ORIGINAL ARTICLE
Adequacy

The association of standard Kt/V and surface area-normalized standard Kt/V with clinical outcomes in hemodialysis patients

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Abstract

Introduction: A previous study demonstrated that the surface area-normalized standard Kt/V (SAstdKt/V) was better associated with mortality than standard Kt/V (stdKt/V). This study investigates the association of SAstdKt/V and stdKt/V with mortality, anemia, and hypoalbuminemia in a larger patient cohort with a longer follow-up period.

Methods: We included adult patients on thrice-weekly hemodialysis in the USRDS database and excluded amputated patients. StdKt/V and SAstdKt/V were calculated from the available single-pool Kt/V. Patients were categorized into five groups according to their stdKt/V and SAstdKt/V: <2.00, 2.00–2.19, 2.20–2.39, 2.40–2.59, and ≥2.60. Hazard ratios (HR) and odds ratios (OR) were calculated using Cox and logistic regression analysis respectively.

Findings: There were 507,656 patients included in the analysis. The patients had a median age of 65.5 years with a median follow-up period of 2 years. Thirty-four percent died during follow-up. HRs for mortality progressively decreased as SAstdKt/V increased in both unadjusted and adjusted models. Unlike SAstdKt/V, HRs were the lowest in the categories with stdKt/V of 2.40–2.59 and they increased in the higher stdKt/V category. The adjusted HR for SAstdKt/V vs. stdKt/V were 0.68 vs. 0.62 in the category of 2.40–2.59, and 0.63 vs. 0.73 in the category of ≥2.60. The adjusted ORs for anemia progressively decreased as SAstdKt/V increased, whereas ORs decreased to the lowest in stdKt/V category 2.40–2.59 and increased in the ≥2.60 category. The adjusted ORs for

hypoalbuminemia progressively decreased as SAstdKt/V and stdKt/V increased which were both 0.45 in 2.40–2.59 category and decreased to 0.29 and 0.42 in the ≥2.60 category.

Discussion: SAstdKt/V is better associated with mortality, anemia, and hypoalbuminemia than stdKt/V. SAstdKt/V is a better parameter in defining hemodialysis dosing which can be calculated by an available online tool. Further studies to determine the optimal SAstdKt/V dose required to achieve improved clinical outcomes with better cost-effectiveness are needed.

Keywords: Adequacy of dialysis, survival, nutrition, anemia

INTRODUCTION

Hemodialysis (HD) adequacy is commonly determined by measuring small-solute clearance using urea Kt/V, where "K" denotes urea clearance, "t" time of dialysis treatment, and "V" urea distribution volume, which equates to total body water.[1] HD patients with single-pool Kt/V (spKt/V) less than 1.2 have worse clinical outcomes and higher mortality.[2,3] A National Institutes of Health-sponsored Hemodialysis study (HEMO) showed that patients who received standard dose vs. high dose spKt/V (1.3 vs. 1.7) had no difference in mortality rate.[4] Data from the HEMO study were reanalyzed and it was found that female patients benefited from the higher dialysis dose. Unsurprisingly, females had a significantly lower "V" than their male counterparts.[5] These results raised questions about the effect of normalizing the dialysis dose normalization for "V."

Since Kt/V is most commonly calculated using a complex mathematical equation which does not allow easy determination of the Kt value alone,[1] practical rescaling would involve multiplying Kt/V with the estimated "V" and then dividing it by the desirable variables instead. Among the alternative variables that have been proposed for Kt/V rescaling, body surface area (BSA) has been a promising option with some physiologic justifications.[6,7] First, the liver is known to be the major organ responsible for uremic toxin metabolism and its volume is best estimated as a function of BSA.[8] Second, normalization of glomerular filtration rate (GFR) with BSA has been used for decades.[9] The scaling of estimated GFR with either BSA or liver volume has been shown to be not significantly different between genders and body sizes, whereas scaling with "V" resulted in significant differences.[10]

The V/BSA ratio was found to be relatively lower in females and males with smaller body size.[6,11,12] Therefore, the rescaling of Kt/V with BSA or surface area (SA)-based dose in these patients would result in lower Kt/Vs than previously calculated. As a result, a volume (V)-based dose would result in less dialysis given to these patients than is truly required. In the HEMO study, female patients in the conventional-dose group had a lower surface-area-normalized standard Kt/V (SAstdKt/V) than male patients in the conventional-dose group, although they had similar standard Kt/V (stdKt/V) results. In addition, females and smaller body-sized patients in the higher dose group had lower mortality rates compared to patients in the conventional-dose group.[12] This result indicates that these patients received inadequate dialysis.

In a prior study of HD patients receiving thrice-weekly HD, the hazard ratio (HR) for 1-year mortality decreased progressively as the SAstdKt/V increased in both genders, while the HR increased in the higher quintiles of stdKt/V.[13] This suggests that SAstdKt/V may perform better than stdKt/V as a measure of dialysis adequacy when evaluating the association between dialysis dose and mortality, especially at extreme values.

Studies determining the relationship between SAstdKt/V and mortality are scarce, and none have been performed for other clinical outcomes. Therefore, we set out to study the association between the HD dose, expressed using stdKt/V and SAstdKt/V, and the clinical outcomes of mortality, anemia, and hypoalbuminemia in a larger cohort with a longer follow-up period.

MATERIALS AND METHODS

Participants and study design

Prevalent HD patients from the United States Renal Data System (USRDS) database[14] with an age of 18–100, who received HD for ≥90 days and did not receive any other renal replacement therapy (RRT) modality were included in the study.

Patients with no monthly data from Consolidated Renal Operations in a Web-enabled Network (CROWNWeb) clinical data file, had an amputation, or who had not received thrice-weekly HD treatments were excluded. The CROWNWeb file contained monthly laboratory and dialysis adequacy results from May 2012 to May 2017. Patients who had at least 1 month of data were included in the analysis. Patients with missing necessary data for SAstdKt/V calculation, such as gender, spKt/V, height, weight, dialysis frequency, and duration were excluded.

The demographics, sequence of dialysis treatment, and death were obtained from patients' medical evidence, treatment history, and death files. Outlier data values were excluded from the analysis (Supplementary Table S1). After exclusion of this data, patients who had no spKt/V, pre- and post-HD weights, dialysis treatment times, or who did not have all these data at the same time-point for SAstdKt/V calculation were excluded.

The vintage of dialysis was calculated as the date of RRT initiation minus the first date of data available on CROWNWeb. As CROWNWeb does not report the date of the labs, only the month and year, we defaulted the date to the first of the month which may lead to values of up to negative 30 days. Patients with negative dialysis vintage or with a date of death occurring before the last reported date from the CROWNWeb clinical data file were excluded (Figure 1).

The primary outcome was mortality and the secondary outcomes were anemia (mean hemoglobin level < 10 g/dL) and hypoalbuminemia (mean serum albumin level < 3.5 g/dL). Deaths were censored at 30 days after the last reported date from the CROWNWeb clinical data file.

Formal modeling

The spKt/V results were collected from the CROWNWeb clinical data file. SAstdkt/V was calculated using the following steps:

Step 1: The equilibrated Kt/V (eKt/V) was calculated using the modified Tattersall Equation.[1,15,16]

$$eKt/V = spKt/V \left(\frac{t}{t + 30} \right)$$

where "t" is the HD treatment time in minutes and 30 is the correction value.

Step 2: The stdKt/V was calculated using the simplified, fixed-volume equation by Leypoldt.[1,17]

$$stdKt/V = \frac{10,080 \frac{1 - e^{-eKt/V}}{t}}{\frac{1 - e^{-eKt/V}}{eKt/V} + \frac{10,080}{Nt} - 1}$$

where "N" = 3, the number of treatments per week.

Step 3: The volume of distribution of urea (V) was calculated using the equation by Watson et al[18]:

Volume of distribution of urea (V)
for males = $2.447 - (0.09156 \times A) + (0.1074 \times H) + (0.03362 \times W)$.
for females = $-2.097 + (0.1069 \times H) + (0.2466 \times W)$.
where "A" is age in years, "H" is height in centimeters, and "W" is post-HD weight in kilograms.

Step 4: The stdKt/V was adjusted with volume change during dialysis using the equation by Chin et al.[19]
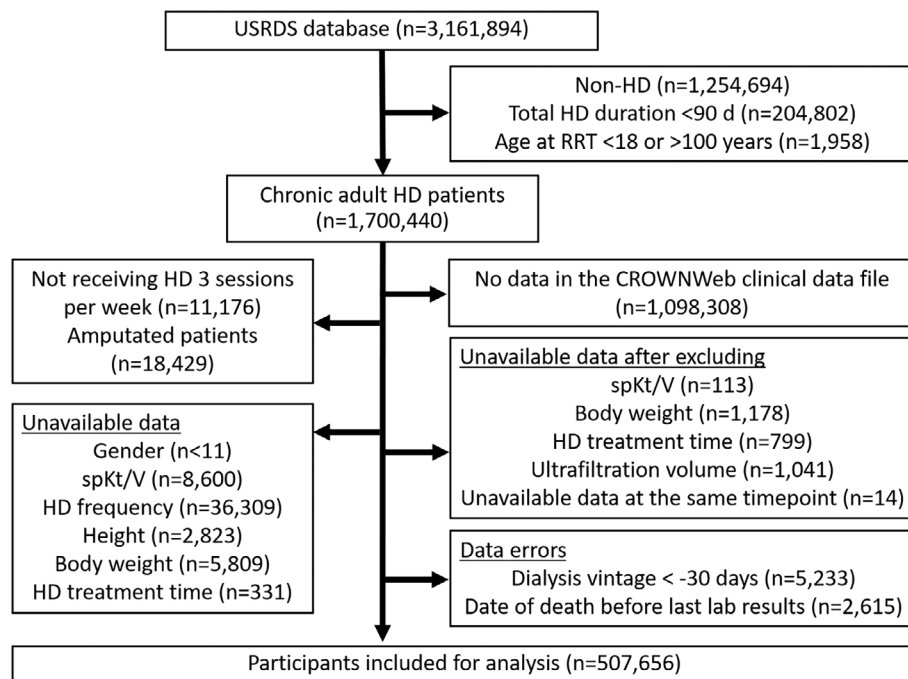
Figure 1 The study flow. HD, hemodialysis; RRT, renal replacement therapy, spKt/V, single-pool Kt/V; USRDS, United States Renal Data System.

$$stdKt/V = \frac{S}{\left(1 - \left(\frac{0.74}{N}\right) \times \left(\frac{UFw}{Vu}\right)\right)}$$

where "N" = 3, the number of treatments per week, "UFw" is weekly fluid removal in mL which can be estimated by multiplying volume of ultrafiltration with 3 (number of treatments per week), and "Vu" is volume distribution of urea in mL from urea kinetic model. Since the urine output and the pre- and post-dialysis BUN were not available from the monthly reported results in the CROWNWeb clinical data file, the urea clearance from residual native function was omitted and the "Vu" is estimated by multiplying V with 0.9.[19] The value of adjusted stdKt/V with this equation will be typically 6–7% higher than the value obtains from step 2.

Step 5: The body surface area (BSA; m^2) was calculated using the equation by DuBois and DuBois[20]:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184.$$

Step 6: The SAstdKt/V was calculated using the equation by Daugirdas et al[1,6]:

$$SAstdKt/V = \frac{stdKt/V}{20} \times \frac{V}{BSA}$$

where 20 is a normalizing factor (population mean V/BSA).

Statistical analyses

The monthly laboratory and dialysis dose measurements were averaged. The baseline data were presented as a percentage and a median (interquartile range, IQR) for categorical and continuous variables, respectively. Baseline descriptive statistics were compared using stdKt/V < 2.0 vs. ≥ 2.0 and SAstdKt/V < 2.0 vs. ≥ 2.0 using Fisher's Exact test for categorical variables and Wilcoxon Rank-Sum test for continuous variables. The mean stdKt/V and SAstdKt/V were categorized into five groups: 1) less than 2.00, 2) 2.00–2.19, 3) 2.20–2.39, 4) 2.40–2.59, and 5) 2.60 or more. The Kaplan–Meier survival analysis was performed, and the survival estimates among the five categories compared by the Log-Rank test. We assumed that the stdKt/V and SAstdK/V levels were steady throughout the follow-up period and used their averaged monthly levels as the variable of interest in the Cox model. The association between outcomes and calculated stdKt/V and SAstdKt/V were determined by Cox proportional hazard models for the primary outcome and logistic regression for secondary outcomes.

The three Cox regression analysis models were adjusted for 1) age, gender, race and Hispanic ethnicity, 2) model 1 plus comorbidities (list of comorbidities provided in Supplementary Table S1), and 3) model 2 plus serum albumin and dialysis vintage. The adjusted odds ratio (OR) for anemia and hypoalbuminemia were adjusted by similar covariates as used for model 3, except not including serum albumin for adjusted hypoalbuminemia. The group with stdkt/V and SAstdKt/V of 2.00–2.19 were used as the reference.

This study was approved by Icahn School of Medicine Program for the Protection of Human Subjects/Institutional Review Board (IRB-18-01255). The analysis was done using Stata/IC 15.1 software (StataCorp, College Station, TX, USA).

RESULTS

Patient and treatment characteristics

There were 3,161,894 patients initially in the study. After applying the exclusion criteria, there were a total of 507,656 patients (Figure 1). The median age was 65.5 (55.8–74.9) years with a median follow-up period of 2.0 (0.9–3.8) years. Fifty-six percent were male, 60% were white, 33% were African American, and 50% of the patients used an AVF or AVG at the time of entry into the analysis. The patients had a median spKt/V of 1.6 (1.4–1.7), eKt/V 1.4 (1.3–1.5), stdKt/V 2.3 (2.2–2.4), and SAstdKt/V 2.4 (2.2–2.5). The SAstdKt/V was greater than the stdKt/V with a mean difference of 0.065. During the follow-up period, 174,748 (34%) patients died.

Compared to patients with stdKt/V ≥ 2.0, those with stdKt/V < 2.0 had a greater proportion of male (74 vs. 56%), white (63 vs. 60%), younger (59.7 vs. 65.7 years), and taller (175 vs. 168 cm) patients. Other differences included BSA (2.1 vs. 1.9 m^2), pre-HD weight (97.7 vs. 79.5 kg), post-HD weight (95.9 vs. 77.3), V (45.9 vs. 38.2 L), and V/BSA (22.1 vs. 20.4 L/m^2) (Table 1).

In contrast, compared to patients with SAstdKt/V ≥ 2.0, those with SAstdKt/V < 2.0 had a lower proportion of male (38 vs. 57%), young (63.8 vs. 65.6 years) and higher proportion of White patients (62 vs. 60%). Other differences included pre-HD weight (81.5 vs. 79.8 kg), post-HD weight (80.1 vs. 77.6 kg), V (37.6 vs. 38.4 L), and V/BSA (19.4 vs. 20.4 L/m^2) (Table 1).

As shown in Supplementary Table S7, higher levels of stdKt/V were associated with increased age and lower indices of body size (height, BSA, V, V/BSA, pre- and post-HD weights). There was a trend toward decreasing of male proportion as the stdKt/V increased. Hemoglobin

Table 1 Characteristics of participants included in the analysis

Characteristics	stdKt/V			SAstdKt/V		
	< 2.0	≥ 2.0	P value	< 2.0	≥ 2.0	P value
Total, n (%)	12,353 (2)	495,303 (98)	—	10,028 (2)	497,628 (98)	—
Male, n (%)	9180 (74)	276,157 (56)	<0.001	3796 (38)	281,541 (57)	<0.001
Age, year, median (IQR)	59.7 (49.6–69.0)	65.7 (55.9–75.0)	<0.001	63.8 (53.3–74.2)	65.6 (55.8–74.9)	<0.001
Race, n (%)			<0.001			<0.001
White	7813 (63)	298,502 (60)		6231 (62)	300,084 (60)	
African American	4036 (33)	163,416 (33)		3344 (33)	164,108 (33)	
Asian	207 (2)	20,110 (4)		240 (2)	20,077 (4)	
Other	297 (2)	13,275 (3)		213 (2)	13,359 (3)	
Hispanic ethnicity, n (%)	1342 (11)	88,017 (18)	<0.001	1034 (10)	88,325 (18)	<0.001
Comorbidities at RRT initiation, n (%)						
Hypertension	10,705 (87)	441,996 (89)	<0.001	8647 (86)	444,054 (89)	<0.001
Diabetes mellitus	7491 (61)	300,141 (61)	0.9	5705 (57)	301,927 (61)	<0.001
Congestive heart failure	3871 (31)	150,901 (30)	0.04	3013 (30)	151,759 (31)	0.3
Atherosclerotic heart disease	1721 (14)	81,275 (16)	<0.001	1447 (14)	81,549 (16)	<0.001
Peripheral vascular disease	1225 (10)	50,833 (10)	0.2	961 (10)	51,097 (10)	0.03
Stroke	797 (6)	44,792 (9)	<0.001	792 (8)	44,797 (9)	<0.001
COPD	1205 (10)	42,829 (9)	<0.001	947 (9)	43,087 (9)	0.006
Smoking	1021 (8)	31,209 (6)	<0.001	754 (8)	31,476 (6)	<0.001
Malignancy	869 (7)	30,377 (6)	<0.001	805 (8)	30,441 (6)	<0.001
AVF or AVG at entry, n (%)	4753 (39)	250,867 (51)	<0.001	3953 (40)	251,657 (51)	<0.001
Duration of follow-up, year, median (IQR)	0.7 (0.2–2.1)	2.1 (0.9–3.8)	<0.001	0.7 (0.2–2.2)	2.1 (0.9–3.8)	<0.001
Dialysis vintage, year, median (IQR)	0 (0–0.2)	0 (0–1.5)	<0.001	0 (0–0.5)	0 (0–1.5)	<0.001
Height, cm, median (IQR)	175 (168–182)	168 (160–175)	<0.001	168 (162–175)	168 (160–175)	<0.001
Body surface area (BSA), m^2, median (IQR)	2.1 (1.9–2.3)	1.9 (1.7–2.1)	<0.001	1.9 (1.7–2.1)	1.9 (1.7–2.1)	<0.001
Hemodialysis parameters, median (IQR)						
Pre-HD body weight, kg	97.7 (81.1–118.2)	79.5 (66.9–95.6)	<0.001	81.5 (67.4–99.0)	79.8 (67.1–96.2)	<0.001
Post-HD body weight, kg	95.9 (79.5–116.1)	77.3 (65.0–93.1)	<0.001	80.1 (66.1–97.4)	77.6 (65.2–93.6)	<0.001
Ultrafiltrate volume, L	1.8 (1.1–2.6)	2.2 (1.6–2.8)	<0.001	1.4 (0.9–2.0)	2.2 (1.7–2.8)	<0.001
Total body volume (V), L	45.9 (39.8–53.5)	38.2 (32.9–44.2)	<0.001	37.6 (32.4–44.4)	38.4 (33.0–44.4)	<0.001
V/BSA, L/m^2	22.1 (20.4–23.5)	20.4 (18.8–21.9)	<0.001	19.4 (18.6–21.5)	20.4 (18.8–22.0)	<0.001
HD treatment time, minutes	201 (180–224)	218 (203–240)	<0.001	185 (169–209)	218 (203–240)	<0.001
spKt/V	1.0 (0.9–1.1)	1.6 (1.4–1.7)	<0.001	1.1 (0.9–1.3)	1.6 (1.4–1.7)	<0.001
eKt/V	0.9 (0.8–1.0)	1.4 (1.3–1.5)	<0.001	0.9 (0.7–1.1)	1.4 (1.3–1.5)	<0.001
stdKt/V	1.8 (1.6–1.9)	2.4 (2.3–2.5)	<0.001	1.9 (1.6–2.1)	2.4 (2.3–2.5)	<0.001
SAstdKt/V	2.0 (1.7–2.2)	2.5 (2.3–2.6)	<0.001	1.9 (1.7–2.0)	2.5 (2.3–2.6)	<0.001
nPCR, g/kg/day	0.9 (0.8–1.0)	0.9 (0.8–1.0)	<0.001	0.7 (0.6–0.9)	0.9 (0.8–1.0)	<0.001
Laboratory values, median (IQR)						
Hemoglobin, g/dL	10.3 (9.5–10.8)	10.6 (10.3–11.0)	<0.001	10.2 (9.5–10.8)	10.6 (10.2–11.0)	<0.001
Serum ferritin, μg/L	428 (243–714)	784 (508–1045)	<0.001	489 (269–801)	782 (504–1043)	<0.001
Iron saturation, %	24 (19–29)	30 (25–35)	<0.001	25 (19–31)	30 (25–35)	<0.001

Table 1 Continued

Characteristics	stdKt/V			SAstdKt/V		
	< 2.0	≥ 2.0	P value	< 2.0	≥ 2.0	P value
Serum albumin, g/dL	3.6 (3.2–3.9)	3.7 (3.5–3.9)	<0.001	3.5 (3.1–3.8)	3.7 (3.5–3.9)	<0.001
Serum calcium, mg/dL	9.2 (8.9–9.5)	9.2 (8.9–9.5)	<0.001	9.3 (8.9–9.6)	9.2 (8.9–9.5)	<0.001
Serum phosphate, mg/dL	5.0 (4.3–5.9)	4.9 (4.4–5.6)	<0.001	4.9 (4.2–5.7)	4.9 (4.4–5.6)	<0.001
Parathyroid hormone, pg/mL	330 (197–527)	315 (220–461)	0.1	314 (186–509)	315 (220–461)	0.2
Death, n (%)	4417 (36)	170,331 (34)	0.002	3967 (40)	170,781 (34)	<0.001
Cardiovascular	2068 (17)	82,483 (17)	0.8	1762 (18)	82,789 (17)	0.01
Myocardial infarction	143 (1)	6765 (1)	0.049	127 (1)	6781 (1)	0.4
Infection	449 (4)	14,503 (3)	<0.001	385 (4)	14,567 (3)	<0.001
Malignancy	144 (1)	5435 (1)	0.5	146 (1)	5433 (1)	0.001

AVF, arteriovenous fistula; AVG, arteriovenous graft; COPD, chronic obstructive pulmonary disease; eKt/V, equilibrated Kt/V, HD, hemodialysis; IQR, interquartile range; nPCR, normalized protein catabolic rate; RRT, renal replacement therapy; SAstdKt/V, surface area-normalized standard Kt/V; spKt/V, single-pool Kt/V; stdKt/V, standard Kt/V; V/BSA, total body water/body surface area ratio.

and serum albumin were relatively stable among all stdKt/V categories.

However, these trends were different in the SAstdKt/V categorization (Supplementary Table S8). Higher levels of SAstdKt/V were associated with increased hemoglobin and serum albumin. There was a trend toward increasing of male proportion as the SAstdKt/V increased. The trend for age and body size indices was not clear.

Primary outcome

The Kaplan–Meier survival curves for mortality among patients in the five categories of stdKt/V (Figure 2a) and SAstdKt/V (Figure 2b) showed significant intracategory differences for both stdKt/V and SAstdKt/V (P value <0.001 by Log-Rank test). The survival outcomes were worst in the lowest categories of stdKt/V and SAstdKt/V. Moreover, survival progressively decreased with lowering of SAstdKt/V. Such a direct, orderly association was not seen with stdKt/V.

In multivariable models, the HRs for mortality progressively decreased as the SAstdKt/V increased in unadjusted and all three adjusted models (Figure 3a–d and Supplementary Table S5). Unlike SAstdKt/V, HRs were the lowest in the categories with stdKt/V of 2.40–2.59, and then HRs increased in the higher stdKt/V categories. In Figure 3d, the adjusted HRs for SAstdKt/V vs. stdKt/V were 0.68 vs. 0.62 in categories of 2.40–2.59, and 0.63 vs. 0.73 in categories of ≥2.60, respectively.

Secondary outcomes

As stdKt/V increased, the unadjusted and adjusted ORs for anemia decreased to their lowest in stdKt/V category
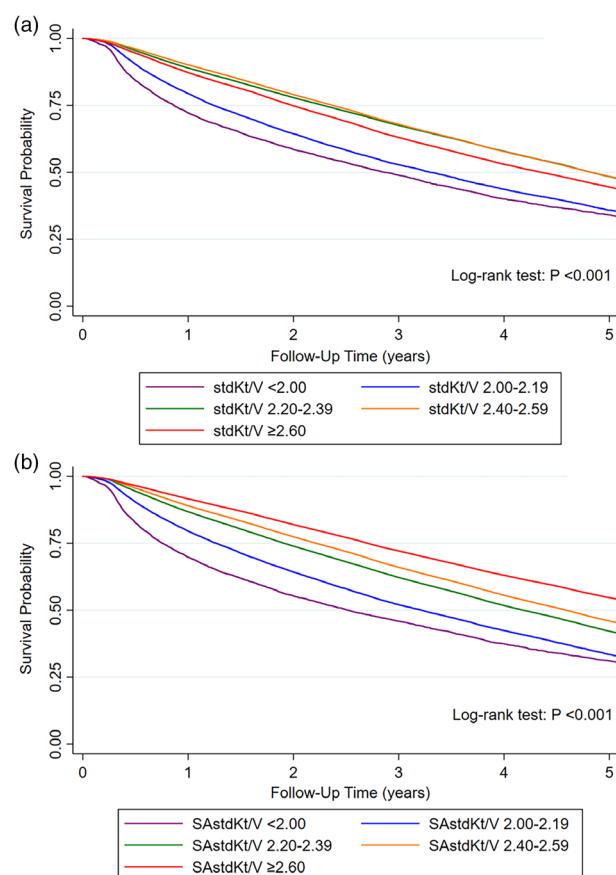
Figure 2 The survival curves for mortality among patients who were in five different categories of standard Kt/V (stdKt/V) (Figure 2a) and surface area-normalized standard Kt/V (SAstdKt/V) (Figure 2b). The number of patients at risk were shown in Table S3 and S4 in supplementary. [Color figure can be viewed at wileyonlinelibrary.com]
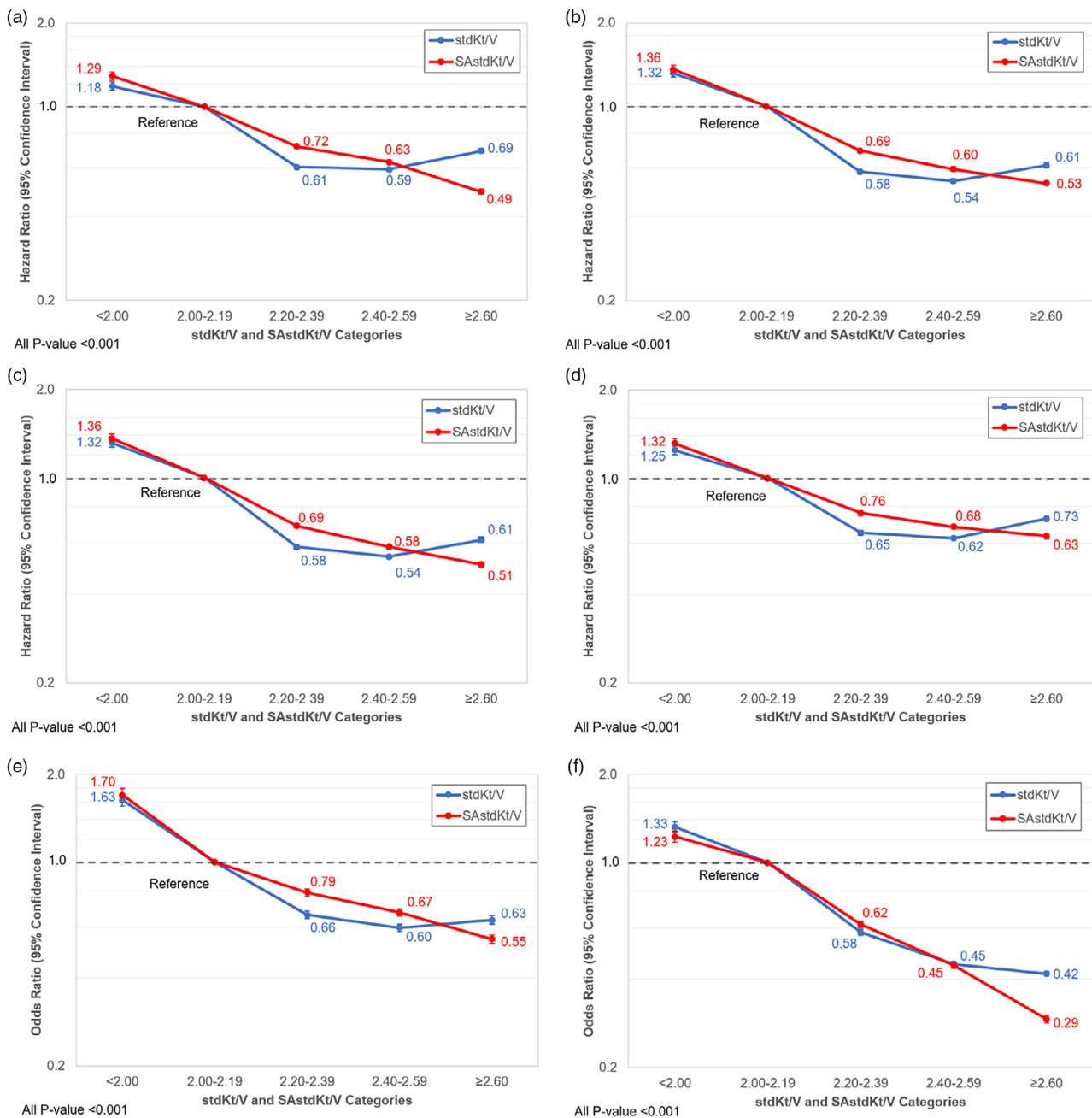
Figure 3 The hazard ratio (HR) and 95% confidence interval for mortality: (a) unadjusted, adjusted by (b) age, gender, race, and Hispanic ethnicity, (c) age, gender, race, Hispanic ethnicity, and comorbidities, and (d) age, gender, race, Hispanic ethnicity, comorbidities, serum albumin, and dialysis vintage. The adjusted odds ratio (OR) and 95% confidence interval for (e) anemia (defined by hemoglobin level of less than 10 g/dL) by age, gender, race, Hispanic ethnicity, comorbidities, serum albumin, and dialysis vintage, and (f) for hypoalbuminemia (defined by serum albumin level of less than 3.5 g/dL) by age, gender, race, Hispanic ethnicity, comorbidities, and dialysis vintage. The group with stdKt/V and SAstdKt/V of 2.00–2.19 were used as reference group. The unadjusted OR for anemia and hypoalbuminemia were shown in Supplementary Figure S1. [Color figure can be viewed at wileyonlinelibrary.com]

2.40–2.59, and then increased in the highest categories. Unlike stdKt/V, the unadjusted and adjusted ORs continuously decreased as the SAstdKt/V increased. (Figure 3e, Supplementary Figure S1 A-B and Table S6).

The unadjusted ORs for hypoalbuminemia progressively decreased to the lowest in 2.40–2.59 category of stdKt/V and increased in the higher category. Whereas the ORs were continuously decreased as the SAstdKt/V increased. The adjusted ORs for hypoalbuminemia progressively decreased as the SAstdKt/V and stdKt/V increased. The ORs were both 0.45 in the 2.40–2.59 categories. The ORs slightly decreased to 0.42 for stdKt/V and more noticeable decreased to 0.29 for SAstdKt/V (Figure 3f, Supplementary Figure S1 C-D and Table S6).

Sensitivity analysis

The Kaplan–Meier survival curves for mortality in both genders showed significantly lower survival probability in patients with stdKt/V and SAstdKt/V < 2.0 (P value <0.001) (Supplementary Figure S2.

DISCUSSION

Our results suggest that SAstdKt/V had a better association with mortality, anemia, and hypoalbuminemia than stdKt/V in a large cohort of chronic HD patients with long-term follow-up. While extremely low and high levels of stdKt/V were found to be associated with worse mortality and anemia, lower levels of SAstdKt/V were associated with worse clinical outcomes and higher levels with increasingly better outcomes. Although the ORs were decreased progressively as SAstdKt/V and stdKt/V increase, the ORs in the highest categories were more noticeably decreased for SAstdKt/V than stdKt/V. These findings are similar to those reported in a previous study by Ramirez et al. which included a smaller cohort and a shorter follow-up period.[13] They found that both unadjusted and adjusted HRs for mortality were decreased as stdKt/V increased and became lowest in patients with stdKt/V level of 2.5 for males and 2.6 for females. HRs for mortality were higher if stdKt/V increased beyond these points. However, better clinical outcomes were associated with higher SAstdKt/V regardless of gender. Our results emphasize the effect of stdKt/V rescaling to SAstdKt/V on mortality. We also demonstrated the effects of rescaling the dialysis dose on anemia and hypoalbuminemia. These associations persisted after adjusting for both gender and the associated clinical variables.

Gender and body size have been shown to be important factors in the mortality of HD patients who received different V-based dialysis doses. Previous studies showed that females and smaller body-sized males required higher dialysis doses according to the SA-based dose in the HEMO study dataset as well as other data sets.[6,11,21] The results from a large observational study and the HEMO study showed that the benefit of increasing V-based dose beyond standard targeted dose were restricted only to females.[5,22] In addition, smaller body-sized HD patients had a higher mortality than larger patients at similar V-normalized dose levels.[23] These results suggested that determining dialysis dose with V-normalized dose might be problematic, particularly in females and smaller body-size patients.

Body composition is also affected by gender and body size, and these factors could be contributing to mortality. Smaller body-sized patients have relatively lower fat mass, muscle mass, and V in proportion to their body weight, but had relatively higher high metabolic rate organs (HMRO) than larger body-sized patients.[24–26] These differences in body compartments result in higher HMRO per V ratio in smaller body-sized patients. This ratio was also found to be higher in female patients.[25] The HMRO mass relates to the protein catabolic rate which indirectly reflects protein intake and uremic toxin generation from proteins. Thus, females and small body-sized patients have higher uremic toxin concentration, and this could be the reason why increasing V-based dialysis dose in these patients may be beneficial.

Our results demonstrated that SAstdKt/V is consistently associated with anemia and hypoalbuminemia. As SAstdKt/V values increased, the median serum albumin, normalized Protein Catabolic Rate (nPCR), and hemoglobin levels progressively increased as well. In contrast, these laboratory parameters were quite steady with stdKt/V values of 2.0 or more (Supplementary Table S7-S8). These trends persisted in the adjusted models (Figure 3 and Supplementary Figure S1). These findings might be explained by rescaling the dialysis dose with BSA leading to a more consistent association between uremic toxin generation and removal (dialysis dose). Smaller body-sized patients and females have relatively higher uremic toxin generation with lower V's.[24–26] Therefore, determining dialysis delivery with V-based dosing could result in inadequately dialyzing these patients.

Prior studies have demonstrated an association with HD dose and several clinical outcomes. Azar et al.

compared nutritional status and biochemical outcomes before and after increasing the HD dose.[27] They found that nPCR, serum albumin, and hemoglobin levels were significantly improved after increasing the HD dose. Moreover, previous studies on HD patients have shown the association between dialysis adequacy and hematocrit,[28–30] as well as serum albumin level.[31,32] Alteration of these factors could affect patient mortality. It has been known that nutritional status, particularly serum albumin, is strongly associated with mortality in HD patients.[33,34] Anemia was also associated with all-cause mortality in patients with CKD either with or without dialysis dependence.[35] Thus, ensuring adequate dialysis clearance could improve the nutritional status, anemia, and mortality of HD patients.

Although previous studies showed a discrepancy in the outcomes between SA- and V-normalized dosing among different body-sized patients and genders, V-normalized targets have been the standard in determining the delivered HD dose and applied to all HD patients.[1] Since SA-based dosing showed better dose–outcome relationships, dialysis dosing should also be determined by SA-based dosing. Our results suggest that using SAstdKt/V (Figures 2 and 3) has a better association with mortality and other clinical outcomes than using stdKt/V. Although the formulae for calculation of SAstdKt/V seems complicated, the calculation can be simply done by using the open-source program, Solute-Solver, which can be found at www.ureakinetics.org.[36] This tool aids in implementing the SAstdKt/V into clinical practice without requiring multiple-step complex calculations. However, our findings have to be interpreted with following caveats: First, since these results came from an observational dataset, there might be several factors that could affect the outcomes other than the effect of HD dosing. Second, residual renal function (RRF) data were unavailable and was assumed to be zero. This could result in potential underestimation of the stdKt/V and SAstdkt/V. Third, it has been known that RRF is associated with lower mortality rates.[37,38] The effects of RRF on mortality were not assessed in this study. Lastly, since we enrolled only the patient with thrice-weekly HD to this study, the association of SAstdKt/V to the outcomes cannot be reassured in other population. We suggest not to apply these findings to the patients who not receive thrice-weekly HD.

In conclusion, we demonstrated that SAstdKt/V showed better association with mortality, anemia, and hypoalbuminemia than stdKt/V. Targeted V-normalized dosing carries the risk of inappropriate dialysis dose modification. Therefore, SAstdKt/V is a better parameter to define HD dosing which can be simply calculated by using an available online tool without requiring multiple-step complex formulae. However, the results should be cautiously interpreted with the aforementioned limitations. Further studies to determine the optimal dialysis SA-normalized dose required to achieve improved clinical outcomes with better cost-effectiveness are needed.

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