Clinical Kidney Journal

Clinical Kidney Journal, 2025, vol. 18, no. 4, sfaf074

https://doi.org/10.1093/ckj/sfaf074
Advance Access Publication Date: 12 March 2025
Original Article

ORIGINAL ARTICLE

Prognosis of non-albuminuric patients with the cardiovascular–kidney–metabolic syndrome

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ABSTRACT

Background. Cardiovascular–kidney–metabolic (CKM) syndrome affects a significant portion of the general population. Urinary albumin-to-creatinine ratio (UACR) is an important indicator of kidney injury. While some studies have indicated associations between UACR within the normal range and mortality outcomes, it remains uncertain whether traditionally normal UACR could help to distinguish the prognosis of CKM patients.

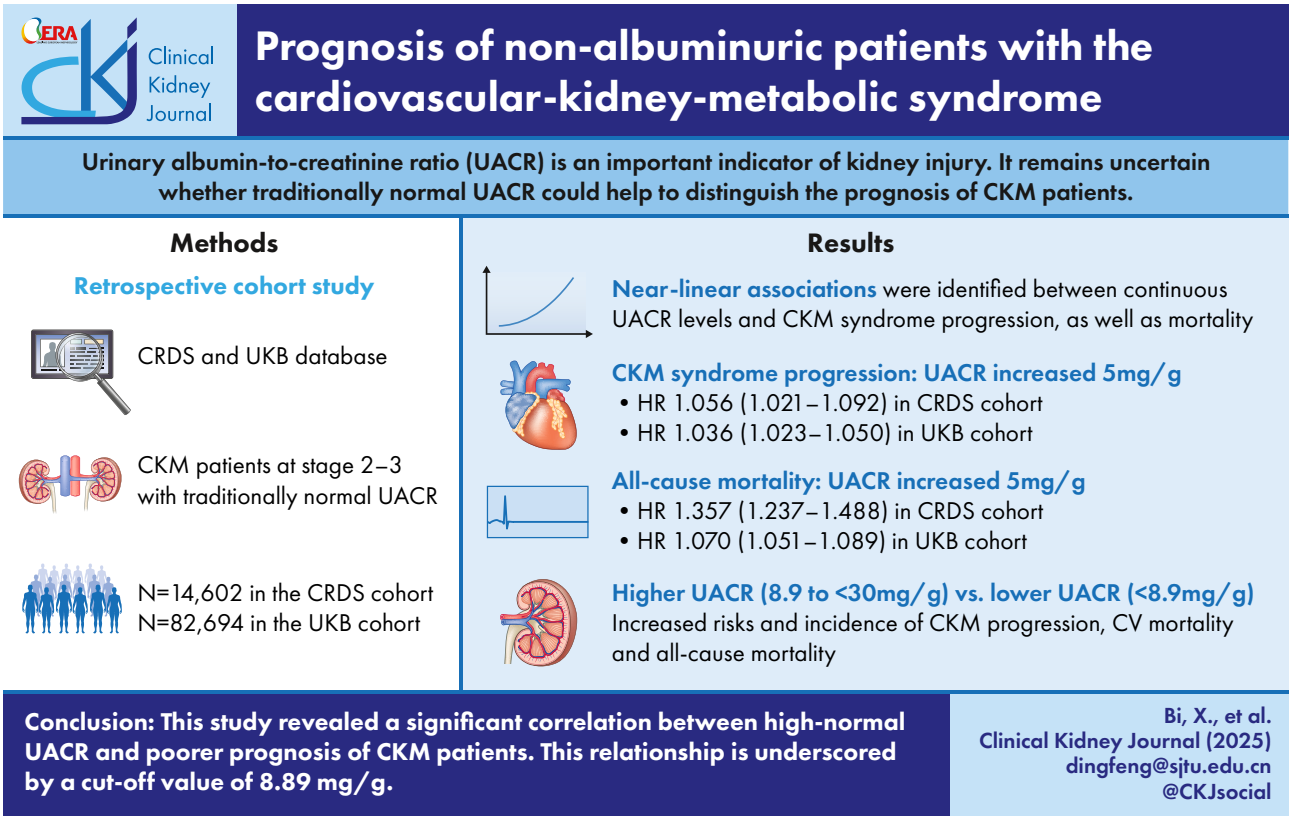
Methods. This cohort study included patients with CKM syndrome at stages 2 and 3 and traditionally normal UACR from the China Renal Data System (CRDS) and UK Biobank (UKB) databases. UACR was treated as a continuous variable and categorized into low-normal and high-normal. The associations were initially assessed in the CRDS database and subsequently validated in the UKB database. Multivariable Cox proportional hazards regression was employed to estimate the associations with UACR. Additionally, subgroup analyses and sensitivity analyses were conducted to enhance the robustness of the results.

Results. The study encompassed a total of 14 602 patients from the CRDS database and 82 694 patients from the UKB database. Near-linear associations were identified between continuous UACR levels and progression to CKM stage 4, as well as all-cause mortality. When compared with the low-normal UACR group, individuals with high-normal UACR exhibited an elevated risk of progression to CKM stage 4 (HR 1.133, 95% CI 1.026–1.250) and increased all-cause mortality (HR 2.321, 95% CI 1.679–3.208) within the CRDS database. These associations were further corroborated in the UKB database. Consistent findings were also observed through subgroup analyses and sensitivity analyses.

Conclusions. The findings indicate that elevated UACR levels within the normal range are significantly associated with poor prognosis among CKM patients at stages 2 and 3. These results underscore the critical role of UACR in identifying high-risk populations, particularly among individuals with metabolic disorders. This information may prove valuable for monitoring and implementing risk intervention strategies for CKM patients.

Received: 18.1.2025; Editorial decision: 5.3.2025

GRAPHICAL ABSTRACT



Keywords: all-cause mortality, cardiovascular disease, metabolic dysfunction, urinary albumin-to-creatinine ratio

INTRODUCTION

Cardiovascular, kidney, and metabolic (CKM) diseases are pathophysiologically interconnected. In 2023, the American Heart Association (AHA) introduced the concept of CKM syndrome to promote multidisciplinary strategies for the prevention, risk stratification, and management of these conditions [1]. CKM syndrome is classified into stages ranging from 0 to 4. CKM stage 4 pertains to patients with established cardiovascular disease (CVD), which often results in a reduced survival rate [2]. According to recent prevalence reports, patients with CKM stages 2 and 3 account for more than half of all CKM patients [3]. It is crucial to identify biomarkers that can effectively monitor therapeutic outcomes and predict the prognosis for these individuals.

Urinary albumin-to-creatinine ratio (UACR) plays an important role in the diagnosis of chronic kidney disease (CKD). A UACR value of 30 mg/g or higher is indicative of kidney injury [4]. Abnormal urinary albumin (UACR >30 mg/g) has been demonstrated to be linked with adverse kidney outcomes, as well as cardiovascular events and increased mortality [5–7]. However, some studies have indicated that UACR within the normal range may also be linked to an increased risk of cardiovascular morbidity and mortality [8, 9]. According to the KDIGO guidelines published in 2024, CKD patients with UACR of 10 mg/g or greater are at higher risk of myocardial infarction, stroke, and atrial fibrillation [10]. Considering the associations between metabolic diseases and kidney dysfunction, UACR may serve as a valuable predictor for the incidence of cardiovascular events in CKM patients at an early stage [11, 12]. It remains uncertain whether high-normal UACR is linked to increased mortality in CKM patients and the specific interval range involved. Therefore, it is crucial to investigate whether varying but traditionally accepted normal UACR ranges can effectively differentiate the prognosis of CKM patients. Such an inquiry would offer valuable insights into the necessity for continuous monitoring of UACR in CKM patients within traditional normal ranges, as well as aid in identifying those at higher risk for progression and mortality at an early stage. The objective of this study was to examine the association between UACR within the normal range and prognosis among Chinese and European populations with CKM stages 2 and 3, while also exploring the interval range necessary for effective differentiation.

MATERIALS AND METHODS

Data source

The China Renal Data System (CRDS), a collaborative initiative between the National Clinical Research Center and the Chinese Center for Disease Control and Prevention (CDC), constitutes a comprehensive nationwide population-based database encompassing over 8 million inpatients and outpatients treated at 28 urban academic hospitals from 1 January 2000 to

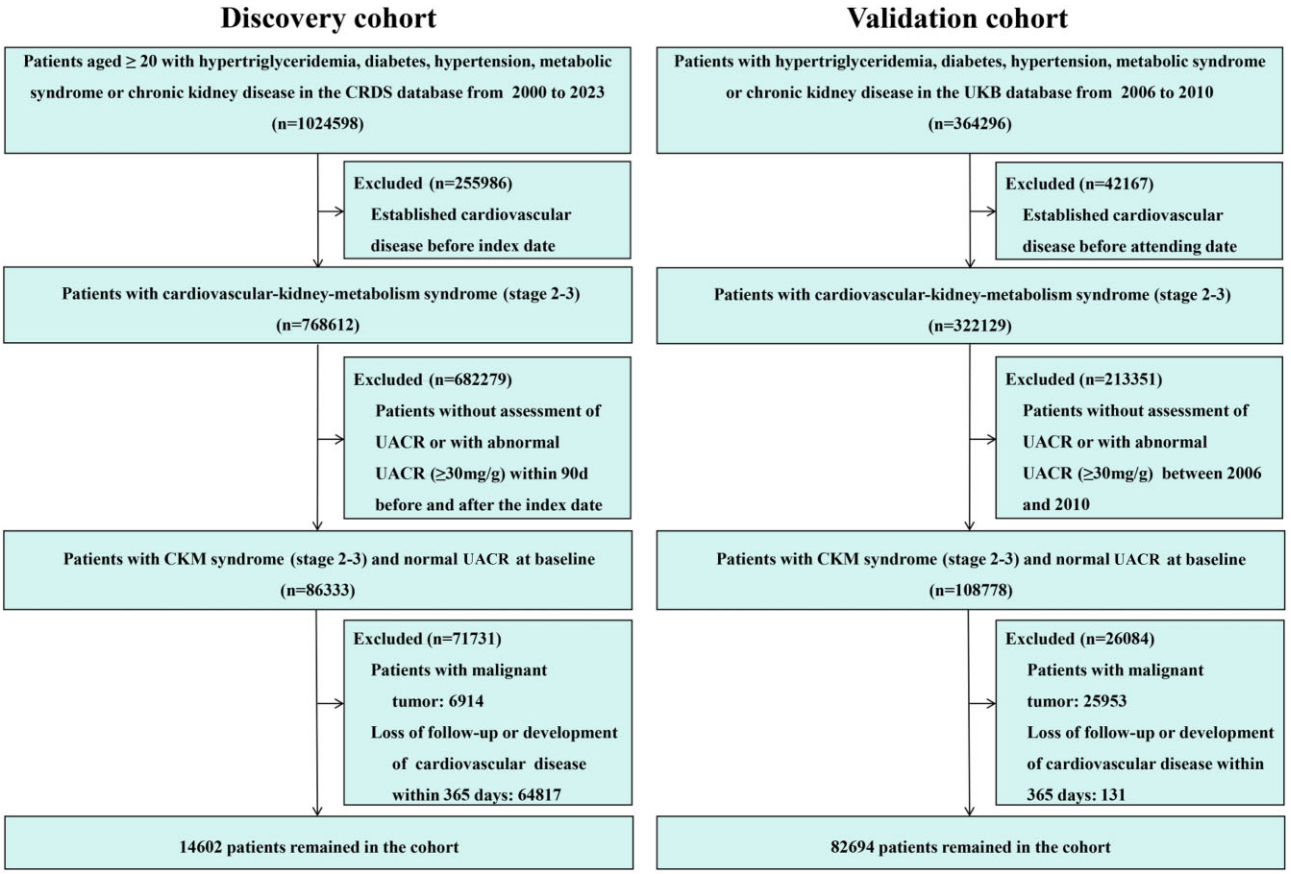


Figure 1: Flow chart of overall study design.

31 December 2023. The accuracy and completeness of this database have been validated through previous studies [13–15]. The recorded data included the demographic characteristics of the patients, vital signs, diagnoses at both admission and discharge, medications administered, surgical details, and laboratory measurements. The UK Biobank (UKB) database recruited over 500 000 individuals aged between 40 and 69 years from 22 assessment centers located across England, Scotland, and Wales during the period from 2006 to 2010.

Study design and participants

Patients with CKM syndrome (stages 2 and 3) were identified from the CRDS and UKB databases (as illustrated in Fig. 1). The diagnostic criteria were as follows: (i) patients met one or more of the five conditions, which included elevated fasting serum triglycerides (≥135 mg/dL), hypertension, diabetes, metabolic syndrome [defined as having three or more of the following: elevated waist circumference, low high-density lipoprotein (HDL) cholesterol levels, fasting serum triglycerides ≥150 mg/dL, elevated blood pressure, or prediabetes], or CKD. For the CRDS cohort, the date when patients first experienced any of these conditions was considered the index date; (ii) patients were required to be over 20 years old; (iii) there was no record of a diagnosis or self-reported history of established CVDs (including coronary heart disease, angina pectoris, myocardial infarction, heart failure, stroke, atrial fibrillation, and peripheral artery disease) prior to the index date for CRDS or attending date for UKB. Patients who did not have an assessment of UACR or exhibited abnormal UACR levels (≥30 mg/g) within 90 days before and after the index date for CRDS or between 2006 and 2010 for UKB were excluded from this study. Additionally, those lost to follow-up or who developed CVDs within 365 days post-inclusion were also excluded. Subsequently, retrospective cohorts were established for further evaluation. The cohort derived from the CRDS database was designated as the discovery cohort while that from the UKB database served as the validation cohort.

Exposure and outcome

The exposure of interest was UACR of participants at baseline. In the CRDS database, baseline UACR was defined as the average value of UACR within 90 days before and after the index date. In contrast, for the UK Biobank (UKB) database, baseline UACR was determined as the ratio between urinary microalbumin and urinary creatinine assessed during the period from 2006 to 2010. The outcome of interest encompassed all-cause mortality and progression to CKM stage 4. The latter indicates an incidence of CVDs, including coronary heart disease, angina, heart attack, heart failure, stroke, atrial fibrillation, and peripheral artery disease, whichever occurred first. For each participant in the CRDS database, cohort end time was marked by either the occurrence of an event of interest or the date of their last medical record. Conversely, in the UKB database, cohort end time corresponded to either the occurrence of an event of interest or one among several other endpoints: death or loss to follow-up, alternatively ending on 31 December 2022 (the conclusion date for

this study), whichever came first. Cardiovascular mortality in the UKB database was defined according to a previous report [16].

Covariates

Categorical variables are presented as counts (or proportions), while continuous variables are reported as medians along with interquartile ranges (IQRs). We gathered demographic information, including age and sex, as well as laboratory parameters such as serum creatinine levels, total cholesterol levels, and HDL-C levels. Additionally, we documented medication usage encompassing anti-hypertensive agents, glucose-lowering agents, and statins. Comorbidities, including hypertension, diabetes mellitus, and CKD, were identified based on diagnoses coded according to the International Classification of Diseases, 10th Revision (ICD-10). Medication classifications were determined using Anatomical Therapeutic Chemical codes. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine values utilizing the Chronic Kidney Disease Epidemiology Collaboration equation. Detailed descriptions of the covariates can be found in Supplementary Tables 1 and 2.

Statistical analysis

The χ^2 test and Kruskal–Wallis test were utilized to assess differences in clinical parameters and baseline characteristics among the groups. In the discovery cohort, multivariable Cox proportional hazards regression models were employed to estimate the hazard ratio (HR) for various outcomes associated with UACR as both a continuous variable (1 mg/g increment or 5 mg/g increment) and a categorical variable (segmentation of UACR). The proportional hazards assumption was evaluated using Schoenfeld residuals. Model 1 was adjusted for age and sex, while model 2 included additional adjustments for comorbidities (hypertension and diabetes), non-HDL cholesterol levels, eGFR, and statin administration. Restricted cubic spline (RCS) models with three knots (at the 10th, 50th, and 90th percentiles) were fitted to explore non-linear associations between continuous UACRs and various outcomes. The cut-off value of UACR was determined at an HR of 1. A likelihood ratio test was conducted to evaluate non-linearity. Absolute risk estimates and risk differences at different time points were calculated using the Kaplan–Meier estimator; corresponding 95% confidence intervals were derived from bootstrap sampling of 1000 samples utilizing a percentile approach. In the validation cohort, competing risk models were applied to estimate HRs for various outcomes related to UACR as either a continuous or categorical variable. Deaths and loss to follow-up were considered competing events against progression to CKM stage 4, whereas loss to follow-up was treated as a competing event against all-cause mortality. Model 1 accounted for age and gender adjustments; model 2 further incorporated adjustments for systolic blood pressure, use of antihypertensive agents, diabetes status, non-HDL cholesterol levels, eGFR values, and statin therapy.

In the subgroup analyses, we conducted the primary analyses stratified by age (<60 vs ≥60 years), gender, eGFR (≥60 vs <60 mL/min/1.73 m^2), hypertension (yes vs no), diabetes (yes vs no), hypertriglyceridemia (yes vs no), and metabolic syndrome (yes vs no) utilizing the continuous variable of urinary UACR. In sensitivity analyses, we excluded patients who experienced loss to follow-up within the initial 3 or 5 years and re-evaluated the associations accordingly.

To address missing data for all covariates, we assumed that the data were missing at random and subsequently imputed the missing values using a random forest algorithm via the missForest package (version 1.5) in R. The proportions of missingness for all covariates were less than 5% in the CRDS database and 20% in the UKB database. All statistical analyses were performed using R version 4.3.1 (R Foundation for Statistical Computing), with a significance level set at 0.05 (two-sided).

RESULTS

Associations of UACR with the prognosis of CKM patients in the discovery cohort

In the discovery cohort, a total of 14 602 patients were included for assessment. Among these participants, 8646 (59.2%) were male, with a median age of 55 years (IQR 45–63 years). As shown in Table 1, cox regression analyses conducted in model 2 revealed that participants exhibited an increased risk of progression to CKM stage 4 and all-cause mortality, with HRs of 1.056 (95% CI 1.021–1.092) and 1.357 (95% CI 1.237–1.488), respectively, per increment of 5 mg/g in UACR after multivariable adjustment. Utilizing restricted cubic spline modeling, a near-linear correlation was identified between UACR and the risk of progression to CKM stage 4 (Fig. 2a), as well as all-cause mortality (Fig. 2b). Based on the RCS curve analysis, participants were categorized into two groups: a low-normal group (≤8.89 mg/g) and a high-normal group (8.90–30 mg/g). Detailed characteristics of the participants according to UACR segmentation are presented in Supplementary Table S3. As shown in Table 2, cox regression analyses indicated that compared with individuals in the low-normal UACR group, those in the high-normal UACR group faced a significantly higher risk of progression to CKM stage 4 (HR 1.133; 95% CI 1.026–1.250 in model 2) and all-cause mortality (HR 2.321;95% CI 1.679–3.208 in model 2). In absolute terms , participants within the low-normal UACR category also demonstrated lower risks for both progression to CKM stage 4 and all-cause mortality, as illustrated in Table 3 (5-year risk differences for progression to CKM stage 4: 6.23%, 95% CI 4.63%–7.84%; and all-cause mortality: 2.47%, 95% CI l.59%–3.33%).

Associations of UACR with the prognosis of CKM patients in the validation cohort

In the validation cohort, a total of 82 694 patients were included for assessment. Among these participants, 45 646 (55.2%) were male, with a median age of 59 years (interquartile range 51–64 years). Detailed characteristics of the participants segmented by UACR are presented in Supplementary Table S4. Competing risk model analyses conducted in model 2 indicated that participants exhibited an increased risk of progression to CKM stage 4, all-cause mortality, and cardiovascular mortality, with HR of 1.036 (95% CI 1.023–1.050), 1.070 (95% CI 1.051–1.089) and 1.076 (95% CI 1.037–1.116), respectively, per increment of 5 mg/g in UACR after multivariable adjustment (as shown in Table 4). To validate the cut-off value identified in the discovery cohort, participants from the UKB database were categorized into low-normal group (≤8.89 mg/g) and high-normal group (8.90–30 mg/g). Compared with those in the low-normal UACR group, individuals within the high-normal UACR group faced a significantly higher risk of progression to CKM stage 4 (HR 1.092; 95% CI 1.056–1.129 in model 2) as well as all-cause mortality (HR 1.151; 95% CI 1.097–1.206) and cardiovascular mortality (HR 1.198; 95% CI 1.084–1.325 in MODEL 2), following multivariable adjustment.

Table 1: HRs of UACR within normal range associated with the prognosis of CKM patients at stages 2 and 3 in CRDS database.

			Unadjusted		Model 1		Model 2	
Outcome		Events/*n*	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Progression to CKM stage 4	Increase 1 mg/g	1646/14 602	1.029 (1.023–1.036)	<.001	1.023 (1.016–1.029)	<.001	1.011 (1.004–1.018)	.002
	Increase 5 mg/g		1.156 (1.120–1.193)	<.001	1.119 (1.083–1.155)	<.001	1.056 (1.021–1.092)	.002
All-cause mortality	Increase 1 mg/g	185/14 602	1.076 (1.058–1.095)	<.001	1.067 (1.048–1.086)	<.001	1.063 (1.043–1.083)	<.001
	Increase 5 mg/g		1.445 (1.323–1.557)	<.001	1.382 (1.263–1.512)	<.001	1.357 (1.237–1.488)	<.001

Model 1 was adjusted by age and gender. Model 2 was adjusted by age, gender, hypertension, diabetes, non-HDL cholesterol, eGFR and administration of statins. UACR, urinary albumin-to-creatinine ratio.

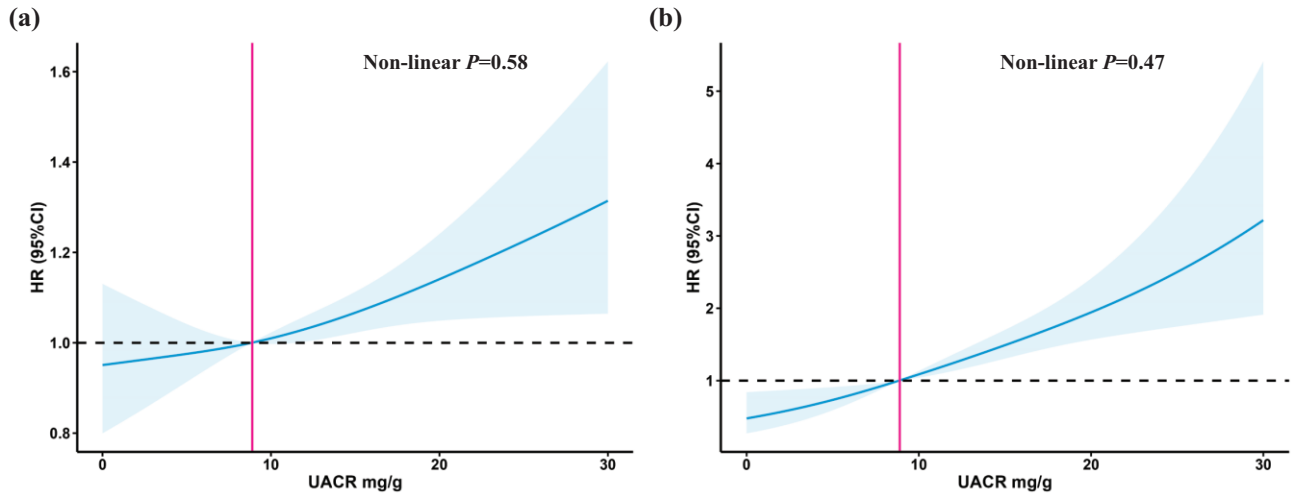


Figure 2: Associations of UACR with progression to CKM stage 4 (**a**) and all-cause mortality (**b**) in CKM patients at stages 2 and 3.

Table 2: Associations of segmentation of UACR with the prognosis of CKM patients at stages 2 and 3 in CRDS database.

		HR (95% CI)		
Subgroup	Events/*n*	Unadjusted	Model 1	Model 2
Progression to CKM stage 4				
UACR low-normal	747/7359	Reference	Reference	Reference
UACR high-normal	899/7243	1.440 (1.306–1.587)	1.312 (1.189–1.447)	1.133 (1.026–1.250)
All-cause mortality				
UACR low-normal	55/7359	Reference	Reference	Reference
UACR high-normal	130/7243	3.027 (2.202–4.162)	2.524 (1.829–3.485)	2.321 (1.679–3.208)

UACRs were grouped into low-normal (≤8.89 mg/g) and high-normal(8.90 to <30 mg/g).
Model 1 was adjusted by age and gender. Model 2 was adjusted by age, gender, hypertension, diabetes, non-HDL cholesterol, eGFR, and administration of statins.

Table 3: Estimated absolute risk and risk differences of progression to CKM stage 4 and all-cause mortality among the participants in CRDS database.

	Progression to CKM stage 4, % (95% CI)	All-cause mortality, % (95% CI)
3 years		
Absolute risk, UACR low-normal	9.07 (8.39–9.78)	0.34 (0.23–0.46)
Absolute risk, UACR high-normal	12.54 (11.71–13.37)	1.04 (0.75–1.32)
Risk difference, UACR high vs low	3.47 (2.57–4.40)	0.70 (0.43–0.94)
5 years		
Absolute risk, UACR low-normal	19.64 (18.32–20.99)	1.26 (0.88–1.66)
Absolute risk, UACR high-normal	25.87 (24.38–27.39)	3.73 (2.88–4.54)
Risk difference, UACR high vs low	6.23 (4.63–7.84)	2.47 (1.59–3.33)
8 years		
Absolute risk, UACR low-normal	31.31 (28.76–33.80)	5.94 (4.10–7.85)
Absolute risk, UACR high-normal	39.29 (36.57–42.09)	15.86 (12.25–19.39)
Risk difference, UACR high vs low	7.99 (5.80–10.23)	9.91 (6.55–13.14)

UACRs were grouped into low-normal (≤8.89 mg/g) and high-normal (8.90 to <30 mg/g).

Table 4: HRs of UACR associated with the prognosis of CKM patients at stages 2 and 3 in UKB database.

Outcome		Events/*n*	Unadjusted		Model 1		Model 2	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Progression to CKM stage 4	Increase 1 mg/g	14 980/82 694	1.010 (1.005–1.015)	<.001	1.008 (1.005–1.011)	<.001	1.007 (1.005–1.010)	<.001
	Increase 5 mg/g		1.075 (1.060–1.090)	<.001	1.060 (1.050–1.070)	<.001	1.036 (1.023–1.050)	<.001
	Category (low as reference)		1.180 (1.140–1.220)	<.001	1.150 (1.110–1.190)	<.001	1.092 (1.056–1.129)	<.001
All-cause mortality	Increase 1 mg/g	7453/82 694	1.024 (1.018–1.030)	<.001	1.016 (1.011–1.021)	<.001	1.013 (1.010–1.017)	<.001
	Increase 5 mg/g		1.120 (1.100–1.140)	<.001	1.091 (1.071–1.111)	<.001	1.070 (1.051–1.089)	<.001
	Category (low as reference)		1.291 (1.230–1.352)	<.001	1.190 (1.140–1.250)	<.001	1.151 (1.097–1.206)	<.001
Cardiovascular mortality	Increase 1 mg/g	1646/82 694	1.029 (1.024–1.034)	<.001	1.024 (1.019–1.028)	<.001	1.015 (1.007–1.022)	<.001
	Increase 5 mg/g		1.153 (1.112–1.194)	<.001	1.132 (1.093–1.162)	<.001	1.076 (1.037–1.116)	<.001
	Category (low as reference)		1.392 (1.260–1.534)	<.001	1.330 (1.210–1.470)	<.001	1.198 (1.084–1.325)	<.001

UACRs were grouped into low-normal (≤8.89 mg/g) and high-normal(8.90 to <30 mg/g).
Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, systolic blood pressure, administration of anti-hypertension agents, diabetes, non-HDL cholesterol, eGFR, and administration of statins.

Subgroup and sensitivity analyses

Subgroup analyses stratified by age (<60 years vs ≥60 years), gender, eGFR (≥60 vs <60 mL/min/1.73 m^2), hypertension (yes vs no), diabetes (yes vs no), hypertriglyceridemia (yes vs no), and metabolic syndrome (yes vs no) demonstrated consistent patterns in the associations between continuous UACR measurements (1 mg/g increment) and progression to CKM stage 4, as well as all-cause mortality, across both the CRDS (Fig. 3a, b) and UKB databases (Fig. 3c, d). In sensitivity analyses, results remained comparable to the primary findings in both the CRDS and UKB databases after multivariable adjustment when excluding patients with short-term follow-up (as shown in Tables 5 and 6). Among participants with more than 3 years of follow-up, those in the high-normal UACR group continued to exhibit a higher risk of progression to CKM stage 4 (HR 1.215, 95% CI 1.028–1.436 in CRDS; HR 1.089, 95% CI 1.051–1.128 in UKB) and increased all-cause mortality risk (HR 1.677, 95% CI 1.015–2.771 in CRDS; HR 1.148, 95% CI 1.093–1.206 in UKB).

DISCUSSION

In this retrospective cohort study, we observed that the risks of progression to CKM stage 4 and all-cause mortality were associated with an increase in UACR among CKM patients who traditionally exhibited normal UACR levels. Furthermore, segmenting UACR values at 8.89 mg/g proved effective in distinguishing the prognosis of CKM patients across both Chinese and European populations. These findings underscore the significance of UACR as a biomarker for early renal dysfunction not only in individuals with CKD but also in those presenting metabolic risk factors such as hypertriglyceridemia, hypertension, diabetes, and metabolic syndrome. Dynamic monitoring of UACR should be considered for CKM patients even when their UACR levels are traditionally deemed normal. Future investigations are warranted to ascertain whether variations in UACR can effectively reflect the impact of interventions on patients with CKM syndrome.

CKM syndrome is proposed as a means to identify patients with metabolic dysfunction or kidney disease, enabling earlier intervention to delay the onset of CVD and reduce mortality rates. UACR exceeding 30 mg/g is traditionally considered one of the indicators of renal dysfunction. For patients diagnosed with CKM syndrome, it is recommended that Renin-Angiotensin System (RAS) inhibitors and Sodium-dependent glucose transporters 2 (SGLT2) inhibitors be administered when UACR levels exceed 30 mg/g [1, 17]. However, apparent renal dysfunction often manifests relatively late in the progression of the disease, particularly among patients with metabolic risk factors. It remains uncertain whether UACR within the normal range is still linked to the development and prognosis of CKM syndrome. Our study represents the first investigation into the associations between UACR within this normal range and both incident CVD and all-cause mortality in CKM patients. We utilized population-based databases to identify correlations between UACR and patient outcomes for those with CKM stages 2 and 3 in the China Renal Data System (CRDS) database, subsequently validating these findings in the UKB database through both continuous measurement and segmentation of UACR. To date, several epidemiological studies have reported positive associations between UACR within normal limits and all-cause mortality [9, 18, 19]. Inoue *et al*. found that UACR ranging from 10 to 30 mg/g and from 5 to 10 mg/g may be associated with an increased risk of all-cause mortality when compared with UACRs of less than 5 mg/g

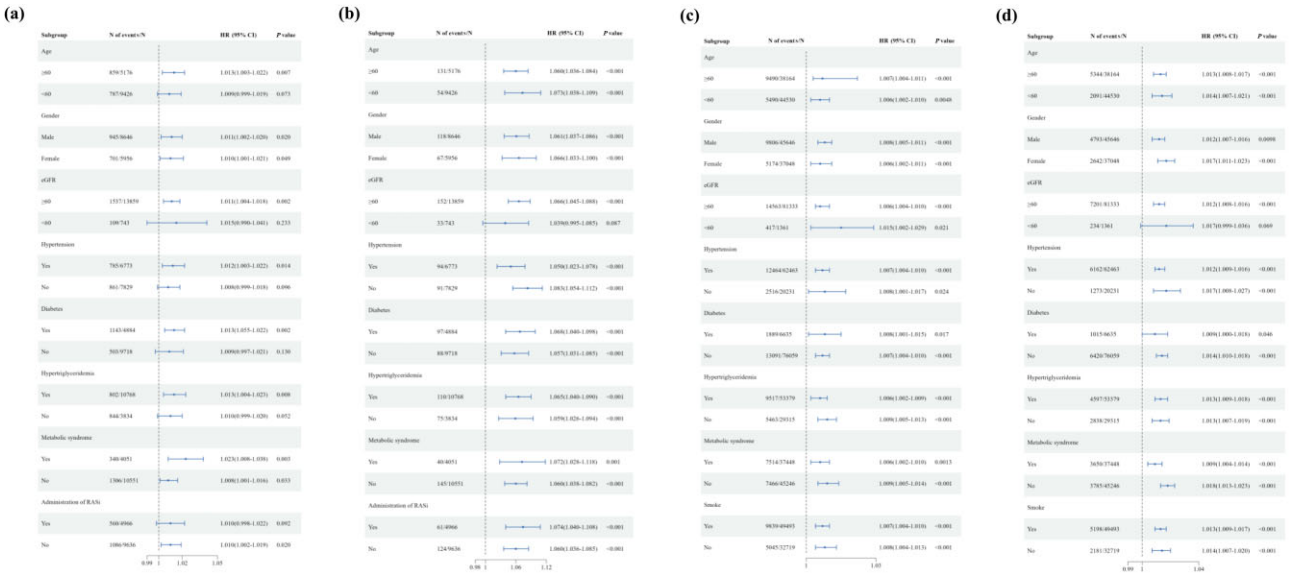


Figure 3: Adjusted hazard ratios of UACR with the risk of progression to CKM stage 4 and all-cause mortality stratified by baseline characteristics in the CKM patients at stages 2 and 3. (**a**) Progression to CKM stage 4 in CRDS database. (**b**) All-cause mortality in CRDS database. (**c**) Progression to CKM stage 4 in UKB database. (**d**) All-cause mortality in UKB database.

Table 5: Adjusted HR associated with progression to CKM stage 4 and all-cause mortality in CKM patients with long-term follow-up in CRDS database.

Outcome	Follow-up duration (years)	Events/*n*	UACR increase 1 mg/g		UACR category (low as reference)	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Progression to CKM stage 4	>3	573/4956	1.017 (1.005–1.028)	0.0051	1.215 (1.028–1.436)	0.0221
	>5	135/1379	1.050 (1.026–1.074)	<.001	1.189 (1.328–2.658)	<.001
All-cause mortality	>3	69/4956	1.064 (1.032–1.098)	<.001	1.677 (1.015–2.771)	0.044
	>5	21/1379	1.119 (1.047–1.197)	<.001	2.470 (0.920–6.633)	0.072

HRs were estimated using Cox proportional hazards model adjusted by age, sex, hypertension, diabetes, nonhdlc, eGFR, and administration of statins.

Table 6: Adjusted HR associated with progression to CKM stage 4 and all-cause mortality in CKM patients with long-term follow-up in UKB database.

Outcome	Follow-up duration (years)	Events/*n*	UACR increase 1 mg/g		UACR category (low as reference)	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Progression to CKM stage 4	>3	13 906/81 284	1.007 (1.004–1.009)	<.001	1.089 (1.051–1.128)	<.001
	>5	11 714/78 605	1.007 (1.004–1.010)	<.001	1.088 (1.048–1.130)	<.001
All-cause mortality	>3	6866/81 284	1.013 (1.009–1.017)	<.001	1.148 (1.093–1.206)	<.001
	>5	5872/78 605	1.010 (1.008–1.016)	<.001	1.132 (1.073–1.194)	<.001

HRs were estimated using competing risk model adjusted by age, gender, systolic blood pressure, administration of anti-hypertension agents, diabetes, non-HDL cholesterol, eGFR, and administration of statins.

in the American population [9]. Sung *et al*. reported that among Korean individuals, a UACR below 30 mg/g is linked to a heightened risk of developing hypertension and adverse mortality outcomes [18]. In addition, Grams *et al*. conducted a large-scale meta-analysis including over 27 million individuals derived from both observational studies and clinical trials [20]. They found that participants with traditionally higher UACR (10–29 mg/g) were at increased risk of adverse outcomes compared with those with UACR less than 10 mg/g, which aligns with our findings. The individuals included in their study primarily comprised the general population and CKD patients, while most participants in our study had metabolic

disorders, indicating some differences between the study populations.

Furthermore, we sought to determine the cut-off value for UACR in CKM patients at stages 2 and 3 in order to differentiate their prognoses. Our findings indicated that patients with a UACR less than 8.89 mg/g were at a lower risk for incident CVD and all-cause mortality. These associations have also been corroborated within the European population. Previous studies have proposed various cutoffs for traditionally normal UACR within the general population [9, 18, 19]. As indicated by both the Grams *et al*. study and our own research, the risks associated with UACR are consistently elevated in conjunction with increasing UACR levels. Therefore, the identification of UACR cutoffs in our study does not imply an absence of risk within lower UACR groups. Rather, it serves to identify patients who are susceptible to early kidney injury, as well as high-risk populations with poor prognoses among CKM patients in clinical practice. This is particular important in this population, as kidney dysfunction plays a significant role in the relationships between metabolic disorder and development of CVDs. In this regard, monitoring of UACR should be emphasized in patients with any metabolic disorder and assessment of dynamic variations in UACR should be considered for CKM patients even with traditionally normal UACR. Given that high-normal UACR may signify early kidney injury and is correlated with the prognosis of CKM patients, it warrants further investigation into whether CKM patients exhibiting high-normal UACR would derive benefits from treatment interventions. Since this study included CKM patients from the Chinese and European populations, caution should be exercised when generalizing the findings to other ethnic groups.

The precise biological mechanisms underlying the adverse effects associated with high-normal UACR remain unclear. Previous studies have indicated that microalbuminuria, resulting from increased permeability of kidney endothelial cells, may serve as an indicator of endothelial dysfunction [21, 22]. In this study, the majority of the included CKM patients presented with metabolic risk factors. Consequently, a high-normal UACR may serve as an indicator of endothelial dysfunction induced by metabolic disturbances, which is recognized as an early pathogenic characteristic associated with cardiovascular morbidities. These morbidities encompass impaired vasodilation, angiogenesis, and barrier function [23]. Other studies have indicated that microalbuminuria may also lead to changes in fibrinogen levels, von Willebrand factor activity, and the activation of tissue factor-induced coagulation [24, 25]. Further investigations into the biological mechanisms underlying UACR, as well as its association with the development and prognosis of CKM syndrome, are warranted based on findings from cross-population epidemiological studies and animal studies.

The strengths of the present study include its utilization of real-world data sources, a large sample size, and participants representing a diverse array of disease phenotype across multiple urban centers in China and Britain. The incorporation of two national cohorts provided a substantial sample size that enhanced the robustness of the results. Furthermore, the linkage to national death registries ensured a more accurate determination of mortality outcomes.

Several limitations of our study warrant consideration. First, there exists a slight discrepancy in the definition of baseline UACR between the two databases. In the CRDS database, average values of UACR near baseline were utilized, whereas in the UKB database single measurement results of UACR were employed. Second, our dependence on ICD-10 diagnostic codes for defining clinical conditions did not fully leverage the clinical precision afforded by laboratory and imaging data. Third, other uncontrolled factors may have influenced the progression of CKM syndrome. For example, dietary influences and certain lifestyle factors were not accounted for in this investigation.

In conclusion, this cohort study involving Chinese and European patients with CKM syndrome revealed a significant association between high-normal UACR and the progression of CKM syndrome, as well as all-cause mortality. This relationship is underscored by a cut-off value of 8.89 mg/g. These findings highlight the critical role of UACR in identifying high-risk populations that may present with traditionally normal UACR values. Such insights could prove invaluable for monitoring and implementing risk intervention strategies for CKM patients in the future.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

FUNDING

This study was supported by the National Key R&D Program of China (No. 2021YFC2500200 and 2021YFC2500204) and the National Natural Science Foundation of China (No. 82200755 and 82470712).

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Received: 18.1.2025; *Editorial decision:* 5.3.2025