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Ultrafiltration Rate, Residual Kidney Function, and Survival Among Patients Treated With Reduced-Frequency Hemodialysis

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Abstract

Rationale & Objective: Patients receiving twice-weekly or less-frequent hemodialysis (HD) may need to undergo higher ultrafiltration rates (UFRs) to maintain acceptable fluid balance. We hypothesized that higher UFRs are associated with faster decline in residual kidney function (RKF) and a higher rate of mortality.

Study Design: Retrospective cohort study.

Setting & Participants: 1,524 patients with kidney failure who initiated maintenance HD at a frequency of twice or less per week for at least 6 consecutive weeks at some time between 2007 and 2011 and for whom baseline data for UFR and renal urea clearance were available.

Predictor: Average UFR during the first patient-quarter during less-frequent HD (<6, 6-<10, 10-<13, and ≥13 mL/h/kg).

Outcome: Time to all-cause and cardiovascular death, slope of decline in RKF during the first year after initiation of less-frequent HD (with slopes above the median categorized as rapid decline).

Analytical Approach: Cox proportional hazards regression for time to death and logistic regression for the analysis of rapid decline in RKF.

Results: Among 1,524 patients, higher UFR was associated with higher all-cause mortality; HRs were 1.43 (95% CI, 1.09–1.88), 1.51 (95% CI, 1.08–2.10), and 1.76 (95% CI, 1.23–2.53) for UFR of 6 to <10, 10 to <13, and ≥13 mL/h/kg, respectively (reference: UFR < 6 mL/h/kg). Higher UFR

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was also associated with higher cardiovascular mortality. Baseline RKF modified the association between UFR and mortality; the association was attenuated among patients with renal urea clearance ≥ 5 mL/min/1.73 m^2. Higher UFR had a graded association with rapid decline in RKF; ORs were 1.73 (95% CI, 1.18–2.55), 1.89 (95% CI, 1.12–3.17), and 2.75 (95% CI, 1.46–5.18) at UFRs of 6 to <10, 10 to <13, and ≥13 mL/h/kg, respectively (reference: UFR < 6 mL/h/kg).

Limitations: Residual confounding from unobserved differences across exposure categories.

Conclusions: Higher UFR was associated with worse outcomes, including shorter survival and more rapid loss of RKF, among patients receiving regular HD treatments at a frequency of twice or less per week.

Less-frequent hemodialysis (HD) schedules, such as twice-weekly HD, have not typically been implemented in the United States until recently.[1] However, the potential benefits, including a more flexible treatment schedule, greater preservation of residual kidney function (RKF), better quality of life, reduced risks related to the dialysis procedure, and comparable survival rates compared with thrice-weekly HD, have motivated clinicians to revisit less-frequent HD regimens.[2–4] Unfortunately, less-frequent HD may also be associated with higher interdialytic weight gain (IDWG). This is primarily due to higher ultrafiltration requirements attributable to a reduced dialysis frequency, even if these can be mitigated by substantial RKF and strict fluid restriction.[5] Additionally, less-frequent HD may result in inadequate dialysis, and criteria have been recently proposed for identifying patients who may be more appropriate for less-frequent HD.[3,6]

Ultrafiltration rate (UFR) is a composite metric of IDWG, treatment time, and postdialysis weight, calculated with each dialysis treatment. High IDWG or short treatment times may necessitate higher UFRs.[7] However, rapid fluid removal may potentially result in repetitive intradialytic hypotension (IDH) episodes, resulting in poor clinical outcomes.[8] Several observational studies have shown that high UFR is associated with increased all-cause and cardiovascular (CV) mortality in conventional HD patients.[9–13]

Although the association between UFR and patient outcomes in thrice-weekly HD patients has been evaluated,[10,11,13,14] the impact of UFR on both RKF and mortality remains uncertain among patients receiving less-frequent HD. Given that there has been growing interest in less-frequent HD schedules and greater prioritization of preservation of RKF,[15] evaluating the association between UFR and clinical outcomes in patients receiving less-frequent HD may be helpful for management and improved prognostication. In this study, we evaluated the association between UFR and mortality as well as decline in RKF among patients receiving less-frequent HD regimens. We also assessed the impact of baseline RKF on the association of UFR and mortality in patients receiving less-frequent HD.

Methods

Study Populations

We performed a retrospective cohort study using a cohort of statistically deidentified adult (aged ≥18 years) patients with kidney failure receiving dialysis in facilities operated by a large dialysis organization at some time between January 2007 and December 2011. Patients

were included in our less-frequent HD cohort if they received HD with a constant treatment schedule of twice or less per week (eg, Tuesday/Saturday or Monday/Friday) for at least 6 consecutive weeks. We excluded patients who did not have baseline data for UFR and renal urea clearance (KRU) at the initiation of less-frequent HD. Patients were followed up from less-frequent HD initiation and censored for death, loss to follow-up, transplantation, dialysis discontinuation, or end of the study period (December 31, 2011).

The study was approved by the Institutional Review Board of the University of California Irvine with a waiver of informed consent because the data contained only statistically deidentified information.

Demographic, Clinical, and Laboratory Measures

Information for age, sex, race/ethnicity, primary insurance, comorbid conditions, type of vascular access, date and cause of death, dialysis prescription, and laboratory variables were extracted from the data. Predialysis blood samples were processed using standardized methods at a central laboratory in Deland, FL, within 24 hours of collection. Repeated measurements of laboratory variables were averaged into patient quarterly means to minimize measurement variability. Patient-quarters were defined as 91-day periods starting from the date of less-frequent HD initiation. The first patient quarter is considered baseline. Laboratory values obtained after the patient ended less-frequent HD, but were within the first 91 days after less-frequent HD initiation, were not included in baseline averaged data.

Exposure and Clinical Outcomes

The exposure of interest was average UFR during the first less-frequent HD patient-quarter (ie, baseline UFR). For patients who received less-frequent HD for a period less than the entire first quarter, baseline UFR was calculated using only data for the period during which the patient received less-frequent HD. We divided baseline UFR into 4 exposure categories (<6, 6-<10, 10-<13, and ≥13 mL/h/kg).[10,12,13] The UFR for each HD treatment was calculated as follows:

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

Our primary outcomes of interest were all-cause mortality and CV mortality. CV mortality was defined as death due to myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, congestive heart failure, pulmonary edema, pulmonary embolus, cerebrovascular accident, and mesenteric ischemia. Our secondary outcome of interest was the difference in RKF between initiation of less-frequent HD and 1 year after its initiation. RKF was defined with KRU using the formula below (where UN is urea nitrogen) adjusted for body surface area and expressed in mL/min/1.73 m^2.[16]

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

Statistical Analysis

Baseline characteristics were obtained across UFR categories. Trends across categories were evaluated using a linear regression analysis or Wilcoxon-type nonparametric trend test. Differences in baseline characteristics between included and excluded patients were compared using standardized differences. Additionally, differences between baseline characteristics of patients who were started on less-frequent HD as their initial dialysis schedule and those who were switched from other dialysis modalities or frequencies to less-frequent HD were also compared using standardized differences.

To assess the association between UFR and mortality, we used Cox proportional hazards regression models to estimate the association of the categorized UFR with mortality using UFR category < 6 mL/h/kg as our referent group. In the analysis of CV death, patients who died of non-CV causes were censored at the time of non-CV death. Three levels of adjustment were used (an unadjusted model that included only UFR; a case-mix–adjusted model that additionally included age, sex, race [white, African American, or others], primary insurance [Medicare, Medicaid, or others], comorbid conditions [diabetes, hypertension, congestive heart failure, and CV disease], vascular access [arteriovenous fistula, arteriovenous graft, central venous catheter, or others], and dialysis vintage [from transition to dialysis until the start of less-frequent HD]; and a fully adjusted model that included all covariates in the case-mix–adjusted model plus baseline RKF, body mass index, white blood cell count, hemoglobin level, serum albumin level, phosphorus level, single-pool Kt/V_{urea} [spKt/V, the urea clearance multiplied by dialysis time and normalized for urea distribution volume], and normalized protein catabolic rate [nPCR]). nPCR was calculated accounting for the contribution of RKF.[17,18] A restricted cubic spline model with 4 knots was used for evaluating the association of the outcome with UFR as a continuous variable. Effect modification by baseline RKF was evaluated by adding an interaction term with UFR into regression models using UFR category < 6 mL/h/kg as reference, followed by subgroup analysis according to baseline RKF (KRU >5 or ≥5 mL/min/1.73 m^2). We also performed subgroup analysis to assess the association of UFR with outcomes in patients with different baseline urine volumes (≥1.0 vs <1.0 L), and according to whether they started on or switched to less frequent HD. For sensitivity analysis, we additionally adjusted for ultrafiltration volume and weekly percentage IDWG separately. Moreover, we also performed the main outcome analysis among the excluded patients with missing data for baseline KRU.

We estimated 1-year KRU slope in patients with at least 1 average KRU data point measured between patient-quarters 2 and 5 besides baseline KRU by a linear mixed-effects model allowing for a random intercept and slope using an unstructured covariance matrix. We defined patients with a rapid decline in RKF as patients having a KRU slope greater than the median for our cohort. We hypothesized that the association between UFR and a rapid decline in RKF may be related to IDH. We defined IDH as HD sessions with absolute nadir systolic blood pressure (SBP) < 90 mm Hg per HD session.[19] We then evaluated the association of UFR with a rapid decline in RKF using logistic regression models with 3 levels of adjustment: unadjusted, case-mix–adjusted, and expanded case-mix–adjusted (case mix + baseline RKF + IDH + nPCR). We additionally adjusted for the interval between

KRU measurements in all hierarchical models to minimize potential bias. The proportion of sessions complicated by IDH was compared using a χ^2 test between patients with and without rapid decline in RKF.

Missing baseline covariates included white blood cell count, serum albumin level, spKt/V, and nPCR. The frequency of missing data was <1% for all variables except for spKt/V (20.5%). We performed multiple imputation methods using sequential generalized regression (known as chained equations). The imputation model included all variables of the fully adjusted model and an outcome variable using 20 imputed data sets. Rubin's combination rules were used to form one set of results.[20] All analyses were carried out using STATA, version 13.1 (StataCorp LP).

Results

Patient Characteristics

Data from 162,849 patients were extracted from a statistically deidentified data set for analysis and 4,629 patients who had ever received less-frequent HD were included in our cohort. Among these, 448 of 4,629 were initiated on less-frequent HD; 4,181 switched from other dialysis modalities or more frequent HD (4,175 patients switched from thrice-weekly HD and their median dialysis vintage was 182 [interquartile range, 91–392] days). Median durations of less-frequent HD were 82 (IQR, 61–146) and 76 (IQR, 55–132) in the incident and switched groups, respectively.

After excluding individuals without data for baseline UFR or baseline RKF, 1,524 patients were available for analysis. Flow diagrams summarize cohort construction (Fig S1A) and show initiation of less-frequent HD, assessment of baseline UFR, and duration of follow-up (Fig S1B). Compared with the 3,105 excluded patients receiving less-frequent HD, the 1,524 patients included in our analytical cohort were more likely to be white and had shorter dialysis vintage and lower spKt/V. However, there were no significant differences in most baseline characteristics between groups (Table S1).

Baseline characteristics of the patients across baseline UFR strata are shown in Table 1. Our cohort consisted of individuals whose mean age was 67 ± 14 (standard deviation) years, 56% of whom were men, and who had a mean UFR of 7.3 ± 4.8 mL/h/kg and median dialysis vintage of 119 days. Patients with higher baseline UFRs were less likely to be white and more likely to have diabetes and congestive heart failure. They also tended to have lower body mass index, lower serum albumin level, lower hemoglobin level, higher serum phosphorus level, and higher nPCR. Higher UFR groups also tended to have lower baseline RKF and urine volume. The trajectory of UFR over time showed a consistent separation across baseline UFR categories (Fig S2).

Incident HD patients who started on less-frequent schedules had a lower prevalence of congestive heart failure and lower hemoglobin level, serum albumin level, baseline RKF, and spKt/V compared with patients who switched from more frequent HD or other dialysis modalities (Table S2).

Association Between UFR and Mortality

Among patients on less-frequent HD, median follow-up was 1.0 (IQR, 0.5–1.9) years. During this period, we identified 329 (16.1 per 100 patient-years) all-cause deaths and 117 (5.7 per 100 patient-years) CV deaths. Our Cox regression analyses showed that baseline UFR had a graded association with both all-cause and CV mortality even after adjusting for confounders (Table 2).

In subgroup analyses, baseline RKF was observed to be a potential effect modifier of the association of baseline UFR with all-cause mortality (P-interaction = 0.005). In individuals with higher RKF at baseline (KRU ≥ 5 mL/min/1.73 m^2), the association between higher UFR and increased mortality was attenuated (Fig 1A and B) compared with individuals with lower RKF (KRU < 5 mL/min/1.73 m^2; Fig 1C and D). The case-mix–adjusted restricted cubic splines also showed consistent results for an association between UFR as a continuous variable and all-cause and CV mortality in subgroup analyses according to RKF (Fig S3).

Subgroup analyses according to urine volume showed similar results. In individuals with larger (≥1.0 L) urine volume at baseline, the association between higher UFR and increased all-cause mortality was slightly attenuated compared with individuals with smaller urine volume (<1.0 L; Fig S4). In an additional subgroup analysis, both incident HD patients who started on less-frequent schedules and patients who switched to less-frequent HD continued to exhibit an association between higher UFR and higher all-cause mortality (Fig S5). However, mortality risk estimates were larger for higher UFRs in the incident group compared with the prevalent group.

As sensitivity analysis, we additionally adjusted for actual ultrafiltration volume and weekly IDWG separately to assess the association of UFR with mortality, and results remained consistent (Table S3). We also examined the association of UFR with mortality in excluded patients with missing data for baseline RKF. Among 1,988 excluded patients with missing data for baseline RKF, higher UFR was still associated with greater mortality risk (Table S4).

UFR and 1-Year Decline in RKF

Among our cohort of 1,524 patients, after excluding 728 individuals with only baseline RKF and 47 who died within the first year, we used a subset of 749 individuals who had repeated measurements of RKF after baseline; numbers of patients with 2, 3, 4, and 5 data points were 350, 279, 73, and 47, respectively. The mean number of measurements used in calculating the slopes was 2.8. Numbers of patients with RKF data in patient-quarters 2, 3, 4, and 5 were 338, 425, 287, and 265, respectively. Median estimated 1-year slope of RKF was −1.76 (IQR, −2.02 to −1.40) mL/min/1.73 m^2 per year. The slope tended to be steeper across higher baseline UFR categories (Table 3; P for trend < 0.001). Of 749 patients, 374 (50%) met our criterion for rapid decline in RKF. Logistic regression analysis revealed that higher UFR was associated with higher odds of rapid decline in RKF even after adjustment (Fig 2).

In subgroup analyses looking at the contribution of baseline RKF, there remained a trend toward higher odds of rapid decline in RKF by an increased UFR for both high and low

baseline RKF levels (Fig 3). Subgroup analyses according to baseline urine volume showed consistent results; higher UFR tended to have increased odds of rapid decline in RKF for both larger and smaller urine volume (Fig S6). In our analysis looking at IDH as a possible mechanism for a more rapid decline in RKF, the proportion of patients experiencing IDH did not differ between patients with and without a rapid decline in RKF (50% and 56%, respectively; P = 0.7), and we did not find any correlation between IDH and change in RKF over time (median KRU slope, −1.73 [IQR, −1.98 to −1.40] and −1.79 [IQR, −2.04 to −1.41] in patients with and without IDH, respectively [P = 0.2]).

Discussion

Among 1,524 patients who had ever received less-frequent HD, we found that higher baseline UFR was associated with increased risk for both all-cause and CV mortality. Interestingly, the association between baseline UFR and mortality was modified by baseline RKF. The association was robust only among patients with KRU < 5 mL/min/1.73 m^2. Moreover, higher UFR was associated with a rapid decline in RKF among less-frequent HD patients.

Previously, associations have been found between higher UFR and higher risk for mortality in conventional thrice-weekly HD[9–11,13]; our findings extend this association to less-frequent HD schedules. UFR is determined by pre-dialysis weight, dry weight (the desired postdialysis weight), and treatment time. Therefore, UFR is not only a reflection of volume flux but also a surrogate for IDWG, body weight, and session time. Although UFR is tightly linked to IDWG, we found that UFR was associated with mortality, independently of IDWG.

Interestingly, we observed that the associations of higher UFR with all-cause and CV mortality were attenuated in those with substantial RKF. Similar tendencies were also shown in the subgroup analysis according to urine volume. Some previous studies identified an association between dialysis adequacy and all-cause mortality that was attenuated among incident HD patients with substantial RKF, suggesting that RKF likely has a positive benefit on patient survival regardless of practice-dependent factors.[21,22] Substantial RKF may contribute to improved survival through its beneficial effects on volume control, reduced inflammation, and greater solute clearance, especially that of middle molecules and protein-bound solutes.[23–26] Given the interrelationship of RKF, UFR, and mortality, patients without substantial RKF should be considered for extended treatment times (including switching to thrice-weekly HD) and possibly a more intense focus on controlling IDWG to minimize UFR.

We also found a dose-dependent association between high UFR and a rapid decline in RKF among less-frequent HD patients. Low RKF and consequently increased IDWG are associated with high UFR, which in turn may lead to further RKF decline. Therefore, our results indicate the vicious cycle between UFR and decline in RKF. We postulated that the association between high UFR and decline in RKF may be due to IDH during HD that results in hypoperfusion to the kidneys with an associated loss of RKF.[27] However, we did not find that IDH (defined as nadir SBP < 90 mm Hg) was associated with a decline in RKF. Despite a decrease in SBP, there are likely other regulatory mechanisms to maintain renal

perfusion that vary between individuals, or the association between high UFR and decline in RKF is mediated by yet unidentified mechanisms.[28–32] Although there is not yet a clear mechanism of why higher UFR is associated with a decline in RKF, our study suggests that clinicians should be wary if a patient has a high UFR, even if the SBP of a patient is stable during HD.

A strength of this study is that it assessed the association of UFR with decline in RKF, as well as mortality, among a relatively large cohort of patients receiving less-frequent HD.

However, this study has several limitations that should be acknowledged. First, although we adjusted for an array of baseline characteristics, we cannot rule out the presence of residual confounding from unmeasured factors. In particular, although we found a consistent association between higher UFR and increased mortality even after adjusting for IDWG, IDWG itself may not completely reflect the extracellular volume status of the patients. Therefore, without adjustment for objective volume status measures, it is possible that the analyses were confounded by extracellular volume status. Furthermore, while we observed a robust association between baseline UFR categories with mortality, UFR may inherently change over time depending on patient conditions, potentially limiting causal inference. However, the change in UFR according to baseline UFR categories was consistently separated during follow-up, suggesting that those with higher UFRs remained at higher UFRs over time and vice versa.

Second, using KRU as an index of RKF could lead to underestimates because of tubular reabsorption of urea. However, our analysis focused more on trends in KRU. Moreover, although the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommendations still suggest obtaining KRU in HD patients to assess RKF,[33] clinical practice has changed and many practitioners are no longer obtaining 24-hour urine collections, limiting the external validity of our study. Also, there is no standard definition of a rapid decline in RKF, and we resorted to using the median KRU slope in our cohort. Although extrapolation of our study to other populations is limited when comparing RKF, our results may be useful in providing a starting point that can help guide future research.

Selection bias with including only patients with baseline KRU data is another limitation to our study. It is possible that patients who do not have a KRU measurement are likely to be those lacking substantial RKF. However, given that RKF appears to be associated with improved outcomes,[34,35] this would likely bias our results toward the null. Moreover, when we repeated the main outcome analysis among 1,988 excluded less-frequent HD patients with missing baseline KRU data, the results suggesting increased mortality (all-cause and CV) with higher UFR remained robust.

Last, our study included less-frequent HD patients who switched from other dialysis modalities, as well as incident HD patients on less-frequent regimens. We could not discern why these individuals were switched from other dialysis modalities or thrice-weekly HD to less-frequent HD. Some individuals may have been “healthier” (with greater RKF requiring less frequent dialysis) and some may have been more frail (resulting in requiring less dialysis per week). However, after accounting for dialysis vintage before transition to less-

frequent HD, higher UFR showed a consistent association with increased risk for mortality in both patients who initially started less-frequent HD and those who switched to less-frequent HD. In addition, less-frequent HD patients with increased IDWG and higher UFRs (≥10 mL/h/kg) may represent a special population, such as those getting hospice or palliative care, and thereby results may be subject to selection bias. However, all patients with higher UFRs switched to thrice-weekly HD after less-frequent HD. Moreover, the median time to death after starting less-frequent HD among higher UFR groups did not differ compared with lower UFR groups (367 vs 375 days, respectively; P = 0.6).

In summary, higher UFR is associated with greater all-cause and CV mortality among patients receiving HD regular treatments at a frequency of twice or less per week, especially those without substantial RKF. Additionally, higher UFR is associated with a rapid decline in RKF among those patients. Future trials are needed to determine whether there is a causal relationship between UFR and patient outcomes among patients receiving less-frequent HD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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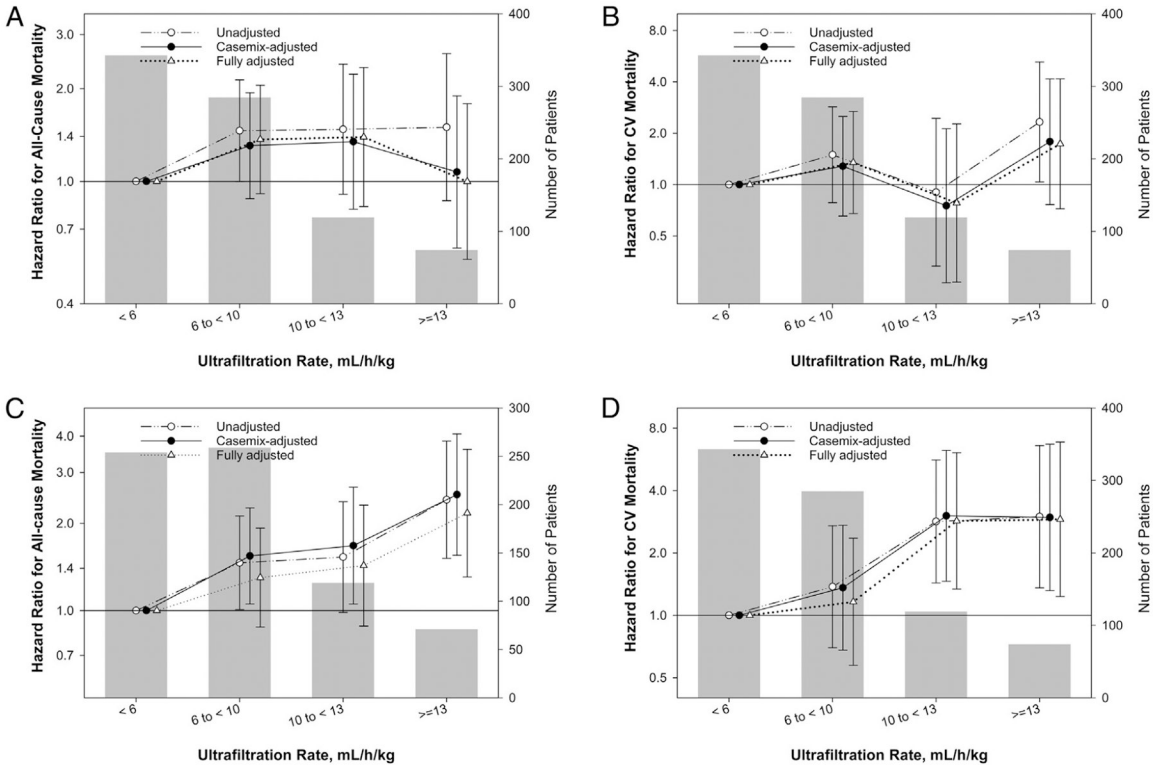

Figure 1.

Ultrafiltration rate and case-mix– and fully adjusted hazard ratios (95% confidence intervals) for all-cause and cardiovascular (CV) mortality stratified by baseline renal urea clearance (A, B) ≥ 5 mL/min/1.73 m^2 and (C, D) <5 mL/min/1.73 m^2 among 1,524 less-frequent hemodialysis patients. Gray bars on figures refer to number of patients in each group.

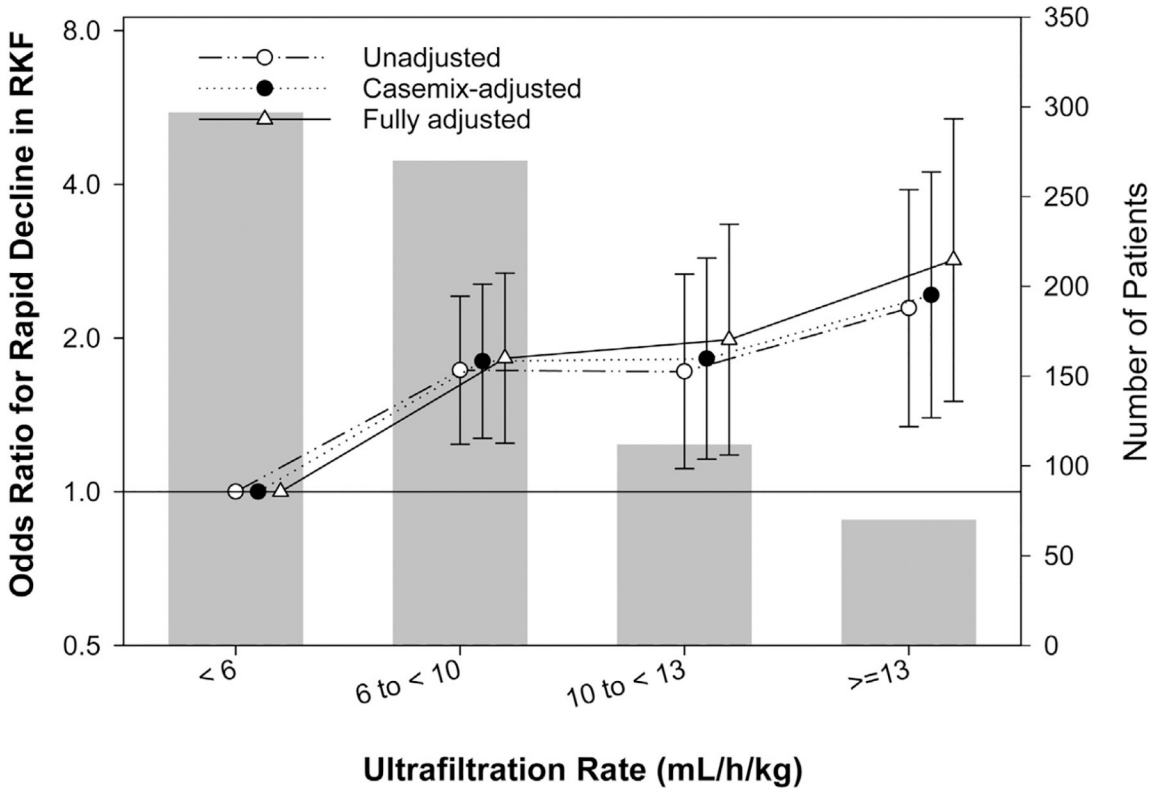

Figure 2.

Ultrafiltration rate and odds ratio for a rapid decline in residual kidney function (RKF) after 1 year using logistic regression model with adjustment for case-mix variables, baseline renal urea clearance (KRU), change in intradialytic systolic blood pressure, normalized protein catabolic rate, and interval between KRU measurements among 749 less-frequent hemodialysis patients. Gray bars on figures refer to number of patients in each group.

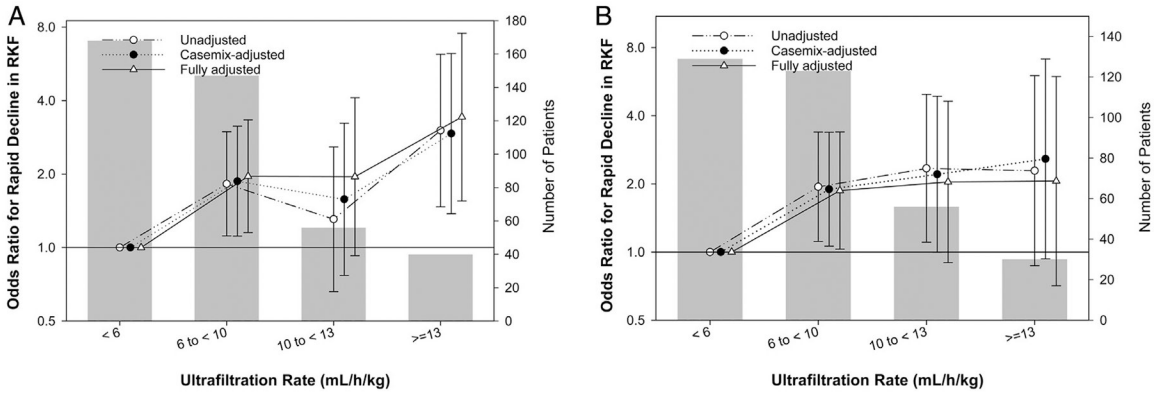

Figure 3.

Ultrafiltration rate and odds ratio for a rapid decline in residual kidney function (RKF) after 1 year stratified by baseline renal urea clearance (KRU) of (A) ≥5 mL/min/1.73 m^2 (n = 411) and (B) <5 mL/min/1.73 m^2 (n = 338) using logistic regression model with adjustment for case-mix variables, baseline renal urea clearance (KRU), change in intradialytic systolic blood pressure, normalized protein catabolic rate, and interval between KRU measurements. Gray bars on figures refer to number of patients in each group.

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Table 1.

Baseline Characteristics of 1,524 Less-Frequent Hemodialysis Patients Stratified by Baseline Ultrafiltration Rate

		Ultrafiltration Rate, mL/h/kg				
Variables	**All Patients**	**<6**	**6-<10**	**10-<13**	**≥13**	***P***
No. of patients	1,524	597 (39%)	544 (35%)	238 (16%)	145 (10%)	
Age, y	67 ± 14	66 ± 14	67 ± 14	67 ± 14	68 ± 15	0.2
Male sex	846 (56%)	303 (51%)	312 (57%)	141 (59%)	90 (62%)	0.003
Race						
White	1,074 (70%)	445 (75%)	374 (69%)	155 (65%)	100 (69%)	0.02
African American	191 (13%)	69 (12%)	75 (14%)	27 (11%)	20 (14%)	0.6
Others	259 (17%)	83 (14%)	95 (17%)	56 (24%)	25 (17%)	0.01
Insurance						
Medicare	860 (56%)	326 (55%)	319 (59%)	139 (58%)	76 (52%)	0.9
Medicaid	72 (5%)	32 (5%)	25 (5%)	6 (3%)	9 (6%)	0.6
Others	592 (39%)	239 (40%)	200 (37%)	93 (39%)	60 (41%)	0.9
Comorbid conditions						
Diabetes	865 (57%)	290 (49%)	332 (61%)	152 (64%)	91 (63%)	<0.001
Hypertension	787 (52%)	306 (51%)	282 (52%)	123 (52%)	76 (52%)	0.8
CHF	528 (35%)	156 (26%)	219 (40%)	88 (37%)	65 (45%)	<0.001
CVD	398 (25%)	157 (24%)	137 (25%)	56 (27%)	48 (26%)	0.4
Vascular access						
AVF	533 (35%)	225 (38%)	177 (33%)	87 (37%)	44 (30%)	0.1
AVG	140 (9%)	47 (8%)	56 (10%)	22 (9%)	15 (10%)	0.3
CVC	788 (52%)	298 (50%)	289 (53%)	120 (50%)	81 (56%)	0.3
Others	63 (4%)	27 (5%)	22 (4%)	9 (4%)	5 (3%)	0.5
Dialysis vintage, d	119 [28–294]	126 [28–364]	119 [28–273]	126 [35–364]	105 [21–217]	0.4
BMI, kg/m^2	25.8 [22.7–30.1]	26.1 [22.8–30.5]	26.7 [23.4–30.8]	25.1 [22.0–29.3]	23.8 [21.3–27.0]	<0.001
KRU, mL/min/1.73 m^2	5.3 [3.2–7.9]	5.6 [3.5–7.8]	5.1 [3.1–7.8]	5.0 [3.0–8.2]	5.0 [3.0–7.6]	0.04
Urine volume, L	1.2 [0.8–1.8]	1.4 [1.0–2.0]	1.2 [0.7–1.8]	1.1 [0.6–1.6]	0.9 [0.6–1.5]	<0.001

Variables	All Patients	Ultrafiltration Rate, mL/h/kg				*P*
		<6	6-<10	10-<13	≥13	
Ultrafiltration, L	1.6 [0.9–2.4]	0.7 [0.4–1.1]	1.9 [1.5–2.4]	2.4 [2.0–3.0]	3.1 [2.5–3.4]	<0.001
Dialysis time, min/session	183 [175–210]	183 [173–210]	185 [178–211]	184 [176–207]	181 [170–186]	0.02
Weekly cumulative IDWG, %	3.2 [1.8–4.9]	1.5 [0.8–2.4]	3.8 [2.7–4.7]	5.2 [4.0–6.3]	6.7 [5.5–8.0]	<0.001
UFR, mL/h/kg	7.3 ± 4.8	2.9 ± 2.6	7.9 ± 1.1	11.3 ± 0.8	16.2 ± 4.7	<0.001
IDH	819 (53.7%)	310 (51.9%)	302 (55.5%)	121 (50.8%)	86 (59.3%)	0.3
Single-pool Kt/V	1.34 ± 0.33	1.32 ± 0.30	1.34 ± 0.36	1.37 ± 0.32	1.35 ± 0.32	0.1
Laboratory variables						
WBC, $\times 10^3/\mu L$	7 [6–8]	7 [6–8]	7 [6–9]	7 [6–8]	7 [6–9]	0.3
Hemoglobin, g/dL	11.6 ± 1.1	11.7 ± 1.1	11.7 ± 1.0	11.6 ± 1.2	11.4 ± 1.2	0.004
Albumin, g/dL	3.8 ± 0.4	3.9 ± 0.4	3.8 ± 0.4	3.8 ± 0.4	3.7 ± 0.4	<0.001
Phosphorus, mg/dL	4.7 ± 1.1	4.6 ± 1.0	4.8 ± 1.1	4.8 ± 1.2	5.0 ± 1.3	0.001
nPCR, g/kg/d	1.0 [0.8–1.2]	1.0 [0.8–1.2]	1.0 [0.8–1.2]	1.1 [0.9–1.2]	1.1 [0.9–1.2]	0.001

Note: Values for categorical variables are shown as percentages; values for continuous variables, as mean ± standard deviation or median [interquartile range]. Conversion factor for phosphorus in mg/dL to mmol/L, ×0.323.

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; CHF, congestive heart failure; CVC, central venous catheter; CVD, cardiovascular disease; IDH, intradialytic hypotension; IDWG, interdialytic weight gain; KRU, renal urea clearance; nPCR, normalized protein catabolic rate; UFR, ultrafiltration rate; WBC, white blood cells.

Table 2.

Unadjusted and Adjusted HRs for All-Cause and Cardiovascular Mortality

	HR (95% CI) for All-Cause Mortality			HR (95% CI) for Cardiovascular Mortality		
UFR	**Unadjusted**	**Case-Mix-Adjusted**	**Fully Adjusted**	**Unadjusted**	**Case-Mix-Adjusted**	**Fully Adjusted**
<6 mL/h/kg	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
6-<10 mL/h/kg	1.48 (1.14–1.93)	1.43 (1.09–1.88)	1.33 (1.01–1.75)	1.46 (0.91–2.32)	1.33 (0.83–2.15)	1.23 (0.76–2.00)
10-<13 mL/h/kg	1.54 (1.12–2.13)	1.51 (1.08–2.10)	1.37 (0.98–1.92)	2.02 (1.19–3.43)	1.87 (1.08–3.21)	1.74 (1.00–3.03)
≥13 mL/h/kg	1.98 (1.39–2.82)	1.76 (1.23–2.53)	1.55 (1.07–2.24)	2.69 (1.53–4.72)	2.23 (1.26–3.97)	2.08 (1.15–3.78)

Note: Case-mix–adjusted model included age, sex, race (white, African American, or others), primary insurance (Medicare, Medicaid, or others), comorbid conditions (diabetes, hypertension, congestive heart failure, and cardiovascular disease), vascular access (arteriovenous fistula, arteriovenous graft, central venous catheter, or others), and dialysis vintage (from transition to dialysis until the start of less-frequent hemodialysis). Fully adjusted model included all covariates in the case-mix–adjusted model plus baseline residual kidney function, body mass index, white blood cell count, hemoglobin level, serum albumin level, phosphorus level, single-pool Kt/V_{urea}, and normalized protein catabolic rate.

Abbreviations: CI, confidence interval; HR, hazard ratio; UFR, ultrafiltration rate.

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Table 3.

Estimated 1-Year KRU Slope According to Baseline UFR Categories

	Decline in Urea Clearance, mL/min/1.73 m^2/y
UFR	
<6 mL/h/kg	−1.70 [−1.92 to −1.30]
6-<10 mL/h/kg	−1.80 [−2.04 to −1.51]
10-<13 mL/h/kg	−1.82 [−2.06 to −1.31]
≥13 mL/h/kg	−1.91 [−2.13 to −1.43]
Total	−1.76 [−2.02 to −1.40]

Note: n = 749. Values are given as median [interquartile range]. *P* for trend < 0.001. Abbreviations: KRU, renal urea clearance; UFR, ultrafiltration rate.