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ORIGINAL ARTICLE

Anemia

A faster decline of residual kidney function and erythropoietin stimulating agent hyporesponsiveness in incident hemodialysis patients

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Abstract

Introduction: Erythropoietin stimulating agents (ESA) hyporesposiveness has been associated with increased mortality in hemodialysis (HD) patients. However, the impact of decline of residual kidney function (RKF) on ESA hyporesposiveness has not been adequately elucidated among patients receiving HD.

Methods: The associations of RKF decline with erythropoietin resistance index (ERI; average weekly ESA dose [units])/post-dialysis body weight [kg]/hemoglobin [g/dL]) were retrospectively examined across four strata of annual change in RKF (residual renal urea clearance [KRU] < −3.0, −3.0 to < −1.5, −1.5 to <0, ≥0 mL/min/1.73 m^2 per year; urinary volume < −600, −600 to<−300, −300 to <0, ≥0 mL/day per year) using logistic regression models adjusted for clinical characteristics and laboratory variables in 5239 incident HD patients in a large US dialysis organization between 1 January 2007 and 31 December 2011.

Findings: The median values of the annual change in KRU and urinary volume were −1.2 (interquartile range [IQR]: −2.8 to 0.1) mL/min/1.73 m^2 per year and −250 (IQR: −600 to 100) mL/day

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per year. A faster KRU decline in the first year of HD was associated with higher odds for ESA hyporesponsiveness: KRU decline of <−3.0, −3.0 to <−1.5, and −1.5 to <0/min/1.73 m^2 per year were associated with adjusted odds ratios (OR) of 2.07 (95% confidence interval [CI]: 1.66–2.58), 1.54 (95%CI: 1.28–1.85), and 1.26 (95%CI: 1.07–1.49), respectively (reference: ≥0 mL/min/1.73 m^2 per year). These associations were consistent across strata of baseline KRU, age, sex, race, diabetes, congestive heart failure, hemoglobin, and serum albumin. Sensitivity analyses using urinary volume as another index of RKF showed consistent associations.

Discussion: A faster RKF decline during the first year of dialysis was associated with ESA hyporesponsiveness and low hemoglobin levels among incident HD patients.

Keywords: Residual kidney function, ESA hyporesponsiveness, erythropoietin stimulating agents, hemodialysis

INTRODUCTION

Anemia is a common complication in patients with chronic kidney disease (CKD), and it has been reported that the prevalence of anemia is nearly universal in dialysis patients.[1, 2] In addition, lower hemoglobin levels are associated with an increased risk for mortality, cardiovascular disease, and poorer quality of life in dialysis patients.[3, 4] Treating anemia with erythropoietin stimulating agents (ESA) has led to a reduction in blood transfusions and an improvement in the quality of life of dialysis patients.[5] However, several clinical trials have raised important safety concerns, including increased mortality, cardiovascular events, and stroke, especially at higher target hemoglobin levels.[6–8] Furthermore, higher ESA dosages have been independently associated with increased risk for mortality than would be expected based upon hemoglobin levels alone.[9, 10] Given these safety concerns, attempts should be made to maintain hemoglobin targets while minimizing mortality and morbidity risks from ESA use.

Previous studies have shown that higher residual kidney function (RKF) and existence of urinary output 1 year after starting dialysis are associated with improved survival and outcomes, including improved maintenance of target hemoglobin levels among dialysis patients considering ESA dose.[11–16] These findings suggest that maintenance of RKF can enable improved anemia control while minimizing ESA use via a physiologically heightened response to ESAs. Many factors are stipulated to influence this physiological response to ESAs, including inflammation, age, sex, and the presence of other comorbid conditions.[17] In order to measure ESA responsiveness, researchers have suggested using the Erythropoietin Resistance Index (ERI), calculated as the weekly weight-adjusted Epogen® (epoetin alfa) dose divided by the hemoglobin level. Lower ERI values reflect improved response to ESAs and have been associated with decreased early mortality compared to patients with higher ERI values.[17]

In this study, we seek to better understand the factors that determine the physiological response to ESAs, specifically the relationship between the change in RKF over time and ESA resistance (as represented by the ERI) among incident hemodialysis (HD) patients using a retrospective cohort analysis of a large dialysis organization based in the United States. A better understanding of this relationship may enable us to target preserved kidney function to improve anemia management among dialysis patients.

MATERIALS AND METHODS

Patients

We retrospectively examined the refined data from a large US dialysis organization for incident thrice-weekly in-center HD patients between 1 January 2007 and 31 December 2011.[18] Included individuals were aged 18 years or older and received HD treatments for 60 or more consecutive days in facilities operated by the dialysis organization. Patients were excluded if they had been treated with other dialysis modalities (i.e., peritoneal dialysis, home HD, twice-weekly in-center HD, or in-center HD requiring more than three treatments per week). We also excluded patients who had missing data on weekly ESA dose, hemoglobin, post-dialysis body weights, and residual urea clearance (KRU) at baseline and year 1. In addition, we excluded patients who had a history of malignancy, non-renal causes of anemia, liver disease, HIV, or prior organ transplantation. Individuals with annual change in KRU values reported at the extremes

(<0.5 or > 99.5 percentiles) were also excluded from the cohort.

Patient follow-up time was divided into patient-quarters representing 91-day periods from the start date of dialysis. Patients were censored at the time of death, transplant, or loss to follow-up. Baseline measurement values were defined as the average laboratory and ESA dosing values in the first patient-quarter while 1-year post transition measurement values were defined as the average laboratory and ESA dosing values in the fifth patient-quarter.

This study was performed in accordance with the Declaration of Helsinki and was approved by the International Review Committees of the University of California, Irvine and the University of Washington, and were exempted from obtaining informed consents.

Demographic, clinical, and laboratory measures

Information on demographics, vascular access type, the presence of comorbidities, and laboratory data was obtained from the dialysis organization's administrative database. Blood samples were obtained before dialysis except for post-dialysis urea. Most laboratory values, including serum urea nitrogen, creatinine, albumin, calcium, phosphorus, and bicarbonate, were measured monthly. Intact parathyroid hormone (PTH) and serum ferritin were measured at least quarterly. All repeated measures for each patient-quarter were averaged to minimize measurement variability.

We used KRU as the index of RKF in all analyses, and the average serum urea concentrations during collection were assumed to be 90% of the pre-dialysis concentrations according to the approach by Daugirdas et al.[19] Serum urea nitrogen was obtained on the closest day within ±28 days of urine collection. Urine collected time was reported as 1440 minutes in 98% of measurements, ranging from 720 to 2880 minutes. We adjusted KRU for body surface area (BSA) expressed as milliliter per minute per 1.73 m^2.[20] Thus, KRU was calculated as follows:

$$\mathrm{KRU}\left(\mathrm{mL/min/1.73^{m^2}}\right) = \frac{\text{urinary urea nitrogen (mg/dL)} \times \text{urinary volume (mL)} \times 1.73(\mathrm{m^2})}{\text{collected time (min)} \times [0.9 \times \text{serum urea nitrogen(mg/dL)}] \times \mathrm{BSA(m^2)}},$$

Annual changes in KRU were calculated by subtracting values at baseline from year 1 (i.e., the fifth patient-quarter).

ESA resistance was expressed as erythropoietin resistance index (ERI), which is calculated as the average weekly epoetin alfa dose (IU)/post-dialysis body weight (kg)/hemoglobin (g/dL).[17, 21, 22] Based on the ERI values at year 1, patients were divided into tertile [first tertile: <6.9; second tertile: 6.9 to <16.6; third tertile: ≥16.6 IU/kg/(g/dL)], and patients belonging to the third tertile (i.e., ≥16.6 IU/kg/[g/dL]) were defined as ESA hyporesponders. Moreover, we defined the patients as having low hemoglobin levels if their hemoglobin was less than 10 g/dL at year 1 despite ESA use.

Statistical analyses

All variables are shown as mean ± standard deviations, median with interquartile range (IQR), or as frequency (proportions) when appropriate. We categorized patients into four groups according to annual change in KRU (<−3.0, −3.0 to< −1.5, −1.5 to<0, and ≥0 mL/min/1.73 m^2 per year) and annual change in urinary volume (<−600, −600 to<−300, −300 to <0, and ≥0 mL/day per year). Differences in baseline characteristics among KRU categories and urinary volume categories were evaluated by nonparametric trend tests. Standardized differences were used to compare differences in baseline characteristics between included versus excluded patients due to the large sample size of this study.[23, 24]

Associations between the annual change in KRU and ESA hyporesponsiveness were examined by multivariate logistic regression models. We used hierarchical adjustment with three models for each analysis as follows: (1) model 1 that included baseline RKF values; (2) model 2 that included model 1 plus age, sex, race/ethnicity, primary insurance, vascular access type, comorbidities (hypertension, diabetes, congestive heart failure (CHF), atherosclerotic heart disease, other cardiovascular disease) and single-pool Kt/V (spKt/V); (3) model 3 that included all of the covariates in model 2 plus body mass index (BMI), normalized protein catabolic rate (nPCR), hemoglobin, serum albumin, creatinine, albumin-corrected calcium, phosphorus, intact PTH, iron saturation, ferritin and total bicarbonate. Covariate adjustment was done using baseline values.

We also examined the association between annual change in KRU and ERI, across strata of baseline KRU (<1.5, 1.5 to <3.0, 3.0 to <6.0, and ≥6.0 mL/min/1.73 m^2) and urinary volume (<300, 300 to <600, 600 to <1200, and ≥1200 mL/day). The linear assumption among covariates were estimated by using restricted cubic spline function with four knots

Table 1 Baseline characteristics of 5239 incident hemodialysis patients according to annual change in KRU

Variable	Total, n = 5239	Annual change in KRU (mL/min/1.73 m^2 per year) <−3.0 n = 1216	−3.0 to <−1.5 n = 1108	−1.5 to <0 n = 1424	≥0 n = 1491	P_{trend}
Age, years	62 ± 14	60 ± 14	63 ± 14	63 ± 15	62 ± 14	<0.001
Men, %	65	74	65	60	61	<0.001
Race, %						
Non-Hispanic white	53	55	53	49	54	0.24
Non-Hispanic black	26	26	24	27	26	0.57
Hispanic	12	10	13	13	12	0.20
Others	9	8	10	12	8	0.78
Primary insurance, %						
Medicare	51	48	50	53	51	0.10
Medicaid	7	7	7	7	6	0.41
Others	43	45	43	40	43	0.21
Access, %						
Central venous catheter (PQ1)	68	65	65	70	71	<0.001
AV fistula/graft (PQ1)	26	29	29	25	24	<0.001
Unknown (PQ1)	5	6	6	5	5	0.34
Central venous catheter (PQ5)	18	19	17	17	18	0.76
AV fistula/graft (PQ5)	81	79	82	82	81	0.79
Unknown (PQ5)	1	2	1	2	1	0.88
Comorbidities, %						
Hypertension	50	46	50	53	50	0.01
Diabetes	69	75	70	65	66	<0.001
Congestive heart failure	45	50	47	44	39	<0.001
Atherosclerotic heart disease	14	16	14	14	14	0.30
Other cardiovascular disease	16	17	16	14	15	0.21
Body mass index, kg/m^2	27.6 (23.9–32.7)	28.7 (24.9–34.4)	27.7 (23.6–32.5)	26.8 (23.6–31.3)	27.4 (23.9–32.6)	<0.001
Post weight (PQ1), kg	84.4 ± 22.8	90.5 ± 24.3	83.1 ± 21.4	80.3 ± 20.8	84.2 ± 23.3	<0.001
Post weight (PQ5), kg	84.3 ± 22.2	89.9 ± 23.3	83.0 ± 21.0	80.4 ± 20.4	84.5 ± 23.0	<0.001
spKt/V (PQ1)	1.59 ± 0.34	1.73 ± 0.39	1.59 ± 0.31	1.55 ± 0.31	1.52 ± 0.31	<0.001
spKt/V (PQ5)	1.73 ± 0.33	1.63 ± 0.31	1.67 ± 0.28	1.72 ± 0.30	1.86 ± 0.38	<0.001
nPCR, g/kg per day	0.90 ± 0.23	0.95 ± 0.24	0.91 ± 0.22	0.89 ± 0.22	0.87 ± 0.22	<0.001
KRU, mL/min/1.73 m^2	3.7 (2.1–5.7)	6.8 (5.2–8.7)	3.9 (3.0–5.2)	2.6 (1.6–3.9)	2.3 (1.2–3.9)	<0.001
Urine volume, mL/day	900 (500–1400)	1400 (1000–1890)	1000 (700–1400)	700 (450–1100)	600 (300–1000)	<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 ± 1.0	0.04
Albumin, mg/dL	3.63 ± 0.41	3.61 ± 0.42	3.62 ± 0.43	3.64 ± 0.40	3.67 ± 0.41	<0.001
Creatinine, mg/dL	6.0 ± 2.2	5.5 ± 1.9	6.1 ± 2.1	6.4 ± 2.5	6.0 ± 2.2	<0.001
Calcium, mg/dL	9.1 ± 0.5	9.0 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.5	0.16
Phosphorus, mg/dL	5.1 ± 1.1	5.0 ± 1.0	5.1 ± 1.1	5.2 ± 1.1	5.0 ± 1.0	0.50
Intact PTH (PQ1), pg/mL	316 (209–470)	308 (205–459)	325 (209–491)	333 (218–484)	305 (202–446)	0.76
Intact PTH (PQ5), pg/mL	275 (201–380)	282 (203–393)	276 (202–379)	272 (201–381)	272 (196–370)	0.03

Table 1 Continued

Variable	Total, n = 5239	Annual change in KRU (mL/min/1.73 m^2 per year) <−3.0 n = 1216	−3.0 to <−1.5 n = 1108	−1.5 to <0 n = 1424	≥0 n = 1491	P_{trend}
Iron saturation (PQ1), %	22 ± 7	22 ± 7	23 ± 7	22 ± 8	22 ± 7	0.51
Iron saturation (PQ5), %	30 ± 10	30 ± 10	30 ± 10	31 ± 10	30 ± 10	0.02
Ferritin (PQ1), ng/mL	247 (142–412)	223 (137–375)	232 (138–393)	260 (146–420)	260 (146–437)	<0.001
Ferritin (PQ5), ng/mL	550 (374–757)	551 (379–753)	548 (370–758)	560 (377–762)	542 (372–750)	0.73
Bicarbonate, mmol/L	23.2 ± 2.5	23.0 ± 2.5	23.0 ± 2.5	23.2 ± 2.5	23.3 ± 2.5	<0.001

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 mean ± standard deviation, medians (interquartile range), or percentage as appropriate. Conversion factors for units: albumin and hemoglobin in grams per deciliter to grams per liter, 10; creatinine in milligrams 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; KRU, renal urea clearance; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; PQ, patient quarter; spKt/V, single-pool Kt/V.

at the 5th, 35th, 65th, and 95th, percentiles of each index. Effect modification of the association between a rapid RKF decline (i.e., <−3.0 mL/min/1.73 m^2 per year in KRU or < −600 mL/day per year in urinary volume) and ESA hyporesponsiveness by baseline age (≥60 or <60 years old), sex, race (white or nonwhite), diabetes, CHF, hemoglobin (≥11.5 or <11.5 g/dL), and serum albumin (≥3.6 or <3.6 g/dL) were examined by including each interaction term into model 3.

The frequency of missing data was low (<1% for most laboratory data, except for creatinine [4%]), and the multiple imputation methods with five datasets were used in all regression analyses. Analyses were conducted using STATA MP, version 13.1 (Stata Corp, College Station, TX, USA).

RESULTS

Patients characteristics at baseline and 1 year

The database contained 133,162 incident hemodialysis patients. A total of 5239 individuals met our inclusion and exclusion criteria (Supporting Information Figure S1). The mean age of the patients was 62 ± 14 years old, and 65% were men, 53% were non-Hispanic white, 26% were non-Hispanic black, and 69% had diabetes. Median baseline KRU was 3.7 (IQR: 2.1–5.7) mL/min/1.73 m^2, and median annual change in KRU was −1.2 (IQR: −2.8 to 0.1) mL/min/1.73 m^2 per year, respectively. In the overall cohort, 1216 (23%), 1108 (21%), and 1424 (27%) patients had annual change in KRU <−3.0, −3.0 to <−1.5, and −1.5 to <0 mL/min/1.73 m^2 per year, respectively. The remaining 1491 (29%) showed a maintained KRU during the first year of HD. Patients with the fastest KRU decline group were younger, more likely to be men, more likely to have diabetes and CHF, had larger BMI, higher spKt/V, nPCR, baseline KRU and urinary volume, slightly lower albumin, and lower ferritin at baseline (Table 1).

Compared with 30,943 excluded patients without KRU data at baseline, the 5239 included patients were more likely to be men, non-Hispanic white, have an arteriovenous fistula as their vascular access, higher BMI, higher spKt/V, higher nPCR, higher urinary volume, higher hemoglobin, higher albumin, higher ferritin, lower bicarbonate, and lower ERI at baseline and at year 1 (standardized difference >0.1). Additionally, compared with 11,742 excluded patients with baseline KRU but not at year 1, the included patients were more likely to be non-Hispanic white, have an arteriovenous fistula as their vascular access, higher spKt/V, higher nPCR, higher KRU, higher urinary volume, higher hemoglobin, and higher albumin (Supporting Information Table S1).

When we assessed the relationship between ESA dose and the annual change in KRU, we found that ESA dose per week among annual change in KRU groups showed no significant difference at baseline. Looking at the relationship between ERI and annual change in KRU, we found that baseline ERI was lower in patients with the fastest KRU decline group (<−3.0 mL/min/1.73 m^2) as

Table 2 Characteristics of ESA dose and ESA resistance index according to annual change in KRU among 5239 incident hemodialysis patients

Variable	Total, n = 5239	Annual change in KRU (mL/min/1.73 m^2 per year)				P_{trend}
		<−3.0 n = 1216	−3.0 to <−1.5 n = 1108	−1.5 to <0 n = 1424	≥0 n = 1491	
ESA dose (PQ1), IU/week	26,400 (16,500–33,000)	26,400 (16,500–33,000)	26,400 (16,500–33,000)	26,400 (16,500–33,000)	26,400 (16,500-34,650)	0.83
ESA dose (PQ5), IU/week	9900 (4400–19,800)	13,200 (6600–22,000)	9900 (4725–19,800)	9900 (4400–19,800)	9900 (4400–19,800)	<0.001
ERI (PQ1), IU/kg/(g/dL)	27.6 (17.9–39.8)	26.0 (16.6–37.2)	27.2 (18.0–39.3)	28.5 (18.8–41.0)	27.7 (18.0–40.8)	<0.001
ERI (PQ5), IU/kg/(g/dL)	10.9 (5.4–21.0)	11.7 (5.7–21.2)	11.4 (5.6–22.2)	11.0 (5.5–21.5)	9.9 (4.8–19.4)	<0.001
ESA hyporesponder, %	33	35	35	34	29	0.001

Values are expressed as medians (interquartile range).
ESA, erythropoietin-stimulating agents; ERI, ESA resistance index; PQ, patient quarter.

compared with the patients with maintained KRU group (≥0 mL/min/1.73 m^2). On the other hand, patients who maintained their KRU had a slightly lower ERI than patients with the fastest KRU decline at year 1 (9.9 vs. 11.7, $p_{trend} < 0.001$). In addition, the proportion of ESA hyporesponders was lower in the maintained KRU group as compared with other groups (Table 2).

Annual change in RKF, ESA hyporesponsiveness, and low hemoglobin levels

The multivariate logistic regression analyses showed a significant association of annual change in KRU with ESA hyporesponsiveness at 1 year after initiation of HD in all models (Figure 1). Patients with faster KRU decline showed higher risks for ESA hyporesponsiveness. Adjusted odds ratios (ORs) in model 3 were 2.07 (95% confidence interval [CI]: 1.66–2.58), 1.54 (95%CI: 1.28–1.85) and 1.26 (95% CI: 1.07–1.49) at <−3.0, −3.0 to <−1.5, and −1.5 to <0 mL/min/1.73 m^2 per year of change in KRU, respectively (reference: KRU ≥0 mL/min/1.73 m^2 per year). Consistent trends were observed in analyses with restricted cubic spline functions according to baseline KRU levels (Figure 2). Patients with rapid KRU decline (<−3.0 mL/min/1.73 m^2 per year) showed an adjusted OR of 1.74 (95% CI:

Figure 1 Annual change in KRU associated with ESA hyporesponsiveness among 5,239 incident HD patients with three levels of adjustment. Model 1: adjusted for baseline KRU. Model 2: adjusted for model 1 +age, sex, race/ethnicity, primary insurance, vascular access type, comorbidities, and single-pool Kt/V. Model 3: adjusted for model 2 + BMI, nPCR, hemoglobin, albumin, creatinine, albumin-corrected calcium, phosphorus, intact PTH, iron saturation, ferritin and total bicarbonate.

1.46–2.07) for the risk of ESA hyporesponsiveness in model 3 (reference: KRU ≥ −3.0 mL/min/1.73 m^2 per year), and this association was observed consistently by age, sex, race, diabetes, CHF, hemoglobin, and serum albumin ($P_{interaction} > 0.15$ for all) (Figure 3). Additionally, patients with the fastest KRU decline showed a significantly higher odds (OR 3.81, 95%CI: 2.02–7.20) for having a hemoglobin level less than 10 g/dL at year 1 (reference: KRU ≥0 mL/min/1.73 m^2 per year) (Supporting Information Figure S2).

Sensitivity analyses using urinary volume as another index of RKF

For sensitivity analyses, we used urinary volume as another index of RKF. The median values of urinary volumes were 900 (IQR: 500–1400) mL/day at baseline, and the median annual change in urinary volume was −250 (IQR: −600–100) mL/day per year. As expected, patients with faster decline in urinary volume over 1 year showed higher odds of ESA hyporesponsiveness (Figure 4). Consistent trends were observed in subgroup analyses according to baseline urinary volume (Supporting Information Figure S3). Patients with rapid decline in urinary volume (<−600 mL/day per year) showed an adjusted OR of 1.40 (95% CI: 1.19–1.65) for the risk of ESA hyporesponsiveness in model 3 (reference: ≥−600 mL/day per year), and this association was not modified by any of the prespecified variables (Supporting Information Figure S4).

DISCUSSION

In this observational study, we found that incident in-center HD patients with faster RKF decline in the first year were associated with higher ERI (lower response to ESAs) and low hemoglobin levels. These associations were robust against additional adjustment for laboratory variables and were consistent across strata of baseline RKF variables, age, sex, race, diabetes, CHF, hemoglobin and serum albumin. This association was also confirmed

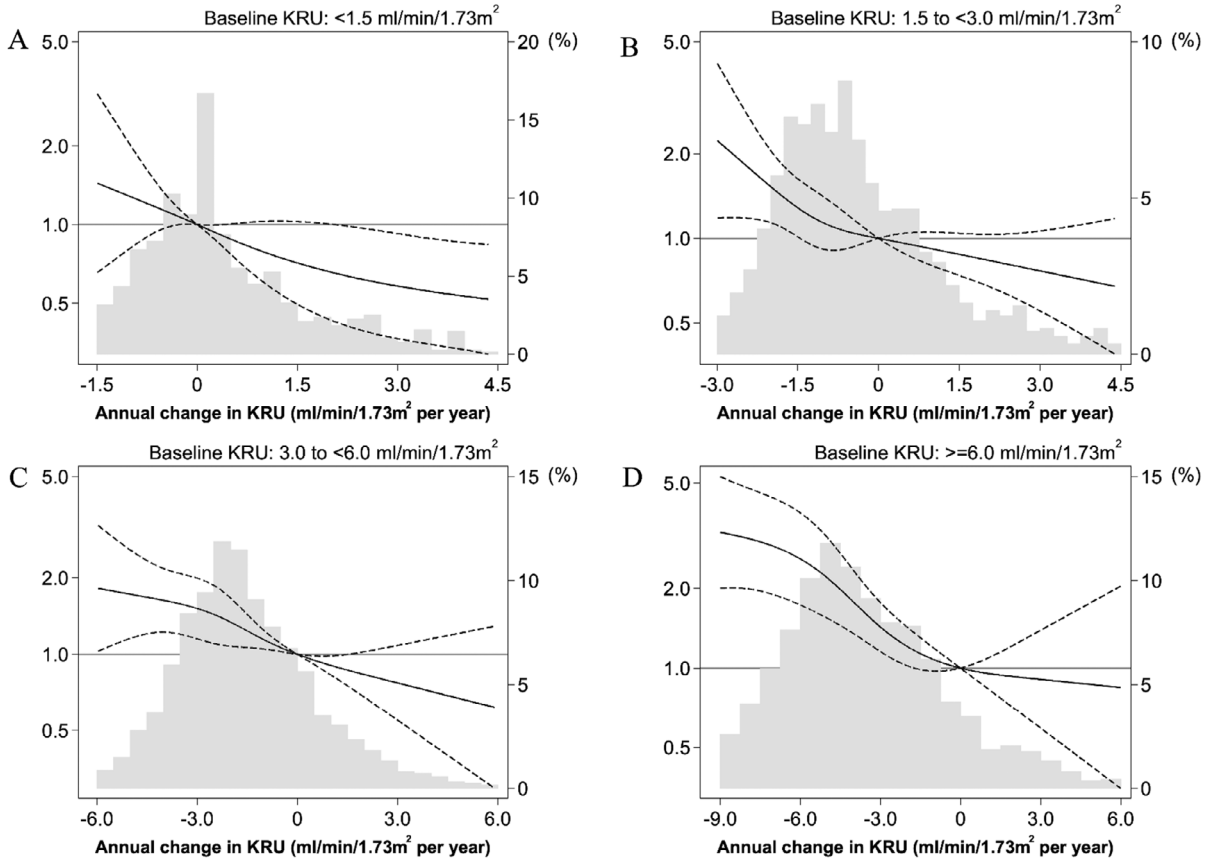

Figure 2 Distributions and model 3 adjusted restricted cubic splines comparing the relationship of annual change in KRU with ESA hyporesponsiveness at year 1 among 5239 incident HD patients stratified by baseline KRU levels.

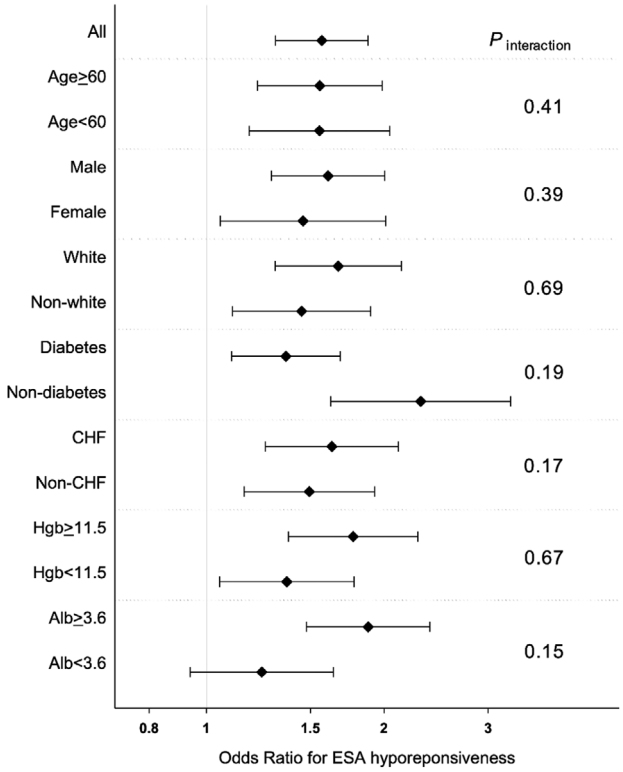

Figure 3 Overall and subgroup analyses of association between rapid decline in KRU (<−3.0 mL/min/1.73 m^2 per year) and ESA hyporesponsiveness among 5239 incident HD patients in model 3 adjustment model (reference; annual change in KRU ≥-3.0 mL/min/1.73 m^2 per year). CHF, congestive heart failure; Hgb, hemoglobin; Alb, albumin.

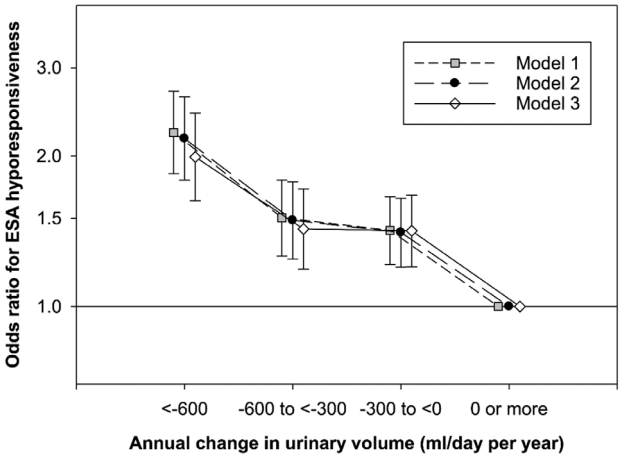

Figure 4 Annual change in urinary volume associated with ESA hyporesponsiveness among 5205 incident HD patients with three levels of adjustment. Model 1: adjusted for baseline urinary volume. Model 2: adjusted for model 1 + age, sex, race/ethnicity, primary insurance, vascular access type, comorbidities, and single-pool Kt/V. Model 3: adjusted for model 2 + BMI, nPCR, hemoglobin, albumin, creatinine, albumin-corrected calcium, phosphorus, intact PTH, iron saturation, ferritin and total bicarbonate.

with using changes in urinary volume as a surrogate for residual kidney function.

Our study supports and extends previous studies that have reported an association between higher RKF and lower requirement for ESAs. In the CHOICE Study, a study of 734 incident HD patients in the United States, patients who reported maintained urinary output ≥250 mL/day during the first year after dialysis initiation showed significantly lower erythropoietin dose requirements than those without urinary output.[12] Another cohort study of 650 HD patients in the United Kingdom showed that the mean ERI over time was 10% to 30% lower in patients with residual urea clearance ≥1 mL/min as compared with those with <1 mL/min.[25] Our study not only verifies the conclusion of the previous US and UK studies, but we also go on to show that a more rapid decrease in RKF over the first year after dialysis initiation is associated higher ERI (i.e., lower ESA responsiveness).

The most common cause of ESA hyporesponsiveness is insufficient iron availability for erythropoiesis, also known as functional iron deficiency.[26] ESAs may precipitate functional iron deficiency in the presence of adequate total body iron stores. The increased erythropoietic rate driven by ESA administration depletes circulating iron at a rate faster than can be replaced from body iron stores despite sufficient total body iron levels to support increased erythropoiesis. In this study, we observed adequate iron stores both at baseline and year 1 as well as similar iron status among annual change in RKF groups. Malyszko et al. reported HD patients with RKF showed significantly higher Kt/V and lower serum hepcidin with similar serum iron, transferrin and iron-binding capacity, ferritin, hemoglobin, hematocrit, and as high-sensitivity C-reactive protein (hsCRP).[27] Although hepcidin levels were not available in our study, patients with maintained KRU during the first year showed higher spKt/V at year 1. These results indicate that dialysis adequacy may be related to ESA hyporesponsiveness, and indeed several studies reported that online hemodiafiltration reduced ERI.[28,29]

We also observed that baseline ERI was higher than those in year 1 regardless of change in KRU. At the time of dialysis initiation, higher ERI levels reflect a decreased response to ESAs, potentially due to higher inflammation in patients who are nearing dialysis initiation. ERI decreases over 1 year as adequate clearance of toxins may

decrease total inflammation resulting in an improved response to ESAs.

We interestingly note that patients with the fastest KRU decline had lower baseline ERI despite no difference with baseline weekly ESA dose compared to the patients in the slow deterioration and maintained KRU groups. We suspect that this may be because patients with the fastest KRU decline also had the highest baseline KRU and urinary volumes. This phenomenon is consistent with a prior observational study which found that patients with higher urinary volumes at baseline showed faster decline in urinary volume during follow-up period.[30]

One of the strengths of our study is large sample size of patients on HD. However, several limitations of this study should be acknowledged. First, the anemia management guidelines changed in 2009 to dissuade providers from prescribing ESAs to maintain normal hemoglobin levels, especially after the CHOIR and TREAT trials showed harm in patients with hemoglobin levels >12 g/dL.[7, 8] As the policy changes were during our study period, we anticipate that this may affect the average hemoglobin levels, ESA dosing, and other anemia treatments. However, ERI should not be affected by the policy changes given ESA dosing is normalized to hemoglobin values. Second, the calculation of RKF is based upon urinary urea nitrogen excretion and may not be accurate given the difficulties in standardizing the timing of urine collection or in collecting 24-hour urine specimens and the use of factor 0.9 for estimating average predialysis serum urea nitrogen. Nevertheless, the population-level associations can be expected from an adequate number of subjects if such errors are not associated with the outcome. Third, several studies have proposed ESA resistance associated with inflammation.[31, 32] However, specific markers for inflammation, such as hsCRP and interleukin-6, were not available in this study. Even though we adjusted for serum albumin and ferritin in multivariate analyses, residual confounding may still be present. Forth, oral medication data were not available. Some medications such as statins and renin-angiotensin aldosterone system (RAAS) inhibitors are expected to influence either hemoglobin levels, ESA responsiveness, RKF or urinary output resulting in residual confounding. Statins have been suggested to improve ESA responsiveness.[33] Although RAAS inhibitors have been suggested to preserve RKF in patients on HD,[34] a randomized controlled trial reported that RAAS inhibitors did not have any effect on RKF in HD patients.[35] Furthermore, diuretics might affect renal output and KRU. Fifth, we realize that blood and urine sample collection and processing variation can lead to measurement bias. While we do not believe the measurement errors would be correlated to the outcome, any errors would likely lead to non-differential misclassification and an underestimation of the effect. Lastly, potential selection bias may exist, because patients with limited or no RKF are less likely to have undergone urine collections.

In conclusion, our analyses suggest an important association between faster decline in RKF and hyporesponsiveness for ESA in incident HD patients. Further research is necessary to test if RKF preservation strategies, including an incremental HD approach, a low-protein diet on nondialysis days, and the use of ultrapure dialysate, can overcome ESA hyporesponsiveness.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplemental Table 1. Baseline characteristics of included and excluded hemodialysis patients.

Supplemental Figure 1. Flow diagram summarizes the criteria used to constitute the analytic cohort.

Supplemental Figure 2. Annual change in KRU associated with low hemoglobin level (<10 g/dl) at year 1 among 5,239 incident HD patients with three levels of adjustment.

Supplemental Figure 3. Distributions and Model 3 adjusted restricted cubic splines comparing the relationship of annual change in urinary volume with ESA hyporesponsiveness at year 1 among 5,205 incident HD patients stratified by baseline urinary volume levels.

Supplemental Figure 4. Overall and subgroup analyses of association between rapid decline in urinary volume (<−600 ml/day per year) and ESA hyporesponsiveness among 5,205 incident HD patients in Model 3 adjustment model (reference; annual change in urinary volume ≥ −600 ml/day per year)