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Impact of cardiovascular-kidney-metabolic (CKM) syndrome multistaging on all-cause and cardiovascular mortality in type 2 diabetes: a retrospective cohort study

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Research Article

Keywords: Cardiovascular-kidney-metabolic syndrome, All-cause mortality, Diabetes, Cardiovascular diseases, causal directed acyclic graph

Posted Date: July 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9843442/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Cardiovascular-kidney-metabolic (CKM) syndrome, introduced by the American Heart Association in 2023, conceptualizes the pathophysiological interplay among cardiovascular disease, chronic kidney disease, and metabolic disorders. Type 2 diabetes (T2D) is a key component, placing individuals at high risk for progression within this framework. However, evidence quantifying the mortality risk across CKM stages in patients with T2D remains limited.

Methods

In this retrospective cohort study, 21,918 adults with T2D from a tertiary hospital in China were included. Directed acyclic graphs (DAGs) are used to guide covariate selection for confounding control. The associations between CKM stages and risks of all-cause and cardiovascular mortality were assessed using Cox proportional hazards models. Subgroup and mediation analyses were performed to further analyze the interactions among these factors. Robustness was evaluated by several sensitivity analyses, including overlap weighting and competing risk models.

Results

Over a median follow-up of 4.2 years, a total of 3,019 deaths occurred. The all-cause mortality increased progressively with advancing CKM stages, from 5.11% at stage 2 to 17.36% at stage 4. Compared with CKM Stage 2, the fully adjusted hazard ratios (HRs) for all-cause mortality were 1.61 (95% CI: 1.36–1.90) for Stage 3 and 1.93 (95% CI: 1.64–2.28) for Stage 4. For cardiovascular mortality, the corresponding fully adjusted HRs were 1.79 (95% CI: 1.32–2.42) for Stage 3 and 2.72 (95% CI: 2.02–3.67) for Stage 4. Mediation analysis showed that Systemic Immune-Inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and Neutrophil-to-Lymphocyte Ratio (NLR) accounted for 10.29%, 13.80%, and 7.67% of the association between CKM stage and all-cause mortality, respectively. These associations remained consistent across sensitivity analyses.

Conclusions

This study provides validated evidence that higher CKM syndrome stages are independently associated with a graded increase in all-cause and cardiovascular mortality among adults with T2D. These findings highlight the need for stage-tailored management strategies to mitigate mortality risk.

Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome, a novel defined health disorder introduced by the American Heart Association (AHA) in 2023, conceptualizes the intricate pathophysiological interplay among cardiovascular disease (CVD), chronic kidney disease (CKD), and metabolic disorders[1]. This syndrome represents a progressive stage, classifying individuals from Stage 0 (no risk factors) to Stage 4 (established CVD). CKM syndrome is a substantial and growing burden on global public health, with its advanced stages being strongly associated with increased risks of all-cause and cardiovascular mortality[2]. Its key components are each significant drivers of worldwide morbidity, mortality, and healthcare costs, both individually and synergistically within the CKM [3,4].

T2D is a core metabolic disorder of CKM. By definition, individuals with T2D are classified at least at CKM Stage 2, indicating the presence of key metabolic risk factors. This population faces a markedly elevated risk of progressing to advanced CKM stages, developing CKD, CVD, or both [5]. For instance, diabetic nephropathy (DKD) accounts for nearly half of end-stage renal

diseases, and renal failure is a major driver of death in diabetic patients[6]. The combined effects of these multiple diseases result in a significantly higher mortality rate for diabetic patients when they have these comorbidities compared to when they have any one disease alone[7]. The unique risk profile and pathophysiology in population with T2D warrant more investigation for refining prognostic stratification. Despite the clear clinical rationale, population-based evidence quantifying the mortality risk across the CKM stages remains limited, particularly within the high-risk cohort of individuals with pre-existing T2D.

To fill this gap, this article explores the association between CKM syndrome stages and all-cause and cardiovascular mortality risk in diabetic patients. Understanding the differences in mortality risk among different CKM stages in this high-risk population may provide valuable clinical insights for early intervention and improved disease management strategies.

Methods

Study population

This study was a retrospective cohort study of patients with diabetes hospitalized at the Second Affiliated Hospital of Wenzhou Medical University in Zhejiang Province, China, from January 1, 2010, to December 31, 2019. Data were obtained from the inpatient electronic medical record system and the China Death Registration Information System. The cohort participants were followed up until death or December 31, 2019, with the first admission date as the baseline. This study strictly adhered to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. After excluding participants younger than 18 years, those with a history of cancer at baseline, and and those with missing data for key variables (creatinine [Cr], total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], systolic blood pressure [SBP], and smoking status), the final analysis included 21,918 participants (Fig. 1).

This retrospective cohort study was reviewed and approved by the Institutional Review Board (IRB) of the Second Affiliated Hospital of Wenzhou Medical University (Approval No.: L-2020-21). The requirement for obtaining individual written informed consent was waived due to the retrospective nature of the study.

Data collection

All patients' baseline data were obtained from the hospital's electronic medical record (EMR) system. The source data included the patient's front-sheet, admission records, first progress notes, operative records, laboratory reports, imaging reports, pathology reports, discharge summary, etc. Clinical physicians conducted face-to-face interviews using a structured questionnaire to collect basic demographic and lifestyle information of the patients, including age, sex, height, weight, alcohol history, smoking history, family history, and medication use. Antihypertensive therapy and antidiabetic therapy were defined based on use of antihypertensive agents and glucose-lowering medications, respectively. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2). White blood cell (WBC), blood platelet (PLT), hemoglobin (Hb) were measured using the Mindray BC-5390 Auto Hematology Analyzer. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides (TG), TC, and HDL-C were determined using a Siemens ADVIA 2400 Chemistry Analyzer. Thyroid-stimulatinghormone (TSH) were measured using the ADVIA Centaur XPT.

Definition of CKM syndrome stages

CKM syndrome was classified into five CKM stages (0–4) according to the AHA Presidential Advisory[1]. Stage 0 was defined as the absence of CKM risk factors, including normal BMI and waist circumference, normoglycemia, normotension, a normal lipid profile, and no evidence of CKD or subclinical or clinical CVD. Stage 1 included individuals with early abnormalities, such as excess adiposity (BMI ≥ 23 kg/m^2), abdominal obesity (waist circumference ≥ 80 cm in women or ≥ 90 cm in men), or impaired glucose regulation (fasting blood glucose 5.6–6.9 mmol/L), but without additional metabolic risk factors, CKD,

or CVD. Stage 2 was characterized by the presence of one or more metabolic risk factors (hypertriglyceridemia ≥ 1.5 mmol/L, dyslipidemia, hypertension, metabolic syndrome, or diabetes), moderate to high-risk CKD, or both. Stage 3 referred to subclinical CVD and included individuals at high predicted risk of CVD (Framingham risk score ≥ 21.5/21.6 in female/male) [8]or with very high-risk of CKD (eGFR < 30 ml/min/1.73 m2). Finally, stage 4 involves individuals with clinical CVD. However, because all participants in this cohort had diabetes at baseline, the present study exclusively included individuals with CKM syndrome stages 2–4.

Definition of outcomes

The primary outcome was all-cause mortality, defined as death from any cause during the follow-up period. The secondary outcome was CVD mortality, defined as death with an underlying cause coded as CVD according to the 10th Revision of the International Classification of Diseases (codes I00–I99). Mortality information was obtained from China's Population Death Registration Information System[9,10]. The participants were followed from baseline until the occurrence of outcome, or December 31, 2019.

Statistical analysis

Baseline characteristics across CKM syndrome stages were compared using analysis of the Kruskal–Wallis test, or the chi-square test. The association between CKM syndrome stages 2–4 and the risk of all-cause and CVD mortality was assessed using Cox proportional hazards regression models, with HRs and 95% confidence intervals reported. CKM stage was also treated as a continuous variable to test for linear trends. Causal graphs were constructed using directed acyclic graphs, and confounding factors were screened (Figure S1). This is an intuitive and rigorous tool for communicating causal questions in clinical and epidemiological studies, thereby informing modeling choices in a systematic and transparent manner[11,12]. Age, gender, drinking, smoking, ALT, AST, TSH, WBC, HB, PLT, Antihypertensive therapy, and antidiabetic therapy were considered potential confounding factors and included in the final model 3. Model 1 was unadjusted; Model 2 was adjusted for age and gender. Subgroup analyses were conducted by age (< 60 vs. ≥60 years), sex (male vs. female), smoking status (yes vs. no), drinking status (yes vs. no). Interactions were assessed using likelihood ratio tests. A mediation analysis was also conducted to aessess the role of inflammatory markers, including SII, SIRI, and NLR, in the association between CKM stage and all-cause mortality. Sensitivity analyses included excluding participants who died within two years of follow-up or who had follow-up < 2 years, and calculating E-values to assess the potential impact of unmeasured confounding[13]. In addition, we repeated the main analysis using a propensity score (PS)-based statistical method—overlap weighting (OW), which aims to reduce confounding bias by assigning different weights to individuals, thereby improving the accuracy of causal inferences[14]. Considering the competing risks between non-CVD mortality and CVD mortality, we also used the Fine-Gray model to further evaluate the relationship between CKM stage and CVD mortality. All analyses were performed using R software (version 4.2.0), and two-sided P values < 0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 21,918 participants were included in the analysis (Table 1), comprising 10,732 (49.0%) men and 11,186 (51.0%) women, with a median age of 58 (52–65) years. These participants were stratified into three groups based on their stages of CKM syndrome at baseline: Stage 2 (n = 3,445), Stage 3 (n = 9,191), and Stage 4 (n = 9,282). The median age increased progressively with advancing CKM stages, from 54 (45–61) years in Stage 2 to 69 (61–76) years in Stage 4, and the proportion of men was higher among those in the later stages. Participants in Stage 3 and Stage 4 tended to have higher values of SBP, DBP, and BMI compared with those in Stage 2. In addition, current drinking and smoking were more frequent in participants with more advanced CKM stages. The prevalence of hypertension and CVD increased sharply from Stage 2 to

Stage 4. All baseline differences among the three stages were statistically significant, as shown by standardized mean differences and P values (all < 0.001).

Table 1
Baseline characteristics of the study population according to different stages of CKM syndrome

Characteristic	CKM syndrome stages			SMD	P value
	CKM Stage 2	CKM Stage 3	CKM Stage 4		
No. of participants	3445	9191	9282		
Gender, %				0.322	< 0.001
Male	1221 (35.4)	5421 (59.0)	5180 (55.8)		
Female	2224 (64.6)	3770 (41.0)	4102 (44.2)		
Age, years	54.00 (45.00, 61.00)	66.00 (59.00, 74.00)	69.00 (61.00, 76.00)	0.917	< 0.001
DBP, mmHg	78.00 (70.00, 85.00)	80.00 (72.00, 88.00)	80.00 (72.00, 89.00)	0.176	< 0.001
SBP, mmHg	128.00 (118.00, 140.00)	148.00 (133.50, 162.00)	149.00 (133.00, 164.00)	0.704	< 0.001
BMI, kg/m2	23.88 (22.04, 26.03)	24.14 (22.37, 26.12)	24.41 (22.67, 26.22)	0.075	< 0.001
ALT, U/L	22.00 (15.00, 37.00)	21.00 (15.00, 32.00)	21.00 (15.00, 31.00)	0.132	< 0.001
AST, U/L	20.00 (16.00, 30.00)	20.00 (16.00, 28.00)	21.00 (17.00, 29.00)	0.047	< 0.001
WBC, g/L	6.60 (5.39, 8.24)	6.86 (5.64, 8.53)	6.96 (5.79, 8.53)	0.064	< 0.001
PLT, $\times 10^9$/L	213.00 (169.00, 257.00)	206.00 (167.00, 252.00)	207.00 (170.00, 249.00)	0.032	0.002
HB, g/L	129.00 (117.00, 141.00)	130.00 (115.00, 141.00)	130.00 (118.00, 142.00)	0.049	< 0.001
TSH, mIU/L	1.55 (1.09, 2.11)	1.62 (1.16, 2.20)	1.61 (1.11, 2.31)	0.085	< 0.001
TG, mmol/L	1.40 (0.98, 2.05)	1.60 (1.13, 2.30)	1.55 (1.12, 2.18)	0.117	< 0.001
HDL_C, mmol/L	1.01 (0.83, 1.24)	0.97 (0.81, 1.17)	0.96 (0.81, 1.15)	0.135	< 0.001
Drinking, %				0.196	< 0.001
no	3030 (88.0)	7068 (76.9)	7381 (79.5)		
yes	415 (12.0)	2123 (23.1)	1901 (20.5)		
Smoking, %				0.340	< 0.001
no	3121 (90.6)	6569 (71.5)	6647 (71.6)		
yes	324 (9.4)	2622 (28.5)	2635 (28.4)		
Antihypertensive therapy, %				0.482	< 0.001

Data are presented as median (interquartile range), or n (%).

BMI, body mass index; DBP, diastolic blood pressure; SBP, Systolic Blood Pressure; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; WBC, white blood cell; PLT, blood platelet; HB, Hemoglobin; TSH, thyroid-stimulatinghormone; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Characteristic	CKM syndrome stages			SMD	P value
	CKM Stage 2	CKM Stage 3	CKM Stage 4		
no	2891 (83.9)	5026 (54.7)	4834 (52.1)		
yes	554 (16.1)	4165 (45.3)	4448 (47.9)		
Antidiabetic therapy, %				0.105	< 0.001
no	1808 (52.5)	4452 (48.4)	5226 (56.3)		
yes yes	1637 (47.5)	4739 (51.6)	4056 (43.7)		
History of CVD, %				0.909	< 0.001
no	3445 (100.0)	9191 (100.0)	4811 (51.8)		
yes	0 (0)	0 (0)	4,471 (48.2)		
History of hypertension, %				0.716	< 0.001
no	2272 (66.0)	2748 (29.9)	1700 (18.3)		
yes	1173 (34.0)	6443 (70.1)	7582 (81.7)		
Data are presented as median (interquartile range), or n (%).					
BMI, body mass index; DBP, diastolic blood pressure; SBP, Systolic Blood Pressure; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; WBC, white blood cell; PLT, blood platelet; HB, Hemoglobin; TSH, thyroid-stimulatinghormone; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.					

Association of CKM stages with the risk of all-cause and cardiovascular mortality

During the median follow-up period of 4.2 years, 3,019 (13.8%) of the 21,918 participants with CKM syndrome died, of whom 1188 (5.4%) died from CVD. The cumulative incidence of both all-cause and cardiovascular mortality increased progressively with advancing CKM stages. As illustrated in Fig. 2, participants in CKM Stage 4 exhibited the highest cumulative all-cause mortality rate, reaching 37.36% (95% CI: 30.68–43.39%) at 10 years, whereas those in Stage 2 had the lowest mortality rate of 12.27% (95% CI: 8.25–16.12%). A similar pattern was observed for cardiovascular mortality: the 10-year cumulative mortality in Stage 4 reached 15.84% (95% CI: 14.20-17.45), with progressively lower risks observed in Stages 3 and 2. Log-rank tests indicated significant differences in both all-cause and cardiovascular mortality across the three CKM stages ($P < 0.0001$).

The associations between CKM stages and all-cause mortality are displayed in Table 2. In the unadjusted model (Model 1), compared with participants in CKM Stage 2, the HRs were 2.78 (95% CI: 2.37–3.26) for Stage 3 and 3.51 (95% CI: 3.01–4.10) for Stage 4 (P for trend < 0.001), indicating a clear stepwise increase in mortality risk with advancing CKM stages. After further adjustment for gender and age (Model 2), the risk estimates were moderately attenuated but the overall trend remained significant. The adjusted HRs were 1.63 (95% CI: 1.38–1.92) for Stage 3 and 1.91 (95% CI: 1.63–2.26) for Stage 4 (P for trend < 0.001). In the fully adjusted Model 3, the HRs were 1.61 (95% CI: 1.36–1.90) for Stage 3 and 1.93 (95% CI: 1.64–2.28) for Stage 4. The positive association between higher CKM stages and elevated mortality risk remained statistically significant after full adjustment (P for trend < 0.001).

Table 2
Associations between different stages of CKM syndrome with the risk of all-cause mortality and CVD mortality

	Events/Total	Model 1		Model 2		Model 3	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality	3019/21918						
CKM Stage 2	176/3445	1.00 (ref)		1.00 (ref)		1.00 (ref)	
CKM Stage 3	1232/9191	2.78 (2.37, 3.26)	< 0.001	1.63 (1.38, 1.92)	< 0.001	1.61 (1.36, 1.90)	< 0.001
CKM Stage 4	1611/9282	3.51 (3.01, 4.1)	< 0.001	1.91 (1.63, 2.26)	< 0.001	1.93 (1.64, 2.28)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
CVD mortality	1188/21918						
CKM Stage 2	51/3445	1.00 (ref)		1.00 (ref)		1.00 (ref)	
CKM Stage 3	424/9191	3.29 (2.46, 4.4)	< 0.001	1.85 (1.37, 2.5)	< 0.001	1.79 (1.32, 2.42)	< 0.001
CKM Stage 4	713/9282	5.36 (4.03, 7.12)	< 0.001	2.77 (2.06, 3.72)	< 0.001	2.72 (2.02, 3.67)	< 0.001
P for trend			< 0.001		< 0.001		< 0.001
Model 1: Unadjusted.							
Model 2: Adjusted for gender and age.							
Model 3: Adjusted for gender, age, smoking, drinking, ALT, AST, TSH, WBC, Hb, PLT, antidiabetic therapy, antihypertensive therapy.							

Similarly, higher CKM stages were significantly associated with increased cardiovascular mortality. In Model 1, compared with CKM Stage 2, the unadjusted HRs for cardiovascular mortality were 3.29 (95% CI: 2.46–4.40) for Stage 3 and 5.36 (95% CI: 4.03–7.12) for Stage 4 (P for trend < 0.001). After adjustment for age and gender (Model 2), the HRs decreased to 1.85 (95% CI: 1.37–2.50) for Stage 3 and 2.77 (95% CI: 2.06–3.72) for Stage 4 (P for trend < 0.001). These associations remained essentially unchanged in the fully adjusted Model 3, with HRs of 1.79 (95% CI: 1.32–2.42) for Stage 3 and 2.72 (95% CI: 2.02–3.67) for Stage 4 (P for trend < 0.001).

Subgroup analyses

Subgroup analyses were performed to assess potential effect modification by age (< 60 vs. ≥60 years), sex (male vs. female), smoking status (yes vs. no), drinking status (yes vs. no), Antihypertensive therapy (yes vs. no), and antidiabetic therapy (yes vs. no) on the associations between CKM stages and mortality outcomes (Fig. 3; Figure S2). No statistically significant interactions were observed between these stratification factors and CKM stages for either all-cause or cardiovascular mortality (P for interaction > 0.05).

Mediation analyses

Mediation analysis showed that systemic inflammatory markers significantly mediated the association between the CKM stages and all-cause mortality (Table 3). After adjusting for multiple covariates, including age, smoking, drinking, ALT, AST,

TSH, Hb, antidiabetic therapy, and antihypertensive therapy, the mediation proportions were 10.29% for SII, 13.80% for SIRI, and 7.67% for NLR (all P < 0.001). Among them, SIRI exhibited the largest mediating effect. Sex-stratified analysis revealed consistently stronger mediation effects in males than in females. Specifically, the mediation proportions in males were 13.37%, 17.00%, and 10.66% for SII, SIRI, and NLR, compared with 8.55%, 11.48%, and 6.02% in females.

Table 3
Mediation analysis on the association between CKM stages and all-cause mortality

Mediator	Gender	Total effect		Indirect effect		Direct effect		Proportion mediated, %
		Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	
SII (Log)	Total	0.54 (0.42, 0.66)	< 0.001	0.04 (0.03, 0.06)	< 0.001	0.50 (0.38, 0.62)	< 0.001	10.29
	Female	0.58 (0.41, 0.75)	< 0.001	0.04 (0.03, 0.06)	< 0.001	0.52 (0.35, 0.69)	< 0.001	8.55
	Male	0.50 (0.33, 0.68)	< 0.001	0.05 (0.03, 0.07)	< 0.001	0.45 (0.27, 0.63)	< 0.001	13.37
SIRI (Log)	Total	0.56 (0.44, 0.69)	< 0.001	0.06 (0.05, 0.08)	< 0.001	0.50 (0.38, 0.62)	< 0.001	13.80
	Female	0.61 (0.44, 0.78)	< 0.001	0.05 (0.03, 0.07)	< 0.001	0.55 (0.39, 0.72)	< 0.001	11.48
	Male	0.51 (0.34, 0.69)	< 0.001	0.07 (0.05, 0.09)	< 0.001	0.44 (0.27, 0.62)	< 0.001	17.00
NLR (Log)	Total	0.57 (0.45, 0.69)	< 0.001	0.03 (0.02, 0.05)	< 0.001	0.53 (0.41, 0.65)	< 0.001	7.67
	Female	0.61 (0.44, 0.78)	< 0.001	0.03 (0.01, 0.05)	< 0.001	0.58 (0.41, 0.75)	< 0.001	6.02
	Male	0.53 (0.35, 0.70)	< 0.001	0.04 (0.02, 0.07)	< 0.001	0.48 (0.31, 0.66)	< 0.001	10.66

SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; NLR, neutrophil-to-lymphocyte ratio;

Models were adjusted for age, smoking, drinking, ALT, AST, TSH, Hb, antidiabetic therapy, antihypertensive therapy.

Sensitivity analyses

Results remained robust when individuals with less than 2 years of follow-up or those who died within 2 years of follow-up were excluded (Table S1-2). To assess the potential influence of unmeasured confounding, E-values were calculated. As shown in Table S3, the E-value for all-cause mortality was 2.60 and 3.28 respectively, which indicates that an unmeasured confounder would need to have a risk ratio of at least 2.60 and 3.28 with all-cause mortality to fully explain away the observed association between CKM stages and all-cause mortality. For cardiovascular mortality, the corresponding E-values were 2.97 and 4.89, indicating that the observed associations were unlikely to be fully explained by unmeasured confounding.

Furthermore, after applying overlap weighting to balance baseline covariates across CKM stages (Figure S2), the associations remained significant. Compared with CKM Stage 2, the HRs for all-cause mortality remained 1.72 (95% CI: 1.43–2.06) for Stage 3 and 2.05 (95% CI: 1.71–2.46) for Stage 4 (Table S4). Similarly, for cardiovascular mortality, the weighted HRs were 1.91 (95% CI: 1.37–2.66) for Stage 3 and 3.04 (95% CI: 2.20–4.20) for Stage 4 (p for trend < 0.001). In addition, competing risk analysis using the Fine-Gray model confirmed the robustness of the association between CKM

stage and cardiovascular mortality (Table S6). Compared to stage 2, the HRs for CVD mortality remained 2.70 (95% CI: 2.00, 3.64) for Stage 4.

Discussion

This large retrospective cohort study provides real-world evidence that the CKM syndrome staging system, recently proposed by the AHA, effectively stratifies mortality risk among adults with T2D. Our analysis demonstrates a strong, graded, and independent association between advanced CKM stages and increased risks of all-cause and cardiovascular mortality. Furthermore, mediation analysis revealed that systemic inflammation partially underlies this association. Our findings validate the prognostic utility of the CKM framework in a high-risk, clinically relevant population and suggest the critical importance of integrated risk assessment and management in diabetes care to mitigate the excessive burden of complications.

Globally, the burden of CKM syndrome is substantially growing, posing a significant and growing public health challenge. In 2021, the worldwide prevalence of its key components increases since 1990 by 92.0% for CKD and 277.9% for diabetes[15]. Meanwhile, CVD is the leading cause of death worldwide, accounting for an estimated 17.9 million deaths in 2019, representing nearly 32% of all global deaths[16]. At the urgent need for effective management strategies for CKM, our study demonstrates that higher CKM stages are associated with a significantly increased risk of all-cause and cardiovascular mortality among patients with T2D. This finding aligns with evidence from multiple recent large-scale epidemiological studies conducted across diverse populations[17–20]. Research involving general populations, nationwide cohorts, and specific disease groups (e.g., individuals with non-alcoholic fatty liver disease or cancer) has consistently confirmed a significant dose-response relationship and a clear risk gradient between advancing CKM stages and increased mortality, particularly from cardiovascular causes. Notably, this association may be even more pronounced in younger populations, highlighting the critical need for early intervention[19]. The markedly elevated mortality observed in our cohort of hospitalized patients with T2D compared to general population estimates.Given that T2D itself is categorized as Stage 2 within the CKM framework, this population is at the center of the interconnected cardiorenal-metabolic pathophysiological network.

The underlying mechanisms driving this mortality increase are multifaceted and synergistic, wherein the combined risk exceeds the simple sum of individual disease components. This synergy is evident by over 40% risk increase of recurrent myocardial infarction in coexisting T2D and CKD, and amplifying cardiovascular events and death[21]. The 10-year mortality risk escalates from 7.7% (T2D alone) or 11.5% (CKD alone) to 31.1% when both conditions are present[7]. Mechanistically, insulin resistance in T2D drives hyperglycemia and dyslipidemia, promoting atherosclerotic plaque formation[21,22]. In addition, metabolic disturbances associated with insulin resistance may trigger low-grade systemic inflammation, characterized by increased production of pro-inflammatory cytokines and endothelial dysfunction, which may further accelerate vascular injury. Persistent microvascular damage may also affect renal structures, leading to glomerular injury and progressive decline in kidney function[23]. Deterioration of renal function which often reflected by reduced eGFR and worsening CKM stage can further exacerbate cardiovascular risk through mechanisms such as accumulation of uremic toxins, anemia, and disturbances in mineral metabolism. These interconnected processes may ultimately contribute to the development of cardiorenal syndrome and increase the risk of mortality[24].

While systemic inflammation is a well-established driver in the pathogenesis of cardiovascular and metabolic diseases, its specific role as a mechanistic link within the novel CKM syndrome framework had been less explored. Our study extends previous findings by quantitatively establishing systemic inflammation as a significant mediator between CKM and mortality, with SIRI showing the strongest effect. This results suggests that chronic inflammation is not only a comorbid feature but also a key biological intermediary through which advanced cardiorenal-metabolic dysfunction translates into increased mortality risk [25–27]. The sex-stratified analysis further revealed that these mediating effects were generally stronger in males, highlighting potential sex differences[28]. Mechanistically, this aligns with evidence that inflammatory state can exacerbate endothelial injury, accelerate atherosclerosis and renal fibrosis, thereby amplifying cardiovascular and overall

mortality risks in patients with advanced CKM stages[25,29]. Consequently, our findings reinforce inflammation as a core component of CKM[30].

Despite its valuable insights, this study has certain limitations. First, the use of the Framingham 10-year risk score to define subclinical CVD may limit generalizability across diverse ethnicities, as this model was derived primarily from White populations and requires validation or recalibration in others[31]. Second, the single-center, hospital-based design may introduce selection bias and constrain the external validity of our findings to broader community or primary care settings. Third, despite multivariable adjustment, residual confounding due to unmeasured factors (e.g., detailed medication adherence, dietary patterns, physical activity, socioeconomic status) cannot be fully excluded. In addition, the substantial age differences across CKM stages may limit comparability between groups. To address this issue, we performed a prespecified sensitivity analysis using propensity score-based overlap weighting, which improved balance in age and other baseline characteristics. The consistent results after OW analysis support the robustness of our findings. However, residual confounding from unmeasured factors cannot be completely excluded. Finally, the retrospective observational design based on EMR data is limited in its ability to establish causality. Future prospective studies and clinical trials are needed to to what extent pragmatic, integrated management strategies guided by CKM staging can mitigate this excess mortality risk in the T2D population.

Conclusion

This large-scale study provides real-world validation that the CKM staging system effectively stratifies graded mortality risk in adults with T2D. Systemic inflammation partially mediates this association further supports the biological plausibility. Clinically, CKM staging could inform more precise, stage-targeted clinical management strategies for T2D to mitigate the excessive mortality burden in this vulnerable population.

Abbreviations

CKM Cardiovascular
kidney-metabolic
CVD Cardiovascular disease

CKD Chronic kidney disease

ALT Alanine aminotransferase

AST Aspartate aminotransferase

BMI Body mass index

T2D Type 2 diabetes

DAGs Directed acyclic graphs

SII Systemic Immune-Inflammation Index

SIRI Systemic Inflammation Response Index

NLR Neutrophil-to-Lymphocyte Ratio

HR Hazard ratios

Cr Creatinine

TC Total cholesterol

TG Triglycerides

HDL-C High-density lipoprotein cholesterol

SBP Systolic blood pressure

DBP Diastolic blood pressure

WBC White blood cell

PLT Blood platelet

Hb Hemoglobin

TSH Thyroid-stimulatinghormone

Declarations

Ethics approval and consent to participate

This study involving human data and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This retrospective cohort study was reviewed and approved by the Institutional Review Board (IRB) of the Second Affiliated Hospital of Wenzhou Medical University (Approval No.: L-2020-21). The requirement for obtaining individual written informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from Zhejiang Provincial Natural Science Foundation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding

This work was supported by grants from Zhejiang Provincial Natural Science Foundation (LQ24H260007). The funders had no role in the study design or in the collection, analysis, and interpretation of the data, writing of the report, or decision to submit the article for publication.

Author Contribution

QS, GZ and HM contributed equally to this work. QS, MY, and YF conceived the idea, designed the study, and drafted the manuscript. KL, YS, and FS supervised and coordinated the study. QS and MY coded the statistical analysis, figures, and

appendix in collaboration with CZ, XZ, QM, and DA double checked the data and results. GM, DL, and CZ obtained funding. All authors have read and approved the final manuscript.

Acknowledgement

We sincerely thank all the patients who participated in this study, as well as the medical professionals who provided support during their hospitalizations.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation

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Figures

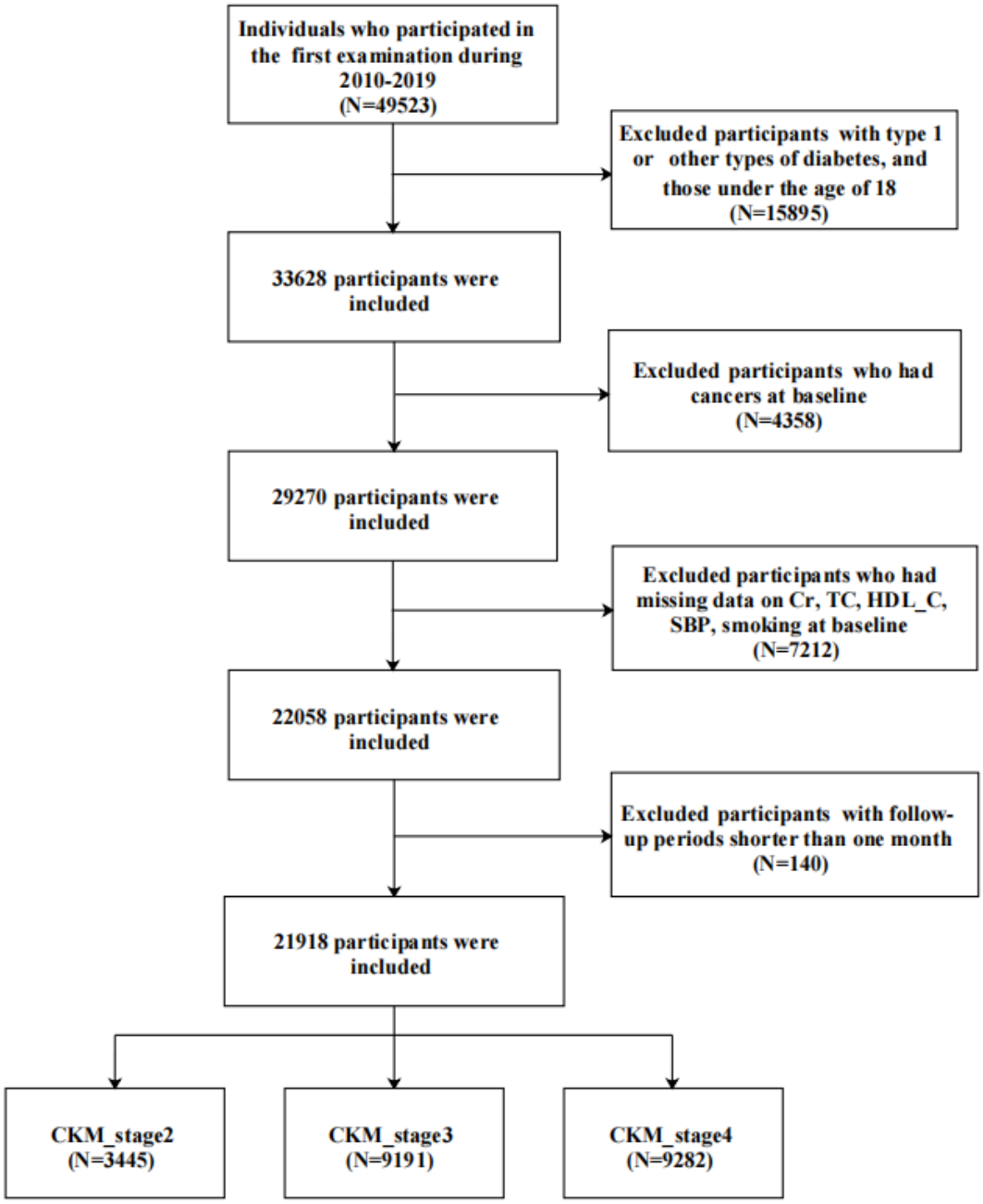


Figure 1

Flowchart of the study population.

TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; CKM, cardiovascular-kidney-metabolic; Cr, Creatinine.

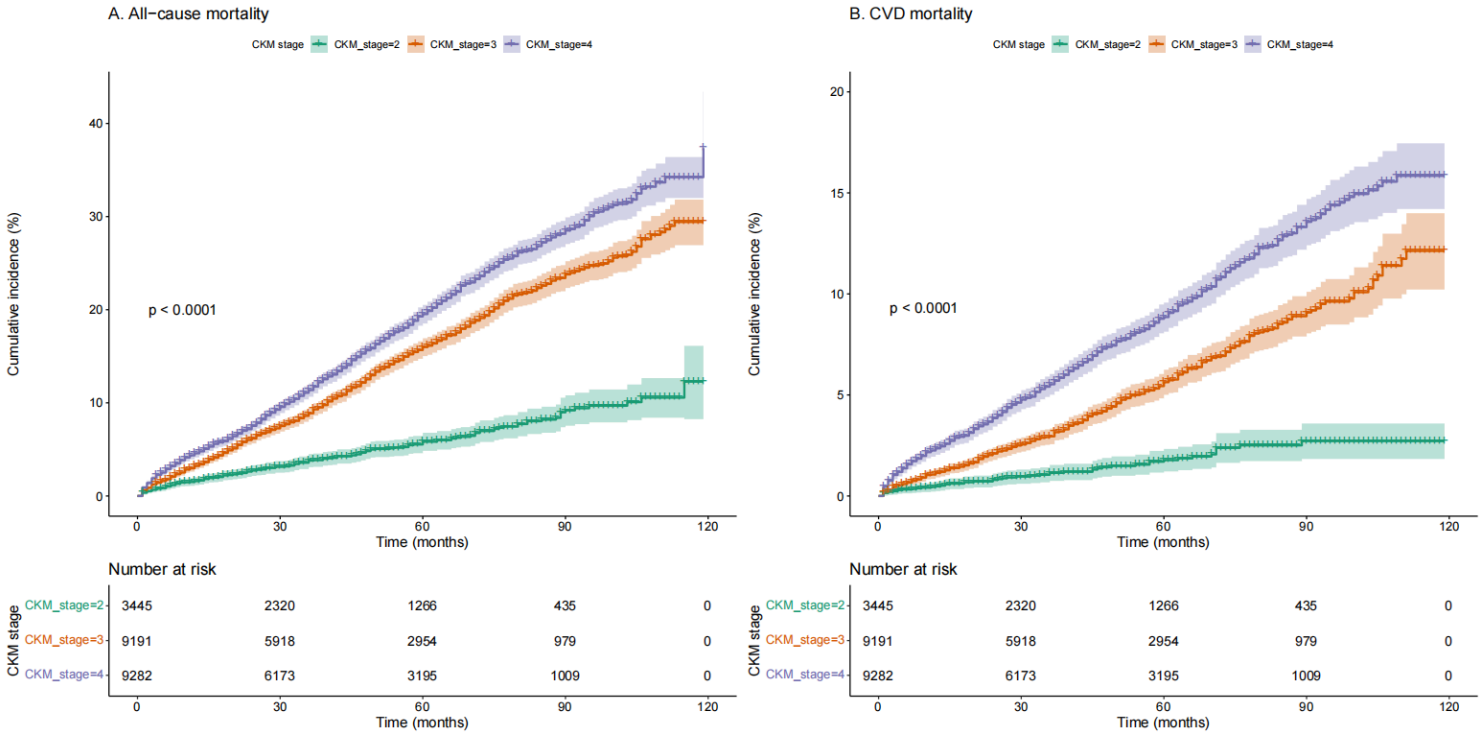


Figure 2

Cumulative incidence of all-cause and CVD mortality stratified by different stages of CKM syndrome. CVD, Cardiovascular Disease.

Subgroups	CKM Stage2(%)	CKM Stage3(%)	CKM Stage4(%)	Stage3 VS 2 HR(95% CI)	Stage4 VS 2 HR(95% CI)	P for interaction
All-cause mortality						
Age,years						0.23
<60	2420 (70.2)	2498 (27.2)	1803 (19.4)	1.69 (1.26, 2.27)	1.80 (1.31, 2.46)	
≥60	1025 (29.8)	6693 (72.8)	7479 (80.6)	1.55 (1.26, 1.92)	1.91 (1.55, 2.35)	
Gender						0.92
Male	1221 (35.4)	5421 (59.0)	5180 (55.8)	1.53 (1.14, 2.06)	1.86 (1.38, 2.50)	
Female	2224 (64.6)	3770 (41.0)	4102 (44.2)	1.66 (1.35, 2.05)	1.98 (1.62, 2.44)	
Drink						0.12
No	3030 (88.0)	7068 (76.9)	7381 (79.5)	1.63 (1.36, 1.95)	1.95 (1.63, 2.33)	
Yes	415 (12.0)	2123 (23.1)	1901 (20.5)	1.23 (0.79, 1.90)	1.51 (0.97, 2.35)	
Smoke						0.27
No	3121 (90.6)	6569 (71.5)	6647 (71.6)	1.60 (1.34, 1.92)	2.01 (1.68, 2.39)	
Yes	324 (9.4)	2622 (28.5)	2635 (28.4)	1.44 (0.81, 2.55)	1.56 (0.88, 2.78)	
Antihypertensive therapy						0.16
No	2891 (83.9)	5026 (54.7)	4834 (52.1)	1.54 (1.28, 1.85)	1.85 (1.54, 2.23)	
Yes	554 (16.1)	4165 (45.3)	4448 (47.9)	2.26 (1.44, 3.56)	2.76 (1.76, 4.33)	
Antidiabetic therapy						0.86
No	1808 (52.5)	4452 (48.4)	5226 (56.3)	1.59 (1.26, 1.99)	1.86 (1.49, 2.34)	
Yes	1637 (47.5)	4739 (51.6)	4056 (43.7)	1.61 (1.26, 2.06)	1.99 (1.56, 2.54)	

Figure 3

Forest plots of subgroup analyses for the association between CKM stages and CVD mortality. HRs were adjusted for gender, age, smoking, drinking, ALT, AST, TSH, WBC, Hb, PLT, antidiabetic therapy, antihypertensive therapy.

Supplementary Files

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- SupplementaryAppendix.docx