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Concordance of outcomes of pairs of kidneys transplanted into different recipients

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Summary

Kidney transplant outcomes are influenced by donor characteristics, including age and gender. Additional donor factors, both genetic and environmental, also influence graft outcome. We aim to assess the strength of donor factors in determining kidney transplant outcomes by comparing paired kidneys from a single donor transplanted into different recipients. We conducted a retrospective cohort study of outcomes of pairs of deceased donor kidneys transplanted in our centre between 1992 and 2008. We examined the relationship within pairs for eGFR at 1 year and at 5 years post-transplant using Spearman's Correlation and the concordance of pairs of transplant kidneys with respect to the occurrence of acute rejection and delayed graft function (DGF). A total of 652 recipient pairs were analysed. Spearman's correlation for eGFR was 0.36 at 1 year and 0.36 at 5 years post-transplant. The incidence of DGF was 11%. The odds ratio of DGF occurring if the contralateral kidney had DGF was 5.99 (95% CI, 3.19–11.25). There is a significant degree of relationship within pairs of kidneys transplanted from the same donor for serum creatinine at 1 year and 5 years post-transplant and also for the occurrence of delayed graft function.

Introduction

Both donor and recipient factors influence graft outcomes. By comparing the clinical course of two kidneys from one donor transplanted into different recipients, the relative contribution of donor factors to kidney transplant outcome can be estimated. Pairs of transplanted kidneys share identical genetic and clinical characteristics up to the time of organ recovery. Previous studies have compared kidney transplant outcomes between recipient pairs for the occurrence of delayed graft function (DGF) and allograft survival [1–3], and found a significant degree of correlation.

Delayed graft function is the need for dialysis during the first week after kidney transplantation. The incidence of DGF after deceased donor kidney transplantation is approximately 25% [4,5]. DGF has been shown to adversely affect kidney transplant outcome. Several studies have demonstrated an association between the occurrence of DGF and both acute rejection and graft failure [6,7]. It also increases length of hospital stay and cost.

Multiple factors are known to contribute to the occurrence of DGF. Donor factors include age [7,8], cause of death and hypertension [9]. Recipient factors include high panel reactive antibody (PRA) [10,11], obesity and number of previous transplants [12]. In addition, peri-operative factors such as prolonged cold ischaemia time (CIT) increase the risk of DGF [6,10,13]. Furthermore, previous paired kidney analyses comparing outcomes between first and second kidneys have demonstrated superior graft outcomes for the first kidney compared with the second kidney transplanted [14,15]. In our study, we seek to investigate the role of additional donor factors that are as yet unmeasured, which contribute to a recipients risk for DGF.

In this study, we retrospectively analysed a national cohort of deceased donor transplant recipients transplanted at a single European centre. In Ireland, all kidney

transplants are carried out in a single centre, the National Renal Transplant Centre. There are a limited number of transplant surgeons and patients are subject to the same immunosuppression protocols. This removes the 'centre effect'. We compared paired kidney recipients for the occurrence of DGF, acute rejection and for eGFR at 1 year and 5 years post-transplant to evaluate the strength of the effect of donor factors on kidney transplant outcome.

Subjects and methods

Inclusion criteria

A retrospective analysis of all first deceased donor kidney transplants in the Republic of Ireland between January 1 1992 and December 31 2008 was performed. In Ireland, all kidney transplants are performed at a single centre, the National Kidney Transplant Unit at Beaumont Hospital, and thus we have a high proportion of kidney pairs to analyse. We excluded living donor recipients, recipients of en bloc kidney transplants and simultaneous pancreas–kidney recipients and included only paired allografts.

Data sources and definition of outcomes

Data at the time of transplant and all follow-up data were attained from the Beaumont Hospital Renal Database (Clinical Vision, 3.4a version 1.1.34.1, Clinical Computing, Cincinnati, Ohio, USA) and the National Renal Transplant Registry. This included information such as donor age, sex and cause of death, recipient details including age, sex, degree of HLA mismatching and PRAs. Post-transplant, all patients received standard immunosuppression with a calcineurin inhibitor, prednisone and either azathioprine or mycophenolate mofetil. Delayed graft function was defined as the need for dialysis in the first week after transplant. Acute rejection was defined as rejection that occurred in the first 3 months after transplantation. Acute rejection was diagnosed by transplant biopsy. During the study period, we did not have an international kidney exchange programme, and thus all kidneys that are transplanted in Ireland come from within our own country. There were no donors after cardiac death.

Statistical analysis

'Kidney A' was chosen randomly and 'kidney B' are the pairs of kidney A. Demographic variables were compared using Pearson Chi-Squared test and Wilcoxon matched pairs Sign-Rank tests. Logistic regression was used to estimate an unadjusted odds ratio for the correlation of the occurrence of delayed graft function within pairs. We performed a logistic regression to estimate odds ratios for DGF in recipients of a donor pair, given that the outcome occurred in the recipient of the contralateral kidney. We estimated attributable risk (AR) to compare the relative proportion of the risk for DGF experienced by recipients with DGF in the contralateral kidney. To calculate AR, the DGF status of one of the pairs of recipients with a common donor was randomly selected as the outcome, and the DGF status of the recipient was the exposure. The AR estimates were adjusted for all factors that are significantly associated with DGF including donor age, donor sex, donor cause of death, recipient age, and recipient sex, degree of HLA mismatching, PRA and cold ischaemia time.

The relationship within pairs for estimated GFR at 1 year and 5 years post-transplant was evaluated using Spearman's Correlation. When at least one kidney required dialysis or failed or serum creatinine was unknown/missing, the pair was excluded. Modification of diet in Renal Disease (MDRD) equation was used to calculate eGFR. Statistical analyses were performed using Stata (version 10; College Station, Texas). Attributable risks in the analysis of DGF were estimated using the PArccs package in R [(C) 2009 The R Foundation for Statistical Computing]. A P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

A total of 1304 recipients (652 pairs) were analysed. The baseline characteristics of the recipients are summarized in Table 1. There were no significant differences between

Table 1. Demographic characteristics of patients.

Variable	Kidney A (n = 652)	Kidney B(n = 652)	P value
Recipient age (years)	43.9 ± 16.1	44.1 ± 15.9	0.84
Recipient sex (%male)	64.3	63.3	0.73
Cold ischaemia time, h	20.6 ± 5.7	20.3 ± 5.6	0.48
No. of HLA Mismatches			
0	3.1%	2.5%	0.35
1–3	63.5%	63.0%	
4–6	33.4%	34.5%	
PRA[1]			
0–10%	82.7	85.7	0.26
11–49%	9.8	8.8	
50–100%	7.5	5.5	
Pre-emptive Transplant	4.3%	5.5%	0.31
Dialysis duration, months	18.2 (10.3, 30.6)	18.5 (10.4, 29.8)	0.65
DGF (%)	11.0	11.4	0.86

Data are expressed as mean ± SD, median (interquartile range) or as proportion (%) 1-PRA, panel reactive antibody.

the recipients. 4.8% of transplants were pre-emptive. Each group has identical donor characteristics because of the use of paired kidneys. Mean donor age was 38.02 ± 14.93. 57.67% of donors were male. The causes of donor death were trauma (41%), intracranial haemorrhage (49%) and other/miscellaneous (10%). Causes of end stage renal disease (ESRD) included glomerulonephritis (26.53%), chronic pyelonephritis (15.49%), polycystic kidney disease (13.65%) and diabetes mellitus (5.21%), other (26.16%) and unknown (12.96%). There were no significant differences between the groups with regard to cause of ESRD.

Graft function and eGFR at 1 year and 5 year post-transplant

Figure 1 is a Kaplan Meier curve of renal allograft survival for kidney pairs. Graft half-life is 12.39 years in kidney A group and 13.12 years in kidney B group. One year graft survival was 91.88% in Kidney A group and 90.35% in kidney B group. We examined the concordance of function in kidney pairs by performing a correlation analysis for eGFR at year 1 and year 5 post-transplant. The results are shown in Figs 2 and 3. The eGFR significantly correlated within pairs at both 1 year and 5 years following kidney transplantation.

Delayed graft function

Delayed Graft Function occurred in 11% of kidney transplant recipients. Within pairs of recipients from the same donor, the odds ratio for DGF occurring if the contralateral kidney had DGF was 5.99 [95% confidence interval (CI) 3.19–11.25, $P < 0.05$]. Both pairs developed delayed graft function in 4% of the donor kidneys. If we randomly select two kidney transplant recipients, the expected incidence of delayed graft function occurring in both patients is 1.2%.

In the adjusted model, when one recipient experienced DGF, donor age was the only statistically significant risk factor for DGF (Table 2).

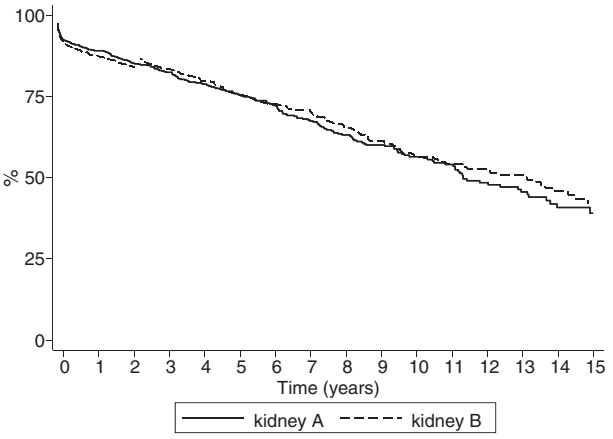

Figure 1 Graft survival in Group A and Group B 'Kidney A' kidneys were chosen randomly and 'Kidney B' kidneys are the pairs of 'Kidney A'.

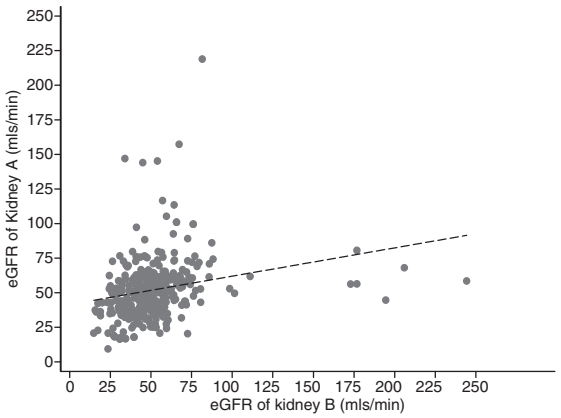

Figure 2 Correlation of eGFR at Year 1 post-transplant: r = 0.36, $P < 0.001$, number of observations = 323.

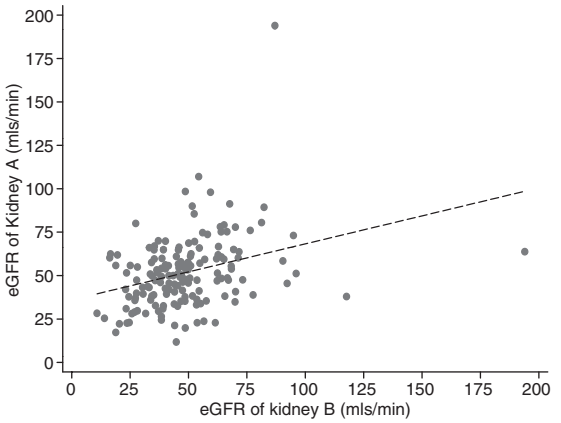

Figure 3 Correlation of eGFR at Year 5 post-transplant: r = 0.36, $P < 0.001$, number of observations = 161.

Attributable risk

Tables 2, 3 and 4 are the odds ratio for DGF, acute rejection and graft failure at 3 years, respectively, when the outcome occurred in the recipient of the contralateral kidney. Table 5 estimates the AR for delayed graft function adjusted for variables in Tables 2, 3 and 4. Attributable risk is the proportion of the incidence of a disease in the exposed that is because of the exposure – in this case, the occurrence of delayed graft function in

Table 2. Odds of DGF given that the recipient of the contralateral donor kidney had DGF.

Variable	Odds ratio (95% CI)	*P* value
Donor cause of death (trauma vs. nontrauma)	0.96 (0.61–1.52)	0.87
Donor Age (vs. <35 years)		
35–49 years	1.63 (0.96–2.74)	0.07
>50 years	2.82 (1.64–4.88)	<0.001
Recipient age(vs. <35 years)		
35–49 years	1.20 (0.68–2.1)	0.53
>50 years	1.42 (0.83–2.42)	0.20
Donor gender (male)	0.98 (0.65–1.46)	0.92
Recipient gender (male)	1.11 (0.75–1.65)	0.61
PRA group (>10% vs. <10%)	1.16 (0.83–1.60)	0.39
Cold ischaemia time(vs. <15 h)		
15–20 h	1.00 (0.50–1.99)	0.99
20–25 h	1.36 (0.69–2.70)	0.37
>25 h	1.28 (0.61–2.71)	0.52
HLA group (vs. 0 mismatch)		
1–3	0.64 (0.23–1.76)	0.38
4–6	0.77 (0.28–2.19)	0.63

Table 3. Odds of acute rejection given that the recipient of the contralateral donor kidney had acute rejection.

Variable	Odds ratio (95% CI)	*P* value
Donor cause of death (trauma vs. nontrauma)	1.03 (0.74–1.45)	0.85
Donor age (vs. <35 years)		
35–49 years	0.91 (0.63–1.39)	0.59
>50 years	1.06 (0.71–1.60)	0.76
Recipient age(vs. <35 years)		
35–49 years	1.31 (0.90–1.90)	0.15
>50 years	0.85 (0.58–1.25)	0.42
Donor gender (male)	0.77 (0.56–1.05)	0.10
Recipient gender (male)	1.02 (0.76–1.38)	0.87
PRA group (>10% vs. <10%)	1.10 (0.85–1.42)	0.48
Cold ischaemia time(vs.<15 h)		
15–20 h	1.53 (0.86–2.71)	0.15
20–25 h	2.17 (1.22–3.87)	0.01
>25 h	2.33 (1.26–4.28)	0.01
HLA group (vs. 0 mismatch)		
1–3	2.20 (0.66–7.42)	0.21
4–6	3.12 (0.92–10.61)	0.07

the contralateral kidney was considered the exposure. The AR for DGF was 0.32 or 32.2% (95% CI 0.237–0.425, $P < 0.05$). The rate of acute rejection was 22.7% in kidney A and 19.3% in kidney B. The AR for acute rejection (Table 5) and graft failure at 1 year was not significant (not shown). The AR for graft failure at 3 years when the mate kidney had failed at 3 years was 0.17 (95% CI 0.04–0.34, $P < 0.05$).

Table 4. Odds of graft failure at 3 years given that the recipient of the contralateral donor kidney had graft failure at 3 years.

Variable	Odds ratio (95% CI)	*P* value
Donor cause of death (trauma vs. nontrauma)	0.77 (0.51–1.15)	0.20
Donor age (vs. <35 years)		
35–49 years	1.48 (0.96–2.28)	0.07
>50 years	1.49 (0.92–2.40)	0.10
Recipient age(vs. <35 years)		
35–49 years	0.69 (0.42–1.14)	0.15
>50 years	1.48 (0.96–2.28)	0.08
Donor gender (male)	0.95 (0.67–1.36)	0.78
Recipient gender (male)	0.84 (0.60–1.18)	0.32
PRA group (>10% vs. <10%)	1.45 (1.10–1.89)	0.007
Cold ischaemia time(vs. <15 h)		
15–20 h	3.39 (1.41–8.12)	0.006
20–25 h	4.28 (1.79–10.26)	0.001
>25 h	3.25 (1.29–8.18)	0.012
HLA group (vs. 0 mismatch)		
1–3	0.53 (0.22–1.31)	0.17
4–6	0.59 (0.23–1.47)	0.26

Table 5. Attributable risk estimates*.

Risk factor	Attributable risk (95%CI)
Delayed graft function in the recipient of the mate kidney	0.32 (0.24–0.43) $P < 0.001$
Acute rejection in the recipient of the mate kidney	0.03 (−0.26 to 0.16) $P = 0.54$
Graft Failure at 3 years in the recipient of the mate kidney	0.17 (0.04–0.34) $P = 0.02$

*AR estimates adjusted for variables associated with DGF, acute rejection and graft failure at 3 years as shown in Tables 2–4.

Discussion

Our study demonstrates a significant degree of relationship between pairs of kidneys from a single donor for early and late transplant outcomes, including delayed graft function, and eGFR at 1 year and at 5 years. To our knowledge, this is the largest study to date evaluating paired kidney transplant outcome and concordance of kidney function in a single centre and in Europe.

Studies on the effect of DGF on long-term graft survival have yielded conflicting results, however, several studies have shown a negative impact of DGF on renal transplant survival [6–8,14]. A previous study at our centre by Giblin *et al.* showed that the graft half-life for a transplant with DGF was 3.56 years compared with 9.9 years for those without DGF [14]. A systematic review and meta-analysis by Yarlagadda *et al.* examined the relationship between DGF and patient survival by combining the results of 21 studies [16]. They found a 41% increase

in graft loss at 3.2 years of follow-up. Yarlagadda also highlighted the variation in the definition of delayed graft function used in studies of DGF in a separate systematic review [17]. The most commonly used definition is that of the need for dialysis in the first week after transplant and this is the definition we have used in our study. Previous studies have also shown that when DGF occurs in one kidney transplant, there is an increased risk of DGF occurring in the mate kidney [1,2]. The results of our study confirm this association.

In our group of patients, the odds of DGF occurring in a kidney transplant when the mate kidney develops DGF is 5.99. Following adjustment for common factors associated with the development of DGF, the AR for DGF when DGF occurred in the mate kidney was 32%. In other words, nearly one-third of the risk for the development of DGF was derived from the exposure to DGF in the mate kidney independent of donor age, sex and cause of death. Thus, there are unmeasured factors within the donor contributing significantly to a patient's risk for DGF. Louvar *et al.* [2] previously calculated adjusted AR estimates and found that exposure to DGF in the mate recipient was a stronger risk factor for DGF than exposure to an expanded criteria donor. We found an even greater AR in our large, single centre, patient group. The adjusted AR for graft failure at 3 years when the mate kidney had failed was 17.9%. The AR for graft failure at 1 year was not significant and this reflects the fact that non donor factors such as surgical complications and immunological risk have a greater impact on early graft loss. Similarly, the AR for acute rejection was not significant and this is because recipient factors play a stronger role in the occurrence of acute rejection.

Gourishankar *et al.* have previously studied 220 pairs of kidneys and shown that kidney pairs have a significant correlation for serum creatinine up to 8 years post-transplant [3]. Six-month graft survival and renal function were reduced in grafts for which the mate kidney had functional impairment (dialysis dependency, low urine output [≤1 l] in the first 24 h post-transplant or day-7 serum creatinine ≥400 μmol/l) even for kidneys, which themselves lacked those criteria. In our study, eGFR at 1 year and 5 years post-transplant were significantly correlated with a spearman's correlation of 0.36. We used eGFR instead of serum creatinine as eGFR better accounts for recipient characteristics. This correlation of kidney function between kidney pairs up to 5 years, and independent of the occurrence of DGF highlights the enduring nature of donor factors effect on kidney transplant outcome. Furthermore, when evaluating transplant dysfunction, the performance of the mate kidney should also be assessed.

In Ireland, all kidney transplants are performed in a single centre. This means we have a high proportion of transplant pairs to analyse. Our DGF rate of 11% compares favourably with international standards. The low mean donor age in our patient group is a factor in the low rate of DGF. The cold ischaemia time was similar in the two groups and this is because kidney A and B were selected randomly, and therefore there was an equal distribution of kidneys that were transplanted first and second. The mean cold ischaemia time during the study period was long because tissue typing was only available during daytime office hours. However, since 2005, a 24-h tissue typing service was introduced and we have seen a progressive decline in overall mean cold ischaemia time to 14.3 h in 2010.

Having adjusted for factors that are known to increase the risk for DGF including donor age and sex, there are other unmeasured donor factors that contribute to a recipient's risk for DGF. These are a combination of environmental and genetic factors. Environmental factors include donor hypertension, terminal creatinine and vasopressor use at time of death.

We propose that genetic variation amongst donors accounts for some of the concordance of kidney function. Previous studies have demonstrated an association between donor genetic polymorphisms and kidney transplant outcome including DGF [18], acute rejection [19] and chronic allograft nephropathy [19]. A study by St Peter *et al.* [18] showed that patients receiving a kidney from a donor who expresses the glutathione-S-transferase M1*B polymorphism either alone or in combination with glutathione-*S*-tranferase M1*A had significantly lower rates of delayed graft function. Moore *et al.* also demonstrated that kidneys from donors with caveolin-1 genotype AA have significantly lower 10-year graft survival because of an increase in transplant kidney fibrosis [20]. This was a candidate gene study.

Further study of genetic associations with kidney transplant outcome is warranted and genome wide association studies could reveal previously unidentified polymorphisms. Tissue injury around the time of organ recovery and up-regulation of inflammatory cytokines during organ reperfusion are involved in the development of DGF [21]. Identification of specific genetic polymorphisms that increase the risk of ischaemia-reperfusion injury could potentially lead to novel therapeutic strategies to reduce the risk of DGF. Identification of genetic polymorphisms that predispose to the development of chronic allograft nephropathy could lead to enhanced surveillance of patients deemed at increased risk and appropriate adjustment of immunosuppression in these patients.

Our study has some notable limitations. First, we have the limitations inherent to any single centre study. However, confining the study to one centre reduces the

confounding effects of multiple surgeons and immunosuppression protocols. Second, there are several clinical factors including donor creatinine and donor hypertension, which can influence risk for DGF and have not been included in our analysis. Even though we have adjusted for a large number of recipient, donor and transplant variables, residual confounding from some of these factors cannot be excluded.

In summary, we found a significant degree of correlation amongst pairs of kidneys transplanted from a single donor for the occurrence of DGF and for eGFR at 1 year and 5 years post-transplant demonstrating that donor characteristics have a significant and enduring impact on kidney transplant outcomes. Further research into the role of donor and recipient genetic polymorphisms in kidney transplant outcome will enhance our understanding of mechanisms underlying graft failure and potentially lead to the identification of novel biomarkers and therapeutic targets.

Authorship

CT: wrote paper. PO: analysed data. MD, CM and PJC: designed paper, critical appraisal.

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