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Authors
Ko, Gang Jee
Obi, Yoshitsugu
Soohoo, Melissa
et al.

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No Survival Benefit in Octogenarians and Nonagenarians with Extended Hemodialysis Treatment Time

Gang Jee Ko[a, b] Yoshitsugu Obi[a] Melissa Soohoo[a] Tae Ik Chang[a, c] Soo Jeong Choi[a, d] Csaba P. Kovesdy[e, f] Elani Streja[a] Connie M. Rhee[a] Kamyar Kalantar-Zadeh[a, g, h]

[a]Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, School of Medicine, Orange, FL, USA; [b]Department of Internal Medicine, Korea University College of Medicine, Seoul, South Korea; [c]Department of Internal Medicine, National Health Insurance Service Medical Center, Ilsan Hospital, Goyangshi, South Korea; [d]Department of Internal Medicine, Soonchunhyang University College of Medicine, Bucheon, South Korea; [e]Division of Nephrology, University of Tennessee, Health Science Center, Memphis, TN, USA; [f]Nephrology Section, Memphis Veterans Affairs Medical Center, Memphis, TN, USA; [g]Department of Medicine, Long Beach Veteran Affairs Health System, Long Beach, CA, USA; [h]Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA, USA

Keywords
Extended treatment session length · Elderly · Mortality · Hemodialysis

Abstract
Background: The population of elderly end-stage renal disease patients initiating dialysis is rapidly growing. Although longer treatment is supposed to benefit for hemodialysis (HD) patients through more solute clearance and slower fluid removal, it is not yet clear how treatment session length affects mortality risk in octogenarians and nonagenarians. ***Methods:*** In a cohort of 112,026 incident HD patients between 2007 and 2011, we examined the association of treatment session length with all-cause mortality, adjusting for demographics and comorbid conditions. We also used restricted spline functions for age to evaluate continuous changes in the association of short (<210 min) and extended (≥240 min) HD treatment (vs. 210 to <240 min) with all-cause mortality over continuous age. ***Results:*** During the first 91 days of dialysis, patients aged ≥80 years tended to have the lowest treatment session length (median [interquartile range] 211 [193–230] min, $r > 0.5$). Longer treatment was associated with better survival in patients <65 and 65 to <80 years but not in octogenarians/nonagenarians. The association of extended treatment (≥240 min) with better survival was attenuated across age and not significant among patients aged ≥80 years with a hazard ratio of 1.10 (95% CI 0.99–1.20). Shorter treatment sessions (<210 min) was associated with higher mortality across all age groups. ***Conclusion:*** Extended HD was not associated with lower mortality among octogenarians and nonagenarians, while it was associated with better survival among younger patients. Further studies are needed to determine the optimal treatment session length in elderly incident HD patients.

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E-Mail karger@karger.com
www.karger.com/ajn

Kamyar Kalantar-Zadeh, MD, MPH, PhD
Professor of Medicine, Pediatrics and Epidemiology, Harold Simmons Center for Kidney Disease Research and Epidemiology, Division of Nephrology and Hypertension, University of California Irvine (UCI) School of Medicine, 101 The City Drive South, City Tower, Suite 400 – ZOT: 4088, Orange, CA 92868-3217 (USA)
E-Mail kkz@uci.edu

Introduction

Despite medical advances and improvements in patient care, the mortality of end-stage renal disease (ESRD) patients on dialysis treatment remains unacceptably high [1]. Although there have been many studies for optimizing treatment session length in hemodialysis (HD) patients as an effort to improve survival by delivering the ideal dose of dialysis and reducing complications [2–7], it has not been clear yet which treatment session length is necessary for achieving better clinical outcomes.

Elderly patients are the fastest growing dialysis population according to the United States Renal Data System [1, 8]. There are several factors that may warrant the need to modify the risk-benefit balance of extended dialysis particularly in this population [9–11]: (1) smaller increases in uremic burden or volumes due to lower dietary intake, compared with those in younger patients; (2) higher risk of HD-related complications; and (3) compromised quality of life by longer dialysis sessions.

Therefore, we examined whether there is a differential association between HD treatment session length and all-cause mortality risk across age groups in a contemporary cohort of incident HD patients.

Materials and Methods

The study was approved by the Institutional Review Boards of the Los Angeles Biomedical Research Institute at Harbor-UCLA and the University of California Irvine Medical Center.

Study Population

We conducted a historical cohort study of incident HD patients receiving dialysis care from a large dialysis organization (LDO) in the United States, with comprehensive longitudinal data on patients' sociodemographics, comorbidities, laboratory tests, dialysis treatment characteristics, clinical events, and vital status. The original source population was a cohort of 208,820 incident dialysis patients receiving care in one of the LDO outpatient facilities over a 5-year period (January 2007 to December 2011). Among 133,162 incident ESRD patients who received dialysis treatment for at least 60 days and were treated only by in-center thrice-weekly HD during the follow-up, we excluded 21,036 patients if they were ≤18 and >100 years old or had missing baseline HD treatment session length data. The follow-up time was divided into patient-quarters (i.e., 91-day periods from the date of first dialysis), where baseline was considered the first 91-day period.

Exposure Ascertainment

Quarterly averaged values of HD treatment session length during the first quarter of dialysis treatment were grouped into the following categories: <180 min, 180 to <210 min, 210 to <240 min, and ≥240 min. Patients were also categorized according to their age at study entry: <65, 65 to <80, and ≥80 years.

Outcome Assessment

The primary outcome of interest was all-cause mortality. Patients were censored for death, kidney transplantation, transfer to a non-LDO dialysis unit, recovery of renal function or dialysis discontinuation, or at the end of the study (December 31, 2011). In the primary analyses, we sought to compare the association of treatment session length with all-cause mortality risk across age groups.

Sociodemographic, Dialysis Treatment, and Laboratory Characteristics

Information regarding sociodemographics (including self-reported race/ethnicity and primary insurance type) as well as comorbid conditions (e.g., diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, other cardiac diseases, cerebrovascular disease, chronic obstructive pulmonary disease, and history of cancer or liver disease) defined by the International Classification of Diseases-9 codes was also obtained from the LDO database. The modified Deyo-Charlson comorbidity index, where we excluded the presence or absence of kidney disease, was also obtained from the LDO database [12, 13].

Blood samples for laboratory tests were collected before dialysis, except for post-dialysis serum urea nitrogen, using standardized techniques in all dialysis clinics. These samples were transported to a central laboratory in Deland, Florida, normally within 24 h, where they were measured using automated and standardized methods. Most laboratory tests were performed monthly, including serum creatinine, albumin, peripheral white blood cell count, total iron binding capacity, calcium, phosphorus, and bicarbonate. Serum intact parathyroid hormone was usually measured at least once per quarter. Hemoglobin was measured weekly to biweekly in most patients. The delivered dialysis dose was calculated by single-pool Kt/V using urea kinetic modeling. The normalized protein catabolic rate (nPCR) was calculated. To minimize measurement variability, all repeated measures for each 91-day interval were averaged, and the quarterly mean values were used in analyses.

Statistical Analysis

Baseline characteristics across age groups and treatment time groups are summarized as proportions, mean ± SD, or medians (interquartile ranges [IQR]) depending on the data type. We used logistic regression to estimate the association between various clinical characteristics and the likelihood of extended treatment session length (treatment session length ≥240 vs. 180 to <240 min) within age groups. We stratified each age group according to the treatment session length, and using Cox proportional hazard models, we compared the association of treatment session length with all-cause mortality risk across age groups using 3 hierarchical levels of adjustment:

(1) Unadjusted model: Included the main predictor, treatment session length

(2) Case-mix adjusted model: Included the unadjusted model covariates as well as age, sex, race/ethnicity, primary insurance type, 10 comorbid conditions (diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, other cardiovascular disease, cerebrovascular disease, dyslipidemia, chronic obstructive pulmonary disease, liver disease, and history of malignancy), dialysis dose as measured by single-pool Kt/V, body mass index (BMI), and ultrafiltration rate (mL/h/kg body weight)

(3) Case-mix + malnutrition-inflammation-cachexia syndrome model: Included the case-mix adjusted model covariates as well as 10 clinically relevant laboratory variables (white blood cell count, hemoglobin, serum albumin, creatinine, bicarbonate, uncorrected calcium, phosphorus, intact parathyroid hormone, total iron binding capacity, and nPCR)

We defined the case-mix model as our preferred model, which included core sociodemographic measures and other confounders of the association between treatment session length and outcomes. The malnutrition-inflammation-cachexia syndrome model was designated an exploratory model, which included confounders as well as potential intermediates on the causal pathway of treatment session length and mortality association. We also conducted subgroup analyses in which we compared the association of short (<210 min) or extended treatment (≥240 min) vs. conventional treatment (210 to <240 min) with mortality across age groups.

Effect modifications of the association between treatment session length (short: <210 min or extended treatment: ≥240 min vs. the standard treatment (210–240 min) and all-cause death by age were examined with restricted cubic spline functions for age in the case-mix adjusted model. The frequency of missing data was low (1%) for most laboratory tests, except for nPCR (4%) and creatinine (4%), and the multiple imputation method with 5 datasets was used in all regression analyses. All analyses and figures were generated with STATA MP, version 13.1 (StataCorp, College Station, TX, USA) and SigmaPlot version 12.5 (Systat Software, San Jose, CA, USA).

Results

Study Population Description

The study population included 112,026 incident HD patients (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000494336). The mean ± SD age of the overall cohort was 63 ± 15 years, and the median treatment session length (IQR) was 211 (193–230) min. The crude all-cause mortality rate of the overall cohort was 135 death events per 1,000 patient-years of follow-up (95% CI 133–136). Across all age groups, the baseline treatment session length distribution showed 3 distinct curves peaking at approximately 180, 210, and 240 min. Patients aged ≥80 years tended to have the lowest baseline treatment session length (median [IQR] 204 [184–217] min), with the highest peak at approximately 180 min, whereas patients aged <65 years had the greatest treatment session length (median [IQR] 214 [199–234] min), with the highest peak at approximately 240 min (Fig. 1). Baseline characteristics of the cohort stratified by age and baseline treatment session length are presented in Table 1. Across all age groups, patients with the highest treatment session length tended to be male; were more likely to be African American and less likely to be Hispanic or Asian; were more likely to use a central venous catheter as their primary vascular access; were more likely to have diabetes, atherosclerotic heart disease, and other cardiovascular diseases; and had higher BMI compared to those in the lowest treatment session length category. Ultrafiltration rate tended to be lower in the extended treatment time group in all age groups. However, intradialytic hypotension was more frequent in the extended treatment time group only in patients aged ≥80 years.

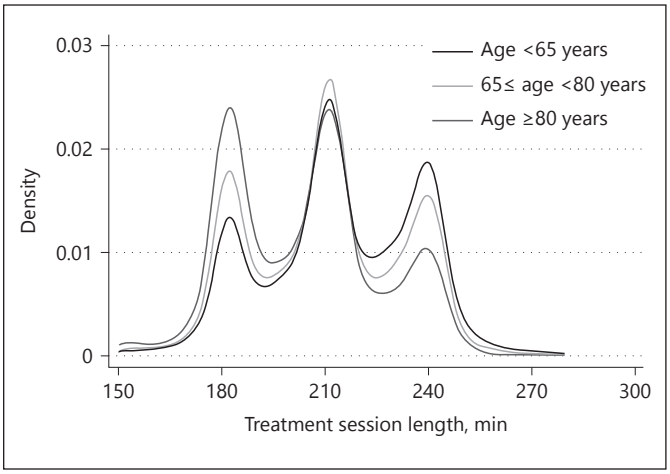

Fig. 1. Distribution of baseline hemodialysis (HD) treatment session length across age groups with age <65, 65 to <80, and ≤80 years in 112,026 incident HD patients.

Clinical Characteristics Associated with Extended Treatment Time Across Age Groups

Table 2 shows the association between clinical characteristics and the likelihood of extended treatment time (treatment session length ≥240 min) across age groups in the case-mix adjusted logistic regression models (reference: treatment session length ≥180 to <240 min). Across all age groups, being female, Hispanic, or Asian; using Medicaid insurance; and having an arteriovenous fistula (AVF)/ arteriovenous graft (AVG) access type were associated with a lower likelihood of extended treatment time. Being African American, having a diagnosis of diabetes or other cardiac disease, and having higher baseline BMI and creatinine values were associated with a higher likelihood of extended treatment time.

Treatment Session Length and All-Cause Mortality Across Age Groups

In the case-mix adjusted Cox regression analysis, there was a linear inverse association in mortality risk with greater treatment session length in patients aged

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Table 1. Baseline characteristics stratified by age and treatment session length in 112,026 incident hemodialysis patients

Characteristics	Age <65 years Treatment time, min				Age 65 to <80 years Treatment time, min				Age ≥80 years Treatment time, min			
	<180	≥180 to <210	≥210 to <240	≥240	<180	≥180 to <210	≥210 to <240	≥240	<180	≥180 to <210	≥210 to <240	≥240
Patient number, *n*	3,962	19,588	25,688	8,816	3,306	14,988	15,830	4,458	1,921	7,079	5,273	1,117
Age, years	50±11	51±11	51±10	51±10	72±4	72±4	72±4	71±4	84±4	84±4	84±3	83±3
Female, %	57	48	38	28	60	52	41	32	59	51	39	27
Race/ethnicity, %												
White	44	37	35	36	58	53	54	57	68	67	68	70
African American	29	34	41	45	19	24	29	30	12	17	20	20
Hispanic	17	21	18	13	13	15	12	8	10	10	7	6
Asian	6	4	2	2	7	5	2	1	7	4	2	1
Others	4	4	4	4	3	3	3	4	3	2	3	3
Primary insurance, %												
Medicare	36	38	40	43	65	66	67	68	70	73	74	73
Medicaid	14	13	10	8	4	3	2	1	2	2	1	1
Others	50	48	49	49	32	31	31	31	28	26	25	26
Access type, %												
Central venous catheter	67	74	77	79	64	71	73	77	67	75	75	78
Arterio-venous fistula	20	15	13	11	22	17	16	12	20	15	14	11
Arterio-venous graft	5	4	3	2	6	5	5	3	7	5	4	3
Others	8	7	7	8	8	7	7	8	6	5	7	8
Comorbidities, %												
Diabetes	52	57	60	63	52	60	63	66	41	45	50	54
Hypertension	45	47	51	54	51	49	50	52	59	58	59	61
Congestive heart failure	37	37	39	42	34	34	35	36	34	32	34	36
Atherosclerotic heart disease	13	12	12	14	15	15	17	18	15	16	17	19
Other cardiac disease	13	12	13	15	15	16	18	21	16	17	19	24
Cerebrovascular disease	1	1	2	2	2	2	2	3	2	2	2	2
COPD	4	4	4	5	6	6	7	8	6	5	6	7
Liver disease	2	2	2	2	1	1	1	2	1	1	1	2
History of cancer	1	1	1	2	4	3	3	4	3	3	4	6
Dyslipidemia	22	23	25	26	24	26	26	29	22	24	26	30
BMI, kg/m^2	25.3 (21.7–30.4)	26.4 (22.7–31.5)	28.2 (24.0–33.9)	30.1 (25.5–37.2)	24.6 (21.4–28.8)	25.9 (22.5–30.1)	27.1 (23.5–31.9)	28.5 (24.6–33.7)	23.2 (20.6–26.4)	23.8 (21.2–27.1)	24.7 (22.1–28.2)	25.7 (23.1–29.1)
Ultrafiltration rate, mL/h/kg BW	7.8 (5.8–10.8)	7.8 (5.6–10.3)	7.1 (5.3–9.3)	6.5 (4.8–8.4)	7.7 (5.4–10.3)	7.4 (5.4–9.6)	6.7 (5.0–8.7)	6.1 (5.0–7.9)	8.0 (5.7–10.5)	7.5 (5.6–9.8)	6.8 (5.1–8.7)	6.2 (4.6–7.9)
Intradialytic hypotension (<90 mm Hg/ session), %	3	2	2	2	4	4	4	5	5	6	6	9
Hemoglobin, g/dL	10.9±1.3	11.0±1.2	11.1±1.2	11.2±1.2	11.0±1.1	11.1±1.1	11.2±1.1	11.2±1.2	11.1±1.1	11.2±1.1	11.2±1.1	11.3±1.1
WBC, 10^3/μL/mL	8.0±2.7	7.8±2.6	7.8±2.5	7.8±2.6	8.0±3.0	7.9±2.8	7.7±2.5	7.8±2.8	7.5±2.8	7.4±2.6	7.4±2.7	7.4±2.6
Albumin, g/dL	3.5±0.6	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.5	3.5±0.4	3.5±0.4	3.5±0.5	3.5±0.4	3.5±0.4	3.4±0.4
Creatinine, mg/dL	6.1±2.5	6.5±2.6	6.7±2.6	6.9±2.7	4.9±1.7	5.2±1.8	5.3±1.8	5.4±1.9	4.5±1.5	4.7±1.5	4.8±1.6	4.8±1.5
Bicarbonate, mEq/L	22.3±2.9	22.9±2.7	23.3±2.6	23.7±2.6	23.3±2.8	3.7±2.6	24.1±2.6	24.3±2.6	23.9±2.7	24.3±2.6	24.5±2.6	24.8±2.5
Calcium, mg/dL	8.6±0.7	8.6±0.7	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6	8.7±0.6
Phosphorus, mg/dL	5.3±1.3	5.2±1.2	5.2±1.2	5.2±1.2	4.7±1.0	4.7±1.0	4.7±1.0	4.6±1.0	4.5±1.0	4.5±1.0	4.4±1.0	4.3±1.0
iPTH, pg/mL	327 (196–521)	343 (243–531)	357 (228–549)	369 (234–564)	276 (169–428)	286 (180–436)	290 (186–441)	292 (189–441)	267 (166–387)	254 (164–380)	259 (167–391)	261 (169–378)
TIBC, mg/mL	229±53	228±50	229±48	231±47	224±50	222±50	222±49	222±49	218±49	214±47	215±46	214±46
nPCR, g/kg/day	0.8±0.3	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2
spKt/V	1.4±0.4	1.4±0.3	1.4±0.3	1.4±0.3	1.5±0.4	1.5±0.3	1.5±0.3	1.5±0.3	1.5±0.4	1.5±0.3	1.6±0.3	1.6±0.3

Values for categorical variables are given as number (percentage); values for continuous variables, mean± SD or median (interquartile ranges)

COPD, chronic obstructive pulmonary disease; BMI, body mass index; BW, body weight; WBC, white blood cell counts; Hgb, hemoglobin; iPTH, intact parathyroid hormone; TIBC, total iron binding capacity; nPCR, normalized protein catabolic rate; spKt/V, single pool Kt/V.

Table 2. Association of clinical characteristics with extended hemodialysis treatment time (treatment session length ≥240 vs. ≥180 to <240 min) among the three age groups (<65, 65 to <80, and ≥80 years) in case-mix adjusted logistic regression models

Factor	Age, years		
	<65 OR (95% CI)	65 to <80 OR (95% CI)	≥80 OR (95% CI)
Socio-demographic factors			
Age, per 5 years	1.00 (1.00–1.00)	0.99 (0.98–1.00)	0.94 (0.93–0.97)
Female (vs. male)	0.48 (0.45–0.51)	0.43 (0.40–0.47)	0.33 (0.28–0.39)
Race: African American (vs. white)	1.17 (1.11–1.25)	1.20 (1.10–1.30)	1.26 (1.05–1.51)
Race: Asian (vs. white)	0.76 (0.70–0.82)	0.62 (0.54–0.70)	0.67 (0.51–0.89)
Race: hispanic (vs. white)	0.64 (0.52–0.80)	0.33 (0.24–0.46)	0.32 (0.17–0.62)
Insurance: medicaid (vs. medicare)	0.69 (0.63–0.75)	0.64 (0.48–0.85)	0.61 (0.30–1.22)
Insurance: other insurance (vs. medicare)	0.91 (0.86–0.96)	0.94 (0.87–1.01)	1.09 (0.93–1.26)
Comorbidity factors			
Diabetes	1.18 (1.11–1.25)	1.12 (1.04–1.21)	1.21 (1.05–1.39)
Hypertension	1.13 (1.07–1.19)	1.06 (0.98–1.14)	1.05 (0.91–1.21)
Congestive heart failure	0.93 (0.88–0.98)	0.91 (0.84–0.98)	1.00 (0.87–1.16)
Atherosclerotic heart disease	1.02 (0.94–1.10)	0.98 (0.88–1.08)	0.96 (0.80–1.15)
Other cardiac diseases	1.10 (1.01–1.20)	1.21 (1.09–1.34)	1.30 (1.09–1.56)
Dialysis related factors			
Access type: AVF (vs. CVC)	0.64 (0.59–0.69)	0.65 (0.58–0.72)	0.62 (0.50–0.77)
Access type: AVG (vs. CVC)	0.55 (0.47–0.65)	0.51 (0.42–0.62)	0.59 (0.41–0.85)
BMI, per 1 kg/m^2	1.06 (1.05–1.06)	1.06 (1.05–1.07)	1.06 (1.05–1.07)
Ultrafiltration, per 1 kg	1.49 (1.45–1.54)	1.50 (1.44–1.57)	1.45 (1.31–1.59)
Pre–HD SBP, per 10 mm Hg	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Laboratory variables			
Hemoglobin, per 1 g/dL	1.13 (1.11–1.16)	1.14 (1.10–1.17)	1.17 (1.10–1.24)
White blood cell counts, per 10^3/μL	0.98 (0.97–0.99)	0.99 (0.98–1.01)	0.99 (0.96–1.01)
Albumin, per 1 g/dL	1.00 (0.95–1.06)	0.92 (0.84–0.99)	0.84 (0.72–0.99)
Creatinine, per 1 mg/dL	1.06 (1.05–1.07)	1.09 (1.07–1.12)	1.09 (1.05–1.14)

AVF, arteriovenous fistula; AVG, arteriovenous graft; CVC, central venous catheter; BMI, body mass index; HD, hemodialysis; SBP, systolic blood pressure.

<65 years, where extended treatment time (≥240 min) was associated with a lower mortality risk (HR [95% CI] 0.91 [0.86–0.97]). Patients aged 65 to <80 and ≥80 years also had a linear inverse association mortality risk as treatment session length increased until <240 min (reference: 210->240 min). However, unlike patients aged <65, the treatment session length ≥240 min was not associated with a lower risk of mortality among patients aged 65 to <80 and ≥80 years (HRs [95% CI] 0.95 [0.90–1.01] and 1.10 [0.99–1.20] respectively; Fig. 2, online suppl. Fig. 2).

Treatment Session Length and Mortality Across Subgroups

Figure 3a and b shows the case-mix adjusted associations between short (<210 min) and extended (≥240 min) treatment session lengths and all-cause mortality (reference: ≥210 to <240 min) across a priori selected subgroups and stratified by age. Compared to the association of mortality with short treatment session length that did not show much difference between age groups (Fig. 3a), there was an incremental change in the association of extended treatment session length with mortality between age groups (Fig. 3b). Extended treatment (≥240 min) compared to standard treatment (≥210 to <240 min) tended to be associated with a lower risk of mortality in those aged <65 years especially in male, African American, non-diabetes, without congestive heart failure, low BMI (≤25), high interdialytic weight gain (IDWG, >3% of body weight), high spKt/V (>1.5), and low albumin (≤3.5 mg/dL). Extended treatment time was not associated with a lower risk of mortality in any subgroups of patients aged 65 to <80 and ≥80 years. In the subgroup of white patients aged ≥80 years, extended treatment (≥240 min) was associated with a higher risk of mortality.

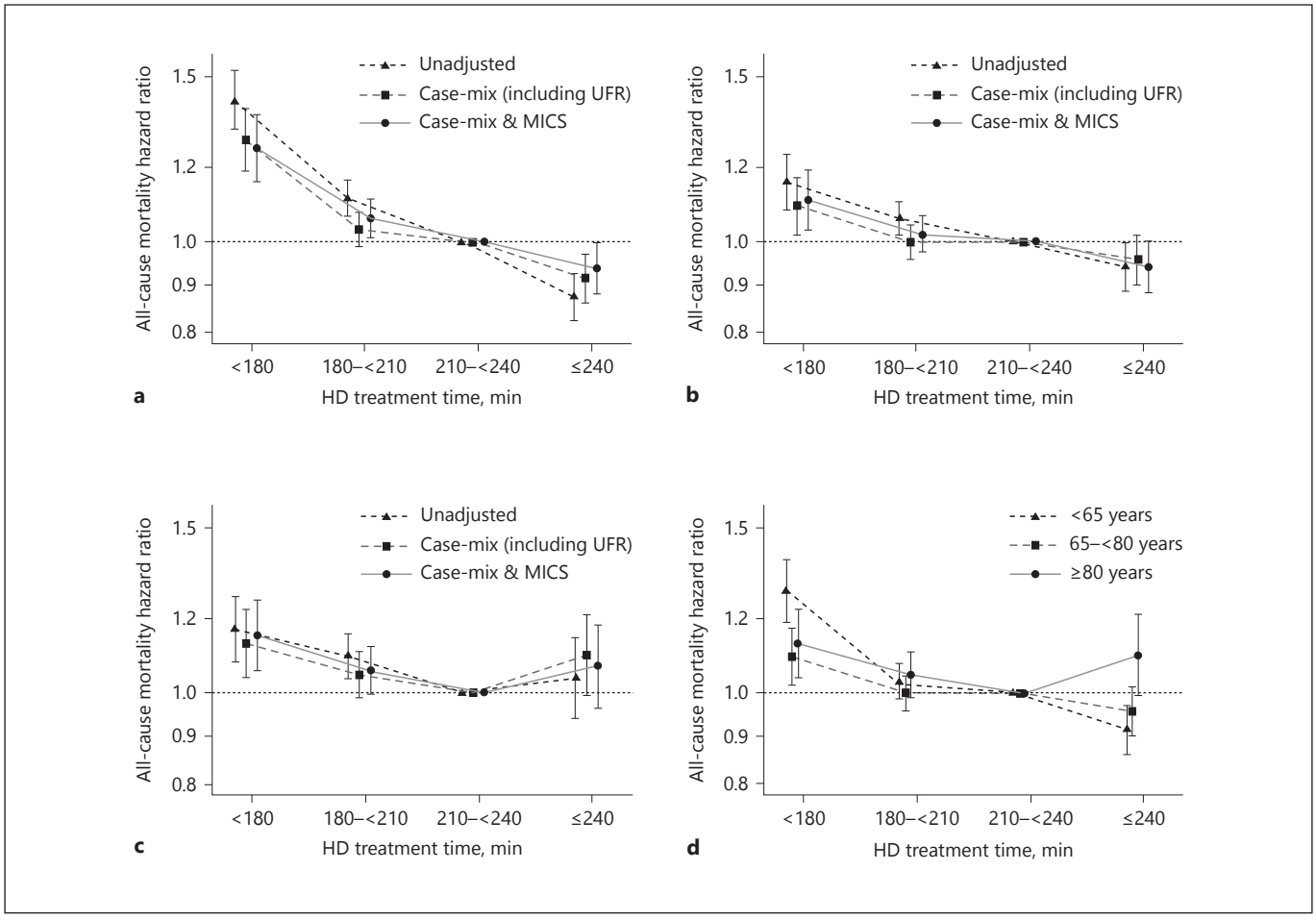

Fig. 2. The hazard ratios for all-cause mortality associated with HD treatment time across the age groups; (**a**) <65 years, (**b**) 65 to <80 years, (**c**) ≥80 years with hierarchical adjustments (see the Methods for detail), and (**d**) the combination of their case-mix adjustment. UFR, ultrafiltration rate; MICS, malnutrition-inflammation-cachexia syndrome.

Effect Modification by Age on the Association of Treatment Session Length with All-Cause Mortality

We then examined the effect modification by age on the association of treatment session length with all-cause mortality in a continuous pattern using a restricted cubic spline function in the case-mix adjusted model. Using patients with standard treatment (≥210 to < 240 min) as reference, treatment session length <210 min was associated with a higher risk of mortality across all ages, though the effect was attenuated along with increase of age (Fig. 4a). Conversely, the HR of all-cause mortality in association with extended treatment session length (≥240 min) was modified by age; lower risk of mortality with extended treatment session length in younger patients was incrementally attenuated across age (Fig. 4b). In a sensitivity analysis using different cut-off values for treatment time, age also did not modify the association of shorter treatment session length (<195 min) with all-cause mortality. However, the association of longer treatment time (≥225 min) with all-cause mortality was modified by age in a similar linear pattern, where it was associated with a higher risk of mortality in those aged 80 years, though it did not reach statistical significance (online suppl. Fig. 3).

Discussion

In a nationally representative cohort of incident US HD patients, we observed an association of longer treatment session length with a lower risk of all-cause mortality in patients aged <65 years, even beyond the

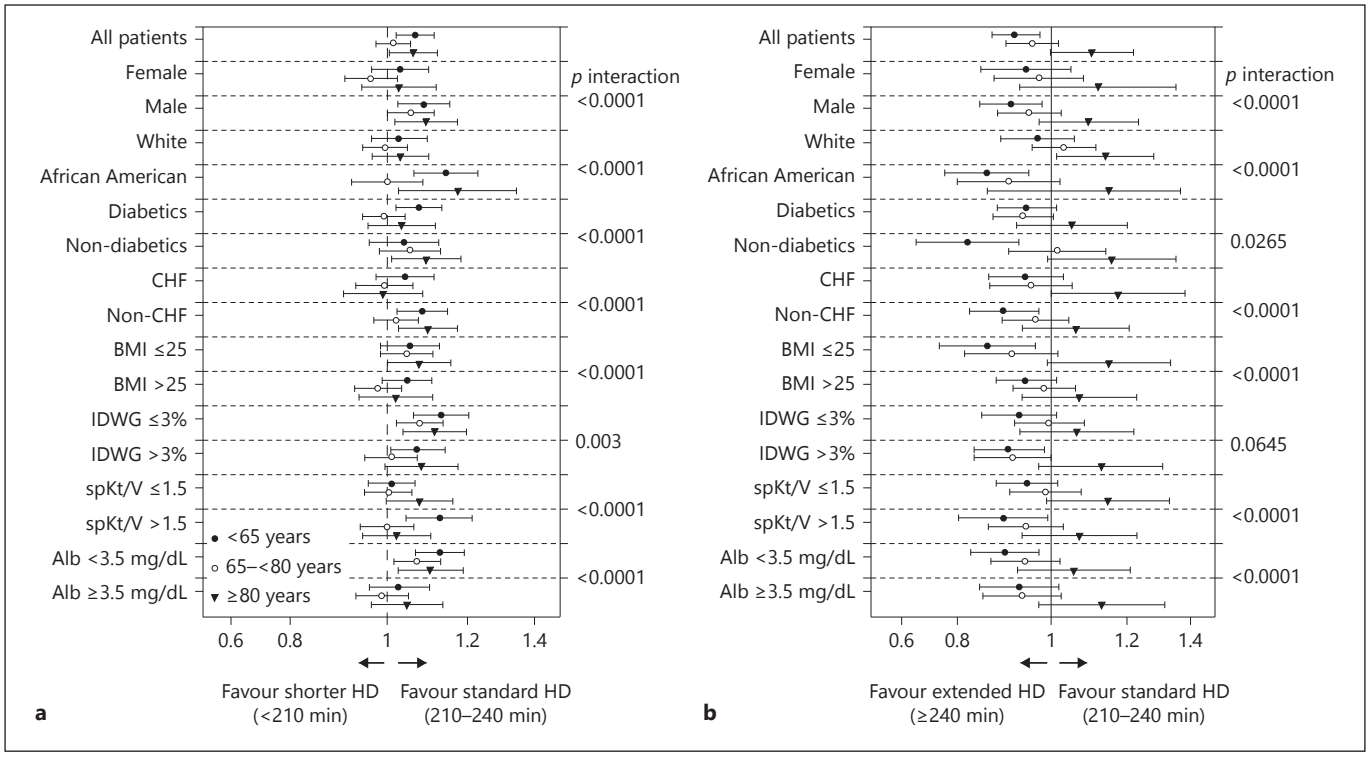

Fig. 3. Subgroup analysis for the association of short treatment time (<210 min, **a**) and extended HD treatment time (≥240 min, **b**) with all-cause mortality across age groups. Treatment session length 210 to <240 min in each age group was used as a reference group. CHF, congestive heart failure; BMI, body mass index; IDWG, interdialytic weight gain; spKt/V, single pool Kt/V; Alb, albumin.

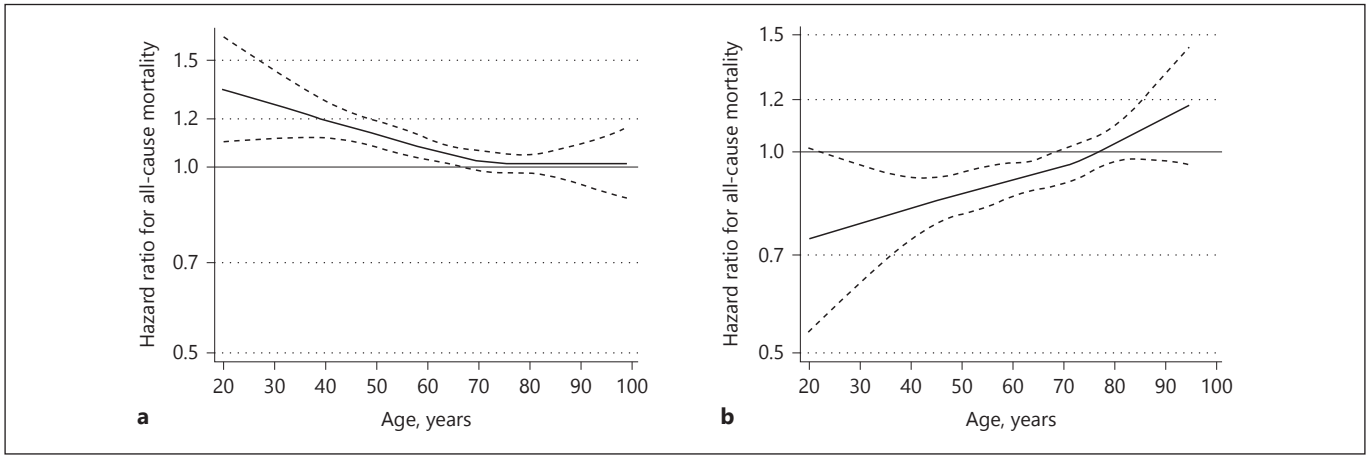

Fig. 4. Change in the association of short HD (treatment session length <210 min, **a**) and extend HD treatment (≥240 min, **b**) with all-cause mortality over age with restricted cubic spline functions in the case-mix adjusted model.

usual treatment session length of ≥240 min per session. However, better survival of patients with extended treatment session lengths ≥240 min was not observed among patients aged 65 to <80 and ≥80 years. Risk for all-cause mortality in patients with an extended treatment session length (≥240 min) was modified by age, whereby a lower risk of mortality was attenuated incrementally across age and tended to be associated with a higher risk of mortality in patients aged ≥80 years, although this did not reach statistical significance.

Despite the existence of clinical practice guidelines and quality improvement programs to achieve optimal delivery of dialysis dose, treatment session lengths have traditionally been shorter in the United States compared with other international counterparts [14]. Although there was a lack of strong evidence based on randomized clinical trials [15, 16] and earlier studies failed to show an association between session length and mortality [17, 18], longer HD treatment sessions have demonstrated benefits in the care [2–4]. Recent publications reported that compared to conventional HD (210–240 min), an extended treatment session of more than 4 h was associated with better survival [6, 7, 19, 20]. But, there have been variable results regarding the association of extended dialysis treatment with mortality [6, 15, 16, 21].

In the present study, increased treatment session length showed a linear association with improved survival in patients aged <65 years and 65 to <80 years, and extended treatment session length (≥240 min) was significantly associated with better survival in patients aged <65 years. However, longer treatment sessions (≥240 min) were not associated with better survival in patients aged 65 and older and showed a higher risk of mortality in the subgroup of white patients aged ≥80 years. Different associations of extended treatment session length ≥240 min with all-cause mortality between patients <80 and ≥80 years were shown uniformly in the subgroup analysis. The association of better survival resulting from extended treatment session lengths ≥240 min was attenuated with increased age. The significance of the association was lost and extended treatment session length was not associated with better survival in patients aged ≥80 years. Longer HD treatment sessions are considered beneficial because they enable the delivery of larger doses of dialysis, which enhances solute clearance, such as phosphorus and unknown potential mediators that cause complications in ESRD [22, 23]. These longer sessions also confer better tolerance in the management of interdialytic weight gain with preferable ultrafiltration rates, which has been known to reduce left ventricular hypertrophy and interdialytic hypotension [20, 24, 25]. However, our findings suggest that the association of longer HD treatment with better survival should be applied carefully, as longer treatments are not advisable for all HD patients. The benefits of extending dialysis treatment time in younger patients for the purpose of reducing the uremic burden and interdialytic weight gain may be diminished in patients aged ≥80 years. Moreover, elderly patients were likely more vulnerable to the higher risk of intradialytic hypotension probably due to higher comorbidities and advanced vascular stiffness when treatment sessions are extended (Table 1). The impact of the excerbated loss of nutrient, such as from hypercatabolism in extended treatment sessions may also be more significant and lead to exceed the advantage of slower and increasing dose of dialysis in older patients [26].

However, shorter treatment sessions (<210 min) were associated with worse survival regardless of age. Worse survival was shown to be associated with shorter treatment (<210 min) in all subgroups, although some of the results were not significant. The adjusted HR ratio analysis also showed worse survival in all age groups. A minimum treatment session length should be recommended to ensure the delivery of a proper dose of dialysis and to avoid such poor outcomes. Such a recommendation would also be helpful to avoid the possibility of an increased ultrafiltration rate due to a shortened dialysis time [27, 28].

The strengths of our study include its examination of a large, nationally representative cohort of dialysis patients, including more than 15,000 patients aged ≥80 years; the examination of incident HD patients whose characteristics are not confounded by survivor bias; and comprehensive availability of detailed, longitudinal patient-level comorbidity, laboratory, and dialysis treatment data. However, several limitations should be mentioned. First, treatment session length data in the first 91 days were used for the analysis to examine the long-term effect of HD treatment time on survival. Though the correlations of treatment session length at baseline with the overall study period were good ($r > 0.5$), baseline value may not reflect changes in session length over the course of follow-up or the impact of these changes on mortality. The overall distribution of treatment session length did not vary considerably across the follow-up period as noted in our previous study [29]. There was a good separation of treatment session length over time between groups divided by baseline treatment time, although the difference in treatment time became smaller, especially during the first 6 months (online suppl. Fig. 4).

Second, cause-specific mortality, which may be helpful to better elucidate the underlying mechanisms of the treatment session length-mortality association, was not examined in this study.

Third, our study results may be subject to residual confounding due to the observational study design and inability to adjust for unmeasured potential confounders. Moreover, a greater mortality risk associated with

shorter treatment time is at least partly explained by indication bias because dying patients are likely to have unstable hemodynamics and low dietary intake and, hence, are likely to receive prescriptions for shorter treatment time in clinical practice. Finally, as with all observational studies, our study did not confirm a causal association between patterns of treatment session length and mortality.

In conclusion, extended treatment session length was not associated with better survival among octogenarians and nonagenarians compared with younger patients. However, a shorter treatment session (<210 min) was associated with higher mortality risk regardless of age. Future studies are needed to determine the underlying mechanisms and to further define the optimal, individualized treatment session length management strategies for specific patient populations.

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Ethics Statement

The study was approved by the Institutional Review Boards of the Los Angeles Biomedical Research Institute at Harbor-UCLA and the University of California Irvine Medical Center.

Disclosure Statement

K.K.-Z. has received honoraria from Genzyme/Sanofi and Shire and was the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA during 2007–2012. Other authors have not declared any conflict of interest.

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Authors Contribution

Research idea and study design: G.J.K., Y.O., C.M.R., E.S., and K.K.-Z.; data acquisition: G.J.K.; data analysis/interpretation: G.J.K., Y.O., C.M.R., E.S., T.I.C., S.J.C., and K.K.-Z.; statistical analysis: G.J.K., Y.O., M.S., E.S., and K.K.-Z.; supervision or mentorship; C.M.R., C.P.K., and K.K.-Z. 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.

References

1 Collins AJ, Kasiske B, Herzog C, Chavers B, Foley R, Gilbertson D, Grimm R, Liu J, Louis T, Manning W, McBean M, Murray A, St Peter W, Xue J, Fan Q, Guo H, Li Q, Li S, Qiu Y, Li S, Roberts T, Skeans M, Snyder J, Solid C, Wang C, Weinhandl E, Zhang R, Arko C, Chen SC, Dalleska F, Daniels F, Dunning S, Ebben J, Frazier E, Hanzlik C, Johnson R, Sheets D, Wang X, Forrest B, Berrini D, Constantini E, Everson S, Eggers P, Agodoa L: Excerpts from the United States Renal Data System 2006 Annual Data Report. Am J Kidney Dis 2007;49(1 suppl 1):A6–7, S1–S296.

2 Marshall MR, Byrne BG, Kerr PG, McDonald SP: Associations of hemodialysis dose and session length with mortality risk in Australian and New Zealand patients. Kidney Int 2006;69:1229–1236.

3 Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, Kimata N, Gillespie BW, Combe C, Bommer J, Akiba T, Mapes DL, Young EW, Port FK: Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int 2006;69:1222–1228.

4 Miller JE, Kovesdy CP, Nissenson AR, Mehrotra R, Streja E, Van Wyck D, Greenland S, Kalantar-Zadeh K: Association of hemodialysis treatment time and dose with mortality and the role of race and sex. Am J Kidney Dis 2010;55:100–112.

5 Brunelli SM, Chertow GM, Ankers ED, Lowrie EG, Thadhani R: Shorter dialysis times are associated with higher mortality among incident hemodialysis patients. Kidney Int 2010;77:630–636.

6 Tentori F, Zhang J, Li Y, Karaboyas A, Kerr P, Saran R, Bommer J, Port F, Akiba T, Pisoni R, Robinson B: Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the dialysis outcomes and practice patterns study (DOPPS). Nephrol Dial Transplant 2012;27:4180–4188.

7 Flythe JE, Curhan GC, Brunelli SM: Shorter length dialysis sessions are associated with increased mortality, independent of body weight. Kidney Int 2013;83:104–113.

8 Paraskevas KI, Bessias N, Koupidis SA, Tziviskou E, Mikhailidis DP, Oreopoulos DG: Incidence of end-stage renal disease in the elderly: a steadily rising global socioeconomic epidemic. Int Urol Nephrol 2010;42:523–525.

9 Tattersall J, Farrington K, Gentile G, Kooman J, Macias Nunez JF, Nistor I, Van Biesen W, Covic A; European Renal Best Practice Guidelines G, the European Union of Geriatric Medicine Societies collaborative group for the production of guidelines on the management of older patients with CKD: Is Kt/V useful in elderly dialysis patients? Pro and Con arguments. Nephrol Dial Transplant 2018;33:742–750.

10 Chazot C, Farrington K, Nistor I, Van Biesen W, Joosten H, Teta D, Siriopol D, Covic A: Pro and con arguments in using alternative dialysis regimens in the frail and elderly patients. Int Urol Nephrol 2015;47:1809–1816.

11 Lee JE, Jo IY, Lee SM, Kim WJ, Choi HY, Ha SK, Kim HJ, Park HC: Comparison of hydration and nutritional status between young and elderly hemodialysis patients through bioimpedance analysis. Clin Interv Aging 2015; 10:1327–1334.
12 Deyo RA, Cherkin DC, Ciol MA: Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.
13 Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML: A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. Am J Med 2000;108:609–613.
14 Kurella M, Chertow GM: Dialysis session length ("t") as a determinant of the adequacy of dialysis. Semin Nephrol 2005;25:90–95.
15 Slinin Y, Greer N, Ishani A, MacDonald R, Olson C, Rutks I, Wilt TJ: Timing of dialysis initiation, duration and frequency of hemodialysis sessions, and membrane flux: a systematic review for a KDOQI clinical practice guideline. Am J Kidney Dis 2015;66:823–836.
16 Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R; Hemodialysis (HEMO) Study Group: Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347:2010–2019.
17 Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. N Engl J Med 1993;329:1001–1006.
18 Held PJ, Port FK, Wolfe RA, Stannard DC, Carroll CE, Daugirdas JT, Bloembergen WE, Greer JW, Hakim RM: The dose of hemodialysis and patient mortality. Kidney Int 1996; 50:550–556.
19 Flythe JE, Curhan GC, Brunelli SM: Disentangling the ultrafiltration rate-mortality association: the respective roles of session length and weight gain. Clin J Am Soc Nephrol 2013; 8:1151–1161.
20 Ok E, Duman S, Asci G, Tumuklu M, Onen Sertoz O, Kayikcioglu M, Toz H, Adam SM, Yilmaz M, Tonbul HZ, Ozkahya M; Long Dialysis Study Group: Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis: a prospective, case-controlled study. Nephrol Dial Transplant 2011;26: 1287–1296.
21 Rivara MB, Adams SV, Kuttykrishnan S, Kalantar-Zadeh K, Arah OA, Cheung AK, Katz R, Molnar MZ, Ravel V, Soohoo M, Streja E, Himmelfarb J, Mehrotra R: Extended-hours hemodialysis is associated with lower mortality risk in patients with end-stage renal disease. Kidney Int 2016;90:1312–1320.
22 Marshall MR, Polkinghorne KR, Kerr PG, Hawley CM, Agar JW, McDonald SP: Intensive hemodialysis and mortality risk in Australian and New Zealand populations. Am J Kidney Dis 2016;67:617–628.
23 Daugirdas JT: Removal of phosphorus by hemodialysis. Semin Dial 2015;28:620–623.
24 Daugirdas JT: Hemodialysis treatment time: as important as it seems? Semin Dial 2017;30: 93–98.
25 Kotanko P, Garg AX, Depner T, Pierratos A, Chan CT, Levin NW, Greene T, Larive B, Beck GJ, Gassman J, Kliger AS, Stokes JB; FHN Trial Group: Effects of frequent hemodialysis on blood pressure: results from the randomized frequent hemodialysis network trials. Hemodial Int 2015;19:386–401.
26 Raj DS, Sun Y, Tzamaloukas AH: Hypercatabolism in dialysis patients. Curr Opin Nephrol Hypertens 2008;17:589–594.
27 Assimon MM, Wenger JB, Wang L, Flythe JE: Ultrafiltration rate and mortality in maintenance hemodialysis patients. Am J Kidney Dis 2016;68:911–922.
28 Flythe JE: Ultrafiltration rate clinical performance measures: ready for primetime? Semin Dial 2016;29:425–434.
29 Mathew A, Obi Y, Rhee CM, Chen JL, Shah G, Lau WL, Kovesdy CP, Mehrotra R, Kalantar-Zadeh K: Treatment frequency and mortality among incident hemodialysis patients in the United States comparing incremental with standard and more frequent dialysis. Kidney Int 2016;90:1071–1079.