Nephrol Dial Transplant (2013) 28: 2146–2155
doi: 10.1093/ndt/gft213
Advance Access publication 5 June 2013

Serum creatinine level, a surrogate of muscle mass, predicts mortality in peritoneal dialysis patients

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Keywords: creatinine, malnutrition, mortality, muscle, peritoneal dialysis

ORIGINAL ARTICLE

ABSTRACT

Background. In hemodialysis patients, higher serum creatinine (Cr) concentration represents larger muscle mass and predicts greater survival. However, this association remains uncertain in peritoneal dialysis (PD) patients.

Methods. In a cohort of 10 896 PD patients enrolled from 1 July 2001 to 30 June 2006, the association of baseline serum Cr level and change during the first 3 months after enrollment with all-cause mortality was examined.

Results. The cohort mean ± SD age was 55 ± 15 years old and included 52% women, 24% African-Americans and 48% diabetics. Compared with patients with serum Cr levels of 8.0–9.9 mg/dL, patients with serum Cr levels of <4.0 mg/dL and 4.0–5.9 mg/dL had higher risks of death {HR 1.36 [95% confidence interval (95% CI) 1.19–1.55] and 1.19 (1.08–1.31), respectively} whereas patients with serum Cr levels of 10.0–11.9 mg/dL, 12.0–13.9 mg/dL and ≥14.0 mg/dL had lower risks of death (HR 0.88 [95% CI 0.79–0.97], 0.71 [0.62–0.81] and 0.64 [0.55–0.75], respectively) in the fully adjusted model. Decrease in serum Cr level over 1.0 mg/dL during the 3 months predicted an increased risk of death additionally. The serum Cr–mortality association was robust in patients with PD treatment duration of ≥12 months, but was not observed in those with PD duration of <3 months.

Conclusions. Muscle mass reflected in serum Cr level may be associated with survival even in PD patients. However, the serum Cr–mortality association is attenuated in the early period of PD treatment, suggesting competing effect of muscle mass versus residual renal function on mortality.

INTRODUCTION

Serum creatinine (Cr) is typically used to estimate glomerular filtration rate (GFR) during a steady state of renal function. However, serum Cr originates from creatine, 95% of which is located in muscle [1, 2]. Although influenced by both muscle mass and GFR, serum Cr level may be used as a surrogate of muscle mass in end-stage renal disease (ESRD) patients among whom there is a balanced distribution of low GFRs [3–10]. In hemodialysis (HD) patients, increased serum Cr level has been associated with greater survival, whereas lower serum Cr level has been associated with increased mortality [10–13]. These findings suggest that low serum Cr level as a proxy of low muscle mass and protein-energy wasting (PEW) may be associated with adverse outcomes in HD patients [6, 14–17].

However, in studies of peritoneal dialysis (PD) patients, there have been variable associations between serum Cr level and mortality [18–20]. One reason for this may be that, compared with HD patients, PD patients have greater preservation of residual GFR [21–24] which is independently associated with mortality [25–27] as well as serum Cr level [28, 29]. In PD patients, total Cr clearance (peritoneal dialytic + renal Cr clearance) may be a greater determinant of serum Cr level than muscle mass and, in this scenario, higher serum Cr level (i.e. a proxy of lower Cr clearance) would relate to increased mortality. In contrast, muscle mass may have a greater influence on serum Cr level and, in this scenario, higher serum Cr level (i.e. proxy of larger muscle mass) would relate to greater survival. In a recent study of PD patients, higher estimated GFR by the Modification of Diet in Renal Disease (MDRD) equation [30, 31] was associated with increased mortality, but measured GFR was not related to mortality [32]. These data suggest that, in PD patients, serum Cr level may in fact be a surrogate of muscle mass, and that low muscle mass is associated with worse outcomes in this context.

We thus hypothesized that elevated serum Cr level as a proxy of large muscle mass may be associated with better outcomes in PD patients. In a large and contemporary cohort of PD patients, we examined the association of baseline serum Cr level and change in serum Cr level during the first 3 months after enrollment with all-cause mortality. In addition, we examined effect modification of PD treatment duration on the serum Cr–mortality association by conducting stratified analyses.

MATERIALS AND METHODS

Patients

We retrospectively examined data from all patients receiving PD treatment from 1 July 2001 to 30 June 2006 (i.e. for 20 consecutive calendar quarters) in a large US dialysis organization, DaVita, Inc. As the dialysis population is a dynamic cohort with a high turnover rate, a non-concurrent cohort was created to include all existing maintenance dialysis patients from the first quarter (q1) and all new patients from subsequent quarters (q2 through q20), which has been described in previous studies [33, 34]. The first (baseline) quarter for each patient was the calendar quarter in which the patient's dialysis duration was >90 days. Dialysis modality (PD versus HD) was ascertained according to the type of treatment patients were receiving at the time of entry into cohort. The follow-up time began on the date of entry into the cohort. Patients were censored at the time of death, renal transplantation, departure from DaVita facilities or end of the study period (30 June 2007). The study was approved by the Harbor-UCLA Medical Center Institutional Review Board with exemption of the requirement for a written consent form.

Demographic and clinical measures

Data from the DaVita database was merged with data from the US Renal Data System (USRDS). Information regarding the date of the first dialysis treatment, race/ethnicity, marital status, insurance and comorbidities was obtained from the USRDS. Race/ethnicity was reported as one of the three mutually exclusive categories: non-Hispanic whites, non-Hispanic African-Americans and Hispanics. In this report, the former two groups are referred to Caucasians and African-Americans, respectively. The following 10 baseline comorbidities were considered: diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, non-ambulatory state and current smoking. The presence of diabetes mellitus was ascertained using data from the DaVita database. Dialysis duration was defined as the time between the first day of dialysis treatment and the first day that the patient entered the cohort. Body weight averaged over 13 weeks during the first (baseline) quarter was used to calculate body mass index (BMI).

Laboratory measures

All laboratory values were typically measured on a monthly basis by automated and standardized methods. Blood samples were transported to the central laboratory center (DaVita Laboratory, Deland, FL) within 24 h. To minimize effects of short-term variations, all repeated measures for each patient during the first quarter were averaged, and the summary estimates were used in all models. Change in serum Cr level (ΔCr) was calculated as the mean serum Cr during the second quarter minus the mean serum Cr during the first quarter.

Statistical analysis

Cox proportional hazards models were used to determine the relationship of baseline serum Cr level (mean serum Cr concentration during the first quarter) and ΔCr level with all-cause mortality. We divided serum Cr levels into seven categories (<4.0, 4.0–5.9, 6.0–7.9, 8.0–9.9, 10.0–11.9, 12.0–13.9, ≥14.0 mg/dL) *a priori*. ΔCr levels were divided into <−1.0, −1.0 to 1.0 and >1.0 mg/dL. For the stratified analyses, PD duration was divided into <3, 3 to <12 and ≥12 months.

For each analysis, three levels of multivariable adjustment were examined: (i) unadjusted models that included the main

Table 1. Baseline characteristics according to serum creatinine level (n = 10 896)

Variables	Serum creatinine (mg/dL)							
	<4.0	4.0–5.9	6.0–7.9	8.0–9.9	10.0–11.9	12.0–13.9	≥14.0	P-value
N	783	2143	2414	2103	1524	965	964	
Age (years)	63 ± 14	61 ± 14	58 ± 15	56 ± 15	52 ± 15	48 ± 14	43 ± 14	<0.001
Gender (% females)	56	53	49	50	45	38	28	<0.001
Race (%)								
Caucasian	65	64	59	52	46	35	21	<0.001
African-American	10	13	18	23	30	39	54	<0.001
Hispanic	15	13	13	13	14	14	15	0.30
Asian	4	4	4	5	4	5	4	0.25
Insurance								
Medicare	69	62	62	68	69	68	76	<0.001
Medicaid	3	3	3	3	4	5	5	<0.001
Other	28	35	35	29	27	26	19	<0.001
Marital status (%)								
Married	61	61	60	59	54	50	48	<0.001
Divorced	6	7	7	10	10	9	8	0.001
Single	17	20	23	23	30	37	42	<0.001
Widowed	16	12	10	8	5	4	2	<0.001
Comorbidity (%)								
PD duration (months)	2 (1–3)	2 (1–4)	3 (1–21)	16 (2–48)	23 (3–55)	28 (8–61)	34 (13–64)	<0.001
DM	68	61	54	47	39	30	21	<0.001
HTN	77	81	80	78	76	74	78	<0.001
IHD	28	22	17	13	11	6	3	<0.001
CHF	32	20	16	15	11	10	6	<0.001

CBVD	9	7	6	4	3	3	1	<0.001
PVD	15	12	8	7	4	3	2	<0.001
COPD	8	4	4	3	2	1	1	<0.001
Non-ambulatory	3	1	1	0	0	0	0	<0.001
Malignancy	6	5	4	3	3	2	1	<0.001
Current smoker	6	6	5	6	5	5	4	0.79
BMI (kg/m^2)	26.1 ± 6.1	26.7 ± 6.3	26.5 ± 6.0	26.3 ± 6.8	25.9 ± 7.1	25.5 ± 7.5	25.8 ± 7.4	<0.001
Laboratory values								
Hemoglobin (g/dL)	12.5 ± 1.5	12.2 ± 1.5	12.1 ± 1.5	11.9 ± 1.5	11.9 ± 1.5	11.8 ± 1.5	11.6 ± 1.6	0.01
Albumin (g/dL)	3.4 ± 0.5	3.4 ± 0.5	3.5 ± 0.5	3.6 ± 0.5	3.7 ± 0.4	3.8 ± 0.4	3.9 ± 0.4	<0.001
TIBC (mg/dL)	243 ± 60	239 ± 57	233 ± 54	223 ± 52	222 ± 51	222 ± 50	223 ± 49	<0.001
Ferritin (ng/mL)	188 (89–374)	209 (101–414)	240 (106–529)	338 (150–691)	355 (142–644)	400 (178–696)	351 (161–669)	<0.001
Ca (mg/dL)	9.1 ± 0.6	9.1 ± 0.7	9.2 ± 0.8	9.3 ± 0.8	9.3 ± 0.8	9.3 ± 0.9	9.3 ± 1.0	<0.001
Phosphorus (mg/dL)	4.0 ± 0.8	4.6 ± 1.0	5.1 ± 1.2	5.6 ± 1.3	6.1 ± 1.6	6.4 ± 1.7	6.8 ± 1.7	<0.001
Total CO_2 (mEq/L)	26 ± 3	25 ± 3	25 ± 3	24 ± 3	23 ± 3	23 ± 3	23 ± 3	<0.001
WBC ($\times 10^3/mm^3$)	7.7 ± 2.7	7.6 ± 2.7	7.7 ± 2.9	7.6 ± 2.4	7.5 ± 2.4	7.3 ± 2.3	6.9 ± 2.2	<0.001
Lymphocyte (%)	19 ± 8.3	19 ± 7.8	19 ± 7.7	19 ± 7.8	20 ± 8.0	21 ± 8.5	22 ± 8.5	<0.001

Categorical variables are reported as percentages; continuous variables are reported as means ± standard deviation or medians (interquartile range). Dialysis duration was defined as the time between the first day of dialysis treatment and the first day that the patient entered the cohort. P-values were estimated by χ^2 test and one-way ANOVA, according to data type. Conversion factors for units: albumin and hemoglobin in g/dL to g/L, ×10; creatinine in mg/dL to µmol/L, ×88.4; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229. No conversion necessary for ferritin in ng/mL and µg/L, and WBC count in $10^3/\mu L$ and $10^9/L$.

DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; CHF, congestive heart failure; CBVD, cerebrovascular disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; TIBC, total iron-binding capacity; WBC, white blood cells.

predictor and the entry calendar quarter (q1 through q20); (ii) case-mix models that included age, sex, diabetes mellitus, race/ethnicity, comorbidities, primary insurance and marital status; (iii) models adjusted for case-mix and malnutrition inflammation cachexia syndrome (MICS) covariates, which included all of the covariates in the case-mix model as well as the following: BMI; serum levels of albumin, calcium, phosphorus, bicarbonate, total iron-binding capacity and ferritin; peripheral white blood cell count, lymphocyte percentage; hemoglobin concentration. The models using ΔCr as the main predictor were additionally adjusted for the baseline serum Cr level. The proportional hazards assumption was assessed by log–log plots and Schoenfeld residuals after model fitting.

Data for age, sex, race, PD duration and diabetes were missing for <1% of the cohort. Data for comorbidities, insurance and marital status had 7.5, 11.5 and 22.1% missing values, respectively. Data for BMI, total iron binding capacity, serum ferritin, peripheral white blood cell count and lymphocyte percentage had 9.3, 1.4, 2.7, 3.1 and 8.8% missing values. The remaining variables had <1% missing values. The missing values were handled using the following approaches: for categorical variables, a missing indicator was created; for continuous variables, the mean or median of existing values was imputed by serum Cr categories. All analyses were carried out with SAS, version 9.3 (SAS Institute, Cary, NC) and STATA, version 12.1 (Stata Corporation, College Station, TX).

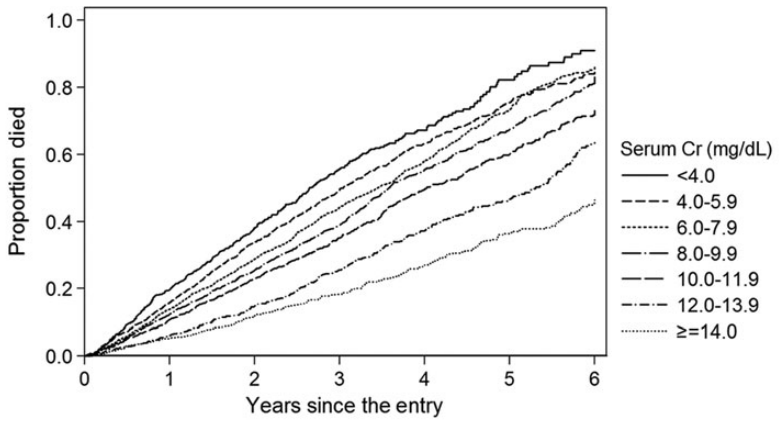
RESULTS

Patient characteristics

During the overall cohort period, 12 734 patients received PD treatment. Among them, patients with missing baseline serum Cr data ($n = 1480$) and incomplete follow-up information ($n = 358$) were excluded, resulting in 10 896 PD patients in the final study cohort. Comparison of demographics between included and excluded patients demonstrated no meaningful differences. Baseline characteristics of the 10 896 PD patients stratified by baseline serum Cr levels are listed in Table 1. Patients with higher serum Cr levels tended to be younger, male, African-American, non-diabetic, and had longer dialysis duration. In patients with lower serum Cr levels, cardiovascular comorbidities, including ischemic heart disease, congestive heart failure, cerebrovascular disease and peripheral vascular disease, were more frequent. Serum albumin and phosphorus levels were positively correlated with serum Cr levels ($r = 0.31$, $P < 0.001$ and $r = 0.51$, $P < 0.001$). Lower hemoglobin and higher ferritin levels were observed with higher serum Cr levels. Lower peripheral white blood cell counts and higher lymphocyte percentages were observed with higher serum Cr levels.

Baseline serum Cr level and all-cause mortality

The mean ± SD duration of follow-up was 2.4 ± 1.6 years during which time a total of 4833 (44%) all-cause deaths were reported {crude mortality rate, 184 deaths [95% confidence interval (95% CI) 179–189 deaths] per 1000 person-years}. Kaplan–Meier curves showed a stepwise decline in deaths with higher serum Cr categories (Figure 1). Compared with patients with serum Cr levels of 8.0–9.9 mg/dL (reference group), decreasing serum Cr levels below this threshold were associated with incrementally higher unadjusted hazard ratios (HR) for all-cause mortality (Table 2). Adjustment for case-mix covariates attenuated the mortality predictability of lower serum Cr levels. However, in fully adjusted (case-mix and MICS) models, serum Cr levels of 4.0–5.9 and <4.0 mg/dL were associated with greater mortality: adjusted HRs 1.19 (95% CI 1.08–1.31) and 1.36 (95% CI 1.19–1.55), respectively. In contrast, higher serum Cr levels ≥10.0 mg/dL were associated



Cr (mg/dL)	Number of patients at risk					
<4.0	783	561	312	150	71	21
4.0–5.9	2143	1628	938	514	267	118
6.0–7.9	2414	1864	1145	685	386	160
8.0–9.9	2103	1657	1135	745	425	220
10.0–11.9	1524	1205	852	583	382	184
12.0–13.9	965	792	569	397	265	143
≥=14.0	964	793	593	442	316	172

FIGURE 1: Kaplan–Meier curves for all-cause mortality according to baseline serum creatinine categories in 10 896 PD patients.

Table 2. Association between baseline serum creatinine level and all-cause mortality (n = 10 896)

Cr (mg/dL)	*N*	Death (%)	Unadjusted HR (95% CI)	Case-mix adjusted HR (95% CI)	Case-mix and MICS adjusted HR (95% CI)
<4.0	783	397 (51)	1.68 (1.49–1.89)	1.13 (1.00–1.28)	1.36 (1.19–1.55)
4.0–5.9	2143	1043 (49)	1.35 (1.24–1.48)	1.06 (0.97–1.16)	1.19 (1.08–1.31)
6.0–7.9	2414	1146 (48)	1.18 (1.09–1.29)	1.02 (0.94–1.11)	1.06 (0.97–1.15)
8.0–9.9	2103	1029 (49)	Ref.	Ref.	Ref.
10.0–11.9	1524	665 (44)	0.80 (0.72–0.88)	0.92 (0.83–1.01)	0.88 (0.79–0.97)
12.0–13.9	965	314 (33)	0.54 (0.48–0.62)	0.73 (0.64–0.83)	0.71 (0.62–0.81)
≥14.0	964	239 (25)	0.37 (0.32–0.42)	0.63 (0.55–0.74)	0.64 (0.55–0.75)

Cr, creatinine; MICS, malnutrition-inflammation cachexia syndrome; HR, hazard ratio; CI, confidence interval.

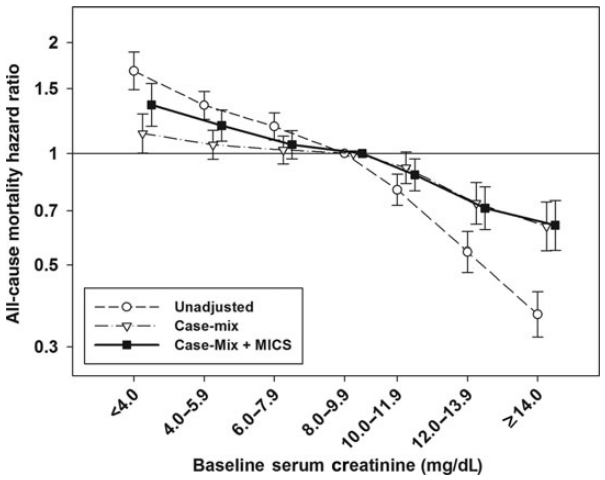


FIGURE 2: Association between baseline serum creatinine level and all-cause mortality in 10 896 PD patients. Note: case-mix models were adjusted for age, sex, diabetes mellitus, race, comorbidities, primary insurance and marital status. Case-mix and MICS models were adjusted for all of the covariates in the case-mix model and BMI, serum albumin, total iron-binding capacity, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, percentage of lymphocyte and hemoglobin concentration. MICS, malnutrition-inflammation cachexia syndrome.

with greater survival when compared with the reference group. Both case-mix and fully adjusted models demonstrated similar HRs with higher serum Cr levels. In fully adjusted models, patients with serum Cr levels of 10.0–11.9, 12.0–13.9 and ≥14.0 mg/dL showed greater survival: adjusted HRs 0.88 (95% CI 0.79–0.97), 0.71 (95% CI 0.62–0.81) and 0.64 (95% CI 0.55–0.75), respectively (Figure 2).

Effect of PD duration on the association between serum Cr level and mortality

The patients were divided by PD duration of <3, 3 to <12 and ≥12 months. Adjusted HRs from fully adjusted models according to serum Cr level and PD duration are presented in Table 3. No association between serum Cr level and mortality was observed in patients with PD duration of <3 months. In patients with PD duration of 3 to <12 months, serum Cr levels of 12.0–13.9 and ≥14.0 mg/dL were associated with a lower mortality risk when compared with serum Cr levels of 8.0–9.9 mg/dL. In patients with PD duration of ≥12 months, there was an overall inverse association between serum Cr level and mortality except in the lowest serum Cr category (<4.0 mg/dL), in which serum Cr levels of 4.0–7.9 mg/dL were associated with higher mortality, whereas higher serum Cr levels >10 mg/dL were associated with a greater survival (Figure 3).

Change in serum Cr level and all-cause mortality

Among 10 896 PD patients, 247 died during the first quarter and 1668 additional patients did not have a serum Cr level in the second quarter, resulting in 8981 patients for this secondary analysis. During the first 3 months after the entry, serum Cr level was stable in 5835 (65%) patients [ΔCr −1.0 to1.0 mg/dL], increased in 2138 (24%) patients [ΔCr >1.0 mg/dL] and decreased in 1008 (11%) patients [ΔCr <−1.0 mg/dL]. Compared with patients with ΔCr of −1.0 to1.0 mg/dL, patients with ΔCr of <−1.0 mg/dL demonstrated higher mortality in the fully adjusted model: adjusted HR 1.16 (95% CI) 1.05–1.28. However, ΔCr >1.0 mg/dL was not associated with a survival benefit (Table 4).

DISCUSSION

In this large and contemporary cohort of 10 896 PD patients, we observed that higher baseline serum Cr levels were associated with greater overall survival. However, this association was modified by PD duration, in which a significant association was observed in patients with PD duration >12 months, but not in those with shorter PD duration. A decline in serum Cr level within the first 3 months of study entry was associated

Table 3. Fully adjusted HRs for all-cause mortality by serum creatinine level and peritoneal dialysis duration (n = 10 896)

Cr (mg/dL)	<3 months (n = 4903)		3-<12 months (n = 1217)		≥12 months (n = 4776)	
	HR	95% CI	HR	95% CI	HR	95% CI
<4.0	1.15	0.93–1.41	0.99	0.64–1.54	1.06	0.79–1.42
4.0–5.9	1.02	0.86–1.21	0.96	0.72–1.27	1.29	1.10–1.52
6.0–7.9	0.98	0.83–1.15	0.95	0.73–1.24	1.14	1.01–1.29
8.0–9.9	Ref.		Ref.		Ref.	
10.0–11.9	1.05	0.83–1.33	0.90	0.66–1.22	0.83	0.74–0.94
12.0–13.9	0.75	0.52–1.09	0.60	0.38–0.95	0.71	0.61–0.83
≥14.0	0.71	0.45–1.13	0.54	0.30–0.98	0.60	0.50–0.72

HR, hazard ratio; CI, confidence interval.

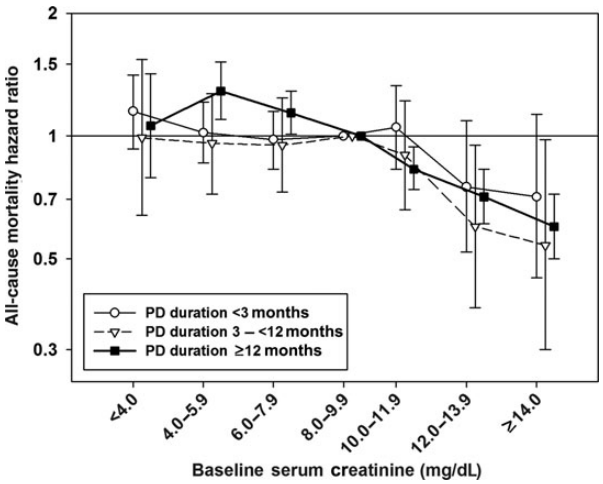


FIGURE 3: Mortality predictability of serum creatinine levels according to peritoneal dialysis duration. The models were adjusted for age, sex, diabetes mellitus, race, comorbidities, primary insurance, marital status, BMI, serum albumin, total iron-binding capacity, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count, percentage of lymphocyte and hemoglobin concentration.

with increased mortality independent of baseline serum Cr level.

PEW is frequently observed in dialysis patients and has been associated with adverse outcomes [14–17]. Because serum Cr is derived from skeletal muscle, it may serve as a biomarker of somatic body protein particularly in ESRD patients with very low GFRs and stable daily protein intake and dialysis dose [3–10]. Several studies in HD patients have demonstrated a linear association between higher serum Cr level with survival [11–13, 35]. This suggests that serum Cr level reflects muscle mass and that low muscle mass resulting from PEW is associated with poor outcomes in HD patients. In addition, some studies evaluating a survival benefit of early start of dialysis showed that a higher estimated GFR based on serum Cr level at dialysis initiation was associated with poorer survival, which could not be fully abolished by adjusting for known confounders such as age, sex, race, comorbidities, hemoglobin and serum albumin level [36–38]. This phenomenon is also likely to be caused by patients with a low muscle mass leading to a low plasma Cr and thus a high estimated GFR [32, 39]. Our results showed that the association between higher serum Cr level with greater survival is still observed in a large PD cohort. A previous study of 140 PD patients demonstrated that age, diabetes, low serum albumin level and low serum Cr level were independent predictors of mortality [18]. Additionally, the Canada–USA Peritoneal Dialysis Study Group reported that percent lean body mass determined from Cr kinetics was associated with survival; among 680 patients divided into tertiles of percent lean body mass (>73, 63–73 and <63%), the 2-year survival probabilities were 88.3, 81.2 and 65.2%, respectively [40]. A recent *post hoc* analysis of data from PD patients enrolled in ADEMEX study demonstrated that every 1 mL/min/1.73 m^2 increase in estimated GFR by the four-variable MDRD equation was associated with a 6% increase in risk of death, but there was no association between measured Cr clearance and survival. This study also demonstrated a negative association between estimated GFR and Cr appearance rates [32]. Our results also suggest that muscle mass plays a predominant role in the serum Cr–mortality association in PD patients, supporting findings from earlier studies. Thus, large muscle mass may be beneficial to survival not only in HD patients, but also in PD patients.

Residual GFR may be better preserved and provide greater contribution to total Cr clearance in PD patients compared with HD patients particularly in patients of shorter dialysis duration [21–24]. Given that residual GFR is an important predictor of survival [25–27], the serum Cr–mortality association may be modified by residual GFR. Because information for residual GFR was unavailable in our database, we compared the mortality predictabilities of serum Cr level among subgroups stratified by PD duration as a proxy of residual GFR. In patients with PD duration of <3 months, an association between serum Cr level and mortality was not observed, suggesting that residual GFR may attenuate this association. In the patients with PD duration of ≥12 months, serum Cr level

Table 4. Association between change in serum creatinine (ΔCr) during the first 3 months after study entry and mortality (n = 8981)

ΔCr (mg/dL)	*N*	Death (%)	Unadjusted	Case-mix adjusted	Case-mix and MICS adjusted
			HR (95% CI)	HR (95% CI)	HR (95% CI)
<(−1.0)	1008	496 (49)	1.36 (1.23–1.50)	1.24 (1.12–1.37)	1.16 (1.05–1.28)
(−1.0) −1.0	5835	2612 (45)	Ref.	Ref.	Ref.
>1.0	2138	888 (42)	1.03 (0.96–1.12)	0.97 (0.90–1.05)	0.98 (0.90–1.06)

ΔCr was calculated as mean of serum Cr for the second quarter minus mean of serum Cr for the first quarter.
MICS, malnutrition-inflammation cahexia syndrome; HR, hazard ratio; CI, confidence interval.

was inversely associated with mortality except among those with serum Cr levels of <4.0 mg/dL. In patients with longer PD duration in whom there is a lower likelihood of residual renal function, there was a robust association between serum Cr level and survival. The absence of an association between low serum Cr level and higher mortality among those with Cr levels <4.0 mg/dL may be related to the small sample size in this subgroup or may have been a reflection of residual GFR preservation in some longer-term PD patients. When employing serum Cr level as a surrogate of muscle mass and prognostic indicator in PD patients, residual GFR and/or dialysis duration should also be considered.

Our results also showed that a decrease in serum Cr level over time was prognostic of increased mortality, independent of baseline serum Cr level. Patients who experienced a 1.0 mg/dL decline in serum Cr level during the first 3 months after study entry had a 16% higher risk of death compared with patients with stable serum Cr levels. Given that residual GFR typically falls with increasing dialysis duration, reductions in serum Cr level more likely reflects loss of muscle mass or poor protein intake, which are consequently associated with increased mortality. However, an increase in serum Cr level did not show a significant association with better survival. It is our opinion that an increase in serum Cr level may be observed with both loss of residual GFR as well as gaining of muscle mass, which may have competing influences on mortality outcome. The association between serum Cr level reductions over time and higher mortality further support the relationship between sarcopenia with mortality in PD patients.

Despite its strength, our study has several limitations which bear mention. First, due to data limitations, we were unable to directly examine residual renal function, peritoneal transport rate, type of PD (continuous ambulatory or automated PD) and delivered dialysis dose (weekly Kt/V or weekly Cr clearance). Although prior evidence has not shown that small-solute clearance within the range achieved in clinical practice has an effect on patient outcomes [41, 42], and a differential association between continuous ambulatory versus automated PD with mortality has not been observed [43–45], we cannot exclude the possibility of bias from lack of data on delivered dialysis dose and type of PD. Second, we did not have information regarding serum C-reactive protein levels, which is independently associated with mortality in PD patients or other inflammatory cytokines [46, 47]. Although we included several other inflammatory surrogate measures, such as total white blood cell count, lymphocyte percentage, serum albumin, total iron-binding capacity and ferritin level, residual confounding cannot be excluded. Third, data on volume status was not available and hence not included in the models. Fourth, although information regarding comorbid conditions was obtained at the time of dialysis initiation and adjusted for in multivariable models, annotation of this information spanned a period of 3–22 months before study entry. Moreover, baseline characteristic data demonstrated that patients with higher serum Cr levels had more favorable comorbid profiles and other nutritional markers than those with lower serum Cr levels, and thus, we cannot exclude residual confounding on the basis of health status. In baseline characteristic, lower hemoglobin and higher serum ferritin levels were observed in patients with higher serum Cr levels. However, it is difficult to explain a reason because data for erythropoiesis stimulating agent and iron dose were not included in this analysis. Last, the muscle mass was not assessed in this study. We did not have estimates of muscle mass such as lean body mass by dual-energy X-ray absorptiometry, bioimpedance analysis or near-infrared interactance,[17, 48] so that could not evaluate an association of the muscle mass and mortality directly. In addition, serum Cr level can be influenced by recent intake of meats. Greater appetite was also reported to associate with better survival in HD patients.[49, 50] It could be a concern that some of the survival benefit associated with higher serum Cr level may be related to the association between better appetite and greater survival in part.

In summary, our findings validate the prognostic value of serum Cr level as a surrogate of muscle mass in a large cohort of PD patients. Higher muscle mass may be associated with greater survival in PD patients as HD patients. However, using serum Cr level to estimate muscle mass should consider residual renal function or at least dialysis duration. Further studies examining efficient strategies for nutritional support are warranted to preserve muscle mass in PD patients.

ACKNOWLEDGEMENTS

We thank DaVita Clinical Research (DCR) for providing the clinical data, analysis and review for this research project.

FUNDING

The study was supported by research grants from the National Institute of Diabetes, Digestive and Kidney Disease of the National Institutes of Health R21 DK 077341 (K.K.Z. and R.M.), a philanthropist grant from Harold Simmons (K.K.Z.) and research grants from DaVita Clinical Research (K.K.Z. and R.M.). M.Z.M. is recipient of the Hungarian Eötvös Scholarship (MÖB/77-2/2012). C.M.R. is supported by an NIH/NIDDK grant (F32 DK093201).

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format. R.M. has received grant support and/or honoraria from Baxter Healthcare and DaVita. A.R.N. is employee of DaVita. K.K.Z. was the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA, during 2007–12. Other authors have declared that no financial conflict of interest exists.

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Received for publication: 3.1.2013; Accepted in revised form: 30.3.2013