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Original Article

Delayed Graft Function, Allograft and Patient Srvival in Kidney Transplantation

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Abstract

Introduction: Delayed Graft Function (DGF) is a common complication of renal transplants and the long-term relation between DGF and survival of patients and grafts is not well established.

Methods: This is a historical cohort study of transplanted patients in Taleghani Hospital of Shahid Beheshti University in Iran between 1994 and 2010. Patients who required dialysis during the first week after transplantation were considered to have DGF. The patients' conditions were updated to determine existing graft function, graft loss or patients' death at one year and five years post transplantation in relation to the presence or absence of DGF.

Results: DGF complicated 67/385 transplants (17.4%). Causes included acute tubular necrosis (58.2%), accelerated rejection (29.9%), transplant renal artery thrombosis (9%) and renal vein thrombosis (3%). More kidneys in the DGF group were procured from cadaveric donors (6% versus 0.9%, P = 0.02). At hospital discharge, patients with DGF had significantly higher mean creatinine level (4.4±2.8 versus 2.0±1.7; P=0.001) compared to other patients. They also had more early acute rejection episodes and more late acute rejection episodes (34.3% versus 2% and 16.4% versus 3%, respectively; P = 0.0001) compared to other patients. The proportion of functioning grafts was significantly lower in the DGF group at 1-year (53.7% versus 95.3%, P = 0.0001) and 5-years (22.4% versus 61.6%, P = 0.001) compared to patients without DGF.

Conclusion: The DGF group had a significantly higher acute rejection rate and an increased risk of graft loss at one and five years.

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Key words: Delayed Graft Function; Graft Survival; Kidney Transplant; Patient Survival

Introduction

Delayed Graft Function (DGF) is a well-known complication that can affect the kidney allograft in the immediate post-transplant period. It may be considered a form of acute kidney injury caused by ischemia reperfusion injury and/or immunological factors [1, 2] that may or may not require dialysis.

Risk factors for DGF in the recipient include male gender, black race, longer dialysis duration, high panel-reactive antibody (PRA) titer, CMV status, number of grafts received and greater degree of HLA mismatching. Donor related risk factors include use of cadaveric donors, older donor age and longer cold ischemia time [3-5]. Most of these variables affect the graft through ischemia-reperfusion injury and immunologic mechanisms. High dosage of calcineurin inhibitors (CNIs) could also prolong or worsen DGF [6].

DGF is a clinical diagnosis based on clinical, radiological, and sometimes histological findings. It increases morbidity by prolonging hospitalization and adds extra cost. It may also lead to premature graft failure. Some studies have indicated an association between DGF and reduced graft survival rates, while others have not found such a relation [7]. The frequency of DGF varies from 4-10% in living donor transplants and 5-50 % in kidneys from cadavers [2-4]. Recent data from US Renal Database System (USRDS) show a 22% incidence rate of DGF in cadaveric allografts [8].

The objective of this study was to assess the frequency of DGF among 385 adult kidney transplant recipients in our center. In addition, the effect of DGF on patients and grafts survival rates was evaluated.

Table1: Comparison of different variables between patients with and without delayed graft function

Variables	DGF	No DGF	P value
Recipients gender(male/female)	41/26	187/131	NS
Recipients age (mean ±SD)	38.31±14	33.74±13.66	NS
Duration of dialysis (mean ±SD)	29.29±25.56	15.26±16.57	NS
PRA status (+/-)	0/67	1/317	NS
Number of transplants (first/second/third)	63/4/0	307/10/1	NS
Source of transplanted organ			
Living related	10 (14.9%)	48 (15.1%)	0.017
Living unrelated	53 (79.1%)	267 (83.9%)	
Cadaveric	4 (6.0%)	3 (0.9%)	
Donor gender(male/female)	56/11	257/61	NS
Donor age (mean ±SD)	29.20±6.65	28.49±6.56	NS

DGF: Delayed Graft Function; PRA: Panel Reactivity Antibody

Methods

The aim of this retrospective study was to evaluate the effect of DGF on survival rates of grafts and patients after adult kidney transplantation. For this purpose, we reviewed the records of all patients who received kidney transplantation at the renal transplantation ward of Taleghani Hospital of Shahid Beheshti University in Iran between1994 and 2010. Collected data included age and gender of donors and recipients, type of transplant donor (cadaver, living related, living unrelated), number of previous transplants, CMV status of donors and recipients, duration of dialysis and results of PRA testing. Patients who required dialysis during the first week after transplantation were considered to have DGF. Allograft function was evaluated by measuring serum creatinine, urea, electrolytes and daily urine output. Rejection episodes were diagnosed clinically after performing color Doppler ultrasonography and renal DTPA isotope scan. The patients' conditions were regularly updated to determine existing graft function, graft loss or patients' death.

Statistical analysis was performed using SPSS (version 16) for windows. Survival rates for patients and grafts with and without DGF were calculated by the Kaplan-Meier method. Survival rates were compared by the Log-Rank test. Means and medians of quantitative variables were compared using student T-test and Mann-Whitney test respectively. Categorical variables were compared using the Chi-square test. All P-values were two-tailed and a P-value <0.05 was considered significant.

Results

The study included 385 renal transplant recipients, 228 of whom were males and 157 were females. Their mean age was 35±14 years. The mean duration of dialysis was 17±18 months (range 0-96 months). PRA was positive in one patient (0.3%). The source of transplanted kidney was a living related donor in 15% (58 patients), living unrelated donor in 83% (320 patients) and cadaveric in 2% (7 patients). This was the first transplant in 96.1% of cases (370 patients), the second transplant in 3.7% (14 patients) and the third transplant in 0.3% (one patient). From 385 donors, 313 were males and 72 were females. The donors' mean age was 29 years. Only one donor and one recipient were positive for CMV. The immunosuppressive regimen included cyclosporine and prednisolone plus either azathioprine or mycophenolate mofetil. Transplantation was performed by one surgical team.

DGF complicated 67/385 transplants (17.4%). Causes of DGF included acute tubular necrosis (58.2%), accelerated rejection (29.9%), transplant renal artery thrombosis (9%) and renal vein thrombosis (3%). Only four patients from the DGF group remained dialysis dependent. When we compared different baseline characteristics of recipients with and without DGF, the only significant difference was in the type of kidney donor. More kidneys in the DGF

Table2: Recipient status at one and five years follow-up

	Total	DGF	No DGF	P value
Status at 1-year				
Functioning graft	339 (88.1%)	36(53.7%)	303(95.3%)	0.0001
Graft loss	33 (8.6%)	26(38.8%)	7(2.2%)	
Death	10 (2.6%)	5(7.5%)	5(1.5%)	
Inconclusive data	3 (0.8%)	0(0%)	3(0.8%)	
Status at 5-year				
Functioning graft	211 (54.8%)	15(22.4%)	196(61.6%)	0.001
Graft loss	60 (15.6%)	33(49.5%)	27(8.5%)	
Death	19 (4.9%)	10(14.9%)	9(2.8%)	
Inconclusive data	95 (24.7%	9(13.4%)	86(27%)	

DGF: Delayed Graft Function

group were procured from cadaveric donors (6% versus 0.9%, P = 0.02) (Table-1). At hospital discharge, patients with DGF had significantly higher mean creatinine level (4.4±2.8 versus 2.0±1.7; P=0.001). They also had more early acute rejection episodes and more late acute rejection episodes (34.3% versus 2% and 16.4% versus 3% respectively; P = 0.0001) compared to other patients. Patient status at one and five years is shown (Table-2). Patients with DGF had significantly worse patient and graft survival rates at one and five years compared to other patients (Figures 1-2).

Discussion

Transplantation is the preferred treatment option for most patients with end stage renal disease (ESRD). It improves the patients' quality of life to a greater extent than hemodialysis and peritoneal dialysis [9]. Today, graft survival has increased with better donor selection and use of newer immunosuppressive agents. Patients with poor graft function in the immediate post-transplant period may require dialysis. The criteria for dialyzing patients in the immediate post-transplant period vary from center to center. However, using dialysis in the immediate post-transplant period as the sole criterion for the diagnosis of DGF would exclude patients with significant residual native kidney function [10].

There are many causes for DGF, such as antibody-mediated rejection, ischemic acute tubular necrosis (ATN), infarction, endothelial damage, acute calcineurin inhibitor toxicity, thrombotic microangiopathy, drug-induced interstitial nephritis and fulminant disease recurrence. In this study, DGF occurred in 17.4% of 385 recipients and ATN was the commonest cause (58.2%). This figure is higher than what was reported by Mihatsch *et al*, who stated that approximately 30% of DGF in their patients was due to ATN or ischemic injury [11]. Several animal studies have shown that DGF due to ATN could reduce graft survival due to nephron mass reduction [12]. Alloimmune responses that are known to be intensified during DGF can also contribute either to acute rejection or to accelerated interstitial nephritis and tubular atrophy, hence reducing graft survival [1]. On the other hand, if DGF is rapidly and completely reversed, there should not be any adverse effect on long-term graft survival [13]. Therefore, early diagnosis of DGF within the first few hours after surgery is crucial. Some techniques utilizing urine or serum biomarkers are able to identify DGF early [14-18]. However, these highly sensitive tests are rarely available at hospital wards. Currently, there is no effective treatment for DGF resulting from ATN. Agents effective for treatment of DGF in animal experiments have been disappointing in clinical setting [19].

DGF predisposes the graft to both acute and chronic rejection [7]. Sri *et al* estimated that DGF is associated with a 38% increased risk of acute rejection in the first year [20]. In the present study we showed that DGF was associated with a higher risk of acute rejection in the first year. Several studies have shown that patients with DGF are at increased risk for graft loss at one, three, and five years compared to patients without DGF [7, 21-23], but

Figure 1: Kaplan Meier patients survival curves for recipients with and without delayed graft function (P = 0.0001)

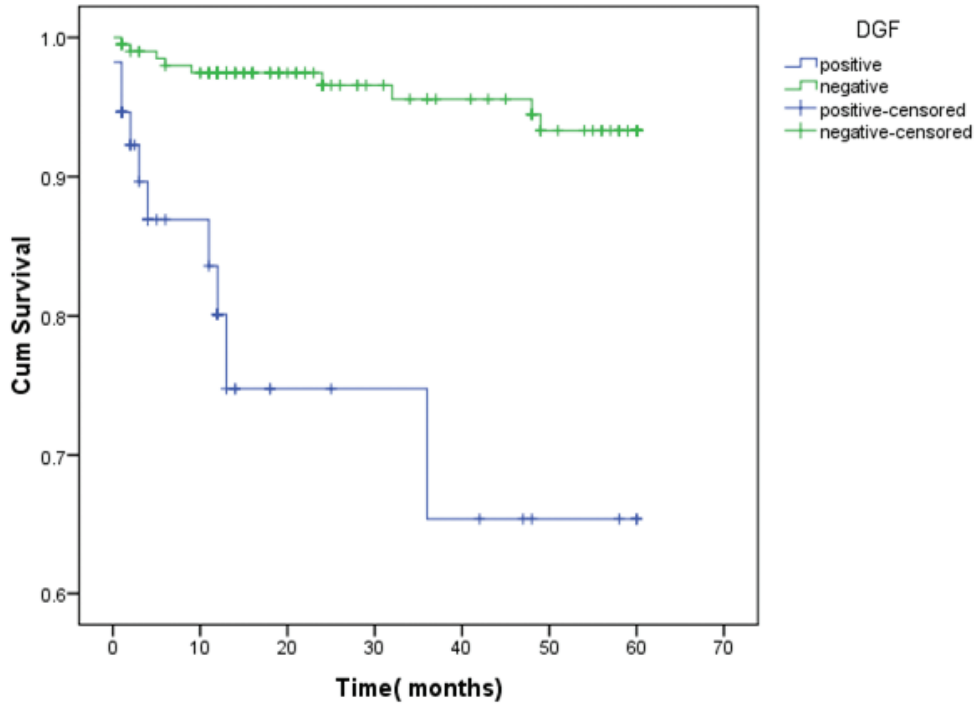
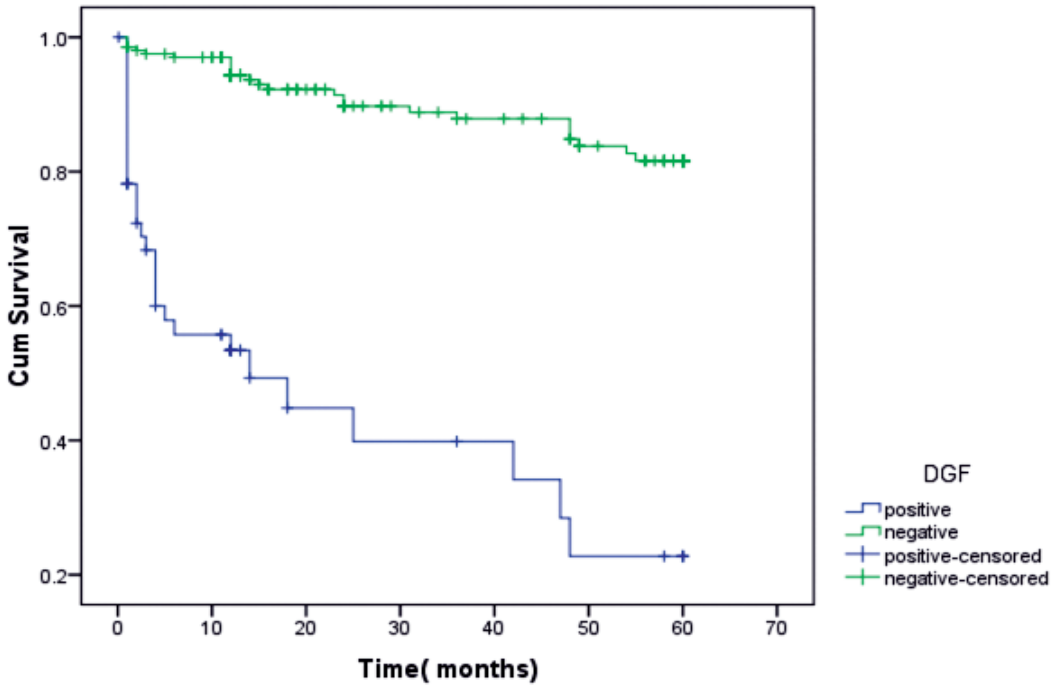


Figure 2: Kaplan Meier graft survival curves for recipients with and without delayed graft function (uncensored for patient death; P = 0.0001)



not with mortality [7, 20]. Nicholson *et al* found that DGF was a significantly more powerful predictive factor for poor graft survival (P = 0.001) than acute rejection occurring in the first 90 days after transplant [24].

Conclusion

In the current study, DGF occurred in 17.4% of 385 kidney transplant recipients and ATN was the commonest etiology. Patients with DGF had a significantly higher acute rejection rates and significantly worse graft and patient survival.

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