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Impact of residual kidney function on hemodialysis adequacy and patient survival

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ABSTRACT

Background. Both dialysis dose and residual kidney function (RKF) contribute to solute clearance and are associated with outcomes in hemodialysis patients. We hypothesized that the association between dialysis dose and mortality is attenuated with greater RKF.

Methods. Among 32 251 incident hemodialysis patients in a large US dialysis organization (2007–11), we examined the interaction between single-pool *Kt*/*V* (sp*Kt*/*V*) and renal urea clearance (rCL_{urea}) levels in survival analyses using multivariable Cox proportional hazards regression model.

Results. The median rCL_{urea} and mean baseline sp*Kt*/*V* were 3.06 [interquartile range (IQR) 1.74–4.85] mL/min/1.73 m^2 and 1.32 ± 0.28, respectively. A total of 7444 (23%) patients died during the median follow-up of 1.2 years (IQR 0.5–2.2 years) with an incidence of 15.4 deaths per 100 patient-years. The Cox model with adjustment for case-mix and laboratory variables showed that rCL_{urea} modified the association between sp*Kt*/*V* and mortality ($P_{interaction}$ = 0.03); lower sp*Kt*/*V* was associated with higher mortality among patients with low rCL_{urea} (i.e. <3 mL/min/1.73 m^2) but not among those with higher rCL_{urea}. The adjusted mortality hazard ratios (aHRs) and 95% confidence intervals of the low (<1.2) versus high (≥1.2) sp*Kt*/*V* were 1.40 (1.12–1.74), 1.21 (1.10–1.33), 1.06 (0.98–1.14), and 1.00 (0.93–1.08) for patients with rCL_{urea} of 0.0, 1.0, 3.0 and 6.0 mL/min/1.73 m^2, respectively.

Conclusions. Incident hemodialysis patients with substantial RKF do not exhibit the expected better survival at higher hemodialysis doses. RKF levels should be taken into account when deciding on the dose of dialysis treatment among incident hemodialysis patients.

Keywords: dialysis adequacy, dialysis dose, hemodialysis, residual kidney function, single-pool *Kt*/*V*

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Single-pool Kt/V_{urea} (sp*Kt*/*V*, the clearance of urea multiplied by dialysis duration and normalized for urea distribution volume) or the urea reduction ratio (URR) is widely used for evaluating dialysis adequacy among patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis. Dialysis dose as expressed in Kt/V_{urea} or URR has been suggested as an important predictor of morbidity and mortality in hemodialysis patients [1–6]. Currently sp*Kt*/*V* is the most frequently applied measure of delivered dialysis dose, where the recommended minimum level is set to 1.2 of sp*Kt*/*V* (equivalent to a URR of 65%) for thrice-weekly hemodialysis patients with little or no residual kidney function (RKF), according to the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) clinical practice guidelines [7].

RKF in ESRD patients may alter the dialysis dose–survival association, and the NKF-KDOQI guidelines in fact suggest that dialysis dose may be reduced for patients with substantial RKF provided that renal urea clearance is periodically measured [7]. Although many studies of peritoneal dialysis patients have shown that the association with better survival is found for greater RKF but not for higher delivered *Kt*/*V* [8–10], evidence for the optimal dialysis dose, either expressed in sp*Kt*/*V* or URR, is still scarce among hemodialysis patients with RKF. This issue is increasing

its importance given that approximately 40% of ESRD patients have an estimated glomerular filtration rate $\geq$10 mL/min/1.73 m^2 at dialysis initiation [11] and given that the rates of RKF decline in hemodialysis patients may be similar to peritoneal dialysis patients under the current standard treatment with biocompatible membranes and bicarbonate buffer [12–14].

Although sp*Kt*/*V* remains a useful and common metric of dialysis adequacy [15] as employed in the ESRD Quality Incentive Program in the USA, the 2015 update in the KDOQI guidelines for hemodialysis adequacy did not make specific recommendations or suggestions on how to reduce the hemodialysis dose according to RKF levels because of lack of evidence [7]. Therefore we investigated the influence of RKF on the association between dialysis dose and mortality in a cohort of incident hemodialysis patients from a large dialysis organization in the USA. We hypothesized that in patients starting hemodialysis therapy with significant RKF, there is little to no association between dialysis dose and survival and that these patients would require lower initial dialysis doses than anuric patients.

MATERIALS AND METHODS

Patients

We retrospectively extracted, refined and examined data from all incident hemodialysis patients who initiated treatment between 2007 and 2011 in facilities operated by a large dialysis organization in the USA. Patients were considered to be on maintenance hemodialysis if they were treated for at least 60 consecutive days and were followed through 31 December 2011. Among 142 419 incident ESRD patients who were treated only by in-center thrice-weekly hemodialysis during the follow-up, we excluded 33 849 patients who died in the first 90 days of dialysis, 9958 who had missing data on baseline (i.e. the first quarter or 91 days of dialysis) variables of body mass index (BMI), hemoglobin, albumin, creatinine, calcium, phosphorus, parathyroid hormone (PTH), iron saturation, ferritin and carbon dioxide, 2470 who had missing data on baseline sp*Kt*/*V*, and 63 891 who had missing baseline data on URR or residual renal urea clearance (rCL_{urea}) (Supplementary data, Figure S1). Our final study population consisted of 32 251 incident hemodialysis patients. The parent study was approved by the University of California Irvine Medical Center and University of Washington. Given the large sample size, anonymity of the patients studied and nonintrusive nature of the research, the requirement for written consent was waived.

Demographic, clinical and laboratory measures

Information on all-cause death, race/ethnicity, primary insurance, vascular access type, comorbidities and laboratory variables were obtained from the electronic database of the dialysis provider. To minimize measurement variability, averaged values of laboratory variables during the first patient-quarter (or the first 91 days of dialysis) within each patient served as baseline data and were used in all models.

Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to the central laboratory in Deland, Florida, USA, typically within 24 h. All laboratory values were measured by automated and standardized methods. Most blood 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 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.

Residual rCL_{urea} was used as the index of RKF in all analyses. The average serum urea concentrations during urine collection were assumed to be 90% of the predialysis concentrations according to the Daugirdas approach [16] and thus rCL_{urea} was calculated as follows:

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

where serum urea nitrogen was obtained on the closest day within $\pm$28 days of urine collection. Urine collected time was reported as 1440 min in 98% of measurements, ranging from 720 to 2880 min. rCL_{urea} was then adjusted for body surface area and expressed as mL/min/1.73 m^2 [17, 18]. Normalized protein catabolic rate (nPCR) was calculated with accounting for rCL_{urea} [19].

Sp*Kt*/*V* or URR was used as the index of hemodialysis adequacy. We used the second-generation logarithmic estimates of sp*Kt*/*V* [20, 21]:

$$\mathrm{SpKt/V} = -\ln\left(R - \frac{0.0174}{PIDI} \times \frac{t}{60}\right) + \frac{(4 - 3.5 \times R) \times 0.55 \times UF}{V},$$

where *R* is the ratio of the pre- and posthemodialysis concentrations of serum urea, *PIDI* is the length of the preceding interdialysis interval (days), *t* is the duration of hemodialysis treatment time (minutes), *UF* is the amount of ultrafiltration (L) during the given hemodialysis session and *V* is the estimated urea distribution volume.

Statistical analyses

Patients were categorized into two groups according to baseline rCL_{urea} strata ($<$3.0 or $\geq$3.0 mL/min/1.73 m^2). The cutoff value of 3.0 mL/min/1.73 m^2 was selected based on the definition of 'substantial RKF' in previous studies and guidelines [22, 23]. Differences in baseline characteristics between included versus excluded patients and between two rCL_{urea} strata were compared by standardized differences due to the large sample size of this study [24, 25]. Since the missing frequency was high in rCL_{urea}, we used inverse probability weighting to mitigate selection bias in our observational study [26]. In short, the probability of having data on rCL_{urea} were calculated among patients with data on all covariates except for rCL_{urea} and nPCR that accounted for rCL_{urea} by a logistic regression model and patients were weighted based on their inverse probabilities. Sp*Kt*/*V* and URR were treated as categorical variables in the primary analyses and their association with all-cause mortality was examined by inverse probability-weighted Cox proportional hazards models.

As the sensitivity analyses, we also examined potential nonlinear relationships by using restricted cubic spline functions with four knots at the 5th, 35th, 65th and 95th percentiles of each index and the reference sp*Kt*/*V* and URR were 1.4 and 0.65, respectively.

For each analysis we employed hierarchical adjustment with four models as follows:

1. Model 1 included baseline sp*Kt*/*V* or URR.
2. Model 2 included the above variables plus case-mix variables including age, sex, race/ethnicity, primary insurance, central venous catheter use, hypertension, diabetes, history of cardiovascular disease (i.e. congestive heart failure, atherosclerotic heart disease, cerebrovascular disease or other cardiovascular disease) and rCL_{urea}.
3. Model 3 included the above variables plus BMI, nPCR, hemoglobin, serum albumin, creatinine, calcium, iron saturation, total bicarbonate and ferritin.
4. Model 4 included the above variables plus serum phosphorus and natural log-transformed intact PTH.

We defined Model 3 as the primary model because serum phosphorus and intact PTH may be located in the pathways between sp*Kt*/*V* and mortality (i.e. intermediates) [27–30]. We also did not include volume parameters such as interdialytic weight gain and ultrafiltration rate in the adjustment models since these factors are considered intermediates. Effect modification of the association between sp*Kt*/*V* or URR and mortality were evaluated by adding a product term between continuous sp*Kt*/*V* and each of *a priori*–defined variables, including baseline age (≥65 or <65 years), gender, race (white or nonwhite), diabetes, presence of congestive heart failure, serum albumin (≥3.6 or <3.6 g/dL) and BMI (≥30 or <30) into Model 3 and by conducting the subgroup analyses in each rCL_{urea} category. Additionally we evaluated the change in the mortality risk associated with low sp*Kt*/*V* (<1.2 versus ≥1.2) over rCL_{urea} levels by including restricted cubic spline functions for rCL_{urea} and their interactions with low sp*Kt*/*V* in Model 3.

The frequency of missing data was 6% for nPCR, and multiple imputation methods with five data sets were used in all regression analyses. Analyses were conducted using STATA MP version 13.1 (StataCorp, College Station, TX, USA).

RESULTS

Baseline characteristics

The cohort included 32 251 incident hemodialysis patients in whom the mean ± SD age was 62 ± 15 years, of which 63% were male, 54% were Caucasian, 28% were African American and 59% were diabetic. Mean baseline sp*Kt*/*V* and URR were 1.32 ± 0.28 and 0.66 ± 0.07, respectively. The median rCL_{urea} was 3.06 [interquartile range (IQR) 1.74–4.85] mL/min/1.73 m^2 and the prevalence of patients with low (<3.0 mL/min/1.73 m^2) and high (≥3.0 mL/min/1.73 m^2) rCL_{urea} levels were 49 and 51%, respectively. Patients with greater rCL_{urea} tended to be male; had lower levels of sp*Kt*/*V*, URR, serum creatinine and phosphorus and had higher levels of nPCR and hemoglobin (Table 1). A total of 7444 (23%) patients died during the median follow-up of 1.2 years (IQR 0.5–2.2) with an incidence of 15.4 deaths per 100 patient-years. Compared with 76 319 excluded patients, 32 251 included patients were more likely to be male, Caucasian and had lower sp*Kt*/*V* and URR levels (standardized difference >0.2; Supplementary data, Table S1). After weighting patients by inverse probability of having data on rCL_{urea} and nPCR, those variables were well balanced between those with versus without rCL_{urea} (Supplementary data, Table S2).

Association of sp*Kt*/*V* and all-cause mortality according to rCL_{urea} strata

There was a trend toward higher mortality risk across higher sp*Kt*/*V* levels in the unadjusted model (i.e. Model 1) in high rCL_{urea} category ($P_{trend} = 0.8$ and <0.001 for the low and high rCL_{urea}, respectively; Figure 1). However, the association between sp*Kt*/*V* and all-cause mortality was significantly modified by rCL_{urea} levels after adjustment for case-mix variables and laboratory variables ($P_{interaction} = 0.01$ and 0.03 for Models 2 and 3, respectively). In Model 3 there was a significant trend toward higher mortality across lower sp*Kt*/*V* categories among patients with low rCL_{urea} ($P_{trend} < 0.001$) but not among those with high rCL_{urea} ($P_{trend} = 0.4$), and the adjusted hazard ratio (aHR) for mortality of the lowest (<1.0) versus the middle (1.2–1.4) sp*Kt*/*V* quintile group was 1.17 [95% confidence interval (CI) 1.00–1.38] and 1.08 (95% CI 0.95–1.23) for patients with low versus high rCL_{urea}, respectively.

We then evaluated the mortality risk associated with low sp*Kt*/*V* (<1.2 versus ≥1.2) over rCL_{urea} levels using spline functions for rCL_{urea} and their interactions with low sp*Kt*/*V* (Figure 2). The risk associated with low sp*Kt*/*V* was higher with lower rCL_{urea}, showing an increased mortality risk in the range of rCL_{urea} <3.0 mL/min/1.73 m^2 with aHRs of 1.21 (95% CI 1.10–1.33) and 1.11 (95% CI 1.04–1.20) at rCL_{urea} of 1.0 and 2.0 mL/min/1.73 m^2, respectively. Meanwhile, low sp*Kt*/*V* was not associated with mortality in greater rCL_{urea} levels with aHRs of 1.06 (95% CI 0.98–1.14) and 1.00 (95% CI 0.93–1.08) at rCL_{urea} of 3.0 and 6.0 mL/min/1.73 m^2, respectively. Consistent associations were observed in Models 2, 3 and 4 (Supplementary date, Figure S2).

In Model 4, which included serum phosphorus and natural intact PTH on top of the variables in Model 3, the modification of the association between sp*Kt*/*V* and mortality by rCL_{urea} was attenuated ($P_{interaction} = 0.06$), which may be due to overadjustment because phosphorus and intact PTH may be at least partly intermediates between sp*Kt*/*V* and mortality.

Subgroup analysis of the association between sp*Kt*/*V* and all-cause mortality according to rCL_{urea} strata

Subgroup analysis of the associations of low (<1.2) and high (≥1.4) sp*Kt*/*V* with mortality were examined in Model 3 (reference 1.2–<1.4). Consistent with the findings above, a significant trend was observed between lower sp*Kt*/*V* categories and higher mortality among patients with low rCL_{urea} ($P_{trend} < 0.001$) but not among those with high rCL_{urea} ($P_{trend} = 0.4$; Figure 3). Among patients with low rCL_{urea}, the

Table 1. Baseline characteristics of 32 251 incident hemodialysis patients stratified by baseline residual rCL_{urea}

Characteristics	Total	rCL_{urea} (mL/min/1.73 m^2)		Standardized difference
		<3.0	≥3.0	
	(n = 32 251)	(n = 15 786)	(n = 16 465)	
CL_{urea} (mL/min/1.73 m^2), median (IQR)	3.06 (1.74–4.85)	1.72 (1.05–2.35)	4.80 (3.80–6.40)	2.03
Urine volume (mL/24 h), median (IQR)	800 (490–1300)	500 (300–700)	1200 (850–1675)	1.74
Age (years), mean ± SD	61.9 ± 14.8	62.3 ± 15.3	61.5 ± 14.3	−0.05
Male, %	63	57	69	0.25
Race, %				
White	54	51	58	0.14
Black	28	31	24	−0.16
Hispanic	11	11	11	−0.02
Asian and others	7	7	8	0.04
Primary insurance, %				
Medicare	51	53	50	−0.06
Medicaid	6	7	6	−0.04
Others	42	40	44	0.08
Vascular access, %				
Central venous catheter	74	77	70	−0.16
AV fistula/graft	22	18	26	0.18
Unknown	4	4	4	0.00
Comorbidities, %				
Diabetes	59	58	61	0.07
Hypertension	51	53	49	−0.08
Congestive heart failure	39	40	38	−0.04
Atherosclerotic heart disease	14	14	14	0.01
Cerebrovascular	2	2	1	−0.02
Other cardiovascular disease	15	16	15	−0.01
Dyslipidemia	26	26	27	0.03
Infection	81	82	81	−0.01
Malignancy	3	3	2	−0.01
spKt/V, mean ± SD	1.32 ± 0.28	1.37 ± 0.28	1.28 ± 0.27	−0.31
Urea reduction ratio (%), mean ± SD	66 ± 7	67 ± 7	65 ± 7	−0.29
Body mass index (kg/m^2), median (IQR)	27.4 (23.6–32.6)	27.3 (23.5–32.7)	27.5 (23.8–32.6)	0.03
Weekday IDWG (kg), median (IQR)	1.7 (1.2–2.4)	1.8 (1.2–2.4)	1.7 (1.1–2.4)	−0.11
Weekend IDWG (kg), median (IQR)	2.4 (1.6–3.3)	2.5 (1.7–3.4)	2.2 (1.5–3.1)	−0.20
Ultrafiltration rate (L/h), mean ± SD	0.59 ± 0.24	0.61 ± 0.23	0.57 ± 0.25	−0.13
nPCR (g/kg/day), mean ± SD	0.98 ± 0.28	0.90 ± 0.25	1.06 ± 0.29	0.58
ESRD reason, %				
Diabetes	47	45	49	0.10
Hypertension	28	31	26	−0.10
Glomerulonephritis	10	10	10	0.00
Cystic kidney disease	2	2	2	0.05
Other	13	13	12	−0.03
Laboratory variables				
Hemoglobin (g/dL), mean ± SD	11.3 ± 1.1	11.1 ± 1.1	11.4 ± 1.1	0.20
Albumin (g/dL), mean ± SD	3.57 ± 0.46	3.54 ± 0.46	3.60 ± 0.45	0.14
Creatinine (mg/dL), mean ± SD	5.9 ± 2.3	6.5 ± 2.6	5.3 ± 1.9	−0.55
Corrected calcium (mg/dL), mean ± SD	9.1 ± 0.5	9.1 ± 0.6	9.1 ± 0.5	0.00
Phosphorus (mg/dL), mean ± SD	5.0 ± 1.1	5.2 ± 1.2	4.8 ± 1.0	−0.28
Intact PTH (pg/mL), median (IQR)	315 (203–478)	332 (213–514)	300 (194–446)	−0.17
Iron saturation (%), mean ± SD	23 ± 8	23 ± 8	23 ± 8	−0.01
Ferritin (ng/mL), median (IQR)	268 (156–448)	281 (165–472)	255 (148–427)	−0.13
Bicarbonate (mEq/L), mean ± SD	23.4 ± 2.6	23.6 ± 2.6	23.2 ± 2.6	−0.15

Conversion factors for units: albumin and hemoglobin in g/dL to g/L, 10; creatinine in mg/dL to mmol/L, 88.4; calcium in mg/dL to mmol/L, 0.2495; phosphorus in mg/dL to mmol/L, 0.3229. No conversion is necessary for ferritin in ng/mL and mg/L. IDWG, interdialytic weight gain.

association between spKt/V and mortality was not modified by baseline age, gender, race, diabetes, presence of congestive heart failure, serum albumin and BMI ($P_{interaction} > 0.05$ for all; Figure 3A). However, among patients with high rCL_{urea} levels, the association between spKt/V and mortality was modified by gender ($P_{interaction} = 0.01$) where low spKt/V was associated with higher mortality risk in female ($P_{trend} = 0.01$) but not in male patients ($P_{trend} = 0.4$; Figure 3B).

Sensitivity analysis using URR

The associations of URR with mortality in Models 1–4 were consistent with those of spKt/V. The Model 3 aHRs of the lowest (<0.60) and highest (≥0.75) URR, when compared with the

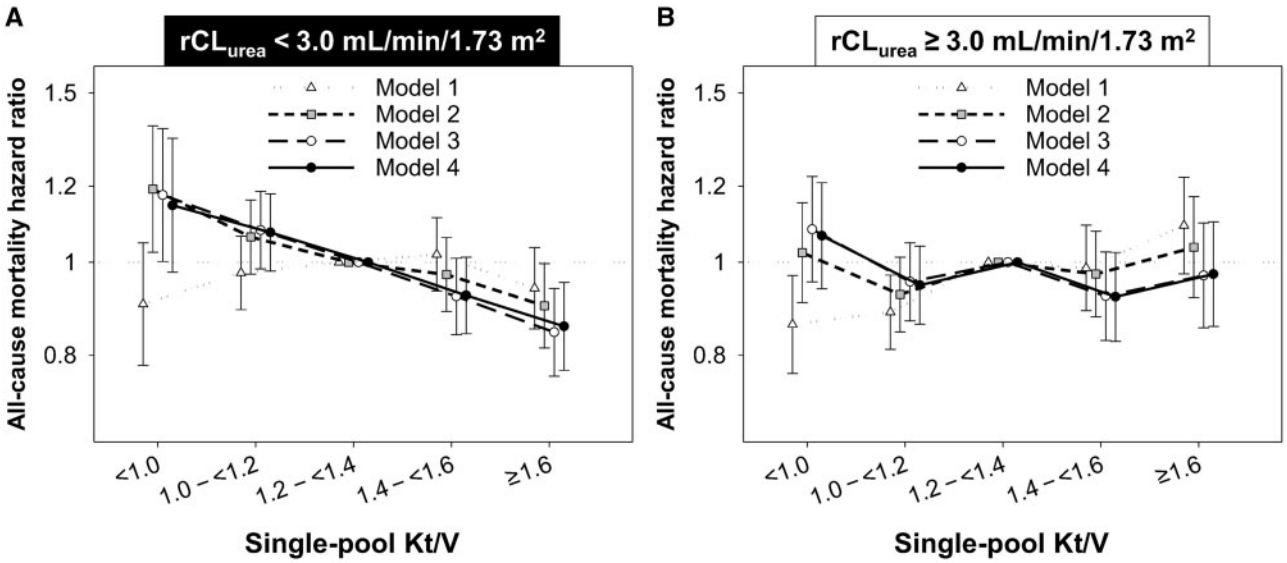

FIGURE 1: Association of baseline sp*Kt*/*V* with all-cause mortality in 32 251 incident hemodialysis patients with baseline rCL$_{urea}$ of (**A**) <3.0 mL/min/1.73 m^2 and (**B**) ≥3.0 mL/min/1.73 m^2 in four adjusted models.

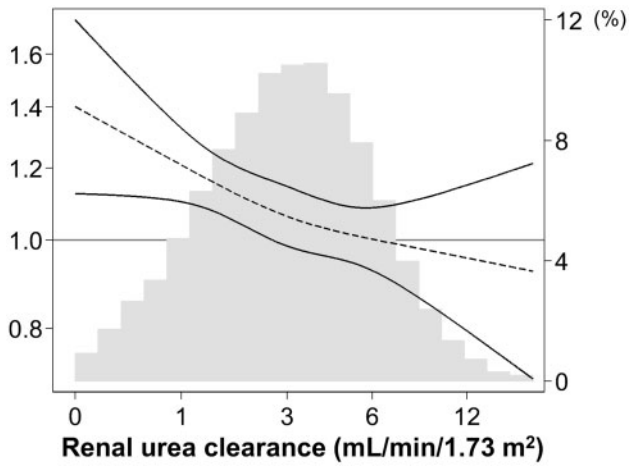

FIGURE 2: The change in the mortality risk associated with low sp*Kt*/*V* (<1.2 versus ≥1.2) over rCL$_{urea}$ levels in 32 251 incident hemodialysis patients.

middle URR (0.65–0.70), were 1.20 (95% CI 1.07–1.35) and 0.86 (95% CI 0.77–0.97), respectively, for patients with low rCL$_{urea}$ (P_{trend}<0.001) and 1.09 (95% CI 0.98–1.22) and 0.95 (95% CI 0.82–1.09), respectively, for patients with high rCL$_{urea}$ (P_{trend}=0.1; Figure 4). Models using spline functions yielded consistent results (Supplementary data, Figure S3).

In subgroup analysis using three URR categories (<0.65, 0.65–<0.70 and ≥0.70), the mortality risk of low URR was further pronounced among patients with low rCL$_{urea}$ whereas the association between low URR and higher mortality was attenuated if serum albumin level was low ($P_{interaction}$ = 0.03) (Figure 5A). Similar to the results based on sp*Kt*/*V*, among patients with high rCL$_{urea}$, there was a significant trend toward lower mortality across higher URR categories when patients were female (P_{trend} = 0.002) but not when patients were male (P_{trend} = 0.5, $P_{interaction}$ = 0.01; Figure 5B).

DISCUSSION

In the present study, the association of a higher sp*Kt*/*V* (or URR) with better survival was observed among patients with low RKF (rCL$_{urea}$ <3.0 mL/min/1.73 m^2) but was attenuated among those with substantial RKF (rCL$_{urea}$ ≥3.0 mL/min/1.73 m^2). The 2006 updates on the KDOQI clinical practice guidelines underscored that the cutoff value of 1.2 for minimum sp*Kt*/*V* can be applied to patients with little or no RKF since it was derived from studies excluding patients with RKF or those assuming no RKF among participants [23, 31, 32]. Our results were consistent with these previous studies in terms of the dialysis dose–mortality association among patients with low rCL$_{urea}$ [28, 33–35]. The 2006 KDOQI guidelines also suggest that the minimum sp*Kt*/*V* can be reduced for patients with substantial RKF based on the urea kinetic model indicating that rCL$_{urea}$ of 2.0 mL/min/1.73 m^2 corresponds to ∼0.67 weekly *Kt*/*V* [23], but there has been little evidence supporting this kinetic model–derived hypothesis. A recent study by Swaminathan *et al.* [36] indicated that ≥4 h of dialysis treatment (versus 3 h) is associated with a lower mortality risk among incident hemodialysis patients. Because dialysis dose increases with longer treatment time, these study results may seem to conflict with ours; however, our study differs by our evaluation of effect modification by RKF.

Our finding that the association of dialysis dose with mortality is strongly dependent on RKF levels is consistent with the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2 study, where lower dialysis dose was incrementally associated with higher mortality only among anuric patients [37]. Both studies included incident hemodialysis patients, but these discrepant cutoff values in rCL$_{urea}$ (i.e. ≥ 3.0 versus <3.0 mL/min/1.73 m^2 in our study and the presence versus absence of RKF in the NECOSAD-2 study) may result from the difference in analytical methods; the NECOSAD-2 study used a time-varying covariate Cox model

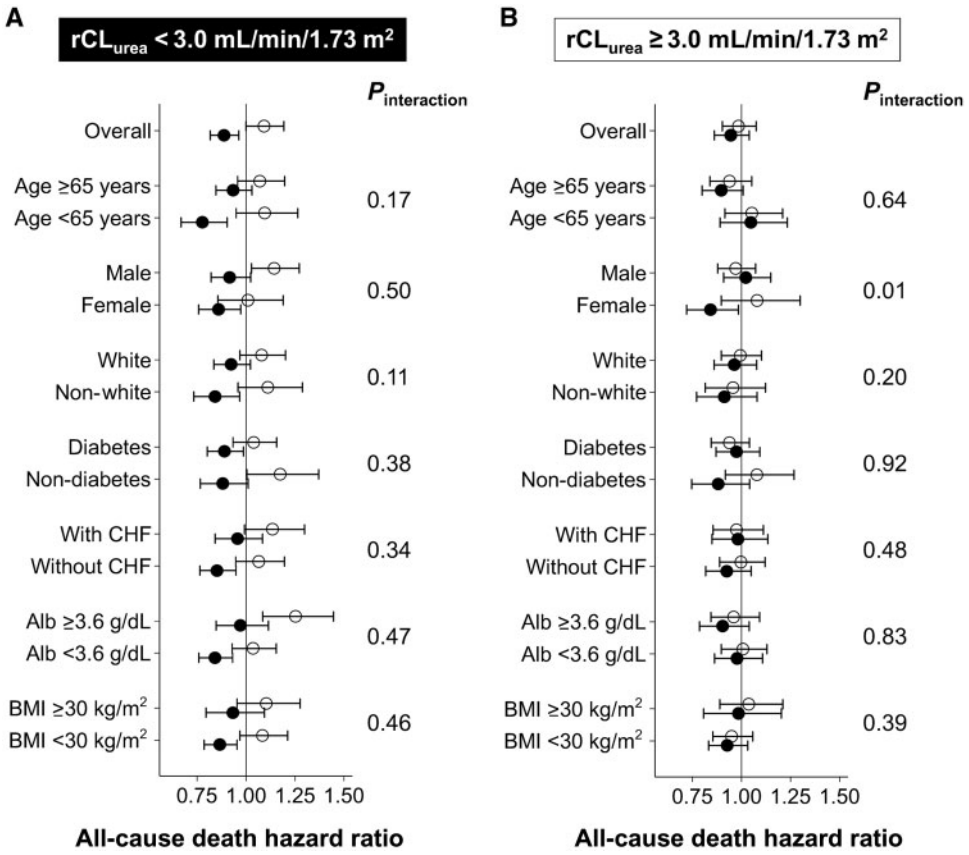

FIGURE 3: Association of baseline URR with all-cause mortality in 32 251 incident hemodialysis patients with baseline rCL$_{urea}$ of (**A**) <3.0 mL/min/1.73 m^2 and (**B**) ≥3.0 mL/min/1.73 m^2 in four adjusted models.

to evaluate short-term associations, while we focused on long-term associations by using a conventional fixed covariate Cox model considering the time frame required for dialysis dose to impact on patient survival.

Given that incident ESRD patients start dialysis at a wide range of RKF levels and that the benefit of greater RKF is substantial even at such small differences as observed in this population, simple dichotomization may not be adequate to untangle the interactions among RKF, dialysis adequacy and survival. The large sample size of this study enabled us to demonstrate that the risk associated with low spKt/V (i.e. <1.2 versus ≥1.2) was linearly attenuated with greater CL$_{urea}$. We also provided specific HRs of low spKt/V for all-cause mortality at different CL$_{urea}$ levels. These detailed data allow us to assess the potential risk associated with low dialysis dose based on the individual RKF level of each patient, which may facilitate tailored dialysis prescriptions in future clinical practice.

Our results are also supported by a recent observational study demonstrating that incident hemodialysis patients on incremental frequency regimens (i.e. starting hemodialysis with a twice-weekly schedule), which is inherently accompanied by reduced dialysis dose, experienced a similar mortality as those with conventional thrice-weekly regimens if patients had substantial RKF [38]. These two studies are complimentary to each other, but the findings of this study can be applicable to a much wider population given that the vast majority of hemodialysis patients in developed countries routinely receive thrice-weekly treatment.

Patients with greater RKF experienced less weekend interdialytic weight gain in this study. Given that an excess of ultrafiltration or intradialytic hypotension in relation to interdialytic weight gain has been associated with higher mortality in both incident and prevalent hemodialysis patients [39–42], more stable intradialytic hemodynamics resulting from less ultrafiltration among patients with greater RKF may partly explain the attenuation in the association between dialysis adequacy and mortality. Additionally, such hemodynamic stability may also preserve more RKF, leading to a positive feedback loop. Other proposed strategies to preserve RKF include avoidance of nephrotoxic agents, a low-protein diet on nondialysis days, the use of ultrapure dialysate and an incremental/infrequent approach to hemodialysis initiation [43].

Higher dialysis dose was consistently associated with lower mortality among women, even if they had substantial RKF. As a urea distribution volume-based scaling of dialysis dose, spKt/V is often overestimated in women, especially in small-size women, due to their relatively less water-rich muscle mass and possibly due to RKF [44–46], whereby women may be underdialyzed under standard spKt/V. Indeed, the Hemodialysis (HEMO) Study suggested that the intensive dialysis dose, compared with the standard dose, reduced mortality and morbidity in women but not in men [27]. A consistent finding was observed among patients with substantial RKF in our study. However, it remains unclear why the interaction between gender and dialysis dose was not observed among patients with little or

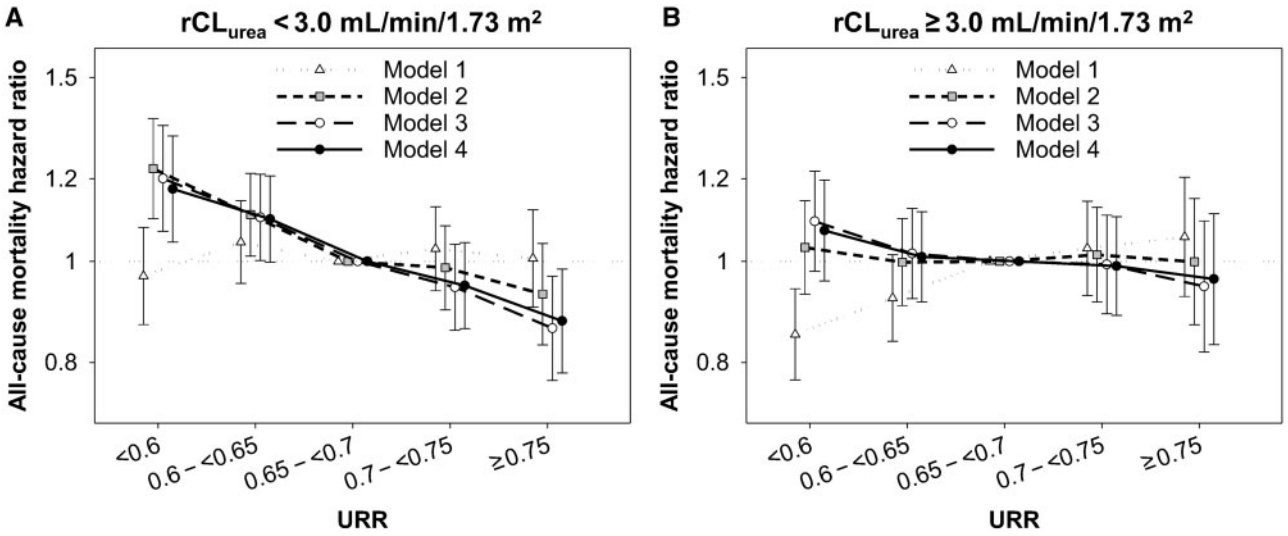

FIGURE 4: Overall and subgroup analysis of association between spKt/V and all-cause mortality in 32 251 incident hemodialysis patients with baseline rCL$_{urea}$ of (**A**) <3.0 mL/min/1.73 m^2 and (**B**) ≥3.0 mL/min/1.73 m^2 in Model 3. Points and bars represent HR estimates and 95% CIs, respectively. Alb, albumin; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus.

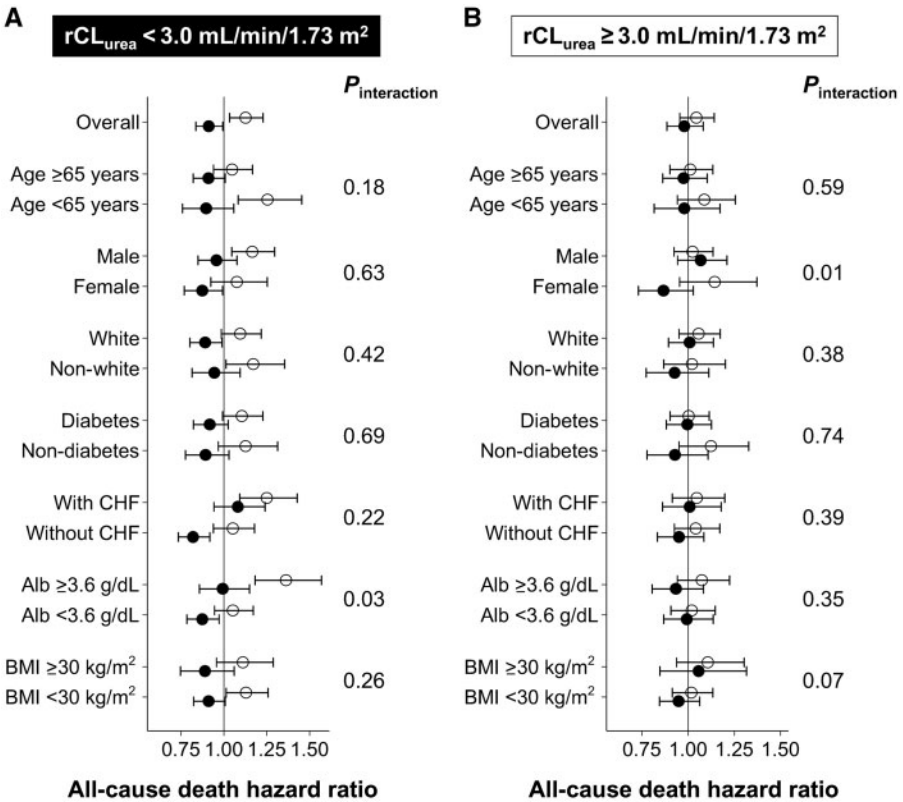

FIGURE 5: Overall and subgroup analysis of association between URR and all-cause mortality in 32 251 incident hemodialysis patients with baseline rCL$_{urea}$ of (**A**) <3.0 mL/min/1.73 m^2 and (**B**) ≥3.0 mL/min/1.73 m^2 in Model 3. Points and bars represent HR estimates and 95% CIs, respectively. Alb, albumin; BMI, body mass index; CHF, congestive heart failure; DM, diabetes mellitus.

no RKF. These results should be considered suggestive due to multiple comparisons and need to be verified in future studies.

Among patients with low rCL$_{urea}$, the association between low URR and greater mortality was attenuated while the association between high URR and lower mortality was pronounced if the patient had low albumin levels. However, these findings were not confirmed by using spKt/V as an index of dialysis dose. Nevertheless, trends of the change in the absolute effect size were similar between URR and spKt/V in either case. A higher threshold of dialysis dose may be necessary for patients with higher serum albumin if they have low or little RKF.

There have been conflicting data among large clinical trials evaluating dialysis dose and frequency. For example, while maintaining lower urea nitrogen concentrations decreased treatment withdrawals and hospitalizations in the National Cooperative Dialysis Study [31], higher dialysis dose did not improve patient survival in the HEMO Study [47]. Additionally, the Frequent Hemodialysis Network reported better survival with daily six-times-per-week in-center hemodialysis [48] and higher mortality with nocturnal six-times-per-week home hemodialysis [29] compared with conventional thrice-weekly in-center hemodialysis. Although the reasons for those inconsistent results remain unclear, it should be noted that clinical trials generally have limited external validity and inadequate statistical power to detect heterogeneity in the treatment effect. The efficacy of higher dialysis adequacy may actually be modified by several factors, including patient body size, dialysis vintage, treatment time, treatment frequency and RKF [7]. Our findings support the potential of RKF as a strong and linear effect modifier, which needs to be examined in further studies. Although, due to the observational nature of this study, we cannot prove causality between dialysis dose and mortality, the currently recommended minimum dialysis dose (i.e. 1.2 in spKt/V) is also based on observational studies and is applicable only in patients with rCL_{urea} <2.0 mL/min/1.73 m^2 [7].

Our study should be qualified for several other limitations. First, there may also be residual confounding or unmeasured confounders such as inadequate predialysis care. Second, spKt/V and URR may have varied over time. We focused on the long-term association of dialysis dose in the early period of dialysis with long-term mortality in this study, and further studies are required to examine the relationships among longitudinal changes in dialysis dose, RKF decline and mortality. Third, RKF may not be accurate given the use of urea clearance, the difficulties in punctual and complete collection of urine samples and the use of factor 0.9 for estimating average predialysis serum urea. Nevertheless, the population-level associations can be estimated from an adequate number of subjects if such errors are not associated with the outcome, and a recent study has shown that the change in rCL_{urea} used in this study was closely related to all-cause mortality [22]. Fourth, medications were not included in the adjustment model. However, in contrast to the peritoneal dialysis population, even renin–angiotensin system inhibitors, the representative renoprotective drug type, do not have any effect on RKF among hemodialysis patients [49]. In addition, potential selection bias may exist since patients with limited RKF are less likely to have undergone urine collections. The employment of inverse probability weighting for having data on RKF is our best effort to mitigate selection bias in this study. Nevertheless, our findings may not be extrapolated to those settings with different practice patterns from the USA, such as dialyzer reuse, inadequate water purification and schedules other than thrice-weekly treatment.

In conclusion, RKF at dialysis start modified the association of initial dialysis dose with all-cause mortality among incident hemodialysis patients. Further research, including clinical trials, is necessary to test if an incremental hemodialysis approach with a reduced dialysis dose by either less treatment time or a less frequent schedule among patients with substantial RKF during the first several months of dialysis is an economic strategy that enhances patients' quality of life without compromising their survival [50, 51].

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

Y.O. was responsible for the research idea and study design. K.K.-Z. was responsible for data acquisition. M.W., Y.O., E.S., C.M.R., J.C., C.H., C.P.K. and K.K.-Z. were responsible for data analysis/interpretation. M.W. and Y.O. were responsible for statistical analysis. C.P.K. and K.K.-Z. provided supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

K.K.-Z. has received honoraria from Abbott, AbbVie, Alexion, Amgen, AstraZeneca, AVEO, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hospira, Kabi, Keryx, Novartis, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi-Aventis, Shire, Vifor, UpToDate and ZS Pharma. Y.O. has received honoraria from Ono and Chugai.

REFERENCES

1. Owen WF Jr, Lew NL, Liu Y *et al.* The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 1993; 329: 1001–1006
2. Parker TF 3rd, Husni L, Huang W *et al.* Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. *Am J Kidney Dis* 1994; 23: 670–680
3. Acchiardo SR, Hatten KW, Ruvinsky MJ *et al.* Inadequate dialysis increases gross mortality rate. *ASAIO J* 1992; 38: M282–M285
4. Collins AJ, Ma JZ, Umen A *et al.* Urea index and other predictors of hemodialysis patient survival. *Am J Kidney Dis* 1994; 23: 272–282

5. Hakim RM, Breyer J, Ismail N *et al.* Effects of dose of dialysis on morbidity and mortality. *Am J Kidney Dis* 1994; 23: 661–669
6. Ajiro J, Alchi B, Narita I *et al.* Mortality predictors after 10 years of dialysis: a prospective study of Japanese hemodialysis patients. *Clin J Am Soc Nephrol* 2007; 2: 653–660
7. Daugirdas JT, Depner TA, Inrig J *et al.* KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update. *Am J Kidney Dis* 2015; 66: 884–930
8. Bargman JM, Thorpe KE, Churchill DN *et al.* Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol* 2001; 12: 2158–2162
9. Termorshuizen F, Korevaar JC, Dekker FW *et al.* The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am J Kidney Dis* 2003; 41: 1293–1302
10. Rocco MV, Frankenfield DL, Prowant B *et al.* Risk factors for early mortality in U.S. peritoneal dialysis patients: impact of residual renal function. *Perit Dial Int* 2002; 22: 371–379
11. Molnar MZ, Ojo AO, Bunnapradist S *et al.* Timing of dialysis initiation in transplant-naive and failed transplant patients. *Nat Rev Nephrol* 2012; 8: 284–292
12. Van Stone JC. The effect of dialyzer membrane and etiology of kidney disease on the preservation of residual renal function in chronic hemodialysis patients. *ASAIO J* 1995; 41: M713–M716
13. Hartmann J, Fricke H, Schiffl H. Biocompatible membranes preserve residual renal function in patients undergoing regular hemodialysis. *Am J Kidney Dis* 1997; 30: 366–373
14. McKane W, Chandna SM, Tattersall JE *et al.* Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. *Kidney Int* 2002; 61: 256–265
15. Daugirdas JT. Kt/V (and especially its modifications) remains a useful measure of hemodialysis dose. *Kidney Int* 2015; 88: 466–473
16. Daugirdas J, Blake PG, Ing TS. *Handbook of Dialysis*. Philadelphia, PA: Lippincott Williams & Wilkins, 2014
17. Clinical practice recommendations for peritoneal dialysis adequacy. *Am J Kidney Dis* 2006; 48(Suppl 1): S130–S158
18. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; 317: 1098
19. Depner TA, Daugirdas JT. Equations for normalized protein catabolic rate based on two-point modeling of hemodialysis urea kinetics. *J Am Soc Nephrol* 1996; 7: 780–785
20. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993; 4: 1205–1213
21. Daugirdas JT, Leypoldt JK, Akonur A *et al.* Improved equation for estimating single-pool Kt/V at higher dialysis frequencies. *Nephrol Dial Transplant* 2013; 28: 2156–2160
22. Obi Y, Rhee CM, Mathew AT *et al.* Residual kidney function decline and mortality in incident hemodialysis patients. *J Am Soc Nephrol* 2016; 27: 3758–3768
23. Hemodialysis Adequacy Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis* 2006; 48(Suppl 1): S2–S90
24. Schacht A, Bogaerts K, Bluhmki E *et al.* A new nonparametric approach for baseline covariate adjustment for two-group comparative studies. *Biometrics* 2008; 64: 1110–1116
25. Austin P. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28: 3083–3107
26. Kurth T, Walker AM, Glynn RJ *et al.* Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol* 2006; 163: 262–270
27. Rocco MV, Dwyer JT, Larive B *et al.* The effect of dialysis dose and membrane flux on nutritional parameters in hemodialysis patients: results of the HEMO Study. *Kidney Int* 2004; 65: 2321–2334
28. Chertow GM, Levin NW, Beck GJ *et al.* In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 2010; 363: 2287–2300
29. Rocco MV, Daugirdas JT, Greene T *et al.* Long-term effects of frequent nocturnal hemodialysis on mortality: the Frequent Hemodialysis Network (FHN) Nocturnal Trial. *Am J Kidney Dis* 2015; 66: 459–468
30. de Francisco AL, Cobo MA, Setien MA *et al.* Effect of serum phosphate on parathyroid hormone secretion during hemodialysis. *Kidney Int* 1998; 54: 2140–2145
31. Lowrie EG, Laird NM, Parker TF *et al.* Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. *N Engl J Med* 1981; 305: 1176–1181
32. Gotch FA, Sargent JA. A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 1985; 28: 526–534
33. NKF-DOQI clinical practice guidelines for hemodialysis adequacy. *Am J Kidney Dis* 1997; 30(3 Suppl 2): S15–S66
34. Lertdumrongluk P, Streja E, Rhee CM *et al.* Dose of hemodialysis and survival: a marginal structural model analysis. *Am J Nephrol* 2014; 39: 383–391
35. Port FK, Pisoni RL, Bommer J *et al.* Improving outcomes for dialysis patients in the international Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol* 2006; 1: 246–255
36. Swaminathan S, Mor V, Mehrotra R *et al.* Initial session duration and mortality among incident hemodialysis patients. *Am J Kidney Dis* 2017; 70: 69–75
37. Termorshuizen F, Dekker FW, van Manen JG *et al.* Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol* 2004; 15: 1061–1070
38. Obi Y, Streja E, Rhee CM *et al.* Incremental hemodialysis, residual kidney function, and mortality risk in incident dialysis patients: a cohort study. *Am J Kidney Dis* 2016; 68: 256–265
39. Htay H, Cho Y, Pascoe EM *et al.* Predictors of residual renal function decline in peritoneal dialysis patients: The balANZ Trial. *Perit Dial Int* 2017; 37: 283–289
40. Liu Y, Ma X, Zheng J *et al.* Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events and residual renal function in dialysis patients: a meta-analysis of randomised controlled trials. *BMC Nephrol* 2017; 18: 206
41. Chou JA, Streja E, Nguyen DV *et al.* Intradialytic hypotension, blood pressure changes and mortality risk in incident hemodialysis patients. *Nephrol Dial Transplant* 2018; 33: 149–159
42. Kim TWCT, Kim TH, Chou JA *et al.* Association of ultrafiltration rate with mortality in incident hemodiaysis patients. *Nephron* 2018; doi: 10.1159/000486323
43. Mathew AT, Fishbane S, Obi Y *et al.* Preservation of residual kidney function in hemodialysis patients: reviving an old concept. *Kidney Int* 2016; 90: 262–271
44. Owen WF Jr, Chertow GM, Lazarus JM *et al.* Dose of hemodialysis and survival: differences by race and sex. *JAMA* 1998; 280: 1764–1768
45. Port FK, Wolfe RA, Hulbert-Shearon TE *et al.* High dialysis dose is associated with lower mortality among women but not among men. *Am J Kidney Dis* 2004; 43: 1014–1023
46. Depner T, Daugirdas J, Greene T *et al.* Dialysis dose and the effect of gender and body size on outcome in the HEMO Study. *Kidney Int* 2004; 65: 1386–1394
47. Eknoyan G, Beck GJ, Cheung AK *et al.* Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347: 2010–2019
48. Chertow GM, Levin NW, Beck GJ *et al.* Long-term effects of frequent in-center hemodialysis. *J Am Soc Nephrol* 2016; 27: 1830–1836
49. Kjaergaard KD, Peters CD, Jespersen B *et al.* Angiotensin blockade and progressive loss of kidney function in hemodialysis patients: a randomized controlled trial. *Am J Kidney Dis* 2014; 64: 892–901
50. Rhee CM, Unruh M, Chen J *et al.* Infrequent dialysis: a new paradigm for hemodialysis initiation. *Semin Dial* 2013; 26: 720–727
51. Kalantar-Zadeh K, Unruh M, Zager PG *et al.* Twice-weekly and incremental hemodialysis treatment for initiation of kidney replacement therapy. *Am J Kidney Dis* 2014; 64: 181–186

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