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ORIGINAL ARTICLE

Estimated glomerular filtration rate at dialysis initiation and subsequent decline in residual kidney function among incident hemodialysis patients

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ABSTRACT

Background. Higher estimated glomerular filtration rate (eGFR) at dialysis initiation, known as earlier start of dialysis, is often a surrogate of poor outcomes including higher mortality. We hypothesized that earlier dialysis initiation is associated with a faster decline in residual kidney function (RKF), which is also associated with higher mortality among incident hemodialysis (HD) patients.

Methods. In a cohort of 4911 incident HD patients who initiated HD over a 5-year period (July 2001 to June 2006), we examined the trajectories of RKF, ascertained by renal urea clearance (KRU), over 2 years after HD initiation across strata of eGFR at HD initiation using case-mix adjusted linear mixed-effect models. We then investigated the association between annual change in RKF and mortality using Cox proportional hazard models.

Results. The median (interquartile range) baseline KRU was 2.20 (1.13–3.63) mL/min/1.73 m^2. The decline of KRU was faster in patients who initiated HD at higher eGFR. The relative changes with 95% confidence intervals (CIs) in KRU at 1 year after HD initiation were −1.29 (−1.28 to −1.30), −1.17 (−1.16 to −1.18), −1.11 (−1.10 to −1.12) and −0.78 (−0.78 to −0.79) mL/min/1.73 m^2 in the eGFR categories of ≥10, 8–<10, 6–<8 and <6 mL/min/1.73 m^2, respectively. The faster decline of KRU at 1 year was associated with higher all-cause mortality (reference: ≥0 mL/min/1.73 m^2): hazard ratios (95% CIs) for change in KRU of −1.5 to <0, −3 to less than −1.5 and less than −3 mL/min/1.73 m^2 were 1.20 (1.03–1.40), 1.42 (1.17–1.72) and 1.88 (1.47–2.40), respectively.

Conclusions. The faster decline of RKF happens with earlier dialysis initiation and is associated with higher all-cause mortality.

Keywords: dialysis, GFR, hemodialysis, MDRD, predialysis

INTRODUCTION

In the USA, there were about 124 000 newly reported cases of end-stage renal disease (ESRD) and >726 000 prevalent patients were on dialysis in 2016. The percentage of incident patients starting dialysis with estimated glomerular filtration rate (eGFR) ≥10 mL/min/1.73 m^2 increased from 13% in 1996 to 43% in 2010 but declined to 39% in 2016. However, the mean eGFR at the initiation of dialysis in 2016 was 9.7 mL/min/1.73 m^2 [1]. The randomized controlled trial (RCT) of early versus late initiation of dialysis [Initiating Dialysis Early and Late (IDEAL)] study [2] found no difference in mortality and did not achieve the desired difference in renal function between the early and late groups; whereby the mean eGFRs were 12.0 and 9.8 mL/min/1.73 m^2 at the time of dialysis initiation in the early and late groups, respectively. In contrast, several observational studies [3–6] and a meta-analysis of cohort studies and RCTs [7] have demonstrated a higher risk of mortality with higher eGFR at the time of dialysis initiation.

One of the potential harms of early dialysis initiation includes the loss of residual kidney function (RKF). Previous studies have shown the rapid decline of RKF during the first 3 months after the initiation of dialysis [8, 9]. The RKF, even at low level, was associated with a lower risk of death in

hemodialysis (HD) patients [10–12]. The graded association between RKF decline at 1 year after dialysis initiation and increased mortality has been observed in a recent cohort of incident HD patients [10]. We investigated the trajectory of RKF over 2 years after HD initiation across different levels of eGFR at the initiation of HD and hypothesized that higher eGFR at the time of dialysis initiation is associated with a more rapid drop in RKF in incident HD patients. We also examined the association between annual change in RKF at 1 year and all-cause mortality.

MATERIALS AND METHODS

Study population

We assessed statistically deidentified data from patients with chronic kidney disease Stage 5 who underwent HD treatment between July 2001 and June 2006 in any of the 580 outpatient dialysis facilities of a large dialysis organization (LDO) in the USA. The baseline quarter for each patient was the earliest calendar quarter in which the patient's HD duration was >90 days. Of the 127 304 patients who underwent HD treatment >90 days during the study period, 108 531 patients with missing eGFR measurements within 60 days prior to HD initiation were excluded. Among the remaining 18 773 patients, patients with missing baseline renal urea clearance (KRU) or KRU at the fourth quarter ($n = 12\,219$), those with missing dialysis vintage or dialysis vintage >3 months ($n = 1595$) and those with outliers of eGFR at the time of HD initiation or baseline KRU (<0.25th or >99.75th percentiles; $n = 48$) were excluded. Therefore, the final study population consisted of 4911 patients for analyses of the trajectory of KRU over the first 2 years of HD across eGFR at the time of HD initiation (Supplementary data, Figure S1). Of the 4911 patients, 3105 patients also had KRU measurements at the fifth patient-quarter and annual change in KRU at 1 year, and we excluded patients with outliers of annual change in KRU at 1 year (<0.25th or >99.75th percentiles; $n = 14$), resulting in 3091 patients for investigating the association of annual change in KRU with survival (Supplementary data, Figure S2). The study was approved by the Institutional Review Committees of the University of California, Irvine and Los Angeles Biomedical Research Institute at Harbor, University of California, Los Angeles. The requirement for a written consent was waived because of the large sample size, patient anonymity and nonintrusive nature of this study.

Demographic, clinical and laboratory measures

The patient cohort has been described previously [13]. Demographic data and the presence of diabetes mellitus (DM) at baseline were obtained from the LDO database. History of preexisting comorbidities and tobacco smoking were derived from Medical Evidence Form 2728 from the United States Renal Data System (USRDS). Available preexisting comorbidities were grouped into nine categories: ischemic heart disease (IHD), congestive heart failure (CHF), other cardiac diseases, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer and nonambulatory state. The level of eGFR at the initiation of HD was estimated on the basis of each patient's serum creatinine reported on Form 2728 within 60 days prior to HD initiation using the Modification of Diet in Renal Disease (MDRD) equation [14].

Information on clinical and laboratory values was obtained from the LDO statistically deidentified data set. Blood samples were drawn using uniform techniques in all LDO facilities and processed at a central laboratory (DeLand, FL, USA) using automated and standardized methods. Most laboratory parameters were measured monthly, including complete blood counts and serum levels of urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, total iron-binding capacity (TIBC) and normalized protein catabolic rate (nPCR). Serum ferritin levels and serum parathyroid hormone concentrations were measured at least quarterly. Corrected serum calcium concentrations were calculated using the following equation: corrected calcium (mg/dL) $= \{0.8 \times [4 - \text{serum albumin (g/dL)}]\} + \text{measured serum calcium (mg/dL)}$. Most blood samples were collected prior to HD except for postdialysis serum urea nitrogen to calculate urea kinetics. The average serum urea concentrations during the collection were assumed to be 90% of the predialysis concentration according to the approach by Daugirdas *et al.* [15] and thus KRU was calculated as follows:

$$\text{KRU (mL/min)} = \frac{\text{urinary urea nitrogen (mg/dL)} \times \text{urinary volume (mL)}}{\text{collected time (min)} \times [0.9 \times \text{serum urea nitrogen (mg/dL)}]}$$

KRU was adjusted for body surface area and expressed as mL/min/1.73 m^2 [16, 17]. The annual changes in KRU at 1 year were calculated by subtracting the KRU values at 1 year (the fifth patient-quarter) from those at baseline (the first patient-quarter). To minimize measurement variability, all repeated measures for each patient during any calendar quarters (i.e. over a 13-week interval) were averaged and used in all models. The averaged values during the first patient-quarter were used as baseline data.

Statistical analyses

Baseline characteristics across eGFR at the initiation of HD were summarized using proportions, means [standard deviation (SD)] or medians [interquartile ranges (IQR)] as dictated by data type. Patients were categorized into four groups according to eGFR at the initiation of HD (<6, 6 to <8, 8 to <10 and ≥10 mL/min/1.73 m^2). Nonparametric trend test was used to evaluate the association of baseline characteristics across eGFR at the initiation of HD. Changes in KRU over time during the first eight patient-quarters (PQ1–PQ8) were examined in linear mixed-effect models with case-mix adjustment. Effect modification of KRU trajectories by categories of eGFR at the initiation of HD was examined by creating the interaction terms (effect modifier variable × patient-quarter follow-up) and comparing model fit with and without interaction terms by Wald test. The case-mix adjusted model included age, sex, race/ethnicity, primary insurance, types of vascular access, presence of DM, nine preexisting comorbidities and history of tobacco smoking. Factors related to nutrition and inflammatory status may be in the causal pathway in the relationship between KRU and these

laboratory parameters; therefore, they were not used as covariates in the analyses. Sensitivity analyses were also conducted in subgroups of patients on the basis of race (White or Non-White), sex, baseline age (<65 or ≥65 years old), presence of DM and heart disease (IHD, CHF and other cardiac diseases). In the sensitivity analyses, patients were categorized into four groups according to their baseline KRU values (<1.2, 1.2 to <2.4, 2.4 to <3.6 and ≥3.6 mL/min/1.73 m^2). Changes in KRU over time during the first eight patient-quarters were examined in linear mixed-effect models with case-mix adjustment, and effect modification of KRU trajectories by baseline KRU categories was examined.

We then evaluated the association of the annual change in KRU at 1 year as a main predictor with subsequent all-cause mortality using Cox proportional hazard regression models and restricted cubic splines. The annual change in KRU at 1 year was calculated subtracting KRU at Year 1 (the fifth patient-quarter) from KRU at baseline (the first patient-quarter). The survival time started from the first day of the fifth patient-quarter (i.e. the 365th day of dialysis) until the end of cohort (30 June 2006). Patients who received a kidney transplant or were lost to follow-up were censored at the time of event. We divided the annual change in KRU at 1 year *a priori* into four categories (less than −3, −3 to less than −1.5, −1.5 to <0 and ≥0 mL/min/1.73 m^2). The category of ≥0 mL/min/1.73 m^2 was designated as the reference group. For each analysis, three models with multivariable adjustment were examined: (i) minimally adjusted model that included baseline KRU; (ii) case-mix adjusted model that included baseline KRU, age, sex, races/ethnicities, primary insurance, types of vascular access, presence of DM and nine comorbidities, history of smoking and baseline single pool Kt/V; (iii) fully adjusted model that included covariates in the case-mix adjusted model plus baseline BMI, nPCR, hemoglobin, albumin, creatinine, corrected calcium, phosphorus, TIBC, bicarbonate, intact parathyroid harmone and ferritin level. Sensitivity analyses were also performed in subgroups of White or non-White patients. Missing covariate data were imputed by the means or medians of the existing values as appropriate. Two-sided $P < 0.05$ were considered to be statistically significant. All statistical analyses were performed using STATA MP, version 13.1 (StataCorp, College Station, TX, USA).

RESULTS

Cohort description

The baseline characteristics of the 4911 incident HD patients stratified by eGFR at the initiation of HD are summarized in Table 1. The mean ± SD age at baseline was 63 ± 15 years old; 41% of the patients were women, 55% were Non-Hispanic White, 25% were African-American and 62% had DM. Their median baseline KRU was 2.20 (IQR = 1.13–3.63 mL/min/1.73 m^2). Patients with higher eGFR at the initiation of HD were more likely to be elderly and Non-Hispanic White, had a higher prevalence of DM, IHD and CHF and had lower serum albumin, creatinine and phosphorus levels at baseline.

Trajectories of RKF according to eGFR at the initiation of HD

In the unadjusted model, trajectories of KRU were significantly different across eGFR at HD initiation strata. Patients with higher eGFR at the initiation of HD had a more rapid decline in KRU over the first 2 years of HD ($P_{Wald} < 0.001$; Figure 1). The association between higher eGFR at the initiation of HD and a faster decrease in KRU persisted in the case-mix adjusted model ($P_{Wald} < 0.001$; Figure 1). In the case-mix adjusted model, the relative annual changes in KRU from baseline (the first patient-quarter) to the fifth patient-quarter were −1.29 [95% confidence interval (CI) −1.28 to −1.30], −1.17 (95% CI −1.16 to −1.18) , −1.11 (95% CI −1.10 to −1.12) and −0.78 (95% CI −0.78 to −0.79) mL/min/1.73 m^2 in the eGFR categories of ≥10 , 8 to <10 , 6 to <8 and <6 mL/min/1.73 m^2, respectively. In the case-mix adjusted model, the association between higher eGFR at the initiation of HD and a more rapid decline in KRU was not significantly modified by race (White or Non-White; $P_{interaction} = 0.85$), sex ($P_{interaction} = 0.27$), baseline age (≥65 or <65 years old; $P_{interaction} = 0.8$), DM ($P_{interaction} = 0.07$) and presence of heart disease ($P_{interaction} = 0.3$; Figures 2 and 3; Supplementary data, Figure S3). Trajectories of KRU were also significantly different across baseline KRU strata. Patients with higher baseline KRU had a faster decline in KRU during the first 2 years of HD ($P_{Wald} < 0.001$ for unadjusted and case-mix adjusted models; Supplementary data, Figure S4).

Annual change in RKF at 1 year and mortality

Cox regression analyses with restricted cubic splines showed a significant association between a more rapid decline in annual change in KRU at 1 year after dialysis initiation and higher risks of all-cause mortality in the fully adjusted model (Figure 4). The hazard ratios (HRs) of all-cause mortality associated with annual change in KRU at 1 year are presented in Table 2. In the fully adjusted model, compared with patients in the reference category of annual change in KRU of ≥0 mL/min/1.73 m^2, death risks were higher in patients with annual change in KRU of −1.5 to <0 mL/min/1.73 m^2 (HR = 1.20; 95% CI 1.03–1.40), −3 to less than −1.5 mL/min/1.73 m^2 (HR = 1.42; 95% CI 1.17–1.72) and less than −3 mL/min/1.73 m^2 (HR = 1.88; 95% CI 1.47–2.40), respectively (Table 2). A similar trend was observed in the subgroup analyses of White and Non-White patients ($P_{interaction} = 0.50$; Figure 4; Supplementary data, Table S1).

DISCUSSION

In this retrospective analysis of data from 4911 incident HD patients from an LDO in the USA, we found that patients with higher eGFR at the initiation of HD had a faster decline in KRU over the first 2 years after HD initiation. These associations were consistent across strata of race, sex, baseline age, DM and presence of heart disease. We also observed a significant association between a faster decline in annual change in KRU at 1 year and higher risks of all-cause death. To our knowledge, this is the first epidemiologic study to examine the association

Table 1. Baseline characteristics of 4911 incident HD patients stratified by eGFR at the initiation of HD

Variables	All	eGFR at the initiation of HD				P-value
		<6 mL/min/1.73 m^2	6 to <8 mL/min/1.73 m^2	8 to <10 mL/min/1.73 m^2	≥10 mL/min/1.73 m^2	
n (%)	4911 (100)	1027 (21)	1106 (22)	1027 (21)	1751 (36)	NA
KRU, mL/min/1.73 m^2	2.20 (1.13–3.63)	1.57 (0.81–2.48)	2.12 (1.13–3.46)	2.45 (1.25–3.85)	2.69 (1.40–4.36)	<0.001
Age, years	63 ± 15	57 ± 15	61 ± 15	64 ± 14	66 ± 14	<0.001
Women (%)	41	46	44	39	37	<0.001
Race/ethnicity (%)						
Non-Hispanic White	55	49	54	58	59	<0.001
African-American	25	26	26	23	25	0.54
Hispanic	15	18	15	15	12	<0.001
Asian and others	5	7	5	4	4	<0.001
Insurance (%)						
Medicare	56	49	55	56	61	<0.001
Medicaid	4	7	5	2	3	<0.001
Others	40	44	40	42	36	<0.001
Vascular access (%)						
AVF	33	34	34	34	30	0.04
AVG	23	18	24	24	25	<0.001
Catheter	44	48	42	42	45	0.31
Comorbidities (%)						
DM	62	46	57	66	72	<0.001
IHD	24	16	21	26	31	<0.001
Cancer	5	5	5	4	5	0.92
CHF	29	19	22	30	39	<0.001
COPD	6	4	5	6	8	<0.001
CVD	8	5	8	7	10	<0.001
Hypertension	82	83	81	84	82	0.65
Other cardiac diseases	5	4	3	5	6	<0.001
PVD	12	7	10	12	16	<0.001
Nonambulatory state	2	1	1	2	2	0.02
Current smoking	5	6	4	5	4	0.04
BMI, kg/m^2	27.9 ± 6.8	27.9 ± 6.5	27.9 ± 6.7	28.0 ± 6.8	27.8 ± 7.1	0.12
spKt/V	1.69 ± 0.41	1.60 ± 0.35	1.67 ± 0.38	1.71 ± 0.38	1.75 ± 0.46	<0.001
nPCR (g/kg/day)	1.05 ± 0.27	1.04 ± 0.26	1.06 ± 0.27	1.06 ± 0.26	1.04 ± 0.27	0.24
Laboratory measures						
Hemoglobin (g/dL)	12.5 ± 1.3	12.5 ± 1.3	12.5 ± 1.2	12.6 ± 1.2	12.6 ± 1.3	0.004
Albumin (mg/dL)	3.72 ± 0.41	3.80 ± 0.38	3.75 ± 0.40	3.71 ± 0.40	3.64 ± 0.41	<0.001
Creatinine (mg/dL)	7.1 ± 2.7	9.4 ± 2.9	7.7 ± 2.3	6.8 ± 2.0	5.5 ± 1.9	<0.001
Calcium (mg/dL)	9.5 ± 0.6	9.5 ± 0.6	9.5 ± 0.6	9.5 ± 0.6	9.5 ± 0.6	0.02
Phosphorus (mg/dL)	5.6 ± 1.3	6.0 ± 1.4	5.7 ± 1.2	5.5 ± 1.2	5.2 ± 1.1	<0.001
Intact PTH (pg/mL)	227 (134–373)	249 (138–438)	229 (123–390)	230 (142–355)	212 (131–337)	<0.001
TIBC (mg/dl)	224 ± 43	223 ± 43	227 ± 43	224 ± 42	224 ± 43	0.96
Ferritin (ng/ml)	231 (120–422)	233 (125–395)	227 (109–412)	226 (123–426)	237 (126–442)	0.05
Bicarbonate (mmol/L)	22.0 ± 2.7	21.4 ± 2.7	21.7 ± 2.9	22.0 ± 2.6	22.4 ± 2.7	<0.001

Data are presented as means ± SDs, medians (IQRs) or percentages as appropriate. The P-value for trend shows the differences in each variable across categories of eGFR at the initiation of HD. eGFR at the initiation of HD was obtained within 60 days prior to initiation of HD. BMI was calculated using postdialysis weight and height. AVF, arteriovenous fistula; AVG, arteriovenous graft; COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; PVD, peripheral vascular disease; BMI, body mass index; spKt/V, single pool Kt/V; intact PTH, intact parathyroid hormone.

between eGFR at HD initiation and change in KRU during the first 2 years of HD.

The RCT of early versus late initiation of dialysis (IDEAL) study [2] showed no difference in mortality between the early (eGFR 10–14 mL/min/1.73 m^2) and late (eGFR 5–7 mL/min/1.73 m^2) groups. However, the limitation of the study is that the researchers could not achieve the degree of separation in renal clearances at the time of dialysis initiation that they intended; therefore, this RCT did not provide a definitive conclusion about the effect of initiation of dialysis at higher eGFR on clinical outcomes [18]. Nevertheless, several observational studies have demonstrated an association of a higher risk of death with higher serum creatinine-based estimates of GFR at the time of dialysis initiation [3–6]. A meta-analysis of cohort studies and trials also found that a 1 mL/min/1.73 m^2 increase in eGFR at dialysis initiation was associated with a 3–4% risk increase in all-cause mortality [7]. One of the potential risks of early start of dialysis is the accelerated loss of RKF. The apparent decline of RKF in dialysis patients has been observed during the first 3 months after the start of dialysis treatment [8, 9]. Our study found that patients with greater eGFR at the time of HD initiation had a more rapid decline in RKF over the first 2 years after the start of HD. The presence of RKF was associated with a lower risk of mortality in HD patients [11, 12]. In a recent longitudinal cohort of incident HD patients, a faster decline in RKF at 1 year after initiating dialysis was associated with higher

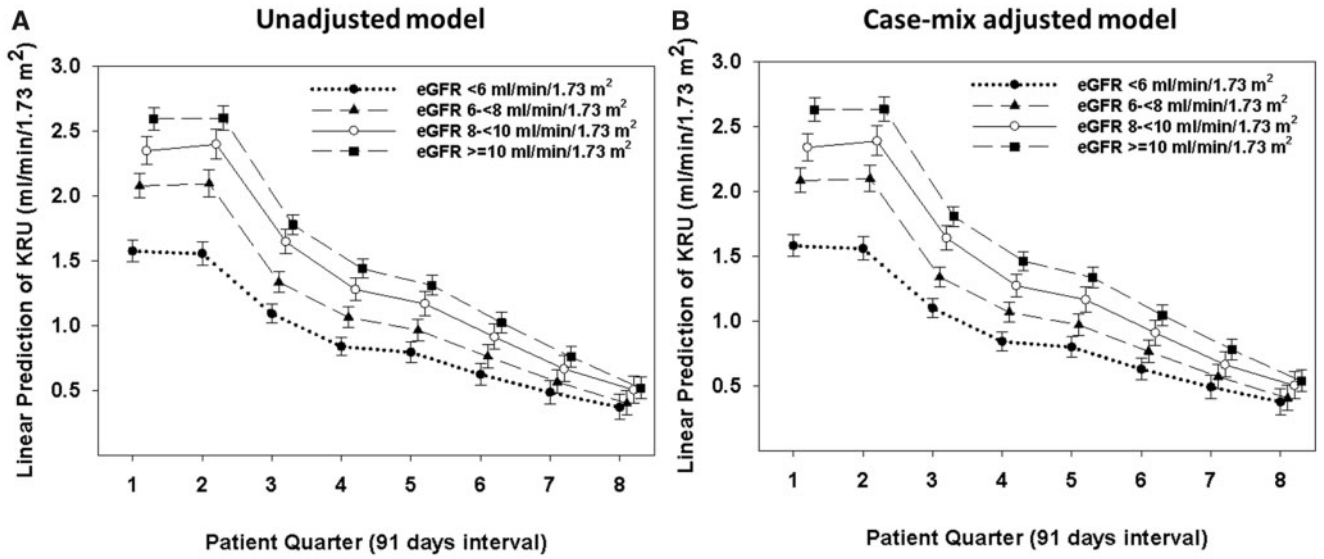

FIGURE 1: Predicted KRU (mL/min/1.73 m^2) at each quarter during the first 2 years of HD in 4911 incident HD patients stratified by eGFR at the time of HD initiation for the unadjusted model (**A**) and case-mix adjusted model (**B**). The case-mix adjusted model included age, sex, race/ethnicity, primary insurance, types of vascular access, presence of DM, nine preexisting comorbidities and history of tobacco smoking.

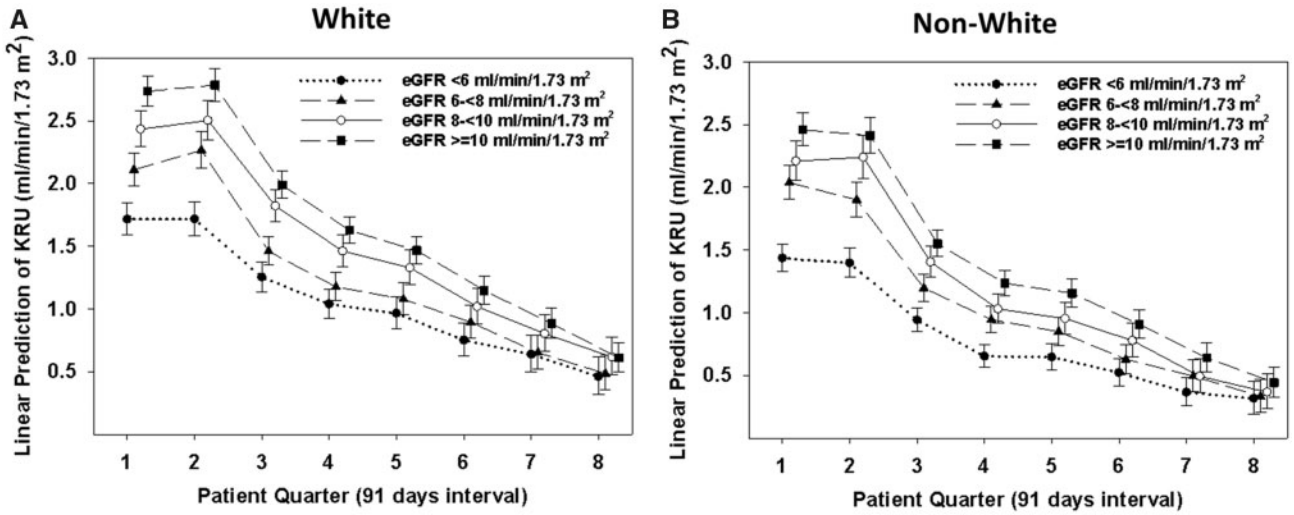

FIGURE 2: Case-mix adjusted mean KRU (mL/min/1.73 m^2) at each quarter during the first 2 years of HD stratified by eGFR at the time of HD initiation in 4911 incident HD patients for White (**A**) and Non-White (**B**) patients. The case-mix adjusted model included age, sex, race/ethnicity, primary insurance, types of vascular access, presence of DM, nine preexisting comorbidities and history of tobacco smoking.

mortality [10]. Similar to the findings in the previous studies [10–12], our study also observed a significant association between a more rapid drop in RKF and a higher risk of all-cause mortality.

The association between a higher eGFR at HD initiation and a faster decline in RKF could be attributable to a vicious cycle of HD-induced RKF decline including HD-induced renal ischemia, aggressive ultrafiltration, intradialytic hypotension and characteristics of HD treatment, which may be more pronounced in patients with higher eGFR at HD initiation. Recently, Marants *et al.* [19] found that renal perfusion decreased during HD, even in the absence of significant hypotension. This reduction in renal perfusion represents a potential renal ischemia, which is repeated during HD sessions and may result in cumulative renal tissue damage and a subsequent decline in RKF. The continual decline in RKF over several HD sessions necessitates an increase in ultrafiltration to account for increased interdialytic weight gain. Nevertheless, higher ultrafiltration rate was associated with a faster decline in RKF among conventional HD dialysis patients [20]. In addition, intradialytic hypotension during HD was negatively associated with RKF after HD initiation [9]. Intradialytic hypotension and aggressive ultrafiltration during HD can also induce myocardial stunning, leading to left ventricular systolic dysfunction among some HD patients [21] and may contribute to greater RKF loss. Assa *et al.* [22] demonstrated that HD-induced regional left ventricular systolic dysfunction may occur shortly after HD treatment begins. Moreover, the characteristics of HD treatments including higher frequency of HD treatments [23–26], a bioincompatible dialysis membrane [27, 28] and

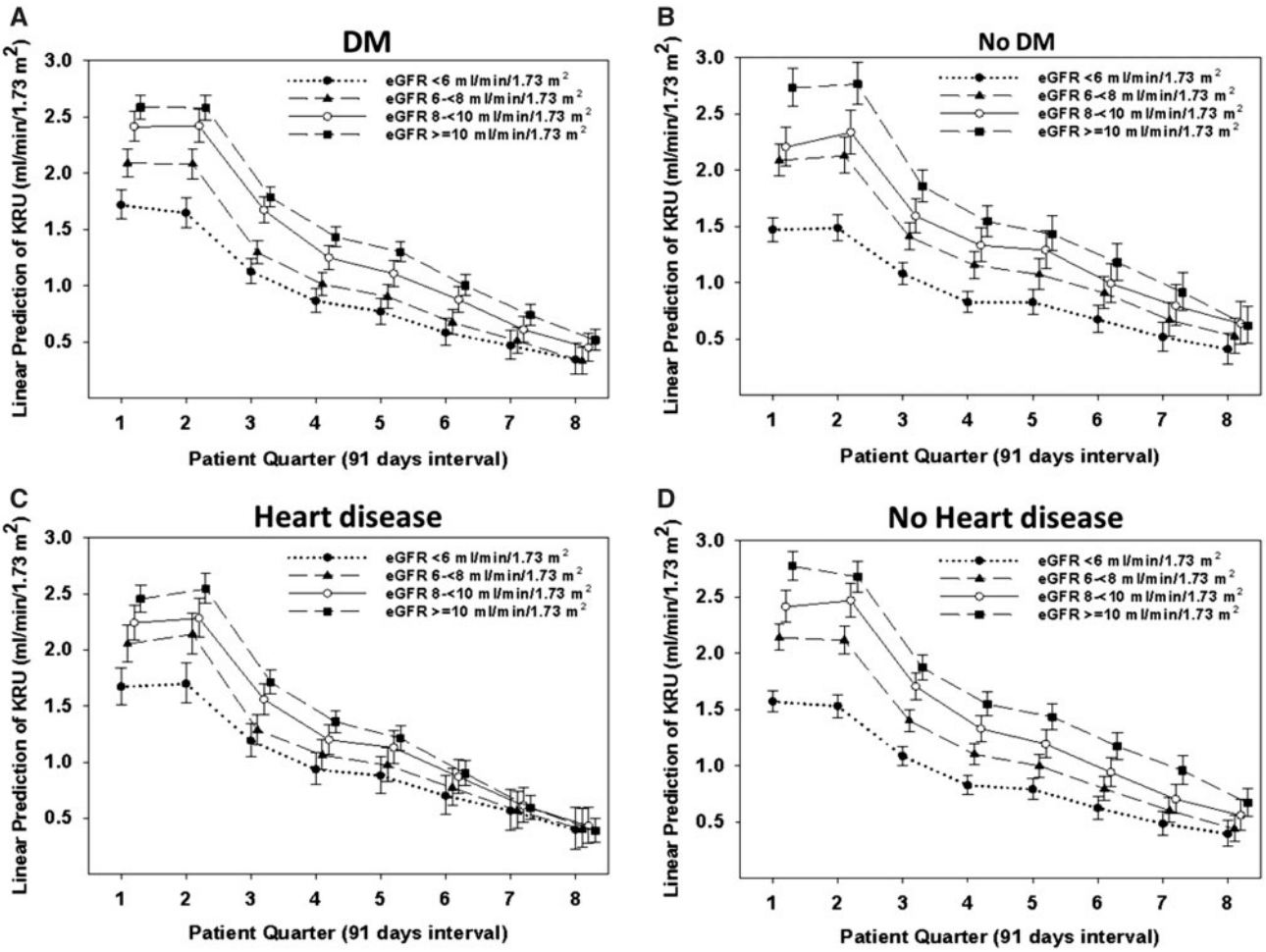

FIGURE 3: Case-mix adjusted mean KRU (mL/min/1.73 m^2) at each quarter during the first 2 years of HD stratified by eGFR at the time of HD initiation in 4911 incident HD patients for diabetic patients (**A**), nondiabetic patients (**B**), patients with heart disease (**C**) and patients without heart disease (**D**). The case-mix adjusted model included age, sex, race/ethnicity, primary insurance, types of vascular access, presence of DM, nine preexisting comorbidities and history of tobacco smoking. Patients with heart disease included those with IHD, congestive heart failure and other cardiac diseases.

microbiological quality of dialysis fluid [29] are associated with RKF decline. Daugirdas *et al.* [23] reported that frequent nocturnal (six times per week) HD was associated with a more rapid decline in RKF compared with conventional (three times per week) HD. Lin *et al.* [24] found that patients who had sufficient urine output and underwent twice-weekly HD had a slower decline of RKF than patients on thrice-weekly HD due to fewer intradialytic hypotension events. Zhang *et al.* [26] observed that patients who initiated with twice-weekly HD for $\geq$6 months had better RKF than patients who started and maintained thrice-weekly HD and the percentage of patients with RKF loss was significantly lower in the twice-weekly group compared with the thrice-weekly group, particularly during the first year of HD initiation. In a recent study by Obi *et al.* [25], the association between incremental HD regimen (defined as twice-weekly HD for >6 weeks during the first quarter) was compared with conventional thrice-weekly HD regimen and the change in RKF and survival were examined. This study found that patients with the incremental regimen exhibited better preservation of RKF and the incremental regimen showed an increased risk of mortality in patients with inadequate baseline KRU $\leq$3 mL/min/1.73 m^2, but not in those with higher baseline KRU [25]. The results of the repetitive exposure of blood to dialysis membranes and to large volumes of dialysis fluids may have negative effects on RKF. Types of dialyzer membranes [27, 28] and microbiological quality of dialysate [29] could influence the rate of decline in RKF. Previous studies found that HD patients who were dialyzed with polysulfone membrane (biocompatible membrane) had a greater preservation of RKF than those who were dialyzed with cellulosic membrane [27, 28]. Schiffl *et al.* observed that HD patients using ultrapure dialysate had less loss of RKF and less inflammation than those using conventional dialysate [29].

There were several limitations in our study. First, we estimated eGFR at HD initiation using the MDRD formula [14]. However, this formula may be inaccurate in estimating renal function in patients with ESRD [30]. This inaccuracy could be due to the fact that there is large interindividual variability in creatinine levels caused by factors such as muscle mass, diet, renal creatinine secretion and extra-renal

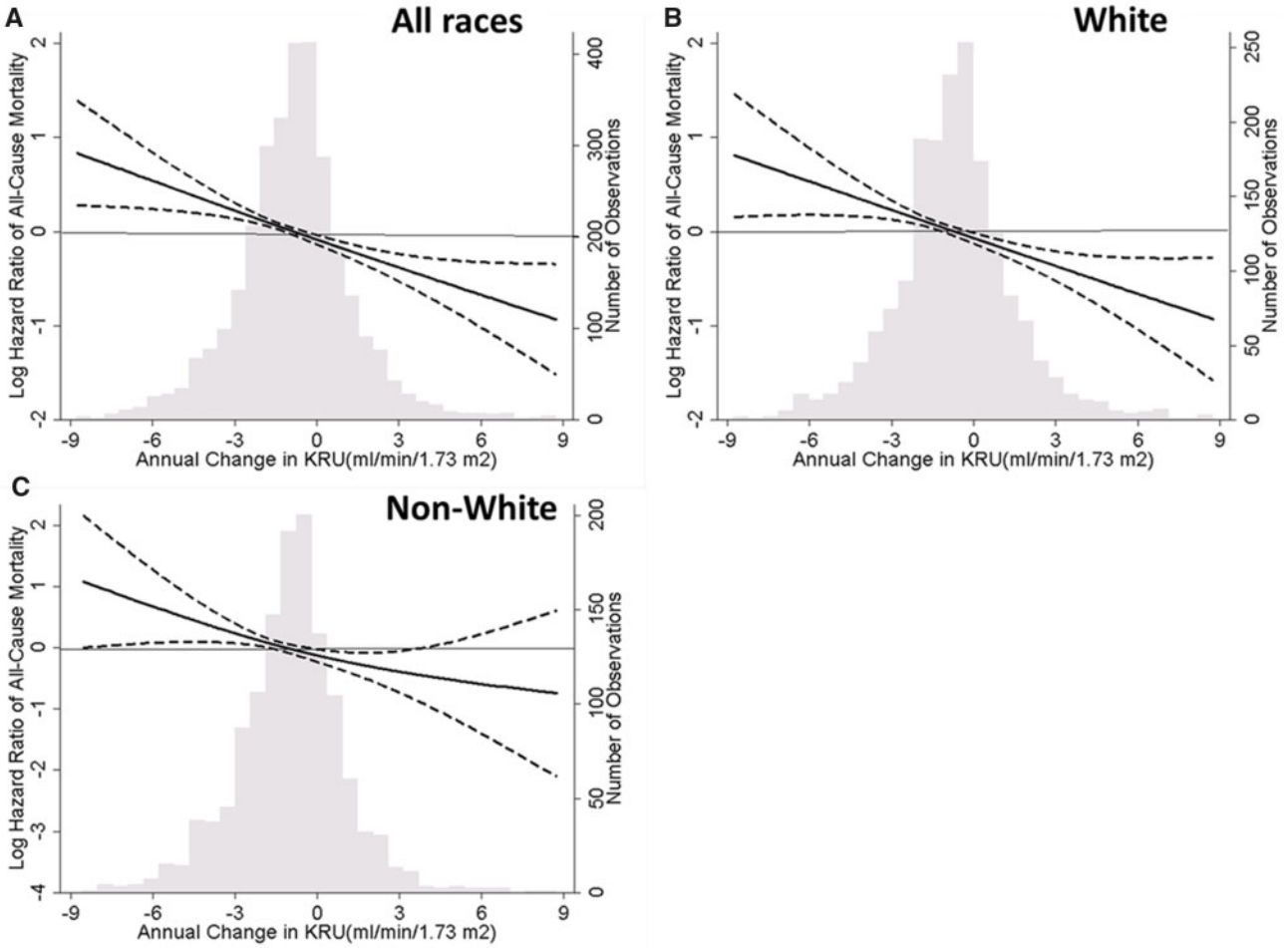

FIGURE 4: Fully adjusted HR for the association between annual change in KRU and all-cause mortality in 3091 incident HD patients for all races (**A**), White (**B**) and Non-White (**C**) patients. Dashed lines represent 95% CI. Annual changes in KRU were calculated subtracting KRUs at Year 1 (the fifth patient-quarter) from those at baseline (the first patient-quarter). The fully adjusted model included baseline KRU, age, sex, race/ethnicity, primary insurance, types of vascular access, presence of DM and nine comorbidities, history of tobacco smoking, baseline single pool Kt/V, body mass index, normalized protein catabolic rate, baseline serum levels of hemoglobin, albumin, creatinine, calcium, phosphorus, total iron-binding capacity, bicarbonate, intact parathyroid hormone and ferritin.

Table 2. HRs (95% CIs) for the association between annual change in KRU and all-cause mortality

Annual change in KRU (mL/min/1.73 m^2)	Minimally adjusted ($n = 3091$)		Case-mix adjusted ($n = 3091$)		Fully adjusted ($n = 3091$)	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Less than −3	1.47 (1.16–1.85)	0.001	1.75 (1.38–2.23)	<0.001	1.88 (1.47–2.40)	<0.001
−3 to less than −1.5	1.11 (0.93–1.33)	0.25	1.31 (1.08–1.58)	0.005	1.42 (1.17–1.72)	<0.001
−1.5 to <0	1.00 (0.86–1.15)	0.95	1.08 (0.93–1.25)	0.34	1.20 (1.03–1.40)	0.02
≥0	1.00		1.00		1.00	

The minimally adjusted model included baseline KRU. The case-mix adjusted model included baseline KRU, age, sex, races/ethnicities, primary insurance, types of vascular access, presence of DM and nine comorbidities, history of smoking and baseline spKt/V. The fully adjusted model included covariates in the case-mix adjusted model plus baseline BMI, nPCR, hemoglobin, albumin, creatinine, corrected calcium, phosphorus, TIBC, bicarbonate, intact PTH and ferritin level. Annual changes in KRU were calculated subtracting KRUs at Year 1 (the fifth patient-quarter) from those at baseline (the first patient-quarter). spKt/V, single pool Kt/V; intact PTH, intact parathyroid hormone; BMI, body mass index.

creatinine elimination, which are not accounted for by the formula [31]. Second, RKF was measured by the use of KRU but not the average of renal urea and creatinine clearances, and the difficulties in complete collection of urine samples could result in inaccurate RKF measurement. The use of factor 0.9 for predialysis serum urea nitrogen for KRU calculation may induce some errors. Third, we lacked information regarding the use of medications such as angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, nephrotoxic drugs, the use of biocompatible dialyzer membrane, ultrapure dialysate fluid and dialysis schedules, which may confound the association between

eGFR at HD initiation and RKF decline. Fourth, linear mixed models did not account for patients who were censored due to kidney transplantation, loss follow-up and death; therefore, the patient numbers at the later time of follow-up may be lower and may lead to selection bias.

In summary, our study demonstrated that patients who initiated HD at higher eGFR had a faster decline in RKF and a more rapid drop in RKF was associated with higher mortality. Further studies are needed to elucidate the mechanisms underlying the association between a faster decline in RKF and higher eGFR at HD initiation.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest. The results presented in this article have not been published previously in whole or part, except in abstract form.

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