Clinica Chimica Acta 489 (2019) 144–153

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Longitudinal progression trajectory of random urine creatinine as a novel predictor of ESRD among patients with CKD

Ching-Wei Tsai[a,b], Han-Chun Huang[b], Ni Tien[c,d], Chih-Wei Chung[b], Hsien-Tsai Chiu[b], Hung-Chieh Yeh[a], Chin-Chi Kuo[a,b,*]

[a] Division of Nephrology, Department of Internal Medicine, China Medical University Hospital and College of Medicine, China Medical University, Taichung, Taiwan
[b] Big Data Center, China Medical University Hospital and China Medical University, Taichung, Taiwan
[c] Department of Laboratory Medicine, China Medical University Hospital and China Medical University, Taichung, Taiwan
[d] Department of Medical Laboratory Science and Biotechnology, China Medical University, Taichung, Taiwan

ARTICLE INFO

Keywords:
Urine creatinine
Trajectory
Chronic kidney disease
Dialysis
Mortality

ABSTRACT

Background: The clinical importance of random urine creatinine concentration in CKD population remains undetermined. Earlier studies found that lower 24-h urine creatinine excretion was associated with the risk of ESRD and all-cause mortality among CKD patients.

Methods: We modeled the longitudinal trajectories of serial random urine creatinine among 4689 CKD patients enrolled in a national registry-based pre-ESRD program between 2003 and 2015 at a tertiary medical center. Other biochemical parameters including kidney function and serum albumin were regularly evaluated. Primary study outcomes were ESRD requiring maintenance dialysis and all-cause mortality.

Results: By group-based trajectory modeling, the urine creatinine trajectories were characterized into three patterns: (1) stable low; (2) medium; and (3) high-declining. The adjusted hazard ratio of incident ESRD and all-cause mortality increased by 6% (95% CI: 1–12%) and 9% (95% CI: 2–17%), respectively, for each 20 mg/dL reduction in baseline random urine creatinine concentration. Consistently, there was a significant inverse linear dose-response relationship between baseline random urine creatinine and incident ESRD, but not all-cause mortality. Compared to patients with "medium" and "high-declining" urine creatinine trajectories combined, the adjusted hazard ratio for incidental ESRD among patients with a "stable-low" trajectory who had serial random urine creatinine concentrations stably below 100 mg/dL was 1.46 (95% CI: 1.00–2.12) after considering the competing risk of death.

Conclusions: Random urine creatinine not only serves as a common urinary concentration corrector but has its own clinical significance in risk stratification and outcome prediction in patients with advanced CKD.

1. Introduction

Random urine creatinine (U-Cr) concentration is commonly used to standardize the variation of random urine analyte concentration from individuals' fluid status. One of the most common urine creatinine-based adjustment in nephrology is albumin-creatinine ratio to approximate daily albumin excretion, which is a classical kidney injury marker and an important predictor of all-cause mortality [1]. Recent studies have raised interest in the independent effects of U-Cr concentration on the progression to end-stage renal disease (ESRD) and risk of mortality in CKD populations [2–4]. All of these studies used 24-h urine specimens to quantify daily U-Cr excretion amount and consistently showed an increased risk of developing ESRD and mortality among CKD patients with lower 24-h U-Cr concentrations. Uremic malnutrition, particularly muscle wasting, has been considered the main contributor [5]. Several mechanisms that induce persistent catabolic state resulting in the erosion of lean body mass and protein degradation has been identified in CKD populations including acidosis, inflammation, and decreased hypothalamic appetite [6]. Muscle wasting has been linked to poor physical performance and cognitive impairment among ESRD patients [7,8]. Although increasing evidence supports the perilous role of muscle wasting in CKD care, the current guidelines has not recommended routinely evaluating sarcopenia based on U-Cr concentrations [9]. Barriers of formulating practical recommendations include

* Corresponding author at: Big Data Center, China Medical University Hospital, China Medical University, Taichung, Taiwan, 2, Yude Rd., North Dist., Taichung City 404, Taiwan.
E-mail address: d25725@mail.cmuh.org.tw (C.-C. Kuo).

https://doi.org/10.1016/j.cca.2018.12.002
Received 30 October 2017; Received in revised form 5 December 2018; Accepted 6 December 2018
Available online 08 December 2018
0009-8981/

the cumbersome 24-h urine collections, the lack of longitudinal trajectory data of 24-h U-Cr, and the unknown feasibility of random U-Cr serving as a reliable marker of muscle wasting or an independent predictor of renal outcomes [10,11].

2. Materials and methods

2.1. Study population

Taiwan's National Health Insurance (NHI) has launched the Project of Integrated Care of CKD since 2002 and specifically targeted on CKD stage 3b to 5 since 2007. This uniquely so-called pre-ESRD Program offers a multidisciplinary approach, involving nephrologists, renal nursing specialists, pharmacists, and dieticians to design an individualized care plan for a wide range of CKD patients toward meeting therapeutic goals of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) guidelines [12]. China Medical University Hospital (CMUH), a tertiary medical center in Central Taiwan, has joined this program since 2003 and prospectively enrolled patients with CKD consecutively who were willing to participate. CKD diagnosis was based on the nephrologist's working diagnosis or according to the criteria of NKF/KDOQI guidelines [12]. Patients in this program were regularly followed up at 12, 8, and 4 weeks, respectively, for CKD stage 3b, 4, and 5, or when necessary. Biochemical measurements including serum creatinine and albumin as well as the random urine albumin or protein were measured at least every 12 weeks or more frequent. All enrolled patients were followed-up until initiation of long-term renal replacement therapy (hemodialysis, peritoneal dialysis, or transplantation), loss to follow-up, death, or December 31, 2015, whichever occurred first.

The index date was defined for each patient as the first day of pre-ESRD program enrollment and patients were required to have at least 6 months of continuous post-enrollment observation. We excluded patients aged < 20 or > 90 y, patients with a dialysis history or illogical data entries and those who had insufficient frequency of U-Cr measurements. This left 4689 participants for the present study (Supplementary Fig. 1). The study has been approved by the Research Ethical Committee/Institutional Review Board of China Medical University.

2.2. Measurement of urine creatinine concentration, specific gravity, and kidney function

Serum and random U-Cr concentrations were measured by the Jaffe rate method at CMUH Central Laboratory using Beckman UniCel® DxC 800 Synchron Clinical Systems (Beckman Coulter Inc.). Urine specific gravity (U-SG) was determined by Clinitek Atlas Urine Chemistry Analyzer (Siemens Healthcare Inc.). The eGFR was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation [13]. The serum creatinine concentration at enrollment was used to define the baseline eGFR and the corresponding CKD stages using the cut-off values: > 90, 60–89.9, 30–59.9, 15–29.9, and < 15 mL/min/1.73m^2. All prospective within-person measurements of U-Cr, serum albumin, and eGFR were considered until the end-points. For instance, the quarterly average concentration of U-Cr was calculated if the patient had more than one measurement of U-Cr within a three-month period and the individual's U-Cr trajectory was modeled based on quarterly average U-Cr measures. The same approach was applied to model the trajectory of serum albumin and eGFR.

2.3. Other variables

Sociodemographic variables collected during the enrollment interview. Smoking status and alcohol consumption were both categorized as current, former, or never. Diabetes mellitus and hypertension were defined by physicians' clinical diagnosis according to the patients' ICD codes and/or the use of glucose-lowering agents. History of cardiovascular disease (CVD) was defined as a documented coronary artery disease, myocardial infarction, stroke or heart failure in the EMRs. All other serum and urine biochemical parameters were determined by UniCel DxC 800 Synchron Clinical Systems (Beckman Coulter Inc.). Random urine dipstick and protein- or albumin-creatinine ratio (PCR or ACR) measurements were used to quantify proteinuria. Proteinuria was defined as in at least two of three consecutive random urine examinations showing urine dipstick $> 1+$ or PCR > 0.5 g/g creatinine or ACR > 0.3 g/g creatinine.

2.4. Statistical analyses

Continuous variables were expressed as mean and SD, being compared using ANOVA whereas categorical variables were expressed as frequency (percentage) and compared through chi-square test. The associations among baseline U-Cr concentration, risk of ESRD, and all-cause mortality were estimated by multivariable Cox regression analysis. Baseline U-Cr concentration was modeled as both a continuous and a categorical (≥ 100 vs. < 100 mg/dL) exposure. We characterized the dose-response relation using a restricted cubic spline model with three knots located at the 10th, 50th, and 90th percentiles of the overall U-Cr distribution.

We used the semiparametric group-based trajectory model (GBTM) to characterize the trajectories of U-Cr. Briefly, the PROC TRAJ macro (developed using SAS software) fits a semiparametric mixture model to longitudinal data using the maximum-likelihood method [14,15]. This approach provides the benefit to discover trajectory patterns when the number of subgroups and other information, such as the shape of trajectories in subgroups, are unknown. We empirically compared one-, two-, three-, and four-group solutions and then optimized the number of subgroups using Bayesian Information Criterion (BIC) values (close to zero indicating a good fit), wherein the shapes of trajectories was determined according to order of the polynomial (linear, quadratic, cubic, etc.). The assignment of U-Cr trajectory subgroups was determined by balancing clinical knowledge against latent hypotheses regarding the existence of distinct trajectories and their number or shape in order to facilitate meaningful interpretation. The determination of U-Cr trajectories was performed prior to analyses pertaining to the risk of dialysis and mortality. Cox proportional hazards modeling was used to evaluate the prospective relationships between U-Cr trajectories and the risk of dialysis and mortality using hazard ratios (HRs) with 95% confidence intervals (CIs). The models were adjusted progressively (see footnotes of Table 2). To characterize the risk of progression to dialysis associated with U-Cr trajectories, we performed competing risk analysis in accordance with the methods outlined by Fine and Gray [16].

Exploratory subgroup analysis was performed based on pre-specified stratification factors including age, sex, diabetes, hypertension, and baseline albumin concentration with cutoff at 3.5 g/dL. Sensitivity analysis was conducted to evaluate the robustness of our findings. Respectively extending the follow-up time to at least one or two years produced consistent results (Supplementary Table 1). We further conducted multiple imputation analysis to verify the robustness of our study results. We used the procedures of PROC MI in SAS 9.4 to perform multiple imputation with fully conditional method (FCS) method, an iterative Markov chain Monte Carlo (MCMC) procedure, to replace the missing values for protein/creatinine ratio (PCR), comorbidities, and medications with imputed values. After ensuring the quality of the imputed database, we used the imputed database to verify the results from “available case analysis” and the findings were consistent in terms of the direction of effect and the effect sizes for both baseline U-Cr values and longitudinal U-Cr trajectories for outcome of progression to ESRD (Supplementary Table 2). Moreover, we additionally applied coarsened exact matching analysis with matching criteria of age, sex, and baseline kidney function to specifically adjust for imbalance kidney

function among U-Cr trajectories followed by statistical adjustment for residual confounders in the stratified Cox regression modeling (Table 2 and Supplementary Tables 2 and 3). To evaluate the performance of U-Cr for the prediction of progression to ESRD, we applied Harrell's C-Statistic to deal the time dependent receiver operating characteristics (ROC) curve for right-censored survival data [17,18]. The 4-variable kidney failure risk equation served as the reference for the predictive performance of new models incorporating the baseline U-Cre values or longitudinal U-Cre trajectories [19]. We also plotted the observed vs predicted risk probability to show the differences in calibrations of all risk models for ESRD.

We also performed urinary dilution correction by Levine's method using U-SG to re-estimate the U-Cr concentration among patients whose U-SG was measured on the same day as the measurement of U-Cr [20]. This method assumes that the relative ratio between the excretion of U-Cr and urinary solutes is consistent regardless the changes in urinary flow and urine solids is roughly proportional to 24 divided by the last 2 digits of the random U-SG [20,21].

$$Specific\ gravity - corrected\ UCr\ values = Urine\ total\ UCr\left(\frac{mg}{dL}\right) \times \frac{(SG-1)_{standardized}}{(SG-1)_{measured}}$$

Although this approach has not been verified in CKD population, the correlation between uncorrected and SG-corrected U-Cr concentration was good (Spearman correlation 0.66, p-value < 0.01). We further examined the correlation between U-Cr and U-SG and found a gradual decrease in correlation concentration with increasing CKD stages with a decreasing trend in the proportion of the highly-concentrated urine (SG > 1.020) (Fig. 1). All statistical analyses were performed in SAS, ver 9.4 (SAS Institute Inc.) and R, vers 3.0.2 (R Foundation for Statistical Computing [www.r-project.org]). The 2-sided statistical significance concentration was set at $\alpha = 0.05$.

3. Results

3.1. Characteristics of various urine creatinine trajectories

Among the 4689 program participants, the median age at enrollment was 67.1 years (IQR: 56.7–75.9), the median follow-up time was 32.1 months, and the median concentration of U-Cr was 93 mg/dl (IQR: 64–133). Three distinct U-Cr trajectories were identified (Fig. 2). We found that 62.8% of enrolled CKD patients had serial U-Cr measurements stably below 100 mg/dl. This pattern was labeled as "stable low" (trajectory 1, n = 2945, 62.8%). Two other trajectories were persistently above the U-Cr concentration of 100 mg/dl and were defined as "medium" (trajectory 2, n = 1386, 29.6%) and "high-declining" (trajectory 3, n = 358, 7.6%) (Fig. 2).

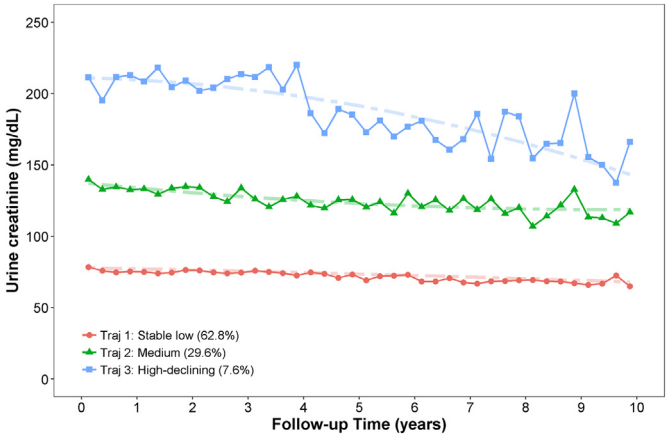


Fig. 2. Urine creatinine trajectories as defined by group-based trajectory modeling (GBTM) of serial quarterly average levels of urine creatinine over the course of chronic kidney disease (N = 4689).

Patients with "medium" and "high-declining" U-Cr trajectories tended to be younger at enrollment, male, a current or past smoker, a current alcohol user, higher educated, with a higher median BMI and a lower median systolic blood pressure, and in CKD status milder than stage 3 compared to those with a "stable-low" U-Cr trajectory (Table 1). As for comorbidities, diabetes and hypertension were prevalent among patients with a "stable-low" U-Cr trajectory. Patients in this group were more likely to use diuretics (51.6%) compared to that of "medium" (39.9%) and "High-declining" (35.5%), respectively. Regarding the use of pentoxyfylline, non-steroid anti-inflammatory agents, contrast media, and ACEI/ARB, the three groups were comparable (Table 1). At enrollment, the median eGFR showed a gradual increase across the ascending U-Cr trajectories, as follows: "stable low" (30.6 mL/min/1.73m^2), "moderate" (45.3 mL/min/1.73m^2) and "high-declining" (52.1 mL/min/1.73m^2) (p-value for trend < 0.001). A similar trend was observed in the concentrations of hemoglobin, albumin, serum sodium, calcium, total cholesterol, low-density lipoprotein (LDL), and triglyceride (TG) across the U-Cr trajectories in an ascending order (Table 1). The opposite trend was observed in the concentration of serum creatinine, serum uric acid, phosphate, hemoglobin A1c and PCR across the U-Cr trajectories in an ascending order (Table 1).

3.2. Dialysis risk, all-cause mortality, and urine creatinine trajectories

During the 15,390 person-years of follow-up, 610 ESRD events and 368 deaths occurred. Incidental ESRD and all-cause mortality were 39.6 and 23.9 per 1000 person-years, respectively. The adjusted hazard ratio

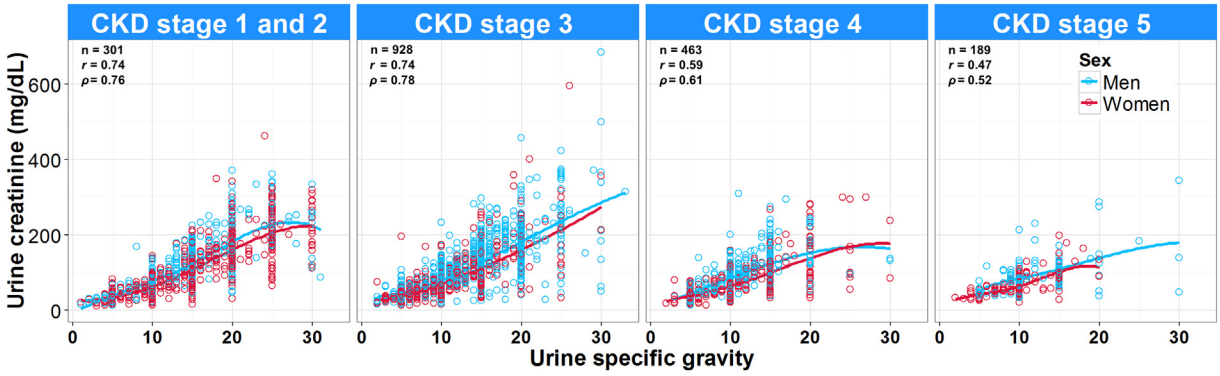


Fig. 1. Scatter plots (with fitting regression line using uniform cubic B-spline with 4 degrees of freedom) illustrating the relationship between the concentration of urine creatinine and the level of urine specific gravity (last two digits of the reported value) by sex and CKD stage(r, Pearson correlation coefficient; ρ, Spearnen correlation coefficient).

Table 1
Baseline demographic and clinical characteristics by urine creatinine trajectories defined by group-based trajectory modeling (GBTM).

Variables	Total (N = 4689)	Trajectory 1: Stable low (n = 2945)	Trajectory 2: Medium (n = 1386)	Trajectory 3: High-declining (n = 358)	P-Value[a]	P for trend[b]
Age at entry (year), median (IQR)	67.1 (56.7, 75.9)	67.9 (57.5, 76.7)	66.4 (55.9, 74.9)	63.0 (52.4, 73.0)	< 0.001	< 0.001
Female, n (%)	1984 (42.3)	1574 (53.5)	351 (25.3)	59 (16.5)	< 0.001	< 0.001
Follow-up duration (month), median (IQR)	32.1 (20.8, 51.4)	30.3 (19.3, 49.2)	35.0 (23.3, 53.9)	34.4 (24.2, 52.4)	< 0.001	< 0.001
No. of urine creatinine records, median (IQR)	6 (4, 11)	6 (3, 10)	7 (4, 12)	6 (4, 11)	< 0.001	< 0.001
BMI (kg/m^2), median (IQR)	24.3 (22.0, 27.1)	23.9 (21.5, 26.7)	25.0 (22.9, 27.5)	25.4 (23.4, 28.0)	< 0.001	< 0.001
SBP (mmHg)	130 (122,140)	131 (123, 144)	130 (120, 140)	130 (120, 139)	< 0.001	< 0.001
DBP (mmHg)	77 (70, 80)	77 (69, 80)	77 (70, 80)	78 (70, 82)	NS	NS
Initial CKD stage, n (%)					< 0.001	NA
1	238 (5.1)	123 (4.2)	91 (6.6)	24 (6.7)		
2	439 (9.4)	195 (6.6)	177 (12.8)	67 (18.7)		
3	2258 (48.2)	1198 (40.7)	821 (59.3)	239 (66.8)		
4	1145 (24.4)	879 (29.9)	241 (17.4)	25 (7.0)		
5	604 (12.9)	547 (18.6)	54 (3.9)	3 (0.8)		
Smoking, n (%)					< 0.001	NA
Never	3849 (82.1)	2511 (85.3)	1079 (77.9)	259 (72.4)		
Former	368 (7.9)	180 (6.1)	142 (10.3)	46 (12.9)		
Current	472 (10.1)	254 (8.6)	165 (11.9)	53 (14.8)		
Alcohol consumption, n (%)					< 0.001	NA
Never	4262 (90.9)	2720 (92.4)	1227 (88.5)	315 (88.0)		
Former	249 (5.3)	139 (4.7)	87 (6.3)	23 (6.4)		
Current	178 (3.8)	86 (2.9)	72 (5.2)	20 (5.6)		
Education level (year), n (%)					< 0.001	NA
< 9	1158 (24.7)	834 (28.3)	262 (18.9)	62 (17.3)		
9 ≤ ~ < 12	1779 (37.9)	1163 (39.5)	494 (35.6)	122 (34.1)		
12 ≤ ~ < 16	1138 (24.3)	650 (22.1)	378 (27.3)	110 (30.7)		
16+	614 (13.1)	298 (10.1)	252 (18.2)	64 (17.9)		
Diabetes, n (%)	1802 (38.4)	1263 (42.9)	438 (31.6)	101 (28.2)	< 0.001	< 0.001
Hypertension, n (%)	2660 (56.7)	1714 (58.2)	746 (53.8)	200 (55.9)	0.024	0.031
Cardiovascular disease, n (%)	1691 (36.1)	1042 (35.4)	512 (36.9)	137 (38.3)	NS	NS
Baseline medication profiles, n (%)						
Pentoxifylline	1142 (24.4)	741 (25.2)	325 (23.5)	76 (21.2)	NS	NS
NSAIDs	1132 (24.1)	688 (23.4)	359 (25.9)	85 (23.7)	NS	NS
Contrast media	652 (13.9)	401 (13.6)	205 (14.8)	46 (12.9)	NS	NS
Anti-hypertension agents						
ACEI	861 (18.4)	566 (19.2)	232 (16.7)	63 (17.6)	NS	NS
ARBs	2113 (45.1)	1330 (45.2)	617 (44.5)	166 (46.4)	NS	NS
Trichlorethiazide	464 (9.9)	317 (10.8)	117 (8.4)	30 (8.4)	0.035	0.017
Furosemide, Spironolactone, Amizide, Indapamide	1734 (37.0)	1200 (40.8)	437 (31.5)	97 (27.1)	< 0.001	< 0.001
Baseline biochemical profiles, median (IQR)						
U-Cr (mg/dl)	93 (64, 133)	74 (54, 97)	133 (106, 162)	195 (154, 232)	< 0.001	< 0.001
eGFR (mL/min/1.73m^2)	37.4 (22.2, 53.0)	30.6 (18.0, 47.6)	45.3 (32.3, 57.0)	52.1 (40.2, 60.2)	< 0.001	< 0.001
Serum creatinine (mg/dL)	1.68 (1.26, 2.64)	1.95 (1.36, 3.11)	1.48 (1.19, 2.01)	1.37 (1.15, 1.63)	< 0.001	< 0.001
Serum uric acid (mg/dL)	7.30 (6.20, 8.40)	7.35 (6.28, 8.50)	7.30 (6.15, 8.40)	6.90 (5.90, 7.83)	< 0.001	< 0.001
Hemoglobin (g/dL)	11.4 (9.9, 13.1)	10.7 (9.4, 12.3)	12.7 (11.1, 14.1)	13.6 (12.5, 14.6)	< 0.001	< 0.001
Serum albumin (g/dL)	4.05 (3.70, 4.30)	4.00 (3.60, 4.28)	4.10 (3.80, 4.40)	4.20 (3.90, 4.45)	< 0.001	< 0.001
Serum sodium (mmol/L)	138 (136, 140)	138 (136, 140)	139 (137, 140)	139 (137, 140)	< 0.001	< 0.001
Serum potassium (mmol/L)	4.20 (3.90, 4.55)	4.25 (3.90, 4.60)	4.15 (3.87, 4.45)	4.09 (3.80, 4.33)	< 0.001	< 0.001
Serum calcium (mg/dL)	8.90 (8.58, 9.25)	8.90 (8.50, 9.20)	9.00 (8.70, 9.30)	9.00 (8.70, 9.30)	< 0.001	< 0.001
Serum phosphate (mg/dL)	4.00 (3.50, 4.55)	4.13 (3.68, 4.70)	3.70 (3.30, 4.20)	3.50 (3.10, 3.90)	< 0.001	< 0.001
Total cholesterol (mg/dL)	184 (159, 211)	183 (157, 210)	185 (161, 211)	189 (165, 211)	0.010	0.003
LDL (mg/dL)	105 (86, 125)	103 (83, 123)	107 (89, 127)	110 (92, 130)	< 0.001	< 0.001
HDL (mg/dL)	41.0 (34.5, 49.1)	41.2 (34.5, 49.9)	40.5 (34.7, 47.7)	39.5 (33.3, 47.8)	NS	0.017
Triglyceride (mg/dL)	136 (96, 197)	135 (94, 195)	136 (98, 200)	147 (102, 209)	0.047	0.028
Triglyceride/HDL ratio	3.50 (2.21, 5.69)	3.37 (2.16, 5.65)	3.67 (2.30, 5.81)	3.63 (2.48, 5.64)	NS	0.033
Hemoglobin A1c (%)	7.03 (6.27, 8.07)	7.14 (6.40, 8.20)	6.85 (6.10, 7.80)	6.85 (6.10, 7.70)	< 0.001	< 0.001
Urine PCR (mg/g)	676 (197, 1888)	1025 (354, 2482)	291 (127, 977)	173 (85, 508)	< 0.001	< 0.001
Urine PCR < 200 mg/g, n (%)	1018 (25.3)	354 (14.2)	493 (41.0)	171 (54.3)	< 0.001	< 0.001

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GBTM, group-based trajectory modeling; HDL, high-density lipoprotein; IQR, inter-quartile range; LDL, low-density lipoprotein; NSAID, nonsteroidal anti-inflammatory drugs; PCR, protein/creatinine ratio; SBP, systolic blood pressure; U-Cr, urine creatinine.

[a] P-values are calculated by Kruskal-Wallis test for continuous variables and Chi-square test for categorical variables.

[b] P-values for trend are calculated by Spearman's correlation for continuous variables and by Cochran-Armitage trend test for binary variables.

(aHR) of incident ESRD and all-cause mortality increased by 6% (95% CI: 1–12%) and 9% (95% CI: 2–17%), respectively, for each 20 mg/dL reduction in baseline random U-Cr concentration (Table 2, model 4). Compared with the patients with baseline U-Cr ≥ 100 mg/dL, the aHRs for incident ESRD and death among those with baseline U-Cr < 100 mg/dL were 1.09 (95% CI 0.84–1.41) and 1.63 (95% CI 1.16–2.29), respectively (Table 2). The corresponding aHRs for progression to ESRD and death became 1.37 (95% CI 1.07–1.74) and 1.13 (95% CI 0.90–1.42), respectively, using data after multiple imputation (Supplementary Table 2). Consistently, there was a significant inverse linear dose-response relationship among baseline U-Cr, incident ESRD, and all-cause mortality (Fig. 3).

As illustrated by the unadjusted Kaplan-Meier survival curve in Fig. 4, patients with the “medium” and “high-declining” U-Cr trajectory

Table 2
Hazard ratios (95% confidence interval) of dialysis and all-cause mortality by baseline serum urine creatinine (U-Cr) concentrations, binary baseline U-Cr with a cut-off point of 100 mg/dl, and U-Cr trajectories.

U-Cr measures	N	Cases	Person-years	Incidence	Crude HR (95% CI)	Model 1	Model 2	Model 3	Model 4	CEM Model
						Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Risk of dialysis[a]										
Baseline UCr (per 20 mg/dL reduction)	4689	610	15,390.0	39.6	1.25 (1.20, 1.29)	1.25 (1.20, 1.30)	1.08 (1.02, 1.13)	1.06 (1.01, 1.12)	1.06 (1.01, 1.12)	1.10 (1.04, 1.16)
Baseline binary U-Cr variable										
U-Cr < 100 mg/dL	2601	467	8263.2	56.5	2.80 (2.32, 3.37)	2.76 (2.25, 3.39)	1.32 (1.04, 1.67)	1.09 (0.84, 1.42)	1.09 (0.84, 1.41)	1.54 (1.15, 2.06)
U-Cr ≥ 100 mg/dL	2088	143	7126.8	20.1	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
U-Cr trajectory group										
Traj 1: Stable-low	2945	539	9244.2	58.3	4.95 (3.87, 6.32)	4.97 (3.82, 6.48)	1.85 (1.33, 2.58)	1.46 (1.00, 2.13)	1.46 (1.00, 2.12)	1.83 (1.28, 2.64)
Traj 2 + 3: Medium + High-declining	1744	71	6145.8	11.6	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
All-cause mortality										
Baseline UCr (per 20 mg/dL reduction)	4689	368	15,404.5	23.9	1.11 (1.07, 1.16)	1.11 (1.06, 1.17)	1.11 (1.04, 1.18)	1.08 (1.01, 1.16)	1.09 (1.02, 1.17)	1.05 (0.99, 1.11)
Baseline binary U-Cr variable										
U-Cr < 100 mg/dL	2601	233	8272.2	28.2	1.52 (1.23, 1.88)	1.68 (1.29, 2.18)	1.52 (1.13, 2.04)	1.59 (1.13, 2.23)	1.63 (1.16, 2.29)	1.22 (0.91, 1.64)
U-Cr ≥ 100 mg/dL	2088	135	7132.3	18.9	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
U-Cr trajectory group										
Traj 1: Stable-low	2945	283	9256.4	30.6	2.31 (1.81, 2.94)	2.04 (1.52, 2.73)	1.45 (1.00, 2.09)	1.17 (0.77, 1.79)	1.22 (0.80, 1.85)	1.59 (1.12, 2.25)
Traj 2 + 3: Medium + High-declining	1744	85	6148.1	13.8	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)

Incidence = No. of incident cases/person-y*1000.
Model 1: Adjusted for age at entry, gender, BMI, smoking status, alcohol consumption, education (n = 4158).
Model 2: Further adjusted for primary etiology, diabetes, hypertension, cardiovascular disease, baseline eGFR, baseline urine creatinine, baseline PCR, and baseline medication use (n = 3547).
Model 3: Further adjusted for baseline albumin and albumin trajectory (n = 2525).
Model 4: Further adjusted for SBP and DBP (n = 2524).
CEM analysis: Adjusted for BMI, smoking status, alcohol consumption, education, primary etiology, diabetes, hypertension, cardiovascular disease, baseline urine creatinine, baseline PCR, baseline medication use, baseline albumin, albumin trajectory (not adjusted in all-cause mortality), SBP and DBP (n = 2670); Coarsened exact matching variables: age, gender, and baseline eGFR.
Abbreviations: CEM, coarsened exact matching; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GBTM, group-based trajectory modeling; HR, hazard ratio; PCR, protein/creatinine ratio; SBP, systolic blood pressure; U-Cr, urine creatinine.
[a] With competing risk analysis for death.

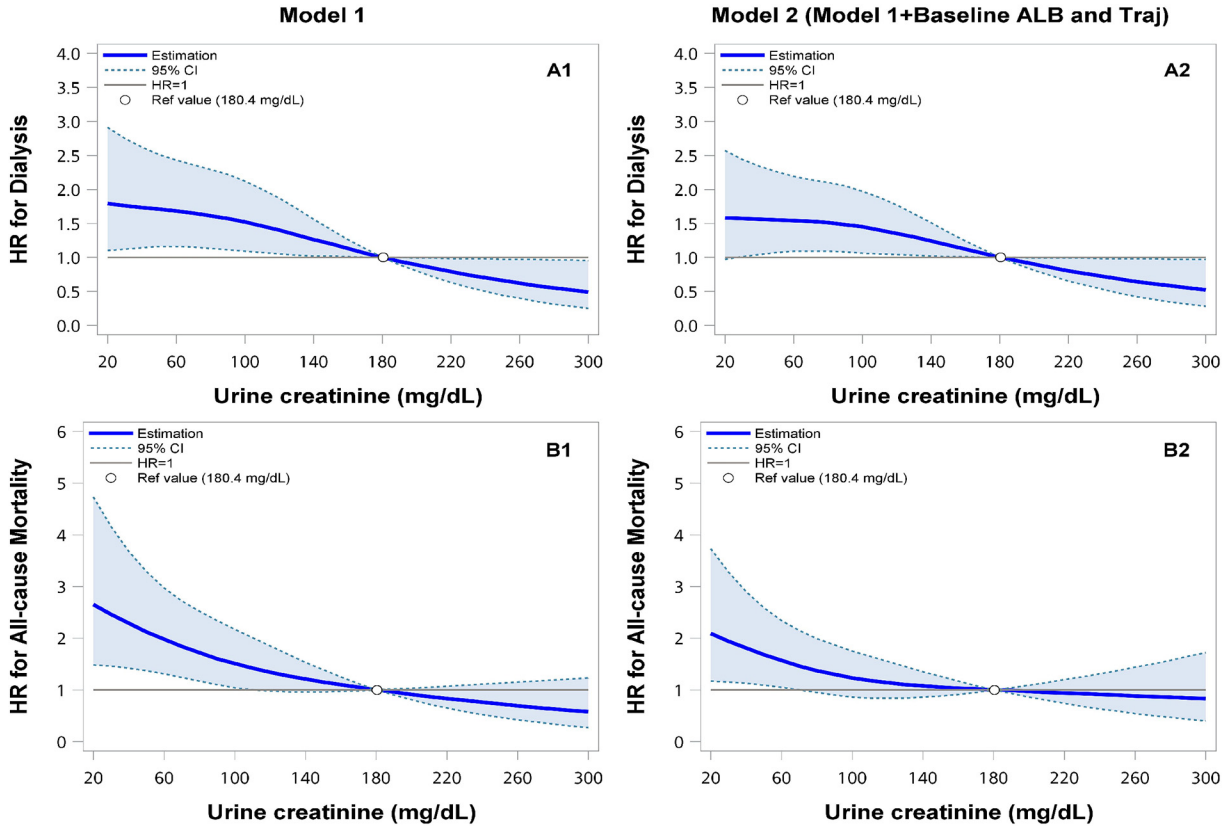


Fig. 3. Hazards ratios for end-stage renal disease (ESRD) requiring dialysis and all-cause mortality by baseline urine creatinine concentration. Solid blue lines represent adjusted hazard ratios based on restricted cubic splines for baseline urine creatinine with knots at 10th, 50th, and 90th percentiles (44.73, 93.3, and 180.4 mg/dL, respectively). The dotted green lines represent upper and lower 95% CIs. The reference was set at 90th percentile of baseline urine creatinine level (180.4 mg/dL). Panel (A1-A2): risk of ESRD requiring dialysis, Panel (B1-B2): all-cause mortality. Model 1: Adjusted for age at entry, gender, BMI, smoking status, alcohol consumption, education, diabetes, hypertension, and cardiovascular disease, primary etiologies of CKD, baseline eGFR, baseline PCR and baseline medication. Model 2: Further adjusted for baseline albumin and albumin trajectory. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

combined had significantly better dialysis-free survival and overall survival (log-rank test, $p < 0.001$). Compared to patients with "medium" and "high-declining" U-Cr trajectories combined, the adjusted hazard ratio (95% CI) for incidental ESRD among patients with a "stable-low" trajectory was 1.46 (1.00–2.12) after considering the competing risk of death (Model 4, Table 2). The effect size and significance of this observed risk were even greater after multiple imputation (aHR 1.70, 95% CI, 1.24–2.34) (Supplementary Table 2). In the same comparison for all-cause mortality, the corresponding adjusted hazard ratio (95% CI) was 1.22 (0.80–1.85). We observed a similar association between U-Cr trajectories and incident ESRD and mortality with regard to age, gender, diabetes, hypertension, and proteinuria (Table 2 and Supplementary Table 2). In the coarsened exact matching analyses, the statistical inferences remained the same as those derived from multiple imputation (Supplementary Table 2). All risk estimates by different statistical approaches are also summarized in the Supplementary Table 2.

3.3. Discrimination and calibration of ESRD risk models that additionally incorporate U-Cr

Fig. 5 summarizes the discrimination performance quantified by Harrell's C-Statistics after adding baseline U-Cr binary status (< 100 mg/dL or not) or longitudinal U-Cr trajectories into the reference 4-variable risk equation. Adding longitudinal U-Cr trajectories to the 4-variable risk model significantly improved the risk discrimination from 0.857 to 0.865 (p-value = 0.02) (Fig. 5). However, the improvement in the prediction performance was not observed if we used the 5-variable risk equation as the reference (Fig. 5). Supplementary Fig. 2 describes the calibration performance of all ESRD risk prediction models. Among all 4-variabe based models, the risk model incorporating with the U-Cr trajectories showed the best calibration.

4. Discussion

This prospective study provides a novel insight into the role of longitudinal trajectory of random U-Cr in the development of ESRD and mortality among CKD patients. We found that patients with serial random U-Cr concentrations stably above 100 mg/dL have better renal and overall survival than those with serial random U-Cr concentrations consistently < 100 mg/dL even after adjustment for patients' albumin longitudinal changes. The results support that random U-Cr can serve as a prognostic factor predicting kidney survival beyond the nutritional status, a key confounding factor in observational studies of kidney disease. Instead of simply being a urinary dilution correction factor like U-SG or osmolality (U-Osm), random U-Cr may have more clinical importance in risk stratification and prognosis assessment. In addition, we found that random U-Cr concentrations progressively decline with increasing CKD stages and so does the correlation with U-SG. These findings imply that using random U-Cr to correct concentrations of random urinary biomarkers may introduce additional confounding and the correction performance may not accurately reflect the 24-h biomarker excretion amount among advanced CKD patients.

The biological and clinical meaning of U-Cr is rarely evaluated in the current literature. Most prior evidence were based on 24-h U-Cr excretion as concentrations of random U-Cr are heavily affected by

Table 3
Hazard ratios and 95% CIs for the risk of progression to dialysis and all-cause mortality when the trajectories of urine creatinine over the course of chronic kidney disease are compared, by patient characteristics at baseline. Adjustment factors were the same as those for model 4 in Table 2.

U-Cr trajectory group	Risk of dialysis[a]				All-cause mortality			
	Events/N	Adjusted HR (95% CI)[a]	Events/N	Adjusted HR (95% CI)[a]	Events/N	Adjusted HR (95% CI)	Events/N	Adjusted HR (95% CI)
		Age < 65 yr (N = 1139)		Age ≥ 65 yr (N = 1382)		Age < 65 yr (N = 1139)		Age ≥ 65 yr (N = 1382)
Traj 1: Stable-low	171/727	1.18 (0.70, 1.98)	168/932	1.73 (0.90, 3.33)	21/727	1.67 (0.55, 5.05)	123/932	1.24 (0.79, 1.96)
Traj 2 + 3: Medium + High-declining	33/416	1.00 (Ref)	14/449	1.00 (Ref)	8/416	1.00 (Ref)	36/449	1.00 (Ref)
	P for interaction = 0.0437				*P for interaction = 0.3858*			
		Female (N = 1073)		Male (N = 1448)		Female (N = 1073)		Male (N = 1448)
Traj 1: Stable-low	172/868	1.63 (0.79, 3.38)	167/791	1.28 (0.82, 1.99)	59/868	1.83 (0.61, 5.52)	85/791	1.15 (0.71, 1.84)
Traj 2 + 3: Medium + High-declining	9/207	1.00 (Ref)	38/658	1.00 (Ref)	5/207	1.00 (Ref)	39/658	1.00 (Ref)
	P for interaction = 0.8461				*P for interaction = 0.6509*			
		Non-DM (N = 1610)		DM (N = 911)		Non-DM (N = 1610)		DM (N = 911)
Traj 1: Stable-low	180/1000	1.34 (0.79, 2.28)	159/659	1.45 (0.82, 2.58)	71/1000	1.19 (0.66, 2.15)	73/659	1.42 (0.74, 2.73)
Traj 2 + 3: Medium + High-declining	27/612	1.00 (Ref)	20/253	1.00 (Ref)	28/612	1.00 (Ref)	16/253	1.00 (Ref)
	P for interaction = 0.8066				*P for interaction = 0.766*			
		Non-HTN (N = 1106)		HTN (N = 1415)		Non-HTN (N = 1106)		HTN (N = 1415)
Traj 1: Stable-low	116/711	1.21 (0.61, 2.40)	223/948	1.39 (0.88, 2.21)	55/711	1.49 (0.75, 2.98)	89/948	1.07 (0.61, 1.90)
Traj 2 + 3: Medium + High-declining	16/397	1.00 (Ref)	31/468	1.00 (Ref)	19/397	1.00 (Ref)	25/468	1.00 (Ref)
	P for interaction = 0.9381				*P for interaction = 0.9191*			
		Albumin < 3.5 g/dL (N = 459)		Albumin ≥3.5 g/dL (N = 2066)		Albumin < 3.5 g/dL (N = 459)		Albumin ≥3.5 g/dL (N = 2066)
Traj 1: Stable-low	106/342	1.64 (0.82, 3.30)	233/1317	1.29 (0.81, 2.06)	43/342	1.78 (0.66, 4.79)	101/1317	1.17 (0.70, 1.94)
Traj 2 + 3: Medium + High-declining	12/116	1.00 (Ref)	35/749	1.00 (Ref)	8/116	1.00 (Ref)	36/749	1.00 (Ref)
	P for interaction = 0.7134				*P for interaction = 0.679*			

Abbreviations: CKD, chronic kidney disease; DM, diabetes mellitus; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GBTM, group-based trajectory modeling; HR, hazard ratio; HTN, hypertension; PCR, protein/creatinine ratio; SBP, systolic blood pressure; U-Cr, urine creatinine.
All models were adjusted for age at entry, gender, BMI, entry year, smoking status, alcohol consumption, education, diabetes, hypertension, cardiovascular disease, primary etiologies of CKD, baseline eGFR, baseline urine creatinine, baseline PCR, baseline albumin, serum albumin trajectories by GBTM, profiles of baseline medication, SBP, and DBP.
[a] With competing risk analysis for death.

hydration status, dietary protein intake, and body anthropometry and composition [22]. Several clinical outcomes have been linked to 24-h U-Cr excretion. In general population, a study in Netherlands demonstrated that 24-h U-Cr excretion was inversely associated with all-cause and cardiovascular mortality [23]. In CKD populations, lower daily U-Cr excretion has been associated with higher risk of arterial stiffness [24], rapid progression of CKD [2,25], and all-cause mortality [2,25]. However, clinical impacts of these findings are limited due to the cumbersomeness and error-prone nature of 24-h urine collection. The main pathogenic mechanism proposed in previous evidence targets on the protein-energy wasting (PEW) related sarcopenia as daily U-Cr excretion was shown to be a good proxy of lean body mass [26]. Yet,

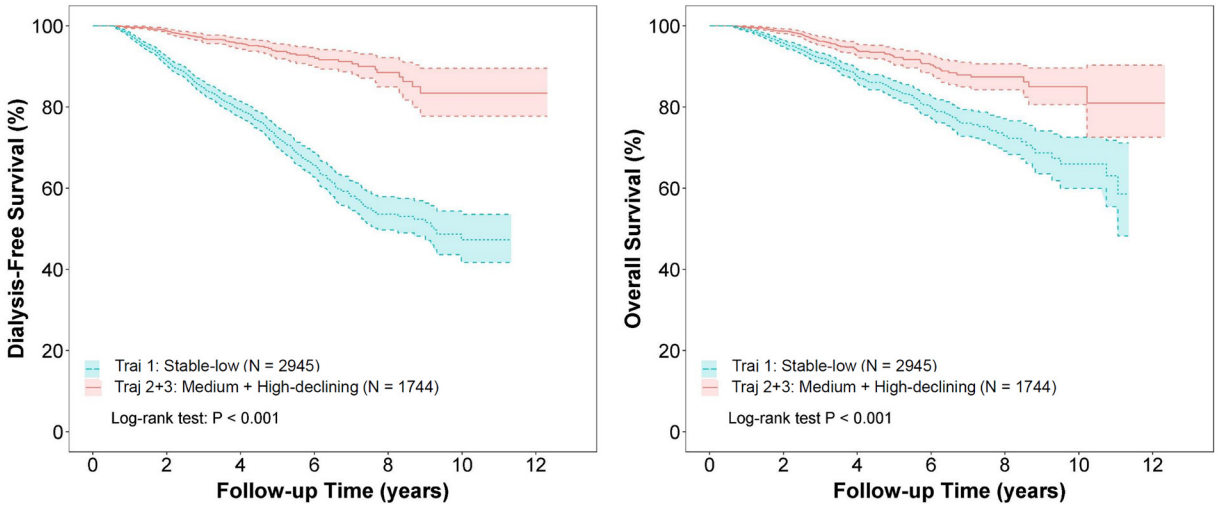
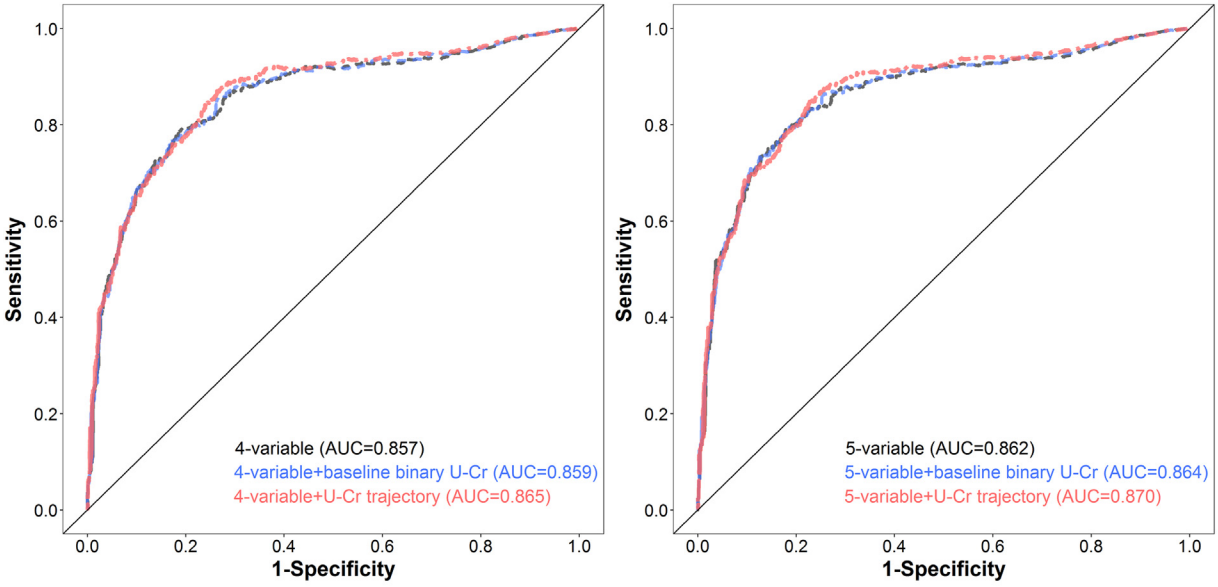


Fig. 4. Kaplan-Meier curves of dialysis-free survival and overall survival, according to urine creatinine trajectories generated by group-based trajectory modeling (GBTM) (N = 4689).



Reference: KFRE with 4 variables (age, sex, eGFR, and PCR)	C-statistic for 5-year mortality	*p*-value for difference from reference model
Reference	0.857	-
Reference + baseline binary U-Cr	0.859	0.2313
Reference + U-Cr trajectory	0.865	0.0249

Reference: KFRE with 5 variables (age, sex, eGFR, PCR and blood pressure)	C-statistic for 5-year mortality	*p*-value for difference from reference model
Reference	0.862	-
Reference + baseline binary U-Cr	0.864	0.3235
Reference + U-Cr trajectory	0.870	0.1309

Fig. 5. Receiver operating characteristic (ROC) curves for 5-year mortality after incorporating baseline binary U-Cr variable (U-Cr ≥ 100 mg/dL vs. < 100 mg/dL) and U-Cr trajectory group (Traj 2 + 3 vs. Traj 1) in the conventional 4-variable Kidney Failure Risk Equation (KFRE) and the 5-varaible KFRE additionally incorporating blood pressure.

studies evaluating the association between U-Cr and lean body mass were most conducted in general population, not CKD population. Also, whether random U-Cr could replace 24-h U-Cr in estimating muscle mass remains undetermined, particularly in patients with CKD. A recent review has pointed that sarcopenia, defined by hand grip strength [27,28], walking speed [29], or low skeletal muscle mass index [28], is associated with all-cause mortality among CKD patients [30]. Our results provide a strong support for further evaluation of the relationships between random U-Cr and sarcopenia defined by various matrices, particularly physical activity. On the other hand, as creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney, it excretion amount should be positively correlated with serum creatinine concentration [31]. Among patients with advanced CKD (persistently high serum creatinine concentration), we found U-Cr is discrepantly low compared to those with better kidney function, which implied that the decreased U-Cr concentration may associate with the greater proportion of nephron loss. Therefore, U-Cr may be a more sensitive marker reflects early significant nephron loss and help distinguish progressing CKD patients from stable patients.

The U-Cr cut-off value of 100 mg/dL is straightforward to clinicians, especially when the reporting unit of laboratory test results (e.g., urine albumin concentration) is mg/L. When U-Cr is exactly 100 mg/dL (or 1 g/L), the random urine albumin concentration will equal to the value derived from urinary albumin-creatinine ratio (ACR, mg/g). If the concentrations of U-Cr are above or below 100 mg/dL, the ACR will be lower or higher than uncorrected random albumin concentrations, respectively. It is the first time to our knowledge that an explicit cut-off value of random U-Cr can be proposed among CKD populations, which greatly improves the practicality of random U-Cr in clinical setting. The present findings motivate future research to explore the feasibility of random urinary albumin concentration in daily practice in patients with CKD. Among patients with diabetes, a recent meta-analysis has shown that random urinary albumin concentration has equivalent diagnostic performance as albumin-creatinine ratio [32]. Carter et al. compared the influences of albumin and creatinine separately on the risk of cardiovascular disease among CKD patients and concluded that the role random urine albumin was more important than random U-Cr [33]. In our study, we found the effect of random U-Cr on the risk of progression to ESRD is independent of baseline protein-creatinine ratio. Whether random U-Cr represents a therapeutic target for slowing CKD progression should be the focus of future research efforts.

Random U-Cr has been served as a urinary dilution correction factor since 1970s as random ACR predicts albumin excretion per kilogram well [34]. However, its correction performance regarding accuracy and reliability remains not well defined especially in patients with advanced CKD. Compared to 24-h urine total albumin amount, ACR may overestimate proteinuria in patients with advanced CKD as U-Cr concentration declines significantly over the course of CKD progression from stage 3 to 5. Indeed, in our study population with CKD stage 4 or 5, U-Cr did not correlate well with U-SG, a conventional urine dilution indicator that is widely used in the quantification of urinary toxicants or biomarkers in environmental epidemiology. This is not unexpected given that U-Cr represents specifically for the concentration of creatinine in the urine sample, whereas U-SG measures the collective number and mass of solutes in the urine. As patients' kidney function advancing to later stages, it is not uncommon that the urine contains much more protein, sugar, and cell debris, which disproportionally maintain U-SG at a relatively high concentration even with concomitantly decreased U-Cr excretion [35]. An alternative biomarker to correct for urine dilution is U-Osm; nonetheless, it is rarely used in clinical nephrology [11,36,37]. Among limited evidence, higher 24-h U-Osm was associated with higher risk of dialysis initiation in a recent study by Plischke et al. [38], while an inverse association was found in the MDRD study [39]. Theoretically, the U-Osm is determined based on the numbers of solutes, regardless of solute type. The key solutes in U-Osmo are electrolytes and urea. An increased urine osmolality may indicate a decreased water concentration in the urine or increased numbers of solutes. In patients with advanced CKD, the relatively high osmolality may be mainly from dietary salt and protein; both are unfavorable for CKD control. The declining but plateaued concentration of U-SG or U-

Osm among patients with renal failure was firstly reported in 1952; however, some assumptions must be met such as constant solute excretion and the urine is free from heavy molecules such as glucose or protein [40]. More importantly, if the tubular concentrating/diluting capacity remains within normal range even in CKD status, the relatively low U-Cr in the condition of isosthenuria would be a signal of uncompensated nephron loss [41]. Indeed, the challenge of elucidating the relationship between dilution markers (U-Cr, U-SG and U-Osm) and renal outcomes is twofold as solute factors should be take into consideration along with solvent factors (e.g., hydration status and renal concentration/diluting ability). In the present study for instance, a low U-Cr may not only indicate a decreased creatinine production from sarcopenia especially in patients with stable CKD or a decreased excretion due to uncompensated nephron loss from the viewpoint of solute concentration. A low U-Cr may also reflect fluid overloading or impaired renal tubular concentrating ability from the perspective of solvent dynamics. The above-mentioned pathogenic mechanisms were all associated with poor kidney outcomes and thus, undoubtedly, deserve future research efforts, particularly in large population studies [42,43].

Our study has several limitations. First, baseline kidney function across U-Cr trajectory groups was significantly different. Patients with a "stable-low" U-Cr trajectory had lower kidney function at baseline. To isolate the independent effect of U-Cr on the outcomes of interest, we not only adjusted for baseline kidney function in the multiple Cox regression modeling but also conducted coarsened exact matching to minimize bias estimation resulting from the baseline eGFR difference across U-Cr groups. Both approaches yielded consistent results that support the robustness of our findings. Second, we did not have 24-h U-Cr excretion data. However, frequently repeated measures of random U-Cr up to median of 6 times over a long-term follow-up should effectively minimize the potential misclassification. Furthermore, the random uncorrected U-Cr concentrations are highly correlated with U-SG-corrected U-Cr. Third, we did not have direct measure of fat-free muscle mass to evaluate the association between sarcopenia and random U-Cr. Also, the fat-free muscle mass could be a critical confounding factor in the relationship between U-Cr and the study outcomes of interests. To best control this confounding, we have carefully adjusted for both baseline albumin and longitudinal changes of albumin during the study follow-up in the full statistical model as serum albumin concentrations and muscle mass are closely related [44]. Fourth, deaths were ascertained using active surveillance rather than using the National Death Registry of Taiwan. Nonetheless, two previous studies evaluating the effectiveness of pre-ERSD programs in Taiwan reported similar mortality rates [45,46]. Fifth, we cannot completely exclude the possibility of residual confounding and overadjustment for variables that could be in the causal pathway.

In conclusion, chronically stable concentrations of random U-Cr below 100 mg/dL are associated with higher risk of rapid progression to ESRD. Random U-Cr not only just serves as a common urinary concentration corrector but has its own clinical significance in risk stratification and outcome prediction. More research is required to validate our findings in other populations such as those with acute kidney injury (AKI) and kidney transplantation and re-evaluate the feasibility and necessity of conventional random U-Cr correction for random urine albumin or protein concentration among patients with advanced CKD.

Acknowledgements

This work was supported by Ministry of Science and Technology, Taiwan, R.O.C. under Grant no. MOST 106-2314-B-039 -041 -MY3 and Department of Medical Research, China Medical University Hospital, Taichung, Taiwan, R.O.C. under Grant no. DMR-106-190.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2018.12.002.

References

[1] B.R. Hemmelgarn, B.J. Manns, A. Lloyd, M.T. James, S. Klarenbach, R.R. Quinn, N. Wiebe, M. Tonelli, N. Alberta Kidney, Disease, relation between kidney function, proteinuria, and adverse outcomes, JAMA 303 (5) (2010) 423–429.
[2] L. Di Micco, R.R. Quinn, P.E. Ronksley, V. Bellizzi, A.M. Lewin, B. Cianciaruso, P. Ravani, N. Alberta Kidney Disease, Urine creatinine excretion and clinical outcomes in CKD, Clin. J. Am. Soc. Nephrol. 8 (11) (2013) 1877–1883.
[3] E. Tynkevich, M. Flamant, J.P. Haymann, M. Metzger, E. Thervet, J.J. Boffa, F. Vrtovsnik, P. Houillier, M. Froissart, B. Stengel, G. Nephrotest Study, Urinary creatinine excretion, measured glomerular filtration rate and CKD outcomes, Nephrol. Dial. Transplant. 30 (8) (2015) 1386–1394.
[4] E. Tynkevich, M. Flamant, J.P. Haymann, M. Metzger, E. Thervet, J.J. Boffa, F. Vrtovsnik, P. Houillier, M. Froissart, B. Stengel, G. Nephrotest Study, Decrease in urinary creatinine excretion in early stage chronic kidney disease, PLoS ONE 9 (11) (2014) e111949.
[5] Y.P. Jadeja, V. Kher, Protein energy wasting in chronic kidney disease: an update with focus on nutritional interventions to improve outcomes, Indian J. Endocrinol. Metab. 16 (2) (2012) 246–251.
[6] X.H. Wang, W.E. Mitch, Mechanisms of muscle wasting in chronic kidney disease, Nat. Rev. Nephrol. 10 (9) (2014) 504–516.
[7] J.C. Kim, K. Kalantar-Zadeh, J.D. Kopple, Frailty and protein-energy wasting in elderly patients with end stage kidney disease, J. Am. Soc. Nephrol. 24 (3) (2013) 337–351.
[8] M.H. Kallenberg, H.A. Kleinveld, F.W. Dekker, B.C. van Munster, T.J. Rabelink, M. van Buren, S.P. Mooijaart, Functional and cognitive impairment, frailty, and adverse health outcomes in older patients reaching ESRD-A Systematic Review, Clin. J. Am. Soc. Nephrol. 11 (9) (2016) 1624–1639.
[9] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease, Kidney Int. Suppl 3 (2013) 1–150.
[10] D.B. Barr, L.C. Wilder, S.P. Caudill, A.J. Gonzalez, L.L. Needham, J.L. Pirkle, Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements, Environ. Health Perspect. 113 (2) (2005) 192–200.
[11] H.C. Yeh, Y.S. Lin, C.C. Kuo, D. Weidemann, V. Weaver, J. Fadrowski, A. Neu, A. Navas-Acien, Urine osmolality in the US population: implications for environmental biomonitoring, Environ. Res. 136 (2015) 482–490.
[12] N.K. Foundation, KDOQI clinical practice guidelines and clinical practice recommendations for 2006 updates: hemodialysis adequacy, peritoneal dialysis adequacy and vascular access, Am. J. Kidney Dis. 48 (supp 1) (2006) S1–S322.
[13] A.S. Levey, J. Coresh, T. Greene, L.A. Stevens, Y.L. Zhang, S. Hendriksen, J.W. Kusek, F. Van Lente, C. Chronic Kidney, Disease Epidemiology, Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate, Ann. Intern. Med. 145 (4) (2006) 247–254.
[14] D.S. Nagin, D. Lynam, S. Raudenbush, K. Roeder, Analyzing developmental trajectories: a semiparametric, Group-Based Approach Psychol. Methods 4 (1999) 139–157.
[15] D.S. Nagin, C.L. Odgers, Group-based trajectory modeling in clinical research, Annu. Rev. Clin. Psychol. 6 (2010) 109–138.
[16] J.P. Fine, R.J. Gray, A proportional hazards model for the subdistribution of a competing risk, J. Am. Stat. Assoc. 94 (446) (1999) 496–509.
[17] F. Harrell, S. Institute, The PHGLM procedure, SAS institute, (1979).
[18] C. Guo, Y. So, W. Jang, Paper SAS462–2017: Evaluating Predictive Accuracy of Survival Models with PROC PHREG, (2017).
[19] N. Tangri, L.A. Stevens, J. Griffith, H. Tighiouart, O. Djurdjev, D. Naimark, A. Levin, A.S. Levey, A predictive model for progression of chronic kidney disease to kidney failure, JAMA 305 (15) (2011) 1553–1559.
[20] L. Levine, J. Fahy, Evaluation of urinary lead determination: I. the significance of the specific gravity, J. Ind. Hyg. Toxicol. 27 (1945) 217–223.
[21] R.J. Graul, R.L. Stanley, Specific gravity adjustment of urine analysis results, Am. Ind. Hyg. Assoc. J. 43 (11) (1982) 863.
[22] K. Kalantari, W.K. Bolton, A good reason to measure 24-h urine creatinine excretion, but not to assess kidney function, Clin. J. Am. Soc. Nephrol. 8 (11) (2013) 1847–1849.
[23] L.H. Oterdoom, R.T. Gansevoort, J.P. Schouten, P.E. de Jong, R.O. Gans, S.J. Bakker, Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population, Atherosclerosis 207 (2) (2009) 534–540.
[24] Y.Y. Hyun, H. Kim, S.A. Sung, S.W. Kim, D.W. Chae, Y.S. Kim, K.H. Choi, C. Ahn, K.B. Lee, Association between urine creatinine excretion and arterial stiffness in chronic kidney disease: data from the KNOW-CKD study, Kidney Blood Press. Res. 41 (5) (2016) 527–534.
[25] F.P. Wilson, D. Xie, A.H. Anderson, M.B. Leonard, P.P. Reese, P. Delafontaine, E. Horwitz, R. Kallem, S. Navaneethan, A. Ojo, A.C. Porter, J.H. Sondheimer, H.L. Sweeney, R.R. Townsend, H.I. Feldman, C.S. Investigators, Urinary creatinine excretion, bioelectrical impedance analysis, and clinical outcomes in patients with CKD: the CRIC study, Clin. J. Am. Soc. Nephrol. 9 (12) (2014) 2095–2103.

[26] G.B. Forbes, G.J. Bruining, Urinary creatinine excretion and lean body mass, Am. J. Clin. Nutr. 29 (12) (1976) 1359–1366.
[27] Y.T. Chang, H.L. Wu, H.R. Guo, Y.Y. Cheng, C.C. Tseng, M.C. Wang, C.Y. Lin, J.M. Sung, Handgrip strength is an independent predictor of renal outcomes in patients with chronic kidney diseases, Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association, Eur. Ren. Assoc. 26 (11) (2011) 3588–3595.
[28] R.A. Pereira, A.C. Cordeiro, C.M. Avesani, J.J. Carrero, B. Lindholm, F.C. Amparo, C. Amodeo, L. Cuppari, M.A. Kamimura, Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality, Nephrol. Dial. Transplant. 30 (10) (2015) 1718–1725.
[29] B. Roshanravan, C. Robinson-Cohen, K.V. Patel, E. Ayers, A.J. Littman, I.H. de Boer, T.A. Ikizler, J. Himmelfarb, L.I. Katzel, B. Kestenbaum, S. Seliger, Association between physical performance and all-cause mortality in CKD, J. Am. Soc. Nephrol. 24 (5) (2013) 822–830.
[30] K. Hirai, S. Ookawara, Y. Morishita, Sarcopenia and physical inactivity in patients with chronic kidney disease, Nephro-Urol. Mon. 8 (3) (2016) e37443.
[31] O. Shemesh, H. Golbetz, J.P. Kriss, B.D. Myers, Limitations of creatinine as a filtration marker in glomerulopathic patients, Kidney Int. 28 (5) (1985) 830–838.
[32] H.Y. Wu, Y.S. Peng, C.K. Chiang, J.W. Huang, K.Y. Hung, K.D. Wu, Y.K. Tu, K.L. Chien, Diagnostic performance of random urine samples using albumin concentration vs ratio of albumin to creatinine for microalbuminuria screening in patients with diabetes mellitus: a systematic review and meta-analysis, JAMA Intern. Med. 174 (7) (2014) 1108–1115.
[33] C.E. Carter, R.T. Gansevoort, L. Scheven, H.J. Heerspink, M.G. Shlipak, P.E. de Jong, J.H. Ix, Influence of urine creatinine on the relationship between the albumin-to-creatinine ratio and cardiovascular events, Clin. J. Am. Soc. Nephrol. 7 (4) (2012) 595–603.
[34] T.M. Barratt, P.N. McLaine, J.F. Soothill, Albumin excretion as a measure of glomerular dysfunction in children, Arch. Dis. Child. 45 (242) (1970) 496–501.
[35] B. Rose, T. Post, Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th ed., McGraw-Hill, New York, 2001.
[36] G.G. Gyamlani, E.J. Bergstralh, J.M. Slezak, T.S. Larson, Urinary albumin to osmolality ratio predicts 24-h urine albumin excretion in diabetes mellitus, Am. J. Kidney Dis. 42 (4) (2003) 685–692.
[37] H.S. Kim, H.W. Cheon, J.H. Choe, K.H. Yoo, Y.S. Hong, J.W. Lee, S.K. Kim, Quantification of proteinuria in children using the urinary protein-osmolality ratio, Pediatr. Nephrol. 16 (1) (2001) 73–76.
[38] M. Plischke, M. Kohl, L. Bankir, S. Shayganfar, A. Handisurya, G. Heinze, M. Haas, Urine osmolarity and risk of dialysis initiation in a chronic kidney disease cohort–a possible titration target? PLoS ONE 9 (3) (2014) e93226.
[39] L.A. Hebert, T. Greene, A. Levey, M.E. Falkenhain, S. Klahr, High urine volume and low urine osmolality are risk factors for faster progression of renal disease, Am. J. Kidney Dis. 41 (5) (2003) 962–971.
[40] R. Platt, Structural and functional adaptation in renal failure, Br. Med. J. 1 (4772) (1952) 1313 7. (contd).
[41] N.S. Bricker, R.R. Dewey, H. Lubowitz, J. Stokes, T. Kirkensgaard, Observations on the concentrating and diluting mechanisms of the diseased kidney, J. Clin. Invest. 38 (3) (1959) 516–523.
[42] R. Agarwal, R.P. Light, J.E. Bills, L.A. Hummel, Nocturia, nocturnal activity, and nondipping, Hypertension 54 (3) (2009) 646–651.
[43] Y.C. Tsai, Y.W. Chiu, J.C. Tsai, H.T. Kuo, C.C. Hung, S.J. Hwang, T.H. Chen, M.C. Kuo, H.C. Chen, Association of fluid overload with cardiovascular morbidity and all-cause mortality in stages 4 and 5 CKD, Clin. J. Am. Soc. Nephrol. 10 (1) (2015) 39–46.
[44] R.H. Mak, A.T. Ikizler, C.P. Kovesdy, D.S. Raj, P. Stenvinkel, K. Kalantar-Zadeh, Wasting in chronic kidney disease, J. Cachexia. Sarcopenia Muscle 2 (1) (2011) 9–25.
[45] I.W. Wu, S.Y. Wang, K.H. Hsu, C.C. Lee, C.Y. Sun, C.J. Tsai, M.S. Wu, Multidisciplinary predialysis education decreases the incidence of dialysis and reduces mortality–a controlled cohort study based on the NKF/DOQI guidelines, Nephrol. Dial. Transplant. 24 (11) (2009) 3426–3433.
[46] Y.R. Chen, Y. Yang, S.C. Wang, W.Y. Chou, P.F. Chiu, C.Y. Lin, W.C. Tsai, J.M. Chang, T.W. Chen, S.H. Ferng, C.L. Lin, Multidisciplinary care improves clinical outcome and reduces medical costs for pre-end-stage renal disease in Taiwan, Nephrology 19 (11) (2014) 699–707.