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Authors

Lee, Yuji
Okuda, Yusuke
Sy, John
[et al.](#)

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Ultrafiltration Rate Effects Declines in Residual Kidney Function in Hemodialysis Patients

Yuji Lee^{a, b} Yusuke Okuda^a John Sy^c Sung Rok Kim^b Yoshitsugu Obi^a
 Csaba P. Kovesdy^{d, e} Connie M. Rhee^a Elani Streja^a Kamyar Kalantar-Zadeh^a

^aHarold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine Medical Center, Orange, CA, USA; ^bDivision of Nephrology, Department of Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, South Korea; ^cNephrology Section, VA Long Beach Healthcare System, Long Beach, CA, USA; ^dDivision of Nephrology, Department of Medicine, University of Tennessee Health Science Center, Memphis, TN, USA; ^eNephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN, USA

Keywords

Hemodialysis · Residual kidney function · Ultrafiltration rate

Abstract

Background: High ultrafiltration rate (UFR) has been associated with increased mortality in hemodialysis (HD) patients. However, the impact of UFR on decline of residual kidney function (RKF) has not been elucidated among patients receiving conventional HD. **Methods:** We performed a retrospective cohort study of 7,753 patients who initiated conventional HD from 2007 to 2011 and survived the first year of dialysis with baseline UFR and renal urea clearance (KRU) data at baseline and 1 year (5th patient-quarter). The primary exposure was average UFR at the 1st patient-quarter from dialysis initiation (<4, 4 to <6, 6 to <9, 9 to <13, and ≥ 13 mL/h/kg). Decline in RKF was defined as the percent change in KRU and decline in urine output during the first year after initiation of dialysis. We used a logistic regression model for rapid decline in RKF and a linear regression model for change in urine volume. **Results:** In our HD cohort, mean baseline UFR

was 7.0 ± 3.1 mL/h/kg, and median (interquartile range) baseline KRU was 3.5 (2.1–5.3) mL/min/1.73 m². There was a graded association between UFR and a rapid decline in RKF; the expanded case mix-adjusted ORs and 95% CIs were 1.21 (1.04–1.40), 1.34 (1.16–1.55), 1.73 (1.46–2.04), and 1.93 (1.48–2.52) for baseline UFR 4 to <6, 6 to <9, 9 to <13, and ≥ 13 mL/h/kg, respectively (reference: <4 mL/h/kg). KRU trajectories showed a greater KRU decline over time in higher UFR categories. Higher UFR was also associated with a greater decline in urine output after 1 year. **Conclusion:** Higher UFR was associated with a rapid decline in RKF among conventional HD patients. Further clinical trials are needed to elucidate a causal effect of UFR on RKF among HD patients.

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Introduction

There has been a growing interest in preservation of residual kidney function (RKF) among hemodialysis (HD) patients alongside endeavors to improve survival

rate and quality of life [1, 2]. Even in small amounts, RKF contributes to volume control and clearance of uremic toxins [3, 4]. In addition, the presence of RKF has been associated with lower concentrations of inflammatory markers and higher levels of nutritional parameters [5–7]. These beneficial effects of RKF may lead to reduced mortality and better quality of life among HD patients [1, 2, 8]. Thus, preserving RKF should be considered when managing HD patients.

Intradialytic parameters, particularly those affecting hemodynamic stability, may play an important role in preserving RKF [9]. Ultrafiltration rate (UFR) during dialysis can impact hemodynamics, and high UFRs may result in intradialytic hypotension (IDH) and hypoperfusion when the UFR exceeds plasma refilling rate [10–12]. Furthermore, systemic hypoperfusion may cause various complications such as myocardial, brain or intestinal ischemia leading to poor outcomes [13–17]. Given its impact on hemodynamics and organ perfusion, we hypothesize that a higher UFR may also lead to a decreased renal perfusion and precipitate loss of RKF. We thereby sought to evaluate the association of baseline UFR with RKF over 1 year after dialysis initiation among incident conventional HD patients.

Methods

Study Population

We examined a statistically deidentified data set of adult (≥ 18 years of age) incident HD patients who received treatment for at least 60 consecutive days in facilities operated by a large dialysis organization in the United States from January 2007 to December 2011. Patients were followed until death, transplantation, loss of follow-up, discontinuation of dialysis or December 31, 2011, whichever occurred first. The follow-up period was divided into patient-quarters (91-day periods from the date of conventional HD initiation). Conventional HD patients were defined as those who received in-center HD and did not receive other dialysis modalities including nocturnal HD, peritoneal dialysis, home HD, less-frequent HD (≤ 2 times per week), or frequent HD (> 3 times per week) for at least 45 days within the first patient-quarter. We excluded patients who had missing data or a null value on baseline UFR or renal urea clearance (KRU), or had missing data on KRU at 1 year (5th patient-quarter). The study was approved by the Institutional Review Board of the University of California Irvine with a waiver of informed consent because it contained statistically deidentified information

Demographic and Laboratory Measurements

Information on age, gender, race/ethnicity, cause of end-stage renal disease (ESRD), primary insurance, comorbidities, dialysis prescription, and laboratory variables were extracted from the statistically deidentified dataset. Predialysis blood samples were processed by standardized methods at a central laboratory in Deland,

Florida, within 24 h of collection. Repeated measures of laboratory variables for each patient during the patient-quarter were averaged to minimize measurement variability. Quarterly means were used in all analyses. Values extracted from the first patient-quarter served as the baseline data.

Exposure and Outcome Definition

The primary exposure was the average UFR in the first-patient-quarter (i.e., baseline UFR), which was calculated as follows:

$$\text{UFR (mL/h/kg)} = \frac{(\text{preHD weight} - \text{postHD weight}) (\text{kg})}{\text{session duration (h)} \times \text{postHD weight (kg)}} \times 1,000 (\text{mL/kg})$$

We then divided baseline UFR into 5 exposure categories (< 4 , 4 to < 6 , 6 to < 9 , 9 to < 13 , and ≥ 13 mL/h/kg) [16].

The primary outcome was the RKF after 1 year from dialysis initiation. RKF was first defined using KRU, which was calculated using the formula below, adjusted for body surface area and expressed as mL/min/1.73 m² [18].

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

Then, the percent change from baseline KRU to the average KRU at the 5th patient-quarter was calculated. We defined a rapid decline in RKF as the percent change in KRU greater than the median for our cohort. Similarly, we assessed the change of urine volume (Δ urine volume) from baseline to the 5th patient-quarter.

Statistical Methods

Baseline characteristics were described across UFR categories, and trends across categories were evaluated using either a linear regression model or a Wilcoxon-type nonparametric trend test, as appropriate.

We first assessed the association between UFR and a rapid decline in RKF using logistic regression models and using UFR category < 4 mL/h/kg as reference. Three hierarchical adjustment models were examined: (1) an unadjusted model; (2) a case mix-adjusted model that included age, gender, race/ethnicity (Caucasian, African American, Hispanic, or other), cause of ESRD (diabetes, hypertension, or other), primary insurance (Medicare, Medicaid, or other), and comorbidities (diabetes, hypertension, congestive heart failure, and cardiovascular disease); (3) an expanded case mix-adjusted model that additionally included baseline KRU, IDH, body mass index (BMI), and normalized protein catabolic rate (nPCR). We defined IDH as HD sessions with absolute nadir systolic blood pressure < 90 mm Hg per HD session. We performed a subgroup analysis to assess if we could elicit any factors that could be contributing to the association between UFR and a rapid decline in RKF using categories of UFR < 4 , 4 to < 9 , and ≥ 9 mL/h/kg (reference, < 4 mL/h/kg). We utilized likelihood ratio testing and the addition of the following interaction terms into our logistic regression model: age (≥ 65 or < 65 years old), gender, race (African American or non-African American), diabetes, congestive heart failure, BMI, baseline KRU (≥ 3 or < 3 mL/min/1.73 m²), nPCR (≥ 0.8 or < 0.8 g/kg/day), and IDH. In sensitivity analysis, we

additionally adjusted for interdialytic weight gain (IDWG) in addition to all covariates included in an expanded case mix-adjusted model. Moreover, we did a sensitivity analysis with the exclusion of BMI in the expanded case mix-adjusted model since body weight was reflected into UFR.

We then attempted to estimate the magnitude and rate of renal function decline over 1 year according to the baseline UFR categories. We utilized a linear mixed-effects model allowing for a random intercept and slope using an unstructured covariance matrix where UFR categories, case mix variables, baseline KRU, and an interaction term between the patient-quarters and UFR categories were included. We also assessed the change in volume over the same year period as a surrogate marker of RKF using a linear regression model with the 3 previously mentioned levels of adjustments.

We assessed missing baseline data in our covariates and found that nPCR had missing data in 3.7% of patients in our cohort. To account for this, we performed multiple imputation methods using sequential generalized regression (known as chained equation). We included expanded case mix variables in the imputation model using ten imputed datasets. The estimates were combined using Rubin's rules [19]. Statistical analyses used STATA, version 13.1 (StataCorp LP, College Station, TX, USA).

Results

Patient Characteristics

Among 147,273 patients receiving conventional HD available for analysis, we excluded 22,427 patients with missing data on baseline UFR. We then excluded 82,848 patients with missing data on baseline KRU and 1,676 patients with zero KRU at baseline. Then, we excluded 32,569 patients with missing data on KRU at the fifth patient-quarter (i.e., the first 91-day period of the second year of dialysis). Our study cohort finally consisted of 7,753 conventional HD patients (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000503918).

In our cohort, mean age was 62 ± 14 years, 65% were male, 56% were Caucasian, 25% were African American, 49% had ESRD due to diabetic nephropathy, and mean baseline UFR level was 7.0 ± 3.1 mL/h/kg, (Table 1). Patients with a higher UFR had lower baseline KRU, lower urine volume, lower BMI, greater nPCR, and greater decrease in intradialytic systolic blood pressure during HD.

Association of Baseline UFR with a Rapid Decline in RKF

The median (interquartile range [IQR]) of KRU at baseline and 1 year was 3.5 (2.1–5.3) and 2.2 (1.0–3.9) mL/min/1.73 m², respectively ($p < 0.001$). The number of patients with rapid decline in RKF was 522 (43%), 950 (48%),

1,393 (50%), 822 (56%), and 189 (59%) for baseline UFR of < 4 , 4 to < 6 , 6 to < 9 , 9 to < 13 , and ≥ 13 mL/h/kg, respectively ($p < 0.001$). Across all levels of adjustment, there was an incremental association between baseline UFR and higher odds of rapid decline in RKF (p for linear trend < 0.001 ; Fig. 1). The expanded case mix-adjusted ORs and 95% CIs were 1.21 (1.04–1.40), 1.34 (1.16–1.55), 1.73 (1.46–2.04), and 1.93 (1.48–2.52) for baseline UFR of 4 to < 6 , 6 to < 9 , 9 to < 13 , and ≥ 13 mL/h/kg, respectively (reference: UFR < 4 mL/h/kg). When we did a sensitivity analysis with the exclusion of BMI in the expanded case mix-adjusted model since body weight was reflected into UFR, the results were unchanged; ORs and 95% CI were 1.21 (1.04–1.40), 1.34 (1.16–1.55), 1.73 (1.47–2.03), and 1.92 (1.48–2.49) for baseline UFR of 4 to < 6 , 6 to < 9 , 9 to < 13 , and ≥ 13 mL/h/kg, respectively (reference: UFR < 4 mL/h/kg). Furthermore, in sensitivity analysis with additional adjustment for IDWG, the results also remained consistent; ORs and 95% CI were 1.21 (1.04–1.41), 1.35 (1.16–1.56), 1.73 (1.46–2.07), and 1.94 (1.47–2.56) for baseline UFR of 4 to < 6 , 6 to < 9 , 9 to < 13 , and ≥ 13 mL/h/kg, respectively (reference: UFR < 4 mL/h/kg).

In subgroup analyses, the association between higher baseline UFR and a rapid decline in RKF was modified by race ($p_{\text{interaction}} = 0.006$); where ORs for UFR ≥ 9 mL/h/kg were drastically attenuated among African Americans (Fig. 2). Although IDH was an effect modifier in the association between UFR and decline in RKF ($p_{\text{interaction}} = 0.02$), the association was consistent with the overall analysis in both patients with and without IDH. However, the association between UFR and a rapid decline in RKF was not modified by age, gender, diabetes, congestive heart failure, BMI, baseline KRU, and nPCR; p values for interaction were 0.842, 0.138, 0.677, 0.517, 0.262, 0.230, and 0.769, respectively.

Association of UFR and RKF Decline through 1 Year

The median (IQR) Δ KRU during the first year after initiation of HD was -1.11 (-2.62 to -0.18) mL/min/1.73 m². When assessing the change in RKF, we found that higher UFR categories exhibited a greater KRU decline over time (Fig. 3). At all time points except baseline (2nd, 3rd, 4th, and 5th patient-quarters), estimated KRU values were lower in higher UFR categories. In particular, 3 months after HD initiation (2nd patient-quarter), decline in RKF was steeper in higher UFR categories; differences in estimated KRU from baseline were -0.02 , -0.25 , -0.41 , -0.70 , and -0.92 mL/min/1.73 m² at UFR of < 4 , 4 to < 6 , 6 to < 9 , 9 to < 13 , and ≥ 13 mL/h/kg, respectively.

Table 1. Baseline characteristics of 7,753 incident conventional hemodialysis patients stratified by baseline UFR

	All patients	UFR, mL/h/kg					p value
		<4	4 to <6	6 to <9	9 to <13	≥13	
n (%)	7,753	1,211 (16)	1,980 (26)	2,768 (36)	1,471 (19)	323 (4)	
Age, years	62±14	62±14	62±14	62±14	61±14	59±15	0.005
Gender, male	65	58	61	68	70	65	<0.001
Race/ethnicity							
Caucasian	56	64	59	55	51	49	<0.001
African American	25	24	26	25	24	18	0.03
Hispanic	10	7	8	11	14	16	<0.001
Others	9	5	7	9	12	17	<0.001
Cause of ESRD							
Diabetes	49	39	47	52	52	51	<0.001
Hypertension	28	29	28	27	29	32	0.9
Others	23	32	24	21	20	17	<0.001
Primary insurance							
Medicare	51	50	49	51	52	52	0.3
Medicaid	6	4	6	6	9	9	<0.001
Others	43	46	45	42	39	39	<0.001
Comorbidities							
Diabetes	68	61	68	71	69	72	<0.001
Hypertension	52	52	55	50	53	52	0.07
CHF	47	38	46	48	53	51	<0.001
CVD	25	24	24	26	28	26	0.1
BMI, kg/m ²	29.2±7.3	31.2±8.2	31.3±7.8	29.1±6.7	26.1±5.4	22.8±3.8	<0.001
KRU, mL/min/1.73 m ²	3.5 (2.1–5.3)	4.0 (2.5–5.8)	3.6 (2.2–5.4)	3.4 (2.1–5.2)	3.1 (1.8–4.9)	3.3 (1.9–4.8)	<0.001
Urine volume, mL	950 (550–1,440)	1,150 (700–1,700)	1,000 (600–1,500)	900 (550–1,400)	800 (500–1,250)	775 (500–1,250)	<0.001
Ultrafiltration, L	2.0±0.9	0.9±0.5	1.7±0.6	2.2±0.7	2.7±0.7	3.1±0.8	<0.001
Dialysis time, min	208 (184–223)	210 (186–230)	211 (188–231)	208 (184–222)	199 (182–214)	185 (180–210)	<0.001
Postdialysis weight, kg	85±24	92±26	92±25	85±22	75±17	64±13	<0.001
Weekday IDWG	2.1 (1.4–2.9)	0.9 (0.5–1.2)	1.5 (1.2–1.8)	2.3 (1.9–2.6)	3.2 (2.8–3.6)	4.3 (3.8–4.9)	<0.001
Weekend IDWG	2.8 (1.9–3.8)	1.1 (0.7–1.6)	2.1 (1.7–2.6)	3.0 (2.5–3.6)	4.2 (3.7–4.9)	5.8 (5.1–6.7)	<0.001
Lowest intradialytic SBP, mm Hg	118±14	118±14	119±14	118±14	118±14	117±14	0.07
IDH	65	62	63	65	69	74	<0.001
nPCR, g/kg/day	0.83±0.22	0.78±0.20	0.80±0.21	0.84±0.21	0.87±0.23	0.92±0.25	<0.001

Values for categorical variables are shown as percentages; values for continuous variables are shown as mean ± SD or median (IQR).

UFR, ultrafiltration rate; ESRD, end-stage renal disease; CHF, congestive heart failure; CVD, cardiovascular disease; BMI, body mass index; IDWG, interdialytic weight gain; KRU, renal urea clearance; SBP, systolic blood pressure; IDH, intradialytic hypotension; nPCR, normalized protein catabolic rate.

Sensitivity Analysis: Urine Output as a Marker of RKF

In our assessment of changes to urine output after the first year on dialysis, the median (IQR) change in urine volume was –250 (–620 to 100) mL. We found higher baseline UFR categories were associated with a greater decline in urine volume during the first year after initiation of HD compared to the reference category (UFR <4 mL/h/kg). After adjusting for case-mix variables, BMI, nPCR, and baseline urine volume, change in urine volume (95% CI) over 1 year was –96 (–56 to –136), –159 (–120 to –198), –229 (–184 to –274), and –268 (–196 to –340) mL at UFR 4 to <6, 6 to <9, 9 to <13, and ≥13 mL/h/kg, respectively (reference: UFR <4 mL/h/kg; Fig. 4).

Discussion

In this study, we demonstrated that higher UFR is associated with incrementally increased odds of rapid decline in RKF, an association that was interestingly attenuated among African Americans. We also found that higher UFR is associated with steeper declines in RKF and a greater decrease in residual urine volume.

Previous studies have shown that UFR levels of ≥9 mL/h/kg are associated with higher mortality [16, 20]. Potential mechanisms underlying this association may be related to circulatory stress and hypotension induced by high UFR. Hypotension may lead to diminished renal blood supply and subsequent nephron loss. Although in our subgroup analysis, IDH was an effect

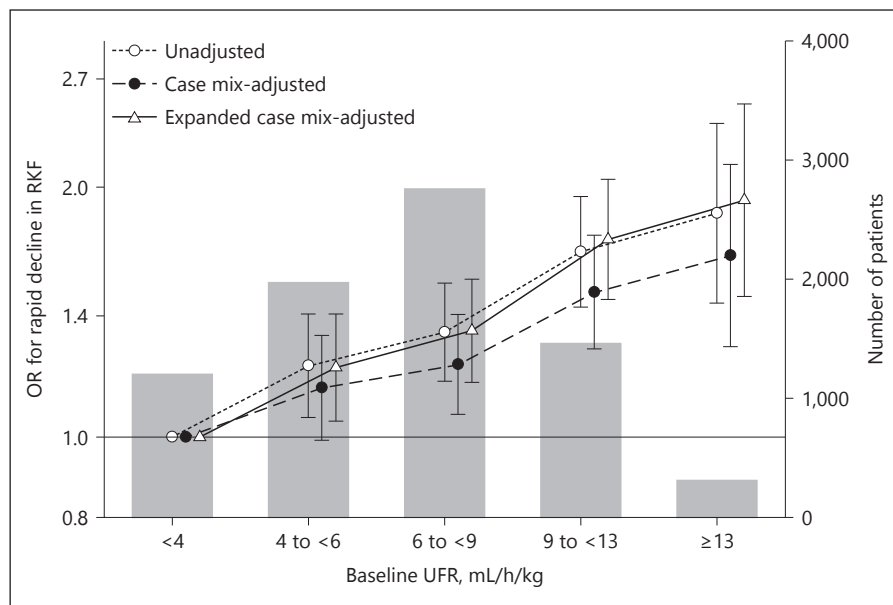


Fig. 1. ORs for rapid decline in RKF with 4 levels of adjustment based upon baseline UFR. RKF, residual kidney function; UFR, ultrafiltration rate.

modifier of the association between high UFR and a decline in RKF, high UFR was associated with a decline in RKF among patients without IDH as well as those with IDH. On the one hand, we hypothesize that despite systemic hypotension, autoregulatory mechanisms maintain adequate renal perfusion [9, 21]. On the other hand, undetected, subclinical hypoperfusion may be occurring despite the absence of systemic hypotension [9, 21, 22]. Unfortunately, our analysis was limited by available data and all episodes of IDH may not have been recorded. Also, our limited definition of IDH may not have captured all clinically relevant episodes of hypotension.

In our study, we also show that individuals exhibit a nonlinear decline in RKF among patients receiving conventional HD. According to the United States Renal Data System 2015 annual data report, a fair number of patients still have RKF at the time of their transition to dialysis [23]. A previous study noted that RKF declines were the greatest within the first 3 months after initiating dialysis [24]. Our analysis not only confirmed that higher UFR is associated with a steeper decline in KRU within the first 3 months but also further goes on to show that this dose-dependent association is continued over the course of the entire year (Fig. 3). Since preservation of renal function may improve survival in dialysis patients, this finding suggests that we should remain cautious about prescribing a high UFR to prevent loss of RKF, especially within the first year after dialysis initiation [2].

The strength of this study is that it showed the impact of high UFR on the decline in RKF in a large cohort of incident conventional HD patients. However, there are several limitations to our study. First, KRU used in this study may not be the best way to measure RKF as it tends to underestimate glomerular filtration rate due to tubular reabsorption. However, our analysis focused on trends in KRU, placing less emphasis on the absolute value of KRU. Second, we only included patients who had KRU data at baseline and 1 year after initiating HD (patients excluded if zero at baseline or missing values at baseline and 1 year). Patients who had limited or no RKF after initiating HD are less likely to have undergone urine collections at 1 year, which might result in potential selection bias. In a sensitivity analysis, we compared our cohort to those who were excluded from the study. We found that the included patients had a higher prevalence of diabetes and congestive heart failure using standardized differences (online suppl. Table 1). Both diabetes and CHF have been associated with a rapid decline in RKF and possibly higher UFR [25, 26]. While we have attempted to adjust for these comorbidities, any residual effect may bias our study results away from the null. Third, even after we adjusted for potential confounders to investigate the association between UFR and RKF, residual confounding may inherently remain due to the inability to measure some potential confounders and the retrospective observational nature of this study. In addition, due to the observational study design, this study could not thoroughly prove a cause

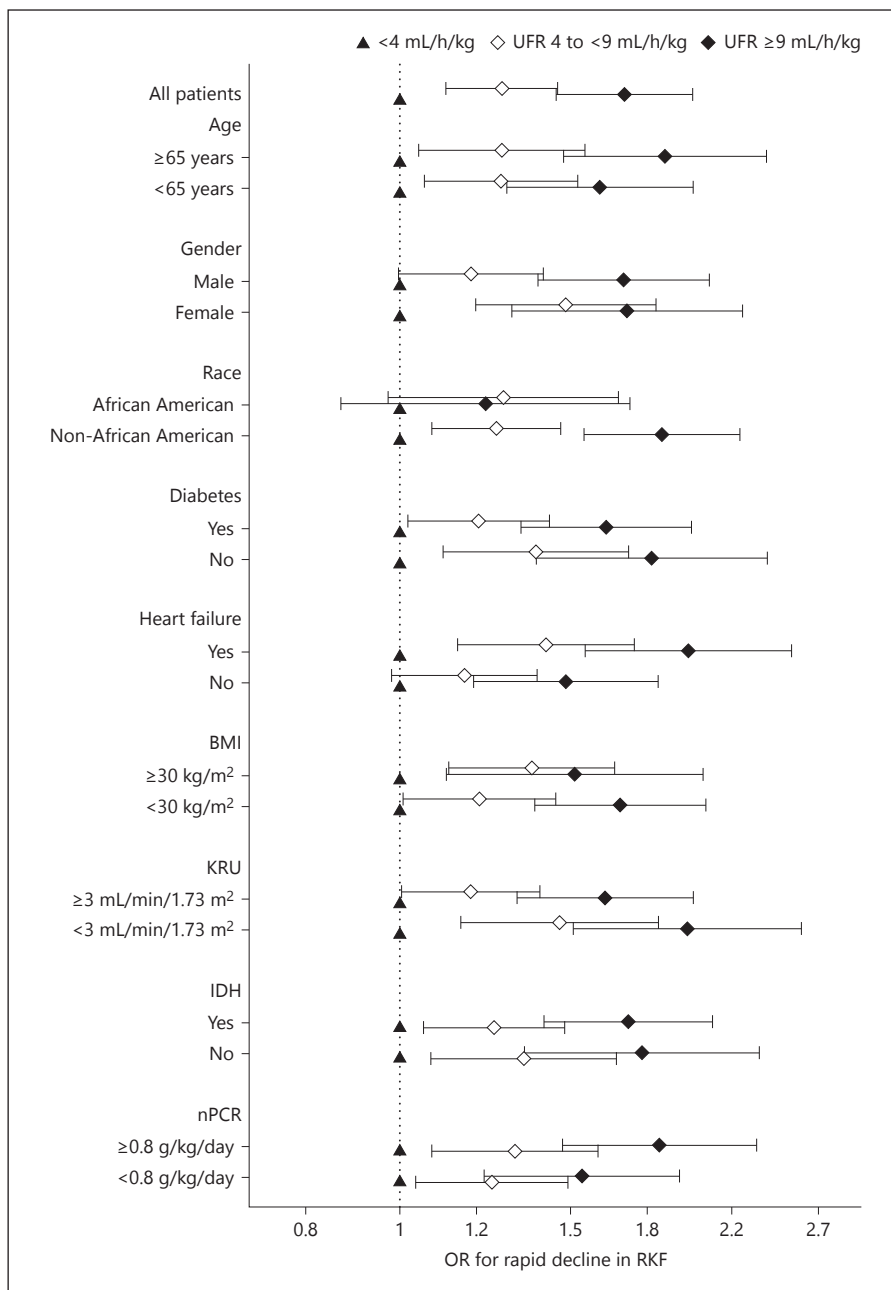


Fig. 2. Subgroup analyses of associations between UFR and rapid decline in RKF in the expanded case mix-adjusted model. Points and bars represent ORs and 95% CIs, respectively. Reference is UFR 4 to <9 mL/h/kg. UFR, ultrafiltration rate; KRU, renal urea clearance; BMI, body mass index; IDH, intradialytic hypotension; nPCR, normalized protein catabolic rate; RKF, residual kidney function.

and effect mechanism. Particularly, although the relationship between higher UFR and rapid decline in RKF remained robust even after adjusting for IDWG, IDWG itself may not thoroughly reflect an objective volume status. Therefore, the analyses might have been confounded by volume status. In addition, the diuretic therapy at the dialysis initiation was not included in our analyses due to lack of data. Diuretic therapy plays a role in increasing urine volume; consequently lowering IDWG and the need for aggressive volume removal in

dialysis patients [27, 28]. However, it is known that diuretics have no effect on renal urea and creatinine clearance in dialysis patients [27, 29, 30]. This suggests that the association of higher UFR with a decline in KRU may be less likely to be confounded by diuretics. While lower UFR appears to be associated with better outcomes in our study, insufficient UFR can also be related to inadequate fluid removal, leading to chronic volume overload and adverse outcomes. Therefore, it remains important to focus on patient factors such as salt and

Fig. 3. Trajectory of KRU over time estimated by the expanded case mix-adjusted linear mixed-effects model. KRU, renal urea clearance.

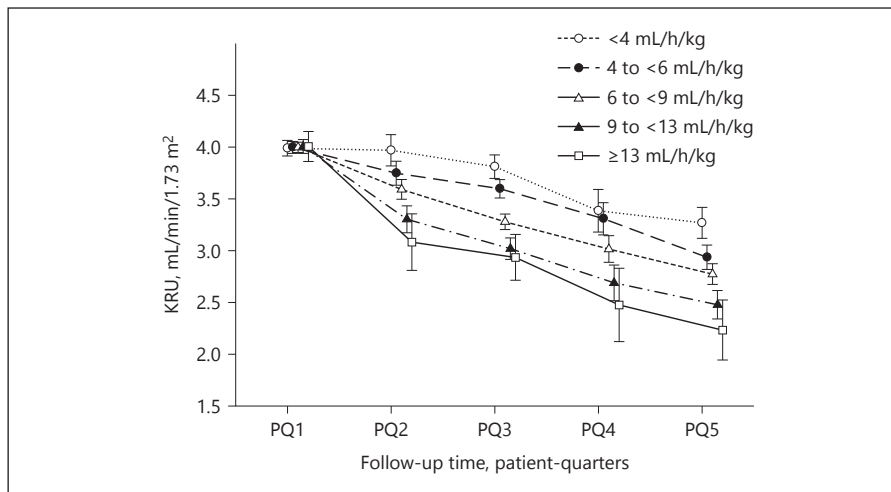
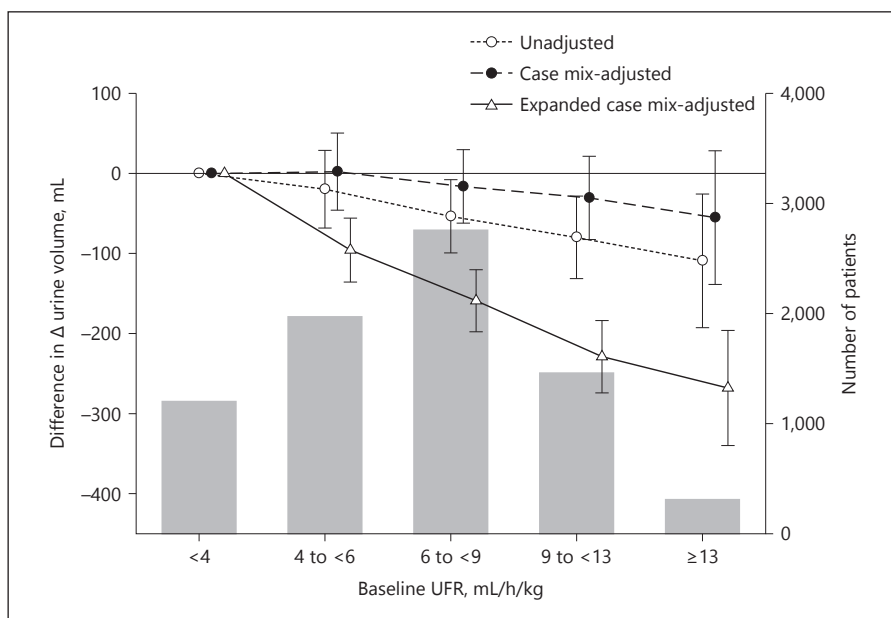


Fig. 4. UFR and difference in Δ urine volume during the first year after initiation of dialysis. UFR, ultrafiltration rate.



fluid restriction to minimize IDWG and enable lower UFRs during dialysis treatments.

In conclusion, high UFR was associated with higher odds of a rapid decline in RKF, lower KRU, and lower urine output after 1 year among patients receiving conventional HD. Further clinical trials are needed to confirm and elucidate a causal effect of UFR on clinical outcomes among conventional HD patients.

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Disclosure Statement

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