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Predictors of Delayed Graft Function in Renal Transplantation

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Keywords
Renal transplantation · Delayed graft function · Complication

Abstract
Purpose: This study aimed to analyze our data on delayed graft function (DGF) and to identify associated factors. ***Methods:*** This is a retrospective case-control study of all patients transplanted in our center over a period of 11 years (January 1, 2003, to December 31, 2014) comparing patients with immediate graft function ($n = 332$) to those with DGF ($n = 165$). DGF was defined as the need for hemodialysis within the first 7 days after transplantation. Donor and recipient characteristics as well as procedural factors were compared by univariate and multivariate logistic regression analyses. ***Results:*** Overall, 33% of patients had DGF. The rate of DGF declined from 2003 to 2011. In cases with DGF, donors and recipients were significantly older ($p = 0.004$ and $p = 0.005$, respectively), had longer cold ischemia times ($p = 0.039$), more revision surgeries ($p < 0.001$), and more HLA mismatches ($p = 0.001$), especially in the DR locus ($p = 0.002$). Neither donor nor recipient gender, waiting time, nor CMV status had any influence. In multivariable analysis, significant risk factors were ischemia time and mismatches at the HLA-DR loci. ***Conclusions:*** DGF is a common complication in renal transplantation which occurred in 33% of our cases. Important factors identified were donor and recipient age, ischemia time, HLA mismatching, and revision surgery.

Introduction

Delayed graft function (DGF) is a frequent occurrence in renal transplantation. Defining DGF as the need for dialysis within the first 7 days of transplantation, the rate of DGF in large registries has been reported to be 25% in deceased donor recipients and up to 5% in living donor recipients [1, 2]. More recently, US registries reported 30.8% of DGF in deceased donor transplantation [3]. Numbers will differ in different registries depending on the definition of DGF used [4].

DGF has been called the "acute kidney injury" of renal transplantation, describing an acute but transient failure of the renal transplant. The mechanisms leading to DGF are not completely understood, but there are indications that complement activation and release of inflammatory

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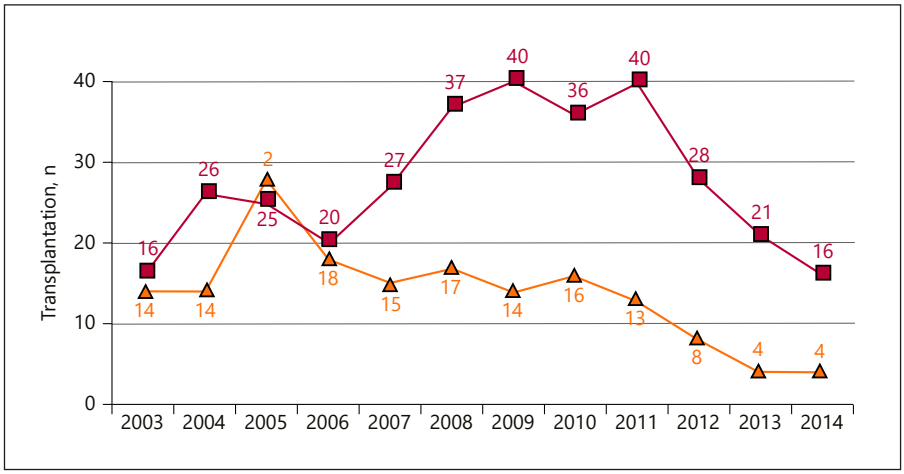

Fig. 1. Transplantations per year grouped by immediate function (red) and DGF (yellow). The decline in transplant numbers from 2012 to 2014 was related to a reduced number of deceased organ donations following negative publicity after irregularities with organ allocation in some German centers. DGF, delayed graft function.

cytokines following ischemia and reperfusion ("reperfusion injury") play an important role [5, 6].

Transplants with DGF also have worse long-term outcomes. DGF is associated with an increased incidence of acute rejection. The risk of graft failure associated with DGF is greatest within 1 year of transplantation in patients who also had an episode of acute rejection [4]. Thus, although DGF is transient, it has implications for the future.

While the reasons for DGF are poorly understood, it is clear that these are likely to be multifactorial. There is no valid treatment for DGF, and clinically, there is no real alternative to being patient. This study was undertaken to analyze factors associated with DGF in our center in order to avoid identifiable risk factors for DGF as far as possible.

Materials and Methods

We performed a retrospective case-control study of all consecutive 531 patients who underwent renal transplantation in our department during an 11-year period from January 1, 2003, to December 31, 2014, comparing patients with immediate graft function versus those with DGF (Fig. 1). The definition used for DGF for the purpose of this study was the need for at least 1 dialysis within the first 7 days after transplantation. Patients with some degree of delay in graft function in whom function appeared within 72 h after transplantation and who did not undergo any dialysis within the first 7 days were excluded from this analysis. Also, patients whose transplant kidney had to be removed due to primary nonfunction and patients who died during the same hospital stay were excluded from analysis. Data were extracted from the hospital records, and the study was approved by the university hospital's internal review board.

Transplantation was done according to the standard extraperitoneal surgical technique with positioning of the transplant into the iliac fossa and vascular anastomosis of the transplant vessels to the common iliac vessels of the recipient. The standard immunosuppression during the entire period was a triple drug regimen with cyclosporine A, mycophenolate mofetil (MMF), and prednisolone, without induction treatment. It was used in 51.2% of patients. The second most commonly used combination was tacrolimus, MMF, and prednisolone (36.0%). A combination of sirolimus, MMF, and prednisolone was used in 3.7%. Deviations from the standard regimen (cyclosporine A, MMF, and prednisolone) were decided on an individual basis.

Thirty-four patients were excluded from analysis due to short-term delay in graft function (see above) or graft removal. The remaining 497 patients were divided into 2 groups: those with DGF (n = 165) and those without (n = 332). A clinical follow-up of 12 months was done for all patients. The 2 groups were compared regarding the following parameters: donor and recipient age, gender, CMV status, HLA mismatches, revision surgeries, transplant biopsies, waiting time, ischemia time, immunosuppression, and serum creatinine levels after 2 weeks, 3 months, and 1 year after transplantation.

All data were stored and analyzed by using Microsoft Excel 2013 and IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were computed for continuous and categorical variables. The statistics computed included mean and standard deviations of continuous variables and are presented as mean ± SD and frequencies and percentages of categorical factors.

Testing for differences of continuous variables between 2 groups was accomplished by the 2-sample t test for independent samples or the Mann-Whitney U test by ranks as appropriate. Test selection was based on evaluating the variables for normal distribution employing the Kolmogorov-Smirnov test. Comparisons between the study groups for categorical variables were done using the Pearson χ^2 test or the Fisher's exact test. The logistic regression model was used to assess the independence of DGF from prognostic factors by computing odds ratios (OR). First, univariate analyses were performed to reveal unadjusted significant associations between prognostic variables and DGF. Thereafter, variables yielding p values ≤0.10 in univariate analyses were entered into the multivariate model to highlight some adjusted associations between the outcome and covariates which were univariate at least of borderline significance. All p values resulted from 2-sided statistical tests, and $p \leq 0.05$ was considered to be significant.

Table 1. Direct comparison of indicator parameters between transplants with immediate function and those with DGF

	Immediate graft function	DGF	*p* value
N (%)	332 (66.8)	165 (33.2)	
Deceased donor, *n* (%)	284 (64.8)	154 (35.2)	
Living donors, *n* (%)	37 (77.0)	11 (23.0)	
Male patients, %	65.4	66.7	0.841#
Waiting time (mean ± SD), years	5.45±3.10	5.82±2.71	0.150*
Recipient age (mean ± SD), years	50.9±13.6	54.3±13.3	0.005*
Donor age (mean ± SD), years	51.4±15.3	55.7±14.4	0.004*
Cadaver donations, %	85.5	93.3	0.012#
Cold ischemia time (mean ± SD), h	12.1±5.88	13.3±5.45	0.039*
HLA mismatches (mean ± SD)	2.58±1.67	3.15±1.64	0.001*
Patients with revision surgeries, %	9.0	21.2	<0.001#
Serum creatinine, mean ± SD (range), µmol/L			
At 2 weeks	183±96.8 (61–894)	277±142 (83–1,095)	<0.001*
At 3 months	164±72.0 (54–741)	235±127 (92–942)	<0.001*
At 12 months	164±75.1 (66–738)	231±147 (60–1,052)	<0.001*
Calculated GFR, mean ± SD, mL/min			
At 2 weeks	40.5 ±18.7	33.03±16.24	<0.001*
At 3 months	44.47±18.6	39.9±17.9	<0.001*
At 12 months	44.7±18.4	42.4±20.9	0.111*

DGF, delayed graft function. * Mann-Whitney U test. # Fisher's exact test.

Results

Immediate graft function occurred in 66.8% of patients (n = 332). In this group, 217 were male (65.4%), 85.5% had received a deceased donor organ (n = 284) and 14.5% a living donor organ (n = 48), the average recipient age was 50.9 ± 13.6 years (range 17–75, SD 13.6), and the average donor age was 51.4 ± 15.3 years (range 4–82, SD 15.3). Of the cadaveric transplantations, 35 were second transplantations and of the living donations 2. Of these, 11 of the cadaveric second transplantations had DGF.

DGF occurred in 33.2% (n = 165) of patients. Of these, 66.7% were male (n = 110), 93.3% had received an organ from a cadaveric donor (n = 154) and only 6.7% (n = 11) one from a living donor, the average recipient age was 54.3 ± 13.3 years (range 17–74, SD 13.3), and the average donor age was 55.7 ± 14.4 years (range 5–83, SD 14.4). The DGF group was significantly older than the non-DGF group (54.3 vs. 50.9 years, p = 0.005). The mean cold ischemia time (CIT) was significantly longer in the DGF group (13.3 h [range 2.20–28.3] vs. 12.1 h [range 1.3–28.3], p = 0.039) (Table 1).

Regarding live donor and cadaveric transplantations, the CITs for transplantation with immediate function were 2.28 ± 0.14 h and 13.8 ± 4.56 h for living donations and cadaveric donations, respectively, and in those with DGF 2.5 ± 0.44 h versus 14.1 ± 4.1 h, respectively. Thus, there was no significant difference in live donor transplantations with and without DGF regarding CIT.

DGF was more common after cadaver donor transplantation than after living donor transplantation (p = 0.012). The number of mismatches according to the Eurotransplant allocation match policy of HLA-A, -B, and -DR loci was numerically higher in the DGF group (mean 3.15 ± 1.64 vs. 2.59 ± 1.67, p = 0.001) (Table 1).

Patients with DGF underwent significantly more surgical revisions (e.g., for hematoma removal, interventions for arterial anastomotic stenosis, and venous thrombosis) than patients in the non-DGF group (35 [21.2%] vs. 30 [9%], p < 0.001). Patients with DGF underwent more transplant biopsies than non-DGF patients (94 [57.0%] vs. 49 [14.8%], p < 0.001).

There were no significant differences found in donor and recipient gender (including the various possible combinations), the pretransplantation waiting time (5.82 ± 2.71 years in DGF patients and 5.45 ± 3.09 years in non-DGF patients, p = 0.150), or the CMV status of donor and recipient (including the combinations). During follow-up, serum creatinine levels at 2 weeks, 3 months, and 12 months after transplantation were significantly higher at all times in DGF patients than in patients with immediate/early graft function (p < 0.001 for each) (Table 1).

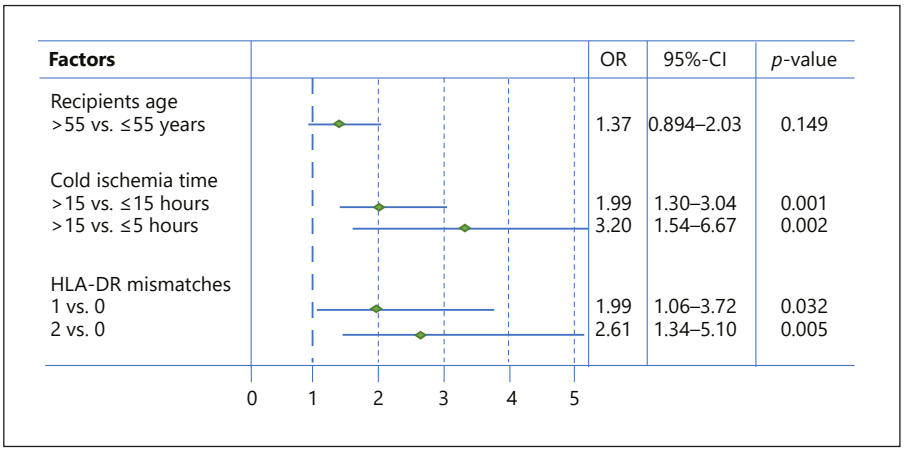

Fig. 2. Multivariate data analysis. Odds ratio with 95% confidence intervals and *p* values.

Calculated GFR was correspondingly lower in patients with DGF (after 2 weeks 33.03 ± 16.2 vs. 40.49 ± 18.7 in transplants with immediate function, respectively). Also, the same difference applied after 3 and 12 months, although all kidneys by then had taken up function. However, the difference at 12 months was clearly smaller and not significant (see Table 1).

In univariate analysis, significant factors indicating DGF were donor age >55 years versus ≤55 years (OR 1.71 [95% CI: 1.17–2.49], $p = 0.005$), CIT over 15 h versus ≤15 h (OR 9.33 [95% CI: 1.9–45.9], $p = 0.006$), 4–6 HLA mismatches ($p = 0.007$) (4 mismatches vs. no mismatches, OR 2.80 [95% CI: 1.38–5.72], $p = 0.005$), 5 mismatches versus no mismatches (OR 3.36 [95% CI: 1.55–7.28], $p = 0.002$), 6 mismatches versus no mismatches (OR 4.73 [95% CI: 1.75–12.8], $p = 0.002$), and mismatches at 1 HLA-DR locus ($p = 0.002$) (1 vs. 0: OR 1.77 [95% CI: 1.1–2.84], $p = 0.018$) or 2 HLA-DR loci (2 vs. 0: OR 2.57 [95% CI: 1.51–4.37], $p < 0.001$). By multivariate analysis, significant factors for DGF were CIT >15 h versus ≤15 h (OR 1.99 [95% CI: 1.30–3.04], $p = 0.001$), CIT >15 h versus ≤5 h (OR 3.20 [95% CI: 1.54–6.67], $p = 0.002$), and mismatches at 1 HLA-DR locus (OR 1.99, 95% CI: 1.06–3.72, $p = 0.032$) or 2 HLA-DR loci (OR 2.61, 95% CI: 1.36–5.09, $p = 0.005$) (Fig. 2).

Discussion

In clinical series, donor and recipient factors associated with DGF most frequently reported for the recipients are male gender, BMI, previous transplantation, and diabetes and for the donor female gender, increased age, and also BMI [5]. Additional factors frequently reported are warm and cold ischemia time, prior sensitization, and number of HLA mismatches [7].

In this retrospective cohort study, the overall rate of DGF of 33% corresponds to the incidence reported in the literature [3, 4]. However, in contrast to larger registry analyses, the rate of DGF in our cohort decreased over the relatively long period from 2003 to 2015. Since our surgical and medical regimens did not change substantially during this time, and both donor and recipient ages and comorbidities increased in accordance with the general development in the German renal transplant populations, we have no plausible explanation for this effect observed in our cohort.

The age of both donors and recipients as well as ischemia time was confirmed in our study as important factors for the development of DGF (Table 1). This has been reported by other studies and registry data before [3, 5, 7]. Ojo et al. [8] reported that for every 6-h increase in CIT, there is a 23% higher risk of DGF. In our cohort, DGF increased substantially with CITs over 15 h. Also, DGF was less common in living donor transplantations in accordance with other reports in the literature.

There was a significant correlation of DGF with revision surgeries and/or interventions in our study. This is not surprising as surgical complications after renal transplantation requiring interventions often lead to transiently impaired transplant function. Also, vice versa, impaired transplant function can lead to complications, so that the correlation probably does not necessarily imply a causal relationship. It is therefore explicable that DGF is associated with more complication-related secondary surgical procedures.

In addition, DGF was related to both donor and recipient age. Kidneys from older donors tend to have more inherent problems (e.g., arterial atherosclerosis), and older recipients

tend to have more comorbidities. Thus, DGF, poor transplant function, and complications after renal transplantation are increasing with increasing donor and recipient age.

HLA matching is an extremely important factor for the success of renal transplantation [6]. Therefore, the significant correlation between HLA mismatching and DGF in our study is not surprising. There was a clear and significant relationship with higher numbers of HLA mismatching seen in our study.

The observation that mismatching at the HLA-DR loci was a highly significant risk factor for DGF in our cohort is a finding that might warrant further analysis. A retrospective study by Sureshkumar et al. [9] suggested that an HLA-DR mismatch should best receive immunosuppression with an induction using depleting antibodies. In our clinical practice, we did not use any induction treatment routinely, and this might have been important.

Of importance is also the observation that patients with DGF had, on average, worse renal function after 12 months compared to those with immediate transplant function. This underscores the fact that DGF has consequences for later transplant function and transplant survival. Transplants with DGF have more episodes of acute rejection and worse long-term outcomes [10].

Despite some understanding about clinical factors promoting DGF, many issues remain poorly understood. Recently, in retrospective analyses similar to ours, early use of diuretics or large volumes of intravenous normal saline solution were reported to be associated with DGF [11, 12]. In contrast, Chaumont et al. [10] reported the absence of perioperative saline loading as predisposing to DGF. Intraoperative color duplex sonography of transplants was reported to show increased peripheral resistive indices as early as 30 min after vascular anastomosis in transplants that later showed DGF [13].

Our study has shortcomings in that not all conceivable contributing factors could be analyzed and in that it is a retrospective analysis with risks of bias. We did not evaluate BMI in our cohort; it is well known that BMI is a risk factor for DGF [14]. However, as a case-control comparison, it confirms the important factors of age and CIT as well as HLA mismatching with a special reference to HLA-DR.

There is no validated treatment for DGF and neither is there a reliable prevention strategy. As we cannot change the donor and recipient populations, we can only aim to keep CITs as short as possible, to avoid surgical complications as best as possible, and to adjust immunosuppression with an eye to patients at risk of DGF. Also, perhaps special attention should be paid to any mismatch at the DR loci if other factors predisposing to DGF are present.

Whether methods to reduce DGF such as graft machine perfusion will be effective is still under debate [15, 16]. Since a randomized, controlled study showed a significant reduction in DGF and an improvement in 3-year graft survival of 4% [17], considerable interest in evaluating this technique has been created which might become part of a strategy to reduce DGF.

Conclusions

DGF is related to donor and recipient age, CIT, and HLA mismatches. The HLA-DR locus may be of particular importance in this respect. Although renal function improved in DGF patients, this is still less good after 12 months than it is in non-DGF patients.

Statement of Ethics

This project of anonymous retrospective patient data review was approved by the Internal Review Board of the University Hospital Rostock (date of approval: January 31, 2016). The study was conducted according to the guidelines of the Declaration of Helsinki. Written informed consent from participants was not required in accordance with local/national guidelines. In the case of retrospective evaluation of existing, internal patient, and examination data, there is only a simple obligation to notify to the Ethics Committee of the University of Rostock. Furthermore, all data have been anonymized.

Conflict of Interest Statement

The authors of this manuscript have no conflicts of interest to disclose.

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Author Contributions

Karoline Kernig supervised data acquisition and analysis, Veronika Albrecht performed data acquisition and analysis, Desiree Dräger reviewed data analysis and drafted the manuscript, Andreas Führer reviewed the data and manuscript, Steffen Mitzner reviewed the data and manuscript, Günther Kundt performed statistical analysis, and Oliver Hakenberg reviewed data and revised the manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (K.K.) upon reasonable request.

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