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Predictive Value of the C-Reactive Protein–Triglyceride–Glucose Composite Index for All-Cause Mortality in General Population: A Dual-Cohort Study Based on NHANES and CHARLS

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Abstract: *Background:* Metabolic dysregulation and chronic inflammation coexist commonly, synergistically increasing cardiovascular and all-cause mortality. Single biomarkers fail to comprehensively assess metabolism-inflammation imbalance. This study first validates the dose-response relationship between CTI (a novel dual-pathway composite biomarker) and all-cause mortality across two cross-continental cohorts. *Methods:* Data from NHANES (n = 7, 752) and CHARLS (n = 9, 352) were integrated. CTI was calculated for all participants. Statistical methods including multivariable Cox model, propensity score overlap weighting, RCS regression, and competing risk model analyzed CTI-mortality correlation. Sensitivity analysis and external validation ensured result robustness. *Results:* Median follow-ups: 11.3 years (NHANES, 1, 260 deaths) and 9 years (CHARLS, 236 deaths). Fully adjusted Model 3: Each 1-unit CTI increase linked to 21% (NHANES: HR = 1.21, 95% CI: 1.12–1.31) and 56% (CHARLS: HR = 1.56, 95% CI: 1.34–1.82) higher all-cause mortality. All-cause mortality surged when CTI > 9.77 (NHANES) or > 7.54 (CHARLS) ($P < 0.001$). Highest CTI quartile had 37% (NHANES) and 221% (CHARLS) higher mortality vs. lowest; effect pronounced in middle-aged and elderly (CHARLS, median age 58). CTI (AUC = 0.61) outperformed TyG or CRP alone. *Conclusions:* CTI, integrating inflammatory and metabolic indicators, effectively identifies high-risk individuals across populations. With population-specific thresholds, it is promising for routine health screening risk stratification, guiding early intervention.

Keywords: C-reactive protein–triglyceride–glucose index (CTI); All-cause mortality; Cardiopulmonary mortality; NHANES; CHARLS; Propensity score overlap weighting; Competing risk model.

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1. Introduction

CVDs are the leading global cause of death. GBD models (2025-2050) project 90.0% higher CVD prevalence, 73.4% higher crude death rate, and 54.7% higher DALYs [1].

This crisis is linked to MetS; > 30% of U.S. adults (especially elderly) meet MetS criteria. 2015-2020 data: ~25% of global general population has MetS, with related treatment costs accounting for > 75% of national medical expenditure[2].

Insulin resistance, MetS's core feature, drives metabolic abnormalities and correlates with multi-organ dysfunction and premature death[3]. TyG index is a simple, reliable insulin resistance biomarker, linked to type 2 diabetes, obesity, CVD[4, 5]. CRP, a classic inflammatory biomarker, reflects infection/tissue damage and correlates with atherosclerosis and adverse cardiovascular outcomes. Metabolic disorders and chronic inflammation interact, forming a pathological network that amplifies organ damage and death risks. Thus, dual-pathway composite biomarkers are clinically valuable for predicting all-cause mortality. Progress has been made in TyG-based composite indices (TyG-WHtR, TyG-WC) with better predictive efficacy than TyG alone[6].

However, single metabolic indicators cannot fully assess metabolism-inflammation imbalance, leading to CTI (integrating CRP and TyG)[7]. Previous studies confirm CTI's value in stroke risk stratification, cancer prognosis, and predicting erectile dysfunction/depression in hypertensive populations[8]. But its association with general population all-cause mortality lacks cross-population, large-sample evidence; mechanisms are underexplored.

This study examines CTI-all-cause mortality dose-response relationship and cross-population consistency using NHANES and CHARLS data.

Objectives: (1) Clarify CTI's independent predictive value; (2) Identify CTI risk thresholds; (3) Reveal modifying effects of age/region.

Hypothesis: CTI independently predicts all-cause mortality with consistent threshold effects across populations; middle-aged and elderly are more sensitive.

Table S1. Baseline characteristics comparison among the CTI quartile groups (CHARLS)

	Overall	Q1	Q2	Q3	Q4	p
n	9352	2852	2950	2028	1522	
Age (mean (SD))	58.0 (9.0)	57.0 (9.2)	58.2 (8.9)	58.5 (9.0)	58.6 (8.9)	< 0.001
Gender (%)						
Female	5179 (55.4)	1508 (52.9)	1639 (55.6)	1186 (58.5)	846 (55.6)	0.002
Male	4168 (44.6)	1342 (47.1)	1309 (44.4)	842 (41.5)	675 (44.4)	
Education, n(%)						
< High school	137 (1.5)	39 (1.4)	38 (1.3)	32 (1.6)	28 (1.8)	0.506
Completed high school	6584 (70.5)	2038 (71.5)	2051 (69.6)	1428 (70.5)	1067 (70.2)	
> High school	2623 (28.1)	773 (27.1)	858 (29.1)	566 (27.9)	426 (28.0)	
Marital status, n(%)						
Married	8394 (89.8)	2571 (90.1)	2648 (89.8)	1814 (89.4)	1361 (89.4)	0.833
Never married	958 (10.2)	281 (9.9)	302 (10.2)	214 (10.6)	161 (10.6)	
Alcohol, n(%)						
Yes	3026 (32.5)	1007 (35.4)	964 (32.8)	569 (28.2)	486 (32.0)	< 0.001
No	6297 (67.5)	1838 (64.6)	1977 (67.2)	1450 (71.8)	1032 (68.0)	
BMI, (kg/m2), (median [IQR])	23.2 [21.0, 25.9]	21.9 [20.1, 23.9]	23.0 [20.8, 25.5]	24.4 [22.0, 26.9]	25.3 [22.8, 28.0]	< 0.001
Laboratory, (median [IQR])						
Wbc	5.9 [4.9, 7.2]	5.5 [4.6, 6.6]	5.9 [4.9, 7.0]	6.2 [5.2, 7.5]	6.7 [5.5, 8.0]	< 0.001
Hemoglobin (g/dl)	14.2 [13.0, 15.5]	14.0 [12.8, 15.3]	14.2 [13.1, 15.4]	14.4 [13.2, 15.7]	14.6 [13.2, 15.8]	< 0.001

Table S1 (Continued)

	Overall	Q1	Q2	Q3	Q4	p
Creatinine (mg/ml)	0.8 [0.6, 0.9]	0.7 [0.6, 0.8]	0.7 [0.6, 0.9]	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	< 0.001
Platelets(10^9/L)	207.0 [162.0, 255.0]	202.0 [161.0, 249.0]	206.0 [161.0, 256.0]	210.5 [165.0, 260.0]	213.0 [167.0, 260.8]	< 0.001
cholesterol (mg/ml)	190.2 [167.0, 214.9]	180.9 [160.4, 203.7]	190.2 [168.2, 212.2]	195.0 [170.5, 221.5]	203.4 [176.7, 234.7]	< 0.001
CTI	8.7 [8.1, 9.2]	7.9 [7.7, 8.1]	8.6 [8.4, 8.7]	9.2 [9.1, 9.4]	10.0 [9.7, 10.4]	< 0.001
Disease status, n(%)						
Hypertension						
Yes	3474 (41.6)	754 (29.7)	1054 (40.1)	891 (49.0)	775 (56.5)	< 0.001
No	4886 (58.4)	1787 (70.3)	1574 (59.9)	929 (51.0)	596 (43.5)	
Diabetes						
Yes	691 (7.4)	73 (2.6)	141 (4.8)	154 (7.6)	323 (21.4)	< 0.001
No	8593 (92.6)	2756 (97.4)	2784 (95.2)	1866 (92.4)	1187 (78.6)	
Asthma						
Yes	295 (3.2)	82 (2.9)	81 (2.8)	72 (3.6)	60 (4.0)	0.087
No	8992 (96.8)	2756 (97.1)	2848 (97.2)	1939 (96.4)	1449 (96.0)	
Permth_int (median [IQR])	9.0 [9.0, 9.0]	9.0 [9.0, 9.0]	9.0 [9.0, 9.0]	9.0 [9.0, 9.0]	9.0 [9.0, 9.0]	< 0.001
Mortality (%)						
Survive	9116 (97.5)	2807 (98.4)	2886 (97.8)	1972 (97.2)	1451 (95.3)	< 0.001
Dead	236 (2.5)	45 (1.6)	64 (2.2)	56 (2.8)	71 (4.7)	

Note: BMI, Body mass index; Wbc, White blood cell count; HGB, Hemoglobin; Plt, Platelet count; CRP, C-reactive protein; CTI, C-reactive protein-triglyceride glucose index; Mortstat, All-cause mortality rate; Permth_int, Follow-up time

2. Materials and methods

2.1. Research Design and Population

Dual-cohort design investigating CTI-all-cause mortality correlation by integrating NHANES and CHARLS data.

The NHANES database is managed by the Centers for Disease Control and Prevention (CDC) of the United States. It adopts a multi-stage stratified sampling design, covering multi-dimensional data including participants' basic information, questionnaire data, physical examination records, and laboratory test results. All participants had signed a written informed consent form. Taking December 31, 2019 as the follow-up deadline, the survival status data were obtained by matching with the death data from the National Center for Health Statistics (NCHS) in the United States. From 2005 to 2018, NHANES included a total of 70, 109 participants, and 7, 752 subjects were ultimately recruited in our study after screening based on the following exclusion criteria: (1) Subjects with missing CTI data (n = 60, 608); (2) Subjects under 18 years old, and/or with missing or unsuitable follow-up information (n = 1, 749).

CHARLS, as a national longitudinal study in China, adopts a multi-stage stratified sampling strategy. Its baseline survey in 2011 covered 450 villages in 28 provinces of China, including 17, 708 middle-aged and elderly individuals. Thereafter, follow-ups were conducted every 2-3 years (2013, 2015, 2018, 2020). The research plan of our study was approved by the Ethics Committee of Peking University, and all participants had signed an informed consent form. The

survival status data were obtained from the 2018 and 2020 mortality questionnaires, and were then screened based on the following exclusion criteria: (1) Subjects with missing CTI data (n = 6, 072); (2) Subjects under 18 years old, and/or with missing or unsuitable follow-up information (n = 2, 284). Ultimately, a total of 9, 352 subjects were recruited.Participants with complete CRP, TG, FPG (for CTI calculation) and mortality follow-up data were included.

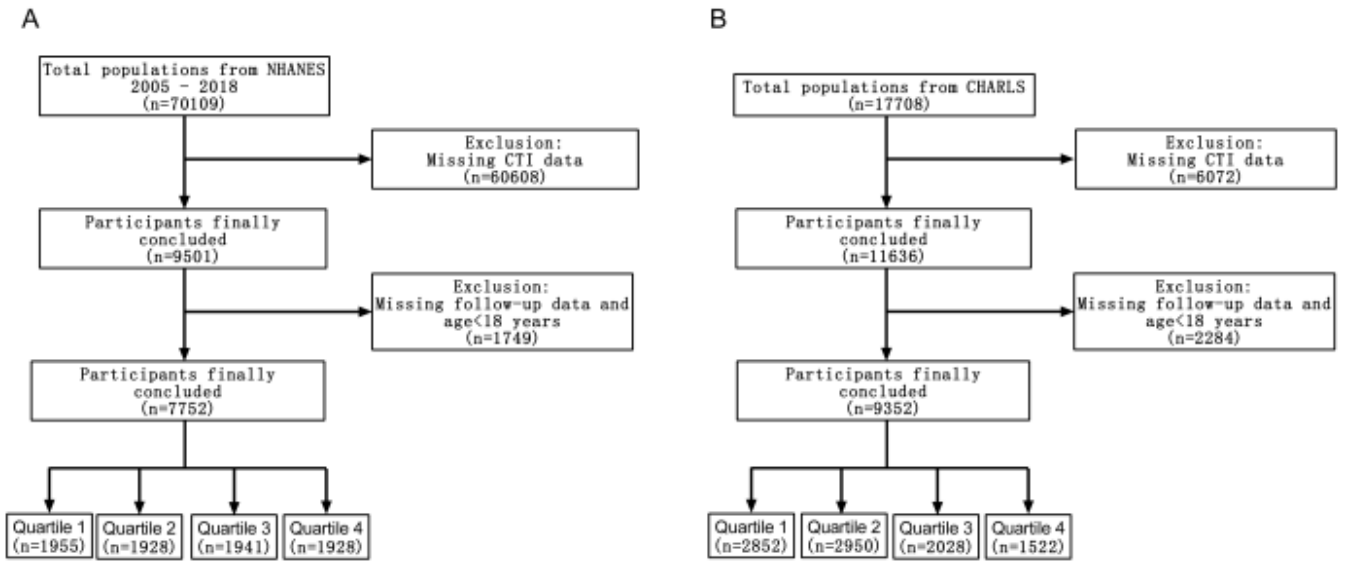

Figure 1. Patient selection process A: Nhanes, B: Charls

2.2. Definition of variables

2.2.1. Independent variable

CTI = 0.412 × Ln (CRP [mg/L]) + Ln (TG [mg/dl] × FPG [mg/dl]/2) (CRP = C-reactive protein; TG = triglycerides; FPG = fasting plasma glucose).

(1) Primary outcome: All-cause mortality (death from any cause during follow-up).

(2) Secondary outcome: Cardiopulmonary mortality (death from cardiovascular/respiratory diseases, classified by ICD codes).

2.2.2. Covariates

The covariates collected from the NHANES cohort include gender, age, education level (below high school/high school/above high school), marital status (married/unmarried), alcohol consumption, body mass index (BMI), white blood cell count, hemoglobin, creatinine, cholesterol level, hypertension status, diabetes status, and asthma status. Hypertension was defined as meeting any of the following criteria: (1) Systolic blood pressure (SBP) ≥ 140 mmHg; (2) Diastolic blood pressure (DBP) ≥ 90 mmHg; (3) Self-reported diagnosis of hypertension by a doctor; (4) Currently in use of antihypertensive drugs. Diabetes was defined as meeting any of the following criteria: (1) Fasting plasma glucose (FPG) ≥ 126 mg/dL; (2) Glycated hemoglobin (HbA1c) ≥ 6.5%; (3) Currently in use of hypoglycemic drugs; (4) Self-reported diagnosis of diabetes by a doctor. Asthma was defined as a self-reported medical history of asthma diagnosed by a doctor.

3. Statistical analysis

3.1. Descriptive statistics

Continuous variables (mean ± SD/median [IQR]); categorical variables (frequency [percentage]).

Continuous variable comparison: t-test/ANOVA (normal distribution), Kruskal-Wallis/Mann-Whitney U test (non-

normal distribution); categorical variable comparison: Chi-square/Fisher's exact test.

Missing data (< 20%) imputed via random forest.

3.2. Hierarchical statistical strategy

(1) Three stepwise adjusted Cox models (CTI as continuous/quartile variable [Q1-Q4, Q1 as reference]): Model 1 (no confounders); Model 2 (Model 1 + sociodemographic/lifestyle variables); Model 3 (Model 2 + clinical indicators). Trend tests.

(2) Four-node RCS regression to explore nonlinear dose-response relationships; two-stage Cox model for threshold analysis.

(3) Stratified analyses by age (≤ 60/> 60 years), gender, and disease status (hypertension/diabetes: yes/no) to assess effect heterogeneity.

(4) Propensity score overlap weighting to balance confounding factors; univariate Cox analysis and Kaplan-Meier survival curve plotting.

(5) E-value analysis to evaluate unmeasured confounder impact.

Cardiopulmonary mortality analysis: Competing proportional hazards model; CIF survival curves; Gray's test; Fine-Gray model.

Predictive efficacy assessment: ROC curves and AUC calculation; DeLong test for pairwise comparisons.

Reverse causal bias reduction: Exclude tumor death cases and subjects with < 2 years of follow-up.

External validation: Conducted via CHARLS.

All analyses using R software (version 4.2.1); two-tailed $P < 0.05$ considered statistically significant.

4. Results

4.1. Study population characteristics

Tables 1 and **S1** summarize baseline characteristics of NHANES and CHARLS cohorts.

NHANES: 7, 752 subjects (mean age 48.6 years, 51.3% male, median CTI 8.9 [8.2, 9.6]); 1, 260 deaths (16.3%) during 135 months of follow-up.

CTI > 9.55 (Q4): 8.4-fold higher diabetes risk (36.0% vs 4.3%), 12-fold higher CRP (6.1 vs 0.5 mg/L), 2.5-fold higher all-cause mortality (21.7% vs 8.8%) vs Q1.

Table 1. Baseline characteristics comparison among the CTI quartile groups(NHANES)

	Overall	Q1 (≤ 8.25)	Q2(8.25 < CTI ≤ 8.91)	Q3(8.91 < CTI ≤ 9.55)	Q4 (9.55 < CTI)	p.overall
n	7752	1955	1928	1941	1928	
Age, yr, (mean (SD))	48.6 (18.7)	41.1 (17.7)	49.3 (18.8)	52.1 (18.5)	52.0 (17.4)	< 0.001
Gender, n(%)						< 0.001
Male	3773 (48.7)	905 (46.3)	1028 (53.3)	925 (47.7)	915 (47.5)	
Female	3979 (51.3)	1050 (53.7)	900 (46.7)	1016 (52.3)	1013 (52.5)	
Education, n(%)						< 0.001
< High school	972 (12.6)	141 (7.2)	220 (11.4)	288 (14.9)	323 (16.8)	
Completed high school	1309 (16.9)	292 (14.9)	330 (17.1)	307 (15.8)	380 (19.8)	
> High school	5458 (70.5)	1521 (77.8)	1377 (71.5)	1344 (69.3)	1216 (63.4)	

Table 1 (Continued)

	Overall	Q1 (≤ 8.25)	Q2(8.25 < CTI ≤ 8.91)	Q3(8.91 < CTI ≤ 9.55)	Q4 (9.55 < CTI)	p.overall
Marital status, n(%)						0.001
Married	4608 (60.6)	1060 (56.7)	1176 (62.1)	1203 (62.4)	1169 (61.1)	
Never married	2995 (39.4)	809 (43.3)	717 (37.9)	724 (37.6)	745 (38.9)	
Alcohol, n(%)						< 0.001
No	6436 (89.2)	1563 (87.2)	1565 (86.8)	1649 (90.6)	1659 (92.3)	
Yes	777 (10.8)	229 (12.8)	238 (13.2)	172 (9.4)	138 (7.7)	
BMI, (kg/m2), (median [IQR])	27.8 [24.2, 32.2]	24.1 [21.5, 27.0]	27.4 [24.2, 30.7]	29.1 [25.8, 33.1]	31.4 [27.5, 36.3]	< 0.001
Laboratory, (median [IQR])						
Wbc, (1000cells/ul)	6.6 [5.5, 8.0]	5.8 [4.9, 6.9]	6.3 [5.3, 7.5]	6.8 [5.7, 8.1]	7.5 [6.3, 8.9]	< 0.001
HGB, (g/dl)	14.3 [13.2, 15.4]	14.1 [13.1, 15.2]	14.4 [13.3, 15.4]	14.3 [13.2, 15.4]	14.3 [13.1, 15.4]	0.001
Plt, (1000cells/ul)	248.0 [209.0, 295.0]	239.0 [205.0, 281.0]	244.0 [206.0, 284.0]	252.0 [210.0, 301.0]	262.0 [218.0, 308.5]	< 0.001
Creatinine, (umol/L)	74.3 [62.8, 88.4]	72.5 [62.8, 85.8]	77.8 [63.6, 88.6]	74.3 [63.6, 88.4]	72.5 [61.9, 88.4]	< 0.001
Cholesterol,（mmol/L）	5.0 [4.3, 5.7]	4.6 [4.0, 5.3]	4.9 [4.3, 5.6]	5.1 [4.4, 5.9]	5.3 [4.6, 6.2]	< 0.001
Tgy (median [IQR])	8.6 [8.2, 9.0]	8.0 [7.7, 8.2]	8.4 [8.2, 8.7]	8.8 [8.5, 9.0]	9.3 [9.0, 9.7]	< 0.001
CRP (median [IQR])	2.0 [0.8, 4.8]	0.5 [0.3, 1.0]	1.5 [0.8, 2.8]	2.9 [1.6, 5.7]	6.1 [3.2, 11.8]	< 0.001
CTI	8.9 [8.2, 9.6]	7.8 [7.4, 8.1]	8.6 [8.4, 8.8]	9.2 [9.1, 9.4]	10.0 [9.7, 10.3]	< 0.001
Disease status, n(%)						
Diabetes (%)						< 0.001
Yes	1316 (17.0)	84 (4.3)	214 (11.1)	324 (16.7)	694 (36.0)	
No	6436 (83.0)	1871 (95.7)	1714 (88.9)	1617 (83.3)	1234 (64.0)	
Asthma (%)						< 0.001
Yes	1038 (13.4)	217 (11.1)	235 (12.2)	291 (15.0)	295 (15.3)	
No	6705 (86.6)	1736 (88.9)	1688 (87.8)	1650 (85.0)	1631 (84.7)	
Hyptersion (%)						< 0.001
Yes	3083 (39.8)	425 (21.7)	736 (38.2)	896 (46.2)	1026 (53.2)	
No	4669 (60.2)	1530 (78.3)	1192 (61.8)	1045 (53.8)	902 (46.8)	
Permth_int (median [IQR])	135.0 [118.0, 156.0]	138.0 [120.0, 159.0]	136.0 [118.0, 155.0]	133.0 [116.0, 154.0]	135.0 [116.0, 156.0]	< 0.001
Mortstat, n(%)						< 0.001
Survive	6492 (83.7)	1782 (91.2)	1621 (84.1)	1580 (81.4)	1509 (78.3)	
Dead	1260 (16.3)	173 (8.8)	307 (15.9)	361 (18.6)	419 (21.7)	
Mortstat1, n(%)						< 0.001
Survive	6492 (83.7)	1782 (91.2)	1621 (84.1)	1580 (81.4)	1509 (78.3)	

Table 1 (Continued)

	Overall	Q1 (≤ 8.25)	Q2(8.25 < CTI ≤ 8.91)	Q3(8.91 < CTI ≤ 9.55)	Q4 (9.55 < CTI)	p.overall
Cardio - Pulmonary Death	383 (4.9)	48 (2.5)	97 (5.0)	111 (5.7)	127 (6.6)	
Other deaths	877 (11.3)	125 (6.4)	210 (10.9)	250 (12.9)	292 (15.1)	

Note: BMI, Body mass index; Wbc, White blood cell count; HGB, Hemoglobin; Plt, Platelet count; CRP, C-reactive protein; CTI, C-reactive protein-triglyceride glucose index; Tgy, triglyceride-glucose; Mortstat, All-cause mortality rate; Mortstat1, Death rates for specific diseases; Permth_int, Follow-up time

CHARLS: 9, 352 subjects (median age 58 years, 55.4% male, median CTI 8.7 [8.1, 9.2]); 236 deaths (2.5%) during 108 months of follow-up.

CTI > 9.55 (Q4): 8.2-fold higher diabetes risk (21.4% vs 2.6%), 2.9-fold higher all-cause mortality (4.7% vs 1.6%) vs Q1.

CTI quartile analysis: Mortality increases with CTI (P < 0.001 for trend) in both cohorts.

Correlation between CTI and All-cause and Cardiopulmonary Mortalities

NHANES Cox models: Model 1 (HR = 1.42, 95%CI: 1.34-1.50, P < 0.001), Model 2 (HR = 1.26, 95%CI: 1.18-1.35, P < 0.001), Model 3 (HR = 1.21, 95% CI: 1.12-1.31, P < 0.001) for all-cause mortality. Model 3 quartile analysis: Q4 vs Q1 (HR = 1.37, 95% CI: 1.12-1.67, P = 0.002) with significant linear trend.

Cardiopulmonary mortality HRs: Model 1 (1.46), Model 2 (1.29), Model 3 (1.24); Model 1 Q4 vs Q1 (2.88-fold, 95% CI: 2.07-4.02, P < 0.001); Model 3 (HR = 1.42, 95% CI: 0.98-2.05, P = 0.063) with marginal trend significance.

Competing risk analysis: Q4 HR = 1.27 (95% CI: 0.87-1.86, P = 0.280).

Table 2. Cox proportional hazard model results

Mortality		Mortality 1		Mortality 2		Mortality 3		Mortality 4	
Group	Characteristic	HR, 95% CI	p-value	HR, 95% CI	p-value	HR, 95% CI	p-value	HR, 95% CI	p-value
Model1	CTI	1.42(1.34, 1.50)	< 0.001	1.41(1.32, 1.50)	< 0.001	1.46(1.32, 1.61)	< 0.001	1.43(1.31, 1.57)	< 0.001
	CTI_q4								
	Q1	—		—		—		—	
	Q2	1.88(1.56, 2.26)	< 0.001	1.85(1.48, 2.31)	< 0.001	2.15(1.52, 3.03)	< 0.001	2.08(1.48, 2.94)	< 0.001
	Q3	2.24(1.87, 2.69)	< 0.001	2.18(1.75, 2.71)	< 0.001	2.49(1.77, 3.49)	< 0.001	2.39(1.71, 3.35)	< 0.001
	Q4	2.64(2.21, 3.15)	< 0.001	2.5(2.02, 3.090	< 0.001	2.88(2.07, 4.02)	< 0.001	2.73(1.96, 3.80)	< 0.001
HR, p for trend		1.99	< 0.001	1.92	< 0.001	2.10	< 0.001	1.32	< 0.001
Model2	CTI	1.26(1.18, 1.35)	< 0.001	1.22(1.12, 1.33)	< 0.001	1.29(1.14, 1.46)	< 0.001	1.23(1.07, 1.41)	0.003
	CTI_q4								
	Q1	—		—		—		—	
	Q2	1.07(0.88, 1.29)	0.493	1.02(0.81, 1.270	0.894	1.16(0.82, 1.64)	0.404	1.17(0.82, 1.65)	0.39
	Q3	1.14(0.95, 1.38)	0.154	1.07(0.85, 1.33)	0.573	1.21(0.86, 1.71)	0.275	1.17(0.83, 1.67)	0.37
	Q4	1.5(1.25, 1.82)	< 0.001	1.35(1.08, 1.69)	0.008	1.53(1.08, 2.17)	0.017	1.4(0.97, 2.01)	0.071

Table 2 (Continued)

Mortality		Mortality 1		Mortality 2		Mortality 3		Mortality 4	
Group	Characteristic	HR, 95% CI	p-value	HR, 95% CI	p-value	HR, 95% CI	p-value	HR, 95% CI	p-value
HR, p for trend		1.34	< 0.001	1.24	0.008	1.34	0.018	1.10	0.075
Model3	CTI	1.21(1.12, 1.31)	< 0.001	1.14(1.04, 1.25)	0.007	1.24(1.08, 1.42)	0.002	1.18(1.02, 1.37)	0.025
	CTI_q4								
	Q1	—		—		—		—	
	Q2	1.07(0.88, 1.29)	0.507	1.01(0.80, 1.26)	0.949	1.18(0.83, 1.67)	0.366	1.16(0.82, 1.64)	0.42
	Q3	1.14(0.94, 1.38)	0.174	1.03(0.82, 1.29)	0.789	1.21(0.85, 1.71)	0.289	1.12(0.79, 1.60)	0.52
	Q4	1.37(1.12, 1.67)	0.002	1.16(0.91, 1.48)	0.224	1.42(0.98, 2.05)	0.063	1.27(0.87, 1.86)	0.22
HR, p for trend		1.25	0.002	1.11	0.222	1.27	0.067	1.07	0.280

Mortality 1: All-cause mortality, Mortality 2: Exclude all-cause death from tumors and death within two years, Mortality 3: Cardio-pulmonary mortality, Mortality 4: Competitive proportional hazard model cardio-pulmonary mortality

Kaplan-Meier curves: Q4 all-cause mortality significantly higher than Q1 (Log rank P < 0.001).

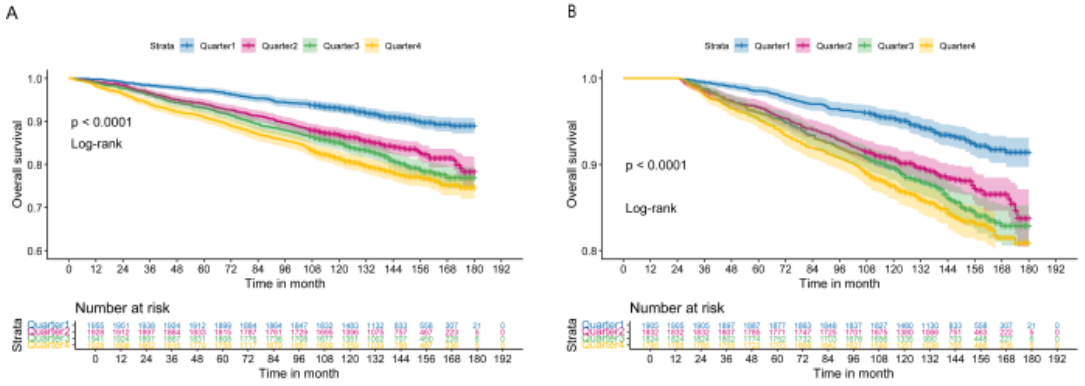

Figure 2. A: Kaplan-Meier survival analysis curves for all-cause mortality; B: excluding tumor death and death within 2 years

Cardiopulmonary mortality curves: Q4 higher at follow-up < 176 months; Q2 higher at follow-up > 176 months.

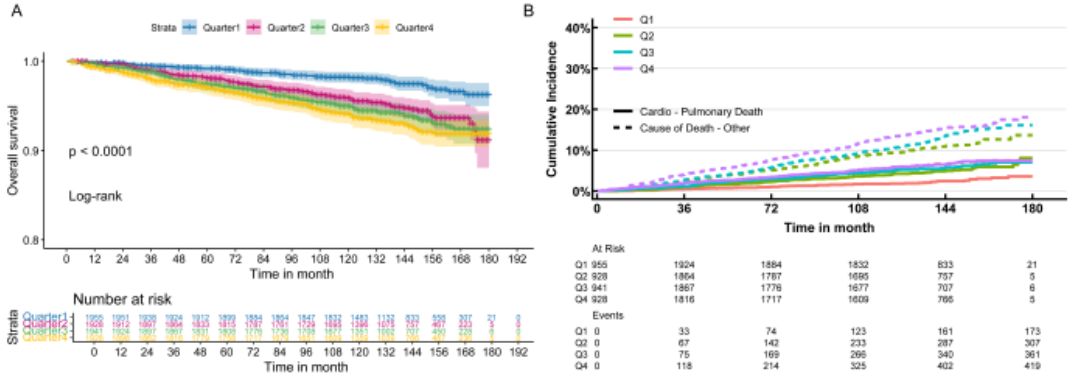

Figure 3. A: Cardiac and lung mortality survival curve; B: Competition proportional hazard model distribution curve

Subgroup analyses: CTI-mortality association stronger in subjects > 60 years old, those with hypertension, and those with diabetes; no gender/asthma influence.

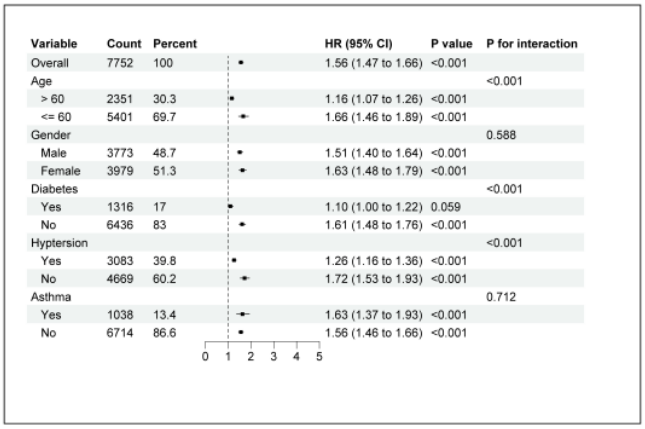

Figure 4. The association of CTI with the all-cause mortality in different subgroups of the population.

Analysis of the Predictive Efficacy and Threshold Effect of CTI

RCS: Linear CTI-all-cause mortality relationship (P for nonlinearity > 0.05).

Threshold effect: CTI > 9.77 (NHANES, HR = 1.49, 95%CI: 1.26-1.76, P < 0.001); CTI > 7.54 (CHARLS, HR = 1.66, 95%CI: 1.43-1.94, P < 0.001).

Table S2. cut-off effect analysis of CTI on all cause mortality in Patient, A: NHANES, B: CHARLS

Outcome	the effect size, 95% CI, P value
NHANES	
Model 1 Fitting model by standard linear regression	1.21(1.13-1.31), < 0.001
Model 2 Fitting model by two-piecewise linear regression	
Inflection point	9.77
< 9.77	1.11(1.01-1.23), 0.039
>9.77	1.49(1.26-1.76), < 0.001
P for likelihood ratio test	0.011
CHARLS	
Model 1 Fitting model by standard linear regression	1.56(1.34-1.82), < 0.001
Model 2 Fitting model by two-piecewise linear regression	
Inflection point	7.54
< 7.54	0.12(0.07-0.57), 0.002
>7.54	1.66(1.43-1.94), < 0.001
P for likelihood ratio test	0.002

Note: ROC curves: CTI (AUC = 0.61) outperforms CRP (0.58) and TyG (0.59) alone (P < 0.05 for pairwise comparisons).

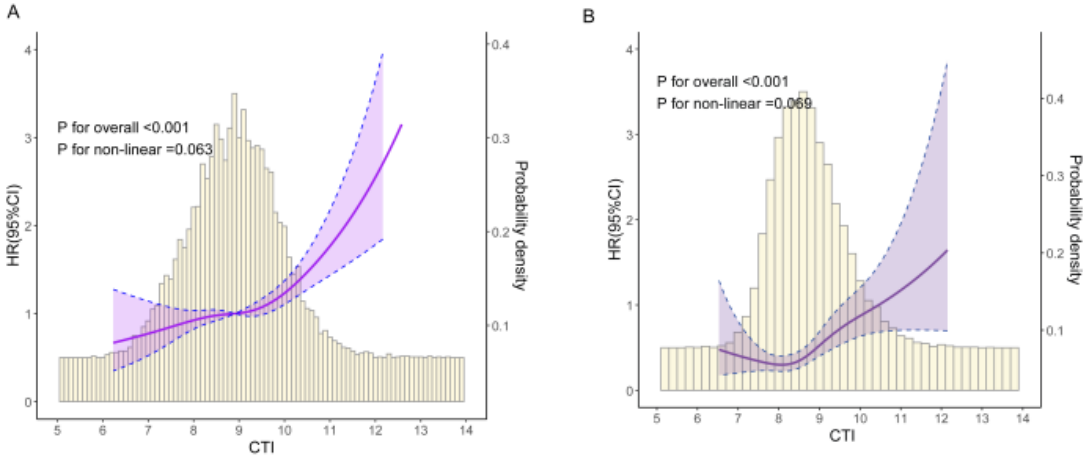

Figure S1. RCS of CTI index with all-cause mortality, A: NHANES; B: CHARLS

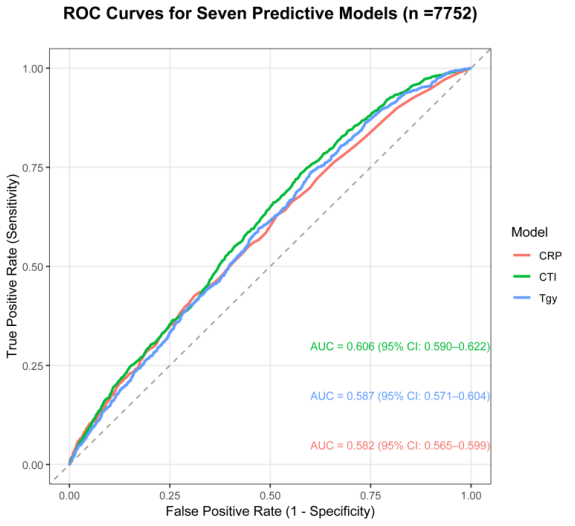

Figure 5. ROC curve analysis of the incremental effect of CTI on all-cause mortality

4.2. Sensitivity analyses

NHANES propensity score overlap weighting: All covariates SMD < 0.1, indicating effective confounder balancing.

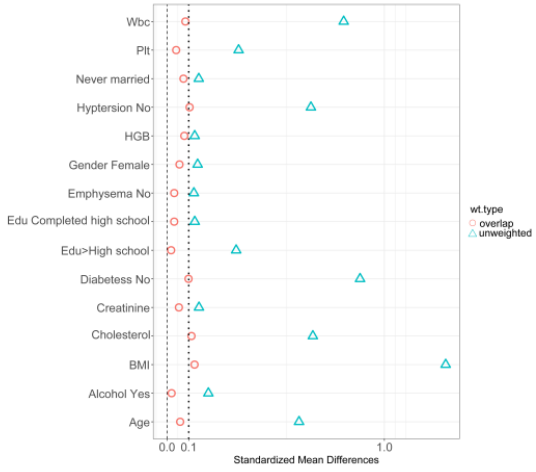

Figure S2. Baseline characteristics balance graph of patients after overlapping weighting(NHANES)

Kaplan-Meier: Q4 all-cause/cardiopulmonary mortality higher than Q1 (Log rank P < 0.001 for both).

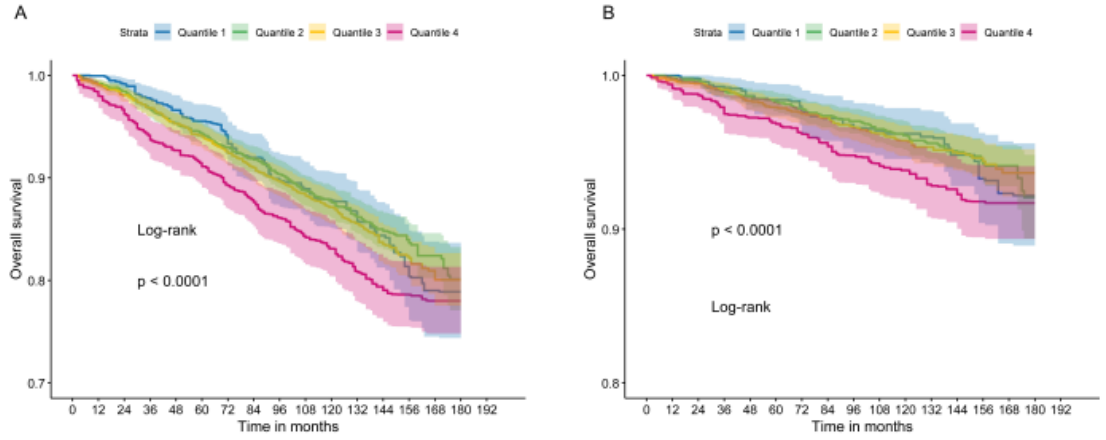

Figure S3. Overlapping weighted survival curves. A: All-cause mortality; B: Cardiopulmonary mortality rate.

Weighted univariate Cox: CTI correlated with all-cause (HR = 1.19, 95% CI: 1.07-1.33, P < 0.001) and cardiopulmonary (HR = 1.27, 95% CI: 1.05-1.53, P < 0.001) mortality.

Table S3. Comparison of baseline features between the CTI quartile groups after overlapping weights

Rowname	Overall	Q1	Q2	Q3	Q4	p	SMD
Age, yr, (mean (SD))	49.64 (18.60)	50.27 (18.24)	49.15 (18.46)	49.25 (18.80)	49.90 (18.88)	0.477	0.036
BMI, (kg/m2), (mean (SD))	28.16 (5.12)	28.50 (6.07)	27.86 (4.83)	27.93 (4.77)	28.33 (4.67)	0.025	0.076
Gender(%)							
Male	51.24	53.14	50.79	50.27	50.74	0.551	0.029
Female	48.76	46.86	49.21	49.73	49.26		
Marital new(%)							
Married/Living with partner	60.26	59.99	61.21	61.78	58.07	0.332	0.042
Never married	39.74	40.01	38.79	38.22	41.93		
Edu(%)							
< High school	12.37	12.44	12.7	12.83	11.49	0.942	0.03
Completed high school	16.01	16.4	15.85	15.29	16.49		
>High school	71.63	71.16	71.45	71.88	72.01		
Alcohol(%)							
No	88.73	88.59	89.04	88.93	88.37	0.951	0.012
Yes	11.27	11.41	10.96	11.07	11.63		
Wbc, (mean (SD))	6.77 (1.85)	6.87 (2.11)	6.71 (1.82)	6.74 (1.69)	6.77 (1.75)	0.444	0.045
HGB, (mean (SD))	14.26 (1.57)	14.26 (1.55)	14.30 (1.56)	14.30 (1.55)	14.18 (1.62)	0.325	0.044
Plt, (mean (SD))	255.73 (71.54)	257.20 (76.60)	255.51 (67.86)	256.01 (69.32)	254.19 (72.12)	0.9	0.022
Creatinine, (mean (SD))	80.03 (35.92)	81.02 (24.14)	79.56 (37.37)	79.06 (35.14)	80.48 (44.12)	0.489	0.033
Cholesterol, (mean (SD))	5.08 (1.05)	5.06 (1.07)	5.12 (1.03)	5.13 (1.02)	5.02 (1.06)	0.043	0.065
Diabetess(%)							
Yes	13.03	15.06	11.73	12.29	13.03	0.159	0.053

Table S3 (Continued)

Rowname	Overall	Q1	Q2	Q3	Q4	p	SMD
No	86.97	84.94	88.27	87.71	86.97		
Hyptersion(%)							
Yes	39.36	42.13	37.06	38.62	39.64	0.13	0.055
No	60.64	57.87	62.94	61.38	60.36		
Emphysema(%)							
Yes	12.43	12.16	11.92	12.64	13.01	0.866	0.019
No	87.57	87.84	88.08	87.36	86.99		

Table S4. Cox proportional hazard model results (after overlap weighting)

Mortality		All-cause mortality		Cardio-pulmonary mortality	
Group	**Characteristic**	**HR, 95% CI**	**p-value**	**HR, 95% CI**	**p-value**
	CTI	1.19(1.07, 1.33)	< 0.001	1.27(1.05, 1.53)	0.014
	CTI_q4				
	Q1	—		—	
	Q2	0.93(0.74, 1.18)	0.560	0.95(0.62, 1.45)	0.799
	Q3	1.00(0.79, 1.27)	0.998	0.94(0.63, 1.49)	0.887
	Q4	1.27(0.98, 1.66)	0.070	1.42(0.89, 2.280	0.142
HR, p for trend		1.20	0.052	1.27	0.142

Weighted CTI quartile analysis: No significant HR differences between Q2-Q4 and Q1. Reverse causal bias reduction: CTI HRs for all-cause mortality in Models 1-3 (1.41, 1.22, 1.14, $P < 0.05$), indicating stable results. Competing risk model: Q3-Q4 cumulative incidence higher than Q1-Q2 ($p < 0.001$); clear risk gradient.

Table S5. Function density distribution diagram of competition proportional hazard model

Group	Characteristic	N	3-year cuminc	6-year cuminc	9-year cuminc	12-year cuminc	15-year cuminc	p-value1
Cardio - Pulmonary Death	CTI_q4							< 0.001
	Q1	1, 955	0.51% (0.27%, 0.92%)	1.0% (0.65%, 1.6%)	1.7% (1.2%, 2.3%)	2.4% (1.8%, 3.3%)	3.6% (2.5%, 4.9%)	
	Q2	1, 928	1.0% (0.66%, 1.6%)	2.3% (1.7%, 3.0%)	3.6% (2.8%, 4.5%)	4.9% (4.0%, 6.1%)	8.1% (5.6%, 11%)	
	Q3	1, 941	1.1% (0.73%, 1.7%)	2.9% (2.3%, 3.8%)	4.4% (3.5%, 5.4%)	5.7% (4.7%, 6.9%)	7.0% (5.7%, 8.6%)	
	Q4	1, 928	2.0% (1.5%, 2.7%)	3.4% (2.7%, 4.3%)	5.2% (4.3%, 6.2%)	6.5% (5.5%, 7.7%)	7.4% (6.2%, 8.8%)	
Cause of Death - Other	CTI_q4							< 0.001

Table S5 (Continued)

Group	Characteristic	N	3-year cuminc	6-year cuminc	9-year cuminc	12-year cuminc	15-year cuminc	p-value1
	Q1	1, 955	1.2% (0.77%, 1.7%)	2.8% (2.1%, 3.6%)	4.6% (3.7%, 5.6%)	6.6% (5.5%, 7.9%)	7.5% (6.2%, 8.9%)	
	Q2	1, 928	2.4% (1.8%, 3.2%)	5.1% (4.2%, 6.1%)	8.5% (7.3%, 9.8%)	11% (9.6%, 13%)	14% (11%, 16%)	
	Q3	1, 941	2.7% (2.1%, 3.5%)	5.8% (4.8%, 6.9%)	9.3% (8.1%, 11%)	14% (12%, 15%)	16% (14%, 18%)	
	Q4	1, 928	4.1% (3.3%, 5.0%)	7.7% (6.5%, 8.9%)	12% (10%, 13%)	16% (14%, 17%)	18% (16%, 20%)	

Adjusted for other deaths, CTI-cardiopulmonary mortality HRs (Models 1-3: 1.43, 1.23, 1.18, P < 0.05).

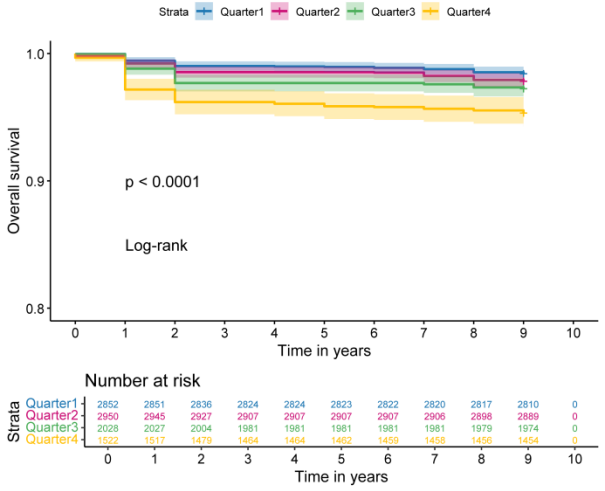

Figure S4. Kaplan-Meier survival analysis curves for all-cause mortality (CHARLS)

Competing risk probability: Q4 3-year cardiopulmonary death risk (2.0% vs 0.51%, P < 0.001); 6-year other cause death risk (7.7% vs 2.8%, P < 0.001).

E-value: Moderate-to-strong result robustness.

Table S6. Cox proportional hazard model results and E-value

Mortality		Mortality 1	Mortality 2	Mortality 3	Mortality 4
Group	Characteristic	E-value, 95% CI	E-value, 95% CI	E-value, 95% CI	E-value, 95% CI
Model1	CTI	2.19(2.01, 2.37)	2.40(2.18, 2.62)	1.28(1.96, 2.66)	2.21(1.92, 2.57)
Model2	CTI	1.83(1.64, 2.04)	1.17(1.49, 1.99)	1.90(1.54, 2.18)	1.76(1.34, 2.11)
Model3	CTI	1.71(1.49, 1.95)	1.54(1.24, 1.81)	1.79(1.37, 2.09)	1.64(1.16, 1.99)

CHARLS Database Validation

CHARLS Models 1-3: Significant CTI-all-cause mortality correlation (HR = 1.50, 1.57, 1.56, P < 0.001).

Quartile analysis: Q4 vs Q1 (HR = 3.21, 95% CI: 2.15-4.79, P < 0.001).

Kaplan-Meier: Q4 all-cause mortality higher than Q1 (Log rank P < 0.001).

Table S7. Cox proportional hazard model results (CHARLS)

Group	Characteristic	HR, 95% CI	p-value
Model1	CTI	1.50(1.31, 1.71)	< 0.001
	CTI_q4		
	Q1	—	
	Q2	1.38(0.94, 2.02)	0.098
	Q3	1.76(1.19, 2.61)	0.005
	Q4	3.02(2.08, 4.39)	< 0.001
Model2	CTI	1.57(1.36, 1.80)	< 0.001
	CTI_q4		
	Q1	—	
	Q2	1.37(0.94, 2.01)	0.105
	Q3	1.78(1.20, 2.65)	0.004
	Q4	3.24(2.22, 4.73)	< 0.001
Model3	CTI	1.56(1.34, 1.82)	< 0.001
	CTI_q4		
	Q1	—	
	Q2	1.41(0.96, 2.07)	0.081
	Q3	1.71(1.14, 2.55)	0.009
	Q4	3.21(2.15, 4.79)	< 0.001

5. Discussions

This cross-continental study confirms CTI as a robust independent predictor of general population all-cause mortality.

6. Key findings

(1) Linear correlation and risk threshold: CTI linearly correlates with all-cause mortality; thresholds 9.77 (NHANES) and 7.54 (CHARLS). CTI above thresholds increases death risk. Threshold differences may stem from demographic, lifestyle, or healthcare system disparities. Defining thresholds provides clinical risk warnings for early intervention.

(2) Cross-cohort validation and age effect: CTI's predictive value confirmed in two cohorts; CHARLS Q4 mortality risk (HR = 3.21) higher than NHANES (HR = 1.37), suggesting middle-aged and elderly are more vulnerable. Age is an important CTI predictive efficacy modifier.

(3) Cardiopulmonary death risk: Elevated CTI linked to increased cardiopulmonary death risk (Model 3 HR = 1.24); competing risk model reduces HR to 1.18. CTI quartile analysis not significant, suggesting subtype-specific effect or sample size limitation.

(4) Consistent mortality correlation: NHANES Q2 highest cardiopulmonary death risk at follow-up > 176 months (possible survivorship bias/confounders). After weighting/E-value analysis, CTI-mortality correlation persists.

7. Mechanisms

CTI integrates CRP (inflammatory pathway) and TyG (metabolic pathway, insulin resistance indicator). CRP activates complement system, promotes endothelial dysfunction/atherosclerosis [9, 10]. TyG is a reliable insulin resistance indicator [11, 12] with wide clinical applications [13]. Concurrent TyG and hsCRP elevation increases cardiovascular/coronary heart disease/stroke risks [14].

Mechanistically: Insulin resistance-induced glucose/lipid disruption exacerbates inflammation; inflammation worsens insulin resistance (vicious cycle) [15], amplifying vascular damage/organ dysfunction and increasing mortality. CTI outperforms single indicators in high-risk individual identification/stratification.

8. Research Advantages and Limitations

Advantages: Cross-continental dual-cohort (n ≈ 17k) validation; identified population-specific thresholds; CTI outperforms single indicators.

Limitations: Observational design (no causal relationship); residual confounders; baseline CTI only; unconsidered confounders (diet, exercise).

Future directions: (1) Expand validation in different races/regions/clinical populations; (2) In-depth mechanism research (dynamic monitoring, multi-omics, RCTs); (3) Develop individualized intervention strategies based on CTI thresholds.

9. Conclusions

This study first establishes CTI as a robust independent predictor of general population all-cause mortality via cross-continental dual-cohort investigation.

Linear dose-response relationship and clear thresholds (9.77 for NHANES, 7.54 for CHARLS) identified; middle-aged and elderly more vulnerable to high CTI-related death risk.

CTI, a simple, economical, routinely measurable indicator, has great potential in clinical risk stratification and public health interventions.

Disclosure statement

The author declares no conflict of interest.

References

[1] Chong D, et al., 2024, Global Burden of Cardiovascular Diseases: Projections from 2025 to 2050. *European Journal of Preventive Cardiology*, zwae281.

[2] Ostrominski JW, et al., 2023, Prevalence and Overlap of Cardiac, Renal, and Metabolic Conditions in US Adults, 1999-2020. *JAMA Cardiology*, 8(11): 1050–1060.

[3] Wheatcroft SB, et al., 2003, Pathophysiological Implications of Insulin Resistance on Vascular Endothelial Function. *Diabetic Medicine*, 20(4): 255–268.

[4] DeFronzo RA, et al., 2015, Type 2 Diabetes Mellitus. *Nature Reviews Disease Primers*, 1: 15019.

[5] Hill MA, et al., 2021, Insulin Resistance and Cardiovascular Disease. *Metabolism*, 119: 154766.

[6] Li S, et al., 2024, Triglyceride-Glucose Related Indices and Mortality. *Cardiovascular Diabetology*, 23(1): 286.

[7] Hu H, et al., 2024, Diabetes Risk Prediction Models. *BMJ Open Diabetes Research & Care*, 12(1): e003680.

[8] Tang S, et al., 2024, C-Reactive Protein-Triglyceride Glucose Index Predicts Stroke in Hypertensive Population. *Diabetology & Metabolic Syndrome*, 16(1): 277.

[9] Koenig W, 2013, High-Sensitivity C-Reactive Protein and Atherosclerotic Disease. *International Journal of Cardiology*, 168(6): 5126–5134.

[10] Wang A, et al., 2017, Cumulative High-Sensitivity C-Reactive Protein Exposure Predicts Cardiovascular Disease Risk. *Journal of the American Heart Association*, 6(10): e005610.

[11] Simental-Mendía LE, et al., 2008, Fasting Glucose and Triglyceride Product as Insulin Resistance Surrogate. *Metabolic Syndrome and Related Disorders*, 6(4): 299–304.

[12] Cui C, et al., 2024, Triglyceride Glucose Index and Modified Indices in Cardiovascular Disease Prediction. *Cardiovascular Diabetology*, 23(1): 185.

[13] Xia X, et al., 2024, Triglyceride-Glucose Index and Atherosclerotic Cardiovascular Disease. *Cardiovascular Diabetology*, 23(1): 208.

[14] Cui C, et al., 2024, TyG Index and High Sensitivity C-Reactive Protein Joint Association with Cardiovascular Disease. *Cardiovascular Diabetology*, 23(1): 156.

[15] Shoelson SE, et al., 2006, Inflammation and Insulin Resistance. *Journal of Clinical Investigation*, 116(7): 1793–1801.