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Research Article

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The C-reactive protein–triglyceride–glucose index and cardiovascular–kidney–metabolic syndrome stages in adults with type 2 diabetes: a retrospective cross-sectional study

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Abstract

Background and aims: Cardiovascular‑kidney‑metabolic (CKM) syndrome arises from the intricate interplay among metabolic dysfunction, chronic kidney disease (CKD), and cardiovascular disease (CVD). The C-reactive protein‑triglyceride‑glucose index (CTI) integrates inflammation and insulin resistance; However,its stage-specific association with CKM syndrome in adults with type 2 diabetes remains unclear. We evaluated the association of CTI with CKM stages and its performance in identifying higher stages.

Methods: This retrospective cross-sectional study included 559 hospitalized adults with type 2 diabetes classified as CKM stage 2 (metabolic risk factors and/or moderate- to high-risk CKD), stage 3 (subclinical CVD or risk equivalents) or stage 4 (clinical CVD). CTI was calculated from high-sensitivity C-reactive protein (hsCRP), triglycerides and fasting plasma glucose. Multinomial logistic regression was used to estimated adjusted stage-specific associations with stage 2 as the reference. Receiver operating characteristic (ROC) analyses compared CTI, its components and clinical models; models for stages 3–4 versus 2 and stage 4 versus 2–3 underwent bootstrap correction and ten-fold cross-validation, whereas stage 3 versus 2 was assessed separately.

Results: CKM stages 2, 3 and 4 included 205, 219 and 135 patients, respectively. Each standard-deviation (SD) increase in CTI was associated with higher adjusted odds of stage 3 (odds ratio [OR] 1.43, 95% confidence interval [CI] 1.12 – 1.84) and stage 4 (OR 4.69, 95% CI 3.36 – 6.55) versus stage 2. Adding CTI to the clinical model raised the bootstrap-corrected area under the ROC curve (AUC) from 0.730 to 0.781 for stages 3 – 4 versus 2 and from 0.717 to 0.837 for stage 4 versus 2 – 3. CTI alone had an AUC of 0.749 for stage 4 versus 2 – 3 but only 0.528 (95% CI 0.473 – 0.583) for stage 3 versus 2; for stages 3 – 4 versus 2, hsCRP alone had a higher AUC than CTI (0.692 versus 0.617).

Conclusions: Higher CTI was associated with more advanced CKM stages. Models incorporating CTI had higher internally assessed AUCs, particularly for stage 4. These findings support further evaluation of CTI as a complementary marker of concurrent CKM burden; however its limited discrimination of stages 2 and 3 and its unestablished external validity constrain its clinical application.

Keywords: C-reactive protein; triglyceride-glucose index; cardiovascular-kidney-metabolic syndrome; type 2 diabetes; retrospective cross-sectional study; albuminuria

1 Introduction

Cardiovascular–kidney–metabolic (CKM) syndrome encompasses the interrelated effects of metabolic dysfunction, kidney disease and cardiovascular disease (CVD). The American Heart Association (AHA) introduced a five-stage framework in 2023 [1,2], followed by detailed diagnostic and management recommendations in the 2026 AHA/ACC/ADA/ASN guideline [3]. CKM abnormalities are common in population surveys [4]. In patients with diabetes, clinical assessment integrates glycemia, kidney function, albuminuria and established CVD [5]. Readily available biomarkers may provide complementary information on this disease burden, although inpatient measurements can be affected by acute illness and treatment.

The C-reactive protein–triglyceride–glucose index (CTI) combines C-reactive protein with the triglyceride–glucose (TyG) index. Initially evaluated for cancer prognosis [6], CTI integrates inflammatory and metabolic measurements. TyG is a surrogate of insulin resistance with imperfect diagnostic accuracy [7] and has been associated with incident heart failure [8]. High-sensitivity C-reactive protein (hsCRP) also provides prognostic information in cardiovascular populations [9]. Whether their combination offers an advantage in adults with type 2 diabetes and CKM syndrome remains uncertain.

Previous studies have associated CTI with incident CVD, advanced CKM and mortality [10–13], as well as transitions among coronary disease, diabetes and chronic kidney disease (CKD) [14]. CTI has also been evaluated in patients hospitalized with stage 4 CKM and acute decompensated heart failure [15] and in adults with diabetes and abnormal bone mineral density [16]. However, broad comparisons of advanced versus earlier CKM stages may not reflect the ability to distinguish adjacent stages in patients who already have metabolic disease. Evidence on stage-specific associations and the relative performance of CTI and its components in this setting is limited.

We examined CTI in relation to CKM stages 2–4 among hospitalized adults with type 2 diabetes. We estimated adjusted stage-specific associations and evaluated performance using receiver operating characteristic (ROC) analysis, including the stage 3-versus-2 comparison. Comparisons with hsCRP, TyG and separately modeled components assessed the performance of the fixed CTI formula. Concurrent kidney abnormality was an exploratory secondary outcome.

2 Methods

2.1 Study design and population

This retrospective cross-sectional study used hospitalization records from First People's Hospital of Huzhou with discharge dates between January 1, 2023 and March 18, 2025. Eligible patients were aged ≥18 years, had type 2 diabetes and CKM stage 2, 3 or 4, and had positive hsCRP, triglyceride and fasting plasma glucose values and complete core covariate data. All eligible records were included in the screening process. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [17].

Hospitalizations were linked by medical record number. Eligibility was assessed for each hospitalization, and the earliest eligible discharge was selected as the index admission for patients with repeated admissions. Ties were resolved by source-record order. Exposure, covariate and outcome data were obtained from the same index hospitalization.

2.2 Data collection and covariate assessment

Demographic and clinical data included age, sex, body mass index (BMI), diabetes duration, smoking and alcohol histories, systolic blood pressure (SBP), fatty liver and medication use. Laboratory variables included hsCRP, triglycerides, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C), estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR). Triglycerides and FPG were measured after a fasting period of at least 8 h. BMI was expressed in kg/m², SBP in mmHg, eGFR in mL/min/1.73 m² and UACR in mg/mmol.

Diabetes duration was expressed in months and log-transformed as ln(1 + duration) for regression analysis. Smoking history, alcohol history and fatty liver were coded as binary variables. Medication variables included lipid-lowering treatment, sodium–glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists and insulin. A combined glucose-lowering treatment variable indicated use of any of the latter three therapies.

2.3 Calculation of CTI

CTI was calculated from hsCRP, triglycerides and FPG using natural logarithms [10]. Triglyceride and FPG concentrations were converted from mmol/L to mg/dL by multiplying by 88.57 and 18.018, respectively. The formula was as follows:

$$CTI = 0.412 \times ln[hsCRP\ (mg/L)] + ln\{[TG\ (mg/dL) \times FPG\ (mg/dL)]\ /\ 2\}$$

The TyG index corresponded to the second term of the CTI formula, and TyG-BMI was calculated by multiplying TyG by BMI. CTI was analyzed as a continuous variable per standard deviation (SD) increase; tertiles were used for descriptive analyses.

2.4 Definition of study outcomes

The primary outcome was CKM syndrome stage among hospitalized patients enrolled in this study.. The American Heart Association (AHA) proposes a five-stage classification system for CKM syndrome according to pathophysiological mechanisms, disease risks and prevention opportunities [1,2]. In the present study, the diagnostic criteria for CKM syndrome were adapted from the AHA standards and modified for hospitalized patient data in this cohort.

Stage 0: Lack of risk factors for CKM Syndrome, emphasizing primary prevention and maintaining cardiovascular health.

Stage 1: Identified by an excess of or malfunctioning adipose tissue, including abdominal fat and overweight/obesity.

Stage 2: Metabolic risk factors, such as type 2 diabetes, hypertension, hypertriglyceridemia, metabolic syndrome, and/or moderate-to-high-risk CKD, are present.

Stage 3: CKM Syndrome is linked to preclinical cardiovascular illness, such as asymptomatic heart failure and subclinical atherosclerotic CVD. Very-high-risk CKD (G4-G5 CKD or the very-high-risk stratum of the KDIGO eGFR-albuminuria grid) and high predicted 10-year CVD risk were also regarded as CVD risk equivalents for stage 3.

Stage 4: CKM Syndrome is linked to clinical CVD, such as peripheral arterial disease, heart failure, stroke, coronary artery disease (CAD), and atrial fibrillation.

Although disease severity differs between stage 3 and stage 4, both represent advanced CKM syndrome and share similar pathophysiological mechanisms. In the current analysis, stages 3-4 were collectively defined as advanced CKM syndrome, whereas stages 0-2 were defined as non-advanced CKM syndrome. The present analysis mainly focused on participants with CKM stages 2-4. Additional binary comparative analyses were performed: stages 3-4 versus stage 2, and stage 4 versus stages 2-3. The 2021 CKD-EPI equation was applied to calculate eGFR.

The exploratory secondary outcome was concurrent kidney abnormality, defined as eGFR < 45 mL/min/1.73 m^2 , UACR > 30 mg/mmol, or receipt of dialysis or kidney transplantation. These thresholds corresponded to G3b or worse renal function and A3-grade albuminuria, respectively [18]. This secondary outcome was ascertained using laboratory measurements and treatment information obtained from the index hospitalization.

2.5 Statistical analysis

Continuous variables were presented as medians and interquartile ranges (IQRs), with age additionally expressed as mean and SD. Categorical variables were summarized as numbers and percentages. Differences among CKM stages were evaluated using the Kruskal–Wallis test for continuous variables and the chi-square test for categorical variables. Pairwise comparisons used the Wilcoxon test with Benjamini–Hochberg adjustment [19]. Spearman correlation analysis assessed correlations between CTI and CKM stage and among CTI, hsCRP and TyG.

Multinomial logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for CKM stages 3 and 4, with stage 2 as the reference. The stage 4-versus-3 contrast was calculated from the model coefficients and their covariance matrix. The proportional-odds assumption was assessed in cumulative-logit models using term-specific likelihood-ratio tests [20]. The core model was adjusted for age, sex, BMI, ln(1 + diabetes duration), HbA1c and LDL-C. The extended model additionally included smoking, alcohol use, SBP, lipid-lowering treatment and the combined glucose-lowering treatment variable. Covariates were selected according to clinical relevance and data availability.

Binary logistic regression was used to examine associations of CTI with advanced CKM syndrome, stage 4 CKM syndrome and concurrent kidney abnormality, using the same adjustment sets. Modified Poisson regression with sandwich standard errors was used to estimate prevalence ratios (PRs) and 95% CIs [21,22]. Restricted cubic splines with three knots at the 10th, 50th and 90th CTI percentiles were fitted to assess nonlinear associations [23]. The median CTI was the reference value, and curves were displayed over the 1st–99th percentiles. Nonlinearity was evaluated using likelihood-ratio tests.

Multinomial model diagnostics included convergence, coefficient finiteness, positive definiteness of the observed-information matrix and variance inflation factors (VIFs). Coefficient stability was evaluated using 1,000 patient-level bootstrap resamples and percentile 95% CIs [24]. Influential observations were ranked using the one-step standardized perturbation of the CTI coefficient and an overall score-based measure. Patients among the five highest-ranked observations under either measure were individually excluded and the models refitted.

Benjamini–Hochberg false discovery rate (FDR) correction was applied separately to four families of tests: the three core-adjusted multinomial contrasts, three core-adjusted binary associations, three CTI-versus-hsCRP AUC

comparisons and nine interaction tests [19]. Analyses used complete data without imputation. Primary analyses were performed in R version 4.6.1. Additional data checks and statistical analyses were performed in Python version 3.12.14 using NumPy version 2.3.5 and SciPy version 1.17.0. Fixed random seeds were used for resampling procedures.

2.6 ROC curve analysis and internal validation

Receiver operating characteristic (ROC) curves were used to assess the performance of CTI, hsCRP, TyG and TyG-BMI in identifying advanced CKM syndrome, stage 4 CKM syndrome and concurrent kidney abnormality. Higher marker values defined the positive direction. Areas under the ROC curve (AUCs) for CTI and hsCRP were compared using the paired DeLong test, with differences expressed as CTI minus hsCRP and reported with 95% CIs [25].

For each binary outcome, five models were evaluated: core covariates alone and core covariates plus log-hsCRP, TyG, CTI, or log-hsCRP and TyG with separately estimated coefficients. Likelihood-ratio tests compared the model containing CTI with the model containing its two components [26]. The same models were evaluated descriptively for stage 3 versus stage 2 using apparent AUCs.

For the three full-sample binary outcomes, AUCs, Brier scores and calibration slopes were assessed with optimism correction using 500 patient-level bootstrap resamples. Ten-fold cross-validation used identical outcome-stratified folds for all competing models, with models refitted in each training fold. Calibration plots compared observed proportions with mean out-of-fold probabilities. Bootstrap correction and cross-validation were not performed for the stage 3-versus-2 model comparisons.

Apparent AUC differences between the core-plus-CTI and core-only models were additionally estimated using 500 paired patient-level bootstrap resamples. Both models were refitted and evaluated in each resample, and percentile 95% CIs were calculated for the AUC differences. These paired-bootstrap differences were evaluated separately from the optimism-corrected AUCs.

2.7 Sensitivity and subgroup analyses

Sensitivity analyses used the last eligible admission, a randomly selected eligible admission with a fixed seed, or all eligible admissions. Analyses of all admissions used generalized estimating equations with an independence working correlation structure and patient-clustered robust standard errors. Additional analyses excluded patients with hsCRP >10 or >20 mg/L, infection-related diagnostic terms, severe kidney impairment (eGFR <30 mL/min/1.73 m² or dialysis/transplantation), or stage 2 records containing coronary calcification or arterial plaque codes. Infection-related records were identified by case-insensitive matching of infection, pneumonia, sepsis or septicemia and their Chinese-language equivalents in diagnostic text. For the imaging-code exclusion analysis, the primary-sample CTI SD was retained when re-estimating the stage 3-versus-2 OR and CTI-alone AUC.

Further analyses winsorized CTI at the 1st and 99th percentiles, applied the extended adjustment set, fitted four-knot splines at the 5th, 35th, 65th and 95th percentiles, and used an alternative CTI formula with division by two outside the logarithm of the triglyceride–glucose product [11]. A broader kidney outcome was defined as eGFR <60 mL/min/1.73 m², UACR ≥3 mg/mmol, or dialysis/transplantation.

Exploratory subgroup analyses were conducted by age (<65 or ≥65 years), sex and BMI (<24 or ≥24 kg/m²) [27]. Age and BMI were retained as continuous covariates within strata, and sex was omitted from sex-specific models. Likelihood-ratio tests assessed interactions of CTI with continuous age, continuous BMI and sex across the three binary outcomes, retaining the corresponding main effects and core covariates.

3 Results

3.1 Characteristics of the study population

Of 596 hospitalization records from 563 patients, three records were excluded for age <18 years and one for hsCRP = 0. The remaining 592 eligible records represented 559 patients. After removal of 33 repeat records, 559 index admissions were included in the analysis; 30 patients had multiple eligible admissions (Supplementary Figure S1). The mean age was 60.7 years (SD 15.1), and 336 patients (60.1%) were male. CKM stages 2, 3 and 4 accounted for 205 (36.7%), 219 (39.2%) and 135 (24.2%) patients, respectively.

Table 1 presents the characteristics of patients according to CKM stage. Patients in higher stages were older and had longer diabetes duration, lower eGFR and higher UACR. HbA1c and LDL-C were lower in stage 4. Concurrent kidney abnormality was present in 148 patients (26.5%), including 113 with eGFR <45 mL/min/1.73 m², 84 with UACR >30 mg/mmol and 43 with dialysis or kidney transplantation; these components were not mutually exclusive.

3.2 CTI distribution and correlations

Median CTI values were 9.89 (IQR 9.20–10.52), 9.95 (9.30–10.69) and 10.98 (10.24–11.56) in CKM stages 2, 3 and 4, respectively (Kruskal–Wallis $P < 0.001$; Figure 1). CTI values did not differ significantly between stages 2 and 3 after adjustment for multiple comparisons (adjusted Wilcoxon $P = 0.32$). The SD of CTI was 1.1405, and the tertile cut points were 9.6916 and 10.6554.

CTI was positively correlated with CKM stage (Spearman $\rho = 0.317$, $P < 0.001$). The correlation coefficients were 0.597 between CTI and hsCRP, 0.882 between CTI and TyG, and 0.192 between hsCRP and TyG (all unadjusted $P < 0.001$; Supplementary Table S1).

3.3 Association between CTI and CKM stages

The proportional-odds assumption was violated for CTI ($P = 0.002$), age, HbA1c and LDL-C (Supplementary Table S1). In the core-adjusted multinomial model, each SD increase in CTI was associated with ORs of 1.43 (95% CI 1.12–1.84) for stage 3 versus 2, 4.69 (3.36–6.55) for stage 4 versus 2 and 3.27 (2.44–4.39) for stage 4 versus 3. All three associations remained statistically significant after FDR correction (Table 2). The corresponding ORs in the extended model were 1.41 (1.09–1.82), 4.71 (3.31–6.69) and 3.33 (2.43–4.57), respectively (Figure 2).

For advanced CKM syndrome versus stage 2 and stage 4 versus stages 2–3, the core-adjusted ORs per SD increase in CTI were 2.02 (95% CI 1.61–2.54) and 3.72 (2.80–4.94), respectively. The corresponding PRs were 1.20 (1.13–1.26) and 1.98 (1.73–2.26) (Supplementary Table S3).

VIFs ranged from 1.04 to 1.25 in the core model and from 1.10 to 1.47 in the extended model. All 1,000 multinomial bootstrap fits converged. The bootstrap 95% CIs for the stage 3-versus-2, stage 4-versus-2 and stage 4-versus-3 ORs were 1.11–1.86, 3.53–7.16 and 2.52–4.60, respectively. All targeted case-deletion models yielded

finite estimates; across nine core-model deletions, the respective OR ranges were 1.43–1.48, 4.66–4.95 and 3.25–3.41 (Supplementary Table S1).

3.4 Association between CTI and concurrent kidney abnormality

Each SD increase in CTI was associated with higher odds and prevalence of concurrent kidney abnormality. The core-adjusted OR was 1.80 (95% CI 1.45–2.23), and the corresponding PR was 1.44 (1.27–1.63) (Supplementary Table S3).

3.5 Restricted cubic spline analysis

The three-knot spline models showed no statistically significant nonlinear associations of CTI with advanced CKM syndrome, stage 4 versus stages 2–3, or concurrent kidney abnormality (P for nonlinearity = 0.813, 0.951 and 0.887, respectively). The corresponding P values in the four-knot models were 0.878, 0.218 and 0.947 (Supplementary Figure S2).

3.6 ROC curve analysis and internal validation

The AUCs of CTI alone for advanced CKM syndrome, stage 4 versus stages 2–3 and concurrent kidney abnormality were 0.617, 0.749 and 0.630, respectively; the corresponding AUCs of hsCRP were 0.692, 0.794 and 0.650 (Figure 3). For advanced CKM syndrome, the CTI-minus-hsCRP AUC difference was −0.075 (95% CI −0.119 to −0.030; P = 0.001; FDR q = 0.003). The differences were −0.046 (−0.092 to 0.000; P = 0.051) for stage 4 versus stages 2–3 and −0.021 (−0.063 to 0.022; P = 0.349) for kidney abnormality.

Among 424 patients in stages 2–3, the AUC of CTI alone for stage 3 versus 2 was 0.528 (95% CI 0.473–0.583). The apparent AUCs were 0.717 for the core model, 0.731 after addition of CTI, 0.735 after addition of log-hsCRP, 0.719 after addition of TyG and 0.739 with separately estimated component coefficients (Supplementary Table S2).

For advanced CKM syndrome, stage 4 versus stages 2–3 and kidney abnormality, the bootstrap-corrected AUCs were 0.730, 0.717 and 0.665 for the core model and 0.781, 0.837 and 0.716 for the core-plus-CTI model, respectively (Table 3). The corresponding AUC increases were 0.051, 0.119 and 0.051. Addition of log-hsCRP yielded AUCs of 0.781, 0.816 and 0.702 (increases of 0.051, 0.099 and 0.037), whereas addition of TyG yielded AUCs of 0.751, 0.793 and 0.696 (increases of 0.021, 0.076 and 0.031).

The paired-bootstrap apparent AUC differences between the core-plus-CTI and core-only models were 0.051 (95% CI 0.024–0.079), 0.114 (0.076–0.149) and 0.049 (0.018–0.088), respectively. All 500 paired-bootstrap fits were successful for each outcome (Table 3). The ten-fold cross-validated AUCs of the core-plus-CTI models were 0.778, 0.836 and 0.709, and the optimism-corrected calibration slopes were 0.955, 0.939 and 0.909, respectively. All 500 validation bootstrap fits were successful for each model. The out-of-fold calibration plots are presented in Supplementary Figure S3.

The models with separately estimated log-hsCRP and TyG coefficients had bootstrap-corrected AUCs of 0.789, 0.847 and 0.716 for the three outcomes, respectively. Compared with the models containing CTI, likelihood-ratio tests gave P = 0.002 for each CKM stage comparison and P = 0.157 for kidney abnormality.

3.7 Sensitivity and subgroup analyses

Positive associations of CTI with the three binary outcomes were observed using alternative admission-selection rules, generalized estimating equations, hsCRP and infection-related exclusions, exclusion of severe kidney impairment, winsorization and extended covariate adjustment (Supplementary Table S3). Exclusion of 133 patients with infection-related diagnostic terms left 426 patients; the adjusted ORs were 2.23 (95% CI 1.70–2.93) for advanced CKM syndrome, 4.13 (2.91–5.88) for stage 4 versus stages 2–3 and 1.54 (1.21–1.97) for kidney abnormality. After exclusion of severe kidney impairment, 478 patients remained, and the adjusted OR for kidney abnormality was 1.45 (1.10–1.91).

Ten patients in stage 2 had positive imaging codes: nine for arterial plaque and one for arterial plaque with coronary calcification. Their exclusion left 549 patients, comprising 195, 219 and 135 patients in stages 2, 3 and 4, respectively. The adjusted OR for stage 3 versus 2 was 1.42 (95% CI 1.10–1.83) per SD increase in CTI. Among the remaining 414 patients in stages 2–3, the AUC of CTI alone was 0.522 (0.466–0.578) (Supplementary Table S2).

The broader kidney outcome definition identified 347 patients (62.1%) and was positively associated with CTI (Supplementary Table S3). The alternative formula yielded a mean CTI of 5.74 (SD 0.76), compared with 10.19 (SD 1.14) using the primary formula. The Spearman correlation between the two CTI measures was 0.962.

For advanced CKM syndrome versus stage 2, the adjusted ORs per SD increase in CTI were 2.82 (95% CI 1.95–4.07) among patients with BMI <24 kg/m² and 1.57 (1.16–2.12) among those with BMI ≥24 kg/m². The interaction between CTI and continuous BMI had P = 0.007 and FDR q = 0.060. None of the nine interactions involving age, BMI or sex remained statistically significant after FDR correction (Supplementary Table S3).

Table 1 Characteristics by CKM stage

Characteristic	Overall n = 559	Stage 2 n = 205	Stage 3 n = 219	Stage 4 n = 135	P
Participants	559	205	219	135	
Age, years	62.00 (51.00–72.00)	53.00 (40.00–65.00)	65.00 (56.00–73.00)	68.00 (61.00–75.00)	<0.001
Age, years, mean (SD)	60.7 (15.1)	52.8 (15.8)	64.1 (12.8)	67.2 (12.1)	—
BMI, kg/m²	24.40 (21.73–27.20)	25.00 (22.20–28.40)	24.40 (21.55–26.69)	23.88 (21.23–25.62)	<0.001
Diabetes duration, months	84.00 (24.00–120.00)	36.00 (6.00–108.00)	108.00 (36.00–126.00)	120.00 (60.00–240.00)	<0.001
HbA1c, %	9.30 (7.65–11.30)	9.90 (8.00–11.30)	9.60 (7.80–11.50)	7.90 (7.15–9.85)	<0.001
LDL-C, mmol/L	2.72 (2.04–3.33)	2.84 (2.22–3.33)	2.80 (2.17–3.46)	2.24 (1.57–3.02)	<0.001
Fasting plasma glucose, mmol/L	9.60 (7.47–12.82)	10.21 (7.82–13.70)	9.56 (7.09–12.65)	8.80 (7.27–12.32)	0.018
Triglycerides, mmol/L	1.76 (1.09–3.08)	1.49 (1.03–2.50)	1.52 (1.05–2.26)	3.28 (1.71–4.67)	<0.001
hsCRP, mg/L	5.20 (2.10–9.37)	3.00 (1.30–5.80)	4.40 (1.80–8.90)	9.56 (7.77–15.35)	<0.001

Characteristic	Overall n = 559	Stage 2 n = 205	Stage 3 n = 219	Stage 4 n = 135	P
eGFR, mL/min/1.73 m²	85.53 (53.56–106.29)	98.37 (73.28–119.89)	84.97 (57.41–102.67)	51.98 (10.54–87.48)	<0.001
UACR, mg/mmol	3.90 (1.77–14.63)	2.50 (1.38–5.30)	4.16 (1.63–9.16)	24.98 (4.57–68.58)	<0.001
CTI	10.17 (9.42–10.91)	9.89 (9.20–10.52)	9.95 (9.30–10.69)	10.98 (10.24–11.56)	<0.001
TyG	9.51 (8.95–10.14)	9.44 (8.89–9.98)	9.34 (8.91–9.88)	10.00 (9.36–10.57)	<0.001
TyG-BMI	229.34 (204.61–265.17)	237.83 (204.63–278.68)	224.94 (202.39–257.79)	232.11 (210.35–258.90)	0.029
Male sex	336 (60.1)	126 (61.5)	127 (58.0)	83 (61.5)	0.714
Smoking history	179 (32.0)	64 (31.2)	78 (35.6)	37 (27.4)	0.262
Alcohol history	86 (15.4)	28 (13.7)	47 (21.5)	11 (8.1)	0.002
Fatty liver	283 (50.6)	110 (53.7)	120 (54.8)	53 (39.3)	0.010
SBP, mmHg	141.00 (126.00–154.00)	138.00 (124.00–150.00)	138.00 (125.50–153.00)	148.00 (134.00–162.50)	<0.001
Recorded lipid-lowering use	107 (19.1)	20 (9.8)	31 (14.2)	56 (41.5)	<0.001
Recorded SGLT2 inhibitor use	121 (21.6)	39 (19.0)	58 (26.5)	24 (17.8)	0.080
Recorded GLP-1 receptor agonist use	42 (7.5)	15 (7.3)	21 (9.6)	6 (4.4)	0.202
Recorded insulin use	246 (44.0)	74 (36.1)	91 (41.6)	81 (60.0)	<0.001
Any of the three glucose-lowering therapies	319 (57.1)	97 (47.3)	129 (58.9)	93 (68.9)	<0.001
eGFR <45	113 (20.2)	16 (7.8)	37 (16.9)	60 (44.4)	<0.001
UACR >30 mg/mmol	84 (15.0)	17 (8.3)	25 (11.4)	42 (31.1)	<0.001
Concurrent kidney abnormality	148 (26.5)	29 (14.1)	46 (21.0)	73 (54.1)	<0.001

Fasting plasma glucose and triglycerides were measured after at least 8 h of fasting. Values are median (IQR) or n (%), unless otherwise indicated. P values are descriptive Kruskal–Wallis or chi-square tests; they are not used to select covariates. All 559 index records had populated core, kidney and extended-covariate fields. Smoking and alcohol indicate recorded history; medication rows indicate recorded use and do not establish uniform treatment timing. The combined glucose-lowering indicator is positive if any SGLT2 inhibitor, GLP-1 receptor agonist or insulin field is positive. Age is additionally shown as mean (SD); the descriptive age P value is reported on the median (IQR) row. Concurrent kidney abnormality at index admission: eGFR <45 mL/min/1.73 m², UACR >30 mg/mmol, or recorded dialysis/kidney transplantation.

Abbreviations: SBP, systolic blood pressure; SD, standard deviation; SGLT2, sodium-glucose cotransporter 2; GLP-1, glucagon-like peptide 1; BMI, body mass index; CKM, cardiovascular-kidney-metabolic; CTI, C-reactive protein-triglyceride-glucose index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose index; UACR, urinary albumin-to-creatinine ratio.

Table 2 Stage-specific CTI associations

Contrast	Unadjusted OR (95% CI)	Core OR (95% CI)	Core P	Core q	Extended OR (95% CI)
Stage 3 vs 2	1.15 (0.93–1.41)	1.43 (1.12–1.84)	0.005	0.005	1.41 (1.09–1.82)
Stage 4 vs 2	2.85 (2.18–3.71)	4.69 (3.36–6.55)	<0.001	<0.001	4.71 (3.31–6.69)
Stage 4 vs 3	2.48 (1.92–3.20)	3.27 (2.44–4.39)	<0.001	<0.001	3.33 (2.43–4.57)

All estimates are per 1 SD higher CTI (1.1405 units), N = 559. Unadjusted, core-adjusted and extended ORs all come from multinomial logistic models. Multinomial ORs compare the odds of membership in the stated stages; they are not cumulative ORs or relative risks. Core adjustment: age, sex, BMI, log(1 + diabetes duration in months), HbA1c and LDL-C. Extended adjustment additionally includes smoking, alcohol use, systolic blood pressure, lipid-lowering treatment and an SGLT2 inhibitor/GLP-1 receptor agonist/insulin indicator. q values cover the three core stage contrasts. Bootstrap coefficient intervals appear in Supplementary Table S1.

Table 3 Internal performance of binary clinical models

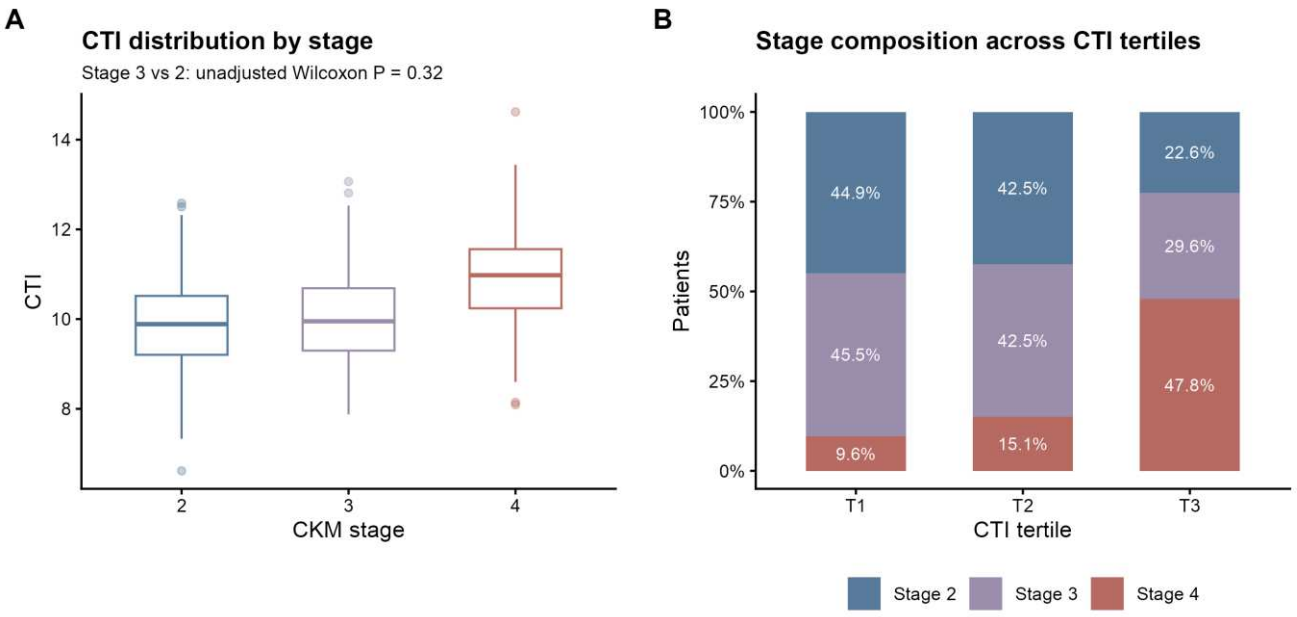
Outcome and model	App. AUC	Corr. AUC	10-fold CV AUC	Corr. Brier	Corr. slope	Apparent AUC difference vs clinical base (paired bootstrap 95% CI)
CKM stages 3–4 vs 2 Clinical base	0.738	0.730	0.727	0.192	0.958	Reference
CKM stages 3–4 vs 2 + log-hsCRP	0.790	0.781	0.779	0.180	0.952	—
CKM stages 3–4 vs 2 + TyG	0.760	0.751	0.749	0.187	0.953	—
CKM stages 3–4 vs 2 + CTI	0.790	0.781	0.778	0.179	0.955	0.051 (0.024–0.079)
CKM stages 3–4 vs 2 + log-hsCRP and TyG	0.799	0.789	0.788	0.177	0.946	—
CKM stage 4 vs 2–3 Clinical base	0.734	0.717	0.716	0.164	0.906	Reference
CKM stage 4 vs 2–3 + log-hsCRP	0.830	0.816	0.819	0.140	0.930	—
CKM stage 4 vs 2–3 + TyG	0.807	0.793	0.790	0.140	0.928	—
CKM stage 4 vs 2–3 + CTI	0.849	0.837	0.836	0.126	0.939	0.114 (0.076–0.149)
CKM stage 4 vs 2–3 + log-hsCRP and TyG	0.860	0.847	0.847	0.123	0.933	—
Concurrent kidney abnormality Clinical base	0.685	0.665	0.662	0.183	0.873	Reference
Concurrent kidney abnormality + log-hsCRP	0.721	0.702	0.694	0.176	0.896	—
Concurrent kidney abnormality + TyG	0.715	0.696	0.692	0.177	0.891	—

Outcome and model	App. AUC	Corr. AUC	10-fold CV AUC	Corr. Brier	Corr. slope	Apparent AUC difference vs clinical base (paired bootstrap 95% CI)
Concurrent kidney abnormality + CTI	0.734	0.716	0.709	0.173	0.909	0.049 (0.018–0.088)
Concurrent kidney abnormality + log-hsCRP and TyG	0.736	0.716	0.708	0.172	0.896	—

N = 559 per model. Clinical base: age, sex, BMI, log(1 + diabetes duration in months), HbA1c and LDL-C; each marker augments that same base. Corrected estimates use 500 patient-level bootstrap resamples, all successful per model. CV uses identical outcome-stratified folds across models. Kidney abnormality is concurrent at index admission. Adjacent-stage models (n = 424) have apparent AUCs only (Supplementary Table S2). These assess internal concurrent classification, not validated future-event prediction. Free-component versus fixed-CTI likelihood-ratio P: 0.002 for each stage threshold; 0.157 for kidney abnormality. App., apparent; Corr., optimism-corrected; CV, cross-validation.

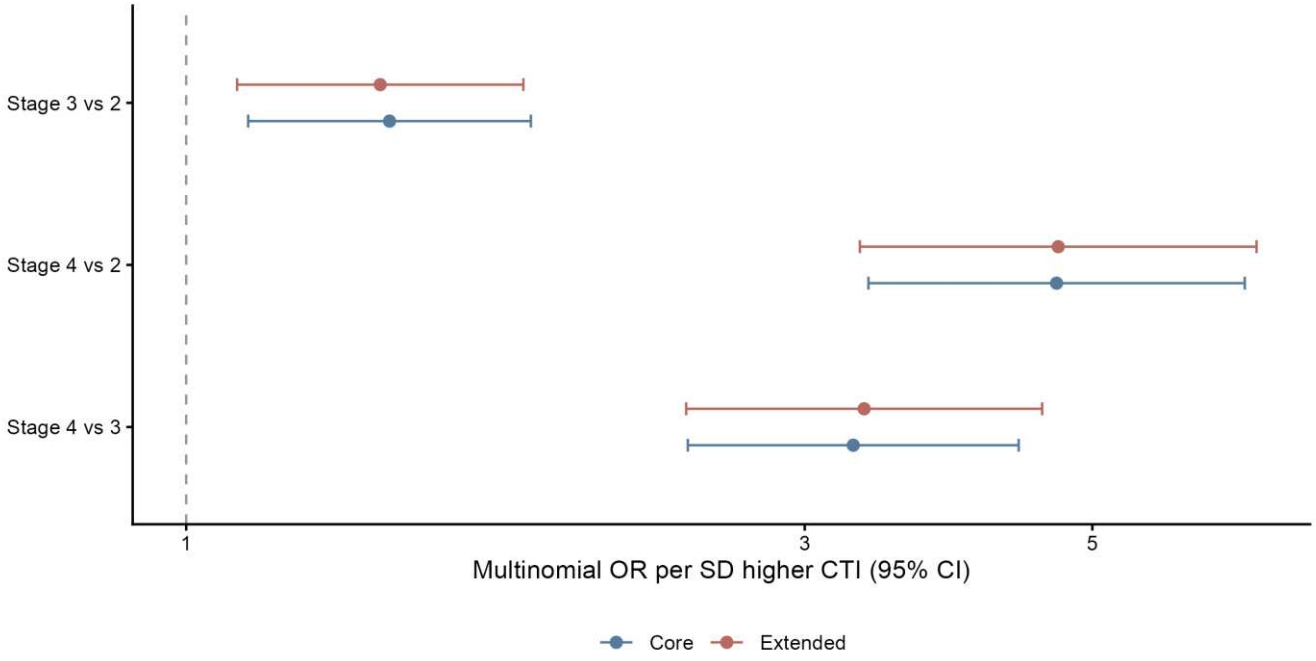
Paired intervals are available only for +CTI; — means not estimated. All 500 paired fits succeeded per outcome. Differences use unrounded AUCs. Both models were refitted and evaluated within each resampled cohort; these apparent-difference intervals are not intervals for corrected AUC differences and do not establish external incremental value. See Supplementary methods.

Figure 1 CTI distribution across CKM stages



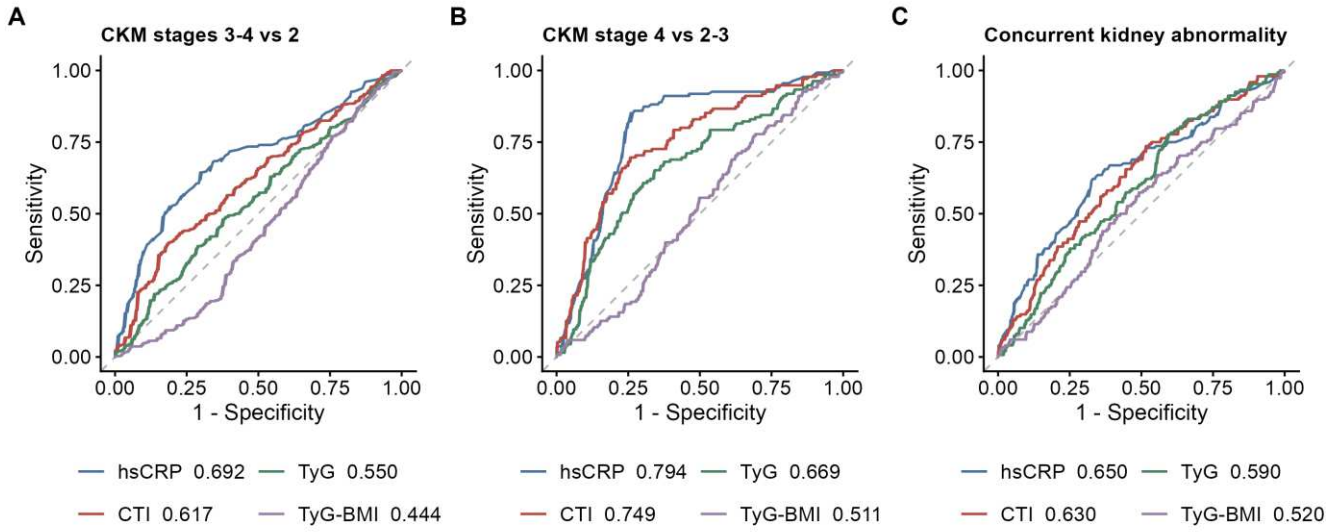
A, Boxplots show the median, interquartile range, 1.5-IQR whiskers and individual outliers. B, Stage proportions within CTI tertiles. Tertile cut points were 9.6916 and 10.6554. N = 559. Displayed percentages may not sum to exactly 100% because of rounding. The figure reports the unadjusted stage 3-versus-2 Wilcoxon P = 0.32; the BH-adjusted P is also 0.32.

Figure 2 Stage-specific adjusted associations



Multinomial odds ratios per SD higher CTI with Wald 95% confidence intervals. N = 559. Core adjustment: age, sex, BMI, log(1 + diabetes duration in months), HbA1c and LDL-C. Extended adjustment additionally includes smoking, alcohol use, systolic blood pressure and the treatment indicators specified in Table 2. The dashed line marks OR = 1.

Figure 3 Single-marker discrimination



ROC curves for A, CKM stages 3–4 versus 2; B, stage 4 versus 2–3; and C, concurrent kidney abnormality at index admission. N = 559 for each analysis. Legend values are apparent unadjusted AUCs. Higher marker values are fixed as the positive direction. Paired CTI–hsCRP differences and confidence intervals are reported in Supplementary Table S2. The stage 4 comparison is not an independent cardiovascular endpoint.

4 Discussion

In this retrospective cross-sectional study of 559 hospitalized adults with type 2 diabetes, higher CTI was associated with more advanced CKM stages after adjustment for clinical covariates (per-SD OR 1.43 for stage 3 and 4.69 for stage 4 versus stage 2), and spline analyses detected no significant nonlinearity (all P for nonlinearity $\geqslant$ 0.218). Models incorporating CTI achieved higher internally assessed AUCs, particularly for stage 4 versus stages 2 – 3 (bootstrap-corrected AUC 0.837 versus 0.717), and the positive associations persisted across most sensitivity analyses. Notably, however, the AUC of CTI alone for stage 3 versus 2 was only 0.528, indicating a clear limitation of CTI as a standalone marker for distinguishing these adjacent stages. Taken together, these findings suggest that CTI may serve as a complementary marker of concurrent CKM burden in adults with type 2 diabetes.

Our findings are consistent with population-based evidence linking CTI to advanced CKM syndrome. Zeng et al. [11] reported adjusted ORs of 1.35 (95% CI 1.20 – 1.48) in NHANES, 1.55 (1.46 – 1.64) in the UK Biobank and 1.42 (1.28 – 1.60) in CHARLS, and their longitudinal analyses further associated CTI with incident advanced CKM (HR 1.22, 95% CI 1.17 – 1.30 in the UK Biobank; HR 1.21, 95% CI 1.01 – 1.46 in CHARLS). Our study addresses a narrower clinical setting in which all patients had type 2 diabetes and stage 2 served as the reference; examining stages 3 and 4 separately showed that the association strengthened with advancing stage within an already affected population. Because of differences in study populations, staging definitions, CTI formulations and scaling, effect sizes cannot be compared directly across studies.

Inflammatory and metabolic markers have also been linked to other complications of diabetes. In 847 middle-aged and older adults with type 2 diabetes, Zhang and Jing [16] reported that higher CTI was associated with osteopenia or osteoporosis (adjusted OR 7.277, 95% CI 4.602 – 11.507; AUC 0.758, 95% CI 0.7254 – 0.7897). In the present study, the discriminative performance of CTI alone varied considerably according to the stage comparison (AUC 0.749 for stage 4 versus 2 – 3 and 0.528 for stage 3 versus 2), suggesting that its performance is specific to the outcome and to the segment of the disease spectrum under evaluation.

Longitudinal studies provide a complementary perspective. Among 5,111 CHARLS participants with CKM stages 0 – 3, Chen et al. [10] documented 555 incident CVD cases, and each SD increase in baseline CTI was associated with an adjusted HR of 1.18 (95% CI 1.07 – 1.30). In 2,000 patients with stage 4 CKM and acute decompensated heart failure, Wang et al. [15] reported higher mortality and major adverse cardiac and cerebrovascular events among patients with diabetes and high CTI than among those without diabetes and with low CTI (adjusted HRs 1.95 and 1.91). These studies link CTI to subsequent outcomes, whereas our study characterizes concurrent differences across CKM stages and therefore cannot establish a prognostic association.

Several lines of evidence may help to explain the association between CTI and CKM burden. CTI reflects overlapping inflammatory and metabolic disturbances that are relevant to the pathophysiology of CKM syndrome. Wu and Huang [28] found that, among 7,904 NHANES participants, the highest TyG quartile was associated with higher odds of advanced CKM than the lowest quartile (adjusted OR 1.94, 95% CI 1.37 – 2.75). Inflammation and insulin resistance contribute to vascular and kidney abnormalities [2], although anti-inflammatory trials have shown that cardiovascular effects depend on the targeted pathway and clinical setting [29,30]. These observations provide

biological context rather than evidence of a CTI-mediated mechanism; moreover, circulating CRP has not been established as a causal therapeutic target [31].

The component comparisons qualify the rationale for a composite index. CTI alone had a lower AUC than hsCRP for stages 3 – 4 versus 2 (0.617 versus 0.692), whereas models containing CTI had numerically higher bootstrap-corrected AUCs for stage 4 versus 2 – 3 than models containing log-hsCRP or TyG (0.837, 0.816 and 0.793, respectively). Models with separately estimated component coefficients yielded an AUC of 0.847 and a better fit than models containing CTI at both cumulative stage thresholds (both P = 0.002). The relative performance of CTI therefore depended on the outcome and the covariates included. A possible explanation is that the published CTI weights, which were derived in a cancer-prognosis setting [6], may not be optimal for patients with type 2 diabetes. Although internal validation supports further evaluation of CTI [24,26].

The exploratory analysis of concurrent kidney abnormality provides additional evidence on concurrent organ involvement (adjusted OR 1.80 and PR 1.44 per SD increase in CTI). Huang et al. [32] observed 262 cases of rapid kidney function decline among 6,888 CHARLS participants over four years, with an OR of 1.18 (95% CI 1.13 – 1.22) per unit of cumulative CTI, and Zhang et al. [33] likewise reported a positive cross-sectional association with prevalent CKD, although the CTI definitions and kidney outcomes differed across studies. Our kidney outcome was defined post hoc using single-admission measurements and dialysis or transplantation status, and chronicity could not be verified [18]; it should therefore be regarded as complementing, rather than independently validating, the staging analysis. Kidney function and albuminuria remain central to clinical assessment, as supported by outcome studies and intervention trials [34 – 36].

The findings for stage 3 versus 2 illustrate the distinction between statistical association and individual-level classification. The adjusted OR estimates the association between CTI and CKM stage conditional on covariates, whereas the AUC of CTI alone describes how well a single marker separates the two groups. When the distributions of the two groups overlap substantially, a significant adjusted association may coexist with limited standalone discrimination. The higher internally assessed AUCs of the multivariable models suggest that CTI provides complementary information, particularly for stage 4, but they provide little support for using CTI alone to identify stage 3.

This study has several strengths. First, it examined stage-specific associations in adults with established type 2 diabetes, in whom broad comparisons of advanced versus earlier stages may not reflect the ability to distinguish adjacent stages. Second, CTI was evaluated alongside its constituent markers. Third, bootstrap optimism correction and cross-validation provided internally validated estimates of model performance.

We also acknowledge several limitations. First, the single-center inpatient sample and possible selection bias may limit generalizability, and the cross-sectional design precludes causal inference. Second, the timing of sampling relative to acute illness and treatment was unavailable; residual confounding and reverse causation therefore cannot be excluded. The attenuation of the kidney association after excluding severe kidney impairment further suggests sensitivity to the disease spectrum analyzed. Third, no subgroup interaction remained significant after FDR correction, so subgroup findings should be regarded as exploratory.

Future studies should use independently adjudicated CKM stages, standardized sampling and multicenter external validation. Comparisons should include CTI, its constituent markers and established clinical assessment tools [37],

with evaluation of calibration and decision-curve analysis for a clearly specified clinical decision [38]. Transparent reporting and appraisal of bias and applicability are essential [39,40]. Longitudinal cardiovascular and kidney outcomes require separate evaluation.

5 Conclusions

In summary, this study shows that higher CTI was associated with more advanced CKM stages in hospitalized adults with type 2 diabetes, and that incorporating CTI into clinical models improved discrimination, particularly for stage 4. As a composite of inflammation and glucose-lipid metabolism, CTI may serve as a readily available complementary marker of concurrent CKM burden and help identify patients with diabetes who warrant more intensive cardiovascular and kidney risk assessment. These findings provide a basis for future longitudinal and multicenter studies to validate CTI and to clarify its incremental value over established clinical assessment before it is adopted in practice.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of Huzhou First People's Hospital (Approval No. 2026KYLL059-01). Individual informed consent was waived by the Ethics Committee due to the retrospective nature of this study.

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated and analysed during the current study are not publicly available due to patient privacy restrictions, but are available from the corresponding author on reasonable request with institutional approval.

Competing interests: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions: Jingyu Zhang: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. Jieya Yang: Data curation, Formal analysis, Validation, Writing – review & editing. Jianfeng Zhan: Methodology, Supervision, Visualization, Writing – original draft. Jiayin Liu: Project administration, Supervision, Validation, Writing – review & editing. Jia Hu: Conceptualization, Project administration, Supervision, Validation, Writing – review & editing.

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