# Impact of Dialysis Modality on Survival after Kidney Transplant Failure

*Jeffrey Perl,* Omar Hasan,† Joanne M. Bargman,‡ Depeng Jiang,§ Yingbo Na,‖ John S. Gill,¶ and S. Vanita Jassal‡*

## Summary

**Background and objectives** An increasing number of patients are returning to dialysis after allograft loss (DAGL). These patients are at a higher mortality risk compared with incident ESRD patients. Among transplant-naïve patients, those treated with peritoneal dialysis (PD) enjoy an early survival advantage compared with those treated with hemodialysis (HD), but this advantage is not sustained over time. Whether a similar time-dependent survival advantage exists for PD-treated patients after allograft loss is unclear and may impact dialysis modality selection in these patients.

**Design, setting, participants, & measurements** We identified 2110 adult patients who initiated dialysis after renal transplant failure between January 1991 and December 2005 from The Canadian Organ Replacement Register. Multivariable regression analysis was used to evaluate the impact of initial dialysis modality on early (2 years), late (after 2 years), and overall mortality using an intention-to-treat approach.

**Results** After adjustment, there was no difference in overall survival between HD- and PD-treated patients (hazard ratio$_{(HD:PD)}$, 1.05; 95% confidence interval, 0.85 to 1.31), with similar results seen for both early and late survival. Superior survival was seen in more contemporary cohorts of patients returning to DAGL.

**Conclusions** The use of PD compared with HD is associated with similar early and overall survival among patients initiating DAGL. Differences in both patient characteristics and predialysis management between patients returning to DAGL and transplant-naive incident dialysis patients may be responsible for the absence of an early survival advantage with the use of PD in DAGL patients.

*Clin J Am Soc Nephrol* 6: 582–590, 2011. doi: 10.2215/CJN.06640810

*Division of Nephrology, St. Michael's Hospital, University of Toronto, Toronto, Canada; †Department of Medicine, Division of General Internal Medicine, Brigham and Women's Hospital, Boston, Massachusetts; ‡Division of Nephrology, University Health Network, University of Toronto, Toronto, Canada; §Applied Health Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital University of Toronto, Toronto, Ontario, Canada; ‖Canadian Institute of Health Information and Canadian Organ Replacement Register, Toronto, Ontario, Canada; and ¶Division of Nephrology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

**Correspondence:** Dr. Jeffrey Perl, St. Michael's Hospital, 3-060, 30 Bond Street, Toronto, Ontario, Canada M5B 1W8. Phone: 416-864-6016; Fax: 416-864-3042; E-mail: Jeff.perl@utoronto.ca

## Introduction

For patients with ESRD, kidney transplantation remains the optimal method of kidney replacement therapy. Overall, transplant recipients have superior survival and quality of life compared with patients treated with dialysis (1,2). Despite improvements in immunosuppression, most kidney transplants still do not provide patients with a lifetime of kidney allograft function, and many patients will either return to dialysis or require repeat transplantation. The increased number of prevalent transplant recipients together with a relatively fixed duration kidney allograft survival, and limited opportunities for repeat transplantation have resulted in an absolute increase in the number of patients returning to dialysis after kidney allograft loss (DAGL) (3). In 2007, 4.1% of new U.S. dialysis patients initiated DAGL, whereas in Canada, these patients comprise 2 to 3% of the annual incident dialysis patient population (3,4). In addition to diabetes mellitus, hypertension, renovascular disease, and unknown causes of ESRD, DAGL is now included among the top five leading individual causes of dialysis initiation.

In both U.S. and Canadian registries, high absolute mortality rates have been observed in patients returning to DAGL (5–8). Using U.S. Renal Data System data, Gill *et al.* (8) reported a 3-year mortality rate of 33%. Not surprisingly, DAGL patients have worse survival compared with patients with ongoing transplant allograft function (5). However, available evidence also suggests that, despite similar comorbidity profiles, the survival of individuals started onto DAGL is poorer than incident transplant wait-listed dialysis patients (9). There are several potential reasons to explain this observation. Compared with incident dialysis patients, these patients may receive suboptimal predialysis care, which may contribute to the morbidity after dialysis reinitiation (8,10). Compared with incident dialysis patients, patients returning to DAGL usually have a longer exposure to uremia and have higher rates of anemia, erythropoietin resistance, and hypoalbuminemia, all factors that have been associated with reduced survival among ESRD patients (11–13). Finally, the presence of a failed allograft has been postulated to be an ongoing source of chronic inflammation, with the latter associated

  

with an increased risk of mortality in dialysis patients (12,14–16). The survival of DAGL patients has primarily been examined in hemodialysis (HD)-treated patients, and few studies have specifically examined the impact of dialysis modality on survival in this patient population. Intriguingly, a few studies have shown favorable outcomes in peritoneal dialysis (PD)-treated DAGL patients (17–19). Badve *et al.* (18) studied patients initiating PD after transplant failure in Australia and New Zealand between 1991 and 1994. After adjustment for comorbidities and age, 309 patients retuning to DAGL had similar mortality, death-censored PD technique failure, and peritonitis-free survival compared with 13,638 transplant-naive patients.

In transplant-naïve patients, the impact of dialysis modality on patient survival has been primarily examined in analysis of registry data (20–33). Although the findings of these studies have been variable, an emerging theme seems to be the time-varying risk of death for PD *versus* HD (24,26,27,33). Equal or lower mortality rates are observed with the use of PD during the first 1 to 2 years of therapy (24,26,27,33). After the first 2 years, some studies suggest that HD seems to confer a survival benefit, particularly among those patients with comorbid conditions (20,34–36). Several factors may explain this observation, including better preservation of residual kidney function (RKF) associated with PD in earlier but not later years (37).

Whether differences in survival between PD and HD transplant-naïve patients also apply to the DAGL population has not been rigorously examined. There are a number of potential differences between DAGL and *de novo* dialysis patients that may modify the impact of dialysis modality on survival. First, DAGL patients have an increased risk of infection caused by the effects of chronic immunosuppression exposure. Septicemia rates in DAGL patients are particularly high during the first few months after starting dialysis, and this may be related in part to the use of temporary HD catheters (38). In some reports, the use of PD has been associated with lower rates of septicemia and bacteremia (39–42). Second, despite being known to nephrologists, transplant failure patients may still receive suboptimal chronic kidney disease (CKD) management before starting dialysis (11). Because initiation of dialysis with PD requires more preparation for dialysis than HD (*i.e.*, because of the requirement for surgical tube placement and patient training), PD patients may receive a greater duration of and more intensive CKD care before dialysis initiation than HD patients, and the benefits of this exposure may differ in transplant naïve and DAGL patients (10). Third, in incident dialysis patients, preserved urine output is a potent predictor of patient survival (43). However, little is known regarding the impact of transplant RKF on survival in DAGL patients. Results of a decision analysis suggest that ongoing preservation of transplant RKF may allow for improved patient survival despite the risks of continuation of maintenance immunosuppression (44). In contrast, rendering a patient anuric after transplant nephrectomy is associated with lower mortality in DAGL patients (16,12). Finally PD offers more independence than HD, and this may secondarily translate to improved adherence with dialysis treatment and outcomes in DAGL patients who are accustomed to the freedom of transplantation.

Given the differences between transplant naïve and DAGL patients, we sought to determine the impact of initial dialysis modality on early (<2 years), late (after 2 years), and overall survival among patients returning to DAGL.

## Materials and Methods

### Study Design

This is a registry-based study of adult patients who initiated dialysis after first kidney transplant failure in Canada between January 1, 1991 and December 31, 2005.

### Data Source

Administrative data were obtained from the Canadian Organ Replacement Register (CORR), a national registry of dialysis and solid organ transplant recipients. CORR captures >95% of all dialysis patients in Canada. Individual-level patient variables and aggregate variables were available for analysis from both the initial transplant and ESRD registration forms. Variables included demographic (age, gender, race) and geographic (treatment region: east, west, central, or Quebec), pretransplant dialysis treatment type, transplant-related variables (length of allograft function, organ type, and cause of allograft loss), and data on comorbid conditions (peripheral vascular disease, stroke, myocardial infarction, a history of coronary artery bypass grafting, diabetes mellitus, malignancy, respiratory disease, and other comorbid illness (likely to affect 5-years survival).

### Patient Population

Derivation of the study cohort is shown in Figure 1. Subjects were included if they were over the age of 18 years at the time of initial kidney replacement therapy, had a first failed kidney transplant, and returned to dialysis after transplant failure between 1991 and 2005. We excluded prevalent patients who had ESRD before the establishment of CORR (1988), patients with a nonrenal solid organ transplant (either associated with or without a kidney transplant), patients who did not require chronic dialysis, and patients initiating dialysis after a second or subsequent

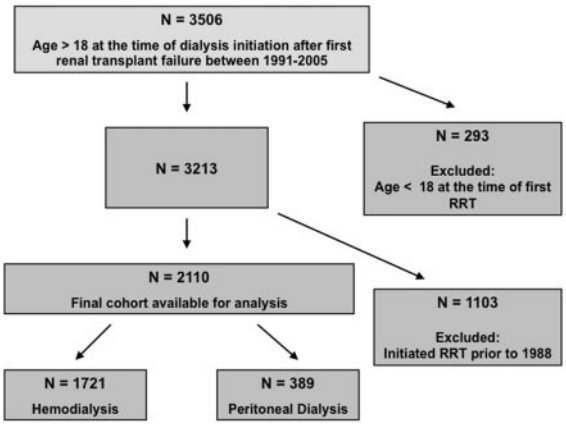


**Figure 1. | Assembly of the study cohort. RRT, renal replacement therapy.**

kidney transplant. The study was approved by the local Research and Ethics Institutional Review Board.

### Data Definitions

Incident dialysis modality, either PD or HD, was determined at the time of first follow-up after first transplant failure. All subtypes of PD were included (intermittent PD, nocturnal intermittent PD, continuous cyclic PD, and continuous ambulatory PD), whereas HD was defined as all conventional HD (3 to 6 hours, two to four times per week) or short daily HD treatments (2 to 3 hours, five to seven times per week), regardless of whether they were done at home, in a satellite unit, or in an in-center unit.

Data on comorbidities and other information were captured at two time points and aggregated: at the time of initial ESRD therapy and at the time of kidney transplantation. Variables indicating the presence of peripheral vascular disease, stroke, myocardial infarction, or a history of coronary artery bypass graft surgery were aggregated to form the variable 'cardiovascular disease' because of the low prevalence of each in a transplant-eligible population (Appendix 1). Similarly, we combined respiratory disease, malignancy, and other systemic illness to form the variable 'other comorbid illness.' Era was defined as the year of dialysis initiation categorized into 5-years time periods: 1991 to 1995, 1996 to 2000, and 2001 to 2005.

### Outcome

The primary outcome of interest was mortality from any cause. Secondary outcomes were early (2 years) mortality and late (after 2 years) mortality. Survival was determined from the date of first dialysis treatment after transplant failure until death. Study subjects were censored if they underwent repeat kidney transplantation or were alive at the end of the observation period (December 31, 2005).

### Sensitivity Analyses

In the primary analysis, study subjects were analyzed in an intention-to-treat manner; patients were not censored if they changed modality treatment assignment during follow-up, and deaths were attributed to the initial dialysis modality. Two additional analyses were performed to test the robustness of our findings. 1) To account for deaths that may be attributable to the effects of initial dialysis modality, survival time was considered only for the duration of exposure to the initial dialysis modality, and patients were censored 60 days after a switch in dialysis modality, and 2) to reduce bias arising from initiation of hemodialysis in an emergency setting, an analysis was performed conditional on patients surviving to day 60 after transplant failure. The subject's dialysis modality (PD *versus* HD) was considered the modality the patient was receiving at day 60.

### Statistical Analyses

Categorical variables were compared using the $\chi^2$ test, $\chi^2$ trend test, and $t$ test or Wilcoxon rank sum test for continuous variables where appropriate. A multivariable Cox proportional hazards model was constructed to obtain covariate-adjusted measures of the association of initial dialysis modality with the rate of death. Model building was performed on the basis of both univariate testing of all covariates for an association with survival and forced entry of variables based on *a priori* knowledge of previous studies examining the impact of dialysis modality on survival (26). Prespecified interaction terms with dialysis modality that were explored included age, gender, the presence of diabetes, and pretransplant dialysis modality. Proportionality of hazards over time was verified for each covariate by testing the interaction between the covariate and a linear function of time. Statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC).

Missing values for the comorbidity covariates (diabetes, cardiovascular disease, and other comorbid illness) ranged from 13 to 20% (Table 1) and did not differ between PD- and HD-treated patients. Missing data were handled in three ways. In the primary model, for the covariates cardiovascular disease, diabetes, and other comorbidities, we created three-level categorical variables with missing values assigned to a separate level (present, absent, and missing). This allowed us to test the impact of missing data on the adjusted hazard ratio (HR). Additional sensitivity analyses were performed using a complete-case analysis by excluding subjects with any missing information and by imputation of missing values as present or absent in separate models.

## Results

### Baseline Characteristics

Table 1 lists the baseline characteristics of the study population. Compared with HD patients ($n$ = 1721, 82%), PD patients ($n$ = 389, 18%) were younger (44.1 ± 11.8 *versus* 47.4 ± 13.1 years), were more likely to be women (53 *versus* 35.8%), and lived farther away from the treating dialysis facility (median distance, 22.1 *versus* 14.5 km for PD and HD, respectively). The most common cause of ESRD in both groups was glomerulonephritis (40.4%). Diabetes mellitus as a cause of ESRD was more common in PD patients (21.6 *versus* 15.2%) than in HD patients. The baseline proportion of comorbidities, length of transplanted allograft function, and median duration of dialysis before first transplantation were similar between the two groups. The majority of patients (55.3%) treated with PD after allograft failure had a history of PD use as a sole dialysis modality before kidney transplantation. The proportion of patients who were treated with more than one dialysis modality before transplantation was similar between groups (22.1 *versus* 22.4%). Patients with a pre-emptive kidney transplant were more likely to be initiated on PD rather than HD after transplant failure (8.5 *versus* 6.4%). Patients returning to dialysis between 1991 and 1995 were more likely to be initiated onto PD compared with those returning in subsequent eras (25.3% compared with 19.2% between 1996 and 2000 and 13.6% between 2001 and 2005).

### Patient Survival by Dialysis Modality

Seven hundred sixteen patients died during the study period (586 HD and 130 PD). Over the period of observation, 140 (36%) of PD patients and 498 (28%) of HD patients received a repeat renal allograft. Overall, the median follow-up was 1043 days (range, 0 to 5822 days). Table 2 summarizes results from the primary analysis. There was

**Table 1. Baseline characteristics of the study cohort at the time of kidney transplant failure**

| Variable | PD ($n$ = 389) | HD ($n$ = 1721) | $P$ |
|---|---|---|---|
| Age at transplant failure years, (mean ± SD) | 44.1 ± 11.8 | 47.4 ± 13.1 | <0.0001 |
| Sex male (no.) (%) | 183 (47.0) | 1105 (64.2) | <0.0001 |
| Caucasian ethnicity, *n* (%) | 315 (80.1) | 1337 (77.7) | 0.16 |
| Primary kidney disease, *n* (%) | | | |
| diabetes mellitus | 84 (21.6) | 261 (15.2) | 0.04 |
| glomerulonephritis | 147 (37.8) | 706 (41.0) | |
| congenital/hereditary | 58 (14.9) | 298 (17.3) | |
| other[a] | 60 (15.4) | 280 (16.3) | |
| unknown | 40 (10.3) | 176 (10.2) | |
| Cause of renal allograft failure, *n* (%) | | | |
| acute rejection | 47 (13.0) | 201 (11.7) | 0.03 |
| chronic allograft nephropathy | 158 (40.6) | 659 (38.3) | |
| recurrence of original disease | 18 (4.6) | 112 (6.5) | |
| graft infection or malignancy | 10 (2.6) | 47 (2.7) | |
| surgical complications | 62 (15.9) | 189 (11.0) | |
| other | 94 (24.2) | 513 (29.8) | |
| Diabetes | | | |
| yes | 89 (22.9) | 310 (18.0) | 0.07 |
| no | 247 (63.5) | 1182 (68.7) | |
| missing | 53 (13.4) | 229 (13.3) | |
| Cardiovascular disease[b] | | | |
| yes | 41 (10.5) | 180 (10.5) | 0.84 |
| no | 296 (76.1) | 1291 (75.0) | |
| missing | 52 (13.4) | 250 (14.5) | |
| Other comorbidities[c] | | | |
| yes | 25 (6.4) | 138 (8.0) | 0.56 |
| no | 287 (73.8) | 1249 (72.6) | |
| missing | 77 (19.8) | 334 (19.4) | |
| Length of graft function (%) | | | |
| <1 year | 145 (37.3) | 548 (31.8) | 0.02 |
| 1 to 5 years | 121 (31.1) | 538 (31.3) | |
| >5 years | 123 (31.6) | 635 (36.9) | |
| Graft type (%) | | | |
| deceased donor | 301 (77.4) | 1366 (79.4) | 0.4 |
| Year of transplant failure (%) | | | |
| 1991 to 1995 | 135 (34.7) | 398 (23.1) | <0.0001 |
| 1996 to 2000 | 136 (35.0) | 571 (33.2) | |
| 2001 to 2005 | 118 (30.3) | 752 (43.7) | |
| Length of pretransplant dialysis (days) | | | |
| median (25th to 75th percentile) | 550 (273 to 1016) | 444 (227 to 743) | <0.0001 |
| Pretransplant dialysis modality (%) | | | |
| PD only | 215 (55.3) | 266 (15.5) | <0.0001 |
| HD only | 55 (14.1) | 960 (55.8) | |
| pre-emptive transplant | 33 (8.5) | 110 (6.4) | |
| >1 modality | 86 (22.1) | 385 (22.4) | |
| Distance from treating center (km) | | | |
| median (IQR) | 22.1 (7.9 to 150.0) | 14.5 (6.1 to 59.7) | <0.0001 |

[a]Other: includes drug induced and renovascular disease as cause of ESRD.
[b]Cardiovascular disease includes a history of coronary artery bypass grafting, peripheral vascular disease, stroke.
[c]Other comorbidities as defined in Appendix 1.

no difference in the unadjusted overall survival ($HR_{[HD:PD]}$, 1.12; 95% confidence interval [CI], 0.93 to 1.35) between patients treated with HD compared with PD and after adjustment for available covariates ($HR_{[HD:PD]}$, 1.05; 95% CI, 0.85 to 1.31; Figure 2). None of the independent variables included in the primary analysis showed significant departure from the proportional hazards assumption. Similarly, there was no difference on the impact of dialysis modality on survival in the first 2 years ($HR_{[HD:PD]}$, 1.18; 95% CI, 0.86 to 1.63) and survival after 2 years ($HR_{[HD:PD]}$, 0.94; 95% CI, 0.70 to 1.30).

Regarding the relationship between dialysis modality and survival, no significant interactions were demonstrated between dialysis modality and the following covariates: age ($P$ = 0.11), diabetes as a primary cause of ESRD ($P$ = 0.85) or as a comorbidity ($P$ = 0.57), gender ($P$ = 0.40), the presence of cardiovas-

**Table 2. Associations between clinical and demographic variables and mortality**

| Variable | Adjusted HR (95% CI) |
|---|---|
| Age (per year increase) | 1.05 (1.04 to 1.06) |
| Sex (female) | 0.95 (0.81 to 1.12) |
| Caucasian ethnicity | 1.10 (0.92 to 1.33) |
| Dialysis year (after transplant failure) | |
| 1991 to 1995 | 1.69 (1.32 to 2.15) |
| 1996 to 2000 | 1.22 (1.00 to 1.48) |
| 2001 to 2005 | 1.0 (ref) |
| Cause of ESRD | |
| diabetes mellitus | 1.70 (1.12 to 2.56) |
| hereditary/congenital | 1.12 (0.88 to 1.42) |
| other | 1.07 (0.85 to 1.34) |
| unknown/missing | 1.18 (0.89 to 1.55) |
| glomerulonephritis | 1.0 (ref) |
| Cardiovascular disease[a] | 1.29 (1.04 to 1.60) |
| Diabetes mellitus[a] | 1.63 (1.11 to 2.40) |
| Other comorbidities[a] | 1.49 (1.16 to 1.91) |
| Length of allograft function | |
| <1 year | 1.0 (ref) |
| 1 to 5 years | 1.54 (1.27 to 3.25) |
| >5 years | 2.07 (1.65 to 2.60) |
| Modality (after kidney allograft failure) | |
| HD | 1.05 (0.85 to 1.31) |
| PD | 1.0 (ref) |
| Pretransplant dialysis duration (per year increase) | 1.05 (0.99 to 1.12) |
| Pretransplant modality | |
| pre-emptive transplant | 0.55 (0.35 to 0.85) |
| PD only | 1.01 (0.82 to 1.24) |
| HD only | 1.0 (ref) |
| >1 modality switch | 1.12 (0.93 to 1.36) |
| Living donor | 1.05 (0.85 to 1.31) |

[a]Individuals with missing data were assumed to be free of disease and thus included in the reference group.

cular disease ($P = 0.24$), pretransplant dialysis modality ($P = 0.06$), and the era of dialysis initiation after kidney allograft loss ($P = 0.61$).

### Impact of Era, Length of Allograft Function, Dialysis Vintage, Pretransplant Modality, and Comorbidities on Survival after Transplant Failure

Era of first kidney transplant failure was associated with improved survival in patients presenting with transplant failure between 2001 and 2005 (reference) compared with 1996 and 2000 (HR, 1.22; 95% CI, 1.00 to 1.48) and between 1991 and 1995 (HR, 1.69; 95% CI, 1.32 to 2.15).

Length of allograft function was inversely proportional to survival after allograft failure. Patients with allograft function >5 years and allograft function between 1 and 5 years had poorer survival compared with patients with allograft loss within the first year after transplantation. Moreover, increased duration of ESRD exposure before transplantation was associated with a trend toward reduced survival on return to DAGL (HR, 1.06; 95% CI, 0.99 to 1.13; per year of pretransplantation dialysis).

Patients treated with preemptive transplantation (HR, 0.55; 95% CI, 0.35 to 0.86) had superior survival compared with patients treated with greater than one dialysis modality before kidney transplantation (HR, 1.12; 95% CI, 0.93 to 1.36), patients treated with PD only (HR, 1.01; 95% CI, 0.82 to 1.24), and patient treated with HD only (reference).

### Sensitivity Analysis

Figure 3 summarizes the results of the sensitivity analyses. Redefinition of the study subject's dialysis modality (PD *versus* HD) using the dialysis modality recorded 60 days after the initiation of dialysis after kidney allograft failure ($n = 472$ PD and 1567 HD) and censoring the 71 deaths that occurred within this 60-day time period resulted in similar survival between patients treated with PD or HD. Similarly, censoring patients at 60 days after a change from initial dialysis modality also did not have a substantive impact on the adjusted survival between PD and HD. Analyses performed to assess the impact of missing data on study results gave similar results to the main model.

## Discussion

This is the first large registry-based study to specifically examine the association between initial dialysis modality and the survival of DAGL patients. We found that the survival was not influenced by initial dialysis modality, with similar effects of dialysis modality on both early and late survival. We also found that factors including the era in which the allograft failed, duration of allograft function, and pretransplant history were associated with survival of patients returning to DAGL. Consistent with these observations, individuals who initially underwent pre-emptive transplantation were found to have the greatest survival of all DAGL patients, suggesting that dialysis vintage (exposure) remains a potent correlate of patient survival even after allograft loss.

Our main finding that patient survival is independent of dialysis modality (PD *versus* HD) is consistent with many (27,33,45–47) but not all (20,21,28,30–32,35,48,49) previously published studies in the dialysis literature. Unlike studies of transplant-naive ESRD patients where dialysis modality may have an effect on patient survival, we found no difference in early, late, and overall survival in patients returning to DAGL treated with PD or HD (21,24,27,32,34,46). Our findings may in part relate to the fact that patients who undergo transplantation are likely younger and healthier at the time of transplantation and therefore are strikingly different from studies of transplant-naïve dialysis patients that include widely heterogeneous groups of patients (8–20), such as those deemed ineligible for kidney transplantation, those of advanced age, and those with complex comorbid disorders (20,24,28,34,35). In keeping with this observation, studies that focused only on incident dialysis patients who were suitable for transplant (*i.e.,* those who were eventually placed on the wait-listed for transplant) had similar results to this study (22,26). This would suggest that the advantages (or disadvantages) of one modality over another might be restricted to other, more vulnerable subgroups. Consistent with our results,

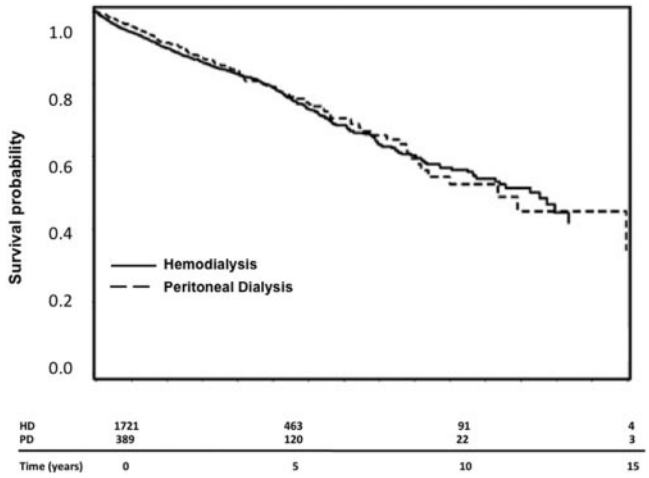


**Figure 2.** | **Adjusted survival curves for patients returning to PD (dashed line) and HD (solid line).**

two smaller, retrospective single-center studies also found little difference in survival between patients treated with PD and HD after kidney transplant failure (50,51). Although small, retrospective studies are of limited generalizability, they allow for detailed collection of patient-level data and potentially better adjustment for case-mix differences.

We initially postulated that allograft function may be better preserved with PD rather than HD, and in turn, patients started onto PD may benefit from better preservation of RKF (37). We therefore tested for proportionality between HD patient survival and PD patient survival, expecting to see a loss of proportionality with time such that there would be a marginally higher early survival in PD patients (over the first 2 years of allograft loss), followed by a reduced survival. This was not observed and was confirmed by an analysis that showed that there was no impact of dialysis modality on early (2 years) and late (after 2 years) survival. Although we had no means of adjusting for RKF at the time of transplant failure, it is possible that the benefits of preservation of transplant residual kidney function on the survival patients returning to DAGL may be different than the impact of native incident residual kidney function. Alternatively, it is possible that patients returning to DAGL are started on dialysis at lower levels of GFR, which may eliminate any early survival advantage traditionally associated with the use of PD. Last, some reports have suggested that there is more accelerated loss of transplant RKF compared with native RKF. This may result in attenuation of the early survival advantage traditionally associated with PD (51). Future studies are needed to evaluate the impact of transplant RKF and

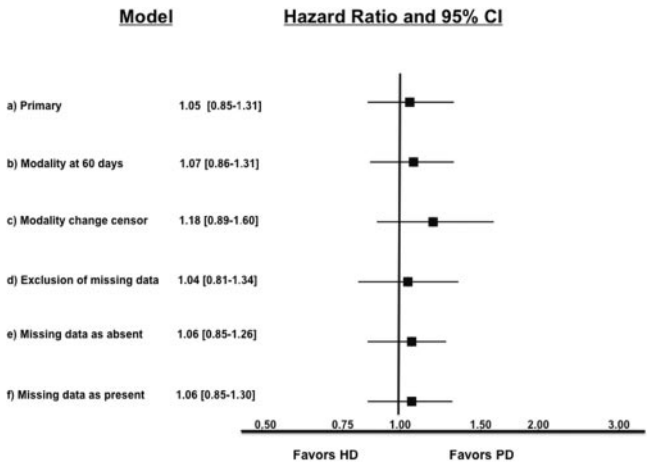


**Figure 3.** | **Results of the sensitivity analyses. Models.** (a) primary, intention-to-treat model. (b) Excluding patients who were censored or died at 60 days after transplant failure. Dialysis modality is taken as the established modality at 60 days after kidney transplant failure. (c) Patients were censored at 60 days after a change in modality. (d) Complete case analysis on patients with all comorbidites documented ($n$ = 1632). (e) Missing comorbidities (diabetes, cardiovascular disease, and other) assigned as absent. (f) Missing comorbidities (diabetes, cardiovascular disease, and other) assigned as present. All models adjusted for age, gender, era of dialysis initiation, cause of ESRD, cardiovascular disease, other comorbidities, diabetes mellitus, pretransplant dialysis duration, pretransplant modality, and region of treatment.

strategies aimed at its preservation on the survival of patients returning to DAGL.

Contemporary cohorts of DAGL patients had better survival than those starting dialysis in earlier eras, independent of dialysis modality. Similar results have been seen in several other incident ESRD populations including incident Canadian dialysis patients (52), U.S. wait-listed dialysis patients (53), and U.S. kidney transplant recipients (53). We attributed this observation to global advances in dialysis care, medications used in transplantation, and overall improved health. We speculate that some of the era effect may be attributable to better predialysis care in patients returning to DAGL and reduced cardiovascular mortality in these patients, particularly given that cardiovascular disease and diabetes are predictive of reduced survival in our cohort.

Unlike data from the U.S. Renal Data System published by Gill *et al.* (8), the data showed that survival after transplant failure was superior in those with the shortest time with a functioning allograft. There are three plausible explanations. First, the duration of allograft function may serve as a proxy for accrued comorbidites during the transplantation period. Second, our study had a longer median follow-up period (>3 years) after transplant failure, making it possible that the length of allograft function, which directly correlates with the duration of exposure to immunosuppression, affects survival only in those who survive long enough to experience the accelerated atherosclerosis associated with continuous immunosuppression. Third, we may be seeing a systematic bias arising from the fact that we included only patients who initiated dialysis after the start of CORR in 1988 (and therefore excluded a cohort of long transplant survivors).

The findings of this analysis need to be interpreted in the context of the study design. As with all analyses of observational data, the major threat to validity in our study is residual confounding. PD requires a surgical procedure and is typically not initiated urgently in unstable patients. In contrast, HD can be initiated emergently using a temporary catheter as dialysis access. Starting HD after transplant failure may be a proxy for other acquired comorbidities (*i.e.*, malignancy) and the acuity of dialysis initiation that both may be risk factors for early mortality after transplant failure. Although we could not assess the absolute impact of comorbidities on dialysis modality choice, we attempted to minimize any bias by performing an analysis using the dialysis modality established at day 60. These analyses did not change the direction or the magnitude of the results of the main analysis. As mentioned previously, we also excluded all patients initiating dialysis before 1988 and therefore systematically excluded a cohort of long-term transplant survivors. Other data, including information about RKF, biochemical values at dialysis initiation, and details of the HD vascular access used at dialysis onset would have been of interest; however, these are not routinely collected in CORR at the time of renal transplant failure and were therefore not available for analysis. The size and scope of our data made it impractical to collect these missing variables from individual patient charts, and therefore, we acknowledge this as a limitation of our results. As with all registry data, large datasets are subject to limitations arising from data surveillance and validity protocols specific to the registry. CORR data are of similar high quality as most registries and are therefore likely to offer clinically useful results (54). We assessed the impact of missing data by performing a series of sensitivity analyses. These showed little change in either the direction of our findings or on the effect size, suggesting that missing data had little on no impact on our overall findings (Figure 3).

Not withstanding these limitations, we showed for the first time in a multicenter study that, compared with HD, PD is associated with similar survival after DAGL. It is interesting to note that, despite this observation, PD was initiated in only 18% of patients, suggesting that PD may be underused in this patient population. We suggest that PD should be considered in these patients because it may offer similar benefits to patients with ongoing allograft function such as autonomy with their own treatment and limited restrictions on travel.

This was a pan-Canadian study with a data source that captures 99% of dialysis patients in Canada and with longitudinal follow-up extending over 14 years, maximizing the generalizability of our results. Our findings provide a basis for the feasibility and safety regarding the use of PD in this patient population. These findings need to be confirmed using a prospective study and in other patient populations, where both patient and PD technique survival may be different than that of our population (19,55,56). Furthermore, these findings will provide a basis for further prospective exploration of modality-specific and transplant-related factors that may influence survival in this patient population.

## Appendix 1

### Definitions of Comorbidities

**1) Diabetes mellitus:**

- Defined as the presence of documented type 1 or type 2 diabetes mellitus

**2) Cardiovascular disease including the presence of at least one of:**

- Cerebrovascular disease: the presence of a cerebrovascular event such as transient cerebral ischemic attack, carotid surgery, cerebral infarct, cerebral hemorrhage, stroke or a cerebrovascular accident.
- Coronary artery bypass grafting/coronary angioplasty: previous coronary artery bypass grafting or previous coronary angioplasty.
- Myocardial infarction: the presence of a confirmed myocardial infarct on the basis of an EKG, cardiac enzymes, echocardiogram, or nuclear medicine scans.
- Peripheral vascular disease: the presence of intermittent claudication at rest or on exercise or previous surgery/internvention including aorto-femoral bypass surgery, femoropopliteal bypass graft, iliac or femoral endarterectomy, angioplasty, direct aortic thrombectomy, abdominal aortic aneurysm repair, or amputation of peripheral extremities (toes, lower legs, etc.).

**3) Other comorbidities including the presence of at least one of:**

- Other serious illness: any other illness that may shorten life expectancy (*e.g.,* AIDS) at the time of starting renal replacement therapy.
- Respiratory disease: clinically significant chronic chest disease requiring medical management before beginning renal replacement therapy. This will usually be described as chronic obstructive lung disease, chronic bronchitis, or emphysema. Patient may be on oral bronchodilators (*e.g.,* Choledyl) or inhalation drugs (*e.g.,* Ventolin).
- Malignancy: malignancy including leukemias and reticuloses, gastrointestinal tract neck and throat urogenital tract, skin, or miscellaneous diagnosed before the initiation of renal replacement.

Adapted from the *Canadian Organ Replacement Register Instruction Manual for Chronic Renal Failure Patients on Renal Replacement Therapy*, Canadian Institute for Health Information, 2007.

**Acknowledgments**

The authors gratefully acknowledge the staff at CORR for maintaining the database and the renal units throughout Canada for submitting information to CORR.

**Disclosures**

J.P. was funded by a Kidney Foundation of Canada Biomedical Fellowship.

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**Received:** August 3, 2010 **Accepted:** October 27, 2010

Published online ahead of print. Publication date available at www.cjasn.org.

See related editorial, "Dialysis Survival after Graft Loss: Are We Finally Comparing 'Apples to Apples'?" on pages 465–466.

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