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Estimated glomerular filtration rate at reinitiation of dialysis and mortality in failed kidney transplant recipients

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Abstract

Background. Recent observational studies and a controlled trial suggest more favorable outcomes upon later dialysis initiation in chronic kidney disease. The role of estimated glomerular filtration rate (eGFR) in predicting outcome at reinitiation of dialysis in failed kidney transplant recipients is unclear.

Methods. Five-year data in a large dialysis organization was linked to the 'Scientific Registry of Transplant Recipients' to identify 747 failed kidney transplant patients with CKD Stage 5, who had restarted dialysis therapy. A propensity score for early (eGFR >10.5 mL/min/1.73m^2) versus late reinitiation of dialysis was fit by logistic regression. The mortality hazard ratio (HR) was estimated across tertiles of the fitted score.

Results. Patients were 44 ± 14 years old and included 42% women. Male gender {odds ratio (OR), [95% confidence interval (CI)]: 1.82 (1.22–2.73)}, diabetes mellitus [OR: 1.75 (1.14–2.68)] and peripheral vascular disease [OR: 3.55 (1.17–10.77)] were associated with higher odds of early dialysis reinitiation. Each mL/min/1.73m^2 higher eGFR was associated with 6% higher death risk in unadjusted model [HR: 1.06 (1.01–1.11)], and although not significant in fully adjusted models [HR: 1.02 (0.96–1.07)], it was significant in some subgroups including women and younger patients. The death HR of higher eGFR across lowest to highest tertiles of propensity score of early dialysis initiation (corresponding healthiest to sickest patients) were 1.10 (0.98–1.24), 1.00 (0.91–1.10) and 0.99 (0.92–1.07), respectively (P for trend <0.05), indicating a trend toward higher mortality risk with earlier dialysis initiation in the healthiest patients.

Conclusions. Earlier return to dialysis therapy in failed kidney transplant patients tends to correlate with worse dialysis survival especially among healthiest and younger patients and women. Additional studies need to verify these findings.

Keywords: eGFR; failed kidney; initiation of dialysis; kidney transplantation; mortality

Introduction

In 1997, the US National Kidney Foundation-Kidney Disease Outcome Quality Initiative (NKF-KDOQI) recommended that dialysis should start at a urea clearance (renal Kt/V_{urea}) of <2.0/week [1]. This corresponds to a glomerular filtration rate (GFR) of ∼10.5 mL/min/1.73m^2. The updated guidelines from 2006 suggest that dialysis should start before chronic kidney disease (CKD) Stage 5 (GFR <15 mL/min/1.73m^2) if patients have symptoms believed to be related to a combination of existing comorbidities and insufficient renal function [2]. In Europe, guidelines from 2002 recommend that dialysis should be started when the GFR is between 8 and 10 mL/min/1.73m^2 [3]. However, the latter guideline has recently been revised and suggests that 'the majority of patients will be symptomatic and need to start dialysis with GFR in the range of 9–6 mL/min/1.73m^2' [4]. Data from the US Renal Data System (USRDS) between 1996 and 2008 showed that the proportion of patients initiating hemodialysis (HD) with an estimated GFR (eGFR) >10 mL/min/1.73m^2 increased from 20 to 52% and those with a starting eGFR of ≥15 mL/min/1.73m^2 increased from 4 to 17% [5, 6]. Interestingly, most of the recent observational trials and a landmark randomized controlled trial failed to show a survival benefit of early initiation of dialysis in CKD patients [5, 7–18].

Contrary to CKD patients, only limited data are available in failed kidney transplant recipients. Failed kidney transplant recipients start dialysis in a worse clinical condition compared to CKD patients in general [19, 20] and also have worse survival on HD [19] and in some cases on peritoneal dialysis [21–26]. The incidence and prevalence of end-stage renal disease (ESRD) due to post-transplant complications have increased substantially from 0.3/million and 3.2/1 million between 1996 and 1998 to 1.3/million and 4.9/1 million between 2006 and 2008,

respectively [27]. Dialysis after kidney allograft loss (DAGL) is among the top five leading individual causes of dialysis initiation after diabetes mellitus, hypertension, renovascular disease and unknown causes of ESRD. In 2007, 4.1% of new US dialysis patients initiated DAGL [28]. To the best of our knowledge, there is only one previous study assessing the association between eGFR at initiation of dialysis and mortality in DAGL patients [29]. In 2002, Gill *et al.*, using USRDS data, examined DAGL in 4741 patients. Each mL/min/1.73m^2 increase in eGFR at reinitiation of dialysis was associated with a 4% increased risk of mortality on dialysis in failed kidney transplant patients [hazard ratio (HR): 1.04, 95% confidence interval (CI): 1.02–1.06] [29]. Factors not considered as potential sources of bias in the study by Gill *et al.*, who was conducted without propensity scoring, included patients' comorbidity, age, gender and other relevant confounders. In the present study, we used a propensity score approach to examine the association of the level of eGFR at the initiation of dialysis [early (eGFR >10.5 mL/min/1.73m^2) versus late reinitiation (eGFR ≤10.5 mL/min/1.73m^2)] with subsequent mortality on dialysis in DAGL patients.

Materials and methods

Patients

We linked data on all DAGL patients who underwent maintenance HD or peritoneal dialysis treatment from July 2001 to June 2006 in one of the outpatient dialysis facilities of a US-based large dialysis organization (DaVita Inc., prior to its acquisition of former Gambro dialysis facilities) with patients listed in the 'Scientific Registry of Transplant Recipients' (SRTR) up to 2007. The study was approved by the Institutional Review Boards of both the Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research. Inclusion criteria were patients who had been undergoing dialysis for at least 90 days, whose dialysis initiation date was listed in USRDS within 30 days of their graft failure date (as listed in SRTR), and who had their initial eGFR level captured in USRDS. The four-variable Modification of Diet in Renal Disease (MDRD) equation was used to assess the eGFR in our present study. In this study, we identified failed transplant recipients who reinitiated dialysis therapy with an eGFR <15 mL/min/1.73m^2 to be consistent with CKD Stage 5 definition.

Clinical and demographic measures

To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, i.e. over a 13-week interval, were averaged and the summary estimate was used in all models. Average values were obtained from up to 20 calendar quarters (q1 through q20) for each laboratory and clinical measure for each patient for up to 6 years of follow-up. The first (baseline) studied quarter for each patient was the calendar quarter in which the patient's dialysis vintage was >90 days. Demographic data and details of medical history were collected, with information on age, gender, race, type of insurance, marital status, height and post-HD dry weight [to calculate averaged body mass index (BMI)]. We captured the date and the cause of death from USRDS.

Laboratory measures

Most laboratory values were measured monthly including serum urea, creatinine, albumin, calcium, phosphorus, bicarbonate and total iron-binding capacity (TIBC). Serum ferritin and intact parathyroid hormone were measured at least quarterly. Hemoglobin was measured at least monthly in essentially all patients and weekly to bi-weekly in most patients. Most blood samples were collected pre-dialysis with the exception of post-dialysis serum urea nitrogen to calculate urea kinetics.

Statistical methods

Data were summarized with descriptive statistics as appropriate. Survival analysis to calculate HRs and 95% CI of all-cause mortality employed Cox proportional hazards regression. For mortality analysis, we censored for loss of follow-up and re-transplantation in all survival analyses. Logistic regression model was employed to estimate the odds ratio (OR) and 95% CI of early (eGFR >10.5 mL/min/1.73m^2) versus late initiation (eGFR ≤10.5 mL/min/1.73m^2) of dialysis. Multivariate logistic regression model was constructed based on theoretical consideration using the available data from literature and results of our univariate analysis. We adjusted for age, gender, BMI, race, type of insurance, comorbidities (diabetes, atherosclerotic heart disease, peripheral vascular disease), serum bicarbonate and normalized protein catabolic ratio as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance.

The propensity score method was used to account for the confounding effects arising from differences in clinical characteristics of patients in whom dialysis was started early (eGFR >10.5 mL/min/1.73m^2) versus late (eGFR ≤10.5 mL/min/1.73m^2). First, factors that seemed to influence the likelihood of early dialysis initiation were studied using logistic regression. On the basis of this logistic regression model, we calculated propensity scores of early dialysis initiation [30, 31]. Multivariate logistic regression model to derive the propensity score for choosing early dialysis initiation the outcome had the area under the receiver operating characteristic curve of 0.65, denoting moderate predictive discrimination with respect to the outcome. Three propensity score strata were created using the 33rd and 66th percentiles as cutoff points.

For each Cox regression analysis, three levels of multivariate adjustment were examined: (i) an unadjusted model that included start eGFR as the predictor; (ii) adjusted models that included the start eGFR as the predictor plus age, gender and diabetes and (iii) fully adjusted models that included start eGFR as the predictor plus age, gender, diabetes, serum albumin, BMI and presence of atherosclerotic heart disease. As sensitivity analysis, we constructed a more parsimonious model that included start eGFR as the predictor and adjusted for the propensity score. Restricted cubic spline graphs were utilized as exploratory data analysis strategies to illustrate systematic relations between initiation level of eGFR and mortality [32]. We have performed subgroup analysis in patients categorized by relevant clinical characteristics. Proportional hazard assumptions were tested using Schoenfeld residuals. All analyses were carried out with STATA version 11.1 (STATA Corporation, College Station, TX).

Results

The original 5-year (July 2001 to June 2006) national database of all DaVita patients included 164 789 adult subjects. Of 16 758 DaVita patients who were identified in the SRTR database, 12 986 had a functioning kidney transplant. From the remaining 3 772 patients with DAGL, we excluded 2897 patients with graft failure whose dialysis initiation date listed in USRDS was >30 days after their graft failure date listed in SRTR and patients who did not have initiation eGFR level in USRDS ($n = 21$) or eGFR was >15 mL/min/1.73m^2 ($n = 107$). We examined the remaining 747 patients who underwent dialysis after loss of kidney transplant during the observation period and who were followed until death, re-transplantation, loss of follow-up or survival until 30 June 2007 (Figure 1). There were 181 deaths (24.2%) and the median follow-up time was 1185 days (interquartile range: 692–1854 days).

Table 1 shows the clinical, demographic and laboratory characteristics of the 747 dialysis patients comparing the early (eGFR >10.5 mL/min/1.73m^2) and late initiation (eGFR ≤10.5 mL/min/1.73m^2) subgroups. Patients in the early initiation subgroup were more likely to be men,

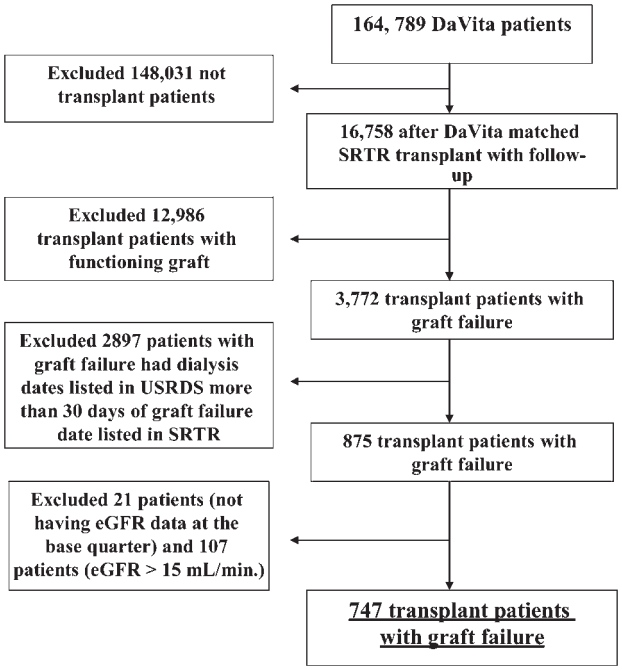

Fig. 1. Flow chart of patients' selection.

insured by Medicare and to be diabetic and have atherosclerotic heart disease, peripheral vascular disease and lower TIBC and phosphorous levels.

Table 2 shows the OR of dialysis start at higher (eGFR >10.5 mL/min/1.73m^2) versus lower (eGFR <10.5 mL/min/1.73m^2) eGFR using multivariate logistic regression analysis. Male gender, presence of diabetes and peripheral vascular disease were associated with increased risk of early initiation of dialysis.

Table 3 shows the HR of death using eGFR upon return to dialysis as the primary predictor. Figure 2A shows the cubic spline model for the unadjusted association of the eGFR at the start of dialysis with mortality. In an unadjusted model, each 1 mL/min./1.73m^2 higher eGFR at dialysis therapy reinitiation was associated with a 6% higher risk of death (HR: 1.06, 95% CI: 1.01–1.11) (Table 3). Figure 2B shows the cubic spline model for the fully adjusted association of the eGFR at the start of dialysis with mortality. In the fully adjusted model, eGFR at the start of dialysis was not associated with the risk of death (HR: 1.02, 95% CI: 0.96–1.07) (Table 3). In a model adjusted for the propensity score, each 1 mL/min./1.73m^2 higher eGFR (indicating earlier dialysis reinitiation) was not associated with greater survival (HR: 1.02, 95% CI: 0.96–1.07).

Table 4 shows the death HR during dialysis therapy based on the starting eGFR as predictor across the tertiles of the propensity score. The eGFR level at the start of dialysis showed an increasing trend toward higher risk of death in the group with low likelihood for dialysis initiation at higher eGFR (HR: 1.10, 95% CI: 0.98–1.24), but not in the moderate (HR: 1.00, 95% CI: 0.91–1.10) or high (HR: 0.99, 95% CI: 0.92–1.07) likelihood groups (P for trend across three tertiles <0.05).

Figure 3 shows unadjusted (Panel A) and fully adjusted (Panel B) death HR (and 95% CI) associated with eGFR across various patient groups. The point estimates were >1 in some subgroups (women and young patients), representing a higher risk of death in patients with early initiation of dialysis in these subgroups.

Discussion

In 747 failed kidney transplant recipients who returned to dialysis therapy between 2001 and 2006, a higher eGFR upon reinitiation of dialysis treatment exhibited a trend toward higher mortality risk especially among the healthiest subgroups, including patients with a lower propensity score of early dialysis initiation, women and younger individuals. Even though patients with early initiation of dialysis appeared sicker (more diabetic and heart disease patients with lower BMI), there was no survival advantage of earlier dialysis therapy at higher eGFR levels in any group. These data may have important clinical and public health policy implications in the long-term management of renal transplant recipients with chronic allograft nephropathy especially with regard to the recommendations for the timing of return to dialysis therapy.

Similar data from CKD patients showed controversial results [33]. From the mid-1970s, some observational studies supported the early initiation of dialysis in CKD patients. However, these studies were small and mainly not adjusted for age and comorbidities, which were different between the early and late subgroups [34–40]. Despite the weak evidence, early initiation was accepted and it was common practice until recently. More recent studies, including a randomized controlled trial, did not support early initiation of dialysis in CKD patients [5, 8, 9, 12, 15–18]. The large multicenter trial from Netherland, the Netherlands Cooperative Study on the Adequacy of Dialysis, was the first observational study which casts doubt on the advantages of early dialysis initiation [7]. Korevaar *et al.* found a small beneficial effect of early dialysis initiation; they observed a gain in survival time of 2.5 months in the first 3 years after the start of dialysis. However, this advantage could have been overestimated because of lead-time bias [7]. This bias was the first potential explanation for previous smaller studies' opposite results. In 2003, Beddhu *et al.* [9] reported that higher eGFR was associated with higher risk of death, but in a subgroup of patients with measured creatinine clearance, there was no association with mortality. Traynor *et al.* [8], on the other hand, reported that higher creatinine clearance at initiation of dialysis was associated with elevated mortality risk. The largest observational study from the USA found a dose-dependent increase in mortality associated with earlier dialysis initiation. After correcting for other factors, compared with those with an eGFR of >5 to 10 mL/min/1.73m^2 at the start of dialysis, patients

Table 1. Baseline characteristics of 747 failed kidney transplant patients who returned to dialysis therapy based on the timing of dialysis reinitiation, i.e. late (eGFR ≤10.5 mL/min/1.73m^2) versus early return to dialysis (eGFR >10.5 mL/min/1.73m^2)[a]

	eGFR ≤10.5 mL/min/1.73m^2	eGFR >10.5 mL/min/1.73m^2	P-value
N (%)	531 (71)	216 (29)	N/A
Deaths (*n*) (crude death rate %)	124 (23)	57 (26)	0.38
Age (years) (mean ± SD)	43 ± 13	45 ± 16	0.11
Gender (% women)	244 (46)	68 (31)	<0.001
Weight (kg) (mean ± SD)	73.3 ± 19.8	72.8 ± 19.2	0.77
Estimated lean body mass (kg) (mean ± SD)	50.5 ± 8.3	49.5 ± 8.2	0.25
BMI (kg/m^2) (mean ± SD)	25.6 ± 5.8	24.9 ± 5.6	0.13
Peritoneal dialysis (*n*) (%)	82 (15)	39 (18)	0.38
Transplant vintage (months) [median (IQR)]	51 (40–70)	56 (45–73)	0.02
Race (%)			
African-American	31	28	0.43
White	45	49	0.25
Hispanic	15	13	0.52
Asian	3	3	0.91
Primary insurance (%)			
Medicare	50	62	0.006
Medicaid	4	3	0.56
Private	10	5	0.03
Other	23	22	0.64
Marital status (%)			
Married	37	44	0.10
Divorced	5	6	0.96
Single	33	32	0.85
Widowed	2	1	0.37
Dialysis vintage (%)			
0–6 Months	10	17	0.01
6–24 Months	23	24	0.83
2–5 Years	27	20	0.05
>5 Years	34	34	0.90
Comorbid conditions (%)			
Diabetes mellitus	28	44	<0.001
Cancer	2	1	0.28
Atherosclerotic heart disease	5	10	0.01
Heart failure	8	9	0.61
Chronic obstructive pulmonary disease	1	2	0.44
Cerebrovascular disease	1	2	0.22
History of hypertension	72	68	0.18
Other heart diseases	1	3	0.17
Peripheral vascular disease	2	5	0.03
Smoker	4	6	0.33
Serum or blood measurement (during the first dialysis quarter)			
Creatinine at quarter base (mg/dL) (mean ± SD)	10.2 ± 3.5	9.2 ± 3.9	0.002
Creatinine at quarter base + 1 (mg/dL) (mean ± SD)	10.9 ± 3.5	10.2 ± 4.0	0.05
Blood hemoglobin (g/dL) (mean ± SD)	11.4 ± 1.7	11.7 ± 1.6	0.08
Albumin (g/dL) (mean ± SD)	3.73 ± 0.48	3.69 ± 0.56	0.44
TIBC (mg/dL) (mean ± SD)	204 ± 47	194 ± 45	0.02
Bicarbonate (mmol/L) (mean ± SD)	22.0 ± 3.6	22.5 ± 3.2	0.17
Calcium (mg/dL) (mean ± SD)	9.2 ± 0.8	9.2 ± 0.8	0.94
Phosphorous (mg/dL) (mean ± SD)	6.2 ± 1.8	5.9 ± 1.6	0.04
Ferritin (ng/mL) [median (IQR)]	376 (199–736)	393 (192–679)	0.82
Protein catabolic rate (g/kg/day) (mean ± SD)	0.95 ± 0.29	0.92 ± 0.27	0.17
WBC (×10^3/μL) (mean ± SD)	7.4 ± 2.7	7.4 ± 2.2	0.99
Lymphocyte (% of total WBC) (mean ± SD)	21 ± 9	22 ± 10	0.84

[a]IQR, interquartile range; WBC, white blood cell.

who initiated dialysis with a higher eGFR experienced a 44% greater mortality risk, whereas those who initiated dialysis at the lowest eGFR (<5 mL/min/1.73m^2) had a 12% lower risk of death [15]. Similar results were reported from the largest observational study from Europe [12]. Data from randomized controlled trials which establish the optimal timing for the initiation of dialysis were lacking until 2010, when the Initiating Dialysis Early and Late (IDEAL) study was published [16, 18]. In this study, patients were randomly assigned either to commence dialysis when the eGFR was 10.0–14.0 mL/min/1.73m^2 (early-start group) or to continue to receive routine medical care and commence dialysis when the eGFR was 5.0–7.0 mL/min/1.73m^2 (late-start group) [18]. During a median follow-up of 3.6 years, 37.6% of early starters

and 36.6% of late starters died (HR for early initiation 1.04, 95% CI: 0.83–1.30; P = 0.75) [16]. Although randomized trials provide the best type of evidence, a question always remains over the generalizability of their results [4, 41]. The mean actual eGFR at the start of dialysis in the IDEAL trial differed only slightly between the two groups (2.2 mL/min by the Cockcroft–Gault equation and 1.8 mL/min by the MDRD equation) [42]. This is a considerably smaller difference compared to what was prespecified by the study protocol and casts doubt on the ability of the study to answer the question it was meant to address.

The main concern of observational studies including ours is the difference between the clinical characteristics and dialysis indications of the early and late initiation groups. Patients with early dialysis initiation were more likely to be men and diabetic, have severe heart failure or coronary heart disease, are less likely to have glomerulonephritis or polycystic kidney disease and have lower serum albumin level and more comorbidity and in summary, they are sicker patients [5, 9, 14, 17]. In our DAGL patients, we found similar results. To handle this potential bias, we used a propensity score in our analysis and we performed subgroup analyses.

A higher eGFR at dialysis initiation was associated with a trend toward higher mortality in healthier subgroups. It is possible that in healthier patients, early dialysis initiation may in fact be harmful. However, eGFR at dialysis initiation was not associated with mortality in sicker subgroups. In these patients, (male, diabetic with peripheral vascular disease) there may be an advantage for early initiation, but further studies are needed to answer this question.

There are some potential factors which can contribute to increased risk of mortality with early dialysis initiation. Thrice-weekly HD treatment may lead to subtle but cumulative mechanical and oxidative stress on the cardiovascular system and engender hemodynamic instability. Burton *et al.* recently showed that HD-induced myocardial stunning is common and may contribute to the development of heart failure and increased mortality in HD patients [43, 44]. In spite of the advances made with more biocompatible membranes, bioincompatibility still remains a problem which may contribute to elevated inflammation/infection and oxidative stress [45]. Moreover, after initiation of dialysis, infection rates are extremely high. Between 1996 and 2001 among a US Medicare cohort of patients who recently started dialysis, the 1-year incidence of infection-related hospitalizations was 32% for those who received HD and 24% for those who received peritoneal dialysis; the 3-year incidence exceeded 50% in both groups [46]. Whereas in the HEMO study, most infection-related hospitalizations were not attributed to vascular access [47], the frequency of access-related infectious hospitalizations was disproportionately higher among patients with catheters compared to grafts or fistulas [47]. Furthermore, there may be repeated bouts of acute tubular necrosis by

Table 2. OR of dialysis reinitiation at higher (eGFR >10.5 mL/min/1.73m^2) versus lower (eGFR <10.5 mL/min/1.73m^2) using multivariate logistic regression analysis, indicating the likelihood of earlier return to dialysis therapy in 747 failed kidney transplant patients[a]

	OR (95% CI)	P-value
Age (+1 year)	1.00 (0.98–1.01)	0.59
Male versus female (reference)	1.82 (1.22–2.73)	0.003
BMI (+1 kg/m^2)	0.97 (0.94–1.01)	0.13
AA race versus White race (reference)	1.00 (0.64–1.56)	0.99
Hispanic race versus White race (reference)	0.91 (0.52–1.60)	0.75
Asian race versus White race (reference)	1.40 (0.48–4.08)	0.54
Medicaid versus Medicare (reference)	0.92 (0.37–2.30)	0.86
Private insurance versus Medicare (reference.)	0.48 (0.23–1.02)	0.06
Other insurance versus Medicare (reference)	0.85 (0.52–1.38)	0.51
Presence of diabetes mellitus	1.75 (1.14–2.68)	0.01
Presence of atherosclerotic heart disease	1.71 (0.75–3.90)	0.20
Presence peripheral vascular disease	3.55 (1.17–10.77)	0.03
Bicarbonate (+1 mmol/L)	1.02 (0.96–1.08)	0.54
nPCR (+1 g/kg/day)	0.75 (0.36–1.55)	0.44

[a]AA, African-American; nPCR, normalized protein catabolic ratio.

Table 3. Death HR using eGFR at dialysis reinitiation in 747 failed kidney transplant patients[a]

	Unadjusted model		Adjusted model[b]		Fully adjusted model[c]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
eGFR (each 1 mL/min/1.73m^2 higher)	1.06 (1.01–1.11)	0.02	1.03 (0.98–1.09)	0.22	1.02 (0.97–1.07)	0.54
Early versus late reinitiation of dialysis	1.27 (0.93–1.74)	0.14	1.03 (0.74–1.43)	0.86	0.95 (0.68–1.33)	0.77
HR of death for other covariates in the above model						
Age (each 1 year increase)	N/A	N/A	1.03 (1.02–1.04)	<0.001	1.03 (1.01–1.04)	<0.001
Gender (male versus female)	N/A	N/A	1.11 (0.82–1.50)	0.50	1.24 (0.91–1.69)	0.18
Presence of diabetes	N/A	N/A	1.86 (1.36–2.55)	<0.001	1.66 (1.20–2.29)	0.002
Serum albumin (each 1 g/dL increase)	N/A	N/A	N/A	N/A	0.44 (0.33–0.59)	<0.001
BMI (each 1 kg/m^2 increase)	N/A	N/A	N/A	N/A	0.99 (0.96–1.02)	0.38
Presence atherosclerotic heart disease	N/A	N/A	N/A	N/A	2.23 (1.44–3.46)	<0.001

[a]The early versus late dialysis reinitiation dichotomy is based on eGFR >10.5 versus ≤10.5 mL/min/1.73m^2. N/A, not applicable.
[b]Model adjusted for age, gender and diabetes.
[c]Model adjusted for age, gender, diabetes, serum albumin, BMI and presence atherosclerotic heart disease.

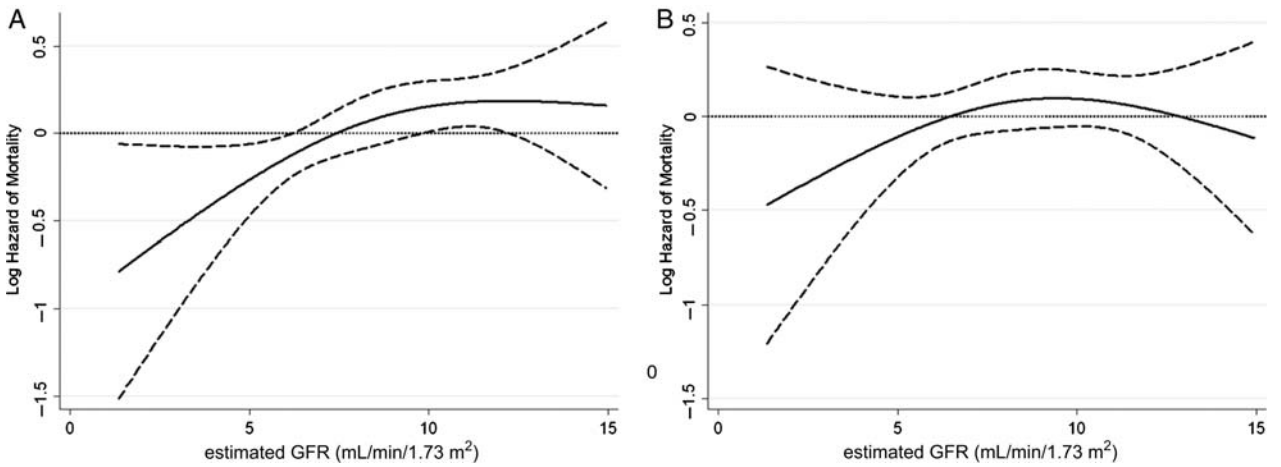

Fig. 2. HR (95% CIs) of death across the entire range of the eGFR level using unadjusted (**A**) and fully adjusted (**B**) Cox regression analyses in 747 long-term failed transplant patients who restarted HD therapy.

Table 4. HR of death using eGFR at dialysis reinitiation as the death predictor across the tertiles of the propensity score (PS) that reflects the propensity to earlier likelihood of return to dialysis therapy[a]

PS tertiles	Unadjusted model		Adjusted model[b]		Fully Adjusted model[c]	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Low likelihood of early initiation ($n = 249$)	1.05 (0.94–1.17)	0.37	1.09 (0.98–1.22)	0.11	1.10 (0.98–1.24)	0.10
Moderate likelihood of early initiation ($n = 249$)	1.01 (0.92–1.11)	0.87	1.02 (0.93–1.12)	0.64	1.00 (0.91–1.10)	0.99
High likelihood of early initiation ($n = 249$)	1.02 (0.95–1.09)	0.56	1.00 (0.93–1.08)	0.95	0.99 (0.92–1.07)	0.82

[a]PS, propensity score.
[b]Model adjusted for age, gender and diabetes.
[c]Model adjusted for age, gender, diabetes, serum albumin, BMI and presence atherosclerotic heart disease.

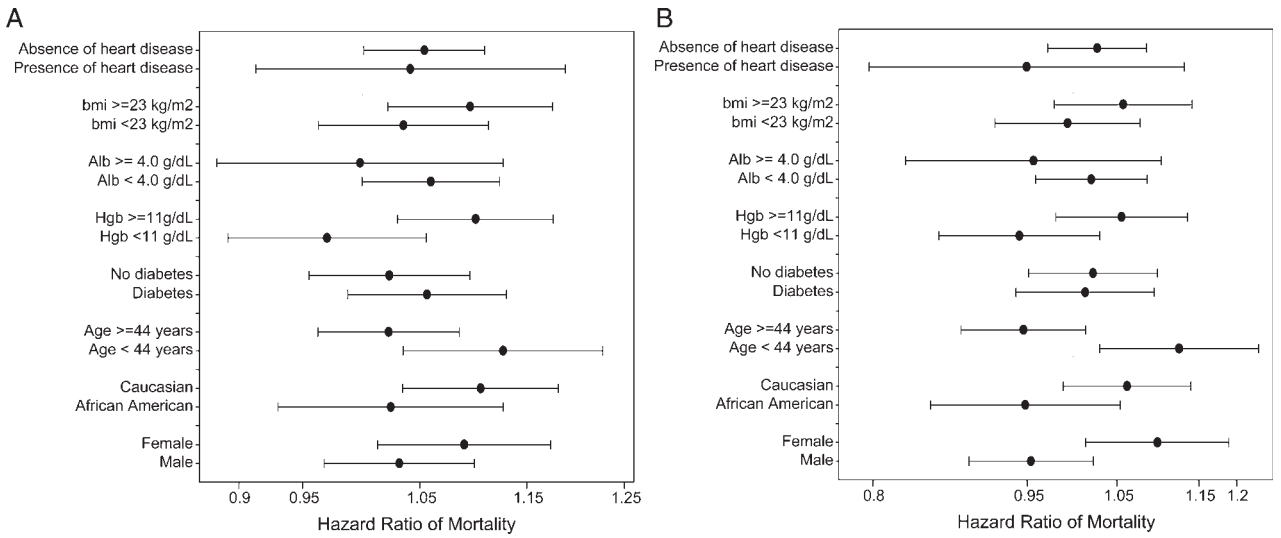

Fig. 3. Multivariate analysis of unadjusted (**A**) and fully adjusted (**B**) Cox regression models showing the HR (and 95% CI as error bars) of death using eGFR at dialysis reinitiation as the death predictor (for each 1 mL/min./1.73m^2 higher eGFR) across different subgroups of patients.

lowering the blood pressure during each HD session [48], resulting in faster loss of residual kidney function and frequent ischemic events upon hypotensive episodes. Exposure to toxic medications may also play role. Patient anxiety which accompanies each HD treatments, along with post-HD fatigue and lightheadedness, may also be harmful [49]. Peritoneal dialysis may be harmful in other ways including substantial protein loss and frequent peritonitis.

There is another factor, which can explain the association of high eGFR and mortality. The eGFR is an inaccurate measure of true GFR in Stage 5 CKD and that it, more accurately, reflects muscle mass (sarcopenia)—not detectable by BMI. High eGFR in Stage 5 CKD largely reflects sarcopenia, not higher renal function [50]. Sarcopenia is in turn a predictor of poor outcomes for patients on HD [51]. The association of high eGFR and mortality might be due to the presence of sarcopenia. Early start by creatinine clearance (a better measure of renal function in Stage 5 CKD) has no adverse effect on mortality risk [9].

Our study has several potential limitations. First, the reported associations do not prove causality. Second, transplant laboratory values (such as serum creatinine) and immunosuppressive and other medical regimens were not available in the SRTR and DaVita database. Third, unmeasured confounders might have an impact on our results. We only had 181 deaths in our cohort, which forced us to use parsimonious models. Fourth, we do not have data about dialysis center characteristics and therefore, we could not adjust for them. Fifth, we did not have the exact data as to which method was used to measure serum creatinine, therefore we did not adjust for the calibration used when we calculated eGFR. Sixth, another important source of bias and error in these studies is the use of eGFR instead of true creatinine clearance (CrCl). Earlier studies showed that patients with low creatinine production were malnourished [52] and that CKD patients with protein-energy wasting including sarcopenia or low meat intake (due to diminished appetite and/or recommended low-protein diet) may have lower serum creatinine levels and perhaps lower creatinine clearance rates but paradoxically higher eGFR per MDRD at dialysis initiation [52]. Indeed, serum creatinine is a good indicator of muscle mass under stable conditions in HD patients [53–56]. Beddhu *et al.* [9] reported that higher initiation eGFR (MDRD), but not higher CrCl, was associated with increased risk of death. Even though in our study we did not find a statistically significant association between higher eGFR at dialysis reinitiation and survival for the entire cohort, our statistical power is limited because among the 3772 failed transplant patients only 747 were included in this study; hence, our generalizability should be qualified. However, we found that higher eGFR was associated with higher death risk at least among women and younger patients. To our knowledge, this is one of the first studies to assess the association between the initiation eGFR and death on dialysis in DAGL patients. Strengths of this study are the relatively uniform dialysis treatment practice pattern across all DaVita clinics, the extensive laboratory and clinical data, the relatively long follow-up time and the multilevel adjustment including via propensity score, which include several important confounders.

Conclusions

In our present cohort of 747 incident HD patients with status post failed kidney transplant, earlier return to dialysis therapy tended to correlate with worse dialysis survival especially among the healthiest and younger patients and women. Whether earlier dialysis reinitiation in failed renal transplant recipients is harmful or not warrants additional studies.

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Conflict of interest statement. None declared.

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