Dose of Hemodialysis and Survival: A Marginal Structural Model Analysis

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Key Words

Hemodialysis dose · Hemodialysis adequacy · Mortality · Survival · Marginal structural model

Abstract

Background: Observational studies have consistently demonstrated the survival benefits of a greater dialysis dose in maintenance hemodialysis (MHD) patients, whereas randomized controlled trials have shown conflicting results. The possible causal impact of dialysis dose on mortality needs to be investigated using rich cohort data analyzed with novel statistical methods such as marginal structural models (MSMs) that account for time-varying confounding and exposure. **Methods:** We quantified the effect of delivered dose of hemodialysis (HD) [single-pool Kt/V (spKt/V)] on mortality risk in a contemporary cohort of 68,110 patients undergoing HD 3 times weekly (7/2001–9/2005). We compared conventional Cox proportional hazard and MSM survival analyses, accounting for time-varying confounding by applying lon-

gitudinally modeled inverse-probability-of-dialysis-dose weights to each observation. **Results:** In conventional Cox models, baseline spKt/V showed a weak negative association with mortality, while higher time-averaged spKt/V was strongly associated with lower mortality risk. In MSM analyses, compared to a spKt/V range of 1.2–<1.4, a spKt/V range of <1.2 was associated with a higher risk of mortality [HR (95% CI) 1.67 (1.54–1.80)], whereas mortality risks were significantly lower with higher spKt/V [HRs (95% CI): 0.74 (0.70–0.78), 0.63 (0.59–0.66), 0.56 (0.52–0.60), and 0.56 (0.52–0.61) for spKt/V ranges of 1.4–<1.6, 1.6–<1.8, 1.8–<2.0, and ≥2.0, respectively]. Thus, MSM analyses showed that the greatest survival advantage of a higher dialysis dose was observed for a spKt/V range of 1.8–<2.0, and the dialysis dose-mortality relationship was robust in almost all subgroups of patients. **Conclusions:** Higher HD doses were robustly associated with greater survival in MSM analyses that more fully and appropriately accounted for time-varying confounding.

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Introduction

Urea kinetic modeling (UKM) with the introduction of the single-pool Kt/V urea ($\text{spKt/V}_{\text{urea}}$) index is a surrogate marker for low-molecular-weight toxin removal. This is the preferred method for measuring the dose of hemodialysis (HD) treatment per patient based on Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines [1–3]. In the Hemodialysis (HEMO) study [4], a randomized controlled trial (RCT) of maintenance HD (MHD) patients, a higher dialysis dose did not confer a survival benefit compared with standard dose. In contrast, most observational studies [5–11] have demonstrated a lower mortality risk associated with a higher HD dose. However, the observed association between a higher HD dose and decreased mortality may be a consequence of confounding by indication and time-varying confounding such as body size and nutritional status. High Kt/V values may result from high Kt (clearance $\times$ time) or small V (i.e. small body size which may reflect nutritional status). Larger patients tend to achieve smaller Kt/V values [11], and large body size is associated with decreased mortality [11, 12]. MHD patients with extremely high achieved Kt/V tend to have protein-energy wasting (PEW) [13, 14], which is correlated to increased mortality [15–17]. These time-varying confounders influence the likelihood of subsequent HD dose and mortality, and they also serve as intermediates in the dose-mortality association.

Application of novel statistical techniques such as marginal structural models (MSMs) may be useful to control for time-varying confounding and to examine the longitudinal exposure effects in observational studies [18]. MSMs are a causal modeling tool that can be fit using inverse-probability-of-treatment weights to remove time-varying confounding and thus, mimic randomization of treatment in the study sample, provided causal assumptions such as conditional exchangeability (no uncontrolled confounding) hold [19]. With sufficient confounding control, and in the absence of measurement error and selection bias, the results of MSMs might be comparable to those obtained in RCTs [18]. We hypothesized that higher Kt/V is associated with greater survival in a large nationally representative cohort of MHD patients. In order to investigate the possible effects of handling time-varying confounding and exposure appropriately, we used both conventional Cox regression and MSM analyses to examine the proposed hypothesis. We used MSMs to account for time-varying laboratory measures and body size, which are both the results and determinants of dialysis dose.

Materials and Methods

Study Population and Data

We extracted and examined data from all patients with end-stage renal disease who underwent HD between July 2001 and June 2006 in any one of the 580 US outpatient dialysis facilities of DaVita Inc. The baseline quarter for each patient was the earliest calendar quarter in which the patient's HD duration was >90 days. Among 127,304 patients who underwent HD for >90 days, we excluded patients age <18 or >99 years or without age data ($n = 580$) and those without spKt/V data for at least two calendar quarters or $\text{spKt/V} <0.8$ or >2.7 ($n = 50,332$). Among the remaining 76,392 patients, we excluded patients whose time on dialysis was <2.5 or >5 h, or who had missing time on dialysis data to exclude short daily or long nocturnal MHD patients ($n = 8,282$). The final study population consisted of 68,110 patients (online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000362285). Due to missing data on time on dialysis between October 2005 and June 2006, we restricted the study cohort period from July 1, 2001 to September 30, 2005. The study was approved by the institutional review committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, and DaVita Clinical Research. The requirement for a written consent was exempted due to large sample size, patient anonymity, and non-intrusive nature of the research.

The creation of the DaVita MHD patient cohort has been described previously [20]. To minimize measurement variability, all repeated measures for each patient during any calendar quarters (i.e. over a 13-week interval) were averaged and used in all models. Clinical measures and laboratory parameters for each patient were obtained during the cohort period (July 1, 2001–September 30, 2005) and patients were followed for outcomes until September 30, 2005. Dialysis duration was defined as the duration of time between the first day of HD treatment and the day that the patient entered the cohort. Demographic data were obtained from the DaVita database. History of preexisting comorbid conditions and tobacco smoking were obtained by linking the DaVita database to the data from Medical Evidence Form 2728 from the US Renal Data System (USRDS). Available preexisting comorbidities were grouped into nine categories: atherosclerotic heart disease, congestive heart failure, other cardiac diseases, hypertension, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, cancer, and non-ambulatory state.

Outcome Measure

All-cause mortality was defined by 'date of death' if it occurred during the cohort period (July 1, 2001–September 30, 2005). Patients who received a kidney transplant, or were lost to follow-up, were coded as censored. The percentages of patients censored for kidney transplantation and being lost to follow-up were 4 and 2%, respectively. The use of one set of censoring weights has been performed in the previous studies [21, 22]. Sensitivity analyses were conducted with consideration of censoring weights for transplantation and loss to follow-up.

Main Predictor or Exposure

spKt/V was calculated monthly by using UKM equations derived from the following equation [2, 23]:

$$\text{Kt/V} = -\ln(R - 0.008 \times t) + [(4 - 3.5 \times R) \times \text{UF/W}],$$

where R is the ratio of post-dialysis to pre-dialysis serum urea nitrogen concentration; t is duration of HD (in hours); UF is the amount of ultrafiltration (in liters) during the HD session, and W is the post-dialysis weight (in kilograms). However, the UKM equations used in DaVita laboratories to calculate spKt/V are more complex, and computational software programs were used. We divided spKt/V values into six a priori categories (<1.2, 1.2–<1.4, 1.4–<1.6, 1.6–<1.8, 1.8–<2.0, and ≥2.0). The spKt/V category of 1.2–<1.4 was designated as the reference group on the basis of the KDOQI recommended dialysis dose for 3 times weekly treated HD patients [1].

Laboratory Measures

Blood samples were drawn using standardized techniques in all DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, Fla., typically within 24 h. All laboratory values were measured using automated and standardized methods in the DaVita Laboratory. Most laboratory parameters were measured monthly, including complete blood cell counts, and serum levels of urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, and total iron-binding capacity (TIBC). The normalized protein equivalent of total nitrogen appearance (nPNA), known as normalized protein catabolic rate, was measured monthly as an indicator of daily protein intake. Serum ferritin levels were measured at least quarterly. Corrected serum calcium concentrations were calculated using the following equation: 'corrected calcium (mg/dl) = {0.8 × [4 – serum albumin (g/dl)]} + serum calcium (mg/dl)'. Most blood samples were collected prior to HD, except for post-dialysis serum urea nitrogen, to calculate urea kinetics.

Statistical Analyses

Survival analyses including conventional Cox proportional hazard regression (baseline and time-averaged models), and inverse-probability-of-treatment-weighted fitting of MSMs were used to examine the impact of spKt/V (main predictor) on all-cause mortality (outcome).

We used conventional Cox proportional hazard regression models to study the associations of baseline spKt/V (baseline model) and time-averaged spKt/V (time-averaged model) with mortality separately. Time-averaged spKt/V was the average of spKt/V obtained from each calendar quarter for each patient during the entire follow-up period. The models were adjusted for entry calendar quarter, age, sex, race/ethnicity (non-Hispanic Caucasians, African-Americans, Hispanics, and Asians), dialysis duration categories (<6 months, 6–<24 months, 2–<5 years, and ≥5 years), primary insurance (Medicare, Medicaid, and others), types of vascular access (arteriovenous fistula, arteriovenous graft, and catheter), presence of diabetes, nine preexisting comorbidities, history of tobacco smoking, body mass index (BMI), serum levels of albumin, TIBC, ferritin, creatinine, phosphorus, calcium, bicarbonate, hemoglobin, peripheral white blood cell (WBC) count, and lymphocyte percentage. The conventional model for time-averaged spKt/V used time-averaged variables, whereas baseline variables were used in the model for baseline spKt/V. All adjusted values were used in the construction of the inverse-probability-of-treatment weights for spKt/V in the MSM described below.

MSM fitted using stabilized weights (SWs) was used to determine the effects of delivered spKt/V on mortality while controlling for the effects of time-dependent confounders affected by previous treatment. The SW used in MSM analysis was calculated as the product of stabilized inverse-probability-of-treatment-weight

(IPTW) and inverse-probability-of-censoring-weight (IPCW). Stabilized IPTW and IPCW were calculated from the ratio of (i) the estimated probabilities of treatment (or censorship) using previous delivered spKt/V, and fixed baseline covariate values (numerator) to (ii) the estimated probabilities of treatment (or censorship) using previous delivered spKt/V, fixed baseline covariates, and time-varying covariates (denominator) as described in the previous studies [21, 24–26]. Logistic regression was used to estimate the numerators and denominators of the IPTW and IPCW. Fixed baseline covariates included age, sex, race/ethnicity, dialysis duration categories, primary insurance, presence of diabetes, nine preexisting comorbidities, history of tobacco smoking, and types of vascular access. Time-varying covariates included the study quarter, BMI, and serum levels of albumin, TIBC, ferritin, creatinine, phosphorus, calcium, bicarbonate, hemoglobin, peripheral WBC count, and lymphocyte percentage. The distribution of SWs in MSM is shown in online supplementary table 1. To decrease the disproportional effect of observations with extremely high weights when fitting to the MSM, SWs were truncated by resetting the values of SWs >99th percentile (>3.11) to the values of 99th percentile (3.11). For analysis with MSMs, a pooled logistic regression model fitted using SWs was used to calculate odds ratios for the odds of dying associated with HD dose. A joint model of longitudinal spKt/V values and time to death was performed separately to assess the impact that longitudinal spKt/V, measured with error, had on the time to death. For joint modeling analyses, the linear mixed effects model and Weibull proportional hazards model were used for the longitudinal submodel and the survival model, respectively. The integration method was adaptive Gauss-Hermite quadrature using five nodes. Gauss-Kronrod 15-point quadrature was used to calculate the cumulative hazard.

Missing values of time-varying covariates (<1% for most laboratory variables) were imputed using the values in the previous quarter, whereas missing data on fixed baseline covariates (<3% for most demographic variables) were imputed by the means or medians of the existing values as appropriate. The same study population was used for the analysis with the time-averaged Cox model, MSM, and joint models. MSM analysis was also performed in subgroups of patients based on baseline age, sex, race/ethnicity, presence or absence of diabetes mellitus, baseline serum albumin level, dialysis duration, and baseline BMI categories. We reported p values from two-sided tests with a significance level set to 0.05. All statistical analyses were performed using Stata version 11.2 (Stata Corp., College Station, Tex., USA).

Results

Cohort Description

The baseline demographics, clinical, and laboratory characteristics of the 68,110 MHD patients stratified by dose of HD (delivered spKt/V) are summarized in table 1. The mean (SD) patient age was 59 (16) years; 45% of the patients were women, 37% were African-American, and 58% were diabetics. Patients with higher spKt/V were more likely to be of older age, female, Hispanic and non-Hispanic Caucasian, and were less likely to be African-

Table 1. Baseline characteristics of 68,110 MHD patients stratified by average spKt/V categories

	Average spKt/V range						
	all	<1.2	1.2–<1.4	1.4–<1.6	1.6–<1.8	1.8–<2.0	≥2.0
Number (%)	68,110 (100)	2,811 (4)	10,972 (16)	24,437 (36)	19,199 (28)	7,604 (11)	3,087 (5)
Age, years	59±16	53±15	56±16	59±16	61±16	62±15	63±16
Female, %	45	24	26	38	55	69	75
<i>Race/ethnicity, %</i>							
Non-Hispanic Caucasian	42	38	41	41	43	44	47
African-American	37	51	45	40	34	25	18
Hispanic	17	10	13	16	19	25	26
Asian	4	1	1	3	4	6	9
<i>Dialysis duration, %</i>							
3–<6 months	54	64	60	52	51	53	59
6–<24 months	18	16	17	19	19	19	17
2–<5 years	18	13	15	19	19	18	15
≥5 years	10	7	8	10	11	10	9
<i>Primary insurance, %</i>							
Medicare	69	63	66	70	71	70	68
Medicaid	6	9	7	6	6	7	6
Other	25	28	27	24	23	23	26
<i>Vascular access, %</i>							
AVF	30	20	28	31	30	29	27
AVG	36	19	27	36	41	43	42
Catheter	34	61	45	33	29	28	31
<i>Comorbidities, %</i>							
Diabetes mellitus	58	62	60	58	57	56	51
Atherosclerotic heart disease	21	19	20	21	21	22	22
Cancer	3.9	3.3	3.7	3.8	4	4.2	4.8
Congestive heart failure*	27	28	27	27	27	28	26
COPD	5	5	5	5	6	6	6
Cerebrovascular disease	7	6	6	7	8	8	7
Hypertension*	79	79	79	80	80	80	78
Other cardiac diseases*	4.5	4.3	4.5	4.6	4.5	4.5	4.2
Peripheral vascular disease*	11	11	11	10	11	11	11
Non-ambulatory state*	2.5	2.7	2.8	2.4	2.4	2.5	2.2
Current smoking	4.9	6	6	4.9	4.5	4.2	3.9
% obesity ^a	26	44	35	28	22	16	11
Time on dialysis, min	215±27	218±30	217±28	215±27	214±27	214±26	213±26
Blood flow rate, ml/min	387±64	369±67	380±65	390±64	390±63	389±63	384±64
Dialysate flow rate, ml/min	754±83	758±77	755±80	754±82	751±87	756±86	760±83
Postdialysis weight, kg	76±21	93±26	86±23	79±20	71±18	65±16	61±16
Height, m	1.68±0.12	1.75±0.11	1.73±0.11	1.69±0.11	1.65±0.10	1.61±0.11	1.59±0.11
Body mass index	27.0±6.9	30.6±8.6	28.7±7.5	27.4±6.8	26.2±6.2	24.9±5.8	24.0±5.7
<i>Laboratory measures (baseline)</i>							
Albumin, g/dl	3.7±0.4	3.6±0.5	3.7±0.4	3.7±0.4	3.7±0.4	3.7±0.4	3.7±0.4
Creatinine, mg/dl	8.4±3.3	9.0±3.9	8.9±3.7	8.8±3.4	8.1±3.0	7.5±2.7	6.6±2.5
TIBC, mg/dl	210±44	209±46	213±45	210±44	209±43	209±43	210±44
Ferritin ^b , ng/ml	385 (179–724)	289 (137–551)	317 (152–624)	388 (180–719)	421 (195–769)	425 (202–784)	424 (206–770)
Bicarbonate, mg/dl	22.0±2.9	21.6±3.0	21.8±2.9	22.0±2.8	22.1±2.9	22.2±2.9	22.2±2.8
Calcium, mg/dl	9.5±0.7	9.4±0.7	9.4±0.7	9.5±0.7	9.5±0.7	9.5±0.6	9.5±0.6
Phosphorus, mg/dl	5.6±1.5	6.1±1.7	5.9±1.5	5.7±1.5	5.5±1.4	5.4±1.4	5.2±1.3
Hemoglobin, g/dl	12.1±1.3	11.7±1.5	11.9±1.4	12.1±1.3	12.1±1.3	12.2±1.2	12.2±1.2
WBCs, ×10 ³ /μl*	7.3±2.3	7.6±2.7	7.3±2.4	7.2±2.3	7.3±2.3	7.3±2.3	7.3±2.1
% lymphocytes	21.1±7.7	20.1±7.7	20.8±7.8	21.2±7.8	21.2±7.7	21.1±7.6	21.3±7.7
nPNA, g/kg/day	0.96±0.25	0.86±0.22	0.91±0.23	0.95±0.24	0.99±0.25	1.01±0.26	1.03±0.28

AVF = Arteriovenous fistula; AVG = arteriovenous graft; COPD = chronic obstructive pulmonary disease. ^a Percentage of patients with BMI ≥30. ^b Median (interquartile range) is used for serum ferritin level. The differences in each variable across average spKt/V categories were estimated by p for trend. All p values are <0.05 unless marked with an asterisk; * p values >0.05.

Table 2. Hazard ratios (95% CIs) for the association between spKt/V categories (reference 1.2–<1.4) and all-cause mortality, obtained from different analytical models

spKt/V range	Baseline model (n = 64,528)			Time-averaged model (n = 68,110)			MSM (n = 68,110)		
	HR	95% CI	p value	HR	95% CI	p value	HR	95% CI	p value
<1.2	1.07	1.02–1.12	0.008	1.31	1.23–1.40	<0.001	1.67	1.54–1.80	<0.001
1.2–<1.4	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.	ref.
1.4–<1.6	1.00	0.96–1.03	0.79	0.69	0.66–0.71	<0.001	0.74	0.70–0.78	<0.001
1.6–<1.8	0.90	0.87–0.94	<0.001	0.57	0.54–0.59	<0.001	0.63	0.59–0.66	<0.001
1.8–<2.0	0.90	0.86–0.95	<0.001	0.54	0.51–0.57	<0.001	0.56	0.52–0.60	<0.001
≥2.0	0.83	0.78–0.88	<0.001	0.52	0.48–0.56	<0.001	0.56	0.52–0.61	<0.001

American patients or to use a catheter. SpKt/V positively correlated with nPNA, but negatively correlated with measures of body size, serum creatinine, and phosphorus levels (table 1). A total of 23,810 patients died [crude mortality rate (95% CI) 159/1,000 (157–161/1,000 person-years)] during a median (IQR) follow-up of 1.98 (1.08–3.3) years.

Conventional Cox Model

The observed association of HD dose with mortality varied according to the applied statistical models. There was a weak negative relationship between baseline spKt/V and mortality, whereas time-averaged spKt/V showed a strong negative association with mortality (table 2; fig. 1). In time-averaged models, compared to a spKt/V range of 1.2–<1.4, those with spKt/V range of <1.2 had an increased mortality risk [HR (95% CI) 1.31 (1.23–1.40)], whereas a survival advantage was associated with spKt/V ≥1.4 [HRs (95% CI) 0.69 (0.66–0.71), 0.57 (0.54–0.59), 0.54 (0.51–0.57), and 0.52 (0.48–0.56) for spKt/V ranges of 1.4–<1.6, 1.6–<1.8, 1.8–<2.0, and ≥2.0, respectively] (table 2). In time-averaged models, a prominent survival benefit of higher dialysis dose was associated with a spKt/V range of 1.6–<1.8, and beyond this range the survival gain was minimal (fig. 1).

MSM and Joint Models

In MSM analysis, higher spKt/V was associated with a lower mortality risk. In comparison to a spKt/V range of 1.2–<1.4, death HRs (95% CI) associated with spKt/V ranges of <1.2, 1.4–<1.6, 1.6–<1.8, 1.8–<2.0, and ≥2.0 were 1.67 (1.54–1.80), 0.74 (0.70–0.78), 0.63 (0.59–0.66), 0.56 (0.52–0.60), and 0.56 (0.52–0.61), respectively (table 2). The greatest survival advantage of a higher dialysis dose was associated with a spKt/V 1.8–<2.0 range, while no further reduction in mortality was observed with

Fig. 1. Hazard ratios (95% CIs) for the associations between spKt/V categories (reference 1.2–<1.4) and all-cause mortality, obtained from baseline, time-averaged, and MSMs.

spKt/V ≥2.0 in MSM analyses (fig. 1). The findings of sensitivity analysis using SWs calculated as the product of IPTW, inverse-probability-of-transplant-weight, and inverse-probability-of-censoring-weight (due to lost follow-up) were similar (online suppl. table 2). The results of the analyses conducted with and without imputation were essentially the same (online suppl. table 3). Sensitivity analyses using a 6-month interval of dialysis duration categories were performed and data were similar (data were not shown here). The greatest survival benefit of spKt/V in the 1.8–<2.0 range appeared to be consistent in almost all subgroups of patients based on demographics (baseline age, sex, race/ethnicity), diabetic status, baseline serum albumin, dialysis duration, and baseline BMI cat-

egories. The trends toward greater survival with a spKt/V range of ≥ 2.0 were observed among patients of Hispanic ethnicity, ≥ 65 years old, with a baseline serum albumin level < 3.8 g/dl, dialysis duration ≥ 1 year, and baseline BMI ≥ 30 kg/m² (fig. 2a–c and online suppl. table 4). The survival benefits of a higher dialysis dose were observed using joint models adjusted for case-mix covariates and malnutrition inflammation complex syndrome (MICS) surrogates (online suppl. table 5).

Discussion

In this retrospective analysis of 68,110 patients receiving 3 times weekly HD treatments lasting 2.5–5 h in a large dialysis organization in the USA, a higher delivered HD dose was associated with lower risk of mortality using causal models known as MSMs to adjust for time-varying confounding. In MSMs, the greatest survival gain with a higher HD dose was observed with a spKt/V range of 1.8– < 2.0 . Similar results were observed in almost all demographic and clinical subgroup analyses using MSMs.

While most prior observational studies [5–11] reported an association between higher HD dose and lower risk of mortality, the HEMO RCT [4] which compared high HD dose (spKt/V 1.71 ± 0.11) with standard dose (spKt/V 1.32 ± 0.09) found no survival advantage of a higher dialysis dose. A secondary analysis of HEMO study using an ‘as-treated’ instead of ‘intention-to-treat’ approach [27] proposed that ‘dose-targeting bias’ might explain these discrepancies between the RCT and previous observational studies. This study [27] showed that larger anthropometric volume over time, comorbidities, and declining serum albumin levels were associated with lower achieved Kt/V values in both high-dose and standard-dose treatment groups. Indeed, PEW [15–17] and small body size [9, 11, 12] have been associated with increased mortality in dialysis patients. The combined effects of body size and dialysis dose on mortality tend to partially cancel each other out due to the tendency of larger and smaller patients achieving a smaller and larger Kt/V, respectively [11]. Larger body size was associated with a lower mortality risk [11, 12]; therefore, the confounded association between body size and dialysis dose might obscure the survival advantage of a higher dialysis dose [11]. In addition, MHD patients who achieved an extremely high urea reduction ratio or spKt/V values tended to be those who were malnourished, further suggesting that the Kt/V-mortality relationship may be confounded by PEW [13, 14].

Our study observed that there was an association between a higher dose of HD and lower death risk when using conventional Cox models. However, these standard statistical methods are subject to major sources of bias such as confounding-by-indication, and time-varying confounding due to nutritional status and body size. Such time-varying confounders influence (1) the likelihood of future treatment (e.g. spKt/V) and (2) future outcome (e.g. mortality) conditional on past treatment, and may subsequently confound the dose-mortality association. Novel statistical techniques such as MSMs may be useful in addressing time-varying confounding. MSMs can be used to estimate the causal effects of a time-varying exposure in the presence of time-varying covariates (that may simultaneously function as confounders and intermediate variables), and are thus referred to as causal models [18, 28].

To our knowledge, ours is the first large epidemiologic study using MSMs to determine the causal relationship between dialysis dose and survival in 3 times weekly treated HD patients, and we adjusted for time-varying confounding including body size and MICS surrogates that might correlate with HD dose and patient outcomes. We observed that a higher dialysis dose was associated with a survival advantage using MSMs, and that the dialysis dose-mortality association was attenuated at a higher dose with a plateau effect for survival beginning at a spKt/V range of 1.8– < 2.0 . MSMs have been used to confirm the survival advantage of activated injectable vitamin D [29] and to determine the effects of levocarnitine on hospitalization in MHD patients [30]. Previous analyses stratified by body size showed a similar association between a higher HD dose and lower risk of mortality in all body-size groups [9, 11]. Furthermore, a recent study using normalization of dialysis dose to body surface area demonstrated an association between a higher surface area-based dialysis dose and increased survival in 3 times weekly treated HD patients [31]. An attenuation in the survival advantage observed with higher dialysis doses may in part be due to electrolyte derangements and/or disequilibrium, arrhythmia, hypotension, and myocardial stunning resulting from higher ultrafiltration vol-

Fig. 2. All-cause mortality hazard ratios (95% CIs) comparing spKt/V categories (reference 1.2– < 1.4) using a MSM stratified by sex, race/ethnicity (a), baseline age, presence or absence of diabetes mellitus, baseline serum albumin levels (b), dialysis duration and baseline BMI categories (c). Low-, medium-, and high-BMI subgroups include patients with a BMI < 18.5 , 18.5– < 30 , and ≥ 30 , respectively. Alb = Serum albumin levels.

(For figure see next page.)

umes [32–34] associated with rapid and vigorous dialysis at unusually high dialysis doses (such as $\text{spKt/V} \geq 2.0$ within 4 h).

Previous observational studies have shown that there are survival benefits associated with a higher HD dose in women compared with men [7, 35], Whites compared with African-Americans [7], and a subgroup analysis in the HEMO study [4] also suggested greater benefits of a higher HD dose in women compared with men. However, a higher HD dose normalized to body surface area showed an association with a lower mortality risk in both men and women, and the dose-mortality curves were similar in shape for both sexes [31]. Similarly, our study found a consistent relationship between higher HD dose and greater survival in almost all subgroups. Our subgroup analyses showed a trend towards greater survival with a $\text{spKt/V} \geq 2.0$ among Hispanic, elderly, hypoalbuminemic, and obese patients, and patients on dialysis ≥ 1 year, but confirmatory studies are needed given the risk of false-positive findings from conducting multiple subgroup analyses.

Strengths of this study include (1) the use of MSM analyses to address potential time-varying confounders such as body size and MICS surrogates that link to both HD dose and patient survival; (2) the large sample size of the cohort; (3) uniform administrative patient care within a large dialysis organization, and laboratory measurements conducted at a single facility, and (4) the use of averaged laboratory measures during any calendar quarter (i.e. over a 13-week period) to minimize measurement variability.

However, several limitations of this study bear mention. First, our study was observational in nature, and we lacked data on patient compliance with HD treatments, types of dialyzer membranes, practice patterns associated with dialysis, and longitudinal data on comorbidities, which may have resulted in residual confounding. Second, residual renal function (RRF) could not be included in the main analysis due to missing data. RRF is associated with better survival in MHD patients [36] and may confound the HD dose-mortality association. However, this association was unchanged in subgroup analysis of patients with dialysis duration ≥ 1 year who were likely to have minimal RRF. Third, we excluded patients without spKt/V data for at least two quarters or those with outliers of spKt/V and this may lead to selection bias. Fourth, we were unable to account for certain markers of inflammation such as C-reactive protein; however, our analyses were adjusted for serum levels of albumin, ferritin, TIBC, WBC count, and lymphocyte percentage, which are

known to be associated with inflammation in dialysis patients [37].

In summary, in a large cohort of 68,110 HD patients treated 3 times weekly, a higher dose of HD was associated with greater survival up to a spKt/V 1.8–<2.0, and no further survival advantage was observed with a $\text{spKt/V} \geq 2.0$ in MSM analyses that more fully and appropriately address important time-varying confounding. The inverse correlation between HD dose and mortality was robust across different subgroups of patients with a spKt/V approaching the 1.8–<2.0 range using MSMs. Further RCTs on survival advantage of HD dose should consider incorporating MSMs in their sensitivity analyses.

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