# Outcomes in Third and Fourth Kidney Transplants Based on the Type of Donor

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**Background.** An increasing number of patients are requiring multiple retransplants. We assessed outcomes of third and fourth kidney transplants, to aid decision making on the most suitable donor type. **Methods.** Data were collected retrospectively for 2561 transplants, including 69 third and 8 fourth, performed from 2000 to 2017. Demographics and outcomes for the combined third/fourth group were compared to first and second transplants. Within the third/fourth kidney transplant group, comparisons were made between deceased donors (n = 39), live donor HLA-compatible (n = 23) and -incompatible (n = 13) transplants, as well as between standard (n = 25) and extended-criteria (n = 14) deceased donor transplants. **Results.** Patient survival did not differ significantly by transplant number ($P = 0.532$), whereas death-censored graft survival declined progressively, from 89% at 5 years in first, 85% in second and 74% in the third/fourth transplant group ($P < 0.001$). Within the combined third/fourth transplant subgroup, 5-year graft survival was found to be 100% in recipients of HLA-compatible live donors, compared to 75% in deceased donors and 53% in HLA-incompatible live donors, although this difference did not reach statistical significance ($P = 0.083$). No significant difference in patient survival ($P = 0.356$) or complication rates ($P = 0.757$) were detected between these groups. For recipients of deceased donors in the third/fourth transplant group, there were no significant differences between standard versus extended-criteria donors for any of the outcomes considered. **Conclusions.** Despite variable functional outcomes, third and fourth kidney transplant recipients experience comparable patient survival rates to first and second transplants, regardless of the donor type. In selected patients, HLA-incompatible live donors and extended-criteria deceased donors should be considered.

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Advances in immunosuppression and perioperative care of kidney transplant patients have resulted in improvements in short- to medium-term outcomes. These achievements have not yet translated into advances in longer-term graft survival.[1] As a result, graft failure is now a common cause of end-stage kidney disease (ESKD) and an increasing proportion of recipients will require multiple transplants throughout their lifetime.[2-4] This has ramifications for the individual and for others waiting for a scarce resource. Retransplantation improves long-term mortality, compared with remaining on dialysis,[5-7] with some evidence that second graft survival rates may be comparable to first transplants.[8,9]

However, third and subsequent transplantations remain a controversial issue, with limited long-term evidence to support it.[10] Arguments against such transplants include the increased risk of infections, malignancies and surgical complications (up to 41%).[11,12] A registry analysis from the United States demonstrated that third transplants have inferior outcomes compared to first kidney transplants, but provide a survival benefit over remaining on the waiting list.[13] This analysis also demonstrated a selection bias toward better quality donors and did not take into account the increasing experience with desensitization protocols and marginal donors. In addition, no such analysis exists from other countries.

Patients requiring such repeated transplants are physiological weaker, surgically more challenging and highly sensitized, compared with the time of their first transplant.[14] Therefore, sensible donor selection is paramount. Within

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current transplant practice, these patients have the difficult choice of either having a prolonged wait for potentially marginal deceased donor, undergoing high-risk desensitization protocols and an incompatible transplant, or entering a donor-recipient national exchange scheme with the possibility of undergoing several unsuccessful "matching runs." The limited series of third and subsequent transplants in the literature have very few live donor recipients or marginal deceased donors to guide clinicians and patients.[15]

The aims of this article were twofold. First, we analyzed overall outcomes in our more heterogenous and contemporary third and fourth transplant recipients. This included comparison with first and second transplants performed at our center. Second, we compared outcomes between the live donor (both HLA/ABO-compatible and -incompatible) and deceased donor transplants. Outcomes in these donor categories tend to vary considerably in de novo transplants, but whether this can be extrapolated to third and fourth transplants has not been explored. Crucially, these options reflect the current options available to clinicians and recipients. We have focused on surgical and immunological aspects throughout.

## MATERIALS AND METHODS

### Patient Cohort and Definitions

All adult patients (age > 18 years) receiving a single kidney transplant between February 2000 and September 2017 at our center were included. Patients were identified using a prospectively maintained database and data collected using medical records. Given the nature of this study, no ethical approval was required. In addition to baseline characteristics, operative information was obtained on the surgical approach, the need for transplant nephrectomy of old grafts and the recipient vessels used for implantation. Patients were followed up until May 2018 for the survival outcomes.

Graft survival was recorded from time of transplant to graft failure (return to dialysis) and censored at patient death-with-a-functioning-graft. Delayed graft function (DGF) was defined as the need for dialysis within the first 7 days posttransplantation, regardless of the indication. Pretransplant sensitization levels were expressed as a calculated reaction frequency (cRF), which is deduced from the proportion of the last 10000 UK blood-group compatible deceased donors exhibiting HLA antigens that react with the patient's serum. Recipients were considered highly-sensitized if they had a cRF greater than 85%. Histological classifications of antibody-mediated rejection (AMR) and T cell–mediated rejection (TCR) were based on the Banff criteria (initially 1997, then 2007 and finally 2013).[16]

### Preoperative Assessment

In addition to the standard preoperative recipient workup, patients receiving their third or subsequent transplant had additional imaging and were discussed on a case-by-case basis in a "complex-cases" multidisciplinary meeting. There were no predefined medical contraindications to retransplantation. All patients were evaluated with an iliac artery and vein duplex scan. Further cross-sectional imaging with computer tomography was performed in the majority of cases, to identify areas of vascular calcification, optimal sites for implantation, pseudo-aneurysms,[17] and the need for previous graft removal. The recipient cutoff for body mass index (BMI) was 35 $kg/m^2$. Patients who had a BMI of 30 to 35 $kg/m^2$ are encouraged to lose weight while they await surgery, but this did not preclude them from transplantation.

All patients underwent a functional cardiac assessment with either a myocardial perfusion scan or dobutamine stress echocardiography. Abnormal tests were referred to a cardiologist for further intervention. Where necessary, recipients were supported in intensive care during the immediate postoperative period.

### Immunosuppressive Protocol for HLA/ABO-compatible Transplants

Since 2010, all recipients at our center were stratified as low, standard or high immunological risk. Before 2010, all HLA/ABO-compatible transplants were treated as standard risk and cyclosporine was used instead of tacrolimus. Low risk protocols applied to first kidney transplants with no HLA antibodies. Standard risk recipients included those of black ethnicity, second or subsequent grafts, and live donors where a wife was receiving a kidney from her husband or a mother receiving a kidney from a child. The induction protocol consisted of basiliximab (20 mg IV) on day 0 and day 4 postoperatively, tacrolimus 0.075 mg/kg (0.125 mg/kg in black patients) twice daily preoperatively and methylprednisolone (1 g IV). The maintenance regime was tacrolimus 0.075 mg/kg (0.125 mg/kg in black patients) twice daily, mycophenolate mofetil (500 mg 4 times a day) and a reducing regime of prednisolone. Target trough tacrolimus levels were 10 to 12 μg/L for the first 2 months, and 8 to 10 μg/L thereafter. In total, 46 patients receiving their third or subsequent transplant were classed as standard immunological risk.

Recipients who were crossmatch negative by flow cytometry but who had donor-specific antibody (DSA) toward the new organ were considered high immunological risk. In addition to the standard maintenance regime, these patients were given alemtuzumab (MabCampath) 30 mg at induction and on day 1 postoperatively. In total, this applied to 17 patients receiving their third or fourth transplant.

### Immunosuppressive Protocols for HLA- or HLA+ABO-incompatible Transplants

Details of our HLA- and ABO-incompatible programs, including pre-operative immunological assessment and treatment, have been previously published.[18,19] In brief, HLA-incompatible or combined HLA+ABO-incompatible transplantation was defined as those with both DSA and a positive flow cytometric crossmatch. Antibody detection was performed using Single Antigen Bead analysis on the Luminex platform (OneLambda, Canoga Park, CA), with the positivity threshold for the bead median fluorescence intensity (MFI) set at greater than 1000. The threshold for performing pretransplant antibody removal was based on a 3-color flow cytometric crossmatch with a relative median fluorescence ratio between the patient's serum and the negative control serum (pool from AB group normal donors) greater than 2.3 for T cells and/or B cells.

Live donor HLA (and ABO)-incompatible recipients had individualized regimes which evolved over time, and included preoperative antibody removal, with either plasma exchange or immunoadsorption techniques, and inhibition of new antibody synthesis with IV immunoglobulin and/or rituximab.[20,21]

### Statistical Analysis

The distributions of continuous variables were assessed using graphical methods, with normally distributed data summarized as mean ± SD and medians and interquartile ranges (IQRs) used otherwise. Comparisons of ordinal and continuous factors by transplant number were performed using Kendall tau and Jonckheere-Terpstra tests, to account for the ordering of the categories, whereas $\chi^2$ tests were used for nominal factors. Survival analyses were performed using Kaplan-Meier curves and univariable Cox regression, with log-rank tests used to make comparisons between groups. Comparisons between donor types used Kruskal-Wallis tests for continuous or ordinal variables, and Fisher exact tests for nominal variables. All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $P$ less than 0.05 deemed to be indicative of statistical significance throughout.

## RESULTS

### Study Population

Between February 2000 and September 2017, our center performed a total of 2562 single kidney transplants. Of these, the majority (n = 2154, 84%) were the recipients' first transplant, with 330 second, 69 third, 8 fourth and a single fifth transplant. The fifth transplant was excluded from further analysis, due to the small sample size in this group. The third and fourth transplant groups were then combined and compared to first and second transplants (Table 1). Recipient age was found to decrease significantly with transplant number, whereas the proportions of females and patients of White ethnicity increased significantly (all $P < 0.001$). The distribution of donor types also changed significantly with transplant number ($P < 0.001$), with 17% of first transplants using donation after cardiac death (DCD) organs, compared with 4% of third and fourth transplants. Recipients of third and fourth transplants were significantly more likely to receive HLAi grafts than first transplants (19% vs 0%, $P < 0.001$), although the total number of HLA mismatches was found to decline significantly with increasing transplant number ($P < 0.001$).

Patients were followed up for a median of 79 months (IQR, 42–128) posttransplant, during which time there were a total of 310 deaths, giving patient survival rates of 98%, 96%, 93%, and 85% at 1, 3, 5, and 10 years, respectively. There were a total of 450 graft losses during the follow-up period, giving death-censored graft survival rates of 94%, 91%, 88%, and 77% and 1, 3, 5, and 10 years, respectively. Patient survival was not found to differ significantly with graft number ($P = 0.532$, Table 2, Figure 1A). However, death-censored graft survival become progressively shorter with increasing transplant number ($P < 0.001$, Figure 1B). Rates at 5 years declined from 89% in first, to 85% in second (hazard ratio, 1.32; $P = 0.038$) and 74% in the combined third/fourth transplant groups (hazard ratio, 2.33; $P = 0.025$).

### Demographics of Third and Fourth Kidney Transplantations

The third and fourth transplants (n = 77) were then assessed in detail (Table 3). In total, 51% (N = 39) of these transplants were derived from deceased donors, of whom 3 were from DCD donors. The remainder were of live donor organs, with 34% (n = 13) being HLA-incompatible and a further 6% (n = 2) being combined HLA+ABO-incompatible. Nineteen donations came from individuals related to the recipients. Of the unrelated donors, 5 donations were as a result of being in the paired/pooled donation scheme, whereas 4 were from nondirected altruistic donations. In the deceased donors group, 14 (36%) were from extended-criteria donors (ECDs)[20] with 1 patient being a combined DCD and ECD donor.

### Surgical Aspects of Third and Fourth Kidney Transplantations

At surgery, an extraperitoneal approach was achieved in 75% (n = 58) of cases, with an intraperitoneal approach employed for the remainder (25%, n = 19). In 2 of these cases, an extraperitoneal approach was converted into an intraperitoneal operation, due to difficulties in gaining exposure safely. In a further 2 cases, a midline approach was used due to difficulties in dissecting the iliac vessels. In 69% (n = 53), the right iliac fossa was used. The orthotopic location was not used.

The majority of the grafts were left kidneys (n = 55, 71%). Twenty (26%)patients underwent a transplant nephrectomy of 1 or more of their previous grafts before their transplant, primarily due to recurrent infections. In 5 further cases, a nephrectomy of an old graft was required at the time of transplantation due to restrictions in space. The donor artery was anastomosed onto the recipient external iliac artery in 69% (n = 53) of cases and onto the common iliac artery in 32% (n = 25). For the venous anastomosis, the recipient external iliac vein was used in 77% (n = 59), common iliac vein in 19% (n = 15), and inferior vena cava in 4% (n = 3) of cases. The implantation of the ureter was performed using a Lich-Gregoir technique in all cases. A transperitoneal approach was required in 15 (19%) cases.

### Outcomes of all Third and Fourth Kidney Transplants

In total, there were 9 deaths in this cohort during our observation period, giving cumulative survival rates of 96%, 92%, 90%, and 83% at 1, 3, 5, and 10 years, respectively. One patient died of a myocardial infarction more than 7 years after his transplant. Another died after a cardiac surgery for an unrelated cause. One patient died of multiorgan failure after a perforated peptic ulcer. Two patients died of nonlymphoid malignancy. One died of metastatic hepatocellular carcinoma. One patient died of multiorgan failure secondary to an infection of unknown origin. The cause of death was unknown in the 2 remaining patients. Of the 9 patients that died, 5 had a functioning graft at the time of death. Specific surgical complications and management in this cohort are detailed in Table 4.

**TABLE 1.**

**Demographics and baseline characteristics of donors and recipients by transplant number**

| | N | Transplant number | | | P |
|---|---|---|---|---|---|
| | | First (n = 2154) | Second (n = 330) | Third/fourth (n = 77) | |
| Recipient factors | | | | | |
| Age, y | 2561 | 47.8 ± 13.6 | 42.6 ± 12.8 | 43.8 ± 10.9 | **<0.001** |
| Sex (% male) | 2561 | 1366 (63%) | 183 (55%) | 33 (43%) | **<0.001**[a] |
| Ethnicity (% white) | 2553 | 1517 (71%) | 262 (80%) | 68 (88%) | **<0.001**[a] |
| Donor factors | | | | | |
| Age | 2559 | 47.6 ± 14.2 | 47.4 ± 13.8 | 44.3 ± 14.6 | 0.196 |
| Type | 2561 | | | | **<0.001** |
| DBD | | 831 (39%) | 135 (41%) | 36 (47%) | |
| DCD | | 362 (17%) | 27 (8%) | 3 (4%) | |
| Living | | 961 (45%) | 168 (51%) | 38 (49%) | |
| Matching/transplant factors | | | | | |
| Mismatches | 2561 | | | | **<0.001** |
| No | | 2072 (96%) | 309 (94%) | 60 (78%) | |
| ABOi | | 79 (4%) | 20 (6%) | 0 (0%) | |
| HLAi | | 3 (0%) | 1 (0%) | 15 (19%) | |
| HLA+ABOi | | 0 (0%) | 0 (0%) | 2 (3%) | |
| Total HLA mismatches | 2465 | | | | **<0.001**[a] |
| 0 | | 189 (9%) | 46 (14%) | 29 (38%) | |
| 1-3 | | 1255 (61%) | 202 (63%) | 33 (43%) | |
| 4-6 | | 624 (30%) | 72 (23%) | 15 (19%) | |

Data are reported as n (%), with *P* values from $\chi^2$ tests, or as mean ± SD, with *P* values from Jonckheere-Terpstra test, unless stated otherwise.
[a]*P* value from Kendall tau.
DBD, donation after brain death.

At the last follow-up, 22 patients had suffered graft failure, giving cumulative death-censored graft survival rates of 86%, 80%, 74%, and 58% at 1, 3, 5, and 10 years, respectively. Five patients (1 living-donor and 4 deceased donors) lost their graft secondary to graft thrombosis. In 4 of these the reasons were thought to be due to technical difficulties. In the fifth, the graft thrombosed after a bleed and low blood pressure after renal biopsy on day 9. One patient lost their graft due to poor compliance. Another lost their graft due to systemic sepsis secondary to a chest infection. Two patients lost their graft within the first 6 months, one due a rapid return of focal segmental glomerulosclerosis and the other due to multiple episodes of AMR. Three patients who received deceased donor kidneys experienced primary nonfunction. The remaining 10 patients (5 living donor and 5 deceased donor recipients) suffered a slow decline in graft function, without an identifiable cause, and returned to dialysis. Further details of causes of graft failure, and comparisons with first and second transplants are reported in Table 5.

Comparisons were then made between the outcomes of those patients receiving their third and fourth transplants (Table 6). No significant differences in either overall ($P = 0.938$) or graft ($P = 0.255$) survival were detected between these groups. Rates of DGF ($P = 0.713$), complications ($P = 0.710$) and both biopsy-proven ($P = 1.000$) and treated ($P = 0.083$) rejection were also similar.

## Analysis Based on the Type of Donor and Immunological Risk in Third and Fourth Kidney Transplants

The combined third/fourth cohort was divided into deceased donor (n = 39), and live HLA-compatible (n = 23)

**TABLE 2.**

**Outcomes of first, second, and third/fourth transplants**

| | N | Transplant numbers | | | P |
|---|---|---|---|---|---|
| | | First (n = 2154) | Second (n = 330) | Third/Fourth (n = 77) | |
| Patient survival | 2561 | | | | 0.532 |
| Rate at 5 y | | 92% | 94% | 90% | |
| Hazard ratio (95% CI) | | — | 0.83 (0.58-1.12) | 1.17 (0.60-2.28) | |
| Death-censored graft survival | 2561 | | | | **<0.001** |
| Rate at 5 y | | 89% | 85% | 74% | |
| Hazard ratio (95% CI) | | — | 1.32 (1.01-1.71) | 2.33 (1.51-3.58) | |

Survival rates are Kaplan-Meier estimates and *P* values are from log-rank tests. Hazard ratios are from univariable Cox regression models, and are relative to the first transplant group. Bold *P* values are significant at $P < 0.05$.

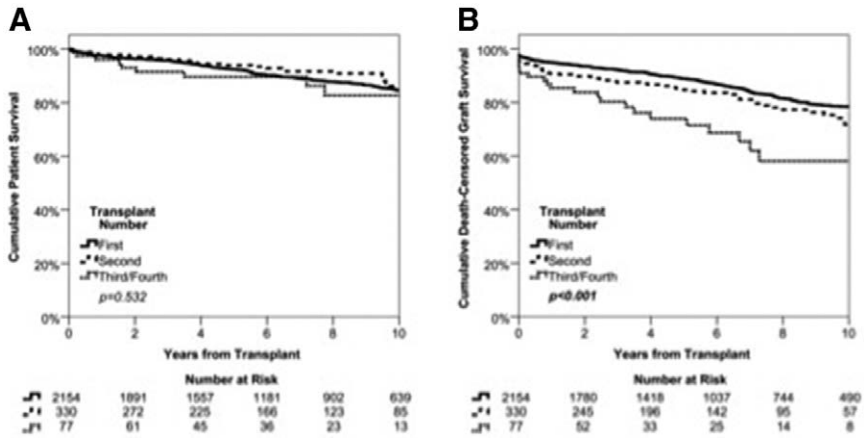


**FIGURE 1.** Kaplan-Meier curves of patient and graft survival by transplant number.

and HLA-incompatible (n = 13) groups. Two combined ABOi+HLAi transplants were excluded, as the possible confounding nature of dual antibody incompatibility is not yet fully realized, and potential differences in treatment strategies may impact on the data presented. The 3 groups were generally similar with respect to patient demographics (Table 7), with the exception of the gender distribution ($P$ = 0.019), with HLA-incompatible live recipients more likely to be male than HLA-compatible ones (77% vs 30%). The lifetime duration of dialysis also differed significantly between the groups ($P$ = 0.001), being longest in HLA-incompatible live recipients (median, 84 months) and shortest in HLA-compatible ones (12 months).

The HLA-incompatible transplants had significantly more HLA mismatches ($P$ = 0.007), with these patients also being significantly more sensitized than the other 2 groups ($P$ = 0.005), whereas deceased donor transplants had a significantly longer cold ischemia time (CIT) ($P$ < 0.001). A total of 4 (17%) HLA-compatible grafts and 13 (33%) deceased donor grafts had pretransplant DSA detectable by beads only, with a negative flow cytometric crossmatch, so proceeded without antibody removal. In patients with pretransplant DSA detectable by beads, there was no significant difference in the reported MFI value pretransplant between the 3 groups ($P$ = 0.847), irrespective of the requirement for antibody removal.

Analysis of patient outcomes (Table 8) found rates of DGF to be significantly higher in the deceased donor group than in the live donor HLA-incompatible or -compatible groups (79% vs 31% vs 17%, $P$ < 0.001). No significant difference in the rates of complications at 3 months ($P$ = 0.757) or biopsy-proven rejection ($P$ = 0.126) were detected between the 3 groups. There was a tendency for a higher rate of treated AMR rejection within 1 year of transplant for the HLA-incompatible live donor group (38% vs 8% in other groups), although this did not reach statistical significance ($P$ = 0.091).

Overall patient survival was not found to differ significantly between the groups ($P$ = 0.356, Figure 2A). Death-censored graft survival at 5 years was 100% in HLA-compatible live donors, compared to 75% in deceased donors and 53% in HLA-incompatible donors (Figure 2B), although this difference did not reach statistical significance ($P$ = 0.083).

**TABLE 3.**

**Demographics and baseline characteristics of donors and recipients in third and fourth transplant groups**

| | | Transplant number | | |
|---|---|---|---|---|
| | N | Third (n = 69) | Fourth (n = 8) | *P* |
| Recipient factors | | | | |
| Age | 77 | 43.9 ± 11.3 | 42.6 ± 7.3 | 0.750 |
| Sex (% male) | 77 | 30 (43%) | 3 (38%) | 1.000 |
| Ethnicity (% white) | 77 | 61 (88%) | 7 (88%) | 1.000 |
| BMI | 64 | 24.8 ± 4.1 | 25.7 ± 4.5 | 0.576 |
| Hypertension | 70 | 36 (57%) | 3 (43%) | 0.692 |
| Myocardial infarction | 70 | 3 (5%) | 0 (0%) | 1.000 |
| Diabetes | 70 | 5 (8%) | 0 (0%) | 1.000 |
| Smoker | 55 | 4 (8%) | 0 (0%) | 1.000 |
| Primary cause of renal disease | 76 | | | 0.278 |
| Reflux nephropathy | | 20 (29%) | 4 (50%) | |
| Glomerulonephritis | | 17 (25%) | 3 (38%) | |
| Congenital/hereditary | | 16 (24%) | 0 (0%) | |
| Autoimmune | | 10 (15%) | 0 (0%) | |
| Unknown etiology | | 5 (7%) | 1 (13%) | |
| Lifetime duration of dialysis, mo | 61 | 48 (14-102) | 7 (0-60) | 0.184 |
| Donor factors | | | | |
| Age, y | 76 | 44.8 ± 14.7 | 40.0 ± 13.9 | 0.384 |
| Type | 77 | | | 0.389 |
| DBD | | 33 (48%) | 3 (38%) | |
| DCD | | 2 (3%) | 1 (13%) | |
| Living | | 34 (49%) | 4 (50%) | |
| Matching/transplant factors | | | | |
| Incompatibility | 77 | | | 1.000 |
| No | | 53 (77%) | 7 (88%) | |
| HLAi | | 14 (20%) | 1 (13%) | |
| HLA+ABOi | | 2 (3%) | 0 (0%) | |
| Total HLA mismatches | 77 | | | 0.449[a] |
| 0 | | 25 (36%) | 4 (50%) | |
| 1-3 | | 30 (43%) | 3 (38%) | |
| 4-6 | | 14 (20%) | 1 (13%) | |
| Pretransplant cRF | 77 | 94 (79-99) | 89 (76-98) | 0.639 |
| cRF > 85 | | 45 (65%) | 4 (50%) | 0.452 |
| CIT, h | 44 | 13 (7-16) | 14 (7-17) | 0.967 |

Data are reported as n (%), with *P* values from Fisher exact tests, mean ± SD, with *P* values from *t* tests, or median (IQR), with *P* values from Mann-Whitney tests, unless stated otherwise. Bold *P* values are significant at $P < 0.05$.

[a]*P* value from Kendall tau.

**TABLE 4.**

**Surgical complications and management in third and fourth transplant recipients**

| Outcomes | n (%) |
|---|---|
| Graft thrombosis | 6 (8%) |
| Loss of graft and nephrectomy | 5 |
| Surgical thrombectomy and graft salvage | 1 |
| Perirenal hematoma | 7 (9%) |
| Surgical evacuation | 6 |
| Conservative + antibiotics | 1 |
| Transplant renal artery stenosis | 4 (5%) |
| Conservative | 2 |
| Angioplasty ± stenting | 2 |
| Lymphocele | 6 (8%) |
| Radiological drainage | 4 |
| Surgical drainage + fenestration | 2 |
| Urinary leak and reimplantation | 1 (1%) |
| Wound dehiscence | 1 (1%) |

Survival outcomes for patients receiving their third and fourth grafts were then compared with the first and second transplants within each donor type (Table 9). This found no significant difference in patient outcomes by graft number within any of the donor type subgroups. An additional subgroup analysis was performed for the recipients of deceased donor organs in third and fourth transplants, to compare outcomes between SCD (n = 25) and ECD (n = 14) organs (Table 10). None of the outcomes considered were found to differ significantly between these 2 groups.

## DISCUSSION

An increasing portion of patients will require 1 or more kidney retransplants over their lifetime.[1] This article sought to provide contemporary information from a heterogeneous (live and deceased donors) cohort of third and fourth transplants and compare outcomes according to donor type.

As a point of comparison, we included first and second transplants, and demonstrated a decline in graft survival with increasing transplant number, but no difference in patient survival. This trend in graft survival has been seen in other studies,[13,21] even when the same donor is used for a first and third kidney transplant.[21] Given similar patient survival and more importantly better outcomes over remaining on the waiting list, we agreed that third or more transplantation should not be discouraged based solely on functional outcomes.

Amongst patients receiving their third transplant in our cohort, patient survival rates are comparable to published data, which range from 76.9% to 96% at 5 years.[10-15,21-28] This reflects an appropriate, yet potentially stringent, donor and recipient selection policy for third or more recipients, compared to overall first kidney transplant patients. Similarly, our graft survival rates for third transplants are also comparable to previously reported data, which range from 53.6% to 76.4% at 5 years.[10-15,21-28] Published data on fourth transplants is rare. In articles with more than 9 patients, 1-year graft survival ranged from 50% to 87%.[10,14,22,23,25,27] Superior results in our cohort should be viewed in the context of a higher proportion of live HLA and HLAi donors.

Third and subsequent transplants can be technically demanding.[14,24,25] Difficulties arise as a result of previously dissected tissue planes and atherosclerotic vessels. We were able to perform an extraperitoneal approach in the majority (75%) of our cases. Orthotopic kidney transplantation has been used successfully in other series[28] but was not required in our cases. With regard to the vascular anastomotic site, Hagan et al[27] reported the need to use common iliac vessels or the aorta/inferior vena cava in half of their recipients. In our series, grafts were implanted onto the external iliac vessels in the majority of cases.

Five patients (7%) underwent a nephrectomy at the time of their fourth transplant, to generate space. This is lower than reported in other case series.[10,24] In most instances, this is not required, as older grafts are usually shrunken. Nevertheless, it is an important preoperative consideration to be discussed with the anesthetic team, as it can add an extra hour of operative time.[22]

Formation of ureteroneocystostomy may be difficult given the previous scarring. Some authors recommend a transperitoneal approach through the midline incision, thus avoiding redissection of an already obliterated extraperitoneal pouch.[28] In our series, a transperitoneal approach was required in 15 cases (19%). Loupy et al reported the need for uretero-ureteric anastomosis in 39% and urological complication rates of 15%.[25] This was not required in any of our third or fourth cases and we observed low urological complication rates.

**TABLE 5.**

**Cause of graft failure in first, second, and third/fourth transplants**

| | Transplant number | | |
|---|---|---|---|
| Cause of failure | First | Second | Third/fourth |
| Unknown cause of graft failure | 127 (35%) | 21 (32%) | 10 (45%) |
| Rejection while taking immunosuppression drugs | 124 (34%) | 20 (30%) | 1 (5%) |
| Primary nonfunction | 17 (5%) | 9 (14%) | 3 (14%) |
| Recurrent primary renal disease | 34 (9%) | 8 (12%) | 1 (5%) |
| Vascular or ureteric operative problems | 31 (9%) | 6 (9%) | 0 (0%) |
| Systemic or localized sepsis related to transplant | 12 (3%) | 0 (0%) | 1 (5%) |
| Rejection due to noncompliance to immunosuppression | 11 (3%) | 0 (0%) | 1 (5%) |
| Vascular (arterial or venous) thrombosis | 5 (1%) | 2 (3%) | 5 (23%) |
| Removal of functioning graft | 1 (0%) | 0 (0%) | 0 (0%) |

**TABLE 6.**

**Comparison of outcomes between third and fourth transplants**

| | Transplant number | | |
|---|---|---|---|
| | Third (n = 69) | Fourth (n = 8) | *P* |
| DGF | 35 (51%) | 5 (63%) | 0.713 |
| Complication rate at 3 mo | 24 (35%) | 2 (25%) | 0.710 |
| Biopsy-proven rejection during observation period | 21 (30%) | 2 (25%) | 1.000 |
| Treated rejection within 1 y | | | 0.083 |
| No | 55 (80%) | 6 (75%) | |
| AMR | 11 (16%) | 0 (0%) | |
| TCR | 3 (4%) | 2 (25%) | |
| Five-year patient survival[a] | | | 0.938 |
| Rate at 5 y | 88% | 100% | |
| Hazard ratio (95% CI) | — | 0.92 (1.12-7.39) | |
| Five year death-censored graft survival[a] | | | 0.255 |
| Rate at 5 y | 73% | 88% | |
| Hazard ratio (95% CI) | — | 0.33 (0.04-2.47) | |

Data reported as n (%), with *P* values from Fisher exact test, unless stated otherwise.
*P* values are significant at $P < 0.05$.
[a]Survival rates are Kaplan-Meier estimates, hazard ratios are from univariable Cox regression models and *P* values are from log-rank tests.

**TABLE 7.**

**Patient demographics by donor type in third and fourth kidney transplantation**

| | N | HLA-compatible live donor (n = 23) | Deceased donor (n = 39) | HLA-incompatible live donor (n = 13)[a] | *P* |
|---|---|---|---|---|---|
| Recipient factors | | | | | |
| Age | 75 | 45.7 ± 11.4 | 44.7 ± 11.0 | 38.8 ± 9.1 | 0.171 |
| Sex (% male) | 75 | 7 (30%) | 14 (36%) | 10 (77%) | **0.019** |
| Ethnicity (% white) | 75 | 19 (83%) | 35 (90%) | 12 (92%) | 0.628 |
| BMI | 62 | 25.1 ± 4.2 | 25.2 ± 4.5 | 24.0 ± 3.5 | 0.806 |
| Primary cause of renal disease | 74 | | | | 0.290 |
| Reflux nephropathy | | 9 (40%) | 12 (32%) | 2 (15%) | |
| Glomerulonephritis | | 7 (30%) | 11 (29%) | 2 (15%) | |
| Other | | 7 (30%) | 15 (39%) | 9 (69%) | |
| Hypertension | 68 | 12 (52%) | 19 (58%) | 7 (58%) | 0.947 |
| Myocardial infarction | 68 | 2 (9%) | 1 (3%) | 0 (0%) | 0.576 |
| Diabetes | 68 | 1 (4%) | 3 (9%) | 1 (8%) | 0.846 |
| Smoker | 53 | 1 (6%) | 2 (7%) | 1 (11%) | 1.000 |
| Duration of dialysis, mo | 59 | 12 (2-36) | 60 (26-120) | 84 (42-120) | **0.001** |
| Graft no | 75 | | | | 0.314 |
| 3 | | 19 (83%) | 35 (90%) | 13 (100%) | |
| 4 | | 4 (17%) | 4 (10%) | 0 (0%) | |
| Donor factors | | | | | |
| Age, y | 74 | 41.0 ± 12.5 | 44.9 ± 16.1 | 47.1 ± 13.9 | 0.450 |
| Matching/transplant factors | | | | | |
| Total HLA mismatches | 75 | | | | **0.007**[b] |
| 0 | | 7 (30%) | 21 (54%) | 1 (8%) | |
| 1-3 | | 9 (39%) | 13 (33%) | 9 (69%) | |
| 4-6 | | 7 (30%) | 5 (13%) | 3 (23%) | |
| Pretransplant cRF | 75 | 88 (83-97) | 92 (64-98) | 99 (95-100) | **0.005** |
| cRF > 85 | 75 | 13 (56%) | 22 (56%) | 12 (92%) | **0.047** |
| CIT, h | 43 | 5 (3-7) | 16 (13-18) | 1 (0-7) | **<0.001** |
| DSA at transplant | 75 | 4 (17%) | 13 (33%) | 13 (100%) | **<0.001** |
| MFI (×1000)[c] | 21 | 14 (8-21) | 10 (4-39) | 14 (14-16) | 0.847 |

Data are reported as mean ± SD or median (IQR), with *P* values from Kruskal-Wallis tests, or as n (%), with *P* values from Fisher exact tests, unless stated otherwise. Bold *P* values are significant at $P < 0.05$.
[a]Excludes n = 2 cases that were combined HBOi and ABOi.
[b]*P* value from a Kruskal-Wallis test, as the factor is ordinal.
[c]For those patients with DSA at transplant.

**TABLE 8.**

**Outcomes by donor type in third and fourth kidney transplantation**

| | HLA-compatible live donor (n = 23) | Deceased donor (n = 39) | HLA-incompatible live donor (n = 13)[a] | *P* |
|---|---|---|---|---|
| DGF | 4 (17%) | 31 (79%) | 4 (31%) | **<0.001** |
| Complication rate at 3 mo | 8 (35%) | 11 (28%) | 5 (38%) | 0.757 |
| Biopsy-proven rejection during observation period | 5 (22%) | 10 (26%) | 7 (54%) | 0.126 |
| Treated rejection within 1 y | | | | 0.091 |
| No | 19 (83%) | 33 (85%) | 8 (62%) | |
| AMR | 2 (3%) | 3 (8%) | 5 (38%) | |
| TCR | 2 (3%) | 3 (8%) | 0 (0%) | |
| Patient survival[b] | | | | 0.356 |
| Rate at 5 y | 96% | 86% | 92% | |
| Hazard ratio (95% CI) | — | 3.51 (0.43-28.6) | 1.43 (0.09-23.0) | |
| Death-censored graft survival[b] | | | | 0.083 |
| Rate at 5 y | 100% | 75% | 53% | |
| Hazard ratio (95% CI) | — | 3.32 (0.74-14.9) | 5.36 (1.08-26.6) | |

Data are reported as n (%), with *P* values from Fisher exact tests, unless stated otherwise. Bold *P* values are significant at $P < 0.05$.
[a]Excludes n = 2 cases that were combined HLAi and ABOi.
[b]Survival rates are Kaplan-Meier estimates, hazard ratios are from univariable Cox regression models, and are relative to the HLA compatible live donor group. *P* values are from log-rank tests.

We experienced surgical complication rates of 35% and 25% in our third and fourth transplant groups, respectively. Despite the presence of highly sensitized recipients, these rates are in keeping with other series. Loupy et al,[25] in 56 third transplants, noted complication rates of 41%. Izquierdo et al[10] (74 third kidney transplants) observed complication rates of 25.5%. Our rates of graft loss due to immediate vascular thrombosis (6%) are marginally higher than that reported in the literature (range, 1.2%–5%)[10,11,21,25,27] and reflects the technical challenges faced during retransplantation.

Within the live donor third/fourth transplants, we experienced 5-year graft survival rates of 100% and 53% in live HLA-compatible (n = 23) and live HLAi-incompatible (n = 13) organs, respectively. Izquierdo et al[10] presented the previous largest single-center experience of live HLA/ABO-compatible donor recipients (n = 14), but did not analyze this group separately. Redfield et al[13] demonstrated 5-year graft survival rates of 79% in their HLA-compatible living donor third transplants. Other than Kim et al,[14] who presented a small group of live HLA-incompatible transplants (n = 4) after desensitization, no other groups have demonstrated outcomes using these donors in third kidney transplantations. At our center, 5-year graft survival for all live donor HLA-incompatible transplants is 69%, with 1-year treated AMR rejection rates of 40%.[18] In this cohort of live donor HLA-incompatible transplants, 5-year graft survival was 53%, with 1-year incidence of treated AMR of 38%. Data from the United States have shown that live donor HLA-incompatible transplantation provides a significant survival benefit for highly sensitized patients over remaining on dialysis.[29] In centers with relevant experience, live donor incompatible transplantation should be considered in selected retransplant patients.

The use of ECDs in second retransplant patients have produced poorer graft compared with the first kidney transplants, with their use being recommended only in highly selected patients.[30] This has not been reported exclusively in third transplant patients. Most centers seem to use better quality donors for third kidney transplants.[13] Although our numbers are small, we showed similar 5-year survival rates between ECD and SCD recipients. Ortiz et al[31] recently showed similar outcomes in ECD and SCD recipients in all retransplant patients. The prudent use of

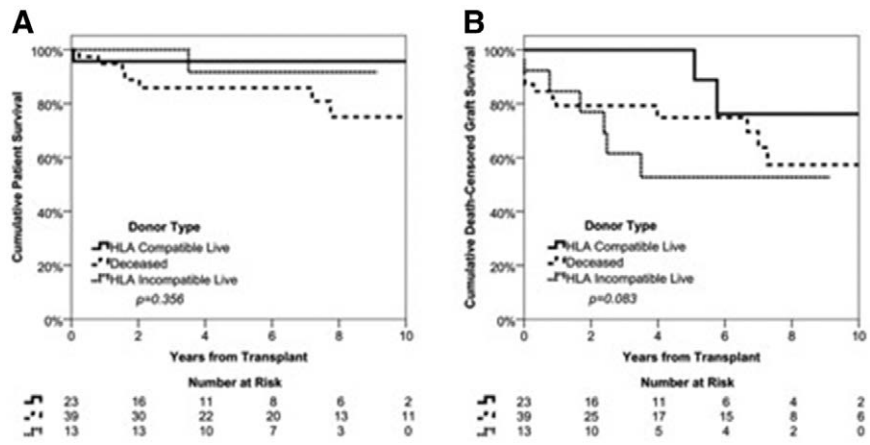


**FIGURE 2.** Kaplan-Meier curves of patient and graft survival by donor type.

**TABLE 9.**

**Outcomes by donor type and transplant number**

| | N | Transplant number | | | P |
|---|---|---|---|---|---|
| | | First | Second | Third/fourth | |
| Patient survival | | | | | |
| HLA-compatible live donor | 1148 | | | | 0.426 |
| Rate at 5 y | | 93% | 95% | 96% | |
| Hazard ratio (95% CI) | | — | 0.65 (0.33-1.28) | 0.69 (0.10-4.98) | |
| Deceased donor | 1394 | | | | 0.703 |
| Rate at 5 y | | 92% | 92% | 86% | |
| Hazard ratio (95% CI) | | — | 0.93 (0.60-1.43) | 1.33 (0.62-2.83) | |
| HLA-incompatible live donor[a] | 17 | | | | 0.882 |
| Rate at 5 y | | 100% | NA[b] | 92% | |
| Hazard ratio (95% CI) | | — | NA[b] | NC[c] | |
| Death-censored graft survival | | | | | |
| HLA-compatible live donor | 1148 | | | | 0.080 |
| Rate at 5 y | | 94% | 88% | 100% | |
| Hazard ratio (95% CI) | | — | 1.62 (1.06-2.49) | 1.18 (0.29-4.80) | |
| Deceased donor | 1394 | | | | 0.084 |
| Rate at 5 y | | 85% | 81% | 75% | |
| Hazard ratio (95% CI) | | — | 1.23 (0.88-1.72) | 1.76 (0.99-3.15) | |
| HLA-incompatible live donor[a] | 17 | | | | 0.321 |
| Rate at 5 y | | 100% | NA[b] | 53% | |
| Hazard ratio (95% CI) | | — | NA[b] | NC[c] | |

Survival rates are Kaplan-Meier estimates, and *P* values are from log-rank tests, comparing across the 3 groups. Hazard ratios are from univariable Cox regression models, and are relative to the first transplant group. *P* values are significant at $P < 0.05$.
[a]Excludes n = 2 cases that were combined HBOi and ABOi.
[b]Not estimable, as there was only 1 patient in the group.
[c]Not calculable, are there were no events in the reference group.

ECDs in third and subsequent retransplant patients needs further evaluation in selected patients. Our series contained only 2 DCD transplants, therefore, no conclusions could be drawn regarding this donor type.

This study was subject to the limitations of selection and survivor bias. In other words, the outcomes presented are based on patients who have survived long enough to undergo third/fourth transplantation, deemed surgical/physiologically safe and appropriately sensitized to receive an offer and undergo retransplantation by our center. In addition, because the sample size was small, the statistical power of the comparisons between groups was low. As a result, only large differences were detectable, meaning smaller but potentially clinically relevant differences may have been missed. This also precluded the use of multivariable analysis, as there were insufficient outcomes to generate reliable models. Consequently, it was not possible to account for baseline differences between patient groups

**TABLE 10.**

**Subgroup analysis of outcomes by type of deceased donor**

| | SCD (n = 25) | ECD (n = 14) | P |
|---|---|---|---|
| Five-year patient survival[a] | | | 0.460 |
| Rate at 5 y | 84% | 92% | |
| Hazard ratio (95% CI) | — | 0.46 (0.05-3.88) | |
| Five-year death-censored graft survival[a] | | | 0.781 |
| Rate at 5 y | 75% | 77% | |
| Hazard ratio (95% CI) | — | 0.83 (0.22-3.19) | |
| DGF | 19 (72%) | 13 (93%) | 0.218 |
| Complication rate at 3 mo | 6 (24%) | 5 (36%) | 0.478 |
| Biopsy-proven rejection during observation period | 6 (24%) | 4 (29%) | 1.000 |
| Treated rejection within 1 y | | | 0.788 |
| No | 22 (88%) | 11 (79%) | |
| AMR | 2 (8%) | 1 (7%) | |
| TCR | 1 (4%) | 2 (14%) | |

Analysis includes only the recipients of deceased donor organs.
Data are reported as n (%), with *P* values from Fisher exact tests, unless stated otherwise. Bold *P* values are significant at $P < 0.05$.
[a]Survival rates are Kaplan-Meier estimates, hazard ratios are from univariable Cox regression models and *P* values are from log-rank tests.

to assess the independence of any significant associations. As with all such historical case series, recipients were subjected to varying immunosuppression protocols.

Given good patient survival across the literature, centers may be encouraged to be less stringent in their donor-recipient selection criteria for third or more transplants.[32] This study supports third and subsequent transplantation using all types of live and deceased donor kidneys when recipients are appropriately selected and counseled.

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