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Outcomes of delayed graft function in deceased donor kidney transplantation: a single center experience

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ABSTRACT

Objective: Delayed graft function (DGF) is related to enhanced acute rejection attacks in the short-term and reduced graft survival and reduced overall survival in the long-term. In this study, we desired to ascertain the outcomes of DGF.

Material and Method: This study is a retrospective cohort study. Two hundred seventy-four patients who underwent a kidney transplant from a deceased donor were included. DGF was described as obtaining dialysis treatment within the first week of transplant. The kidney recipients were divided into groups DGF+ (Group 1) and DGF- (Group 2). Two groups were compared in terms of risk factors which were based on donor and recipient characteristics. Short-term outcomes, long-term graft survival and recipient survival results were compared.

Results: The incidence of DGF was 50.3%. The rate of donors with expanded criteria donor (ECD) was 37.3%. Mean glomerular filtration rate (GFR) at one year after kidney transplantation was 57.5 ml/dk/1.73m² for Group 1, and 73 ml/dk/1.73m² for Group 2 ($p<0.001$). There was no statistically significant difference between the groups in terms of graft loss and mortality at one year. There was no statistically significant difference between groups in terms of graft and recipient survival.

Conclusion: DGF did not negatively impact graft survival and recipient survival at one year and long-term, although it was associated with prolonged hospitalization and increased acute rejection in the early period.

Keywords: Delayed graft function, kidney transplantation, graft survival

INTRODUCTION

The need for dialysis in the first week after kidney transplantation is described as delayed graft function (DGF). Although the incidence of DGF varies widely due to various definitions in the literature (19-70%), it is around 25-30% (1,2). The activation of immunological pathways triggered by ischemic damage is one of the best-known mechanisms of DGF. The main physiopathological factors affecting the development of DGF are; donor-related (ischemic injury, inflammatory response) and recipient-related (reperfusion injury and immune response) (3).

In the last few decades, the use of allografts from marginal deceased donors to expand the cadaveric organ pool is a mandatory tendency by kidney transplant teams around world (3). Allograft donation from deceased donors after cardiac arrest is not applied routinely in our country; however, the use of those allografts results in an increased risk of DGF development (4). DGF is associated with prolonged hospitalization, worse kidney function, and increased acute rejection attacks in the early postoperative period (5,6). In a meta-analysis, DGF has been associated with 38% increased risk of acute rejection and 41% increased risk of graft loss in an average follow-up of 3.2 years. While many studies have shown that DGF is associated with decreased graft survival and decreased recipient survival (7-9), some other studies was found no association between DGF and graft survival, although it was associated with reduced kidney function (10,11).

Many risk factors have been argued to cause in DGF development, such as transplant-related (cold and warm ischemia time, sensitization, HLA mismatch), donor-related (age, body mass index, ethnicity, deceased donor after cardiac death, method of operation), recipient-related (age, sex, duration of dialysis, previous transplant history, presence of PRA, diabetes mellitus) and perioperative processes related (induction, anesthesia) (4,12).

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In this retrospective cohort study, we aimed to reveal the impact of DGF on short-term and long-term outcomes of kidney transplant recipients who received grafts from deceased donors.

MATERIAL AND METHOD

The study was approved by Yeni Yüzyil University Science, Social and Non-Invasive Health Sciences Research Ethics Committee (2020/06-473). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

In our retrospective cohort study, we contained patients who had kidney transplants from deceased donors, between 2008-2020. Kidney transplant patients who were followed for more than one year were included in the study. Patients with hyperacute rejection, primary nonfunctioning kidney, and multiple organ transplants were excluded. Kidney recipient and donor characteristics were obtained from medical records. Renal recipients were divided into two groups: DGF+ (group 1) and DGF- (group 2). Donor data included age, sex, body mass index (BMI), cause of death, history of diabetes mellitus (DM) and hypertension (HT), number of days in intensive care, creatinine level that belongs to a patient at admission time to hospital, and most recent creatinine level. Recipient data included age, sex, BMI, disease-causing end-stage renal disease, dialysis modality, dialysis duration, Class I-II PRA, HLA mismatch, cold ischemia time (CIT), biopsy-proven acute rejection (BPAR), length of hospital stay after transplantation, graft survival and recipient survival.

Definitions

Delayed graft function: The need for dialysis in the first week after kidney transplantation is described as DGF.

Expanded criteria donor (ECD): ECD was described as the presence of one of the following characteristics (13).

1.Donor aged ≥60 years,

2.Donor aged 50-59 years and additionally, in the presence of two of the following three features,

a. Cerebrovascular cause of death
b. Creatinine>1,5 mg/dl
c. Hypertension

Clinical Outcomes

In the present study the outcomes were biopsy-proven acute rejection (within 100 days after kidney transplantation), GFR (Glomerular Filtration Rate) at one year post-transplantation, graft loss within one year, short-term mortality (the patients who died within one year after kidney transplantation), the time it took to reach the best kidney function graft survival, and recipient survival.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 21.0. The variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. The Mann-Whitney U test was used to compare donor and recipient characteristics that they were not normally distributed between groups. The effect of DGF on graft survival and recipient survival was investigated using the Log-Rank test. The Kaplan-Meier survival estimates were calculated. A 5% type-1 error level was used to infer statistical significance.

RESULTS

In the present study, the incidence of DGF was 50.3% (n=135). The mean donor age and median donor age of Group 1 and Group 2 were 50.82±18.4 and 52 (12-87) years, 41.3±21.1, and 42 (1-86) years, respectively. Mean recipient age and median recipient age of Group 1 and Group 2 were 45.3±12 and 46 (10-66) years, and 40.3±16.3 and 43 (2-68) years, respectively. When kidney recipients age and donors age were compared according to groups, there was a statistically significant difference between Group 1 and Group 2 ($p<0.001$ and $p=0.036$).

When Group 1 and group 2 were compared according to donor BMI, a statistically significant difference was found. Median BMIs of groups 1 and 2 were 26.1 (16.5-41) and 25.1 (13.9-47), respectively ($p=0.012$). A statistically significant difference was found when Group 1 and 2 were compared according to kidney recipient BMI. Median BMIs of groups 1 and 2 were 23.6 (13.9-35) and 23.6 (12.9-38.3), respectively ($p=0.036$).

When the groups were evaluated in terms of donor diseases, Group 1 had a higher prevalance of DM and HT more than Group 2 ($p=0.001$). When creatinine level at admission time to hospital and recent creatinine values were evaluated, recent creatinine was statistically significant in terms of DGF development ($p=0.004$). The rate of donors with ECD was 37.3% (100/268). In Group 1, 59% of donors (n=59) were ECD, and this difference between the two groups was statistically significant ($p=0.029$).

Mean duration of dialysis 112.2±65 months. Duration of dialysis in Group 1 higher than in Group 2 ($p=0.018$). In terms of dialysis modality, we found that DGF developed statistically significantly more often in HD patients than in PD patients ($p=0.001$).

Mean and median duration of cold ischemia time of all patients were 14.7±4.3 and 14 (7-32) hours, respectively.

Cold ischemia time was statistically significant in the development of DGF (p=0.002). The presence of HLA mismatch, Class I, and Class II PRA in kidney recipients were not statistically significant in the development of DGF. Donor and recipient characteristics according to groups are given in **Table 1.**

Table 1. Donor and recipient characteristics according to groups

	Grup 1 (n=135)	Grup 2 (n=133)	
Donor Related Risk Factors**			
Age, years	52 (12-87)	42 (1-86)	0.000*
Sex, female/male (m%)	83/52 (38.5%)	78/55 (41.3%)	0.636
BMI (kg/m^2)	26.1 (16.5-41)	25.1 (13.9-47)	0.012
Cause of death			
CVE	68 (52.3%)	62 (47.7%)	0.119
Head trauma	48 (46.6%)	55 (53.4%)	
Hipoxia	9 (81.8%)	2 (18.2%)	
Other	10 (41.7%)	14 (58.3%)	
Comorbidities			
HT	31 (56.4%)	24 (43.6%)	0.001
DM	19 (86.4%)	3 (13.6%)	
No	56 (41.5%)	79 (58.5%)	
Unknown	29 (51.8%)	27 (48.2%)	
Creatinine level (mg/dl)			
Admisson to hospital cr	0.82 (0.37-3.6)	0.78 (0.19-3.7)	0.073
Terminal cr	1.23 (0.3-8)	1.01 (0.2-5.7)	0.004
Intensive care stay (days)	4 (2-45)	4 (1-10)	0.562
Expanded Criteria Donor			
Yes	59 (59%)	41 (41%)	0.029
No	76 (45.2%)	92 (54.8%)	
Recipient Related Risk Factors			
Age, years	46 (10-66)	43 (2-68)	0.027
Sex, female/male (m%)	81/54 (40%)	72/61 (45.8%)	0.332
BMI (kg/m^2)	23.6 (13.9-35)	23.6 (12.9-38.3)	0.036
Primary Disease			
DM	19 (61.3%)	12 (38.7%)	0.218
HT	28 (54.9%)	23 (45.1%)	
GN	19 (61.3%)	12 (38.7%)	
Other	68 (45.9%)	80 (54.1%)	
Dialiysis Modality			
PD	4 (17.4%)	19 (82.6%)	0.001
HD	130 (54.4%)	109 (45.6%)	
Duration of dialysis (months)	120 (39-264)	108 (6-264)	0.018
HLA Mismatch			
0	4 (50%)	4 (50%)	0.409
1-5	127 (49.8%)	128 (50.2%)	
6	4 (80%)	1 (20%)	
PRA Categories			
Class I and Class II negative	100 (54.1%)	85 (45.9%)	0.150
Class I or Class II positive	19 (38.8%)	30 (61.2%)	
Class I and Class II positive	16 (47.1%)	18 (52.9%)	
Graft Related Risk Factor			
Cold ischemia time (hours)	14 (7-21)	14 (8-23)	0.002

*p<0.001 **Numbers are given as median and minimum, maximum, and percentages by row.
CVE:Cerebrovascular event, HT: Hypertension, DM:Diabetes mellitus, GN:Glomerulonephritis,
PD:Peritoneal dialysis, HD:Hemodialysis, HLA:Human leukocyte antigen, PRA:Panel reactive antibody, cr:Creatinine

There was no difference between the two groups in terms of induction therapy (ATG or IL-2 Ab) and maintenance immunosuppressive treatments (p=0.051 and p=0.349). When the two groups were compared in terms of the time it took to reach the best kidney function, we found that patients in Group 1 took longer to reach the best kidney function than patients in Group 2. (p<0.001). After kidney transplantation, the length of hospital stay of Group 1 was 23.5 (5-46) days, while the duration of hospitalization of Group 2 was 10 (6-23) days. This difference was statistically significant (p<0.001). Biopsy proven acute rejection developed in 24 out of 135 patients (17.8%) in Group 1, and 10 out of 133 patients (7.5%) in Group 2 in the early period, and this difference was found to be statistically significant (p=0.019). The short-term outcomes are given in **Table 2** by groups. At one year, Group 1 had a mean (range) GFR of 57.5 ml/dk/1.73m^2 (8-132) and Group 2 had a mean (range) GFR of 73 ml/dk/1.73m^2 (20-133) and the difference was statistically significant (p <0.001). There was no statistically significant difference between the groups in terms of graft loss and mortality at one year.

Table 2. Short-term clinical outcomes according to groups

**	Grup 1 (n=135)	Grup 2 (n=133)	
Time it took to reach best kidney function (days)	195 (6-1320)	62 (5-490)	0.000*
Length of hospital stay (days)	23.5 (5-46)	10 (6-23)	0.000*
Biopsy proven acute rejection			
Yes	24 (70.6%)	10 (29.4%)	0.019
No	111 (47.4%)	123 (52.6%)	
GFR at one year (ml/dk/1.73 m^2)	57.5 (8-132)	73 (20-133)	0.000*
Mortality at one year			
Yes	13 (48.1%)	14 (51.9%)	0.967
No	122 (50.6%)	119 (49.4%)	
Graft loss at one year			
Yes	8 (53.3%)	7 (46.7%)	1.0
No	127 (50.2%)	126 (49.8%)	

*p<0.001 **Numbers are given as median and minimum, maximum, and percentages by row. GFR: glomerular filtration rate

Mean and median of follow-up time in all recipients and in recipients with DGF were 56.9±35.7, 50 (0-143) months, 54.4±35.7, 49 (0-143) months, respectively. While graft loss developed in 13.4% (36/268) of all patients, this rate was 17% (23/135) and 9.8% (13/133) in Group 1 and Group 2, respectively. While 17.9% (48/268) of all patients died, mortality rate was 20% (27/135) and 15.8% (21/133) in Group 1 and Group 2, respectively.

Figure 1 shows the Kaplan-Meier analysis results in terms of graft survival, and there was no statistically significant difference between the groups (p=0.141). **Figure 2** shows the Kaplan-Meier analysis results in terms of recipient survival, and there was no statistically significant difference between the groups (p=0.665).

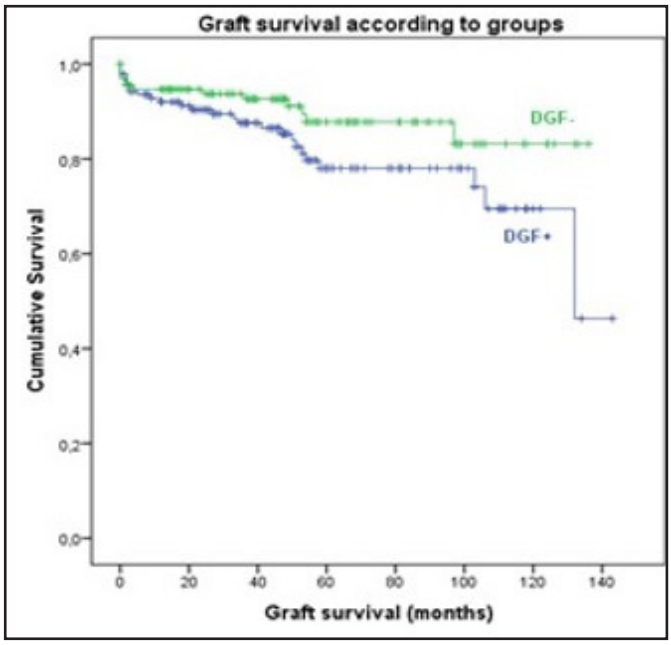

Figure 1. Graft survival according to delayed graft function

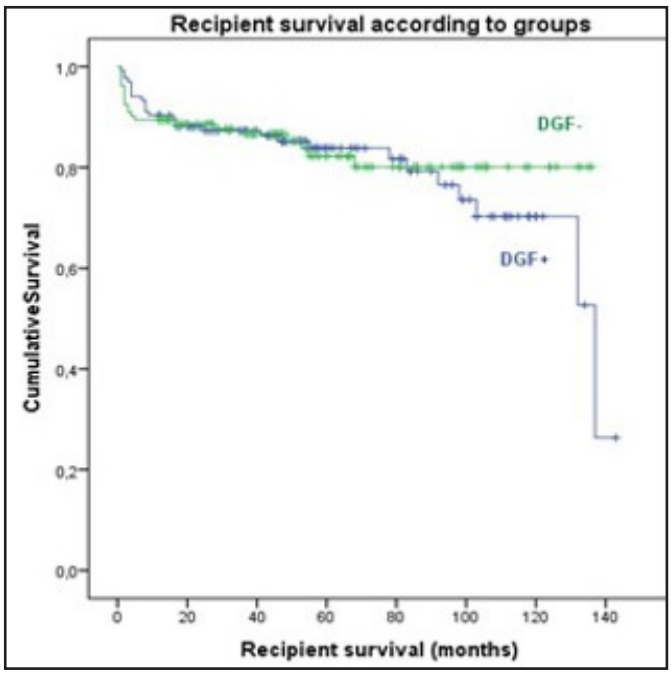

Figure 2. Recipient survival according to delayed graft function

DISCUSSION

Delayed graft function appears as a clinical outcome of all processes in the pre-harvesting period, organ protection phase, and reimplantation phase. Donor-related factors such as low perfusion, infection, and cytokine release triggered by brain death result in adverse effects on the kidney. Low perfusion during the organ preservation period creates ischemic damage, especially in the tubular area, and also causes the release of various proteins and antigens that activate immune pathways as a result of vascular endothelial damage. DGF develops as a result of processes such as tubular damage caused by ischemia,

complement activation, accumulation of free radicals, and increased proinflammatory cytokines as a result of reperfusion injury developed after reimplantation (3,4).

Although many studies have shown the associations between DGF and prolonged hospitalization, early acute rejection, and loss of graft in the short term after kidney transplantation (5-9), these are not apparent in the long-term. In the present study, we have shown that despite the high frequency of DGF (50.3%), it did not negatively affect graft loss and mortality rate within the first year, long-term graft survival, and recipient survival.

The incidence of DGF was significantly higher in studies from our country (20-57.8%) (10,14-18) than the incidence reported in international literature (25-30%) (1,2). In our study, the incidence of DGF (50.3%) was found to be similar to our national studies. The higher frequency of DGF in our transplant center may have been due to the more acceptance of kidney donors with ECD. While the frequency of ECD varies from 28 to 40.5% in international literature (19-21), in our study, it was 39.5% in all patients and 59% in the group that developed DGF.

One of the negative consequences of DGF is prolonged hospitalization after transplantation. In this study, we found the length of hospital stay was significantly longer in DGF+ group, similar to the data in the literature (5-9).

In the present study, BPAR rate that developed within 100 days after kidney transplantation was found to be higher in the group with DGF compared to the group without DGF (17.8% vs 7.5%). Yarlagadda et al. (5) found that the development risk of BPAR was 38% in the group that developed DGF, and in the study conducted by Lai et al. (6) BPAR developed in 60.8% of the group that developed DGF.

One of the most important results of our study is that kidney function continues to recover after the early period in both groups. Patients with DGF achieved the best kidney function an average of 133 days later compared to those without DGF. This effect may have been due to the long-term healing of inflammatory damage resulting from ischemic injury and the immune system response mounted by the recipient. Induction therapy used in the kidney transplant procedure and early maintenance high immunosuppressive therapy may also impair the recovery process.

In the present study, we found that GFR at one year post-transplantation of the DGF group was significantly lower than the group without DGF, but the graft loss was not different among the two groups at one year. Similarly, we did not find any difference between the two groups in terms of recipient survival at one year. In a recent meta-analysis, DGF was found to be a risk factor for graft loss in the 1st year (HR 1.89, 95% CI, 1.46-2.47) (22). In this meta-analysis, six factors were found to be associated with graft loss: donor age, deceased donor, number of HLA mismatches, recipient age, and DGF as a risk factor for one year graft loss. In this meta-analysis, DGF was considered a moderate level risk factor due to serious inconsistencies in the studies included in the analysis. Also, authors commented that each of the identified risk factors had a small effect.

In this study, as shown in **Figures 1 and 2**, DGF+ group accured more graft loss (23 vs 13) and patient death (27 vs 21). However, there was no statistically significant difference between the two groups in the long-term.

In the meta-analysis that Yarlagadda et al. (5) analyzed 33 studies, DGF was found to be associated with graft loss after 3.2 years of follow-up, however they also showed that it didn't negative impact recipient survival after 5 years of follow-up. Lai et al. (6) determined that graft survival was lower in the group with DGF at 1st year and 3rd years, but they did not find difference in terms of recipient survival. In the previously reported study from Turkey by Kara et al. (10), there was no difference in graft survival and recipient survival between the groups with and without DGF in the 1st year. Helfer et al. (7) determined that GFR was found to be statistically significantly higher in the group with DGF in the first 4 years after kidney transplantation, while 5 years later this difference was reduced and became insignificant. They demonstrated that longer DGF duration (>14 days) was associated with graft loss and worse kidney function.

Although the short-term negative results of DGF have been revealed in many studies, its effects on graft survival and recipient survival in the long term do not yet remain clear. There are many factors affecting graft survival and recipient survival, such as infection, acute rejection, recipient age, immunological risk status, and comorbidities. In our study, although GFR was lower in the group that developed DGF at one year, there was no significant difference between two groups in terms of graft loss. The reason may have been due to high number of ECDs in both groups. In our study, we showed that improvement in kidney function lasted longer in the group that developed DGF (195 versus 62 days). The fact that the recovery period of DGF continues beyond the early stage of kidney transplant may signify that the adverse effects of DGF are less common in the long term.

The present study has a few limitations. First, it is a retrospective study accomplished at a single center. Furthermore, although we have used the most widely preferred definition of DGF in the literature, postoperative dialysis indication is a subjective decision. The fact that DGF definition is not standardized in the literature has led to significant differences in center-specific incidences

of DGF, and this directly affects the results. Therefore, our DGF definition in this study directly affected our results. Some studies have revealed that patients with shorter DGF duration have similar results with patients that did not develop DGF and that patients with longer DGF duration have worse kidney outcomes (6,23,24). With more studies evaluating the effect of DGF duration on kidney and patient outcomes, the uncertainty generated by various DGF definitions in this area can be reduced. If the DGF duration were included in our study, the results would most likely be different.

CONCLUSION

Our study showed that DGF did not negatively affect graft survival and recipient survival in the first year and long-term, although it was associated with prolonged hospitalization and increased acute rejection in the early period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Yeni Yüzyil University Science, Social and Non-Invasive Health Sciences Research Ethics Committee (2020/06-473).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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