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Residual Kidney Function Decline and Mortality in Incident Hemodialysis Patients

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ABSTRACT

In patients with ESRD, residual kidney function (RKF) contributes to achievement of adequate solute clearance. However, few studies have examined RKF in patients on hemodialysis. In a longitudinal cohort of 6538 patients who started maintenance hemodialysis over a 4-year period (January 2007 through December 2010) and had available renal urea clearance (CL_{urea}) data at baseline and 1 year after hemodialysis initiation, we examined the association of annual change in renal CL_{urea} rate with subsequent survival. The median (interquartile range) baseline value and mean \pm SD annual change of CL_{urea} were 3.3 (1.9–5.0) and -1.1 ± 2.8 ml/min per 1.73 m^2 , respectively. Greater CL_{urea} rate 1 year after hemodialysis initiation associated with better survival. Furthermore, we found a gradient association between loss of RKF and all-cause mortality: changes in CL_{urea} rate of -6.0 and $+3.0$ ml/min per 1.73 m^2 per year associated with case mix–adjusted hazard ratios (95% confidence intervals) of 2.00 (1.55 to 2.59) and 0.61 (0.50 to 0.74), respectively (reference: -1.5 ml/min per 1.73 m^2 per year). These associations remained robust against adjustment for laboratory variables and ultrafiltration rate and were consistent across strata of baseline CL_{urea} , age, sex, race, diabetes status, presence of congestive heart failure, and hemoglobin, serum albumin, and serum phosphorus levels. Sensitivity analyses using urine volume as another index of RKF yielded consistent associations. In conclusion, RKF decline during the first year of dialysis has a graded association with all-cause mortality among incident hemodialysis patients. The clinical benefits of RKF preservation strategies on mortality should be determined.

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In patients with ESRD, residual kidney function (RKF) contributes to achievement of adequate solute clearance and is associated with health and patient survival.^{1,2} RKF, even at such low levels as in patients undergoing maintenance dialysis, substantially contributes to solute clearance, particularly for protein-bound solutes and middle molecules,^{3,4} and among patients undergoing peritoneal dialysis, it has been shown that residual renal clearance is more strongly associated with survival versus dialysis clearance.^{5–8} Although this may also be

the case in patients on hemodialysis, there is paucity of such data. Other benefits conferred by RKF

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include better fluid and metabolic homeostasis, less severity of mineral and bone abnormalities, and greater endogenous production of erythropoietin and calcitriol.^{7–12} These factors allow for greater fluid and dietary liberalization in this population and may prevent common complications in patients with ESRD, such as left ventricular hypertrophy, arterial media calcification, and congestive heart failure.

The importance of RKF in patients on peritoneal dialysis is widely known, but only a few studies have examined RKF in patients on hemodialysis, despite the fact that up to 45% of patients in the United States initiate maintenance dialysis at eGFRs >10 ml/min per 1.73 m².^{13,14} Paucity of prior study in this area may, in part, be because of misconceptions that RKF declines rapidly after starting maintenance hemodialysis, when, in fact, the rates of RKF decline in patients on hemodialysis may be similar to those in patients on peritoneal dialysis if the current standard biocompatible membranes and bicarbonate buffer are used.^{15–17} In addition, timed urine collections for patients undergoing maintenance hemodialysis are labor intensive, and hence, they are not performed routinely. This is likely another important reason for the paucity of studies of RKF in patients on hemodialysis.

To address this knowledge gap, we studied a large national cohort of incident hemodialysis patients in the United States for 5 years to determine which clinical factors at the time of initiation of hemodialysis predict preserved RKF at 1 year and quantitatively investigate the association of annual change in RKF with survival. We hypothesized that faster decline in RKF has a dose-dependent association with higher mortality, irrespective of baseline RKF or comorbid conditions, in incident hemodialysis patients.

RESULTS

Baseline Demographic, Clinical, and Laboratory Characteristics

Compared with the 44,416 excluded patients who lacked baseline residual renal urea clearance (CL_{urea}; or KRU) data, the 6538 included patients were more likely to be men and non-Hispanic white; were more likely to have an arteriovenous fistula as their vascular access; and had larger body mass index, lower single-pool Kt/V (spKt/V), higher hemoglobin, higher albumin, lower bicarbonate, and lower ferritin at baseline (Supplemental Table 1). Additionally, compared with the 16,357 excluded patients who had CL_{urea} data at baseline but not at year 1, the included patients were more likely to be non-Hispanic white; were more likely to have an arteriovenous fistula as their vascular access; and had greater RKF, higher hemoglobin, and higher albumin at baseline. The mean ± SD age of the final study cohort was 62 ± 14 years old, of which 65% were men, 56% were non-Hispanic white, 25% were non-Hispanic black, and 68% were diabetic (Table 1). Their median baseline renal CL_{urea} was 3.4 (interquartile range [IQR], 2.1–5.1) ml/min per 1.73 m².

Predictors of Annual Decline in RKF

Renal CL_{urea} rates at 1 year after initiation of hemodialysis were lower than baseline levels (*P* for signed rank test <0.001); median renal CL_{urea} was 2.1 (IQR, 0.9–3.6) ml/min per 1.73 m², and mean ± SD annual change in renal CL_{urea} was -1.1 ± 2.8 ml/min per 1.73 m². In the overall cohort, 1134 (17%), 1444 (22%), and 2073 (32%) patients had change in renal CL_{urea} <−3.0, −3.0 to <−1.5, and −1.5 to <0.0 ml/min per 1.73 m², respectively, and 1887 (29%) showed maintained or increased CL_{urea} during the first year of dialysis (Table 1).

After adjustment for case mix characteristics and baseline value, factors associated with less decline in renal CL_{urea} included non-Hispanic white; presence of atherosclerotic heart disease; higher body mass index, hemoglobin, albumin, and corrected calcium; and normalized protein catabolic rate (nPCR) <0.8 g/kg per day at baseline, whereas older age, diabetes, presence of congestive heart failure, and higher creatinine, phosphorus, intact parathyroid hormone (PTH), and iron saturation at baseline were associated with faster decline in renal CL_{urea} (Table 2). Consistent findings were observed in the fully adjusted model, whereas the association with faster CL_{urea} decline became significant in women and higher serum bicarbonate rates. In the sensitivity analyses, where patients with baseline CL_{urea} <1.5 ml/min per 1.73 m² were excluded (Supplemental Table 2), atherosclerotic heart disease was not associated with annual change in CL_{urea}. Additionally, nPCR and intact PTH lost their significance in the fully adjusted model.

RKF at 1 Year and Survival

A total of 1046 patients died during the follow-up period after year 1 until the end of the study (December 31, 2011). There was a significant trend toward lower mortality with higher renal CL_{urea} (*P*_{trend} <0.001 across all models). Compared with patients who had renal CL_{urea} of 3.0 to <6.0 ml/min per 1.73 m² at 1 year after hemodialysis initiation, those who had renal CL_{urea} of 1.5 to <3.0 and <1.5 ml/min per 1.73 m² experienced higher mortality, which remained significant after adjusting for case mix characteristics (hazard ratio [HR], 1.26; 95% confidence interval [95% CI], 1.08 to 1.47 and HR, 1.67; 95% CI, 1.44 to 1.94, respectively) or body mass index and laboratory variables at 1 year after hemodialysis initiation (Figure 1). The mortality risk in patients who had renal CL_{urea} of ≥6.0 ml/min per 1.73 m² at year 1 was not significantly different in the unadjusted model and the case mix adjustment model, but it was lower in the fully adjusted model (HR, 0.74; 95% CI, 0.57 to 0.97).

Annual Change in RKF and Survival

Cox regression analyses with restricted cubic spline functions showed a significant association of annual change in renal CL_{urea} with all-cause mortality in the minimally adjusted, case mix-adjusted, and fully adjusted models (Figure 2); patients with faster CL_{urea} decline showed higher risks of mortality. Case mix-adjusted HRs were 2.00 (95% CI, 1.55 to 2.59), 1.25 (95% CI, 1.16 to 1.35), 0.81 (95% CI, 0.73 to 0.91),

Table 1. Characteristics of 6538 incident hemodialysis patients who have urine collection data at both baseline and 1 year after initiation of dialysis stratified by annual change in renal CL_{urea}

Variable	Total, n=6538	Annual Change in Renal CL_{urea}			P_{trend} Value	
		<-3 ml/min per 1.73 m ² , n=1134; 17%	-3 to <-1.5 ml/min per 1.73 m ² , n=1444; 22%	-1.5 to <0 ml/min per 1.73 m ² , n=2073; 32%		≥0 ml/min per 1.73 m ² , n=1887; 29%
Renal CL_{urea} , ml/min per 1.73 m ²	3.4 (IQR, 2.1–5.1)	6.2 (IQR, 5.2–7.9)	3.9 (IQR, 3.0–5.0)	2.6 (IQR, 1.7–3.8)	2.4 (IQR, 1.3–3.7)	<0.001
Urine volume, ml/d	900 (IQR, 550–1400)	1478 (IQR, 1100–1900)	1075 (IQR, 750–1450)	750 (IQR, 500–1200)	650 (IQR, 400–1050)	<0.001
Age, yr	62±14	61±14	62±14	62±15	63±14	0.001
Men, %	65	74	66	62	61	<0.001
Race, %						
Non-Hispanic white	56	57	55	53	58	0.46
Non-Hispanic black	25	23	25	26	25	0.13
Hispanic and others	19	20	20	21	16	<0.01
Primary insurance, %						
Medicare	52	50	48	54	52	0.04
Medicaid	7	7	7	7	6	0.22
Others	42	43	44	39	42	0.15
Access, %						
Central venous catheter	68	68	64	68	72	0.001
AV fistula/graft	27	27	30	27	23	<0.001
Unknown	5	5	6	5	5	0.95
Comorbidities, %						
Hypertension	52	48	51	55	53	<0.01
Diabetes	68	74	71	66	66	<0.001
Congestive heart failure	47	52	48	47	43	<0.001
Atherosclerotic heart disease	16	17	16	15	17	0.98
Other cardiovascular disease	18	19	17	18	18	0.82
Body mass index, kg/m ²	27.7 (IQR, 24.0–32.8)	27.8 (IQR, 24.4–32.8)	27.8 (IQR, 23.8–32.6)	27.4 (IQR, 23.9–32.4)	27.7 (IQR, 24.2–33.2)	0.98
spKt/V	1.30±0.27	1.23±0.26	1.28±0.27	1.32±0.26	1.34±0.28	<0.001
Ultrafiltration rate, L/h	0.58±0.24	0.60±0.24	0.59±0.25	0.59±0.23	0.56±0.23	<0.001
nPCR, g/kg per d	1.0±0.3	1.11±0.29	1.05±0.28	0.99±0.27	0.95±0.27	<0.001
Laboratory variables						
Hemoglobin, g/dl	11.5±1.0	11.6±1.0	11.6±1.0	11.5±1.0	11.5±1.1	0.02
Albumin, mg/dl	3.64±0.42	3.59±0.44	3.62±0.43	3.65±0.40	3.67±0.41	<0.001
Creatinine, mg/dl	6.0±2.2	5.2±1.8	6.0±2.1	6.4±2.4	6.0±2.2	<0.001
Calcium, mg/dl	9.1±0.5	9.1±0.5	9.1±0.5	9.1±0.5	9.1±0.5	<0.01
Phosphorus, mg/dl	5.1±1.1	4.9±1.0	5.1±1.1	5.2±1.1	5.0±1.0	0.08
Intact PTH, pg/ml	313 (IQR, 207–461)	292 (IQR, 195–420)	326 (IQR, 208–485)	328 (IQR, 218–482)	303 (IQR, 201–441)	0.31
Iron saturation, %	23±8	22±7	23±7	22±8	23±8	0.80
Ferritin, pg/ml	243 (IQR, 140–403)	219 (IQR, 136–364)	230 (IQR, 132–380)	249 (IQR, 141–401)	258 (IQR, 148–437)	<0.001
Bicarbonate, mmol/L	23.2±2.5	23.1±2.5	23.1±2.5	23.1±2.5	23.4±2.5	0.003

All repeated measures from each patient during the first patient-quarter (the first 91 days of dialysis) were averaged, and the quarterly means are presented. Values are expressed as means±SDs, medians (IQRs), or percentages as appropriate. Conversion factors for units: albumin and hemoglobin in grams per deciliter to millimoles per liter, 88.4; calcium in milligrams per deciliter to millimoles per liter, 0.2495; and phosphorus in milligrams per deciliter to millimoles per liter, 0.3229. No conversion is necessary for ferritin in nanograms per milliliter and milligrams per liter. AV, arteriovenous.

Table 2. Association of baseline characteristics with annual change in residual renal CL_{urea} among 6538 incident patients on hemodialysis

Variables	Case Mix-Adjusted Model		Fully Adjusted Model	
	β (95% CI)	P Value	β (95% CI)	P Value
Baseline renal CL_{urea} per 1.0 ml/min per 1.73 m ²	-0.62 (-0.65 to -0.59)	<0.001	-0.70 (-0.74 to -0.67)	<0.001
Age, yr				
<50	-0.11 (-0.26 to 0.05)	0.17	0.17 (0.01 to 0.32)	0.04
50 to <60	-0.16 (-0.29 to -0.02)	0.03	-0.04 (-0.18 to 0.10)	0.56
60 to <70	Reference		Reference	
70 to <80	-0.08 (-0.22 to 0.06)	0.25	-0.19 (-0.33 to -0.05)	<0.01
≥80	-0.29 (-0.46 to -0.11)	0.001	-0.48 (-0.66 to -0.30)	<0.001
Men	-0.01 (-0.12 to 0.10)	0.90	0.26 (0.15 to 0.38)	<0.001
Race/ethnicity				
Non-Hispanic white	Reference		Reference	
Non-Hispanic black	-0.34 (-0.45 to -0.22)	<0.001	-0.15 (-0.28 to -0.02)	0.02
Hispanic and other	-0.32 (-0.44 to -0.19)	<0.001	-0.10 (-0.22 to 0.03)	0.14
Medicare as primary insurance	-0.03 (-0.13 to 0.07)	0.61	-0.04 (-0.14 to 0.05)	0.39
Central venous catheter use	0.09 (-0.01 to 0.19)	0.06	0.19 (0.09 to 0.29)	<0.001
Comorbidities				
Hypertension	-0.03 (-0.13 to 0.07)	0.53	-0.01 (-0.11 to 0.09)	0.86
Diabetes	-0.16 (-0.27 to -0.05)	0.004	-0.20 (-0.31 to -0.08)	0.001
Congestive heart failure	-0.31 (-0.41 to -0.21)	<0.001	-0.27 (-0.37 to -0.18)	<0.001
Atherosclerotic heart disease	0.18 (0.03 to 0.34)	0.02	0.19 (0.04 to 0.34)	0.01
Other cardiovascular disease	0.01 (-0.13 to 0.16)	0.87	-0.02 (-0.16 to 0.12)	0.77
spKt/V per SD	0.01 (-0.05 to 0.06)	0.79	0.01 (-0.05 to 0.07)	0.79
Body mass index per SD	0.09 (0.04 to 0.15)	0.001	0.08 (0.02 to 0.14)	<0.01
nPCR, g/kg per d				
<0.8	0.27 (0.12 to 0.43)	<0.001	0.19 (0.04 to 0.34)	0.01
0.8 to <1.0	0.04 (-0.09 to 0.18)	0.54	-0.01 (-0.14 to 0.12)	0.87
1.0 to <1.2	Reference		Reference	
≥1.2	-0.04 (-0.18 to 0.11)	0.64	0.02 (-0.12 to 0.16)	0.76
Laboratories				
Hemoglobin per SD	0.07 (0.02 to 0.12)	<0.01	0.05 (-0.01 to 0.10)	0.09
Albumin, g/dl				
<3.2	-0.56 (-0.70 to -0.41)	<0.001	-0.73 (-0.89 to -0.58)	<0.001
3.2 to <3.6	-0.28 (-0.40 to -0.16)	<0.001	-0.36 (-0.48 to -0.24)	<0.001
3.6 to <4.0	Reference		Reference	
≥4.0	0.07 (0.03 to 0.12)	0.002	0.34 (0.20 to 0.48)	<0.001
Creatinine per SD	-0.39 (-0.45 to -0.33)	<0.001	-0.38 (-0.45 to -0.31)	<0.001
Calcium per SD	0.07 (0.03 to 0.12)	0.002	0.08 (0.03 to 0.13)	0.002
Phosphorus per SD	-0.30 (-0.35 to -0.25)	<0.001	-0.17 (-0.22 to -0.11)	<0.001
Intact PTH, pg/ml				
<160	0.28 (0.12 to 0.44)	0.001	0.12 (-0.04 to 0.28)	0.14
160 to <320	0.23 (0.11 to 0.34)	<0.001	0.13 (0.01 to 0.24)	0.03
320 to <640	Reference		Reference	
≥640	-0.25 (-0.38 to -0.12)	<0.001	-0.13 (-0.26 to 0.00)	0.04
Iron saturation per SD	-0.05 (-0.10 to 0.00)	0.04	-0.07 (-0.12 to -0.02)	<0.01
Ferritin, ng/ml				
<200	-0.09 (-0.23 to 0.04)	0.18	-0.11 (-0.24 to 0.03)	0.12
200 to <400	-0.05 (-0.19 to 0.09)	0.49	-0.05 (-0.19 to 0.09)	0.46
400 to <800	Reference		Reference	
≥800	0.19 (-0.08 to 0.45)	0.16	0.25 (-0.01 to 0.51)	0.06
Bicarbonate per SD	0.01 (-0.04 to 0.06)	0.60	-0.13 (-0.18 to -0.08)	<0.001

Case mix variables included baseline urine volume, age, sex, race/ethnicity, primary insurance, central venous catheter use, comorbidities, and spKt/V.

and 0.61 (95% CI, 0.50 to 0.74) at -6.0, -3.0, \pm 0.0, and +3.0 ml/min per 1.73 m² per year of change in CL_{urea} , respectively (reference: -1.5 ml/min per 1.73 m² per year). These

associations were robust against additional adjustment for baseline ultrafiltration rate and its annual change. Consistent trends were observed in subgroup analyses according to

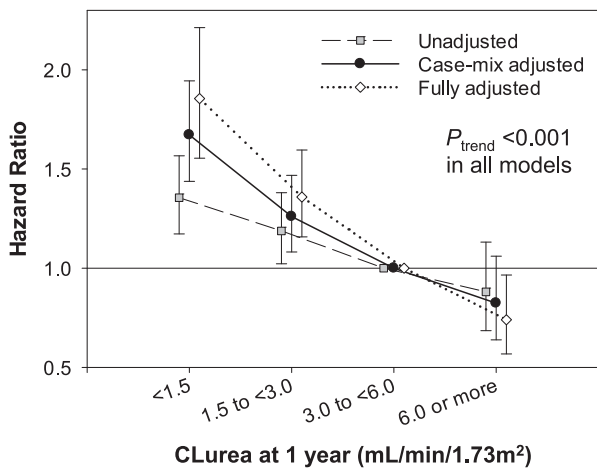


Figure 1. Renal CL_{urea} and all-cause mortality risk in incident hemodialysis patients. The mortality risk associated with renal CL_{urea} at 1 year after initiating dialysis among 6538 incident hemodialysis patients (2007–2010) with three levels of adjustment. There was a significant trend toward lower mortality of higher renal CL_{urea} (P for trend <0.001 across all models).

baseline CL_{urea} (Figure 3). Rapid CL_{urea} decline (>3.0 ml/min per 1.73 m^2 per year) also showed a case mix-adjusted HR of 1.62 (95% CI, 1.27 to 2.07) for all-cause mortality. This association was not modified by baseline age (≥ 65 or <65 years

old), sex, race (white or nonwhite), diabetes, presence of congestive heart failure, hemoglobin (≥ 11.5 or <11.5 g/dl), serum albumin (≥ 3.6 or <3.6 g/dl), and serum phosphorus (≥ 5.0 or <5.0 mg/dl; $P_{interaction} > 0.20$ for all) (Figure 4).

Sensitivity Analyses Using Urine Volume as Another Index of RKF

Median baseline urine volume was 900 (IQR, 550–1400) ml/d (Supplemental Table 3). Median urine volume at year 1 was 650 (IQR, 380–1100) ml/d, and mean \pm SD annual change in urine volume was -240 ± 610 ml/d. Compared with factors related to annual decline in CL_{urea} , older age, non-Hispanic black, diabetes, presence of congestive heart failure, lower body mass index, lower serum albumin, higher serum creatinine, and higher serum phosphorus were consistently associated with faster decline in urine volume, irrespective of the adjustment model. Women, lower serum calcium, and higher serum bicarbonate also showed significant relationships to faster annual decline in the fully adjusted model (Supplemental Table 4). These findings were confirmed in the sensitivity analyses, where patients with baseline urine volume <300 ml/d were excluded (Supplemental Table 5).

There was a significant trend toward lower mortality at higher urine volume ($P_{trend} < 0.001$ across all models) (Supplemental Figure 1). Annual change in urine volume showed a significant association with all-cause mortality in all models,

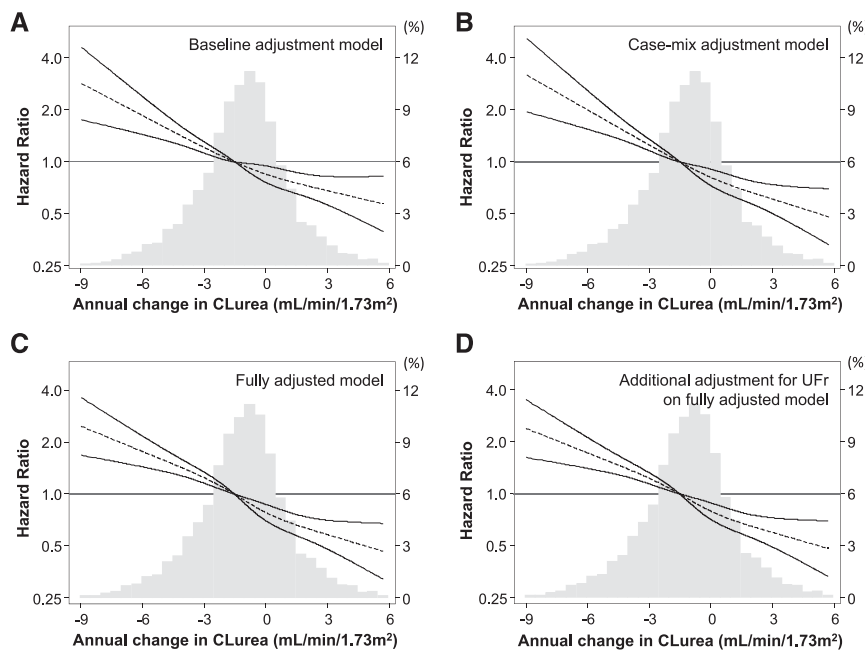


Figure 2. Distributions and restricted cubic splines comparing the relationship of annual change in residual renal CL_{urea} with all-cause mortality among 6538 incident hemodialysis patients (2007–2010): (A) baseline renal CL_{urea} adjustment model, (B) case mix adjustment model, (C) fully adjusted model, and (D) additional adjustment for baseline ultrafiltration rate (UFR) and its annual change on the fully adjusted model. Annual changes in renal CL_{urea} were calculated subtracting values at year 1 (the fifth patient-quarter; the first 91 days of the second year of dialysis) from those at baseline (the first patient-quarter; the first 91 days of the first year of dialysis). Dashed and solid lines represent HR estimates and 95% CIs, respectively.

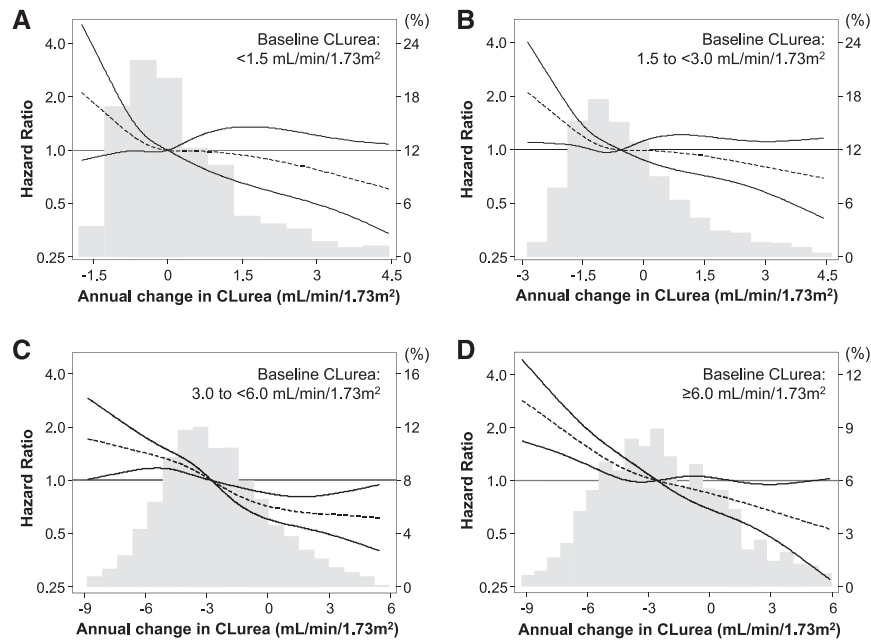


Figure 3. Distributions and case mix-adjusted all-cause death HRs of annual change in renal CL_{urea} by using restricted cubic splines among 6538 incident hemodialysis patients (2007–2010) stratified by baseline CL_{urea} levels: (A) <1.5 ml/min per 1.73 m², (B) 1.5 to <3.0 ml/min per 1.73 m², (C) 3.0 to <6.0 ml/min per 1.73 m², and (D) ≥ 6.0 ml/min per 1.73 m². Annual changes in renal CL_{urea} were calculated subtracting values at year 1 (the fifth patient-quarter; the first 91 days of the second year of dialysis) from those at baseline (the first patient-quarter; the first 91 days of the first year of dialysis). Dashed and solid lines represent HR estimates and 95% CIs, respectively.

including adjustment for ultrafiltration rate and its annual change (Supplemental Figure 2); patients with faster decline in urine volume showed higher risk of mortality. Consistent trends were observed in subgroup analyses according to the baseline urine volume categories shown (Supplemental Figure 3). Rapid decline in urine volume (>600 ml/d per year) also showed higher mortality risk in the case mix adjustment model, and this association was not modified by any of the prespecified variables ($P_{interaction} > 0.20$ for all) (Supplemental Figure 4).

DISCUSSION

Among 6538 incident hemodialysis patients who had available urine data at the time of hemodialysis initiation and 1 year afterward from a large dialysis organization in the United States, greater renal CL_{urea} rates at year 1 were associated with better survival. Additionally, annual decline in renal CL_{urea} showed a gradient association with all-cause death. These associations were robust against additional adjustment for laboratory variables and ultrafiltration rate, and they were consistent across strata of baseline RKF, age, sex, race, diabetes, congestive heart failure history, hemoglobin, serum albumin, and serum phosphorus. Sensitivity analyses using urine volume as another index of RKF yielded consistent associations.

Given the exclusion of RKF from the assessment of hemodialysis adequacy in the recent End-Stage Renal Disease

Quality Incentive Program,¹⁸ the findings from our study are both timely and relevant. At this time, the only metric considered in the ascertainment of hemodialysis adequacy is $spKt/V$, with a threshold of ≥ 1.2 . However, many patients early in their course of ESRD may retain substantial RKF, which may have an important bearing on their achievement of adequate clearance and volume removal, leading to better clinical outcomes. Furthermore, individualizing hemodialysis prescriptions according to RKF may allow for the reductions in dialysis treatment time and frequency, which may favorably affect patients' quality of life and reduce medical costs.^{19–21}

Although several investigators addressed the importance of RKF preservation, even in patients on hemodialysis, evaluation of change in RKF using at least two measurements separated by a reasonably long time interval is needed to overcome lead time bias. In a cohort study of 734 incident hemodialysis patients from the United States conducted in the late 1990s, RKF was qualitatively examined by questionnaire (urine volume ≥ 250 or <250 ml/d) in a prospective manner.¹⁰ Of these patients, 260 (35%) responded at both baseline and 1 year, and patients who reported maintained urine volume ≥ 250 ml/d during the first 1 year of dialysis showed better survival than those who lost urine output. The Netherlands Cooperative Study on the Adequacy of Dialysis Study Group prospectively examined 609 and 1191 patients new to peritoneal dialysis and hemodialysis, respectively, and showed that full loss of RKF was associated with higher mortality,

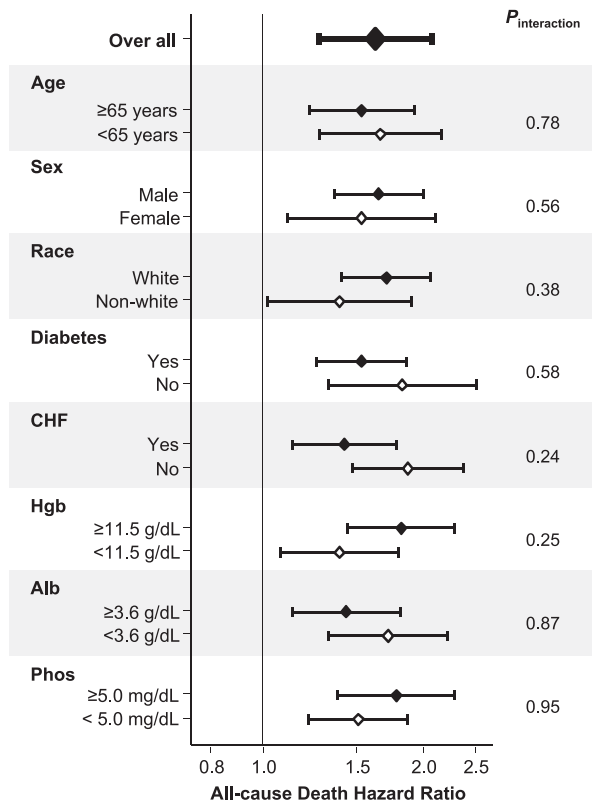


Figure 4. Overall and subgroup analyses of associations between rapid decline in residual renal $CL_{urea} > 3$ ml/min per 1.73 m² per year and all-cause mortality among 6538 incident hemodialysis patients (2007–2010) in the case mix adjustment model. Annual changes in renal CL_{urea} were calculated subtracting values at year 1 (the fifth patient-quarter; the first 91 days of the second year of dialysis) from those at baseline (the first patient-quarter; the first 91 days of the first year of dialysis). Points and bars represent HR estimates and 95% CIs, respectively. Alb, albumin; CHF, congestive heart failure; Hgb, hemoglobin; Phos, phosphorus.

irrespective of modality, hemodialysis, or peritoneal dialysis.²² However, when RKF was not fully lost, there was no significant association between RKF and mortality. Despite some discrepancies in results, partly because of differences in study populations, thresholds used to define RKF, and statistical modeling approaches (traditional Cox models used to evaluate long-term association in the former versus marginal structural model used to evaluate short-term association and account for time-dependent confounding in the latter), our study consistently shows the survival benefit of preserved RKF using a larger national representative cohort of incident hemodialysis patients. Rapid decrease in RKF has also been identified as an independent risk factor for all-cause death in patients on peritoneal dialysis.²³

We observed large variations in annual change in RKF and identified several predictors of preserved RKF at 1 year after hemodialysis initiation after adjustment for baseline RKF values and case mix characteristics. Compared with a previous report by Moist *et al.*,⁹ women, nonwhite race, diabetes, and

history of congestive heart failure were consistent risk factors of RKF decline. Although renin-angiotensin system inhibitors have been suggested to preserve RKF in patients on hemodialysis,^{9,24} medication information was not available in our study. However, a recent randomized, controlled trial found no significant difference in RKF decline over time with use of the angiotensin receptor blocker irbesartan versus placebo in patients undergoing hemodialysis.²⁵ Although the not removing water strategy with hemodialysis may maintain urine volume, it also increases BP, left ventricular mass index, and cardiovascular events,²⁶ suggesting the importance of individualized volume management to avoid both congestive heart failure and intradialytic hypotension.^{9,27} Other potential strategies include avoidance of nephrotoxic agents, ultrapure dialysis fluid,²⁸ online hemodiafiltration,^{29,30} diuretic use,^{31,32} and incremental hemodialysis regimens.^{19–21,33–35}

A substantial number of patients in this study increased their renal CL_{urea} rate during the first 1 year of hemodialysis treatment. Although it may be partly caused by measurement error as with large decreases in RKF, subgroup analyses and sensitivity analyses excluding subjects with low baseline RKF yielded consistent results. Additionally, a US Renal Data System special study has shown that congestive heart failure and AKI are among the most common reasons of hospitalization at hemodialysis initiation,³⁶ and approximately 5% of incident hemodialysis patients recovered their kidney function with successful discontinuation of dialysis treatment in 2008 and 2009.³⁷ The prevalence of recovery of renal function is increasing over time and may be underestimated if patients continue dialysis without re-evaluation of RKF after recovery of their renal function.

We acknowledge several other limitations in this study. First, cause-specific death was not available in this study. Second, RKF measurement is not accurate given the use of CL_{urea} and not the average of renal urea and creatinine clearances and the difficulties in complete collection of urine samples and its punctuality in patient daily life. The use of factor 0.9 for predialysis serum urea nitrogen for renal CL_{urea} calculation might have also induced errors to some extent. Nevertheless, the population-level associations with clinical outcomes can be estimated from an adequate number of subjects if such errors are not associated with the outcome. Third, available RKF measures may not be representative of those in the entire hemodialysis population, because patients on dialysis with limited or no RKF are less likely to have undergone urine collections, especially at 1 year after hemodialysis initiation. This potential selection bias might have resulted in missing patients who lost RKF during the first 1 year of dialysis, and thus, the mortality risk of RKF decline might be underestimated. Additionally, although we adjusted for only baseline patient characteristics and not those at year 1 to avoid overadjustment, RKF decline could also be an intermediary between adverse events (*e.g.*, cardiovascular events and infection) during the first year of dialysis and subsequent mortality. Indeed, the mortality risk of RKF decline was attenuated to some extent after adjusting

for body mass index and laboratory variables at both baseline and 1 year, but it still remained significant (data not shown). Although it is hard to estimate the net effect of the former and the latter limitations, our results met seven of nine of the criteria by Hill³⁸ (*i.e.*, temporal relationship, strength, dose-response relationship, consistency, biologic plausibility, coherence, and reasoning by analogy), suggesting a possible causal relationship between RKF decline and all-cause death in patients on hemodialysis.

In conclusion, decline in RKF, both renal CL_{urea} and urine volume separately, shows a graded association with higher mortality among incident hemodialysis patients. Future trials are warranted to test the clinical benefits of RKF preservation strategies, including maintaining diuretic use and the incremental hemodialysis regimen.

CONCISE METHODS

Patients

We retrospectively extracted, refined, and examined data from all incident hemodialysis patients who were ages ≥ 18 years old and received hemodialysis treatment for ≥ 60 consecutive days in facilities operated by a large dialysis organization (DaVita, Inc.) in the United States from January 1, 2007 to December 31, 2010.³⁹ Patients were followed until December 31, 2011, and the follow-up time was divided into patient-quarters (91-day periods from date of first dialysis). For each patient-quarter, patients were assigned the conventional hemodialysis modality if they did not receive treatments other than thrice weekly hemodialysis (*i.e.*, peritoneal dialysis, less frequent in-center hemodialysis, home hemodialysis, frequent in-center hemodialysis, or nocturnal in-center hemodialysis) for at least 45 days within the patient-quarter.

To examine RKF and the changes during the first 1 year of hemodialysis, we used all incident in-center hemodialysis patients between 2007 and 2010 who were alive at year 1 and had measured renal CL_{urea} at the start of dialysis and year 1. First, we excluded patients who were censored or ever treated with peritoneal dialysis, nocturnal hemodialysis, or home hemodialysis during the first 1 year of dialysis. Second, we identified 22,895 incident hemodialysis patients with baseline CL_{urea} data from 67,311 patients who were assigned only conventional hemodialysis for the first four patient-quarters. Among them, 6538 patients also had RKF measurements at the fifth patient-quarter (*i.e.*, the first 91-day period of the second year of dialysis) and were included in this study (details in Supplemental Figure 5). This study was approved by the Institutional Review Committees of the Los Angeles Biomedical Research Institute at Harbor–University of California, Los Angeles; the University of California, Irvine Medical Center; and the University of Washington.

Demographic, Clinical, and Laboratory Measures

The information on all-cause death, race/ethnicity, primary insurance, access type, the presence of comorbidities, and laboratory variables was obtained from the electronic database of the dialysis provider. To minimize measurement variability, all repeated measures

for each patient during any given patient-quarter (91 days) were averaged, and the quarterly means in each quarter were used in all analyses. The averaged values during the first patient-quarter (the first 91 days of dialysis) served as baseline data.

Blood samples were drawn using uniform techniques in all dialysis clinics and transported to the central laboratory (Deland, FL) typically within 24 hours. All laboratory values were measured by automated and standardized methods. Most laboratory values were measured monthly, including serum urea nitrogen, creatinine, albumin, calcium, phosphorus, and bicarbonate. Serum ferritin and intact PTH were measured at least quarterly. Hemoglobin was measured at least monthly in essentially all patients and weekly to biweekly in most patients. Most blood samples were collected predialysis with the exception of the postdialysis urea, which was obtained to calculate urea kinetics.

The average serum urea concentrations during the collection were assumed to be 90% of the predialysis concentrations according to the approach by Daugirdas *et al.*,⁴⁰ and thus, renal CL_{urea} was calculated as follows:

$$\text{renal } CL_{\text{urea}} \text{ (ml/min)} = \frac{\text{urinary urea nitrogen (mg/dl)} \times \text{urinary volume (ml)}}{\text{collected time (min)} \times [0.9 \times \text{serum urea nitrogen (mg/dl)}]}$$

where serum urea nitrogen was obtained on the closest day within ± 28 days to urine collection. Observations with $CL_{\text{urea}} > 15$ ml/min or urine volume > 3000 ml/d were excluded from this study. Among the eligible 23,111 CL_{urea} observations, urine collected time was reported as 1440 minutes in 22,716 observations (98%), ranging from 720 to 2880 minutes. Serum urea nitrogen was measured on the same day of urine collection in 22,520 (97%) patients. The differences between our calculated CL_{urea} and CL_{urea} reported from the large dialysis organization were within ± 0.01 ml/min in 22,445 observations (97%) (Supplemental Figure 6). Renal CL_{urea} was then adjusted for body surface area and expressed as milliliters per minute per 1.73 m^2 .^{1,41} Annual changes in renal CL_{urea} and urine volume were calculated by subtracting values at year 1 (the fifth patient-quarter; the first 91 days of the second year of dialysis) from those at baseline (the first patient-quarter; the first 91 days of the first year of dialysis). spKt/V delivered by dialysis was calculated using urea kinetic modeling equations.⁴² nPCR was calculated taking renal CL_{urea} into account.⁴³

Statistical Analyses

Renal CL_{urea} was used as the index of RKF in the primary analyses, and urine volume was used in the sensitivity analyses. Differences in baseline characteristics between included versus excluded patients were compared by standardized differences because of the relatively large sample size of this study.^{44,45} Patients were categorized into four groups according to annual change in renal CL_{urea} (< -3.0 , -3.0 to < -1.5 , -1.5 to < 0.0 , and ≥ 0.0 ml/min per 1.73 m^2) or urine volume (< -600 , -600 to < -300 , -300 to < 0.0 , and ≥ 0.0 ml/d), and the association with each patient characteristic was evaluated by non-parametric trend test. Linear regression with robust estimation was used to identify the predictors of annual change in RKF. Survival

analysis with Cox regression was used to estimate association between the exposure variable (*i.e.*, RKF at year 1 or annual change in RKF) and all-cause mortality. Annual changes in RKF (*i.e.*, CL_{urea} and urine volume) were modeled as continuous variables, and their relationship with all-cause death was estimated using restricted cubic spline functions with four knots at the 5th, 35th, 65th, and 95th percentiles of each index. In the primary analyses, -1.5 ml/min per 1.73 m² and -300 ml/d were used as references for changes in CL_{urea} and urine volume, respectively. Median values were used as references in each subgroup analysis. The first day of the fifth patient-quarter (*i.e.*, 364th day of dialysis treatment) was used as the entry day of each patient. Proportional hazards assumptions were tested using log-log against survival plots and Schoenfeld residuals.

Models were examined with three levels of adjustment as listed below.

1. Unadjusted model or minimally adjusted model that included baseline RKF values.
2. Case mix-adjusted models that included the above plus age, sex, race, ethnicity (non-Hispanic black, non-Hispanic white, Hispanic, or other race/ethnicity), primary insurance (Medicare and others), central venous catheter use, and six comorbidities (hypertension, diabetes, presence of congestive heart failure, atherosclerotic heart disease, other cardiovascular disease, and spKt/V).
3. Fully adjusted models that included all of the covariates in the case mix model plus body mass index, nPCR, and nine laboratory variables (hemoglobin, serum albumin, creatinine, albumin-corrected calcium, phosphorus, iron saturation, total bicarbonate, and natural log-transformed intact PTH and ferritin).

When evaluating the association of RKF indices at 1 year after hemodialysis initiation with mortality, we used primary insurance, vascular access type, and laboratory variables obtained from the same period (*i.e.*, the fifth patient-quarter). For analyses of the association between annual changes in RKF indices and all-cause mortality, baseline variables were used to avoid overadjustment, because those variables at year 1 may have been influenced by change in RKF (*i.e.*, intermediaries between RKF decline and all-cause death). Additional adjustment for ultrafiltration rate at baseline and its annual change was conducted on the fully adjusted model to unfold how fluid removal may affect the RKF-mortality association.

Linear assumption among covariates was examined by using restricted spline functions and a likelihood ratio test for goodness of fit.⁴⁶ For linear regression analyses where annual change in RKF was used an outcome, age, nPCR, and serum concentrations of albumin, intact PTH, and ferritin retained one or more spline functions (*i.e.*, nonlinear association) and thus, were categorized irrespective of models as follows: five groups of age (<50 , 50 to <60 , 60 to <70 , 70 to <80 , and ≥ 80 years old), four groups of serum albumin (<3.2 , 3.2 to <3.6 , 3.6 to <4.0 , and ≥ 4.0 g/dl), five groups of serum calcium (<8.5 , 8.5 to <9.0 , 9.0 to <9.5 , 9.5 to <10.0 , and ≥ 10.0 mg/dl), four groups of intact PTH (<160 , 160 to <320 , 320 to <640 , and ≥ 640 pg/ml), and four groups of serum ferritin (<200 , 200 to <400 , 400 to

<800 , and ≥ 800 ng/ml). In the Cox regression analyses, significant spline functions were kept instead of categorizing variables and used in the multivariate models.

Effect modification of the association between annual RKF decline (*i.e.*, >3.0 ml/min per 1.73 m² in CL_{urea} or >600 ml/d in urine volume) and all-cause death by baseline age (≥ 65 or <65 years old), sex, race (white or nonwhite), diabetes, presence of congestive heart failure, hemoglobin (≥ 11.5 or <11.5 g/dl), serum albumin (≥ 3.6 or <3.6 g/dl), and serum phosphorus (≥ 5.0 or <5.0 mg/dl) were examined by including each interaction term into case mix adjustment models. The frequency of missing data was low ($<1\%$ for most laboratory tests, except for nPCR [4%] and creatinine [4%]), and the multiple imputation method with five datasets was used in all regression analyses. Analyses were conducted using STATA MP, version 13.1 (StataCorp, College Station, TX) and SAS, version 9.4 (SAS Institute Inc., Cary, NC).

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