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Non-linear relationship between urinary creatinine and diabetic kidney disease: implications for clinical practice

Huihong Cao[1], Li Song[1], Xiaojun Wang[2] and Haochen Guan[3*]

Abstract

Objective This study aims to investigate the relationship between urinary creatinine (UCr) and the risk and severity of Diabetic Kidney Disease (DKD) in patients with Type 2 Diabetes Mellitus (T2DM). The goal is to establish UCr as a potential biomarker for early DKD detection and severity assessment.

Methods A retrospective cross-sectional analysis was conducted using medical records of T2DM patients. Patients were classified into groups with and without DKD, and relevant clinical data, including demographic, blood, and urine parameters, were collected. Logistic regression and receiver operating characteristic (ROC) curve analysis evaluated the association between UCr levels and DKD. Curve fitting and threshold effect model were used to further evaluate the relationship between UCr and the incidence and severity of DKD.

Results A total of 302 T2DM patients were analyzed, with 137 diagnosed with DKD. Significant differences in clinical parameters were observed between the DKD and non-DKD groups, particularly in UCr, urine albumin levels, and eGFR. UCr levels demonstrated a strong association with DKD. Moreover, a non-linear relationship was identified, with specific inflection points indicating different correlation patterns of UCr with DKD occurrence and progression.

Conclusion The findings of this study highlight the potential of UCr as a valuable biomarker for early detection and assessment of DKD in T2DM patients. Incorporating UCr measurements into routine clinical practice could enhance early identification of patients at risk for kidney complications, leading to timely intervention and improved patient outcomes.

Keywords Diabetic kidney disease, Type 2 diabetes Mellitus, Urinary creatinine, Biomarker, Early detection, Renal function

*Correspondence:
Haochen Guan
hcguan777@163.com
[1]Department of Endocrinology of Shanghai Minhang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai, China
[2]Shanghai Key Laboratory of Clinical Geriatric Medicine, Huadong Hospital Affiliated to Fudan University, Shanghai, China
[3]Department of Nephrology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, Anhui Province, China

Introduction

Diabetic Kidney Disease (DKD) is one of the most common and serious complications among diabetic patients, particularly prevalent in those with Type 2 Diabetes Mellitus (T2DM) [1, 2]. The occurrence of DKD significantly impacts the quality of life of patients and is linked to cardiovascular health and overall prognosis. Increasingly, global research has demonstrated that early identification and intervention for DKD are crucial for improving patient outcomes [3].

In recent years, urine creatinine (UCr) has garnered attention as a routine marker of kidney function [4, 5]. Variations in UCr levels can reflect the status of renal function; however, its role in the early screening and risk assessment of DKD has not been fully elucidated. Studies indicate that changes in urinary creatinine excretion may be associated with tubular dysfunction, a condition that exhibits certain specificity in diabetic patients [6, 7]. Therefore, understanding the relationship between UCr and DKD, as well as its impact on the incidence and severity of DKD, is essential for improving clinical management and patient prognosis.

This study aims to explore the relationship between UCr and the risk and severity of DKD in patients with T2DM. By comparing clinical data between patients with and without DKD, we hope to establish UCr as a potential biomarker with clinical value in predicting the onset of DKD and assessing its severity. Through a detailed analysis of the relationship between changes in UCr and DKD, we aim to provide new insights for the early identification and intervention of diabetic kidney disease, thereby enhancing the overall health and quality of life of diabetes patients. This research will also contribute to a theoretical framework for understanding the interplay between UCr levels and DKD, potentially informing early screening and management strategies in clinical practice.

Materials and methods

Subjects

This study is a retrospective cross-sectional analysis, collecting medical records of diagnosed Type 2 Diabetes Mellitus (T2DM) cases from October 2023 to December 2023 at the First Affiliated Hospital of USTC and from December 2022 to August 2024 at the Integrated Traditional and Western Medicine Hospital in Minhang District, Shanghai. The diagnostic criteria are as follows: (1) For T2DM diagnosis: According to the classification provided by the American Diabetes Association established in 2017; (2) For Diabetic Kidney Disease (DKD) diagnosis: Based on the clinical practice guidelines released by the National Kidney Foundation in 2012, which require the exclusion of other factors causing renal impairment, with an estimated Glomerular Filtration Rate (eGFR) < 60 mL/(min · 1.73 m^2) and/or a urine albumin-to-creatinine ratio (UACR) ≥ 30 mg/g. The exclusion criteria include: (1) Type 1 diabetes or other specific types of diabetes; (2) Urinary tract infections or use of medications that affect urinary protein; (3) Acute renal failure with a rapid decline in eGFR or a rapid increase in UACR within a short period; (4) Other acute complications of diabetes; (5) Acute obstructive renal injury; (6) Urinary system disorders; (7) Isolated renal hematuria or hematuria with proteinuria; (8) Significant abnormal casts. Based on the above criteria, patients were classified into groups with and without DKD among those with solely T2DM. For patients with DKD, the Kidney Disease: Improving Global Outcomes (KDIGO) classification was used to categorize them into stages I to V. The research protocol has been approved by the hospital's ethics committee (2024-RE-426) [8].

Data extraction

Clinical pathological and demographic variables were collected from patients, including gender, age, height, weight, and history of hypertension (HBP). Blood and urine samples were collected upon admission for routine renal and liver function tests, with each specimen analyzed by the clinical laboratory within 2 h of collection. Specific measurements included hemoglobin (Hb), glycated hemoglobin (HbA1C), urine albumin (UALB), urine creatinine (UCr), UALB/UCr ratio, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum creatinine (SCr), blood urea nitrogen (BUN), serum uric acid (SUA), blood glucose (BG), serum albumin (ALB), and eGFR. As well as clinical variables, epidemiological data, clinical assessments, and laboratory tests were collected during the same visit for each patient.

Statistical analysis

All statistical analyses were conducted using R software (http://www.R-project.org), with a significance level set at $P < 0.05$. Initially, the Kolmogorov-Smirnov test was used to determine the normal distribution of variables. A one-way analysis of variance or two-tailed Student's t-test was used for normally distributed data, while a Mann-Whitney U test was used for non-parametric data comparisons. Furthermore, multiple logistic regression models were used to evaluate the relationship between UCr and DKD, and the area under the receiver operating characteristic (ROC) curve was calculated to assess the significance of uric acid in the diagnosis of T2DM. A two-segment linear regression model with smoothing functions was applied to investigate the role of UCr in predicting the likelihood of DKD and its grading of KDIGO. A "trial-and-error" method was commonly employed to identify the threshold or inflection point, starting with a lower value and progressing to a higher

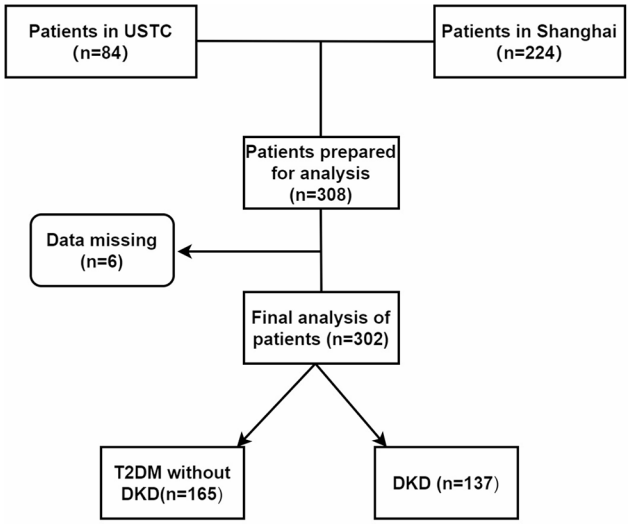

Fig. 1 Study flow chart

one. Following analysis, we used the values resulting in the highest specificity and sensitivity to identify outliers.

Results

Study participants

Initially, 308 patients were enrolled in the study, but due to data missing in 6 cases, the final analysis included 302 T2DM patients, comprising 165 patients without Diabetic Kidney Disease (DKD) and 137 patients with DKD (Fig. 1). The demographic data of the participants are presented in Table 1. Among the enrolled T2DM patients, there were more males than females, with an overall average age of 60.215 years. The proportion of patients with hypertension was significantly higher in those with DKD compared to those without. Additionally, patients with DKD were significantly older than those without DKD. No significant differences were observed in height, weight, or BMI between the DKD and non-DKD groups.

Table 1 Characteristics of the patients with T2DM with and without DKD

Variables	Total	T2DM without DKD	DKD	*P*-value
No.	302	165	137	
Age (years)	60.215 ± 12.520	58.503 ± 12.647	62.277 ± 12.093	0.009
Gender				0.204
male	201 (66.556%)	115 (69.697%)	86 (62.774%)	
female	101 (33.444%)	50 (30.303%)	51 (37.226%)	
Height (cm)	165.258 ± 8.539	165.699 ± 8.715	164.726 ± 8.323	0.325
Weight (kg)	68.932 ± 11.997	69.152 ± 12.088	68.667 ± 11.926	0.727
BMI (kg/m^2)	25.119 ± 3.764	25.115 ± 3.517	25.300 ± 4.052	0.672
Hb (g/L)	135.142 ± 19.344	140.097 ± 17.349	129.175 ± 19.990	< 0.001
HbA1C (%)	9.304 ± 2.276	9.375 ± 2.328	9.218 ± 2.218	0.552
UALB (mg/L)	136.074 ± 406.947	15.120 ± 8.977	281.749 ± 572.102	< 0.001
UCr (μmol/L)	9507.964 ± 5579.446	11127.564 ± 5387.009	7557.350 ± 5185.425	< 0.001
UALB/UCr (mg/g)	195.090 ± 727.107	13.455 ± 6.897	413.848 ± 1040.102	< 0.001
TC (mmol/L)	4.604 ± 1.260	4.610 ± 1.180	4.597 ± 1.355	0.934
TG (mmol/L)	1.920 ± 1.853	1.928 ± 2.105	1.910 ± 1.503	0.932
HDL (mmol/L)	1.172 ± 0.309	1.177 ± 0.301	1.166 ± 0.320	0.762
LDL (mmol/L)	3.076 ± 0.937	3.100 ± 0.900	3.046 ± 0.982	0.619
SCr (μmol/L)	74.705 ± 46.115	62.648 ± 16.922	89.226 ± 63.028	< 0.001
BUN (mmol/L)	6.280 ± 2.747	5.399 ± 1.498	7.341 ± 3.452	< 0.001
SUA (μmol/L)	327.173 ± 97.331	302.464 ± 87.617	356.931 ± 100.383	< 0.001
BG (mmol/L)	9.261 ± 4.844	8.880 ± 4.283	9.720 ± 5.425	0.134
ALB (g/L)	38.264 ± 12.466	38.839 ± 11.113	37.572 ± 13.934	0.380
eGFR	106.894 ± 70.760	117.830 ± 84.660	93.723 ± 46.032	0.003
HBP				< 0.001
no	123 (40.728%)	85 (51.515%)	38 (27.737%)	
yes	179 (59.272%)	80 (48.485%)	99 (72.263%)	
Grading of KDIGO				
II			57 (41.606%)	
III			62 (45.255%)	
IV			14 (10.219%)	
V			4 (2.920%)	

Table 2 Association between each variable and DKD

Variables	Statistics	DKD OR/β (95% CI)	*P*-value
Gender			0.205
male	201 (66.556%)	1.0	
female	101 (33.444%)	1.364 (0.844, 2.204)	
Age (years)	60.215 ± 12.520	1.025 (1.006, 1.045) 0.00991	0.009
Height (cm)	165.258 ± 8.539	0.987 (0.961, 1.013)	0.324
Weight (kg)	68.932 ± 11.997	0.997 (0.978, 1.016)	0.726
BMI (kg/m^2)	25.199 ± 3.764	1.013 (0.954, 1.076)	0.671
HBP			< 0.001
no	123 (40.728%)	1.0	
yes	179 (59.272%)	2.768 (1.708, 4.486)	
Hb (g/L)	135.142 ± 19.344	0.968 (0.955, 0.981)	< 0.001
HbA1C (%)	9.304 ± 2.276	0.970 (0.878, 1.072)	0.551
UALB (mg/L)	136.074 ± 406.947	1.107 (1.077, 1.139)	< 0.001
UCr (μmol/L)	9507.964 ± 5579.446	1.000 (1.000, 1.000)	< 0.001
UALB/UCr (mg/g)	195.090 ± 727.107	1.211 (1.153, 1.271)	< 0.001
TC (mmol/L)	4.604 ± 1.260	0.992 (0.829, 1.188)	0.934
TG (mmol/L)	1.920 ± 1.853	0.995 (0.880, 1.125)	0.932
HDL (mmol/L)	1.172 ± 0.309	0.892 (0.427, 1.862)	0.761
LDL (mmol/L)	3.076 ± 0.937	0.940 (0.737, 1.199)	0.618
SCr (μmol/L)	74.705 ± 46.115	1.029 (1.017, 1.040)	< 0.001
BUN (mmol/L)	6.280 ± 2.747	1.430 (1.262, 1.620)	< 0.001
SUA (μmol/L)	327.173 ± 97.331	1.006 (1.004, 1.009)	< 0.001
BG (mmol/L)	9.261 ± 4.844	1.037 (0.989, 1.087)	0.137
ALB (g/L)	38.264 ± 12.466	0.991 (0.971, 1.012)	0.392
eGFR	106.894 ± 70.760	0.988 (0.981, 0.994)	< 0.001

Comparison of blood and urine indicators between patients with and without DKD

Table 1 summarizes the comparison of blood and urine parameters between patients with and without DKD. Patients with DKD exhibited higher levels of UALB, UALB/UCr, SCr, SUA, and BUN. Conversely, patients with DKD had significantly lower levels of Hb, UCr, and eGFR compared to the non-DKD group.

Relationship between UCr and DKD

Table 2 demonstrates the relationships between DKD and several variables. Among these variables, UCr levels were closely associated with DKD. Table 3 presents these relationships further, based on multivariate analysis. Specifically, multivariate analysis indicated a strong association between UCr levels and DKD (β = 0.999; 95% CI: 0.998–0.999; $P < 0.001$). After adjusting for confounding factors such as gender, age, hypertension history, height, weight, and BMI, the results remained consistent, confirming that UCr levels are a risk factor for DKD (β = 0.989; 95% CI: 0.985–0.992; $P < 0.001$). The diagnostic value of UCr for DKD patients (ROC curve) is illustrated in Fig. 1. Our findings indicate that UCr levels performed best in diagnosis, with an AUC value of 0.724, specificity of 0.787, and sensitivity of 0.576 (Fig. 2).

A nonlinear relationship was detected between UCr levels and the incidence of DKD (β = 0.999, 95% CI: 0.998–0.999) as well as with KDIGO grading (OR = -0.003, 95% CI: -0.005 to -0.001). When UCr is below the inflection point of 17,421 μmol/L, the UCr level is negatively correlated with the incidence of DKD. However, when UCr is equal to or greater than 17,421 μmol/L, the predicted dose-response curve shows a positive correlation between UCr levels and the incidence of DKD (Table 4; Fig. 3). Similarly, regarding DKD grading, when UCr is below the inflection point of 4,616 μmol/L, the UCr level negatively correlates with KDIGO grading. Conversely, when UCr is equal to or greater than 4,616 μmol/L, UCr levels positively correlate with KDIGO grading (Table 5; Fig. 4).

Discussion

DKD remains one of the most common and concerning complications of T2DM, posing significant challenges to patient management and quality of life [9, 10]. The findings of this study highlight the potential importance of UCr as an early biomarker for the detection and assessment of DKD risk. Our results demonstrate a significant association between UCr levels and the occurrence and severity of DKD, emphasizing its clinical relevance in routine diabetes care.

We observed a non-linear relationship between UCr levels and DKD, suggesting that UCr may serve as an early alert signal for renal dysfunction in patients with T2DM. Specifically, the likelihood of developing DKD seems to decrease when UCr levels are below the threshold of 17,421 μmol/L, indicating that UCr may reflect the compensatory function of the kidneys. However, when UCr levels exceed this threshold, there is a positive correlation with DKD progression, suggesting that increased creatinine excretion may indicate potential tubular dysfunction and renal stress. This finding is particularly important, as early intervention is crucial for slowing the progression of kidney damage and improving patient outcomes.

Table 3 Multivariate regression for effect of UCr levels on DKD

Variable	Non-adjusted		Model I		Model II	
UCr	β(95% CI)	P-value	β(95% CI)	P-value	β(95% CI)	P-value
	0.999(0.998, 0.999)	< 0.001	0.999 (0.987, 0.996)	< 0.001	0.989 (0.985, 0.992)	< 0.001

Model I adjusted for age and gender. Model II adjusted for age, gender, height, weight, BMI and history of hypertension. CI, confidence interval

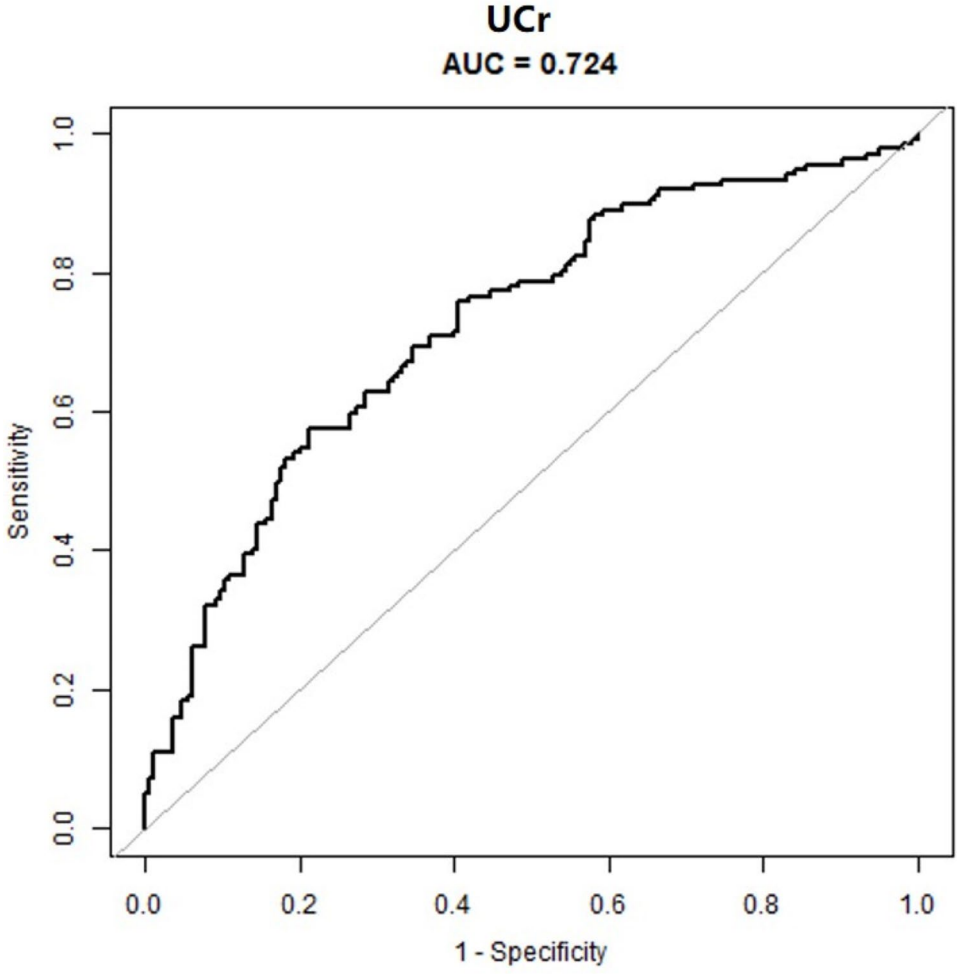

Fig. 2 Diagnostic value of UCr levels were evaluated using ROC analysis when patients with DKD

Table 4 The threshold effect of UCr levels on incidence rate of DKD

	β(95% CI)	*P*-value
UCr<17,421 μmol/L	0.999 (0.998, 0.999)	< 0.001
UCr ≥ 17421μmol/L	1.002 (1.000, 1.004)	0.239

Adjusted for age, gender, height, weight, BMI and history of hypertension. CI, confidence interval

Butt et al. emphasized the importance of elevated creatinine levels as a marker of kidney disease progression in diabetic patients, as well as its association with other kidney function markers such as blood urea nitrogen and glomerular filtration rate [11]. Their research supports the significance of urinary creatinine levels as a critical indicator for diagnosing and monitoring DKD, aligning with the necessity for comprehensive metabolic assessments in the management of diabetic patients. Additionally, Zhou et al. explored the application of the urine C-peptide creatinine ratio in assessing β-cell function in T2DM patients under varying kidney function conditions [12]. Although this study did not specifically target DKD, it underscored the role of urinary creatinine in evaluating diabetes-related complications, highlighting the broader relevance of UCr levels in diabetes management.

Furthermore, the statistical association between UCr and DKD underscores its potential value as a screening tool. Given that UCr measurement is relatively simple and non-invasive, regular UCr assessments could enable healthcare providers to identify high-risk patients earlier. Early identification of patients who may benefit from interventions, such as diabetes control, lifestyle modifications, or pharmacotherapy, could mitigate or delay the onset of severe renal complications. While UACR and eGFR are established biomarkers for DKD, our findings highlight the potential complementary role of UCr in clinical practice. UACR primarily reflects glomerular filtration, while eGFR estimates overall kidney function. In contrast, our data suggest that UCr provides additional information, particularly reflecting tubular function, revealing a non-linear relationship with DKD incidence and progression not fully captured by UACR or eGFR alone. The identification of UCr inflection points may

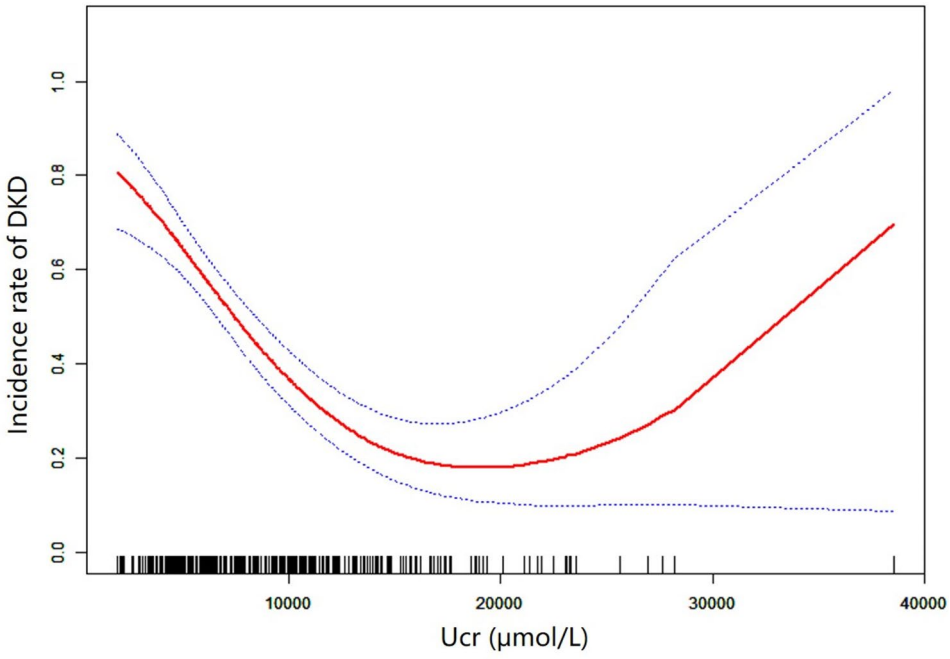

Fig. 3 Association of UCr levels with incidence rate of DKD
Adjusted data for incidence rate of DKD plotted against UCr levels with a curve indicating the shaped relationship between UCr levels and incidence rate. A threshold UCr of 17,421 μmol/L existed for regulation of UCr. This figure illustrates the non-linear relationship between UCr levels and the incidence rate of DKD. A two-segment linear regression model was used to identify an inflection point at 17,421 μmol/L. Below this threshold, UCr levels show a negative correlation with DKD incidence; above this threshold, a positive correlation is observed. This suggests a potential regulatory role for UCr in DKD development

Table 5 The threshold effect of serum uric acid levels on grading of KDIGO assessments

	β(95% CI)	*P*-value
UCr<4616μmol/L	-0.003 (-0.005, -0.001)	0.005
UCr<4616μmol/L	0.000 (0.000, 0.000)	0.270

Adjusted for age, gender, height, weight, BMI and history of hypertension. CI, confidence interval

enhance early detection of DKD, enabling more timely interventions. A combined approach, using UCr in conjunction with UACR and eGFR, might lead to a more accurate risk stratification and more tailored management strategies. Future studies are needed to evaluate the clinical utility and cost-effectiveness of incorporating UCr into routine DKD monitoring.

The implications of this study extend to clinical management strategies for T2DM patients. Current guidelines typically emphasize the importance of monitoring kidney function through eGFR and the UALB/UCr [13, 14]. However, as more evidence supports the role of UCr, incorporating UCr assessment into existing monitoring protocols may be prudent [15, 16]. Doing so could enhance the sensitivity of early DKD detection, facilitating more timely and targeted therapeutic interventions. These thresholds suggest that regular monitoring of UCr levels in individuals with T2DM could facilitate earlier detection of those at higher risk of developing DKD. Patients whose UCr levels consistently exceed the identified thresholds might benefit from more frequent monitoring, earlier nephrology referral, and the proactive implementation of DKD preventative strategies, such as optimized glycemic control and blood pressure management. Furthermore, the observed non-linear relationship between UCr levels and DKD severity suggests that treatment strategies could potentially be tailored based on a patient's UCr level relative to these thresholds. However, it is crucial to acknowledge that these findings require validation in larger, prospective studies before they can be confidently incorporated into routine clinical practice. Future research should focus on evaluating the predictive performance of these thresholds in diverse populations and determining the optimal strategies for their clinical application. In recent advancements in biomarker research, the role of urinary Smad1 has emerged as a promising indicator for predicting the onset of mesangial matrix expansion in diabetic nephropathy [17]. This study highlights the significance of urinary Smad1 as a novel biomarker that may serve as an early warning sign for changes in kidney structure associated with DKD.

Our multivariate model adjusted for age, gender, BMI, and hypertension, several unadjusted factors may influence the observed relationship. For instance, the use of ACE inhibitors or diuretics could impact urinary creatinine excretion and confound the association between

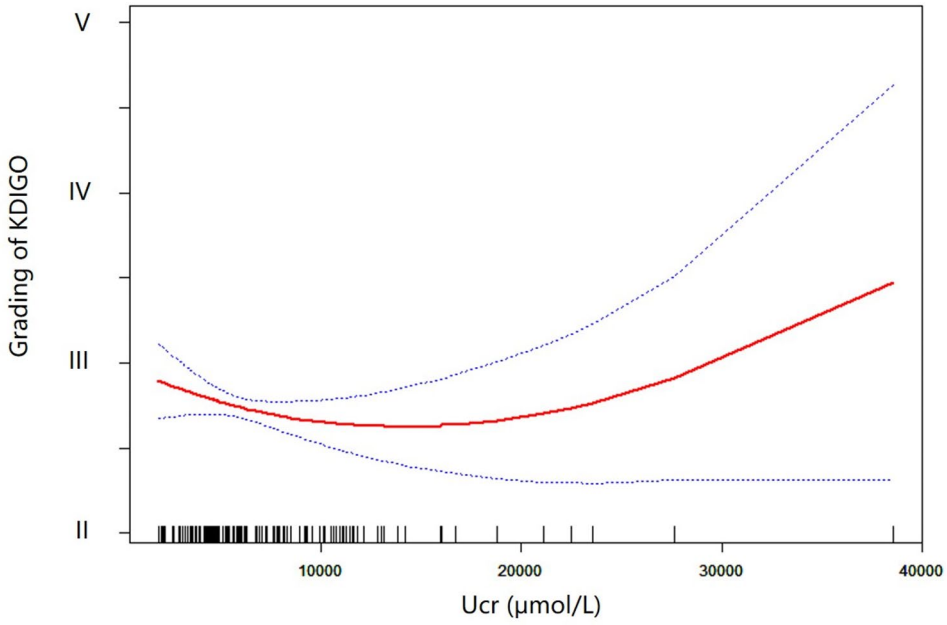

Fig. 4 Association of UCr levels with grading of KDIGO
The nonlinear relationship between UCr levels and grading of KDIGO was observed, and a threshold UCr of 4616 μmol/L existed for regulation of UCr. This figure shows the non-linear relationship between UCr levels and the grading of CKD according to the KDIGO classification. A two-segment linear regression model revealed an inflection point at 4616 μmol/L. Below this threshold, UCr levels exhibit a negative correlation with KDIGO grading; above this threshold, a positive correlation is observed. This indicates a potential threshold effect of UCr on DKD progression

UCr and DKD. Furthermore, longer duration of diabetes is known to increase DKD risk, and the presence of comorbidities such as cardiovascular disease could also influence kidney function. Although we did not fully adjust for these factors, we believe that our large sample size and rigorous methodology mitigate the potential for significant confounding bias. However, future research should consider more comprehensive data collection on medication use, diabetes duration, and the prevalence of various comorbidities to provide a more nuanced understanding.

In discussing the treatment and management strategies for DKD, it is important to highlight the renoprotective effects of SGLT2 inhibitors, incretin-related drugs such as GLP-1 receptor agonists, and mineralocorticoid receptor antagonists (MRA). These drugs have been demonstrated in several clinical studies to slow the progression of DKD. Firstly, GLP-1 receptor agonists have shown protective effects on the glomerular endothelium damaged by diabetes, although this effect might be inhibited by the activation of PKCβ [18]. Additionally, incretin-based therapy is widely recognized for its benefits in preventing vascular complications associated with diabetes [19]. Secondly, SGLT2 inhibitors not only alleviate renal burden by lowering blood glucose levels but also provide renal protection by reducing intraglomerular pressure and mitigating inflammatory pathways [20]. Moreover, MRAs such as finerenone have shown efficacy in improving renal outcomes in diabetic patients with low eGFR [21]. Overall, existing and emerging therapeutic strategies confer renal protection through various mechanisms, and an optimal combination of these medications might enhance therapeutic benefits for high-risk patients [22].

While this study provides important insights, further research is needed to validate the predictive value of UCr across different populations and stages of DKD. Longitudinal studies could offer greater understanding of the fluctuations in UCr levels as renal function changes, potentially revealing patterns that could enhance predictive capabilities. Additionally, exploring the biochemical mechanisms associated with UCr and DKD may provide valuable information for developing targeted therapies. We acknowledge the limitations inherent in a retrospective study design. The potential for unmeasured confounders and the possibility of selection bias are limitations that could affect the generalizability of our findings. To mitigate these limitations and strengthen the conclusions, we plan to conduct a prospective cohort study to validate our findings in an independent population. This prospective study will allow for more rigorous control of confounding variables and provide more robust evidence for the clinical utility of UCr in early DKD detection.

In conclusion, this study reinforces the position of UCr as a promising biomarker for the early detection and management of DKD in T2DM patients. As the medical community continues to seek more effective monitoring strategies and interventions to improve renal outcomes,

UCr may play a pivotal role in clinical practice, enhancing the quality of patient care and health outcomes in the diabetic population. By prioritizing UCr assessment, clinicians may increase opportunities to preserve renal function and improve the quality of life for patients at risk for DKD.

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Author contributions
Huihong Cao and Li Song contributed equally to this work. H.C.G., H.H.C. and L.S. wrote the main manuscript text and X.J.W prepared Fig. 1, 2, 3 and 4. All authors reviewed the manuscript.

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Data availability
The data that support the findings of this study are available from USTC, but restrictions apply to the availability of these data, which were used under licence for the current study and so are not publicly available. The data are, however, available from the authors upon reasonable request and with the permission of USTC.

Declarations

Ethical approval
The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of USTC (2024-RE-426).

Consent to Publish
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. All authors agreed to submit this version.

Competing interests
The authors declare no competing interests.

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