

## Original Paper

# Prognosis of Dialysed Patients after Kidney Transplant Failure

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## Key Words

Dialysis • Graft failure • Renal transplant • Survival analysis

## Abstract

**Background/Aims:** Patients with a failed kidney transplant represent a unique, high-risk chronic kidney disease population that is increasing in number, and may be sub-optimally managed. Our aim was to compare the survival of patients with failed allografts to patients with native kidney failure and to assess whether their survival is affected by the graft resection.

**Methods:** Kaplan-Meier and Cox-regression survival analyses were performed on the data of 57 patients with graft failure and of 123 transplant-naive haemodialysed patients. **Results:** After adjustment for age and gender, there was no statistically significant difference in the mortality of patients in the two groups. The 43 patients, who had a transplanted kidney nephrectomy had a statistically not significant survival benefit over non-nephrectomised patients (age and gender adjusted hazard ratio: 0.56 95 % confidence interval: 0.24-1.58, p-value: 0.18).

**Conclusion:** Elective graft resection is a safe, effective alternative for both the treatment and the prevention of the chronic inflammatory state associated with a failed kidney transplant.

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## Introduction

Patients with a failed kidney transplant represent a unique chronic kidney disease (CKD) population that is increasing in number, and that is at high risk of morbidity and mortality because of a prolonged history of CKD that may be sub-optimally managed [1]. A number of

recent studies have shown that the mortality rate in this population is higher than among age-matched incident dialysis patients, patients listed for primary transplantation, and patients with a functioning transplant [2]. Five former cohorts did not find a significant difference in mortality between patients starting dialysis with graft failure (GF) and transplant naive patients on dialysis treatment (HD) [3-8]. There is no clear indication about the optimal timing for starting dialysis after graft failure. We can only rely on the indications available for the general population of patients with CKDs (K/DOQI recommendations), based on clinical symptoms and biochemical changes. In fact, many reports on patients with renal allograft failure tell us that dialysis often started at GFR levels far below the optimal suggested threshold [9-11]. Evidence regarding the effect of transplanted kidney nephrectomy is controversial. Mortality associated with graft resection ranges from 0 to 39% [12]. Lopez-Gomez et al. concluded that maintaining a failed graft represents a chronic inflammatory state, independently from the presence or absence of any overt symptom [13]. A more recent paper using the USRD registry found that transplanted kidney nephrectomised patients had a consistent survival advantage over non-nephrectomised patients (mortality rate ratio: 0.89) if the graft survival was longer than 1 year [14]. Goldfarb-Rumyantzev et al. found that preemptive re-transplantation increases the risk of graft failure and has no effect on recipient survival [15]. Another argument raised against graft resection has been the observation that graft removals may be followed by a rise in anti-HLA antibodies, which may have a negative effect on the subsequent transplantations [16]. Transplanted kidney nephrectomy has long been indicated in hyperacute rejection or in case of technical complications of transplant surgery, though the role of allograft nephrectomy outside these indications has been controversial. Routine nephrectomy of failed allografts has been practiced, as well as leaving asymptomatic grafts in situ and continuing immunosuppression. The purported benefits of leaving grafts in situ are erythropoietin production by the failed allograft and retention of residual renal function, though there is no evidence to support such a benefit, rather about increased mortality following allograft loss [17-19]. The return to haemodialysis has been demonstrated to lead to deep depression that is often undervalued by nephrologists, and the opportunity for psychiatric help is seldom offered to these patients [20].

In our study we compared the characteristics and survival of patients with graft failure readmitted to dialysis (reHD group) to transplant-naive dialysed patients (HD group) and assessed whether their survival was affected by the removal of the failed graft.

## Materials and Methods

### *Selection and Description of Participants*

Demographic data were collected on all patients retrospectively by chart review at baseline. We enrolled 180 patients who started dialysis between 2000-2005, of whom 123 had had no kidney transplantation previously, 12% were waiting-listed for transplantation and 57 were transplanted patients with graft failure (20 of them (35%) were waiting-listed again). In Hungary the proportion of waiting-listed patients is rather low. That derives not only from inadequate patient education but also from the low activity for deceased donor kidney transplants.

Transplanted patients received a cadaver kidney between 1991 and 2002 in the Centre of Transplantation, Medical & Health Science Centre, University of Debrecen. Recipients who received organs other than kidneys, and patients younger than 18 years were excluded from the study. Laboratory data obtained at baseline included the following: hemoglobin levels (Hb), GFR, calcium (Ca), phosphate (P), cholesterol (chol), triglycerides (Tg). Follow-up data were obtained annually from the general practitioners of the patients and also from the dialysis centres of the four Hungarian counties where the patients lived. They were followed till death or till 15 December 2010.

Resected kidney transplant specimens were routinely sent to the pathology department for microscopic examination. Specimens were subjected to standard histologic review by a staff pathologist using routine techniques [21].

**Table 1.** Baseline characteristics of patients in the HD and in the re-HD groups

	HD group (N=126)	re-HD group (N=57)	p-value
Male (%)	55.3	64.8	0.2
Age (yr)	62.4 (13.1)	44.1 (12.0)	p<10 <sup>-3</sup>
Cause of chronic renal failure*			0.03
GN	21.8	39.3	
DN	23.4	17.9	
APCD	13.7	10.7	
CPN	4.8	12.5	
Vascular disease	21.8	8.9	
Miscellaneous	14.5	10.7	
GFR (mL/min/1,72 m <sup>2</sup> )	9.2 (5.7)	10.3(4.7)	0.2
Hb (g/L)	99.5 (21.1)	92.1 (16.9)	0.02
Ca (mmol/L)	2.08 (0.32)	2.13 (0.30)	0.3
P (mmol/L)	1.87 (0.62)	1.73 (0.53)	0.2
Total cholesterol (mmol/L)	5.20 (1.53)	5.80 (2.47)	0.05
Triglyceride (mmol/L)	2.06 (1.32)	2.02 (1.12)	0.8
Proportion of statin users (%)	27.7	12.5	0.01

Numbers are percentages for categorical and means (SD) for continuous variables. Data about patients in the re-HD were obtained at the time of returning to dialysis. GN: glomerulonephritis, DN: diabetic nephropathy, APCD: adult polycystic disease, CPN: chronic pyelonephritis, GFR: glomerular filtration rate, Hb: haemoglobin, Ca: calcium, P, phosphate. \* In the reHD group data refer to the cause of the failure of the native kidney

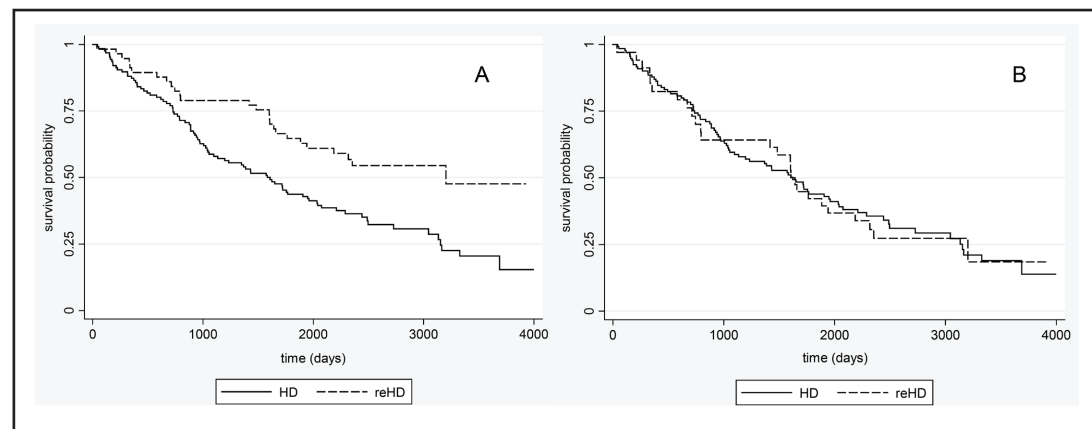
We used Kaplan-Meier analysis and log-rank test to compare the survival of patients in the HD and in the reHD groups from the start of the dialysis. We adjusted for age and gender in Cox-regression. We performed a similar analysis to compare the survival of patients with graft failure whose graft was removed (43 patients) and those whose graft was not removed (14 patients). Additionally, we compared the clinical characteristics of patients in the HD and reHD groups. We used the two-sample t-test to compare continuous and the  $\chi^2$ -test to compare categorical variables.

## Results

The comparison of the HD and the reHD groups revealed several differences. Patients in the reHD group had lower haemoglobin level and higher GFR (Table 1). The proportion of patients taking statins was larger in the HD group. Patients in the HD group were significantly older. In the crude analysis patients in the reHD group had a much better survival (hazard ratio 0.51, 95% CI: 0.33-0.59) (Figure 1). However, after adjustment for age and gender there was no difference in the survival probability of the two groups (hazard ratio reHD versus HD group: 1.09, 95% CI: 0.64-1.87) (Figure 1). The characteristics of the reHD group are presented in Table 2. Non-compliance in the table means that the patients did not have control visits in the transplantation centre or at their general practitioners, or stopped taking their immunosuppressive drugs that led to rejection. Two patients committed suicide in the non-graftectomised group. In 43 patients transplanted kidney nephrectomy was performed within 1 year (average: 262 days) after restarting HD. Death within 1-year after readmission to dialysis was 6.97% in the graftectomised and 21.42 % in non-graftectomised group. The indications of the graft nephrectomy were the followings: acute rejection or severe inflammation (in 17 cases), symptoms or signs of severe anaemia (in 12 cases), elective nephrectomies without major symptoms (diuresis less than 500 ml/day) (in 14 cases). Nephrectomised patients had a consistent but statistically not significant survival advantage (crude hazard ratio = 0.50 95 % confidence interval: 0.22-1.12, p=0.09; after adjustment for age and gender hazard ratio: 0.56, 95 % CI: 0.24-1.32, p=0.18). Of the reHD patients 34.8 % were re-transplanted, although none of them had preemptive re-transplant.

**Table 2.** Characteristics of and events in the re-HD group

	Graftectomised patients (N=43)	Non-graftectomised patients (N=14)
Age at restarting dialysis (years)	42.8	42.4
Male (%)	62.5 %	78.5 %
Number of retransplantation	15 (34.8%)	2 (14.3%)
Non-compliance	3 (6.97%)	3 (21 %)
Number of death within 1-year after readmission to dialysis	3 (6.97%)	3 (21.42%)
Number of death over 1 year after readmission to dialysis	10 (23.25 %)	7 (50%)
Number of suicide	0	2 (14.3 %)



**Fig. 1.** Survival of patients with graft failure readmitted to dialysis (re-HD group) compared to transplant-naïve patients (HD patients); A: crude analysis; B: after adjustment for age and gender.

Our clinical policy for tapering immune suppressive therapy after return to dialysis was the following: (1) antiproliferative drugs (azathioprine, mycophenolate-mofetil, sirolimus) should be the first drugs to be discontinued when irreversible graft failure is established, (2) tapering and withdrawal of calcineurin inhibitor over a brief period (1-3 weeks) of the graft failure followed a chronic and slow progression, and a longer period (4-8 weeks) if the graft failure followed more acute immunologic events, (3) slow tapering of steroids with possible withdrawal (in a few months) maintaining the same dose of steroid for 1 month, then halving the steroid dose in every month until complete withdrawal.

Histologic examination of the resected kidney transplants was available for 37 of the 43 cases. In all 37 cases, there was evidence of chronic rejection characterized by the existence of variable degrees of glomerulitis and tubulitis. Characteristic findings included presence of chronic interstitial mononuclear cell infiltrate (1), subendothelial lymphocytic and monocytic cellular infiltrate (2), intimal vascular fibrosis (3), moderate to severe interstitial fibrosis (4). None of the specimens had viral inclusions or findings suggestive of an infection. A summary of the major histologic findings is provided in Table 3.

## Discussion

The first important finding of our study was that after adjustment for age and gender, patients with graft failure readmitted to dialysis and transplant-naïve dialysed patients had similar survival. Our observation is in line with the findings of former cohorts studying this question [3-8].

With a larger numbers of patients entering long-term dialysis after failed kidney transplant worldwide, optimal management of the failed allograft is an increasingly

**Table 3.** Summary of the histopathological findings in 37 resected kidney transplant specimens

Findings	Negative	Mild	Moderate-severe
Chronic inflammation (interstitial mononuclear infiltrate)	0	19	18
Acute inflammation (interstitial PMN infiltrate)	24	11	2
	Present	Absent	
Arteriopathy (intimal hyperplasia, parietal thickening)	19	18	
Vascular thrombosis (arterial and venous thrombi)	25	12	

important question. There is not a consensus about the optimal management of the failed renal allograft. Our second important finding is that removal of the failed kidney transplant provided a non significant survival benefit. That result is in agreement with observations made by Ayus et al. They have demonstrated that surgical removal of the failed allograft and discontinuation of immunosuppressant medications may improve survival following a failed renal allograft [22].

Some caution needs to be taken when our results are interpreted. Firstly, our sample size was not large enough to have a precise estimate of the hazard ratio comparing the mortality of transplant-naive dialysed patients and of patients readmitted to dialysis. Although our data did not provide statistical evidence for the difference in the survival probability, it cannot exclude even a reasonably large difference. Secondly, confounding by indication may partially explain the survival benefit of graftectomy. Thirdly, removal of the failed allograft may limit opportunities for repeat transplantation by increasing cytotoxic antibody levels, and may be associated with an increased risk of repeat transplant failure [1]. However, other investigators have not reported an increase in antihuman leukocyte antigen (anti-HLA) antibodies after nephrectomy [16, 23]. Elective transplanted kidney nephrectomy, in the hands of the proper surgical team is a safe, an effective alternative for the treatment of the chronic inflammatory state associated with a failed kidney transplant. We should emphasise that all patients who return to HD following kidney allograft loss should be screened for evidence of chronic inflammation. This should include assessment of erythropoietin resistance, hypoalbuminaemia, and elevated ferritin and CRP levels. Patients with a failed graft represent a challenging clinical problem. Optimal timing of the start of the dialysis after graft loss and avoiding an underdiagnosed uraemic state might reduce morbidity and mortality [24]. Appropriate management of CKD-related complications, including treatment of metabolic bone disease, management of hyperkalemia, acidosis, and anemia, is another important component of CKD care. The risk of complications related to the retained allograft may be higher in patients with shorter durations of allograft function, especially those with graft survival of less than 1 year, those with cytotoxic antibodies prior to the primary transplant, those with a history of rejection or rejection as the cause of transplant failure, and those with an HLA-mismatched primary transplant. It may be also helpful to determine the cytotoxic antibody level at the time of transplant failure to inform decision-making regarding immunosuppressant drug withdrawal after transplant failure [1].

## Conclusion

In summary, the patient with a failed graft enters no-man's-land where all of the physicians (transplant nephrologists, transplant surgeons, dialysis nephrologists) should be involved in the management. A consensus between the transplant team and the dialysis team is crucial to determine which treatment is the most effective in reducing long-term mortality in this high risk population in the dialysis clinic.

### Conflict of Interests

The authors of this manuscript state that they have no conflicts to declare.

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