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Original Investigation

Timing of Peritoneal Dialysis Initiation and Mortality: Analysis of the Canadian Organ Replacement Registry

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Background: Several observational studies of hemodialysis patients show an association between early dialysis therapy initiation and increased mortality. Few studies have examined this association among peritoneal dialysis patients.

Study Design: Retrospective cohort study.

Setting & Participants: A cohort of 8,047 incident peritoneal dialysis patients who started dialysis therapy in 2001-2009 and were treated in Canada.

Predictor: Estimated glomerular filtration rate (eGFR) at dialysis therapy initiation. Defined early, mid, and late starts as eGFR >10.5, 7.5-10.5, and <7.5 mL/min/1.73 m^2, respectively.

Outcomes: Time to death.

Measurements: Proportional piecewise exponential survival models to compare mortality (overall and early) for the 3 predictor groups.

Results: Between 2001 and 2009, the proportion of patients starting peritoneal dialysis therapy as early starts increased from 29% (95% CI, 26%-32%) to 44% (95% CI, 41%-47%). Compared with the late-start group, the overall mortality rate was not higher for the early- (adjusted HR, 1.08; 95% CI, 0.96-1.23) or mid-start (adjusted HR, 0.96; 95% CI, 0.86-1.09) groups. However, when examined yearly, patients in the early-start group were significantly more likely to die within the first year of dialysis therapy compared with those in the late-start group (adjusted HR, 1.38; 95% CI, 1.10-1.73), but not in subsequent years.

Limitations: Bias and residual confounding may have influenced the observed relationship between predictor and outcome.

Conclusions: Patients are initiating peritoneal dialysis therapy at increasingly higher eGFRs. Contrary to most observational studies assessing hemodialysis, the early initiation of peritoneal dialysis therapy, at eGFR > 10.5 mL/min/1.73 m^2, is not associated with increased mortality.

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INDEX WORDS: Estimated glomerular filtration rate (eGFR); mortality; peritoneal dialysis; retrospective cohort study; timing.

Globally, patients are initiating dialysis therapy at higher levels of estimated glomerular filtration rate (eGFR).[1-5] A recent randomized controlled trial suggests that "early" dialysis therapy initiation (at higher eGFRs) offers no improvement in survival, quality of life, or hospitalization rates compared with "late" or deferred dialysis.[6] Results were similar for both hemodialysis (HD) and peritoneal dialysis (PD) patients.[7] However, the difference in eGFRs at initiation between the early- and late-start groups was smaller than planned (only 2.2 mL/min/1.73 m^2), and therefore the trial was not conclusive. In contrast, a large body of observational evidence suggests that early dialysis therapy initiation (at eGFR > 10.5 mL/min/1.73 m^2) is associated with increased mortality.[2,8-11] The optimal time to initiate dialysis therapy has been a matter of controversy, and traditional criteria based on measures of kidney function (such as eGFR) are fraught with limitations. Although some believe that the observed association between early dialysis therapy initiation and mortality is explained by greater comorbid conditions in those with early initiation,[12-14] others recommend delaying dialysis therapy in asymptomatic patients until eGFR decreases to <9 mL/min/1.73 m^2.[15,16]

Perhaps because PD patients constitute a minority of dialysis patients, <11% of the global dialysis population,[17] data are scant regarding the relationship between early PD therapy initiation and mortality. Patient comorbid conditions and dialysis technique may influence the association between early dialysis therapy initiation and mortality, and results from early-start studies in HD patients are not generalizable

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to PD patients.[18] On average, PD patients tend to have fewer comorbid conditions and fewer late referrals than HD patients.[12,18,19] PD is associated with different mortality risks than HD.[18,20] Evaluating the relationship between timing of dialysis therapy initiation and mortality in PD patients may provide additional insight into the potential risks and/or benefits of early initiation.

We analyzed data from the Canadian Organ Replacement Register (CORR) to examine national trends in PD therapy initiation and mortality between 2001 and 2009. We examined trends in timing of PD therapy initiation, determined the characteristics of patients in whom dialysis therapy was initiated earlier versus later, and evaluated whether timing of dialysis therapy initiation is associated with mortality.

METHODS

Data Source

We analyzed data from the CORR, a validated national registry maintained by the Canadian Institute for Health Information.[21] The CORR contains data for the incidence, prevalence, treatment changes, and outcomes of long-term dialysis patients and solid-organ transplant recipients in Canada.[22,23] Dialysis service providers collect the data by completing survey forms for each patient at the initiation of dialysis therapy and yearly thereafter; a change of status form captures information for mortality, transplantation, and dialysis modality change. We analyzed all incident PD patients (aged $\geq$ 18 years at dialysis therapy initiation) who had a recorded value for serum creatinine at dialysis therapy initiation and who received PD as their first form of renal replacement therapy between January 1, 2001, and December 31, 2009. We analyzed patients receiving continuous ambulatory PD and automated PD.

Measures and Definitions

We used the last recorded serum creatinine (SCr) value before dialysis therapy initiation and calculated eGFR using the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation ($186 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ [if female] $\times 1.21$ [if black]).[24] We divided patients into 3 groups based on eGFR at dialysis therapy initiation and defined each as follows: early start, eGFR $>$ 10.5 mL/min/1.73 m^2; mid start, eGFR of 7.5-10.5 mL/min/1.73 m^2; and late start, eGFR $<$ 7.5 mL/min/1.73 m^2. These stratifications were based on guideline cutoff values and previous studies.[4,6,25,26] We documented the presence or absence of coronary artery disease (defined as angina, myocardial infarction, angioplasty, or coronary artery bypass surgery), peripheral vascular disease, hypertension, diabetes mellitus (types 1 and 2), and cerebrovascular disease in 3 categories: yes, no, and unknown (the categories for no and unknown constituted the reference group) and estimated the burden of comorbid disease using the end-stage renal disease comorbidity index.[27] We defined late referral as a patient having first seen a nephrologist less than 3 months before dialysis therapy initiation. Serum albumin concentration was estimated from the last recorded measurement before dialysis therapy initiation.

Statistical Analysis

We followed up cohort members from dialysis therapy initiation until death, loss to follow-up, transplantation, or end of the observation period (December 31, 2009). Patients continued to be followed up in their respective groups after modality switch (ie, from PD to HD). We compared patients' characteristics using χ^2 and t tests, as appropriate. We used a proportional piecewise exponential survival model to compare mortality for the early- and mid-start groups relative to the late-start group. The mortality association between the early- and mid-start groups versus the late-start group was assessed overall and in 1-year increments for 5 years. We adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the following variables: age (years), sex, ethnicity, body mass index (kilograms per meter squared), serum albumin (grams per liter), primary diagnosis, late referral, end-stage renal disease comorbidity index, era (calendar year of dialysis therapy initiation), comorbid conditions, and treatment province. We conducted 3 preplanned sensitivity analyses. First, we constructed a marginal structural model with inverse probability of treatment and censoring weighting.[18,28-30] This technique adjusts for all measured covariates using a single summary propensity score that simultaneously adjusts for the effect of informative censoring from differential likelihood of kidney transplantation across comparison groups. We calculated propensity scores based on each patient's probability of initiating dialysis therapy late (at eGFR $<$ 7.5 mL/min/1.73 m^2) using all available covariates.[31] Because this exposure variable had 3 levels (early, mid, and late start), we ran 2 separate multivariable logistic regression models to calculate propensity scores (early versus late start and mid versus late start). We used receiver operating characteristic curves to test the discriminatory capacity of each model. We derived stabilized censoring weights based on each patient's probability of remaining transplant free in each successive 1-year interval. In the final model, we weighted each observation by: (1) the inverse propensity score and (2) stabilized censoring weights. We conducted 2 other sensitivity analyses: (1) to examine the effect of early mortality, which may disproportionately affect the least healthy patients, we censored patients who died within 90 days of dialysis therapy initiation (this also would exclude those who would have died regardless of dialysis therapy initiation); and (2) to examine the impact of modality switches, we censored patients 60 days after switching from PD to HD. We used the SAS statistical software package, version 9.2 (SAS Institute Inc), for all analyses.

RESULTS

Participant Characteristics

We identified 8,413 adults in whom PD therapy was initiated between 2001 and 2009; a total of 366 were excluded due to missing data for serum creatinine, leaving 8,047 in the analytic sample. Patient characteristics, overall and across comparison groups, are shown in Table 1. Overall, patients were 57% men with a mean age of 61 $\pm$ 15 (SD) years. Mean eGFR at dialysis therapy initiation was 10.1 $\pm$ 4.8 mL/min/1.73 m^2. There were 2,994 (37.2%), 2,670 (33.2%), and 2,383 (29.6%) patients categorized in the early-, mid-, and late-start groups, respectively.

With few exceptions, baseline comorbid conditions and risk factors were greater in the early-start group (Table 1). Those in the early-start group were older; were more likely to be men, have a higher comorbidity index score, and have diabetes, coronary heart disease, peripheral vascular disease, pulmonary edema, lung disease, or a malignancy or other serious disease; and were least likely to receive a kidney transplant during follow-up. However, late referral was more common in the late-start group (19%)