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### Permalink

<https://escholarship.org/uc/item/39d585m1>

### Journal

Journal of Renal Nutrition, 27(1)

### ISSN

1051-2276

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### Publication Date

2017

### DOI

10.1053/j.jrn.2016.07.001

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Peer reviewed

# Concurrence of Serum Creatinine and Albumin CrossMark With Lower Risk for Death in Twice-Weekly Hemodialysis Patients

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**Objective:** Markers of better nutritional status including both higher levels of serum albumin (as a measure of visceral proteins) and creatinine (as a measure of the muscle mass) are associated with lower mortality in conventional (thrice weekly) hemodialysis patients. However, data for these associations in twice-weekly hemodialysis patients, in whom less frequent hemodialysis may confound nutritional predictors, are lacking.

**Design and Subjects:** We identified 1,113 twice-weekly and matched 4,448 thrice-weekly hemodialysis patients from a large national dialysis cohort of incident hemodialysis patients over 5 years (2007-2011). Mortality risk, adjusted for potential confounders, was examined across two-by-two combinations of serum creatinine (<6 vs. ≥6 mg/dL) and albumin (<3.5 g/dL vs. ≥3.5 g/dL) for each treatment frequency yielding a total of 8 groups.

**Results:** Patients were aged 70 ± 14 years and included 48% women and 55% diabetics. Using the thrice-weekly hemodialysis patients with creatinine ≥ 6 mg/dL and albumin ≥ 3.5 g/dL as reference, patients with creatinine <6 mg/dL and albumin <3.5 g/dL had a 1.8-fold higher risk of mortality (hazard ratio: 1.75, 95% confidence interval: 1.33-2.30) in twice-weekly and 2.2-fold increased risk of mortality (hazard ratio: 2.21, 95% confidence interval: 1.81-2.70) in thrice-weekly hemodialysis patients, respectively in fully adjusted models adjusted for demographics, comorbidities, and markers of malnutrition and inflammation. A test for interaction showed that there was no significant difference in albumin creatinine mortality associations between twice-weekly and thrice-weekly hemodialysis patients (*P*-for-interaction = .7667).

**Conclusions:** Surrogate markers of higher visceral protein and muscle mass combined may confer greatest survival in both twice-weekly and thrice-weekly hemodialysis patients.

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## Introduction

CHRONIC KIDNEY DISEASE and end-stage renal disease (ESRD) are recognized as global public health problems.<sup>1,2</sup> More than 400,000 people in the United States receive hemodialysis treatment for

ESRD, among whom, approximately 100,000 initiate hemodialysis each year.<sup>3</sup> In ESRD patients, serum creatinine may be used as a surrogate of muscle mass,<sup>4-11</sup> and higher serum creatinine level has been found to be associated with better survival.<sup>11-14</sup> Serum albumin, as

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Support: The work in this article has been performed with the support of the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute for Health Research grants R01-DK95668 (K.K.-Z.), K24-DK091419 (K.K.-Z.), R01-DK078106 (K.K.-Z.). K.K.-Z. is supported by philanthropic grants from Mr. Harold Simmons, Mr. Louis Chang, Dr. Joseph

Lee, and AVEO. C.P.K. is supported by the National Institute of Diabetes, Digestive and Kidney Disease grants R01-DK096920 and U01-DK102163. C.M.R. is supported by the National Institute of Diabetes, Digestive and Kidney Disease grant K23-DK102903.

Financial Disclosure: K.K.-Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, AVEO, Chugai, DaVita, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, ZS Pharma. C.P.K. has received honoraria from Sanofi-Aventis, Relypsa and ZS Pharma.

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<http://dx.doi.org/10.1053/j.jrn.2016.07.001>

a measure of visceral proteins, is also a powerful predictor of outcomes in patients with ESRD.<sup>15</sup> However, most previous studies on these factors had largely focused on patients using a thrice-weekly hemodialysis regimen. Notably, recent data have found that “infrequent dialysis” or twice-weekly regimens does not necessarily confer greater mortality risk when compared with thrice-weekly therapy.<sup>16,17</sup> Although the survival differences associated with twice- versus thrice-weekly hemodialysis may be related to patient selection bias,<sup>16</sup> patients on a less frequent hemodialysis regimen are also more likely to have better nutritional status, have higher serum albumin values, and possibly lower muscle mass based on serum creatinine values. Few studies have compared the clinical outcome in twice- versus thrice-weekly hemodialysis patients according to concurrent nutritional status of both visceral protein and muscle mass. We hypothesized that survival advantages of higher serum albumin and creatinine combined will hold in twice-weekly hemodialysis patients.

## Materials and Methods

### Patients

We extracted and examined data from all patients with ESRD who received dialysis therapy from January 2007 to December 2011 in a large dialysis care organization in the United States (DaVita Inc.). The study was approved by the institutional review committees of the University of California Irvine, Los Angeles Biomedical Research Institute at Harbor-UCLA, and the University of Washington. Given the large sample size, anonymity of the patients studied, and noninvasive nature of the research, the requirement for written consent was waived. During the study period, a total of 208,820 patients initiated dialysis. We excluded 46,149 patients in whom dialysis duration lasted less than 60 days total. Among the remaining 162,671 patients, we excluded 24,944 patients who had missing treatment information and 7,871 patients with missing creatinine or albumin during the first 91 days of dialysis (baseline). An additional 563 patients were excluded for missing censoring information. We then identified 1,123 twice-weekly and 117,625 thrice-weekly hemodialysis patients during the baseline quarter. We 1:4 matched twice-weekly to thrice-weekly hemodialysis patients by age, gender, race/ethnicity, diabetes status, and facility region. The final matched study cohort consisted of 1,113 twice-weekly and 4,448 thrice-weekly hemodialysis patients (Fig. 1).

### Demographic and Clinical Measures

All data were obtained from electronic medical records at DaVita Inc. The following comorbid conditions were considered: diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, cerebrovascular disease, other cardiovascular disease, chronic obstructive pulmonary disease, history of cancer, and alcohol abuse.

Race and ethnicity determinations were based on self-identification of the race and ethnicity with which they most closely identified, according to the definitions set forth by the US Census Bureau and the Federal Office of Management and Budget.<sup>18,19</sup>

### Laboratory Values

In all DaVita Inc. dialysis clinics, blood samples were drawn using standardized techniques and were transported to a central laboratory in Deland, FL, typically within 24 hours, where measurements were made using automated and standardized methods. Serum creatinine, phosphorus, calcium, urea, albumin, bicarbonate, and total iron-binding capacity were measured monthly. Serum parathyroid hormone and ferritin were measured at least quarterly. Hemoglobin was measured weekly to biweekly in most patients. Delivered dialysis dose was estimated with single-pooled Kt/V using the urea kinetic model. Body mass index (BMI) was calculated as post-dialysis body weight in kilogram divided by height in meter squared ( $\text{kg}/\text{m}^2$ ). Baseline laboratory measurements were averaged during the first 3 months (91 days) of dialysis treatment to attenuate an effect of short-term variation in laboratory measurements. We used a validated creatinine-based formula to estimate baseline lean body mass in all hemodialysis patients.<sup>20</sup> The formula is as follows: estimated lean body mass (kg) =  $0.34 \times \text{serum creatinine (mg/dL)} + 5.58 \times \text{gender (1 if female; 0 if male)} + 0.30 \times \text{weight (kg)} + 0.67 \times \text{height (inch)} - 0.23 \times \text{urea reduction ratio} - 5.75$ .

Patients were divided into 4 categories based on baseline measurements: serum creatinine <6 mg/dL and albumin <3.5 g/dL; serum creatinine  $\geq$  6.0 mg/dL and albumin <3.5 mg/dL; serum creatinine <6.0 mg/dL and albumin  $\geq$  3.5 g/dL; and serum creatinine  $\geq$  6.0 mg/dL and albumin  $\geq$  3.5 g/dL. Patients with the highest serum creatinine and albumin were considered as the reference group.

### Statistical Methods

Descriptive data were summarized using proportions, mean ( $\pm$ standard deviation), and medians (interquartile range) as appropriate. Data across groups were compared using analysis of variance, Kruskal-Wallis, or chi-square tests where appropriate. We analyzed the relationship between all-cause mortality and baseline concurrent serum creatinine and albumin, using Cox proportional hazard models. Patients were followed up from patients' first date of dialysis until death or censoring due to renal transplantation, transfer to another dialysis facility, or end of the study period (December 31, 2011).

Three models of analyses were examined: (1) an unadjusted model that included only the categorical groupings of serum creatinine and albumin, the main predictor variable, and calendar quarter of entry; (2) case-mix adjusted models that additionally included age, gender, race/ethnicity (non-Hispanic white, African American, Hispanic, Asian, and other), previously listed comorbidities,

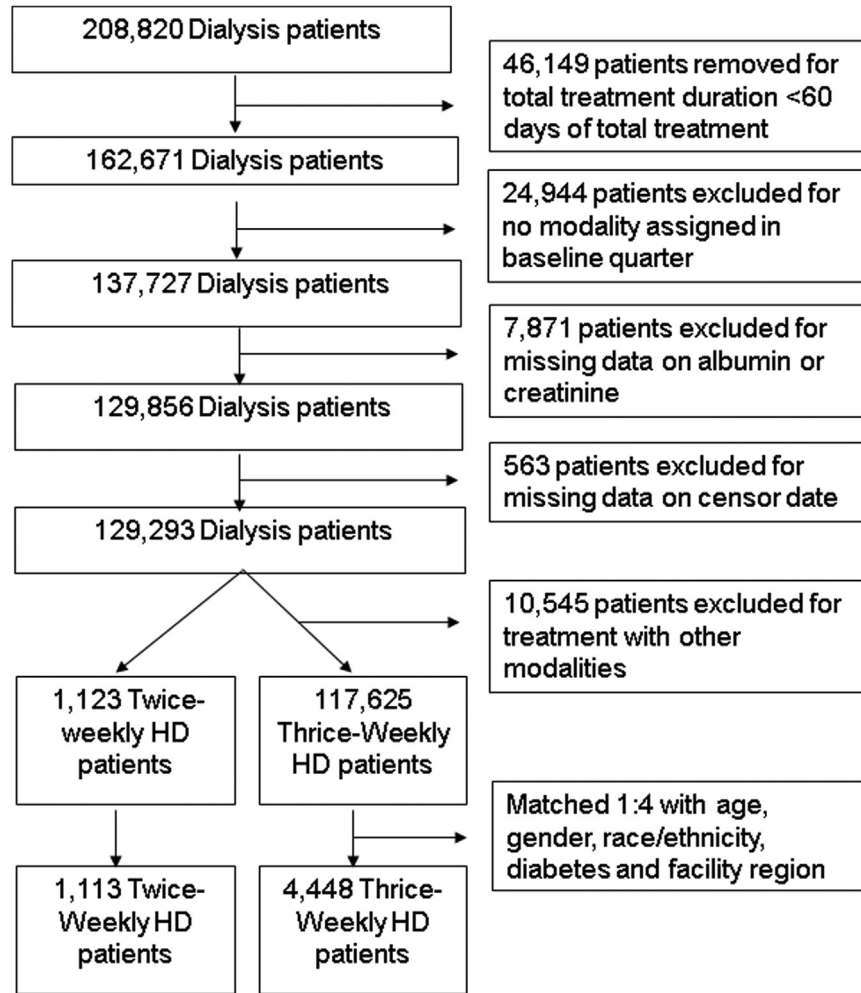


Figure 1. Cohort construction.

and primary insurance; and (3) case-mix plus malnutrition-inflammation complex syndrome (MICS) adjusted models, which included all the covariates in the case-mix model as well as 11-surrogates of nutritional and inflammatory status: BMI, hemoglobin, serum levels of calcium, phosphorus, parathyroid hormone, potassium, ferritin, iron saturation ratio, total iron-binding capacity, bicarbonate, and peripheral white blood cell count. *P*-for-interaction was tested using Wald's test. In sensitivity analyses, associations between creatinine albumin groups with mortality were evaluated in a matched cohort, which was additionally matched for creatinine albumin exposure category groups. All analyses were carried out with SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina). Matching procedures were completed using SAS (SAS Institute Inc, [www.sas.com](http://www.sas.com)) macro GMATCH based on the greedy algorithm created by Bergstralh et al.<sup>21</sup> Missing covariate data (under 1% for most laboratory and demographic variables) were imputed by means or medians of recorded values.

## Results

### Baseline Demographics and Clinical Characteristics

The study cohort included a total of 5,561 twice and thrice-weekly hemodialysis patients after matching. Baseline characteristics stratified by each concurrent serum level of creatinine and albumin category are presented in Table 1. The mean ( $\pm$  standard deviation) age was  $70 \pm 14$  years, and 48% were women. At baseline, 55% of hemodialysis patients had diabetes mellitus, and 49% had hypertension. The mean body weight, estimated lean body mass, and BMI in 5,561 hemodialysis patients was  $76 \pm 21$  kg,  $64 \pm 7$  kg and  $27 \pm 7$  kg/m<sup>2</sup>, respectively. Patients with higher concurrent levels of serum creatinine and albumin were younger, male, and had higher body weight, estimated lean body mass, BMI, serum levels of phosphorus, parathyroid hormone, and a higher prevalence of hypertension and lower prevalence of diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease.

**Table 1.** Baseline Characteristics Stratified by Concurrence of Serum Creatinine and Albumin in the Total Cohort of After Matched Hemodialysis Patients (n = 5,561)

Variables	After Match Hemodialysis Patients					P Value
	Total	Cr < 6.0 and ALB < 3.5	Cr ≥ 6.0 and ALB < 3.5	Cr < 6.0 and ALB ≥ 3.5	Cr ≥ 6.0 and ALB ≥ 3.5	
N	5,561	1,731	554	2,222	1,054	
Age (y)	70 ± 14	72 ± 13	65 ± 15	72 ± 12	63 ± 15	<.0001
Gender (female %)	48	55	39	50	37	<.0001
Race/ethnicity (%)						
Non-Hispanic white	64	66	53	71	52	.0012
African American	13	11	18	10	20	.0001
Hispanic	12	12	14	10	13	.7321
Asian	8	8	10	7	10	.5915
Other	3	3	5	3	5	.2296
Primary insurance (%)						
Medicare	59	63	58	60	48	<.0001
Medicaid	5	5	6	3	7	<.0001
Other	36	32	36	36	45	<.0001
Weight (kg)	75.6 ± 20.7	73.4 ± 20.8	76.8 ± 20.0	75.7 ± 20.5	78.6 ± 21.2	<.0001
eLBM (kg)	64.4 ± 7.3	63.5 ± 7.2	65.8 ± 7.1	63.9 ± 7.0	66.4 ± 7.5	<.0001
BMI (kg/m <sup>2</sup> )	27.0 ± 6.6	26.6 ± 6.8	26.9 ± 6.5	27.2 ± 6.5	27.4 ± 6.6	.0004
Laboratory values						
Ca (mg/dL)	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.6	9.1 ± 0.5	9.0 ± 0.6	<.0001
P (mg/dL)	4.8 ± 1.1	4.5 ± 1.0	5.4 ± 1.2	4.5 ± 0.9	5.6 ± 1.1	<.0001
K (mEq/L)	4.4 ± 0.5	4.3 ± 0.5	4.6 ± 0.6	4.4 ± 0.5	4.6 ± 0.5	<.0001
PTH (pg/mL) (IQR)	340.9 (174.5-423.0)	291.5 (147.0-366.3)	395.2 (210.0-479.0)	308.0 (162.6-392.0)	463.0 (245.8-566.7)	<.0001
WBC (×10 <sup>3</sup> /μL)	7.8 ± 2.8	8.2 ± 3.2	8.3 ± 2.9	7.5 ± 2.6	7.6 ± 2.3	<.0001
HGB (g/dL)	11.2 ± 1.1	11.0 ± 1.1	10.9 ± 1.2	11.4 ± 1.0	11.3 ± 1.1	<.0001
ALB (g/dL)	3.5 ± 0.5	3.1 ± 0.3	3.2 ± 0.3	3.8 ± 0.2	3.9 ± 0.3	<.0001
CO <sub>2</sub> (mEq/l)	23.5 ± 0.8	24.3 ± 2.7	23.1 ± 2.6	23.6 ± 2.7	22.3 ± 2.6	<.0001
Cr (mg/dL)	5.2 ± 2.1	4.1 ± 1.1	7.4 ± 1.3	4.3 ± 1.0	7.9 ± 1.8	<.0001
nPCR (g/kg/d)	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	<.0001
Fe (ng/mL; IQR)	376.3 (166.0-465.3)	422.6 (180.0-521.0)	451.9 (188.5-533.5)	342.1 (157.0-426.0)	332.6 (151.0-406.0)	<.0001
ISAT (%)	23.0 ± 8.9	22.7 ± 9.3	23.9 ± 11.2	22.7 ± 8.0	23.4 ± 8.9	.2441
TIBC (μg/dL)	227.8 ± 48.7	203.2 ± 46.6	204.1 ± 41.1	246.8 ± 44.7	240.4 ± 40.6	<.0001
Comorbidities (%)						
DM	54.5	59.5	56.1	53.8	45.0	<.0001
ASHD	14.5	14.8	13.4	14.7	14.5	.9432
CHF	35.9	37.8	38.6	35.9	31.1	.001
HTN	49.4	46.3	52.3	49.0	54.1	.0006
CVD	1.8	1.7	1.6	1.9	1.6	.9856
Other cardiovascular disease	16.2	17.6	15.3	16.6	13.7	.0217
COPD	4.8	6.2	4.7	4.1	4.1	.0024
History of cancer	2.5	2.8	2.3	2.3	2.5	.4247
Alcohol abuse	0.1	0.1	0	0.1	0.2	.6623

ALB, albumin; ASHD, atherosclerotic heart disease; BMI, body mass index; Ca, calcium; CHF, congestive heart failure; CO<sub>2</sub>, carbon dioxide combining power; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CVD, cerebrovascular disease; DM, diabetes mellitus; eLBM, estimated lean body mass; Fe, ferritin; HGB, hemoglobin; HTN, hypertension; IQR, interquartile range; ISAT, iron saturation ratio; K, potassium; nPCR, normalized protein catabolic rate; P, phosphorus; PTH, parathyroid hormone; TIBC, total iron-binding capacity; WBC, white blood cells.

Note: Categorical variables are given as percentage; continuous variables as mean (standard deviation) or median (IQR) as appropriate. Laboratory measures are represented as averages of repeated measures during the first quarter of entry to cohort.

P value was estimated by 1-way analysis of variance or Kruskal-Wallis test for continuous variables or chi-square test for categorical variables.

Conversion factors for units: calcium in mg/dL to mmol/l, ×0.2495; phosphorus in mg/dL to mmol/l, ×0.3229; hemoglobin and albumin in g/dL to g/L, ×10; TIBC in μg/dL to μmol/l, ×0.179. No conversion necessary for intact PTH in pg/mL and ng/L, WBC count in 10<sup>3</sup>/μL and 10<sup>9</sup>/L, and ferritin in ng/mL and μg/L.

### Baseline Demographics and Clinical Characteristics According to Concurrence of Serum Creatinine and Albumin Among Twice-Weekly and Thrice-Weekly Hemodialysis Patients

After matching on age, gender, race/ethnicity, diabetes status, and facility region, our cohort comprised 1,113 twice-weekly and 4,448 thrice-weekly hemodialysis patients. There were no significant differences in demographics before and after matching for twice-weekly hemodialysis patients. However, compared with the entire cohort of thrice-weekly hemodialysis patients, the matched thrice-weekly patients were older, more likely to be women, non-Hispanic white or Asian, and used Medicare as primary insurance (Table S1). They also had a lower body weight, estimated lean body mass, BMI, serum creatinine and parathyroid hormone level, and a lower prevalence of diabetes mellitus, hypertension, and congestive heart failure, but a higher prevalence of other cardiovascular disease.

In the matched cohort, and in both twice- and thrice-weekly hemodialysis groups, patients with a higher concurrence of serum creatinine and albumin were more likely to be younger, men, less likely to be non-Hispanic white, less likely to use Medicare as primary insurance, had higher body weight, estimated lean body mass, BMI, serum levels of phosphorus and parathyroid hormone, lower serum level of ferritin, a higher prevalence of hypertension, and lower prevalence of diabetes mellitus, congestive heart failure, and chronic obstructive pulmonary disease (Table 2).

Compared with twice-weekly hemodialysis patients, the thrice-weekly patients had a higher mean body weight ( $76 \pm 21$  vs.  $75 \pm 20$  kg), estimated lean body mass ( $65 \pm 7$  vs.  $64 \pm 7$  kg), and BMI ( $27.1 \pm 6.6$  vs.  $26.8 \pm 6.6$  kg/m<sup>2</sup>). Notably, this trend was also seen in each category of combined serum creatinine and albumin level.

### Mortality Outcome According to Concurrence of Serum Creatinine and Albumin

Figure 2 and Table S2 show the association of combined serum albumin and creatinine levels with mortality in the matched cohort, according to lower levels and then higher levels of albumin. Compared with the reference group (serum creatinine  $\geq 6.0$  mg/dL and albumin  $\geq 3.5$  g/dL), patients with the lowest concurrence of serum creatinine and albumin (serum creatinine  $<6.0$  mg/dL and albumin  $<3.5$  g/dL) had a 3.2-fold increased risk of crude mortality (hazard ratio [HR]: 3.22; 95% confidence interval [CI]: 2.73–3.80) in unadjusted models. Associations between lower albumin and higher creatinine and then lower creatinine and higher albumin followed a linear trend toward comparatively lower mortality risk. These relationships remained robust after further adjustments in subsequent case-mix and case-mix and MICS models.

The same linear trend was also present in both 1,113 twice- and 4,448 thrice-weekly hemodialysis cohorts independently ( $P$ -for-interaction = .7667). In twice-weekly hemodialysis patients, compared with the reference group (serum creatinine  $\geq 6.0$  mg/dL and albumin  $\geq 3.5$  g/dL), patients in the group with the lowest levels of serum creatinine and albumin ( $<6.0$  mg/dL and  $<3.5$  g/dL, respectively) had a 2.9-fold increased risk of crude mortality (HR: 2.94; 95% CI: 1.92–4.52; Fig. 3, Table S3). In thrice-weekly hemodialysis patients, compared with the reference group (serum creatinine  $\geq 6.0$  mg/dL and albumin  $\geq 3.5$  g/dL), patients in the lowest concurrent level of serum creatinine and albumin ( $<6.0$  mg/dL and  $<3.5$  g/dL, respectively) had a 3.3-fold increased risk of crude mortality (HR: 3.25; 95% CI: 2.72–3.89; Fig. 4, Table S4). This relationship remained robust after further adjustment for case-mix and case-mix and MICS models especially among the thrice-weekly matched hemodialysis patients.

### Mortality Outcome According to Concurrence of Serum Creatinine and Albumin in Twice-Weekly Hemodialysis Patients

Figure 5 and Table S5 show results of a combined analysis, comparing both modality and concurrence of creatinine and albumin in 8 groups and using the thrice-weekly hemodialysis patients with the highest concurrence serum creatinine and albumin (serum creatinine  $\geq 6.0$  mg/dL and albumin  $\geq 3.5$  g/dL) as the reference group. In this analysis, twice- and thrice-weekly hemodialysis patients with the lowest concurrence of serum creatinine and albumin ( $<6.0$  mg/dL and  $<3.5$  g/dL, respectively) had a 2.3-fold (HR: 2.31; 95% CI: 1.78–3.00) and 3.3-fold (HR: 3.27; 95% CI: 2.74–3.91) higher mortality risk, respectively. Twice-weekly hemodialysis patients with highest concurrent serum of creatinine and albumin had 20% (HR: 0.80; 95% CI: 0.53–1.19) lower death risk in comparison to the reference group, albeit nonsignificant. After adjustment for case-mix and MICS markers, the relationship between mortality and concurrence serum of creatinine and albumin remained robust among especially thrice-weekly hemodialysis patients.

Results for sensitivity analyses, which additionally matched for baseline concurrent serum albumin and creatinine groups, showed similar results (Table S6),  $P$ -for-interaction = .6949.

## Discussion

In a diverse contemporary matched cohort of 5,561 hemodialysis patients dialyzed either twice or thrice weekly, we found an inverse relationship between concurrence of serum creatinine and albumin and mortality, independent of dialysis frequency. Concurrence of higher serum creatinine and albumin was associated with the greatest survival, whereas the concurrence of lower serum creatinine and albumin had the highest mortality in both the twice- and

**Table 2.** Baseline Characteristics Stratified by Concurrence of Serum Creatinine and Albumin Among Twice-Weekly (n = 1,113) and Thrice-Weekly (n = 4,448) Hemodialysis Patients

Variables	Twice-Weekly HD					Thrice-Weekly HD					P Value
	Total	After Matched				Total	After Matched				
		Cr < 6.0 and ALB < 3.5	Cr ≥ 6.0 and ALB < 3.5	Cr < 6.0 and ALB ≥ 3.5	Cr ≥ 6.0 and ALB ≥ 3.5		Cr < 6.0 and ALB < 3.5	Cr ≥ 6.0 and ALB < 3.5	Cr < 6.0 and ALB ≥ 3.5	Cr ≥ 6.0 and ALB ≥ 3.5	
N	1,113	285	55	580	193	4,448	1,446	499	1,642	861	
Age (y)	70 ± 14	70 ± 13	64 ± 15	72 ± 13	63 ± 15	70 ± 14	72 ± 12	65 ± 15	72 ± 12	63 ± 15	<.0001
Gender (female %)	48	54	42	50	35	48	55	38	50	37	<.0001
Race/ethnicity (%)											
Non-Hispanic white	64	63	51	68	57	64	67	53	72	51	.0012
African American	13	14	7	10	21	13	11	20	10	20	.0001
Hispanic	12	13	16	11	10	12	11	14	10	14	.7321
Asian	8	7	18	8	8	8	8	9	7	10	.5915
Other	3	2	7	4	3	3	3	4	2	5	.2296
Primary insurance (%)											
Medicare	60	67	56	61	47	59	63	58	60	49	<.0001
Medicaid	4	5	5	4	5	5	5	7	3	8	<.0001
Other	36	28	38	36	48	36	33	35	36	44	<.0001
Weight (kg)	74.7 ± 20.3	73.0 ± 21.9	73.8 ± 20.5	74.2 ± 19.4	79.1 ± 20.5	75.8 ± 20.8	73.4 ± 20.5	77.2 ± 20.0	76.2 ± 20.9	78.5 ± 21.3	<.0001
eLBM (kg)	63.7 ± 7.0	62.8 ± 7.4	64.2 ± 7.1	63.2 ± 6.5	66.4 ± 7.3	64.6 ± 7.3	63.6 ± 7.2	66.0 ± 7.1	64.1 ± 7.2	66.4 ± 7.5	<.0001
BMI (kg/m <sup>2</sup> )	26.8 ± 6.6	26.8 ± 8.0	26.6 ± 6.2	26.7 ± 6.2	27.3 ± 5.8	27.1 ± 6.6	26.6 ± 6.5	27.0 ± 6.5	27.4 ± 6.7	27.4 ± 6.8	.0004
Laboratory values											
Ca (mg/dL)	9.1 ± 0.5	9.1 ± 0.5	9.0 ± 0.6	9.1 ± 0.5	9.0 ± 0.7	9.1 ± 0.5	9.1 ± 0.5	9.1 ± 0.6	9.1 ± 0.5	9.0 ± 0.6	<.0001
P (mg/dL)	4.7 ± 1.0	4.6 ± 0.9	5.6 ± 1.2	4.5 ± 0.8	5.5 ± 1.1	4.8 ± 1.1	4.5 ± 1.0	5.4 ± 1.2	4.5 ± 0.9	5.6 ± 1.1	<.0001
K (mEq/L)	4.4 ± 0.5	4.4 ± 0.5	4.6 ± 0.5	4.4 ± 0.5	4.6 ± 0.6	4.4 ± 0.5	4.3 ± 0.5	4.6 ± 0.6	4.4 ± 0.4	4.6 ± 0.5	<.0001
PTH (pg/mL)	341.1	320.3	398.2	304.3	466.2	340.9	285.8	394.8	309.3	462.3	<.0001
(IQR)	(172.0-421.0)	(151.0-399.0)	(218.7-512.0)	(163.8-379.8)	(235.0-577.6)	(175.4-424.3)	(146.5-361.5)	(209.3-478.5)	(161.2-394.0)	(249.0-564.8)	
WBC (×10 <sup>3</sup> /μL)	7.5 ± 2.8	7.9 ± 3.1	7.5 ± 2.0	7.5 ± 3.0	7.1 ± 2.0	7.9 ± 2.8	8.2 ± 3.2	8.4 ± 3.0	7.5 ± 2.5	7.7 ± 2.3	<.0001
HGB (g/dL)	11.2 ± 1.0	11.1 ± 1.0	10.8 ± 0.9	11.3 ± 1.0	11.2 ± 1.1	11.2 ± 1.1	11.0 ± 1.1	10.9 ± 1.2	11.4 ± 1.1	11.3 ± 1.1	<.0001
ALB (g/dL)	3.7 ± 0.4	3.1 ± 0.3	3.2 ± 0.2	3.9 ± 0.2	4.0 ± 0.3	3.5 ± 0.4	3.1 ± 0.3	3.1 ± 0.3	3.8 ± 0.2	3.9 ± 0.2	<.0001
CO <sub>2</sub> (mEq/L)	22.8 ± 2.8	23.8 ± 2.7	21.6 ± 2.6	22.8 ± 2.8	21.4 ± 2.4	23.7 ± 2.7	24.4 ± 2.7	23.3 ± 2.6	23.8 ± 2.6	22.5 ± 2.6	<.0001
Cr (mg/dL)	4.8 ± 2.0	3.7 ± 1.1	7.3 ± 1.2	4.1 ± 1.1	7.8 ± 1.9	5.3 ± 2.1	4.2 ± 1.1	7.5 ± 1.3	4.3 ± 1.0	8.0 ± 1.8	<.0001
nPCR (g/kg/d)	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	<.0001
Fe (ng/mL; IQR)	328.9	393.4	407.7	303.9	286.2	388.2	428.3	456.8	355.6	343.0	<.0001
(IQR)	(146.7-410.0)	(176.3-485.7)	(122.5-476.0)	(138.5-389.0)	(143.8-344.3)	(170.7-482.0)	(184.0-530.3)	(190.3-542.5)	(164.9-439.0)	(154.5-419.5)	
ISAT (%)	22.3 ± 7.3	22.4 ± 8.0	23.7 ± 9.6	21.9 ± 6.8	22.8 ± 7.3	23.1 ± 9.3	22.7 ± 9.5	23.9 ± 11.3	23.0 ± 8.3	23.5 ± 9.2	.2441
TIBC (μg/dL)	237.9 ± 46.6	209.9 ± 43.4	223.1 ± 41.1	252.5 ± 44.0	239.7 ± 39.7	225.3 ± 48.9	201.9 ± 47.1	202.1 ± 40.6	244.8 ± 44.8	240.6 ± 40.9	<.0001
Comorbidities (%)											
DM	54.5	64.6	63.6	52.6	43	54.5	58.5	55.3	54.2	47.9	<.0001
ASHD	14.9	15.1	9.1	15.5	14.5	14.5	14.7	13.8	14.4	14.5	.9432
CHF	30.8	30.2	34.5	32.8	24.9	37.1	39.3	39.1	37	32.5	.001
HTN	52	48.1	69.1	50.3	58	48.8	45.9	50.5	48.5	53.2	.0006
CVD	1.8	1.4	1.8	2.1	1.6	1.8	1.8	1.6	1.8	1.6	.9856

(Continued)

**Table 2.** Baseline Characteristics Stratified by Concurrence of Serum Creatinine and Albumin Among Twice-Weekly (n = 1,113) and Thrice-Weekly (n = 4,448) Hemodialysis Patients (Continued)

Variables	Twice-Weekly HD				Thrice-Weekly HD				P Value	
	After Matched		After Matched		After Matched		After Matched			
	Cr < 6.0 and ALB < 3.5	Cr ≥ 6.0 and ALB < 3.5	Cr < 6.0 and ALB ≥ 3.5	Cr ≥ 6.0 and ALB ≥ 3.5	Cr < 6.0 and ALB < 3.5	Cr ≥ 6.0 and ALB < 3.5	Cr < 6.0 and ALB ≥ 3.5	Cr ≥ 6.0 and ALB ≥ 3.5		
Total	14.2	15.8	14.5	13.6	13.5	16.7	18	17.6	13.7	.0217
Other cardiovascular disease										
COPD	3.8	4.9	1.8	3.6	3.1	5.1	6.4	4.3	4.3	.0024
History of cancer	2.1	2.8	0	2.1	1.6	2.6	2.8	2.4	2.7	.4247
Alcohol abuse	0.2	0.4	0	0.2	0	0.1	0.1	0.1	0.2	.6623

ALB, albumin; ASHD, atherosclerotic heart disease; BMI, body mass index; Ca, calcium; CHF, congestive heart failure; CO<sub>2</sub>, carbon dioxide combining power; COPD, chronic obstructive pulmonary disease; Cr, creatinine; CVD, cerebrovascular disease; DM, diabetes mellitus; eLBM, estimated lean body mass; Fe, ferritin; HGB, hemoglobin; HTN, hypertension; IQR, interquartile range; ISAT, iron saturation ratio; K, potassium; nPCR, normalized protein catabolic rate; P, phosphorus; PTH, parathyroid hormone; TIBC, total iron-binding capacity; WBC, white blood cells.

Note: Categorical variables are given as percentage; continuous variables as mean (standard deviation) or median (IQR) as appropriate. Laboratory measures are represented as averages of repeated measures during the first quarter of entry to cohort.

P value was estimated by 1-way analysis of variance or Kruskal-Wallis test for continuous variables or chi-square test for categorical variables.

Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229; hemoglobin and albumin in g/dL, ×10; TIBC in μg/dL to μmol/L, ×0.179. No conversion necessary for intact PTH in pg/mL and ng/L, WBC count in 10<sup>3</sup>/μL and 10<sup>9</sup>/L, and ferritin in ng/mL and μg/L.

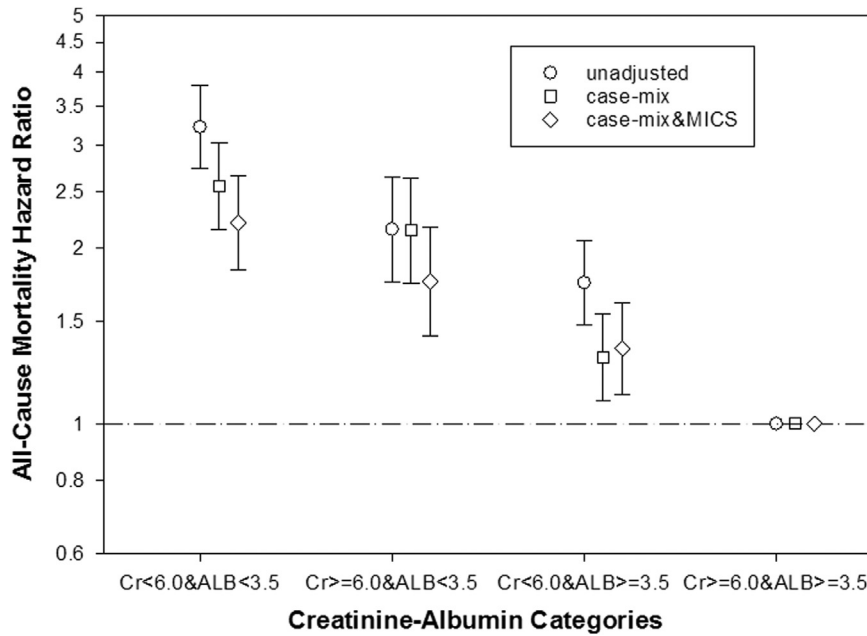
thrice-weekly hemodialysis patients. Furthermore, these inverse associations were still present after adjustment for case-mix covariates as well as nutritional and inflammatory markers. Our findings present an important observation regarding the role of concurrent serum creatinine and albumin when comparing mortality risk between twice-weekly versus thrice-weekly hemodialysis patients.

Many patients with kidney disease and ESRD including those undergoing hemodialysis treatment experience protein-energy wasting.<sup>7,22</sup> Protein-energy wasting and inflammation, which are hence referred to collectively as the MICS, are associated with poorer quality of life and higher morbidity and mortality in hemodialysis patients. Several studies<sup>23-25</sup> have underlined the prognostic significance of protein-energy wasting as a strong predictor of morbidity and mortality independent of other risk factors in hemodialysis patients. Protein nutritional status is determined by visceral and somatic protein stores<sup>26</sup>; and evaluation of muscle mass is an important method to assess protein nutritional status.<sup>14,27-29</sup> Serum creatinine level has been shown to be a reliable indicator of muscle mass and somatic protein mass and can be a crucial and useful marker of nutritional assessment in hemodialysis patients.<sup>26</sup> Previous studies had found that higher serum creatinine level among hemodialysis patients is associated with better survival.<sup>11-13</sup>

Moreover, serum albumin is an indicator of visceral protein stores, and low serum albumin is an important sign of protein-energy wasting. Studies have suggested that serum albumin is a reliable marker of nutritional status in ESRD patients<sup>30,31</sup> and a prognostic variable due to its strong association with long-term outcomes.<sup>32,33</sup> Presence of a low serum albumin in patients often triggers a search for potentially reversible causes of malnutrition or inflammation and therapeutic interventions that generally consist of measures to increase the enteral protein and energy intake.<sup>34</sup> Furthermore, both serum albumin and creatinine would benefit from increases in protein energy intake and thereby improve survival in hemodialysis patients. The impact of combined higher creatinine and albumin levels on mortality in hemodialysis is not well known and has not been studied in patients receiving less frequent hemodialysis treatments (twice weekly).

On the basis of established guidelines and recommendations, thrice-weekly hemodialysis has been regarded as the standard renal replacement therapy for ESRD patients and is therefore the most prevalent dialysis treatment modality in ESRD patients in the United States.<sup>22</sup> Data from a national sample have found that approximately 4% of hemodialysis patients in the United States are treated with twice per week hemodialysis.<sup>16</sup> This study also identified factors predictive of twice-weekly hemodialysis, among which were lower serum creatinine levels and higher serum albumin. Other factors listed included older age, Caucasian race, female gender, lower BMI, and higher residual renal function at dialysis start. In our study, patients

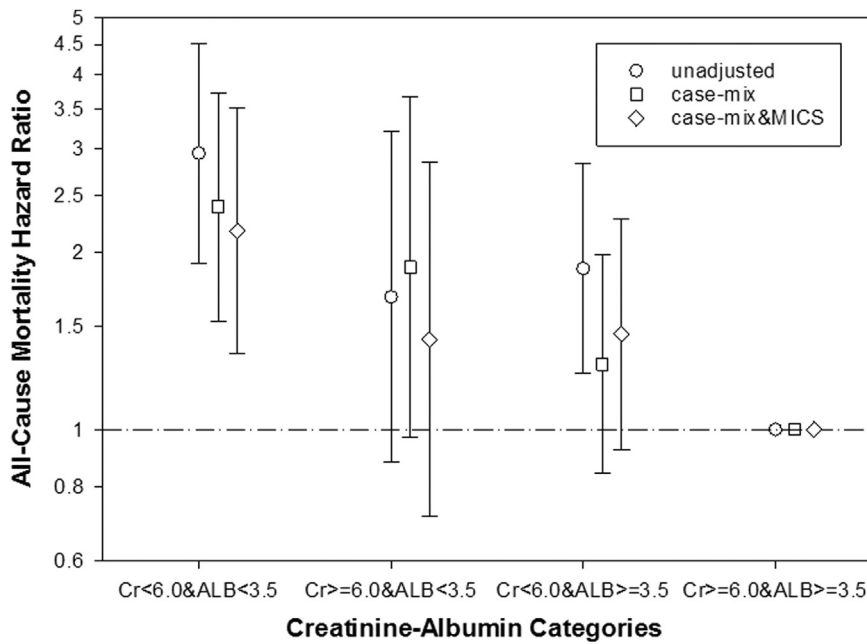




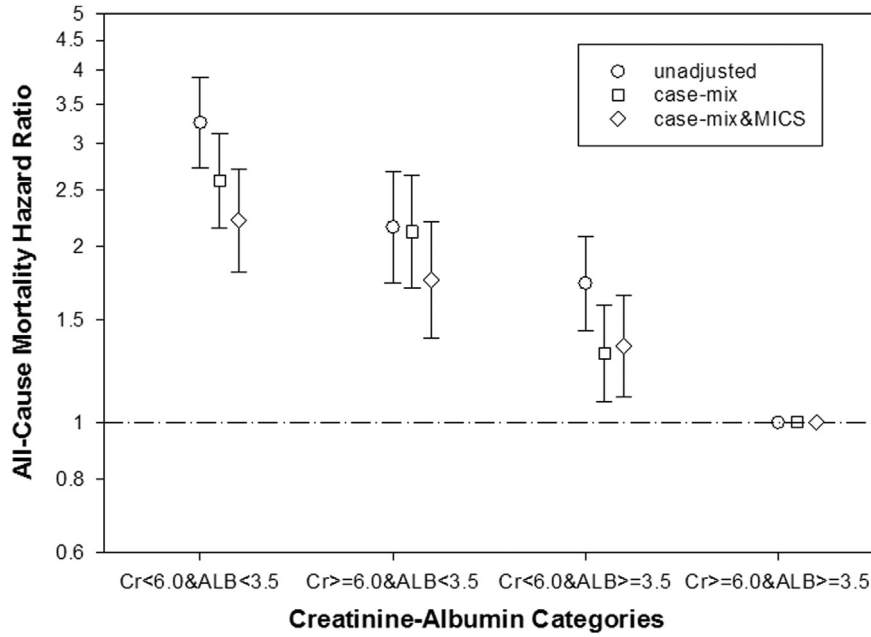
**Figure 2.** Baseline survival hazard ratio over 5 years according to concurrence of serum creatinine (mg/dL) and albumin (g/dL) in the total cohort of after matched hemodialysis patients (n = 5,561). See text for the list of covariates in multivariate adjustment. MICS, malnutrition-inflammation complex syndrome.

were matched on age, race, gender, diabetes, and facility region. Baseline BMI between the two dialysis frequency groups was also similar (Table S1). In sensitivity analysis,

which presented with similar results, patients were additionally matched on baseline concurrent serum albumin and serum creatinine groups. The results of our study



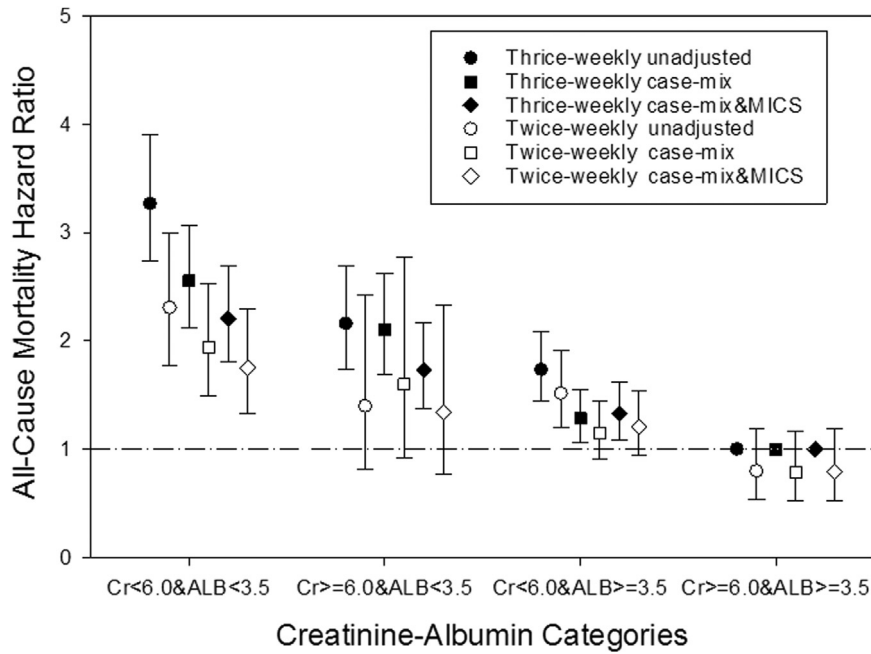
**Figure 3.** Baseline survival hazard ratio over 5 years according to concurrence of serum creatinine (mg/dL) and albumin (g/dL) in after matched twice-weekly hemodialysis patients (n = 1,113). See text for the list of covariates in multivariate adjustment. MICS, malnutrition-inflammation complex syndrome.



**Figure 4.** Baseline survival hazard ratio over 5 years according to concurrence of serum creatinine (mg/dL) and albumin (g/dL) in after matched thrice-weekly hemodialysis patients (n = 4,448). See text for the list of covariates in multivariate adjustment. MICS, malnutrition-inflammation complex syndrome.

show that once these potential selection bias factors are balanced across groups, a higher concurrence level of serum creatinine and albumin, representing a better nutri-

tional status and a lower inflammatory state, leads to better survival in both twice- and thrice-weekly hemodialysis patients.



**Figure 5.** Baseline survival hazard ratio over 5 years according to concurrence of serum creatinine (mg/dL) and albumin (g/dL) among after matched twice-weekly (n = 1,113) and thrice-weekly (n = 4,448) hemodialysis patients. The reference groups are categories in which creatinine  $\geq$  6.0 mg/dL and albumin  $\geq$  3.5 g/dL in thrice-weekly hemodialysis patients. See text for the list of covariates in multivariate adjustment. MICS, malnutrition-inflammation complex syndrome.

The strength of our study is the use of large contemporary nationally representative incident dialysis population with the ability to match 1:4 on a number of potential confounders including age, gender, race/ethnicity, diabetes, and facility region. However, some limitations should be considered. First, we could not obtain sufficient data related to residual kidney function. Second, we did not have comprehensive data that may affect hemodialysis patient outcomes, such as ultrafiltration rate, dialysis access type, hospitalizations, and other known or unknown confounders. Models were only adjusted for known and measured confounders, and therefore, we could not eliminate the possibility of residual confounding.

## Conclusion

Low serum creatinine and albumin levels are associated with highest mortality, and higher visceral protein and muscle mass combined is associated with better survival in both twice- and thrice-weekly hemodialysis patients. Twice-weekly hemodialysis patients have a similar risk for death according to the same levels of nutritional status and muscle mass when compared with thrice-weekly hemodialysis patients.

## Practical Application

Among the thrice-weekly hemodialysis patients, higher serum albumin and creatinine have lower mortality risk; twice-weekly hemodialysis patients who have the same nutritional status confer a similar survival benefit.

## Acknowledgments

The authors express their sincere appreciation to DaVita clinics that ensure the extensive data collection on which their work is based. They thank DaVita Clinical Research for their commitment to clinical research.

The abstract of this report has been presented as a poster at the Kidney Week, American Society of Nephrology, November 11–16, 2014, in Philadelphia, PA, US.

## Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1053/j.jrn.2016.07.001>.

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