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Renal allograft loss in the first post-operative month: causes and consequences

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Abstract: Early transplant failure is a devastating outcome after kidney transplantation. We report the causes and consequences of deceased donor renal transplant failure in the first 30 d at our center between January 1990 and December 2009. Controls were adult deceased donor transplant patients in the same period with an allograft that functioned >30 d. The incidence of early graft failure in our series of 2381 consecutive deceased donor transplants was 4.6% (n = 109). The causes of failure were allograft thrombosis (n = 48; 44%), acute rejection (n = 19; 17.4%), death with a functioning allograft (n = 17; 15.6%), primary non-function (n = 14; 12.8%), and other causes (n = 11; 10.1%). Mean time to allograft failure was 7.3 d. There has been a decreased incidence of all-cause early failure from 7% in 1990 to <1% in 2009. Patients who developed early failure had longer cold ischemia times when compared with patients with allografts lasting >30 d ($p < 0.001$). Early allograft failure was strongly associated with reduced patient survival ($p < 0.001$). In conclusion, early renal allograft failure is associated with a survival disadvantage, but has thankfully become less common in recent years.

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Renal allograft loss in the first month post-transplantation is an uncommon, but devastating outcome for patients. It occurs in approximately 5% of first transplants (1) and has a range of etiologies. Vascular accidents, such as thrombosis of a renal vein or artery, are typically early phenomena post-transplantation and usually catastrophic (2, 3). They are frequent causes of early allograft loss accounting for at least a third of all allograft failures within 90 d (2). The reported incidence of allograft thrombosis ranges between 1.6% and 6% (2–4). Other causes include acute rejection, primary non-function, and recurrence of primary disease. Over the last 20 yr, early kidney transplant outcomes have improved significantly (5). Improved technical approaches and new advances in immunosuppression and antibody definition have improved the outcome associated with the procedure (6, 7). Nevertheless, early transplant loss still remains a significant cause of morbidity. The aims of our study were to report the incidence and changing etiology of early renal transplant failure over the past 20 yr at our center. We also sought to compare these patients to those whose allograft functioned for more than one month with respect to patient characteristics and survival.

Methods

Patients

Our institution is the only renal transplantation center in the Republic of Ireland, performing 150–170 transplants per yr. We conducted a retrospective analysis of all adult (≥18 yr), deceased donor kidney-only transplants between 1 January 1990 and 31 December 2009 and identified those which failed during the first 30 d. Allograft failures were divided into four-yr periods for comparison (1990–1993, 1994–1997, 1998–2001, 2002–2005 and 2006–2009). The percentage of pre-emptive transplants increased during the time period from approximately 1% to 8% by 2006–2009. A diagnosis of primary non-function was reserved for grafts that were perfused, but never functioned. Also, at least one biopsy was performed to exclude other causes. Patients receiving their fourth and subsequent

transplants were excluded from the study as the risk of allograft failure was felt to be exceptionally high. Demographic and outcome data were collected from our prospectively updated transplant database.

Transplant operations

Transplants were performed in the setting of a negative complement-dependent cytotoxicity (CDC) cross-match and a negative CDC plus flow cytometry cross-match from 2002 onwards. Organs were perfused *in-situ* using University of Wisconsin solution and generally recovered using cold storage at 4°C. From 2007, machine perfusion was employed for expanded criteria kidneys. Operations were performed using a standard surgical technique with end to side anastomosis to recipient external or common iliac vessels using a Carrel patch. Multiple renal arteries were dealt with using a neo-Carrel patch or side to side anastomosis for similar sized arteries. Vena caval extension was routinely used for all right-sided kidneys to obtain additional length for the right renal vein, as described by Chopin et al. (8). Peri-operative heparin prophylaxis against venous thromboembolism was not routinely used nor was intraoperative heparin from 1999 onwards. Transplant isotope scanning was generally performed as a definitive diagnosis if allograft thrombosis was suspected. Regular biopsies were performed if graft function deteriorated. Transplant nephrectomy was performed as soon as a non-correctable graft failure was identified. Panel reactive antibody (PRA) was determined by use of the CDC assay, NIH Basic technique (9).

Initial medications

Prior to 2005, antibody induction in the form of anti-thymocyte globulin was reserved for high immunological risk patients (highly sensitized, repeat transplants). From 2005, basiliximab induction was routinely administered to all recipients. Initial immunosuppression consisted of a calcineurin inhibitor (cyclosporine [4 mg/kg twice daily; prior to 2001] or tacrolimus [0.1 mg/kg twice daily; 2001 onwards]), an anti-metabolite (azathioprine [2 mg/kg daily; prior to 2002] or mycophenolate mofetil [500 mg twice daily; 2002 onwards]) and steroids. Cyclosporine doses were adjusted to achieve troughs of 200–250 ng/mL and tacrolimus doses were titrated to troughs of 10–12 ng/mL in the early post-transplant period. Patients at risk for CMV disease (recipient, donor or both CMV seropositive) received CMV prophylaxis from 1992 onwards. This consisted of acyclovir up until 1998, valaciclovir from 1998 until 2004 and valganciclovir used since then (dosage adjusted for renal function). All patients received co-trimoxazole for Pneumocystosis prophylaxis.

Statistical analysis

The two groups (allograft survival <30 and >30 d) were compared for patient survival using proportional hazards regression. Patient survival was conducted from the end of 30 d post-transplant and analyzed for first transplants only. Multi-factorial analysis was performed to test for independence of early allograft failure on patient outcome in the presence of several confounding variables. Kaplan–Meier methods were used to calculate patient survival and also to determine estimated time to re-transplant for early graft failure. Demographic variables were compared with controls using Pearson chi-square or Wilcoxon rank-sum tests. A p-value of <0.05 was considered to be statistically significant.

Results

There were 2381 consecutive deceased donor transplants performed during the study period. Two cases of early allograft failure on the fourth or subsequent transplant were excluded. A total of 109 allografts failed within 30 d of transplantation giving an overall incidence of 4.6%. However, the incidence has become less common over time, from >6% in 1990–1993 to 1.75% in 2006–2009 (Fig. 1). In univariate analysis, patients who developed early failure were older (44.4 vs. 47.0 yr, $p = 0.042$) and had a longer cold ischemia time (CIT; 23 vs. 20 h; $p < 0.001$) when compared with patients with allografts lasting >30 d (see Table 1). The mean donor age was higher in the early failure group (40.2 vs. 37.2 yr; $p = 0.043$) although the percentage of pediatric donors (<18 yr) used was greater (13.0% vs. 10.4%). The early failure group had a lower mean number of HLA mismatches (2.6 vs. 2.9; $p = 0.043$). In a multivariate model, only cold ischemic time was significantly associated with early allograft failure (Table 2).

Etiology of allograft failure

The most common cause of early allograft loss was renal vessel thrombosis, occurring in 48 allografts (44% of total early failures). Thirty cases (62.5% of thromboses) were due to venous thrombosis, 11

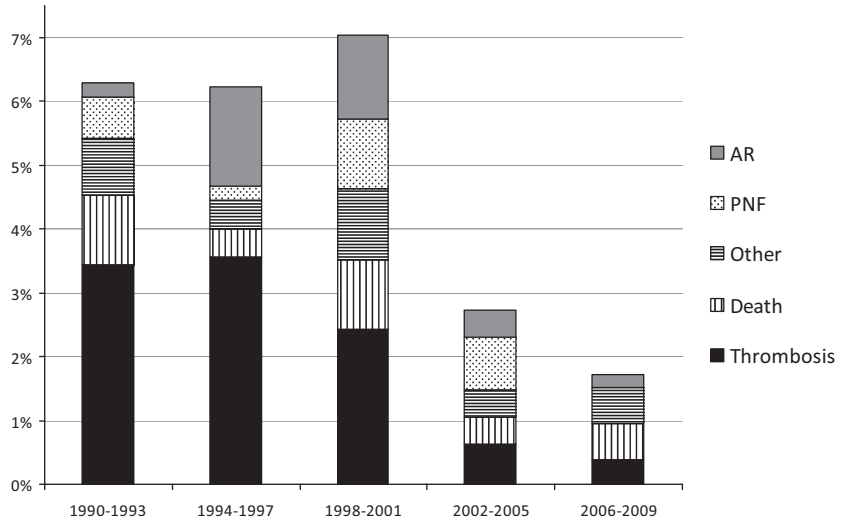

Fig. 1. Etiology of early allograft failure as a percentage of total transplants in specified period.

Table 1. Patient characteristics (means unless specifies)

Variable	Early allograft failure group	Allograft survival >30 d	p-value
Recipient age (SD)	47 (13.4)	44.4 (14.3)	0.0416
Donor age (SD)	40.2 (15.4)	37.2 (15.4)	0.0430
Sex (% M)	57	64	0.126
HLA mismatches (SD)	2.6 (1.5)	2.9 (1.4)	0.0430
CIT (SD)	23 (6.6)	20.4 (5.99)	<0.001
Diabetes (%)	4.6	5.8	0.592
% PRA group[a]	67.0/11.9/21.1	71.3/13.3/15.4	0.279
% First transplant	82	84	0.577

SD, standard deviation; CIT, cold ischemia time.
[a]Panel reactive antibodies (groups 0–10%, 11–49%, 50–100%).

Table 2. Multivariate model of factors which may influence early allograft loss

Variable	Odds ratio	Odds ratio 95% confidence interval	p-value
Recipient age (per yr)	1.013	0.997–1.029	0.118
Donor age (per yr)	1.010	0.995–1.024	0.185
Male recipient sex	0.732	0.486–1.102	0.135
Male donor sex	0.730	0.486–1.096	0.129
HLA mismatches	0.883	0.763–1.022	0.095
CIT	1.069	1.039–1.100	<0.001
PRA group	1.160	0.872–1.542	0.309
Re-transplant	0.800	0.427–1.500	0.487
Diabetes mellitus	0.614	0.220–1.714	0.352

CIT, cold ischemia time.

(23%) were due to arterial thrombosis, and in seven cases (14.5%) both vessels were thrombosed. There was no history of venous thromboembolism in 34 patients with eight cases unknown/insufficient data. Of the remaining six cases, three had a pulmonary embolism prior to their transplant, one patient had previously clotted their polytetrafluoroethylene (PTFE) graft when on dialysis and two patients developed a lower limb DVT post-nephrectomy. Hemoglobin levels at the time of transplant were similar between patients with an allograft thrombosis (11.4 g/dL; IQR 9.3–12.2 g/dL), patients with other causes of early failure (11.3 g/dL; IQR 9.3–12.85 g/dL), and patients with allograft survival >30 d (11.3 g/dL; IQR 9.8–12.5 g/dL; p = 0.967).

Acute rejection was the diagnosis in 19 cases (17.4%). The type of injury was classified as acute cellular rejection (n = 3), antibody-mediated rejection (n = 6), mixed picture (n = 7) and unclassified (n = 3). Death with a functioning allograft occurred in 17 patients (15.6%). The causes of death were cardiovascular (n = 8), sepsis (n = 3), hemorrhage (n = 2), hepatic failure, (n = 1) and unknown (n = 3). Primary non-function was the cause in 14 cases (12.8%). Tubular necrosis was the dominant pathological finding in these cases where the transplant never functioned. Eleven allografts (10.1%) failed due to other causes, including transplant hemorrhage (n = 6), sepsis (n = 2), recurrence of primary disease (n = 1), de novo thrombotic microangiopathy (n = 1), and one unknown cause. There was a striking reduction in all-cause early transplant failure and particularly of allograft thrombosis over the study period (see Fig. 1). There were also steep reductions in failures due to acute rejection since 1994–1997.

Excluding death with a functioning allograft, 36 transplants failed between implantation and the first post-operative day and 57 had failed within the first week (out of 92 total failures in 30 d). The mean time to all-cause graft failure was 7.3 d.

Re-transplantation

The median time to re-transplantation in the early allograft failure group was 3.02 yr (see Fig. 2). In total, 71% of patients were eventually re-transplanted. At our center, patients with an early allograft failure may be prioritized for another organ depending on the clinical circumstances (10). If deemed medically suitable, patients can be immediately re-listed and may be offered an ABO-compatible (non-identical) allograft if one becomes available. This occurred in seven patients from this cohort who were re-transplanted prior to hospital discharge.

Patient survival

In the early graft failure group, survival at 1, 5, 10 and 15 yr after transplant surgery was 84%, 68%, 67%, and 46%, respectively. In the continued allograft function group, the corresponding figures were 98%, 90%, 78%, and 66% (see Fig. 3). A multifactorial model identified death-censored early allograft failure ($p < 0.001$), presence of diabetes mellitus ($p < 0.001$), and recipient ($p < 0.001$) and donor age ($p = 0.008$) as significant predictors of patient survival (see Table 3).

Discussion

The most common cause of early renal allograft failure in our series was renal vessel thrombosis which is consistent with other reports (2, 3). In this study, allograft thrombosis was responsible for approximately 44% of all early (<30 d) graft failures and accounted for 52% of causes when death with a functioning graft was excluded. It is also clear from our results that the allograft is most at risk during the first week post-transplantation.

In recent years, there has been a decrease in the overall number of early renal allograft failures at our center and a decrease individually in failures due to allograft thrombosis, acute rejection, and primary non-function. The improvement in failures due to acute rejection is assumedly due to more sensitive cross-matching techniques as well as the employment of modern immunosuppression with the introduction of tacrolimus, mycophenolic acid, and more recently antibody induction therapy. The lower rate of allograft thrombosis is encouraging and possibly due to improved surgical technique and cross-matching technologies. The absence of primary non-function as a cause of early allograft loss is difficult to explain, but may be a result of

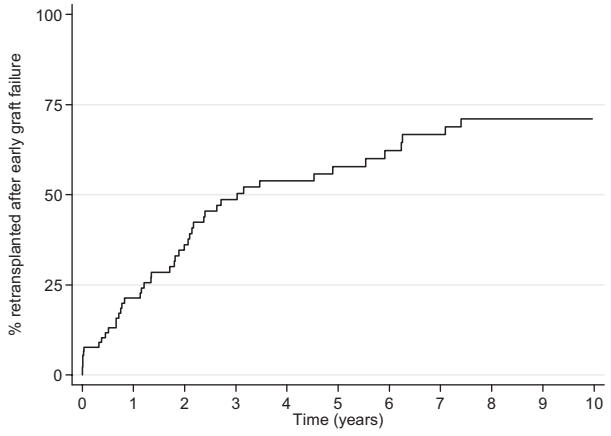

Fig. 2. Time to re-transplantation in early allograft failure patients.

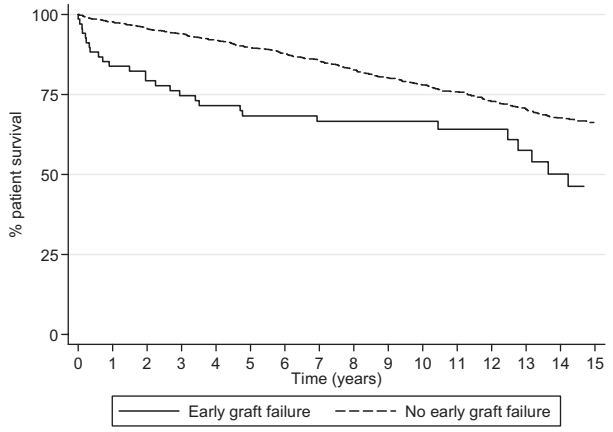

Fig. 3. Patient survival between the early renal allograft failure group and the controls.

Table 3. A multifactorial model of patient survival

Variable	Hazard ratio	Confidence interval	p-value
Early graft failure	2.14	1.41–3.25	<0.001
Recipient age (per yr)	1.06	1.05–1.07	<0.001
Male recipient sex	1.16	0.93–1.46	0.186
HLA mismatches	1.08	0.99–1.17	0.073
Diabetes mellitus	3.13	2.26–4.35	<0.001
Male donor sex	1.03	0.83–1.28	0.758
Donor age (per yr)	1.01	1.00–1.02	0.008
PRA group[a]	1.09	0.91–1.30	0.347
CIT	1.01	0.99–1.03	0.146

HLA, human leukocyte antigen; CIT, cold ischaemia time.
[a]Panel reactive antibodies (groups 0–10%, 11–49%, 50–100%).

more judicious donor selection or perhaps an improved effort to accurately diagnose the cause of organ loss in recent times.

Primary allograft thrombosis can be due to donor and recipient factors as well as issues regarding organ recovery and surgical implantation. The donor right kidney has been associated with an increased risk of allograft thrombosis (2). The reason for this has been speculated to be due to the short vein and long artery of the right kidney (11). The short vein may cause problems with positioning of the kidney especially in larger patients. Moreover, the length of the right renal artery can sometimes lead to kinking of the vessel. However, we have recently demonstrated no difference in outcome between left and right deceased donor kidney pairs where vena caval extension was routinely used to provide additional length for the right kidney anastomosis (12), as in this study. Pediatric patients, who were not included in our study, are at increased risk of allograft thrombosis due in part to the small size of the recipient vessels (13). Other technical problems such as vessel torsion or intimal injury during organ procurement may act as a nidus for thrombosis. Due to a lack of precise data, these issues could not be fully explored in our study.

The association between prolonged CIT and early allograft failure is not surprising. CIT has long been associated with delayed graft function (DGF). In other series, it was also found that CIT was strongly associated with DGF, with a 23% increase in the risk of DGF for every six h of CIT ($p < 0.001$) (14). Acute transplant rejection occurred more frequently in the allografts with DGF. A prolonged CIT has also been associated with long-term allograft dysfunction (15) as well as with allograft thrombosis itself (10). Our report reenforces the message to keep CIT as short as possible during kidney transplantation.

The mean HLA mismatches were marginally lower in the early graft failure group. This result may be surprising as the importance of HLA matching has been demonstrated in other series (16). The detrimental effect of HLA mismatching in the context of CIT has also been suggested. Connolly et al. (17) showed that zero HLA-DR mismatched grafts showed significantly enhanced survival over those with 1 HLA-DR mismatch at one yr (92.8% vs. 84.5%) and at five yr (88.3% vs. 73.9%), if CIT was < 26 h ($p = 0.0009$). However, most of the transplant failures in our series occurred very early and were not immunologically mediated. There is a lack of modern literature on the effect of HLA matching on allograft outcome in the first 30 d. Therefore, the lower degree of HLA mismatching in the early failure group (mean 2.6 vs. 2.9) may be a chance occurrence. There was no association between early allograft failure and donor sex, presence of diabetes mellitus, and number of previous transplants.

Variables that were significantly associated with decreased patient survival included early allograft loss, presence of diabetes mellitus, and increasing recipient and donor age. These associations are perhaps not surprising, although it does highlight the deleterious effect that an early allograft loss has to the patient. It is clear from the survival curve that the adverse survival effect is evident immediately post-transplant failure. Moreover, reports of mortality with increasing donor age are not consistent with some studies, showing no association between older donor age and patient survival (18, 19) despite expanded criteria donors showing a reduced patient survival (20).

Waiting times on the on the renal transplant pool continue to rise (21). In Ireland, the median waiting time was between eight and 15 months depending on blood group, for those with a low level of sensitization, during the period between 2000 and 2005 (22). In this series, the median time to re-transplantation following an early allograft failure was three yrs with almost 30% of patients never getting re-transplanted. During the 1990s, waiting times for renal transplantation in Ireland was generally less than one yr, so it is evident that our early failure patients faced significant barriers to re-transplantation. Despite this, the eventual rate of re-transplantation compares well to other reports (23). It is well recognized that longer waiting times for kidney transplantation translates into shorter patient survival (24). This may explain some of the increased mortality experienced by the early failure patients.

There are some limitations to this study. We acknowledge the inherent weaknesses of any retrospective, single center study. Moreover, over the study period, surgical and immunological practices have undoubtedly developed and immunosuppressant agents have been modernized. This can lead to issues when comparing patients from different eras. However, confining the study to one center reduces the confounding effects of multiple surgeons and multiple peri-operative protocols, and the long study period has allowed us to assess the change in the outcome over time.

Early renal allograft failure is a catastrophic event for patients and was associated with reduced patient survival. Encouragingly, early transplant failure has become less common in recent years, driven particularly by lower rates of allograft thrombosis and failures due to acute rejection.

Authors' contributions

Dr. Paul J. Phelan: wrote article, performed study, study design. Mr. Patrick O'Kelly: analyzed data. Mr. Munir Tarazi, Mr. Nadim Tarazi: collected data, wrote paper. Dr. M. Ridhwaan Salehmohamed: collected data. Ms. Dilly Little, Dr. Colm Magee: critical revision. Prof. Peter J. Conlon: study design, final approval submitted version.

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