ORIGINAL ARTICLE

Journal of Cachexia, Sarcopenia and Muscle 2022; **13**: 1704–1716
Published online 7 March 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/jcsm.12951

Paradoxical mortality of high estimated glomerular filtration rate reversed by 24-h urine creatinine excretion rate adjustment: sarcopenia matters

Pei-Yu Kao[1], Hung-Chieh Yeh[2,3,4], Ying-Fang Hsia[4], Ya-Luan Hsiao[5], Jie-Sian Wang[2,3], David Ray Chang[2,3], Shih-Ni Chang[4], Hsiu-Yin Chiang[4] & Chin-Chi Kuo[2,3,4]*

[1]*Division of Chest Surgery, Department of Surgery, China Medical University Hospital and College of Medicine, China Medical University, Taichung, Taiwan;* [2]*Division of Nephrology, Department of Internal Medicine, China Medical University Hospital and College of Medicine, China Medical University, Taichung, Taiwan;* [3]*AKI-CARE (Acute Kidney Injury Clinical Advancement, Research and Education) Center, Department of Internal Medicine, China Medical University Hospital and College of Medicine, China Medical University, Taichung, Taiwan;* [4]*Big Data Center, China Medical University Hospital and College of Medicine, China Medical University, Taichung, Taiwan;* [5]*Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*

Abstract

Background Muscle wasting may explain the paradoxical mortality of patients with high estimated glomerular filtration rates (eGFRs) derived from equation methods. However, empirical evidence and solutions remain insufficient.

Methods In this retrospective cohort study, we compared the performance of equation methods for predicting all-cause mortality; we used 24-h creatinine clearance (24-h CrCl), equation-based eGFRs, and a new eGFR estimating equation weighting for population 24-h urine creatinine excretion rate (U-CER). From 2003 to 2018, we identified 4986 patients whose data constituted the first 24-h CrCl measurement data in the Clinical Research Data Repository of China Medical University Hospital and were followed up for at least 5 years after careful exclusion. Three GFR estimation equations [the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Modification of Diet in Renal Disease (MDRD) Study, and Taiwanese MDRD], 24-h CrCl, and 24-h U-CER–adjusted eGFR were used.

Results A high correlation was observed among the eGFR levels derived from the equation methods (0.995–1.000); however, the correlation decreased to 0.895–0.914 when equation methods were compared with the 24-h CrCl or 24-h U-CER–adjusted equation-based eGFR. In the Bland–Altman plots, the average discrepancy between the equation methods and the 24-h CrCl method was close to zero (maximal bias range: 5.12 for the Taiwanese MDRD equation vs. 24-h CrCl), but the range in limit of agreement was wide, from ±43.7 mL/min/1.73 m^2 for the CKD-EPI equation to ±54.3 mL/min/1.73 m^2 for the Taiwanese MDRD equation. A J-shaped dose–response relationship was observed between all equation-based eGFRs and all-cause mortality. Only 24-h CrCl exhibited a non-linear negative dose–response relationship with all-cause mortality. After adjustment for 24-h U-CER in the statistical model, the paradoxical increase in mortality risk for an eGFR of >90 mL/min/1.73 m^2 returned to null. When 24-h U-CER was used directly to correct eGFR, the monotonic non-linear negative relationship with all-cause mortality was almost identical to that of 24-h CrCl.

Conclusions The 24-h U-CER–adjusted eGFR and 24-h CrCl are viable options for informing mortality risk. The 24-h U-CER adjustment method can be practically implemented to eGFR-based care and effectively mitigate the inherent confounding biases from individual's muscle mass amount due to both sex and racial differences.

Keywords Estimated glomerular filtration rate; Urine creatinine excretion rate; Creatinine clearance; Sarcopenia; Mortality

Received: 21 May 2021; Revised: 21 January 2022; Accepted: 1 February 2022
**Correspondence to: Chin-Chi Kuo, MD, PhD, Kidney Division and Big Data Center, China Medical University Hospital and College of Medicine, China Medical University, 2, Yude Road, North District, Taichung 404, Taiwan. Phone: 886-4-22052121 ext. 2501. Email: chinchik@gmail.com*
Drs Pei-Yu Kao and Hung-Chieh Yeh contributed equally in this study and both serve as the co-first authors.

Introduction

Accurately estimating the glomerular filtration rate (GFR) is crucial in the daily medical practice tasks of determining the diagnosis and trajectory projection of kidney disease, drug dosing and monitoring, and assessing population health risk.[1,2] Measured GFR (mGFR) is conventionally determined by quantifying exogenous inulin clearance, which requires continuous intravenous infusion and multiple blood and urine collections. Although widely regarded as the gold standard for measuring kidney function, measuring inulin clearance is costly, cumbersome, and invasive, preventing its use in daily practice. Conceptualized nearly a century ago, endogenous 24-h creatinine clearance (CrCl), however, has long been used to estimate kidney function and has served as an aid in drug dosing.[2–4] Although 24-h CrCl is a more accurate marker for estimating kidney function than serum creatinine (S-Cre) alone, 24-h CrCl tends to underestimate GFR in cases of incomplete 24-h urine collection and tends to overestimate GFR when the degree of tubular secretion of creatinine is high.[4,5] Although 24-h CrCl is useful in estimating GFR in patients with sarcopenia or malnutrition, problems with its reliability, particularly at low GFR levels due to variations in the tubular secretion of creatinine, and its inconvenience limit its clinical practicality.[6,7]

In 1998, Coresh *et al*. were the first to suggest that the precision of estimating GFR by using the Cockroft–Gault formula is not inferior to that of the 24-h CrCl method. However, a review identified a wide acceptable margin of error [±30% variation between estimated GFR (eGFR) and mGFR] that may be not feasible for evaluating the precision of the eGFR equations.[8] Several researchers have argued that the eGFR derived from the most commonly used equations, namely, the Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, tend to underestimate mGFR by approximately 20 mL/min/1.73 m^2 cross-sectionally and reflect only 25% of kidney functional decline based on mGFR trajectories.[8] Furthermore, a paradoxically increased risk of mortality was found among patients with an eGFR of $>$100 mL/min/1.73 m^2 measured using both the MDRD and the CKD-EPI equations.[9] The latest 2012 Kidney Disease Improving Global Outcomes guidelines suggest that eGFR be calculated using the CKD-EPI equation except when an alternative eGFR equation yields more precise results.[10] Several countries, such as Taiwan, China, and Japan, have developed locally derived eGFR equations to increase the diagnostic validity in their own populations.[11–13] However, no study has systematically compared the value of calculating eGFR with equations by using 24-h CrCl in terms of mortality prognostication. The 24-h CrCl method includes the 24-h urine creatinine excretion rate (24-h U-CER), which is widely accepted as a practical tool for measuring muscle mass.[14] Decreased muscle mass is the main residual confounding factor that contributes to the high eGFR–high mortality paradox despite the lack of direct evidence.[9,15] To address this gap in knowledge, we enrolled patients with 24-h CrCl data in the electronic medical records of the largest medical centre in central Taiwan to evaluate the equation-based eGFRs and the 24-h CrCl in terms of CKD classification concordance and the predictive performance of 5-year all-cause mortality. We hypothesized that adjusting the equation-based eGFR values with the 24-h U-CERs can reverse the paradoxically high mortality associated with high eGFR.

Methods

Study population

In 2017, the Big Data Center of China Medical University Hospital (CMUH) established the CMUH Clinical Research Data Repository (CRDR), which carefully verified and validated data from various clinical sources to unify trackable patient information generated during health care processes. Between 1 January 2003 and 31 December 2018, the CMUH-CRDR documented the medical records of 2 873 887 patients who had sought care at CMUH. Detailed information on the CMUH-CRDR is available elsewhere.[16] All patients enrolled in the CMUH-CRDR were followed up until 31 December 2018 or death, whichever occurred earlier. This study was approved by the Big Data Center of CMUH and the Research Ethics Committee/Institutional Review Board of CMUH (CMUH105-REC3-068).

In this study, we included inpatients and outpatients aged 18–90 years with clinically indicated 24-h CrCl quantification between 2003 and 2018. Patients with a history of acute kidney injury requiring renal replacement therapy (RRT), end-stage renal disease (ESRD) requiring RRT, nephrectomy, cardiopulmonary–cerebral resuscitation, kidney transplantation, or cancer; an index CrCl of $>$200 mL/min/1.73 m^2; or a total urine amount of $<$400 mL/day were excluded. We specifically enrolled patients with a $<$36-h difference between the measurement of S-Cre and 24-h urine collection (mean difference: 11 ± 12 h). *Figure* 1 illustrates the detailed case selection process. Supporting Information, *Table* S1 lists the *International Classification of Diseases* codes for comorbidities. The index date was defined as the day on which the 24-h CrCl test was performed.

Equations to estimate glomerular filtration rate

Serum creatinine levels were measured using the Jaffe rate method at CMUH Central Laboratory by using a Beckman UniCel DxC 800 immunoassay system (Beckman Coulter Inc., Brea, CA, USA). All S-Cre results were calibrated to an isotope dilution mass spectrometry reference. The eGFR

DOI: 10.1002/jcsm.12951

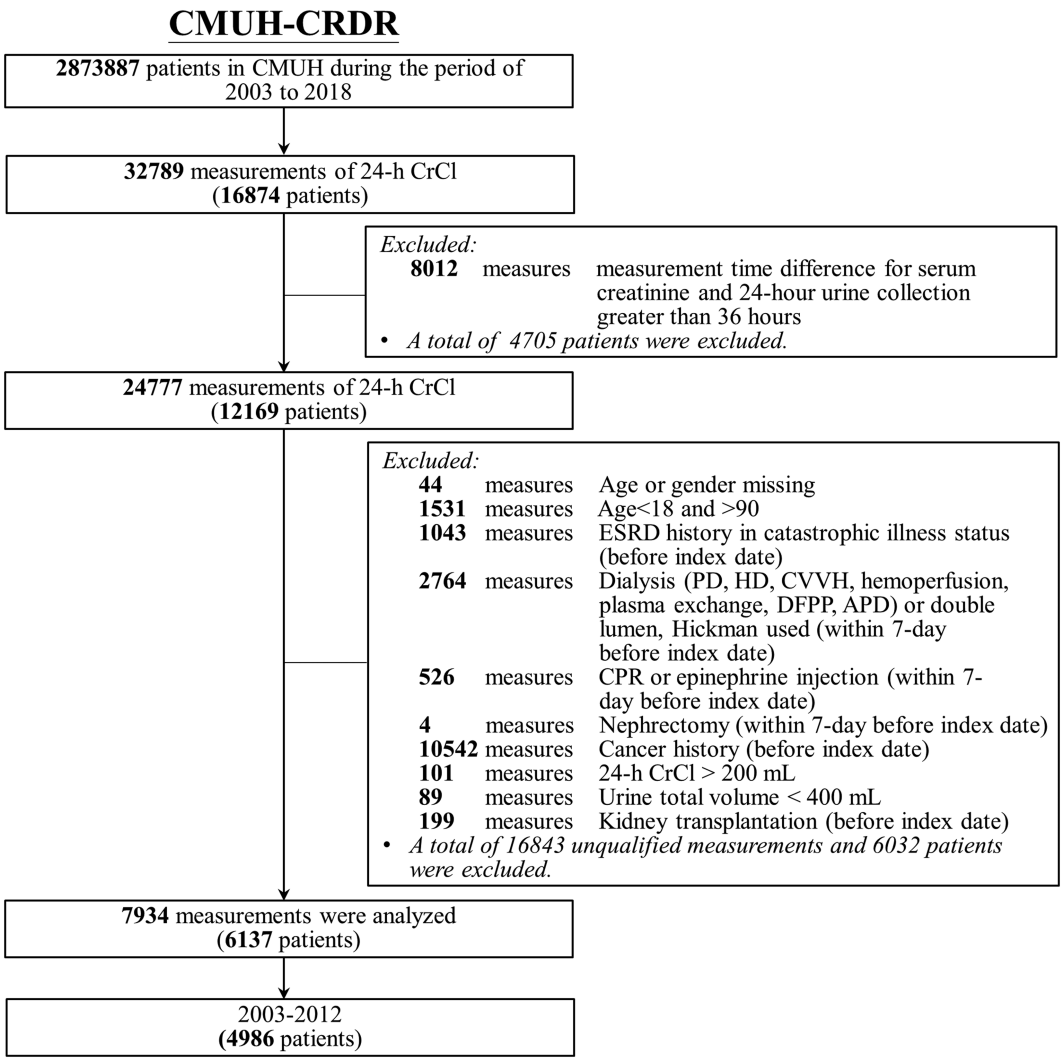

Figure 1 Flow diagram of patient selection.

was calculated using the MDRD Study equation [eGFR = 186 × S-Cre$^{-1.154}$ × age$^{-0.203}$ × 1.212 (if Black) × 0.742 (if female)],[17] the CKD-EPI equation [eGFR = 141 × min(S-Cre/κ, 1)$^{\alpha}$ × max(S-Cre/κ, 1)$^{-1.209}$ × 0.993^{age} × 1.018 (if female) × 1.159 (if Black)],[18] and the Taiwanese MDRD formula.[13] The 24-h CrCl was calculated using the following formula:

$$\frac{\mathrm{U}\ -\ \mathrm{Cre}}{\mathrm{S}\ -\ \mathrm{Cre}} \times \frac{\text{urine volume (mL)}}{1440\ (\text{min})}$$

The S-Cre levels for calculating the 24-h CrCl were used to define the baseline eGFR level and the corresponding CKD stages by using the following cut-off values: >90, 60–89.9, 30–59.9, 15–29.9, and <15 mL/min/1.73 m^2. To control for the confounding effect of muscle mass on the equation-based eGFRs, we proposed a new formula for 24-h U-CER–adjusted eGFR, which was calculated by multiplying eGFR (e.g. using the CKD-EPI equation) by the ratio of the individual 24-h U-CER divided by the age-specific (20–40, 40–65, and ≥65 years) and sex-specific population median 24-h U-CER.

Other variables

Sociodemographic variables, such as age, sex, and body mass index (BMI), were collected from the CMUH-CRDR.[19] Baseline comorbidities, medications, and biochemical measures were determined from information in the CMUH-CRDR within a 1-year window before the index date of the 24-h CrCl.[19] The dates of all-cause death were verified at the Health and

Welfare Data Center of the Ministry of Health and Welfare of Taiwan. The urine protein-to-creatine ratio (uPCR) or urine albumin-to-creatinine ratio (uACR) was used to quantify proteinuria. uACR was converted to uPCR by using the following equation derived from a Japanese population study[20]:

$$\ln(\mathrm{ACR}) = 1.32 \times \ln(\mathrm{PCR}) - 2.64$$

Statistical analysis

Continuous variables are expressed as medians and inter-quartile ranges (IQRs) and were compared using the non-parametric Kruskal–Wallis test, whereas categorical variables are expressed as frequencies (percentages) and were compared using the χ^2 test. We constructed a correlation matrix plot to describe the distribution and relationship among all types of eGFR, including 24-h U-CER–adjusted equation-based eGFR, which was evaluated using Spearman's correlation analysis. To assess the agreement of any paired continuous eGFR based on 24-h CrCl and equation methods, we used a Bland–Altman plot to visualize bias, as defined by the mean difference of the selected pair, limits of agreement estimated by mean difference ± 1.96 standard deviations of the difference, and proportional bias quantified using the regression of the mean difference between paired measures on the average of the paired measures.[21] The concordance of CKD stage was evaluated by comparing CKD stages classified by pairing different GFR estimations, including those generated through 24-h CrCl and equation-based methods. Upward staging indicated that the CKD stage defined by the reference method (*Y*-axis label) was reclassified into a less severe stage by another method (*X*-axis label). In contrast, downward staging implied reclassification into a more severe CKD stage. We systematically evaluated the associations of the 24-h CrCl, equation-based eGFR, and the 24-h U-CER–adjusted eGFR with the risk of all-cause mortality by using multiple Cox proportional hazards models. We characterized the dose–-response relationship by using a restricted cubic spline model with three knots located at the 10th, 50th, and 90th percentiles of the overall distribution for each GFR scale and adjusted for age, sex, cardiovascular disease, diabetes mellitus, systolic blood pressure, total cholesterol, BMI, and uPCR at baseline. Because of the missing data (*Table* S2), we performed multiple imputations with the Multivariate Imputation by Chained Equations package in R and set the number of imputations to 20 and the number of iterations to 100. All statistical analyses were performed using SAS (Version 9.4, SAS Institute, Cary, NC, USA) and R (Version 3.5.1, R Foundation for Statistical Computing, Vienna, Austria). The two-sided statistical significance level of α was set to 0.05.

Results

Clinical characteristics of the study population

On the basis of eGFRs derived from the CKD-EPI equation, the study population could be evenly grouped into five CKD stages. Patients with advanced CKD (Stages 3–5) were substantially older, more likely to be male, and had a higher prevalence of diabetes, hypertension, and cardiovascular disease than those with early CKD (Stages 1–2). Fifty-four percent of the study population had a normal weight, and patients with CKD Stage 5 were less likely to be overweight or obese (*Table* 1). Although patients with advanced-stage CKD were unlikely to be prescribed non-steroidal anti-inflammatory drugs (NSAIDs) or radiocontrast agents, the frequency of NSAID use was higher than 25%. The trends of anti-platelet, anti-diabetic, and anti-hypertensive medications were consistent with the comorbidity trends across all CKD stages (*Table* 1). An increase in serum phosphorus and uPCR or uACR and a decrease in haemoglobin and albumin were observed as the CKD stage worsened. The density plot of each GFR calculation method stratified by sex revealed that the majority of patients in the study population had an eGFR of $<$60 mL/min/1.73 m^2, and a large portion had an eGFR of $<$30 mL/min/1.73 m^2. However, two density peaks were noted in the equation-based methods, forming a notch between the eGFRs of 30 and 60 mL/min/1.73 m^2 among female patients (*Figure* S1).

Correlation of estimated glomerular filtration rate and chronic kidney disease classification concordance among different estimating approaches

The average estimated levels of kidney function derived from both the equation-based methods and the 24-h CrCl method were comparable for patients with CKD Stages 2–5. However, for CKD Stage 1, the average eGFR levels calculated using the Taiwanese MDRD equation were lower than those calculated using the other equations and the 24-h CrCl method (*Table* 2). Generally, men had significantly greater 24-h U-CER than women, and the median of 24-h U-CER significantly decreased with an increase in age and CKD stage (*Table* 2). The scatter plots revealed a high correlation between the eGFR levels derived from the equation methods (0.995–1.000), particularly for patients with an eGFR of $<$60 mL/min/1.73 m^2 derived from the CKD-EPI equation. However, the correlation decreased to 0.895–0.914 when equation methods were combined with the 24-h CrCl or 24-h U-CER–adjusted equation-based eGFR (*Figure* S2). In the Bland–Altman plots, the average discrepancy between the equation methods and the 24-h CrCl method was close to

Table 1 Baseline demographic and clinical characteristics according to the baseline stage of CKD derived from $eGFR_{CKD\text{-}EPI}$

Characteristic[a]	Total (N = 4986)	CKD stage (N = 4986)	
		CKD Stage 1 (N = 1221)	CKD Stage 2 (N = 929)
Demographic information			
Age (year)	59.2 (45.8, 71.8)	42.2 (30.6, 53.3)	57.0 (47.1, 69.3)
Body mass index (kg/m^2)	23.8 (21.2, 26.7)	23.3 (20.4, 26.4)	23.9 (21.4, 27.0)
Weight status category[d]	1460 (29.3)		
Underweight	109 (7.5)	29 (10.5)	11 (6.0)
Normal weight	789 (54.0)	147 (53.3)	100 (54.4)
Overweight	421 (28.8)	75 (27.2)	57 (31.0)
Obesity	141 (9.7)	25 (9.1)	16 (8.7)
Female	2379 (47.7)	706 (57.8)	416 (44.8)
Baseline comorbidities[e]			
Diabetes mellitus	1585 (31.8)	248 (20.3)	275 (29.6)
Hypertension	1770 (35.5)	178 (14.6)	291 (31.3)
Cardiovascular disease	1234 (24.8)	89 (7.3)	189 (20.3)
History of medication use[f]			
NSAIDs	1768 (35.5)	504 (41.3)	366 (39.4)
Contrast	919 (18.4)	287 (23.5)	214 (23.0)
Anti-platelet	1374 (27.6)	165 (13.5)	216 (23.3)
Aspirin	1051 (21.1)	113 (9.3)	165 (17.8)
Dipyridamole	296 (5.9)	60 (4.9)	48 (5.2)
Ticlopidine/clopidogrel	1140 (22.9)	115 (9.4)	174 (18.7)
Anti-hypertension agents	3572 (71.6)	594 (48.7)	576 (62.0)
ACEIs	1354 (27.2)	159 (13.0)	203 (21.9)
ARBs	1046 (21.0)	99 (8.1)	143 (15.4)
Trichlormethiazide	390 (7.8)	40 (3.3)	59 (6.4)
Diuretics	2510 (50.3)	377 (30.9)	340 (36.6)
Alpha-blocker	726 (14.6)	47 (3.9)	76 (8.2)
Beta-blocker	1302 (26.1)	169 (13.8)	187 (20.1)
CCB	2069 (41.5)	208 (17.0)	294 (31.7)
Anti-diabetes agents	1877 (37.7)	280 (22.9)	321 (34.6)
OAD	1284 (25.8)	204 (16.7)	251 (27.0)
Insulin	1211 (24.3)	173 (14.2)	169 (18.2)
Baseline biochemical profiles[g]			
Serum creatinine (mg/dL)	1.4 (0.9, 3.1)	0.7 (0.6, 0.8)	1.0 (0.9, 1.1)
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)	49.4 (17.6, 88.8)	107.0 (98.9, 118.5)	75.7 (68.2, 82.9)
Blood urea nitrogen (mg/dL)	26.0 (14.0, 54.0)	11.0 (8.0, 15.0)	16.0 (12.0, 21.0)
Serum uric acid (mg/dL)	7.1 (5.7, 8.7)	5.8 (4.6, 7.3)	6.5 (5.2, 7.9)
Serum calcium (mg/dL)	8.3 (7.8, 8.9)	8.6 (8.0, 9.0)	8.4 (7.9, 8.9)
Serum phosphate (mg/dL)	4.2 (3.3, 5.3)	3.4 (2.8, 4.1)	3.2 (2.7, 3.7)
Serum albumin (g/dL)	3.3 (2.8, 3.9)	3.4 (2.8, 4.1)	3.4 (2.8, 4.1)
Haemoglobin (g/dL)	11.1 (9.4, 12.9)	12.5 (11.0, 14.0)	12.3 (10.4, 13.8)
Total cholesterol (mg/dL)	184.0 (151.0, 226.0)	189.0 (157.0, 231.0)	190.5 (153.5, 230.0)
Triglyceride (mg/dL)	129.0 (87.0, 193.0)	123.0 (80.0, 194.0)	123.0 (82.0, 189.0)
Urine creatinine (mg/dL)	49.5 (35.2, 69.3)	52.5 (35.6, 74.3)	54.9 (36.3, 76.4)
Urine PCR (mg/g)	1260.4 (267.4, 3872.3)	330.1 (100.5, 1696.4)	409.6 (111.1, 1839.5)
Urine ACR (mg/g)	574.0 (77.9, 4349.3)	170.6 (23.9, 1396.7)	163.3 (34.4, 841.2)
Systolic blood pressure (mmHg)	138.0 (118.0, 160.0)	124.0 (111.0, 144.0)	132.0 (114.0, 151.0)
Diastolic blood pressure (mmHg)	76.0 (66.0, 88.0)	76.0 (67.0, 87.0)	76.0 (66.0, 87.0)
Outcome			
Mortality	2712 (54.4)	312 (25.6)	385 (41.4)
5-year mortality	1916 (38.4)	223 (18.3)	260 (28.0)

ACEIs, angiotensin-converting-enzyme inhibitors; ACR, albumin-to-creatinine ratio; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; OAD, oral anti-diabetic; PCR, protein-to-creatinine ratio.

[a]Categorical variables are presented as frequency (%) and continuous variables are presented as median (inter-quartile range), if not otherwise specified.

[1b]*P*-values are calculated by Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables.

[2c]*P*-values for trend are calculated by Spearman's correlation for continuous variables and by Cochran–Armitage trend test for binary variables.

[3d]Definitions based on World Health Organization: underweight: body mass index (BMI) $<$ 18.5, normal weight: 18.5 $\leq$ BMI $<$ 25, overweight: 25 $\leq$ BMI $<$ 30, obesity: BMI $\geq$ 30.

[4e]Definition: diabetes mellitus, hypertension: ICD code and medication within 1 year before index date; cardiovascular disease: ICD code within 1 year before index date.

[5f]Medication use within 1 year before index date.

[6g]Biochemical value measured within 1 year prior to and closest to the index date.

DOI: 10.1002/jcsm.12951

Table 1 (continued)

Characteristic[a]	CKD stage (*N* = 4986)			*P*-value[b]	*P* for trend[c]
	CKD Stage 3 (*N* = 1020)	CKD Stage 4 (*N* = 731)	CKD Stage 5 (*N* = 1085)		
Demographic information					
Age (year)	65.7 (54.7, 75.0)	69.6 (56.2, 77.2)	66.4 (55.4, 75.2)	<0.0001	<0.0001
Body mass index (kg/m^2)	24.6 (22.2, 27.9)	23.9 (21.8, 26.8)	23.4 (21.0, 26.1)	<0.0001	0.5521
Weight status category[d]				0.0419	-
Underweight	15 (5.4)	15 (6.4)	39 (8.0)		
Normal weight	131 (47.1)	127 (53.8)	284 (58.4)		
Overweight	94 (33.8)	72 (30.5)	123 (25.3)		
Obesity	38 (13.7)	22 (9.3)	40 (8.2)		
Female	370 (36.3)	317 (43.4)	570 (52.5)	<0.0001	0.0048
Baseline comorbidities[e]					
Diabetes mellitus	383 (37.6)	287 (39.3)	392 (36.1)	<0.0001	<0.0001
Hypertension	432 (42.4)	338 (46.2)	531 (48.9)	<0.0001	<0.0001
Cardiovascular disease	328 (32.2)	284 (38.9)	344 (31.7)	<0.0001	<0.0001
History of medication use[f]					
NSAIDs	349 (34.2)	270 (36.9)	279 (25.7)	<0.0001	<0.0001
Contrast	197 (19.3)	120 (16.4)	101 (9.3)	<0.0001	<0.0001
Anti-platelet	340 (33.3)	273 (37.4)	380 (35.0)	<0.0001	<0.0001
Aspirin	272 (26.7)	206 (28.2)	295 (27.2)	<0.0001	<0.0001
Dipyridamole	62 (6.1)	52 (7.1)	74 (6.8)	0.1562	0.0149
Ticlopidine/clopidogrel	296 (29.0)	236 (32.3)	319 (29.4)	<0.0001	<0.0001
Anti-hypertension agents	796 (78.0)	622 (85.1)	984 (90.7)	<0.0001	<0.0001
ACEIs	338 (33.1)	286 (39.1)	368 (33.9)	<0.0001	<0.0001
ARBs	285 (27.9)	204 (27.9)	315 (29.0)	<0.0001	<0.0001
Trichlormethiazide	100 (9.8)	74 (10.1)	117 (10.8)	<0.0001	<0.0001
Diuretics	507 (49.7)	480 (65.7)	806 (74.3)	<0.0001	<0.0001
Alpha-blocker	157 (15.4)	158 (21.6)	288 (26.5)	<0.0001	<0.0001
Beta-blocker	305 (29.9)	235 (32.2)	406 (37.4)	<0.0001	<0.0001
CCB	462 (45.3)	390 (53.4)	715 (65.9)	<0.0001	<0.0001
Anti-diabetes agents	430 (42.2)	353 (48.3)	493 (45.4)	<0.0001	<0.0001
OAD	321 (31.5)	228 (31.2)	280 (25.8)	<0.0001	<0.0001
Insulin	250 (24.5)	255 (34.9)	364 (33.6)	<0.0001	<0.0001
Baseline biochemical profiles[g]					
Serum creatinine (mg/dL)	1.5 (1.3, 1.8)	2.6 (2.3, 3.1)	5.7 (4.4, 7.7)	<0.0001	<0.0001
$eGFR_{CKD\text{-}EPI}$ (mL/min/1.73 m^2)	44.1 (36.9, 52.0)	21.8 (18.0, 25.4)	8.4 (5.8, 11.5)	<0.0001	<0.0001
Blood urea nitrogen (mg/dL)	24.0 (18.0, 34.0)	42.0 (31.0, 58.0)	72.0 (55.0, 94.0)	<0.0001	<0.0001
Serum uric acid (mg/dL)	7.2 (5.9, 8.7)	7.7 (6.5, 9.3)	8.2 (6.7, 9.6)	<0.0001	<0.0001
Serum calcium (mg/dL)	8.4 (7.9, 8.9)	8.4 (7.8, 8.8)	8.1 (7.6, 8.6)	<0.0001	<0.0001
Serum phosphate (mg/dL)	3.5 (2.9, 4.1)	4.0 (3.4, 4.8)	5.1 (4.2, 6.3)	<0.0001	<0.0001
Serum albumin (g/dL)	3.4 (2.8, 4.0)	3.2 (2.7, 3.8)	3.3 (2.9, 3.8)	<0.0001	<0.0001
Haemoglobin (g/dL)	11.7 (10.0, 13.2)	10.5 (9.2, 11.9)	9.3 (8.2, 10.6)	<0.0001	<0.0001
Total cholesterol (mg/dL)	186.0 (154.0, 225.0)	176.0 (145.5, 223.0)	180.0 (146.0, 219.0)	0.0042	0.0001
Triglyceride (mg/dL)	139.5 (93.0, 207.0)	129.5 (87.0, 195.5)	131.0 (92.0, 188.0)	0.0066	0.0257
Urine creatinine (mg/dL)	51.2 (36.3, 72.2)	47.2 (34.3, 64.4)	44.7 (33.8, 58.8)	<0.0001	<0.0001
Urine PCR (mg/g)	994.0 (291.8, 3543.5)	1961.7 (646.7, 4902.3)	3004.6 (1472.8, 6283.2)	<0.0001	<0.0001
Urine ACR (mg/g)	1110.4 (119.2, 8037.1)	4159.4 (461.9, 14 664.8)	2313.4 (758.7, 5566.8)	<0.0001	<0.0001
Systolic blood pressure (mmHg)	139.0 (118.0, 159.0)	141.0 (121.0, 165.0)	147.0 (128.0, 169.0)	<0.0001	<0.0001
Diastolic blood pressure (mmHg)	77.0 (66.0, 87.0)	75.0 (66.0, 88.0)	77.0 (65.0, 88.0)	0.9702	0.8856
Outcome					
Mortality	613 (60.1)	574 (78.5)	828 (76.3)	<0.0001	<0.0001
5-year mortality	399 (39.1)	432 (59.1)	602 (55.5)	<0.0001	<0.0001

ACEIs, angiotensin-converting-enzyme inhibitors; ACR, albumin-to-creatinine ratio; ARBs, angiotensin receptor blockers; CCB, calcium channel blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; OAD, oral anti-diabetic; PCR, protein-to-creatinine ratio.

[a]Categorical variables are presented as frequency (%) and continuous variables are presented as median (inter-quartile range), if not otherwise specified.

[b]*P*-values are calculated by Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables.

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

[d]Definitions based on World Health Organization: underweight: body mass index (BMI) < 18.5, normal weight: $18.5 \leq$ BMI < 25, overweight: $25 \leq$ BMI < 30, obesity: BMI ≥ 30.

[e]Definition: diabetes mellitus, hypertension: ICD code and medication within 1 year before index date; cardiovascular disease: ICD code within 1 year before index date.

[f]Medication use within 1 year before index date.

[g]Biochemical value measured within 1 year prior to and closest to the index date.

DOI: 10.1002/jcsm.12951

Table 2 The distribution of kidney function estimated by equation methods, 24-h CrCl, and the 24-h U-CER–adjusted method, serum creatinine, and 24-h urine creatinine by baseline CKD stage according to $eGFR_{CKD\text{-}EPI}$

Characteristic[a]	Total (N = 4986)	CKD stage (N = 4986)	
		CKD Stage 1 (N = 1221)	CKD Stage 2 (N = 929)
eGFR (mL/min/1.73 m^2)			
CKD-EPI	49.4 (17.6, 89.0)	107.0 (98.9, 118.3)	75.7 (68.1, 82.9)
MDRD	50.5 (18.8, 87.3)	110.1 (96.1, 128.6)	74.7 (67.4, 80.5)
Taiwanese MDRD	46.8 (19.0, 77.1)	95.3 (84.2, 109.8)	66.9 (60.9, 71.7)
24-h U-CER–adjusted eGFR (mL/min/1.73 m^2)			
CKD-EPI	46.7 (16.1, 92.8)	111.8 (89.9, 134.0)	81.6 (61.1, 102.3)
MDRD	48.3 (17.6, 93.7)	116.3 (93.5, 140.1)	81.5 (61.7, 101.0)
Taiwanese MDRD	45.1 (17.6, 82.7)	100.5 (81.2, 120.1)	73.0 (55.6, 90.0)
24-h CrCl (mL/min)	46.3 (18.3, 89.0)	109.0 (88.3, 131.4)	74.4 (56.1, 94.7)
Serum creatinine (mg/dL)	1.4 (0.9, 3.1)	0.7 (0.6, 0.8)	1.0 (0.9, 1.1)
24-h urine creatinine (mg/day)	959.8 (681.2, 1265.0)	1062.6 (823.2, 1369.6)	1065.3 (747.0, 1398.3)
Male	1155.6 (852.8, 1494.8)	1343.9 (1007.7, 1694.0)	1267.2 (944.0, 1642.5)
Age groups (years)			
18–45	1502.8 (1165.5, 1815.6)	1523.3 (1215.2, 1796.3)	1633.6 (1236.0, 1960.8)
45–65	1248.4 (948.8, 1550.2)	1265.4 (1006.4, 1518.0)	1416.2 (1051.2, 1669.2)
≥65	954.6 (694.5, 1188.7)	736.6 (549.0, 1134.3)	998.9 (709.3, 1188.2)
Female	795.0 (580.6, 1025.9)	940.6 (753.2, 1139.4)	873.5 (629.1, 1089.0)
Age groups (years)			
18–45	993.8 (818.0, 1200.0)	1017.6 (841.3, 1212.8)	1024.5 (871.9, 1222.1)
45–65	835.9 (640.3, 1044.2)	873.4 (688.2, 1062.6)	963.2 (736.3, 1155.4)
≥65	628.1 (480.0, 802.5)	684.5 (420.3, 836.0)	649.5 (480.7, 826.8)

eGFR, estimated glomerular filtration rate.
[a]Categorical variables are presented as frequency (%) and continuous variables are presented as median (inter-quartile range), if not otherwise specified.
[1b]*P*-values are calculated by Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables.
[2c]*P*-values for trend are calculated by Spearman's correlation for continuous variables and by Cochran–Armitage trend test for binary variables.

zero (maximal bias range: 5.12 for the Taiwanese MDRD equation vs. 24-h CrCl), but the range in limits of agreement was wide, spanning from ±43.7 mL/min/1.73 m^2 for the CKD-EPI equation to ±54.3 mL/min/1.73 m^2 for the MDRD equation (upper panel of *Figure* 2 and *Figure* S3). Ranges of bias and limits of agreement became wider when using 24-h U-CER–adjusted $eGFR_{CKD\text{-}EPI}$ as the reference (lower panel of *Figure* 2 and *Figure* S3). In addition to the MDRD equation, the CKD-EPI and Taiwanese MDRD equations exhibited mild proportional bias, indicating that the equation methods tended to overestimate GFR (using 24-h CrCl as a reference) when the mean eGFR was below approximately 60 mL/min/1.73 m^2 and tended to underestimate GFR when the mean eGFR was ≥60 mL/min/1.73 m^2. The overlap of the 24-h CrCl CKD Stage-2 and Stage-4 circles inside the CKD Stage-3 band suggest a discordance in CKD classification between the equation methods and the 24-h CrCl method (*Figure* 2 and *Figure* S3). The discordance in CKD classification was evident when the stages of CKD derived from the equation-based methods were compared with those derived from the 24-h CrCl, particularly for the combination of the Taiwanese MDRD equation and the 24-h CrCl. Among patients with CKD Stage 5, as derived from the equation methods, approximately 15.8–18% could be reclassified as having CKD Stage 4 by using the 24-h CrCl method (upper panel of *Figure* 3, and *Figures* S4 and S5). Tendencies for the 24-h CrCl to reclassify CKD Stages 3 and 4 both upward (20.3–23.8%) and downward (15.1–18.1%) were also observed (upper panel of *Figure* 3, and *Figures* S4 and S5). Such discrepancies were more noticeable when referencing 24-h U-CER–adjusted $eGFR_{CKD\text{-}EPI}$ (lower panel of *Figure* 3, and *Figures* S4 and S5). The CKD classification was consistent among pairs of equation-based methods, particularly for the combination of the CKD-EPI and MDRD equations. The proportion of CKD Stage 3 defined by the Taiwanese MDRD equation was notably and upwardly reclassified as CKD Stage 2 by the CKD-EPI and MDRD equations. For CKD Stage 4, it was likely to be downwardly reclassified as CKD Stage 5 by the CKD-EPI and MDRD equations (*Figure* S6).

Association between all-cause mortality and estimated glomerular filtration rate according to different estimating approaches

After adjustment for potential confounders, a J-shaped dose–response relationship was observed between the equation-based eGFRs and 5-year all-cause mortality, indicating that mortality risk substantially increased when eGFR was below 30–40 mL/min/1.73 m^2 and the CKD-EPI and Taiwanese MDRD equations were used or below approximately 50 mL/min/1.73 m^2 when the MDRD equation was used. After adjustment, an eGFR of >75 mL/min/1.73 m^2 was consistently associated with a high risk of all-cause mortality regardless

Table 2 (continued)

Characteristic[a]	CKD stage (N = 4986)			P-value[b]	P for trend[c]
	CKD Stage 3 (N = 1020)	CKD Stage 4 (N = 731)	CKD Stage 5 (N = 1085)		
eGFR (mL/min/1.73 m^2)					
CKD-EPI	44.1 (36.9, 52.0)	21.6 (18.0, 25.3)	8.4 (5.9, 11.5)	<0.0001	<0.0001
MDRD	45.8 (38.5, 53.4)	23.1 (19.5, 26.8)	9.3 (6.6, 12.6)	<0.0001	<0.0001
Taiwanese MDRD	42.8 (36.6, 49.2)	22.9 (19.7, 26.3)	10.0 (7.3, 13.2)	<0.0001	<0.0001
24-h U-CER–adjusted eGFR (mL/min/1.73 m^2)					
CKD-EPI	45.0 (33.7, 60.1)	21.0 (15.3, 27.0)	7.2 (4.5, 11.1)	<0.0001	<0.0001
MDRD	47.2 (34.7, 60.8)	22.7 (16.4, 29.1)	8.1 (5.0, 12.2)	<0.0001	<0.0001
Taiwanese MDRD	44.3 (32.8, 56.5)	22.5 (16.5, 28.6)	8.7 (5.5, 12.8)	<0.0001	<0.0001
24-h CrCl (mL/min)	45.7 (33.9, 60.1)	23.2 (16.8, 30.0)	9.3 (6.0, 13.6)	<0.0001	<0.0001
Serum creatinine (mg/dL)	1.5 (1.3, 1.8)	2.6 (2.3, 3.1)	5.7 (4.4, 7.7)	<0.0001	<0.0001
24-h urine creatinine (mg/day)	993.3 (718.6, 1316.8)	871.2 (621.5, 1163.3)	777.0 (572.4, 1037.5)	<0.0001	<0.0001
Male	1144.8 (885.6, 1466.4)	1037.7 (812.6, 1355.3)	961.4 (701.4, 1265.0)	<0.0001	<0.0001
Age groups (years)					
18–45	1563.5 (1219.4, 1780.8)	1476.6 (1040.0, 1852.6)	1208.0 (830.9, 1562.6)	0.0002	0.0256
45–65	1300.8 (975.1, 1648.0)	1084.5 (896.8, 1431.5)	1080.0 (820.8, 1359.0)	<0.0001	<0.0001
≥65	1024.1 (764.8, 1234.1)	942.8 (719.3, 1240.1)	853.1 (645.5, 1067.2)	<0.0001	0.002
Female	758.5 (569.4, 974.4)	672.0 (512.4, 873.3)	655.5 (482.5, 842.4)	<0.0001	<0.0001
Age groups (years)					
18–45	1040.0 (808.0, 1173.8)	927.1 (640.3, 1035.2)	825.1 (604.8, 1030.1)	0.0016	0.0093
45–65	867.1 (633.6, 1044.0)	741.0 (578.1, 964.6)	740.2 (572.1, 950.0)	<0.0001	<0.0001
≥65	662.6 (524.6, 854.6)	632.2 (495.7, 793.4)	601.6 (444.0, 758.4)	0.0296	0.0105

eGFR, estimated glomerular filtration rate.
[a]Categorical variables are presented as frequency (%) and continuous variables are presented as median (inter-quartile range), if not otherwise specified.
[b]P-values are calculated by Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables.
[c]P-values for trend are calculated by Spearman's correlation for continuous variables and by Cochran–Armitage trend test for binary variables.

of the equation used (*Figure* 4, green line, and *Figure* S7, left panel). However, a non-linear inverse dose–response relationship between the 24-h CrCl and all-cause mortality was identified (*Figure* S7, right panel). Because sarcopenia limits the accuracy of the equation methods, we statistically adjusted for 24-h U-CER, which can estimate muscle mass, and the paradoxical increase in mortality risk at an eGFR > 75 mL/min/1.73 m^2 returned to null (*Figure* 4, blue line, and *Figure* S7, middle panel). When using the direct correcting approach of 24-h U-CER–adjusted $eGFR_{CKD\text{-}EPI}$, the dose–response relationship was almost identical to what was observed for the 24-h CrCl (*Figure* 4, red line, and *Figure* S7, right panel). In addition, the eGFR threshold for 5-year all-cause mortality was consistently 60 mL/min/1.73 m^2.

Discussion

Our findings demonstrate that only the 24-h CrCl exhibited a monotonic non-linear negative relationship with all-cause mortality, whereas an inverted U-shaped association was observed between all equation-based eGFRs and all-cause mortality. The U-shaped curve between the equation-based eGFRs and mortality reverted to a monotonic non-linear curve after the direct adjustment of the equation-based eGFRs for the 24-h U-CERs, implying that sarcopenia contributes to the paradoxical mortality phenomenon in patients with high eGFR.

The primary limitations of the equation-based eGFRs were the underestimation of kidney function in patients with advanced CKD and an overestimation of kidney function in patients with muscle wasting syndrome caused by various factors, such as malnutrition, chronic inflammation, and aging. The consistent confirmation of the U-shaped and J-shaped relationships between the equation-based eGFRs and all-cause mortality suggests a potential misclassification of kidney function by the equations.[9,22–24] Although the CKD-EPI cystatin C equation has been used to complement the inherent limitations of using S-Cre,[25] the paradoxical mortality when eGFR was high could not be completely eliminated, as was the case in our observations of the models even after additional adjustment for 24-h U-CER.[26] In contrast, the dose–response curves of the 24-h U-CER–adjusted eGFRs and the 24-h CrCl consistently indicated a protective effect against mortality when patients had a high eGFR. Our study is the first to propose normalizing the eGFR derived from the CKD-EPI equation by using 24-h U-CER; this method not only provides mechanistic insight into the relationship between high eGFR and mortality but also offers an alternative approach to estimating kidney function, particularly for older adults (≥70 years) and patients with frailty or muscle wasting syndrome. Our findings also challenge the emphasis on low-protein diets in halting the progression of CKD because the findings suggest that the link between

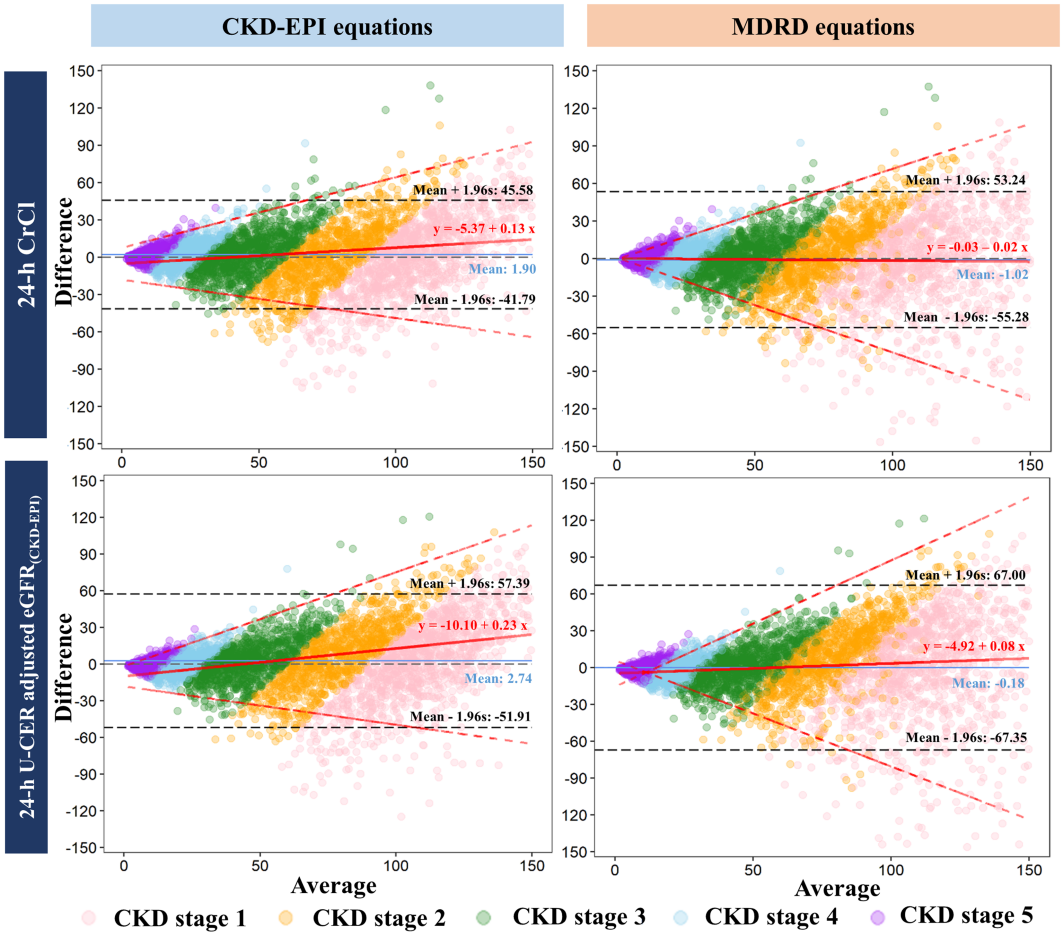

Figure 2 Bland–Altman plots of 24-h CrCl and eGFR calculated by CKD-EPI and MDRD equations (upper panel), 24-h U-CER–adjusted $eGFR_{CKD\text{-}EPI}$ vs. the two equation-based eGFRs (lower panel).

low-protein intake and muscle wasting leads to an overestimation of improvements in kidney function and increases the risk of mortality.[27,28] Our previous study indicated that patients with advanced CKD with random urine creatinine (U-Cre) consistently <100 mg/dL have a high risk of progression to ESRD.[29] Whether random U-Cre can be used similarly to 24-h U-CERs to perform muscle mass adjustments for equation-based eGFRs requires further research.

An inverse association exists between 24-h U-CERs and all-cause mortality in both general and CKD populations.[30,31] In a large general population cohort conducted in the Netherlands, the doubling of U-CER was independently associated with a low risk of all-cause mortality, even after adjusting the model for S-Cre levels.[30] Among patients with CKD, a decreasing U-CER (per 100 mg/day) was independently associated with all-cause mortality after adjustment for eGFR.[31] However, a high mGFR has been associated with a substantial protective effect against all-cause mortality.[32] This observation of high kidney function estimated by either the 24-h CrCl or the muscle mass–adjusted CKD-EPI eGFR may have independent prognostic implications. Almost all S-Cre–based equations for estimating GFR contain inherent bias because of the strong correlation between S-Cre and muscle mass, which introduces non-renal factors, such as sarcopenia from chronic inflammation, into the causal pathway between GFR and all-cause mortality. Therefore, controlling for the confounding effects of muscle mass by using the population-weighted 24-h U-CERs to correct equation-based methods is rational, and the undervalued 24-h CrCl test should receive proper attention from guideline creators.[33]

Our results support the regular monitoring of 24-h U-CERs among patients with CKD with a wide range of kidney function because it provides an accurate risk assessment of all-cause mortality. For the general population, further research is required to characterize the variations in 24-h U-CER and to identify influential factors, such as dietary content. Patients with CKD may benefit from routine 24-h U-CER measurements at the beginning of CKD care and at annual follow-ups thereafter or whenever the stage of CKD changes. The key conceptual difference between 24-h U-CER–adjusted eGFR and 24-h CrCl is that we used 24-h U-CER to adjust for total muscle mass rather than simply to ap-

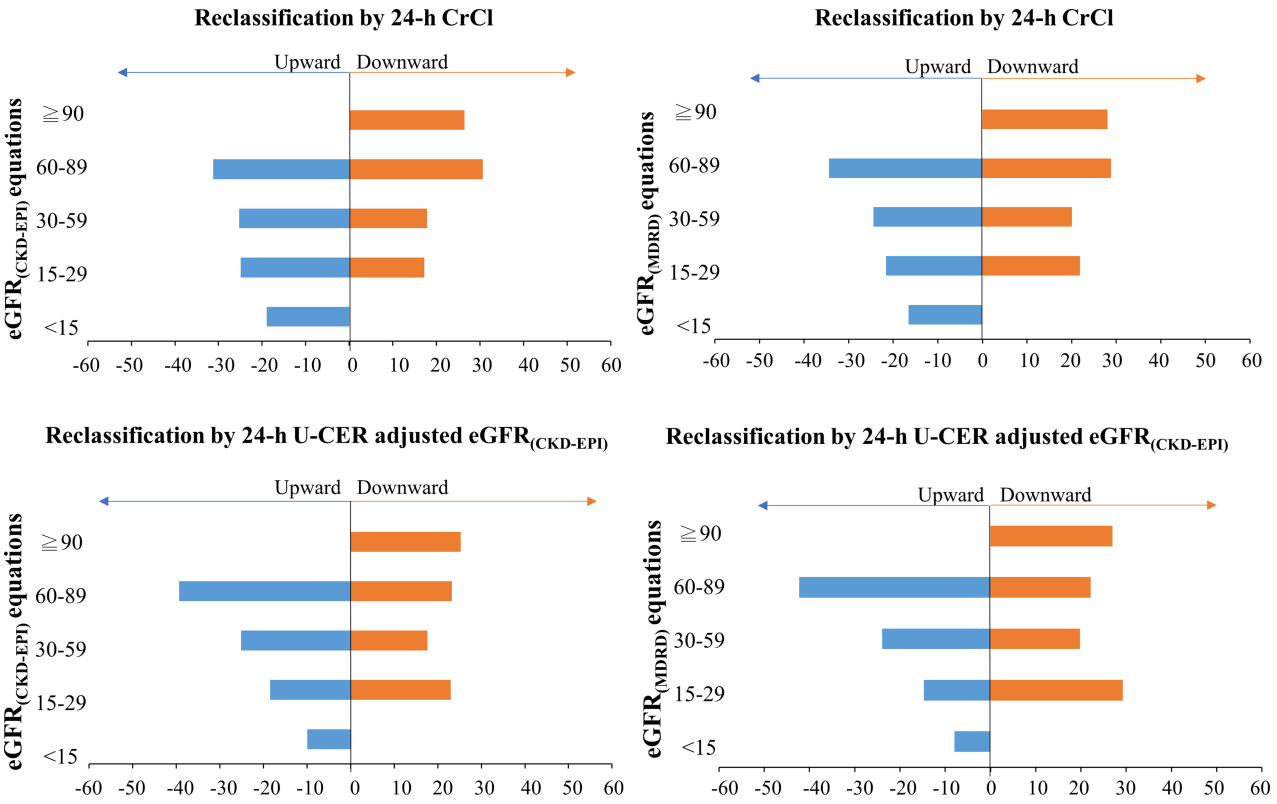

Figure 3 Reclassification of CKD stage based on the eGFRs derived from CKD-EPI and MDRD equations with 24-h CrCl (upper panel) and 24-h U-CER–adjusted $eGFR_{CKD\text{-}EPI}$ (lower panel).

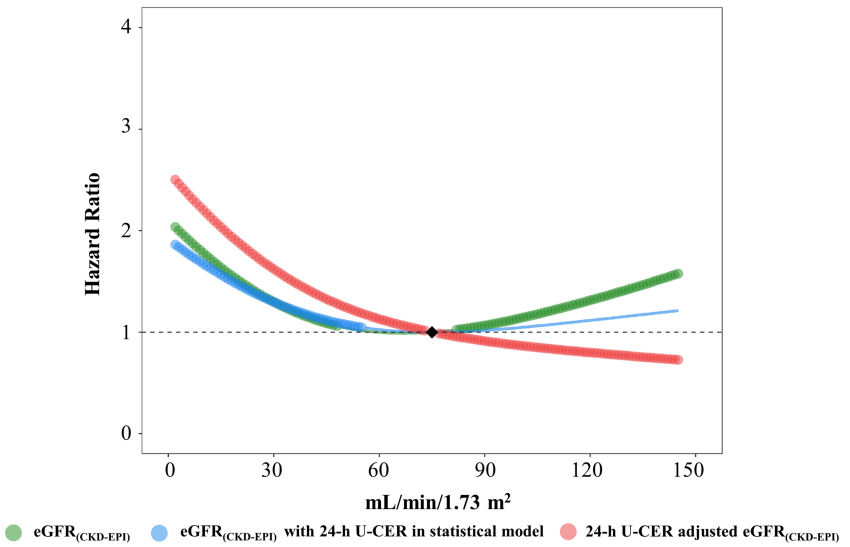

Figure 4 Hazard ratios (HRs) for 5-year all-cause mortality according to eGFRs derived from CKD-EPI and 24-h U-CER–adjusted $eGFR_{CKD\text{-}EPI}$. Solid lines represent adjusted HRs based on restricted cubic splines for each kidney function measurements with knots at the 10th, 50th, and 90th percentiles. Reference is set to 75 mL/min/1.73 m^2 and indicated by a black diamond. Adjustment variables are age, sex, history of cardiovascular disease, diabetes mellitus, systolic blood pressure, total cholesterol, body mass index, and uPCR. Solid circles indicate that the adjusted HR at the indicated eGFR level is significant when compared with the reference point. Green circles and line indicate $eGFR_{CKD\text{-}EPI}$. Blue circles and line indicate further adjustment for 24-h U-CER in the statistical model. Red circles and line indicate 24-h U-CER–adjusted $eGFR_{CKD\text{-}EPI}$.

DOI: 10.1002/jcsm.12951

proximate GFR, which may be biased by tubular secretion of creatinine. Unlike 24-h CrCl, which may overestimate real GFR due to tubular creatinine secretion, 24-h U-CER summarizes creatinine excretion from both glomerular filtration and tubular secretion. This measurement approximates daily body creatinine production when S-Cre is in a steady state. Introducing total muscle mass into the equation-based GFR estimations would help clinicians remain aware of the nutritional status of patients with CKD on a low-protein diet, particularly in older adults. The strategy of applying 24-h U-CER adjustment for equation-based GFR estimations also balances the cumbersomeness of 24-h CrCl measurements. If the 24-h U-CER remains stable over a clinically meaningful period, such as 1 year or 6 months,[34] using 24-h U-CER to correct equation-based eGFRs can be a convenient method for controlling the confounding effects of muscle mass and avoid unwanted intra-individual comparisons between 24-h CrCl and eGFR. Among 479 patients of our study population who had repeat measurements of 24-h U-CER within 1 year after the index date, we observed that the intra-class correlation coefficient was 0.815, which further supports the stability of 24-h U-CER (*Table* S3). The latest Kidney Disease Outcomes Quality Initiative guidelines recommend assessing albumin, normalized protein catabolic rate, and body composition through dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analyses to evaluate protein energy wasting levels in patients with CKD, despite the low evidence grade.[35] Whether 24-h U-CER can serve as a nutritional indicator for patients with CKD remains uncertain. Whether 24-h U-CER can be used to monitor excessive muscle loss over the course of CKD by revealing patients' responses to various low-protein diet intensities can also be investigated.

Despite the strength of the large sample size taken from a real-world practical setting, this study has several limitations. First, mGFR data were unavailable. However, this reference standard is rarely obtained in daily practice. Second, the study lacked the direct quantification of muscle mass with DXA. Future studies can replicate our results by quantifying muscle mass through DXA and comparing the cost-effectiveness of the 24-h U-CER and DXA methods. Third, because of a large proportion of missing data for body surface area (BSA), we did not calculate BSA-adjusted 24-h CrCl. However, BSA adjustment for 24-h CrCl is a controversial approach, particularly in the hospital-based population, where the impacts of misclassifying body height and weight cannot be ignored.[36–38] Fourth, it is likely that residual confounding by indication could not be completely eliminated by adjusting for an extensive set of patients characteristics, as the 24-h urine collections were performed among patients with some form of or who were suspected of having kidney disease. However, the primary aim of the present study was to compare the association patterns between different GFR estimations and all-cause mortality, not determine causality. Fifth, a high number of the source population members were excluded due to missing 24-h urine collection, and the study population excluded patients with ESRD or a history of RRT, kidney transplantation, cancer, or nephrectomy and was composed exclusively of Taiwanese citizens, limiting the generalizability of the results and the feasibility of comparisons. We encourage other investigators to validate the effectiveness of our new approach by conducting studies in different ethnic populations and health care systems.

In conclusion, our study offered the first empirical evidence confirming the role of sarcopenia in the paradoxical mortality pattern in patients with high equation-based GFRs. The weighing of the enrollees' muscle mass effectively corrected the bias in the estimations of the commonly used GFR equations. The nephrology community should re-evaluate the practical role of annual 24-h U-CERs in the current CKD care model.

Acknowledgements

We appreciate the data exploration, statistical analysis, manuscript preparation, and the support of the iHi Clinical Research Platform from the Big Data Center of CMUH. We would like to thank the Health and Welfare Data Science Center (HWDC), Ministry of Health Welfare, and Health Data Science Center, China Medical University Hospital, for providing administrative, technical, and funding support. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle*.[39]

Conflict of interest

P.-Y.K., H.-C.Y., Y.-F.H., Y.-L.H., J.-S.W., D.R.C., S.-N.C., H.-Y.C., and C.-C.K. declare that they have no conflict of interest.

Funding

This study was supported by grants from the Ministry of Science and Technology, Taiwan (Grant Numbers: MOST 108-2314-B-039-038-MY3, MOST 110-2321-B-468-001, and MOST 110-2314-B-039-013) and the China Medical University Hospital, Taiwan (Grant Numbers: DMR-HHC-110-5, DMR-111-206, and DMR-111-207). This study was not sponsored by industry.

Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

References

1. Swedish Council on Health Technology A. *SBU Systematic Review Summaries*. Stockholm: Swedish Council on Health Technology Assessment (SBU) Copyright (c) 2013 by the Swedish Council on Health Technology Assessment; 2013.
2. Hudson JQ, Nolin TD. Pragmatic use of kidney function estimates for drug dosing: the tide is turning. *Adv Chronic Kidney Dis* 2018;**25**:14–20.
3. Tobias GJ, Mc LR Jr, Hopper J Jr. Endogenous creatinine clearance. A valuable clinical test of glomerular filtration and a prognostic guide in chronic renal disease. *N Engl J Med* 1962;**266**: 317–323.
4. Inker LA, Perrone RD. Calculation of the creatinine clearance. UpToDate. 2020
5. van Acker BA, Koomen GC, Koopman MG, de Waart DR, Arisz L. Creatinine clearance during cimetidine administration for measurement of glomerular filtration rate. *Lancet* 1992;**340**:1326–1329.
6. Jones GRD, Lim E-M. The National Kidney Foundation guideline on estimation of the glomerular filtration rate. *Clin Biochem Rev* 2003;**24**:95–98.
7. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006;**354**:2473–2483.
8. Luis-Lima S, Porrini E. An overview of errors and flaws of estimated GFR versus true GFR in patients with diabetes mellitus. *Nephron* 2017;**136**:287–291.
9. Matsushita K, Mahmoodi BK, Woodward M, Emberson JR, Jafar TH, Jee SH, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD Study equation for estimated glomerular filtration rate. *JAMA* 2012;**307**: 1941–1951.
10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. Chapter 2: definition, identification, and prediction of CKD progression. *Kidney Int Suppl* **3**: 63–72.
11. Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006;**17**:2937–2944.
12. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Tsukamoto Y, et al. Modification of the Modification of Diet in Renal Disease (MDRD) Study equation for Japan. *Am J Kidney Dis* 2007;**50**:927–937.
13. Chen LI, Guh JY, Wu KD, Chen YM, Kuo MC, Hwang SJ, et al. Modification of Diet in Renal Disease (MDRD) Study and CKD Epidemiology Collaboration (CKD-EPI) equations for Taiwanese adults. *PLoS ONE* 2014;**9**: e99645, https://doi.org/10.1371/journal.pone.0099645
14. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. *Am J Clin Nutr* 1983;**37**:478–494.
15. Kalantari K, Bolton WK. A good reason to measure 24-hour urine creatinine excretion, but not to assess kidney function. *Clin J Am Soc Nephrol* 2013;**8**: 1847–1849.
16. Chiang HY, Lin KR, Hsiao YL, Huang HC, Chang SN, Hung CH, et al. Association between preoperative blood glucose level and hospital length of stay for patients undergoing appendectomy or laparoscopic cholecystectomy. *Diabetes Care* 2021;**44**: 107–115.
17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;**130**: 461–470.
18. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**: 604–612.
19. Yeh HC, Lo YC, Ting IW, Chu PL, Chang SN, Chiang HY, et al. 24-hour serum creatinine variation associates with short- and long-term all-cause mortality: a real-world insight into early detection of acute kidney injury. *Sci Rep* 2020;**10**:6552, https://doi.org/10.1038/s41598-020-63315-x
20. Yamamoto K, Yamamoto H, Yoshida K, Niwa K, Nishi Y, Mizuno A, et al. The total urine protein-to-creatinine ratio can predict the presence of microalbuminuria. *PLoS ONE* 2014;**9**: e91067, https://doi.org/10.1371/journal.pone.0091067
21. Giavarina D. Understanding Bland Altman analysis. *Biochem Med (Zagreb)* 2015;**25**: 141–151.
22. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, et al. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005;**352**:2049–2060.
23. Chronic Kidney Disease Prognosis C, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010;**375**: 2073–2081.
24. Shastri S, Sarnak MJ. Chronic kidney disease: high eGFR and mortality: high true GFR or a marker of frailty? *Nat Rev Nephrol* 2011;**7**:680–682.
25. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med* 2012; **367**:20–29.
26. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 2013;**369**:932–943.
27. Menon V, Kopple JD, Wang X, Beck GJ, Collins AJ, Kusek JW, et al. Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis* 2009;**53**:208–217.
28. Lucas PA, Meadows JH, Roberts DE, Coles GA. The risks and benefits of a low protein-essential amino acid-keto acid diet. *Kidney Int* 1986;**29**:995–1003.
29. Tsai CW, Huang HC, Tien N, Chung CW, Chiu HT, Yeh HC, et al. Longitudinal progression trajectory of random urine creatinine as a novel predictor of ESRD among patients with CKD. *Clin Chim Acta* 2019; **489**:144–153.
30. Oterdoom LH, Gansevoort RT, Schouten JP, de Jong PE, Gans RO, Bakker SJ. Urinary creatinine excretion, an indirect measure of muscle mass, is an independent predictor of cardiovascular disease and mortality in the general population. *Atherosclerosis* 2009;**207**:534–540.
31. Di Micco L, Quinn RR, Ronksley PE, Bellizzi V, Lewin AM, Cianciaruso B, et al. Urine creatinine excretion and clinical outcomes in CKD. *Clin J Am Soc Nephrol* 2013;**8**: 1877–1883.
32. Sundin PO, Sjostrom P, Jones I, Olsson LA, Udumyan R, Grubb A, et al. Measured glomerular filtration rate does not improve prediction of mortality by cystatin C and creatinine. *Nephrol Dial Transplant* 2017; **32**:663–670.
33. Effersoe P. Relationship between endogenous 24-hour creatinine clearance and serum creatinine concentration in patients with chronic renal disease. *Acta Med Scand* 1957;**156**:429–434.
34. John SG, Sigrist MK, Taal MW, McIntyre CW. Natural history of skeletal muscle mass changes in chronic kidney disease stage 4 and 5 patients: an observational study. *PLoS ONE* 2013;**8**:e65372, https://doi.org/10.1371/journal.pone.0065372
35. Ikizler TA, Burrowes JD, Byham-Gray LD, Campbell KL, Carrero JJ, Chan W, et al. KDOQI Clinical Practice Guideline for Nutrition in CKD: 2020 update. *Am J Kidney Dis* 2020;**76**:S1–S107.
36. Geddes CC, Woo YM, Brady S. Glomerular filtration rate—what is the rationale and justification of normalizing GFR for body surface area? *Nephrol Dial Transplant* 2008;**23**:4–6.

37. Flegal KM, Kit BK, Graubard BI. Bias in hazard ratios arising from misclassification according to self-reported weight and height in observational studies of body mass index and mortality. *Am J Epidemiol* 2018;**187**:125–134.

38. Delanaye P, Radermecker RP, Rorive M, Depas G, Krzesinski JM. Indexing glomerular filtration rate for body surface area in obese patients is misleading: concept and example. *Nephrol Dial Transplant* 2005; **20**:2024–2028.

39. von Haehling S, Morley JE, Coats AJS, Anker SD. Ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle. *J Cachexia Sarcopenia Muscle* 2021;**12**: 2259–2261.