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Predictors and outcomes of delayed graft function after living-donor kidney transplantation

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Summary

Delayed graft function (DGF) following deceased donor kidney transplantation is associated with inferior outcomes. Delayed graft function following living-donor kidney transplantation is less common, but its impact on graft survival unknown. We therefore sought to determine risk factors for DGF following living-donor kidney transplantation and DGF's effect on living-donor kidney graft survival. We analyzed living-donor kidney transplants performed between 2000 and 2014 in the UNOS dataset. A total of 64 024 living-donor kidney transplant recipients were identified, 3.6% developed DGF. Cold ischemic time, human leukocyte antigen mismatch, donor age, panel reactive antibody, recipient diabetes, donor and recipient body mass index, recipient race and gender, right nephrectomy, open nephrectomy, dialysis status, ABO incompatibility, and previous transplants were independent predictors of DGF in living-donor kidney transplants. Five-year graft survival among living-donor kidney transplant recipients with DGF was significantly lower compared with graft survival in those without DGF (65% and 85%, respectively, $P < 0.001$). DGF more than doubled the risk of subsequent graft failure (hazard ratio = 2.3, 95% confidence interval: 2.1–2.6; $P < 0.001$). DGF after living-donor kidney transplantation is associated with inferior allograft outcomes. Minimizing modifiable risk factors may improve outcomes in living-donor kidney transplantation.

Introduction

Delayed graft function (DGF) occurs in approximately 25% of deceased donor (DD) kidney transplants transplantation [1,2]. There is clear evidence that DGF after DD kidney transplantation is associated with inferior graft survival [3–6]. In general, the reported incidence of DGF is low in living-donor (LD) kidney transplants, ranging between 1% and 8% [7,8]. However, the effect of DGF on LD kidney transplant outcomes remains controversial [8,9]. A number of recipient and donor variables have been identified as risk factors for DGF for patients with DD grafts [2,10]. However, factors associated with DGF following LD kidney transplantation, and the outcomes of DGF for LD recipients remain unknown. The aim of this study was to investigate predictors for DGF after LD kidney transplantation and to determine the impact of DGF on LD allograft outcomes.

Methods

Patients

After approval from the Health Sciences University of Wisconsin Institutional Review Board, we analyzed adult, LD kidney transplants performed between the years of 2000 and 2014. Data were obtained from the OPTN registry via UNOS. The clinical and research activities being reported are consistent with the Principles of the Declaration of

Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Exclusion criteria

Graft losses secondary to technical failures, hyperacute rejection, and primary nonfunction were excluded from the analysis. Multiple organ transplant recipients were excluded.

Definition of DGF

DGF was defined as having received dialysis within 1 week of transplantation. Serum creatinine measurements were not available for analysis.

Graft loss

Time to allograft loss was calculated by determining the date of transplantation and subtracting this from the date of allograft loss as reported by UNOS.

Statistical analysis

Kaplan–Meier survival analyses were used to determine allograft and patient survival rates. Regression models were constructed to compare risk factors for both DGF (logistic regression) and 5-year allograft failure (Cox regression). Variables that where statistically significant ($P < 0.05$) in the univariate analysis were entered into the multivariable model. In our primary analyses, multivariate models were constructed using patients with complete data. To demonstrate that eliminating patients with incomplete data did not significantly affect the primary relationships of interest, we conducted sensitivity analyses with multiple imputations of missing covariates for variables missing >5% of data. Sensitivity analyses were performed in which missing values were imputed using values corresponding to the 90%, 10%, and mean among patients who did have data for these variables. These secondary analyses demonstrated similar results when compared with the primary analyses and are not included in this report. Variables were compared between groups using one-way ANOVA, *t*-tests, and chi-squared tests, as appropriate. All analyses were performed using SPSS version 22 (SPSS Inc, Chicago, IL, USA).

Results

Incidence of DGF

Of the 64 042 adult, living-donor kidney transplants, 2282 (3.6%) developed DGF (Table 1). Living-donor recipients with DGF were more often male, African American, diabetic (35.3% vs. 26.1%, $P < 0.001$). Those with DGF also had more human leukocyte antigen (HLA) mismatches (<0.001), had higher body mass index (BMI) (28.4% vs. 26.9, $P < 0.001$), were more highly sensitized with panel reactive antibody (PRA) levels of 16.7% compared with 13.2% ($P < 0.001$), and were more likely to have had a previous kidney transplant (11.3% vs. 9.1%, $P < 0.001$). Mean donor age was higher (42.1 years vs. 40.9 years, $P < 0.001$), and donors were more likely to be African American (21.3% vs. 14.6%, $P < 0.001$) in those recipients who had DGF than in their counterparts without DGF.

Table 1. Recipient characteristics.

	No DGF	DGF	*P* value
Patients	61760	2282	
Mean age of recipient, years (SD)	45.97 (15.1)	46.46 (15.1)	ns
Male recipient (%)	37360 (60.5)	1510 (66.2)	<0.001
Recipient race (%)			
White	40178 (65.0)	1343 (59.0)	<0.001
Black	9016 (14.7)	487 (21.3)	
Other	12566 (20.3)	458 (19.7)	
HLA mismatch (%)			
0	4922 (8.0)	132 (5.8)	<0.001
1	3117 (5.1)	99 (4.5)	
2	9889 (16.1)	342 (15.2)	
3	16585 (27.1)	573 (25.3)	
4	9465 (15.5)	371 (16.4)	
5	11234 (18.3)	468 (20.7)	
6	6041 (9.9)	276 (12.2)	
PRA, mean (SD)	13.6 (25.6)	16.7 (29.2)	<0.001
ABO incompatibility (%)	751 (1.2)	41 (1.8)	0.017
Median wait time, days (range)	204 (0–6769)	238 (0–4643)	<0.001
Preemptive transplant (%)	26570 (43)	482 (21)	<0.001
Previous kidney transplant (%)	5634 (9.1)	259 (11.3)	<0.001
Recipient diabetes (%)	15886 (26.1)	794 (35.3)	<0.001
Recipient BMI (SD)	26.9 (5.5)	28.4 (6.0)	<0.001
Rejection in first year (%)	4713 (7.6)	418 (17.8)	<0.001
Length of stay, days (SD)	5.9 (13.9)	13.9 (15)	<0.001

BMI, body mass index; DGF, delayed graft function; HLA, human leukocyte antigen; PRA, panel reactive antibody; SD, standard deviation.

Patients with DGF experienced, on average, longer cold ischemic time (CIT) (2.2 h vs. 2.6 h, $P < 0.001$) and greater shipping distances (15.7 mi vs. 21.8 mi, $P = 0.033$), as compared to recipients who did not experience DGF. The majority of LD kidney transplants performed were not shipped (97.4% nonshipped compared to 2.6% shipped) and therefore experienced little to no CIT and obviously no shipping distance. This likely accounted for the low CIT and shipping distances seen in both groups. Therefore, examining just those kidneys that were shipped ($n = 1698$), the average CIT was longer in those recipients who experienced DGF, 6.8 h vs. 9.0 h, $P = 0.04$. For shipped kidneys,

the mean distance was greater in recipients that experienced DGF compared to those that did not, but this did not meet statistical significance, 578.9 mi vs. 725.4 mi, $P = 0.092$ (Table 2).

We next compared the median creatinine (cr) level preoperatively, and at the last donor follow-up postdonation, in an attempt to quantify weather there was any difference between those recipients with DGF and those without DGF. The mean preoperative cr for recipients with DGF was 0.88 compared to 0.87 for recipients without DGF ($P = 0.282$). The mean cr at last donor follow-up for recipients with DGF was 1.23 compared to 1.24 for recipients without DGF ($P = 0.276$) at a median follow-up time of 5 months (0–43 months). Additionally, the postoperative presence of urine protein on urinalysis was not statistically different between the two groups (3.9% vs. 5.4%, $P = 0.198$).

DGF risk factors

Univariate analysis revealed a number of recipient factors associated with DGF in LD transplant. Pretransplantation dialysis, previous kidney transplant(s), PRA, ABO incompatibility, history of diabetes, BMI, recipient gender, and African American recipient race were independent predictors of DGF after LD kidney transplantation (Table 3). With regard to donor factors, CIT, shipping distance, donor age, BMI, and African American donor race were associated with DGF. Lastly, performing a right donor nephrectomy and open nephrectomy represented a risk factor for DGF. In a multivariate analysis, all parameters except shipping distance and African American donor race remained significant (Table 3).

Table 2. Donor characteristics.

	No DGF	DGF	*P* value
Mean donor, age, years (SD)	40.93 (11.3)	42.1 (11.8)	<0.001
Male (%)	24624 (39.9)	938 (41.1)	
Donor race (%)			
White	40178 (65.1)	1343 (58.9)	<0.001
Black	9016 (14.6)	487 (21.3)	
Other	12566 (20.3)	452 (19.8)	
Mean CIT, hours (SD)	2.2 (5.3)	2.6 (5.8)	0.019
Mean CIT of shipped kidneys, hours (SD)	6.8 (5.4)	9.0 (7.1)	0.04
Mean shipping distance, miles (SD)	15.7 (147.1)	21.8 (181.2)	0.033
Mean shipping distance of kidneys shipped, miles (SD)	578.9 (705.0)	725.4 (762.8)	0.092
Laparoscopic nephrectomy (%)	53928 (87.7)	1903 (83.9)	<0.001
Right kidney (%)	7589 (12.3)	378 (16.6)	<0.001

CIT, cold ischemia time; DGF, delayed graft function; mi, miles; SD, standard deviation.

Outcomes: allograft and patient survival

Five-year actuarial allograft survival was inferior for those patients who experienced DGF when compared to patients who did not experience DGF (65% vs. 85%, respectively, $P < 0.001$). In a multivariate analysis, controlling for donor and recipient factors, DGF was identified as one of the strongest predictors of inferior graft survival (hazard ratio = 2.3; 95% confidence interval: 2.1–2.6; $P < 0.001$, Table 4). DGF was also associated with inferior patient survival. The overall actuarial patient survival over the study period was 67.8% for patients that did not have DGF compared to 56.7% that did have DGF.

Outcomes: rejection rates

A total of 17.8% of patients who had DGF developed rejection within 1 year, as compared to only 7.6 percent in those who did not have DGF, $P < 0.001$. Despite this observation of increased rejection in DGF kidneys, we did not observe an increase in graft loss secondary to rejection between the two groups. A total of 18% of kidneys with DGF failed secondary to acute rejection and 22.2% from chronic rejection. This compares to 24.2% and 30.9% of kidneys without DGF that failed secondary to acute and chronic rejection, respectively ($P < 0.001$).

Outcomes: hospital length of stay

The mean length of hospital stay was 13.9 days for living-donor kidneys recipients with DGF, as compared to only to 5.9 days for recipients of living-donor kidneys without DGF, $P < 0.001$.

Discussion

DGF in recipients of DD kidney transplants is associated with inferior outcomes [3–6], but the impact of DGF on LD kidney transplantation outcomes is less clear. LD kidney transplantation has a well-established survival benefit over DD kidney transplantation. Identifying modifiable pretransplantation risk factors of DGF (e.g., CIT) is important for optimization of long-term graft outcomes. This issue is of increasing importance, as LD kidneys are now experiencing increased CIT with national exchange programs [11].

We identified risk factors for the development of DGF, many which not surprisingly are similar to those described for DD kidney transplantation [2,10]. In a univariate analysis, we identified that donor factors (shipping distance,

Table 3. Risk factors for DGF in living-donor kidneys.

Variable	Univariate	*P* value	Multivariate	*P* value
CIT >12 h	1.447 (1.093–1.916)	0.010	1.377 (1.216–1.643)	0.037
Distance>2000 mi	2.040 (1.071–3.884)	0.030	ns	ns
HLA mismatch >4	1.256 (1.155–1.366)	<0.001	1.296 (1.167–1.439)	<0.001
Donor age >50 yp	1.210 (1.103–1.328)	<0.001	1.261 (1.123–1.417)	<0.001
PRA>80	1.518 (1.304–1.767)	<0.001	1.484 (1.215–1.812)	<0.001
ABO incompatibility	1.486 (1.082–2.041)	0.014	1.517 (1.047–2.197)	0.027
Diabetes	1.542 (1.412–1.685)	<0.001	1.418 (1.269–1.585)	<0.001
Recipient BMI >25	1.439 (1.315–1.574)	<0.001	1.331 (1.185–1.496)	<0.001
Donor BMI >25	1.295 (1.178–1.423)	<0.001	1.171 (1.046–1.312)	0.006
Female recipient gender	0.783 (0.717–0.855)	<0.001	0.785 (0.701–0.879)	<0.001
African American recipient	1.587 (1.432–1.759)	<0.001	1.399 (1.229–1.585)	<0.001
African American donor	1.437 (1.286–1.605)	<0.001	ns	ns
Previous kidney transplant	1.275 (1.117–1.456)	<0.001	1.210 (1.007–1.454)	0.042
Laparoscopic nephrectomy	0.733 (0.653–0.822)	<0.001	0.769 (0.657–0.901)	0.001
Right nephrectomy	1.417 (1.266–1.587)	<0.001	1.413 (1.216–1.643)	<0.001
On dialysis	2.818 (2.545–3.120)	<0.001	2.725 (2.399–3.096)	<0.001

BMI, body mass index; CIT, cold ischemia time; DGF, delayed graft function; HLA, human leukocyte antigen; mi, mile.

CIT, etc.), recipient factors (PRA, etc.), and technical factors (right side donor nephrectomy) increased the risk of developing DGF after living-donor kidney transplantation. In a multivariate analysis, all parameters except shipping distance and African American donor race remained significant. We speculate that shipping distance failed to remain significant in the multivariate analysis because shipping distance acted as a surrogate marker for CIT.

Specifically addressing CIT, in our multivariate analysis, CIT stratified at greater or <12 h was found to be the time point most associated with DGF in LD kidney transplants. Other authors have tried to address the effect of CIT on the outcomes of LD kidney transplant. Prior to paired kidney exchanges; Simpkins *et al.* addressed the impact of CIT on living-donor kidneys to demonstrate the feasibility of shipping living-donor kidneys [8]. The authors examined the effects of CIT on living-donor kidneys by querying the UNOS database. CIT in this study was largely due to logistical delays in performing the recipient operation. Authors found that the majority of kidneys in this study had a CIT that was quite short, <2 h with an upper limit of 8 h. They found a trend toward increased rates of DGF with increased CIT; however, it was not statistically significant and was not observed to affect long-term graft outcome [8]. Segev *et al.* reported on the initial shipping experience and found no DGF in the initial 50 living-donor kidneys which were shipped and subsequently transplanted [12]. In this study, the average CIT was 7.2 h. We observed similar findings but were able to see a statistically significant impact of CIT>12 h on rates of DGF in our multivariate analysis. This difference was likely detected due to the larger numbers of shipped kidneys included in our study. We identified 1698 shipped kidneys compared to the 50 previously reported. The average cold time for shipped kidneys that experienced DGF was 9.0 h compared to 6.8 h for shipped kidneys that did not have DGF, $P = 0.04$. Collectively, our data support keeping CIT <12 h in LD kidney transplants to reduce the risk of DGF. Furthermore, this may prove to be even more important in LD kidney transplant that have additional risk factors identified. For example, in a LD kidney transplant from an older donor (age>50), into a higher BMI (BMI>25), sensitized (PRA>80), diabetic, African American recipient, minimizing CIT to <12 seems prudent given the data presented in this report. It is currently unclear from our data what an optimal CIT would be in a donor/recipient pair with additional risk factors identified for DGF. For example, in the above hypothetical transplant scenario of an older donor into an obese, sensitized, diabetic, African American recipient CIT may be best kept as low as possible, maybe even substantially <12 h. These data merely serve as a starting point, more work needs to be performed to determine optimal combinations of donor and recipient factors in order to maintain excellent graft outcomes four our patients.

Additionally, we observed that DGF in LD kidney recipients has significantly reduced 5-year actuarial graft survival. In an adjusted analysis, DGF was the strongest risk factor for 5-year graft failure. Therefore, identifying predictors of DGF is important because it may facilitate early intervention and ultimately prevention of DGF after LD kidney transplantation. Because of the elective nature of LD transplantation minimizing potential risk factors for DGF may prove to be more easily accomplished than for DD kidney transplantation. In the context of burgeoning national kidney exchanges, in addition to the continued expansion of living-donor indications into older and higher risk donors,

Table 4. Risk factors for living-donor kidney graft loss.

Variable	Univariate	*P* value	Multivariate	*P* value
Recipient age	1.004 (1.003–1.006)	0.010	1.003 (1.001–1.005)	0.006
Donor age	1.008 (1.006–1.010)	<0.001	1.009 (1.007–1.012)	<0.001
PRA	1.004 (1.003–1.005)	<0.001	1.002 (1.001–1.004)	<0.001
Diabetes	1.447 (1.377–1.521)	<0.001	1.321 (1.235–1.413)	<0.001
BMI recipient	1.015 (1.011–1.019)	<0.001	1.006 (1.000–1.011)	0.045
BMI donor	1.010 (1.005–1.015)	<0.001	ns	ns
Female donor	1.155 (1.101–1.212)	<0.001	1.164 (1.094–1.239)	0.001
African American recipient	1.622 (1.533–1.716)	<0.001	1.282 (1.111–1.478)	<0.001
African American donor	1.601 (1.509–1.698)	<0.001	1.219 (1.049–1.417)	0.01
Previous kidney	1.275 (1.184–1.374)	<0.001	1.197 (1.074–1.333)	0.001
Transplant on dialysis	1.732 (1.646–1.823)	<0.001	1.598 (1.495–1.708)	<0.001
ABO incompatibility	1.493 (1.244–1.793)	<0.001	ns	ns
HLA mismatch	1.060 (1.045–1.075)	<0.001	1.054 (1.034–1.073)	<0.001
CIT	1.005 (1.001–1.010)	<0.001	ns	ns
Laparoscopic nephrectomy	0.891 (0.837–0.949)	<0.001	ns	ns
Right nephrectomy	1.097 (1.025–1.173)	0.007	ns	ns
DGF	3.065 (2.826–3.323)	<0.001	2.308 (2.073–2.568)	<0.001

BMI, body mass index; CIT, cold ischemia time; DGF, delayed graft function; HLA, human leukocyte antigen; PRA, panel reactive antibody.

these predictive factors may prove essential for maintaining and maximizing long-term outcomes. For example, if a potential recipient with numerous risk factors for DGF was identified, minimizing modifiable risk factors such as CIT and/or donor age may improve recipient long-term allograft survival. One way to address these issues is to build into the LD exchange software risk factors such as those identified in this report. Presently, there are multiple exchange programs, some of which are based on geography. There are different models for producing a match, which for example include PRA, blood type, and unacceptable antigens [11]. However, here we have identified a larger number of potentially important variables which may be helpful to include as well. Not only would the inclusion of more predictors of DGF lead to better outcomes but also it may lead to more cost effective care. The average length of hospital stay for LD kidneys with DGF was significantly longer, 13.9 days verses 5.9 days for kidneys without DGF.

A point that warrants discussion is the importance of technique (specifically right-sided nephrectomy and open nephrectomy) in determining rates of DGF. In our center when necessary, we perform laparoscopic right donor nephrectomy with successful outcomes, and therefore, we were surprised by the finding that right donor nephrectomy was associated with an increased risk of DGF. We were likely able to detect this small difference (12.3% vs. 16.8%) because of the size of our dataset. However, the meaning of this result is not exactly clear but may be due to longer operative times in both the donor and recipient operations. For some centers, a right nephrectomy may be more technically challenging, and with the resultant shorter renal vein, the recipient operation too can incur longer warm times. The majority of nephrectomies were performed laparoscopically (87.0%); however, open nephrectomy was also associated DGF. It is unclear from the data if many of these open nephrectomies were failed laparoscopic attempts which could be associated with longer procurement times, hemodynamic instability, and/or more blood loss thus explaining the higher rates of DGF, or were they planned open nephrectomies. Moreover, to better understand these findings, information such as warm ischemia time, revascularization time, and vascular complexity would be helpful in future studies.

Another unexpected finding was that recipient female gender was associated with a reduced risk of DGF. It may be that in our analysis, female recipient status was a surrogate of more favorable recipient health, or perhaps of size mismatch favoring the female recipient. It is tempting to speculate that the female recipient milieu is more resistant to ischemia reperfusion injury than males [13,14], although it is difficult to draw conclusions in this regard.

It is not entirely clear from our analysis what precisely is the relationship between DGF and immunological graft injury. We acknowledge that it is interesting that many immunological risk factors (i.e., re-transplant, PRA, HLA matching, ABO incompatibility) are more prevalent in the DGF group. Thus, it begs the question—is early rejection triggering DGF, or rather, DGF triggering rejection in those patients at higher immunological risk? It is difficult to address this question in the confines of our study, but we do know from the published DD literature [4,5], and our data supports this in LD as well, that DGF is associated with acute rejection. The likely reality is that in LD, as in

DD, DGF is the sum result of multiple factors, and when possible it is best to minimize those modifiable risk factors in order to best optimize graft outcomes. Furthermore, these data would support increased attention to be given to individuals with DGF after LD transplant to prevent future graft loss. These patients may benefit from modifications in their induction and maintenance immunosuppression regimens and close monitoring of graft function for several years after LD transplant.

This was an analysis of a multicenter, self-reported data in UNOS. These data harbor inherent limitations, as do most large data base studies. While one of the many benefits of a study with large numbers is the ability to detect small differences between groups, such differences need to be interpreted appropriately. Here, we were able to detect several differences between the group of patients who experienced DGF, and those who did not. Regardless, if the factors were included into the mathematical model for donor-recipient matching, their value may be marginalized by the parameters that carry substantially more statistical weight. Thus, it is plausible that, for some patients, the addition of the metrics with lower odds ratios would not alter the donor–recipient match, and thus, not affect the incidence of DGF and ultimately graft failure in LD kidney transplant. However, we were able to successfully identify other parameters with a more pronounced effect on graft outcome, which are not presently included in the matching system. The matching algorithm should focus on variables which lead to an appreciable difference in patient outcome, and these should change over time as we identify factors that significantly predict graft outcomes. Lastly, there are multiple definitions for DGF that exist in the literature. Dialysis within the first week of transplant is the most commonly used by transplant centers. This definition tends to favor those patients who are already on dialysis. In addition, this definition underestimates the actual rate of DGF in preemptive transplants because many will not require (or may have delayed) postoperative dialysis initiation.

Lastly, information on kidney function, in addition to pre- and postoperative cr and proteinuria, such as measured GFR, birthweight, and kidney volume are lacking from our analysis and would certainly serve to strengthen it. Such data would enable for us to be able to address a key unanswered question of organ quality, that is, nephron mass and ability to withstand and regenerate from the injury of transplant and DGF. That being said, we did not observe differences in pre- and postoperative cr and the presence of postoperative proteinuria in the two donor groups. Additionally, donor factors such as increased age, BMI were associated with DGF, which could be viewed as surrogate markers for organ quality. It is clear however that more granular study is needed to be able to draw any definitive conclusions.

Conclusion

In conclusion, the cause of DGF after living-donor kidney transplantation is multifactorial. As is evident from this analysis, numerous donor, recipient, and technical factors contribute to an individual's risk for DGF after LD transplant. Attention to and optimization of these risk factors may lead to better long-term allograft outcomes in LD kidney transplant recipients.

Authorship

RRR: designed, performed research study, analyzed data and wrote the paper. JRS: performed research study, analyzed data and wrote the paper. TJZ: performed research study, analyzed data and wrote the paper. BLM: performed research study, analyzed data and collected data. DBK: performed research study, analyzed data and wrote the paper. AD: designed, performed research study, analyzed data and wrote the paper. BCA: performed research study, analyzed data and wrote the paper. MM: designed, performed research study, analyzed data and wrote the paper.

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