Factors Associated With Delayed Graft Function and Their Influence on Outcomes of Kidney Transplantation

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ABSTRACT

Background. One of the main postoperative complications of kidney transplant is delayed graft function (DGF), which means absence of graft function after transplant or the need for dialysis during the first week post procedure. The occurrence of DGF currently in our hospital is high and has been attributed to a combination of many factors. The aim of this study was to evaluate the factors associated to DGF and their influence in the outcome of kidney transplants.

Methods. Historical cohort of 150 patients transplanted with live or deceased donor kidneys from 2011 to 2013.

Results. DGF was associated to time in dialysis and the number of recipient pre-transplant transfusions, donors age, serum creatinine level, use of vasoactive drugs in the donor, distance from place of organ retrieval and transplant center, and duration of cold ischemia time. DGF influenced post-transplantation outcome in regard to length of stay in intensive care, length of hospital stay, acute rejection episodes, and higher creatinine levels at discharge. Patients and graft survival were shorter in the DGF group.

Conclusions. There are multiple factors related to DGF, the most important being those related to donors, and organ storage. The most important factor related to the recipient was the dialysis vintage. We did not find a correlation between DGF and HLA-compatibility. DGF consequences are important, including worse graft function and survival, as well as impact in recipient morbidity and mortality.

KIDNEY transplantation is currently the treatment of choice for patients with chronic kidney disease (CKD), because it improves survival as well as quality of life in comparison to dialysis. One of the main complications of kidney transplantation is delayed graft function (DGF), which has many definitions but means the absence of graft function immediately after transplantation or the need for dialysis during the first week posttransplantation [1–8].

Since the 1990s, many factors have been related to DGF. However, the studies differ in regard to the methodologies used. DGF has been attributed to a combination of toxic, immunologic, and ischemic factors [1].

The occurrence of DGF at the Hospital São Lucas da PUCRS (HSL/PUCRS) is high, and it is mandatory to verify the actual numbers of patients with of this complication, because many studies suggest worse graft outcome due to DGF after kidney transplantation. Therefore, this study sought to verify the factors associated with DGF and its influence on graft outcome.

METHODS

A historic cohort study was conducted at HSL/PUCRS. The cohort was a random sample of 150 consecutive kidney transplant recipients between the years 2011 and 2013, independent of donor

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type and not necessarily on dialysis before the transplantation, more than 13 years of age, and followed up for 12 months after transplantation.

The sample included patients who underwent kidney transplantation and who were more than 13 years of age. Data collection was performed by means of an instrument that included variables that might be related to DGF. Patient follow-up was 12 months after the transplantation. In cases in which postsurgical dialysis was needed, the procedure was conducted according to the routine in the Nephrology Unit, with the criteria defined by the assisting physician. We used the definition of DGF as the need for dialysis in the first week after kidney transplantation. The group that presented with DGF was named DGF1, and the group that did not present with DGF was named DGF0.

Data were analyzed using the Statistical Program for Social Sciences, version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). P values of $<.05$ were considered significant. Categorical data were described as frequencies and percentages. For continuous variables, averages and standard deviations or medians and interquartile ranges were calculated. Nonparametric Mann-Whitney tests were used for proportion differences between common variables comparing donors and recipients. The Fisher exact test was used when there was the intention of identifying dependent relations between 2 or more groups of categorical variables. The study was previously analyzed and approved by the University Research Ethics Committee.

RESULTS

Of the 150 patients analyzed, 83 (55.3%) had DGF. The most used posttransplantation dialysis technique was hemodialysis, in 74 patients (89.2%). The average number of dialysis sessions per patient was 5.3, and 50% needed up to 3 sessions. The average time on dialysis after transplantation was 14 days; however, in 50% of the cases, it was not more than 7 days.

Recipient and Donor Factors Related to DGF

Recipients. Of the patients included in the study, 85 (56.7%) were male, and 127 (84.7%) were of white ethnicity. The average age was 48.4 ± 13.7 years. Most patients had ideal weight at surgery (62 patients, 41.3%), with a body mass index (BMI) of up to 25.

Among the most prevalent CKD etiologies was diabetes mellitus, in 39 patients (26.0%), undetermined in 33 (22.0%), hypertension in 28 (18.7%), and glomerulopathies in 27 (18.0%).

Five patients (3.34%) received preemptive transplantation, and for the patients who already were in dialysis, hemodialysis was the most common modality (123 patients, 82.0%). The average time on dialysis before transplantation was 40.3 months; in 50% of the cases the time on dialysis was of less than 26 months. The average waiting time was 13.2 months, but 50% of the patients had the transplant in less than 9.5 months.

In the laboratory evaluation DGF1 versus DGF0, 24 hours after transplantation, we found that serum potassium (5.2 ± 1 mEq/L vs. 4.4 ± 0.7 mEq/L, $P < .001$), and serum creatinine (8 ± 2.7 mg/dL vs. 6.5 ± 2.9 mg/dL, $P = .001$) were higher in DGF1, with a lower postoperative urinary output. We analyzed immediate postoperative DGF1 urinary volume as compared to DGF0, 0 (0–10) mL vs. 0 (0–250) mL, $P < .001$, in 24 hours, 275 (101–801) mL vs. 2380 (1485–4344) mL, $P < .001$, in 48 hours, 477 (205–1535) mL vs. 4962 (2930–8370) mL, $P < .001$, and in 72 hours posttransplantation, 855 (310–2100) mL vs. 7015 (4827–11,440) mL, $P < .001$, respectively, and observed that urinary volume in DGF1 was always lower.

Donors. Most kidney donors were male (80, 53.3%) and of white ethnicity (50, 33.3%). Information regarding "race" was not available in 96 (64%) patients' records. The average donor age was 43.3 ± 15.3 years. An attempt was made to calculate donors' BMI, but this information was not available in most records.

The most prevalent cause of death was hemorrhagic stroke, in 49 (37.2%) donors. In 78 (52.0%) records, there was no information on donors' use of vasoactive drugs; however, the variable was not ignored due to its correlation with DGF. The number of kidney donors 50 to 59 years of age 41 (27.3%), with 19 (12.7%) being 60 years or older.

A significant association between donor age and DGF was found ($P = .025$). It was noted that in DGF1, 53% of the donors were younger than 50 years, whereas 47% of the patients received organs from donors who were 50 years or older. In DGF0, 65.6% of the patients received kidneys from donors younger than 50 years, and 34.4% received kidneys from donors 50 years or older.

There was no significant difference in donor/recipient HLA compatibility between DGF1 and DGF0 ($P = .662$). The variables concerning the kidney donors are listed in Table 1.

When some of the variables were categorized, a significant association between the organ origin and the occurrence of DGF was evident, since in DGF0, 64.2% of the donated organs came from less than 100 km from the transplanting hospital, and in DGF1 only 36.0% of the organs donated came from less than 100 km of the hospital ($P = .002$).

Kidney donors with expanded criteria are those older than 60 years of age or donors between 50 and 59 years with 2 of 3 criteria: hypertension; creatinine above 1.5 mg/dL or estimated glomerular filtration rate (eGFR) (Cockroft/Gault) between 50 and 70 mL/min/m^2 at admission; or hemorrhagic stroke as the cause of death [9]. We analyzed the list of donors with expanded criteria in DGF1 vs. DGF0 and noted that there was no difference statistic in the occurrence of DGF with 17 (20.5%) vs. 11 (16.4%) ($P = .525$).

The categorical variables concerning kidney donors, donated organs, and kidney recipients comparing DGF1 vs. DGF0 are described in Table 2.

Influence of DGF on Kidney Transplantation Outcome

Table 3 depicts the statistical difference in all variables related to the characteristics of admission for both groups, always unfavorable to DGF1. Creatinine at discharge and

Table 1. Variables Concerning Kidney Donors (N = 150)

Variable	DGF		P
	DGF1	DGF0	
Age (y)*	46 ±13.8	40 ± 16.5	.025
Donor age group: n (%)			
<40 years	25 (30.1)	35 (52.2)	.060
40–49 years	19 (22.9)	9 (13.4)	
50–59 years	26 (31.3)	15 (22.4)	
≥60 years	11 (13.3)	8 (11.9)	
No information	2 (2.4)	0 (0.0)	
Donor type: n (%)			
Deceased	82 (98.8)	50 (74.6)	<.001
Living related	1 (1.2)	13 (19.4)	
Living unrelated	0 (0.0)	4 (6.0)	
Donor initial creatinine (mg/dL)†	0.9 (0.7–1.4)	0.9 (0.7–1.0)	.266
Donor final creatinine (mg/dL)†	1.6 (1.1–2.7)	1.1 (0.9–1.6)	.001
Use of vasoactive drugs: n (%)	31 (37.3)	27 (40.3)	.002
Cardio-respiratory arrest: n†	0 (0–5)	0 (0–0)	.127
HLA compatibility in mismatch: n†	4 (3–4)	3 (3–4)	.662
Duration of cold ischemia (h)†	26 (23–30)	16 (13–25)	<.001
Duration of warm ischemia (min)†	55 (50–61.5)	51.5 (45–60)	.076

P value was obtained by Fisher or Mann-Whitney test. *P* values less than .05 are significant.

Abbreviations: DGF1, patient group presenting with DGF (delayed graft function, defined as need for dialysis in first week after kidney transplantation; DGF0, patient group not presenting with DGF; HLA, human leukocyte antigen.

*Average and standard deviation.

†Median and interquartile interval.

Table 2. Categorical Variables Concerning Kidney Donors, Donated Organs, and Kidney Transplant Recipients

Variable	DGF		P
	DGF1	DGF0	
BMI (kg/m^2): n (%)			
Recipient BMI >25	47 (56.6)	31 (46.6)	.214
Donor BMI >25	11 (13.3)	6 (9.0)	.380
Cause of donor's death: n (%)			
Nontraumatic	54 (72.0)	32 (64.0)	.344
Traumatic	21 (28.0)	18 (36.0)	
Origin of donated organ: n (%)			
<100 km from hospital	30 (36.1)	43 (64.2)	**.002**
>100 km from hospital	41 (49.4)	17 (17.9)	
Cell reactivity panel: n (%)			
<10%	39 (47.0)	40 (59.7)	.436
11%–50%	17 (20.5)	10 (14.9)	
>50%	11 (13.3)	8 (11.9)	
Previous transfusions: n (%)			
0	24 (28.9)	40 (59.7)	**.001**
1–5	27 (32.5)	12 (17.9)	
>5	32 (38.6)	15 (22.4)	
Acute rejection: n (%)			
Yes	19 (22.9)	6 (9.0)	**.023**
No	64 (77.1)	61 (91.0)	

P values obtained using Fisher exact test. *P* values less than .05 are significant.

Abbreviations: BMI, body mass index; DGF1, patient group presenting with DGF (delayed graft function, defined as need for dialysis in first week after kidney transplantation; DGF0, patient group not presenting with DGF.

3 months after transplantation proved higher in DGF1 as compared to DGF0, being respectively 4.8 ± 2.5 mg/dL vs. 2.5 ± 1.7 mg/dL ($P < .001$) and 2.4 ± 1.8 mg/dL vs. 1.5 ± 0.5 mg/dL ($P < .001$). Graft as well as patient survival was shorter in DGF1 as compared to DGF0 (277 ± 131 days vs. 347 ± 45 days, $P < .001$, and 323 ± 92 days vs. 350 ± 44 days, $P = .025$).

Estimated GFR was described using the Cockcroft-Gault equations and estimated GFR according to the equation derived from the study Modification of Diet in Renal Disease (MDRD) [10], as recommended by the National Kidney Foundation [11], in DGF1 versus DGF0 at different times, and a correlation of GFR in kidney transplant outcome was verified, DGF1 GFR versus DGF0 GFR at discharge, 3 months, 6 months, and 12 months post kidney transplant was always better.

Graft and Patient Survival

Of the 150 patients who underwent transplantation, 18 died before 12 months, a survival rate of 88.0%. In DGF1, 14 patients died before 12 months, and in DGF0, 4 patients died before 12 months. Survival was 83.1% in DGF1 and 94.0% in DGF0. Mantel-Cox statistics point to evidence of significant survival differences between the patients groups in regard to the presence of DGF ($\chi^2 = 4.182$, $P = .041$).

DISCUSSION

This study evaluated the occurrence of DGF in kidney-transplanted patients in the HSL/PUCRS. Among the factors associated with DGF in regard to recipients are longer time in dialysis and pretransplantation transfusions, and in regard to donors are age, type (deceased vs. living), final serum creatinine, and use of vasoactive drugs, as well as time of cold ischemia. Also, patients who received kidneys donated from more than 100 km away from the hospital experienced a higher rate of DGF. Indication of dialysis in the first week posttransplantation was for patients with elevated serum creatinine and potassium, and decreased urinary volume, usual indications for the

Table 3. Characteristics of Patients' Hospital Stays

Variable	DGF		P
	DGF1	DGF0	
ICU length of stay (days)	3.0 (2.0–4.0)	2.0 (2.0–3.0)	**.017**
Length of hospital stay (days)	18.0 (13.0–26.0)	10.0 (7.0–13.0)	**<.001**
Number of admissions in 12 months	2.0 (1.0–4.0)	2.0 (1.0–4.0)	.726
Creatinine at hospital discharge	4.17 (2.84–6.43)	2.1 (1.5–2.8)	**<.001**
GFR at discharge, Cockcroft-Gault (mL/min)	19.8 (14.1–26.3)	41.5 (29.5–53.2)	**<.001**
GFR at discharge MDRD (mL/min)	16.0 (11.0–24.0)	33.5 (25.0–47.0)	**<.001**

Data are median and interquartile interval. *P* value obtained by nonparametric Mann-Whitney test. *P* values less than .05 are significant.

Abbreviations: DGF1, patient group presenting with DGF (delayed graft function, defined as need for dialysis in first week after kidney transplantation; DGF0, patient group not presenting with DGF; ICU, intensive care unit; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease equation.

procedure. The influence of DGF in graft outcome is associated with many factors, such as length of stay in intensive care, length of hospital stay, lower pre- and postoperative estimated GFR, episodes of acute rejection, and shorter graft survival as well as patient survival.

There are many definitions of DGF, and the use of a standard definition is suggested, with the objective of achieving interventions able to revert DGF so that, in the future, its occurrence no longer interferes with graft or patient survival [11]. The most frequently used definition for DGF in the studies published previously is the need for dialysis in the first week posttransplantation [1–8], which was also adopted in the present study for data analyses. Therefore, if a DGF standard definition is established by the need for dialysis in the first week posttransplantation, the criteria for the indication of dialysis in the postoperative period after kidney transplantation should be listed. The indications for dialysis in this study were high postoperative serum creatinine and potassium, as well as low urinary volume.

No difference was found in the occurrence of DGF in the group that received preoperative hemodialysis when compared to the group of patients who received peritoneal dialysis. A retrospective study with 325 patients concluded that the occurrence of DGF was higher in the pretransplantation hemodialysis group (49.5%) when compared to the group of patients who had peritoneal dialysis (30.6%) ($P = .01$) and that the variables "donor gender and age" and duration of cold ischemia did not correlate with DGF [8].

In the United States, using the same criteria adopted in Brazil in 2009 for donors with expanded criteria, an 18.3% increase in the number or organs collected and 15% in kidney transplantations was observed. The use of those organs did not correlate with graft survival. DGF remained unaltered with their use, as in this study, which did not find a correlation between the occurrence of DGF when organs from donors with expanded criteria were used. It is possible that the use of mechanical perfusion is more beneficial than static storage by cold temperature, and that its use is associated with decreased loss of kidneys from deceased donors [12], in accordance with other, previous studies reporting a reduction in the occurrence of DGF with this practice [13,14].

The duration of warm ischemia was not correlated with the occurrence of DGF, which is different from one study in which the duration of warm ischemia was longer in DGF [15].

In regard to donor-related variables, statistical differences were found in the occurrence of DGF depending on age, deceased donor final serum creatinine, use of vasoactive drugs, duration of cold ischemia, and distance of the donated organs, a variable not described in previous papers. The duration of cold ischemia was an important factor in the occurrence of DGF, as previously reported. One study with 2525 patients found that longer duration of cold ischemia was related to shorter graft and patient survival [16]. The influence of the duration of cold ischemia with the occurrence of DGF, present in 31.1% of the patients, was described in a study that did not detect the influence of HLA compatibility in graft survival but did find a correlation of the occurrence of DGF with donor age, donor final creatinine value, and the implantation of kidneys from female donors in male recipients [7]. This last variable was described in 2012, in a study in which transplantation of kidneys from female donors to male recipients impaired the early outcome of kidney grafts and increased the risk for graft loss, possibly due to the smaller number of nephrons in female kidneys [17]; nevertheless, no correlation was found between DGF and kidneys from female donors implanted in male recipients in our study. In addition, no correlation between DGF and HLA compatibility was found, suggesting that DGF mechanisms are not primarily related to immunological aspects [7]. A retrospective study with 831 patients in which 25% had DGF found factors related to worse graft outcomes when associated with pretransplantation time in dialysis, donor age, donor type, and HLA compatibility. In this study, there was no correlation between DGF and the panel of cell reactivity or previous transfusions in the recipients; the duration of cold ischemia did not differ in the 2 groups [19], contrary to our findings and to the findings of other studies in which the groups who presented with DGF had a longer duration of ischemia [7,16].

Length of hospital stay was longer for DGF1 than for DGF0. In regard to this variable, a study also correlates length of stay as an important influence for DGF [4,19], in addition to other, similar findings. In that study, the occurrence of the complication was 35.5%, and time in pretransplantation dialysis was also related to DGF; nevertheless, no relation was found to the panel of cell reactivity in the donor, or HLA compatibility [19].

The preoperative time in dialysis, the donor final creatinine value, the use of vasoactive drugs by the donor, and the duration of cold ischemia are associated with DGF, as previously observed [20]. In a report similar to ours but that included 761 patients in a retrospective study, it was noted that besides the factors above, donor age, hospital length of stay, acute rejection, and creatinine value for transplanted patients at the time of discharge are factors related to DGF [4].

The occurrence of DGF is significant, but varies according to the definition used. A retrospective study also described the high occurrence of DGF in 53% of patients, but used as the definition of DGF the need for dialysis for more than 7 days posttransplantation. The study associated only the creatinine value at discharge with DGF [21]. When defined as the need for dialysis up to 7 days after transplantion in a retrospective study that analyzed 570 patients among whom DGF occurred in only 8.4%, the complication was related to donor age as an important factor for its occurrence [5]. A study in the 1990s that defined DGF as creatinine clearance equal or less than 10 mL/min/1.73 m^3 concluded that the patients with DGF who did not reach a creatinine clearance of 10 mL/min/1.73 m^3 or more in 6 days after transplantation and who did not have dialysis during that period (12%) had a significantly worse outcome for the graft than those who

reached a creatinine clearance of 10 mL/min/1.73 m^3 or more in a period shorter than 6 days [22].

The variable acute rejection and GFR were also related to DGF. The estimated GFR according to the Cockroft/Gault equation and MDRD were calculated at different times to better verify their relation with the complication. Posttransplantation GFR of less than 60 mL/min/1.73 m^3 12 months after the procedure is highly associated with worse clinical results such as acute rejection and death [23]. The relation of DGF with shorter graft and patient survival was the most important factor found. Previous studies already pointed out important factors related to DGF, such as graft as well as patient survival [4,5,16]. Others analyzed graft and patient survival after kidney transplantation and concluded that DGF had no effect on graft survival [19,21,22] and/or patient survival [8,19,20,24].

In conclusion, the factors associated with DGF that were observed in this study are related to aspects relating both to kidney recipients and to donors. The consequences of the graft outcome are important, because they correlate with a shorter survival for graft and patient alike.

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