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Original Article

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Risk Factors of Delayed Graft Function in Transplantation of Mate Kidneys

Mehmet Ası Oktan[1], Cihan Heybeli[1], Zekai Serhan Derici[2], Mehtat Ünlü[3], Hayri Üstün Arda[1], Özcan Uzun[1], Serkan Yıldız[1], Caner Çavdar[1], Aykut Sifil[1], Ali Çelik[1]

[1]Division of Nephrology, Department of Internal Medicine, Dokuz Eylül University School of Medicine, İzmir, Turkey
[2]Department of General Surgery, Dokuz Eylül University School of Medicine, İzmir, Turkey
[3]Department of Pathology, Dokuz Eylül University School of Medicine, İzmir, Turkey

Abstract

Objective: The goal of this study was to identify risk factors among donor characteristics that affect delayed graft function (DGF) in paired kidney transplants.
Materials and Methods: A retrospective analysis of 35 paired kidney transplants, which were performed between 1993 and 2017 was conducted. Risk factors for DGF were determined using logistic regression analysis.
Results: In univariate analysis, cold ischemia time, donor age, anti-timocyte globulin use, donor serum creatinine, and DGF in the mate kidney were significantly associated with DGF development. In the multivariate regression model, cold ischemia time (OR 1.21; 95% 1.02-1.44, p=0.029) and DGF in the mate kidney (OR 13.65, 95% 3.42-54.42, p<0.001) were independent predictors of DGF in the recipient. In patients with DGF, renal functions are negatively affected, calcineurin toxicity development is facilitated, and allograft loss is increased.
Conclusion: There is a significant degree of relationship between pairs of kidneys transplanted from the same donor for the occurence of DGF. In patients with allograft dysfunction, assessment of the function of the mate kidney and comparison with that of the recipient is essential.
Keywords: Cold ischemia time, delayed graft function, renal transplantation

Corresponding Author: Mehmet Ası Oktan ✉ mehmetasioktan@hotmail.com
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INTRODUCTION

In 2017, there were approximately 97,000 patients registered on the United Network for the Organ Sharing (UNOS) kidney transplant waiting list in the United States (1). According to the 2019 data of the Turkey Ministry of Health (TDIS), approximately 22,500 patients await kidney transplant (2). Unfortunately, approximately 5% of patients die each year awaiting organs (3). Owing to the huge shortage of organ donation, it is important to improve graft outcomes and prolong patient survival.

The most common complication of kidney transplantation is allograft dysfunction. Delayed graft function (DGF) refers to the need for dialysis during the first week after kidney transplantation. Some authors define DGF as the development of acute renal failure after kidney transplantation. The presence of DGF has a major adverse impact upon both short- and long-term allograft survival. In a study of 518 patients from the United Kingdom, multivariate analysis found that DGF was the principal factor underlying kidney survival at one year; in comparison, acute rejection, HLA matching, degree of sensitization, and retransplantation did not significantly affect short term survival (4). As a result of a meta-analysis performed by Yarlagadda et al. (5), it was stated that for prevention and treatment of DGF, clinicians should be aggressive regarding both short- and long-term renal transplant outcomes.

DGF can occur in up to 30% of deceased donor recipients (6). Multiple factors are known to contribute to the occurrence of DGF. Recipient-donor related and perioperative factors include increased donor age, female kidneys transplanted into male recipients, donation after

cardiac death, prolonged cold ischemia time, and high sensitization of the recipient (7-8).

In this study, we aimed to investigate the factors that contribute to DGF. Moreover, concordance of outcomes of kidney pairs and graft survival were evaluated in patients with DGF.

MATERIALS AND METHODS

Patients and Study Design

A retrospective cohort analysis of deceased donor kidney transplants in our clinic between 1993 and 2017 was performed. During this period (1992-2018), a total of 422 kidney transplants were performed, 191 of which were cadaveric and 231 of them were from living donors. Of the 191 transplantations, 70 of them were mate kidney transplants. We excluded living donor recipients and recipients of en bloc kidney transplants. We included only paired deceased allografts from 35 donors into 70 recipients. The outcomes of these transplantations were analyzed for donor risk factors that affect DGF and concordance of outcomes of kidney pairs. The study protocol was approved by Dokuz Eylül University Local Research Ethics Committee (February 02, 2019; 2019-04/31).

Data and Definitions of Outcomes

Data at the time of transplant and during follow-up were obtained from the hospital database and the archived records. DGF was defined as a less than 50% reduction in serum creatinine levels within 48 hours after transplantation and the need for dialysis in the first week of posttransplant. There was no difference in patient selection, surgical technique, and follow-up principles for years. Renal biopsy was performed according to clinical necessity. In patients who developed DGF, renal biopsy was performed for the differentiation of acute rejection if the graft functions had not recovered. Our clinic has no protocol biopsy practice. The diagnosis of acute rejection and chronic allograft injury was based on the current Banff classification. Calcineurin inhibitor toxicity was defined based on clinical clues with appropriate histopathological examinations of the kidney allograft biopsy specimen.

Induction and Maintenance Drug Regimen

Induction therapy was provided to all cadaveric kidney recipients according to the transplantation protocol of our clinic. All kidney recipients received mycophenolic acid, calcineurin inhibitor, and prednisolone as maintenance treatment after induction with anti-thymocyte globulin (ATG), lymphoglobin, or basiliximab. The type of induction immunosuppressive agent was determined by clinicians. Calcineurin inhibitor was initiated after sufficient diuresis and recovery of graft function (serum creatinine value <3mg/dL) in all kidney recipients.

Statistical Analysis

Demographic variables were compared using chi squared test. Univariate and multivariate analyses were used to analyze the data. Logistic regression analysis was used to estimate an adjusted odds ratio for correlation of the occurrence of DGF. Statistical analysis was performed using IBM Statistical Package for the Social Sciences 22.0 version (IBM SPSS Corp.; Armonk, NY, USA). A p-value of 0.05 was considered to be statistically significant.

RESULTS

Patient Characteristics

Recipients

The mean age of the recipients was 40.5±13.5 years and 57.1% were men. Hemodialysis was performed as the renal replacement therapy prior to transplantation of recipients, at a rate of 67.1%. The mean duration of dialysis was 49.4 months.

Donors

The mean donor age was 37.3±15.7 and 34.3% of donors were men. Intracranial hemorrhage resulted in more than half of the donor deaths. There were no donations after cardiac death. Half of the recipients had DGF.

Donor age, donor serum creatinine, and cold ischemia time were higher in patients with DGF than those in patients without DGF. The mean follow-up time was 117.3±68.1 months in all recipients. The baseline and follow-up characteristics of all recipients and a comparative analysis between patient groups with or without DGF are shown in Table 1.

Graft Function

Serum creatinine at hospital discharge was higher in patients with DGF. Although renal function improved over time in patients with DGF, serum creatinine levels were higher during follow-up (Figure 1). Furthermore, chronic allograft injury, allograft loss, and mortality were more frequently observed in patients with DGF.

Chronic allograft injury was significantly lower in patients with at least one Class 2 (DR/DQ) HLA compliance (24.5% vs 53.8% p: 0.049). Biopsy-proven calcineurin toxicity was significantly higher in patients with DGF.

Main Points

- Cold ischemia time and presence of DGF in the mate kidney are independent risk factors for developing DGF in a deceased kidney transplant recipient.
- In patients with allograft dysfunction, assessment and comparison of the function of the mate kidney is essential, it can provide precious clues in improving allograft dysfunction.
- Reducing DGF will increase organ and patient survival so provide positive results for organ shortage.

Table 1. The baseline and in the follow-up characteristics of all recipients and a comparative analysis between patient groups with or without DGF

Variables	All patients (n=70)	DGF positive (n=35)	DGF negative (n=35)	p
Recipient age, mean±SD	40.5±13.5	39.8±13.2	41.2±14	0.581
Male recipient, n (%)	40 (57.1)	21 (60)	19 (54.2)	0.629
Dialysis modality				0.799
HD, n (%)	47 (67.1)	24 (68.5)	23 (65.7)	
PD, n (%)	23 (32.9)	11 (31.5)	12 (34.3)	
Dialysis vintage, months, mean±SD	49.4±68.3	59.9±92.6	39±26.3	0.883
Donor age, years, mean±SD	37.3±15.7	44.2±14.2	30.5±14.4	<0.001
Male donor, n (%)	24 (34.3)	13 (37.1)	11 (31.4)	0.615
Donor death due to cerebrovascular event, n (%)	40 (57.1)	23 (65.7)	17 (48.5)	0.147
Donor serum creatinine, mg/dl, mean±SD	0.97±0.48	1.09±0.54	0.83±0.37	0.047
Cold ischemia time, hour, mean±SD	15.8±5.1	17.7±5.58	13.9±3.78	0.003
HLA mismatches, n, mean±SD	3.5±1.2	3.5±1.3	3.5±1.0	0.666
PRA, n (%)				N/A
<%10	70 (100)	35 (100)	35 (100)	
>%10	0 (0)	0 (0)	0 (0)	
Serum creatinine at hospital discharge, mg/dL, mean±SD	1.53±0.66	1.72±0.8	1.34±0.43	0.032
Serum creatinine at last visit, mg/dL, mean±SD	2.51±2.14	2.91±2.4	2.14±1.83	0.217
Primary non-functional graft, n (%)	1 (1.4)	0	1	1
Acute rejection, n (%)	16 (22.9)	8 (22.8)	8 (22.8)	1
Chronic allograft injury, n (%)	21 (30)	14 (40)	7 (20)	0.068
Allograft loss, n (%)	20 (28.6)	13 (37.1)	7 (20)	0.112
ATG for induction, n (%)	30 (42.8)	20 (57.1)	10 (28.5)	0.016
CNI based treatment, n (%)	65 (92.8)	30 (85.7)	35 (100)	0.054
mTOR inh.-based treatment, n (%)	4 (5.7)	4 (11.4)	0 (0)	0.114
Modification during maintenance, n (%)	31 (44.2)	18 (51.4)	13 (37.1)	0.229
CNI toxicity, n (%)	15 (21.4)	12 (34.2)	3 (8.5)	0.009
MPA side effect, n (%)	46 (65.7)	25 (71.4)	21 (60)	0.314
Opportunistic infection, n (%)	20 (28.5)	12 (34.2)	3 (8.5)	0.290
Mortality during follow-up, n (%)	15 (21.4)	9 (25.7)	6 (17.1)	0.382
Follow-up time, months, mean±SD	117.3±68.1	100±65.1	134.9±67.4	0.036

CNI: calcineurin inhibitor; MPA: mycophenolic acid; HLA: human leukocyte antigen; ATG: anti-timocyte globülin; N/A: not applicable; SD: standart deviation; DGF: delayed graft function

Delayed Graft Function

DGF occured in 50% of kidney transplant recipients. Within pairs of recipients from the same donor, the odds ratio for DGF occurrence if the contralateral kidney had DGF was 13.65 (p<0.001). Both pairs developed DGF in 14.2% of the donor kidneys.

When DGF is observed in both mate kidneys, the risk factors for DGF are more evident. The higher donor age and the longer the cold ischemia period, increases the risk of developing DGF in both kidneys from cadaver.

When we evaluated 10 mate kidneys, each with DGF in one mate kidney, in terms of recipients and donor age, dialysis vintage, HLA compliance, and cold ischemia time, no statistical difference was found between the patients who developed DGF and those who did not. In these 10 patients, the duration of cold ischemia (14.2-hour vs 14.4-hour, p=0.747) was slightly longer

Table 2. Clinical characteristics of kidney pairs based on delayed graft function

Variables	No DGF (n=30)	DGF in one kidney (n=10)	DGF in both kidney (n=30)	p
Recipient age, years, mean±SD	40.9±14.5	36.6±12.5	41.5±13	0.588
Male recipient, n (%)	17 (56.6)	7 (63.6)	16 (55.1)	0.888
Dialysis modality, n (%)				0.521
HD	19 (63.3)	9 (81.8)	19 (65.5)	
PD	11 (36.6)	2 (18.2)	10 (34.4)	
Donor age, years, mean±SD	29.8±14.1	35.6±15.4	45.9±13.6	0.001
Male donor, n (%)	8 (26.6)	6 (54.4)	10 (34.4)	0.249
Donor death due to cerebrovascular event, n (%)	15 (50)	4 (36.3)	21 (72.4)	0.070
Donor serum creatinine, mg/dL, mean±SD	0.83±0.39	0.89±0.32	1.13±0.58	0.119
Cold ischemia time, hour, mean±SD	13.86±3.71	14.98±4.9	18.2±5.6	0.008
HLA mismatches, n, mean±SD	3.3±1.1	4.1±0.5	3.4±1.3	0.128
Serum creatinine at hospital discharge, mg/dL, mean±SD	1.37±0.43	1.17±0.39	1.83±0.82	0.016
Serum creatinine at last visit, mg/dL, mean±SD	2.04±1.76	2.88±2	2.92±2.53	0.467
Acute rejection, n (%)	7 (23.3)	2 (18.1)	7 (24.1)	0.920
Chronic allograft injury, n (%)	5 (16.6)	4 (36.3)	12 (41.3)	0.103
Allograft loss, n (%)	4 (13.3)	5 (45.4)	11 (37.9)	0.045
ATG for induction, n (%)	8 (26.6)	3 (27.2)	19 (65.5)	0.006
CNI toxicity, n (%)	2 (6.6)	3 (27.2)	10 (34.4)	0.03
Mortality during follow-up n (%)	5 (16.6)	3 (27.2)	7 (24.1)	0.686

DGF: delayed graft function; HLA: human leukocyte antigen; ATG: anti-timocyte globülin; CNI: calcineurin inhibitor

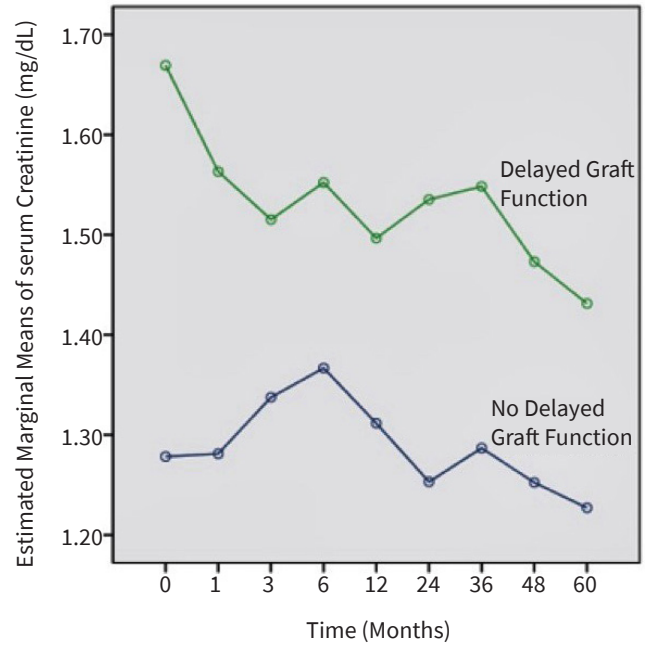

Figure 1. Estimated marginal means of serume creatinine in patients with delayed graft function or not.

in patients with DGF, but it was not found be statistically significant with respect to DGF.

We could not find any impact of performing left or right kidney and first or second transplantation on DGF. Serum creatinine levels at hospital discharge were higher in patients with DGF in both kidneys (Table 2).

In the multivariate analysis, every 10-year increase in donor age increased the risk of DGF by 44% and every one-hour increase in cold ischemia time increased the risk of DGF development by 21% (Table 3). In the Pearson's Chi-squared test, when DGF was observed in one patient, the risk of developing DGF in the mate kidney was 82.8% ($p<0.001$). The same concordance was not observed in terms of acute rejection and allograft loss.

DISCUSSION

The main finding of our study was that cold ischemia time and presence of DGF in the mate kidney are independent risk factors for developing DGF in a deceased kidney transplant recipient. The study shows that there is a strong relationship for development of DGF between the kidney pairs. The odds of DGF occurring in a kidney transplant is 13.65% when the mate kidney de-

Table 3. Univariate and multivariate analysis of variables related to delayed graft function

Variables	Univariate (OR 95% CI)	p	Multivariate (OR 95% CI)	p
Cold ischemia time, per hour	1.19 (1.06-1.33)	0.003	1.21 (1.02-1.44)	0.029
Donor age, per decade	1.92 (1.23-2.68)	0.001	1.44 (0.82-2.51)	0.204
Anti-timocyte globulin	3.33 (1.24-9.0)	0.017	1.19 (0.26-5.46)	0.828
Donor serum creatinine	3.56 (1.04-12.19)	0.043	1.01 (0.17-5.95)	0.992
DGF in the mate kidney	29.0 (7.97-105.55)	<0.001	13.65 (3.42-54.42)	<0.001

DGF: delayed graft function

velops DGF. Although this relationship was revealed in previous studies (9-11), such a strong correlation has been emphasized for the first time. We believe that this high ratio is due to the high rate of DGF in our recipients.

Traynor et al. (11) reported that DGF occurred in 11% of deceased kidney transplant recipients. Furthermore, the odds ratio for DGF occurring if the contralateral kidney had DGF was 5.99, and DGF developed in both pairs in only 4% of the recipients. In another study in the United States, the DGF rate was 24% when one recipient experienced DGF, and the odds ratio of DGF in the contralateral kidney was 3.02 (12). In our study, when the DGF rate was 50% in both pairs, DGF developed in 41% of the recipients. Based on these two studies, we think that our previous interpretation is acceptable. The odds ratio shows that when evaluating kidney transplant dysfunction, the performance of the mate kidney should also be assessed. We think that the high rate of DGF in our patients was because of our diagnostic criteria for DGF. In a study from France, which used the creatinine clearance for diagnosing DGF, incidence of DGF was 63% (13). Ichikawa et al. (14) used the need for dialysis and urine output for diagnosing DGF and reported that the DGF incidence was 82%. In addition to the diagnostic criteria, this high incidence was due to the fact that the kidneys are procured only after cardiac arrest in Japan. In the literature based on various criteria for dialysis requirement and/or changes in creatinine levels. The choice of definition can alter the estimated incidence by more than two-fold as reported by Mallon et al. (15).

The short- and long-term adverse effects of DGF on allograft functions were clearly evaluated in a meta-analysis by Yarlagadda et al. (5). The study demonstrated that DGF is associated with a 41% increased risk in graft loss and is also associated with a 38% increased risk of acute rejection in the first year and results in a higher serum creatinine concentration at 3.5 years of follow-up (5). Parallel to this meta-analysis, allograft loss rate is higher in our recipients who had DGF than in those who did not (40% vs 13.3% p<0.045). Moreover, serum creatinine levels at hospital discharge and during a five-year follow-up period were higher in patients with DGF. In our study, no relationship was found between DGF and acute rejection.

In patients with DGF, ischemia reperfusion injury causes damage to the tubular epithelium. In the acute phase, this presents as acute renal failure. Alloreactivity, which is triggered by the healing process in long-term DGF causes the development of chronic allograft injury (16-17). Supporting this hypothesis, decreased graft survival was reported in kidneys with DGF in comparison to controls (7). A study from Ireland has shown a negative impact of DGF on kidney transplant survival. Giblin et al. (18) reported that the graft half- life for a transplant with DGF was 3.56 years compared to 9.9 years for that without DGF. UNOS data from 64,024 living donor kidney transplant recipients, 2,282 of whom had DGF, showed DGF to be the strongest predictor for five-year graft loss (19). These comprehensive studies have demonstrated that there is a significant association between DGF and chronic allograft injury.

Another important point is that we preferred a calcineurin inhibitor based regimen for maintenance immunosuppressive treatment in the majority of our patients (92.8%). The presence of DGF did not seem to affect the choice of maintenance treatment. A prospective study was conducted to evaluate the effects of sirolimus versus cyclosporine in recipients of kidneys from expanded criteria donors. Use of sirolimus instead of a calcineurin inhibitor showed no positive effect on DGF, and graft survival was numerically lower in the sirolimus group (20). In another randomized study by Flechner et al. (21), the occurrence and length of DGF was not significantly different between the sirolimus and cyclosporine groups in renal transplant recipients. The study was terminated early because of high acute rejection rates in the sirolimus arm. However, in our study, the biopsy-proven calcineurin toxicity rate was higher in patients with DGF (34.2% vs 8.5% p<0.009) and calcineurin toxicity tended to increase in patients with DGF in both kidneys. A small retrospective study found that converting calcineurin therapy to sirolimus in patients with prolonged DGF helped salvage renal graft function (22). Thus, in patients with DGF in both mate kidneys, early conversion of calcineurin to sirolimus may be considered. More prospective studies are needed for stronger evidence on using mTOR inhibitors in such patients.

ATG acts on a wide range of immune and non-immune targets, adhesion molecules, and chemokine receptors (23), and it has

been suggested that ATG could suppress ischemia reperfusion injury. In our recipients, the duration of cold ischemia was found to be longer (14.5 h vs 17.4 h, p=0.03), and serum donor creatinine levels were higher (1.1 mg/dL vs. 0.84 mg/dL, p=0.16) in patients whose received ATG for induction. Therefore, patients who received ATG may have had more confounding factors for the development of DGF. In addition, according to our clinical protocol, ATG was initiated a day after the kidney transplant in order to avoid infusion-related reactions. In another report by Goggins et al. (24), patients who received the first dose intraoperatively had a significantly lower rate of DGF (14.8% vs 35.5% p<0.05). In our study, DGF was more common in patients who received ATG (57.1% vs 28.5% p<0.016). Clinical features of patients receiving ATG and delayed application time of ATG can be interpreted as reasons for more frequent DGF occurrence in this patient group and why DGF is more common with ATG treatment.

Toronyi et al. (25) reviewed the outcome of kidney transplantations in which both kidneys were retrieved from the same donor, and the age of the donor between 16-40 and 41-65 ages was compared. Short term outcomes of transplanted kidneys were worse in the high donor age group. In our patient group, the mean age of the patients who developed DGF was higher than those who did not (44.2 vs 30.5 years, p<0.001). It appears from this analysis that the age of the donor is a significant factor in the short-term outcome of transplanted kidneys.

Kyllönen et al. (26) evaluated the outcomes of 816 paired kidney transplantations from 408 cadaveric donors. The patients were divided into two groups (mean cold ischemia time 22 vs 28 h). DGF was found to occur more frequently in the group with longer cold ischemia time (22% vs 35% p<0.005) (26). The same results were also observed in our paired transplantation: the cold ischemia time was found to be much shorter in patients without DGF (13.8 h vs 18.2 h p<0.008). Cold ischemia time showed a significant influence on graft function in both short- and long-term results.

Limitations

There are some limitations to this study. Firstly, this is a retrospective observational study and there are several clinical factors including donor body mass index and donor hypertension, which can influence the risk for DGF and have not been included in our analysis. Secondly, we could not describe donor factors with the kidney profile index because of inadequate clinic parameters. The reasons for the low numbers of mate kidney transplantations during this period are: firstly the second kidney from the same cadaver was presented to another transplant center because of national transplantation policy. Secondly, although the number of transport centers has increased over the years, there has been no increase in the number of donations from cadavers at the same rate. Therefore, if the sample size was larger, more generalizable results could have been obtained.

The development of DGF in the mate kidney can be expressed as a cumulative effect of donor dependent factors. Achieving normal hemodynamics, oxygenation, and metabolic balance of the donor are essential to prevent DGF (27). Creation of moderate hypothermia in the donor before harvest is useful (28), and it is important to start the initial immunosuppressive therapy immediately intraoperative or after reperfusion (24).

The desire for widespread use of organ preservation machines (29), biomarkers for prediction of DGF (30), and efforts to develop molecules and antibodies that target ischemia-reperfusion injury are promising for reducing the development of DGF (31).

CONCLUSION

Efforts to reduce DGF will reduce the burden on social security, most importantly with increasing organ and patient survival, and this will also lead to a reduction in the number of patients waiting for a kidney transplant.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Research Ethics Committee of Dokuz Eylül University (Approval Date: February 20, 2019; Approval Number: 2019-04/31).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

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