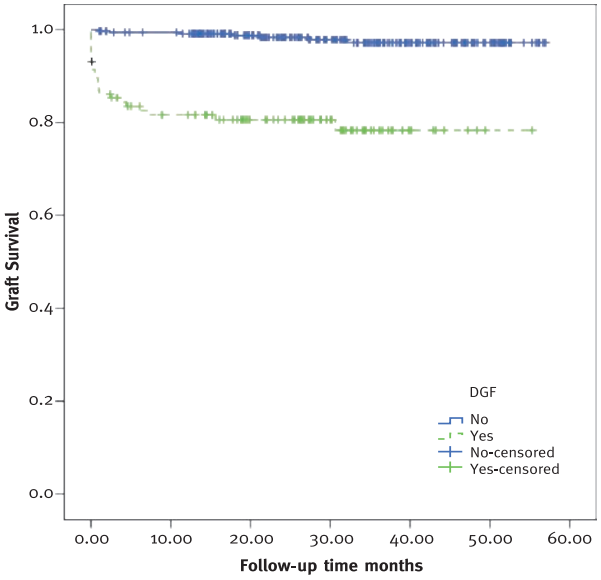

Figure 3

Patient survival in both groups; comparison of the Kaplan-Meier curves showed no significant differences using log-rank test (p=0.106)

the two groups (p<0.001), although between groups 1 and 2 there was no statistically significant difference in the 3-year patient survival rate: 94.6% and 84.5% respectively (p=0.106) (Fig. 3).

DISCUSSION

It is well recognised that graft dysfunction immediately posttransplant can vary from a subtle slowing of the expected decline in SCr to a frank oliguria requiring dialysis for days to weeks. Much has been written about the most severe form of graft dysfunction (DGF) that represents the far end of spectrum of posttransplant graft dysfunction.

Several definitions of DGF have been applied in the current literature. Many studies have defined DGF as the need for dialysis during first posttransplantation week[12]. In most series the frequency of DGF ranges from 5 to 50% in deceased-donor kidney transplants[1-3].

Regarding our study we applied the previous definition, observing DGF among 117 patients (24.8%) which was not satisfactory, but still relatively lower than in other studies[2,11].

DGF is usually the result of a multifactorial event in which immunologic factors also play a role[2]. It generally leads to a more complex postoperative clinical course for recipients. There are prolonged hospital stays leading not only to higher costs but also to an adverse effect on recipients' rehabilitation[8,13].

Several factors have been reported as risk factors for DGF including prolonged CIT, increased donor and recipient age, high PRA levels, prior renal transplant and other donor and recipient associated risks[1,3,4,9,11,14-16].

Our analysis confirmed this expectation: donor age ≥50 years, higher recipient time on dialysis and number of HLA haplotypes matches ≤3 were significant risk factors for DGF.

The importance of prolonged CIT as risk factor for DGF has already been shown. Previous reports showed an increased risk for DGF with every 6 hours of cold ischaemia[16,17].

Our study reinforces that it is critical to reduce CIT. We think that efforts to reduce CIT can also reduce the incidence of DGF, with long-term impacts on graft function and survival.

Donor age has also been demonstrated to be an independent predictive factor for DGF in many reports. In our study older donors ≥50 years were associated with a greater risk for DGF. Considering donor SCr level, many reports have demonstrated an important association with DGF[17]. We also observed this relationship.

Regarding our study, CIT ≥20 hours, older donor age ≥50 years, higher recipient time on dialysis, donor SCr ≥1.5 mg/dL and HLA matches ≤3 were strongly associated with a greater risk for DGF, causing prolonged hospital stay time. All other analysed parameters did not show association with DGF.

However, the long-term effects of DGF are more controversial. Several studies have reported negative influences on long-term graft survival, while other authors have not claimed such an association[6,9-11]. Chatziantoniou and Dussaule reported that completely reversible DGF should have no effect on long-term graft survival[7].

In our analysis, DGF had a significant impact on short- and long-term outcome posttransplant. In the short term, DGF was associated with an increased risk for AR.

Recently, a systematic review and meta-analysis documented 15 studies showing that patients who experienced DGF faced a higher risk of experiencing an episode of AR after transplantation compared to those without DGF[2]. The follow-up time for most of these studies was 1 year. Increased AR rates then negatively affect long-term results.

Additionally, we found than mean SCr at 1 year posttransplant was significantly higher in recipients with DGF, similar to what was also documented in several studies[2]. In this regard, DGF is an important clinical outcome after kidney transplantation, one that needs to be addressed by funding agencies, trialists and clinicians[2].

As expected, the occurrence of DGF was associated with prolonged hospital stay, higher incidence of AR episodes and worse graft function after 1 year follow-up.

In our study death-censored 3-year graft survival between the two groups was significantly different. Although there was no association seen between DGF and mortality, it should be mentioned that 3 years is a relatively short follow-up period when looking for an important outcome like patient survival. As DGF eventually leads to graft loss, it will cause patients to resume dialysis.

It is known that the survival of patients with a transplanted kidney is better than that of patients on dialysis, and so it is likely that, if the patients were followed for longer than 3 years, we would have seen difference in survival of patients who lost their graft. One study reported that mortality in the DGF group was already higher and related to higher infections due to aggressive immunosuppression employed to salvage the failing graft[18].

DGF is both an outcome of a renal allograft and a predictor for its subsequent course[2].

Our study emphasises and quantifies the detrimental association between DGF and important graft outcomes such as graft survival, acute rejection and renal function.

In an era of tremendous shortage of kidneys for transplantation, every effort should be made to improve the survival of the transplanted kidneys. Therefore, it is imperative that we implement strategies to reduce the incidence of DGF in an effort to improve long-term graft survival[2].

Conflict of interest statement. None declared.

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