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Association Between the C-Reactive Protein–Triglyceride Glucose Index and All- Cause Mortality in Critically Ill Patients with Acute Ischemic Stroke: A Retrospective Cohort Study

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Abstract

Objective

To investigate the association between the C-reactive protein-triglyceride-glucose index (CTI) and all-cause mortality in critically ill ischemic stroke patients, and to evaluate its prognostic value.

Methods

A retrospective cohort analysis was conducted comprising 476 critically ill patients with a confirmed diagnosis of ischemic stroke, drawing upon data extracted from the MIMIC-IV database covering the period 2008–2022.The CTI was calculated using the formula: $0.412 \times \ Ln\ (CRP\,[mg/L]) + Ln\ (TG\,[mg/dl] \times \ FPG\,[mg/dl])/2$. The principal endpoint was all-cause mortality at 3 months, with mortality at 1 year designated as the secondary outcome. Cox proportional hazards regression, restricted cubic spline modeling, and stratified subgroup analyses were applied to examine the link between CTI and mortality. The predictive capacity of the CTI was compared with that of the conventional TyG index through receiver operating characteristic (ROC) curve analysis.

Results

The median CTI was 6.1 (IQR: 5.4–6.8). Mortality rates at 3 months and 1 year were 21% and 28%, respectively. Following multivariable adjustment, each 1-unit increment in CTI corresponded to a 37% elevated risk of 3-month mortality (hazard ratio [HR] 1.37, 95% confidence interval [CI] 1.06–1.78; P = 0.017). Relative to the lowest CTI tertile, the highest tertile conferred an 84% elevated risk of 3-month mortality (HR 1.84, 95% CI 1.07–3.17; P = 0.027).Restricted cubic spline analysis indicated a linear relationship between CTI and mortality (P for nonlinearity > 0.05). Subgroup analysis revealed that the association between CTI and 3-month mortality was stronger in patients with sepsis (P for interaction < 0.05). The predictive performance of CTI for 3-month (AUC = 0.627) and 1-year (AUC = 0.644) mortality was significantly superior to that of the TyG index (AUC = 0.563 and 0.546, respectively; P < 0.05).

Conclusion

The CTI serves as an independent predictor of both 3-month all-cause mortality and 1-year mortality in critically ill ischemic stroke patients. It exhibits superior prognostic discrimination relative to the conventional TyG index, indicating potential utility as an accessible instrument for clinical risk stratification and personalized therapeutic management.

Key points

C-reactive protein-triglyceride-glucose index, acute ischemic stroke, all-cause mortality, MIMIC-IV database

Introduction

Ischemic cerebrovascular events arise from stenotic or obstructive pathological changes affecting intracranial or extracranial arteries, ultimately precipitating parenchymal injury attributable to compromised perfusion and oxygen deprivation. Epidemiological data indicate that approximately 7.6308 million new cases of ischemic stroke occurred worldwide in 2019, representing an 87.55% increase compared with 1990[1]. Ischemic stroke remains one of the foremost contributors to global mortality and morbidity [2]. Among these, severe ischemic stroke imposes the greatest burden on both individuals and society. Although intravenous thrombolysis (IVT) and mechanical thrombectomy (MT) can improve the functional prognosis of ischemic stroke, their efficacy is constrained by narrow therapeutic time windows. Therefore, identifying novel biomarkers for early diagnosis and risk stratification of severe stroke patients with poor prognoses holds substantial clinical significance for timely recognition and intervention. Insulin resistance (IR) denotes diminished responsiveness of target tissues to physiological insulin concentrations—a biochemical definition now widely accepted in the academic community [3], empirical studies have demonstrated that IR serves as a critical pathogenic factor in the development of metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), atherosclerosis, and type 2 diabetes mellitus (T2DM). [4]. IR has been established as a risk factor for stroke. The TyG index, constructed by integrating fasting plasma glucose concentrations with circulating triglyceride measurements, functions as a validated proxy for assessing insulin resistance in clinical and research settings. Extensive empirical evidence indicates that the TyG index correlates with stroke incidence[5][6], recurrence rate, disability rate[7], and mortality[8] [9].

Inflammatory responses are closely related to the development of atherosclerotic strokes[10][11] and are also correlated with the risk of stroke recurrence[12]. Elevated C-reactive protein (CRP) levels indicate the presence of an inflammatory state, and CRP is widely utilized in research on cardiovascular disease and systemic inflammation[13]. In the context of ischemic stroke, CRP functions as both an inflammatory marker and a pathogenic factor implicated in vascular endothelial dysfunction, atherosclerosis, and thrombosis[14] [15], and has also been linked to post-stroke complications[16] [17]. Empirical investigations have identified a robust correlation between elevated C-reactive protein concentrations and the clinical severity as well as long-term outcomes of cerebral ischemia, wherein increased CRP values typically parallel aggravated symptomatology and unfavorable recovery trajectories.[18].

Presently, elevated TyG index values together with increased C-reactive protein concentrations are widely acknowledged as contributing determinants to the pathogenesis of cerebrovascular disorders. The C-Reactive Protein-Triglyceride-Glucose Index (CTI) —a composite biomarker synthesizing the triglyceride-glucose index with C-reactive protein—demonstrates robust links to cardiometabolic dysfunction, incident cardiovascular disease, and adverse fatal outcomes.[19]–[23] [24]. While CTI has been shown to correlate with ischemic stroke incidence[25], its association with post-stroke outcomes, especially among critically ill patients, remains poorly defined, with limited empirical evidence available in the existing literature [26] .This study aims to assess the predictive utility of CTI regarding overall mortality risk in severely ill patients diagnosed with ischemic stroke, employing extensive clinical records from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database.

Materials and methods

Data source

Data for this retrospective cohort analysis were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.0)—an open-access repository comprising prospectively gathered clinical records of sequential admissions to intensive care units (ICUs) at Beth Israel Deaconess Medical Center during 2008–2022. Data retrieval was conducted via Navicat Premium 17 following a predefined extraction protocol. The lead investigator (H.S.) completed the National Institutes of Health “Protecting Human Research Participants” training (certification ID 1741944) and obtained institutional data use authorization. The study protocol was approved by the Institutional Review Board of Beth Israel Deaconess Medical Center, with waiver of informed consent granted due to the deidentified, open-access nature of the data. All personal identifiers were replaced with randomly assigned codes to preserve anonymity. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study Population

Patients aged ≥ 18 years with a diagnosis of acute ischemic stroke (AIS), confirmed by International Classification of Diseases, Ninth/Tenth Revision (ICD-9/10) codes, were identified from the MIMIC-IV database (version 3.0). Inclusion criteria required an index hospitalization accompanied by ICU admission. Exclusions included: ICU stays < 24 hours, non-initial hospital presentations, and missing key biomarker data including triglycerides (TG), glucose and C-reactive protein (CRP). After applying these criteria, the final cohort consisted of 476 patients (Fig. 1).

Data collection

Baseline data obtained within the first 24 hours following ICU admission comprised: (1) Demographic characteristics: age, sex, and race; (2) Illness severity indices: Glasgow Coma Scale (GCS), Acute Physiology Score III (APS III), Logistic Organ Dysfunction System (LODS), Oxford Acute Severity of Illness Score (OASIS), Systemic Inflammatory Response Syndrome (SIRS) score, and Sequential Organ Failure Assessment (SOFA); (3) Vital signs: heart rate (HR), mean blood pressure (MBP), respiratory rate (RR), temperature, and peripheral oxygen saturation (SpO_2);(4) Laboratory parameters: red blood cell count (RBC), hemoglobin(Hb), platelets (PLT), white blood cell count (WBC), creatinine, anion gap, glucose, TG ,CRP and triglyceride-glucose index (TyG);(5) Comorbidities: Charlson Comorbidity Index (CCI), acute coronary syndrome(ACS), chronic heart failure (CHF), chronic pulmonary disease (CPD), diabetes mellitus (DM),hypertension, atrial fibrillation (AF), acute kidney injury (AKI) and sepsis;(6) Treatment: administration of vasopressin, statins, angiotensin-converting enzyme inhibitors (ACEIs), antiplatelet agents, performance of endovascular thrombectomy, and initiation of mechanical ventilation (MV).

Exposure and outcome

The primary exposure variable was the CTI index, a composite index derived from TG, glucose and CRP, calculated using the following formula:
$0.412 \times \ Ln\ (CRP\,[mg/L]) + Ln\ (TG\,[mg/dl] \times \ FPG\,[mg/dl])\,/2.$ And TyG was also calculated as: $Ln\,(TG\,[mg/dl] \times FPG\,[mg/dl]/2.$

The principal endpoint was all-cause mortality at 3 months, with mortality at 1 year designated as the secondary outcome.

Statistical Analysis

Baseline characteristics were summarized across the full cohort and stratified by CTI category. Continuous variables were presented as medians with interquartile ranges (IQRs) and compared through Kruskal-Wallis testing, whereas categorical variables were expressed as frequencies (percentages) and evaluated with Pearson's χ^2 tests. Descriptive statistics were produced using the gtsummary package in R.

Time-to-event analyses incorporated Kaplan-Meier survival estimations for overall mortality across CTI trichotomous divisions, with the exposure variable examined as both metric and nominal attributes. Multivariable Cox proportional hazards regression was subsequently employed to derive hazard ratios and corresponding 95% confidence intervals through three hierarchical confounding control strategies: Model 1 (unadjusted), Model 2 (adjusted for age, gender, race), and Model 3 (further adjusted for age, gender, race, SOFA, ACS, CHF, AF, HP, Statin).Trend tests across tertiles used median values per category in regression models. Potential nonlinear dose-response relationships were examined using restricted cubic splines (RCS) with four knots positioned at the 5th, 35th, 65th, and 95th percentiles. Predefined subgroup analyses evaluated consistency across age (< 70 vs. ≥70 years), gender, race, GCS (3–12 vs. 13–15), DM, CHF, sepsis, MV, and other comorbidities; interaction terms tested effect modification.

Discriminatory capacity was compared between CTI and the TyG index—both covariate-adjusted per Model 3—through receiver operating characteristic (ROC) curve analysis. Temporal dynamics of predictive performance were assessed using time-specific ROC curves generated at 3-month and 1-year follow-up intervals; statistical significance of differences in AUC values was determined with the time ROC package.

Sensitivity analyses compared results from four multiple imputation methods—Predictive Mean Matching (PMM), mean substitution, Classification and Regression Trees (CART), and Random Forest (RF)—for missing covariate data.

All analyses used R version 4.4.3; statistical significance was defined as two-sided $P < 0.05$.

Results

Study Population and Baseline Characteristics+

The final analytic sample comprised 476 critically ill patients diagnosed with acute ischemic stroke, identified from the MIMIC database following application of predefined exclusion criteria. (Fig. 1): exclusions included non-index hospital/ICU admissions (n = 4518), short ICU stays (< 24h, n = 386), and missing CTI data (n = 2926).

Demographically, the median age was 67.5 years (IQR: 54.9–79.5); participants were nearly evenly split between males (49.4%, n = 242) and females, with half identifying as White (50%, n = 238). Median baseline CTI was 6.1 (IQR: 5.4–6.8). Key severity indicators included median GCS of 14.0 (IQR: 11.0–15.0), APS III of 37.0 (IQR: 26.0–50.0), LODS of 3.0 (IQR: 1.0–5.5), SIRS score of 2.0 (IQR: 2.0–3.0), SOFA score of 3.0 (IQR: 1.5–5.0), and CCI of

6.0 (IQR: 4.0–8.0). Clinically, 12% had ACS and 12% underwent thrombectomy. Observed mortalities were 21% at 3 months and 28% at 1 year (Table 1).

Table 1
Baseline Characteristics and Clinical Outcomes categorized by CTI index

Characteristic	Overall	CTI			p-value[2]
	N = 476[1]	Low	Medium	High	
		N = 159[1]	N = 158[1]	N = 159[1]	
CTI	6.1 (5.4, 6.8)	5.1 (4.7, 5.4)	6.1 (5.8, 6.4)	7.0 (6.8, 7.3)	< 0.001
Demographic					
Age, years	67.5 (54.9, 79.5)	68.4 (53.3, 81.1)	67.7 (57.9, 81.0)	66.6 (54.0, 75.9)	0.4
Gender, n (%)					0.12
Female	234 (49%)	86 (54%)	80 (51%)	68 (43%)	
Male	242 (51%)	73 (46%)	78 (49%)	91 (57%)	
Race, n (%)					0.7
Non-White	238 (50%)	75 (47%)	82 (52%)	81 (51%)	
White	238 (50%)	84 (53%)	76 (48%)	78 (49%)	
Clinical score					
GCS	14.0 (11.0, 15.0)	14.0 (12.0, 15.0)	14.0 (11.0, 15.0)	14.0 (11.0, 15.0)	0.7
APSIII	37.0 (26.0, 50.0)	29.0 (21.0, 40.0)	37.5 (26.0, 49.0)	46.0 (34.0, 62.0)	< 0.001
LODS	3.0 (1.0, 5.5)	2.0 (1.0, 4.0)	4.0 (2.0, 5.0)	5.0 (3.0, 8.0)	< 0.001
OASIS	31.0 (25.0, 37.0)	28.0 (23.0, 32.0)	31.5 (25.0, 38.0)	35.0 (28.0, 40.0)	< 0.001
SIRS	2.0 (2.0, 3.0)	2.0 (1.0, 2.0)	2.0 (2.0, 3.0)	3.0 (2.0, 3.0)	< 0.001
SOFA	3.0 (1.5, 5.0)	2.0 (1.0, 3.0)	3.0 (2.0, 5.0)	5.0 (3.0, 8.0)	< 0.001
Vital signs					
HR, beats/min	78.9 (68.9, 90.8)	70.5 (65.1, 80.6)	81.4 (72.1, 90.9)	86.0 (77.3, 98.0)	< 0.001

[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

CTI, C-reactive protein-triglyceride glucose index, GCS, Glasgow Coma Scale; APS III, Acute Physiology Score; LODS, logistic organ dysfunction system; OASIS, oxford acute severity of illness score; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; HR, heart rate; MBP, mean blood pressure; RR, respiratory rate; Temp, temperature; SpO2, percutaneous oxygen saturation; RBC, red blood cell; Hb, hemoglobin; PT, platelet; WBC, white blood cell; TG, triglycerides; CRP,C-reactive peptide; TyG, triglyceride-glucose index; CCI, Charlson comorbidity index; OMI, Old myocardial infarction; CHF, chronic heart failure; CPD, chronic pulmonary disease; ACS, acute coronary syndrome; CHF, chronic heart failure; CPD, chronic pulmonary disease; DM, diabetes mellitus; HP, hypertension; AF: atrial fibrillation; AKI, acute kidney injury; ACEI, angiotensin converting enzyme inhibitors; CRR, continuous renal replacement therapy; MV, mechanical ventilation

Characteristic	Overall	CTI			p-value[2]
	N = 476[1]	Low	Medium	High	
		N = 159[1]	N = 158[1]	N = 159[1]	
MBP, mmHg	86.7 (79.3, 95.1)	90.2 (82.0, 99.4)	86.6 (78.5, 95.1)	83.4 (76.6, 90.7)	< 0.001
RR, beats/min	19.2 (17.0, 21.9)	18.1 (16.4, 20.1)	19.1 (17.0, 21.7)	21.1 (18.7, 24.5)	< 0.001
Temp, °C	36.9 (36.7, 37.1)	36.9 (36.7, 37.0)	36.9 (36.7, 37.1)	37.0 (36.8, 37.4)	< 0.001
SpO2, %	97.0 (95.7, 98.1)	96.9 (95.8, 98.0)	97.0 (95.7, 98.4)	96.9 (95.8, 98.0)	0.9
Lab variables					
RBC, 10^{12}/L	4.2 (3.7, 4.6)	4.4 (3.9, 4.7)	4.3 (3.7, 4.7)	4.0 (3.4, 4.4)	< 0.001
Hb, g/dL	12.4 (10.6, 13.8)	12.9 (11.7, 13.9)	12.6 (11.1, 14.3)	11.6 (9.6, 13.4)	< 0.001
PT,10^9/L	222.5 (176.5, 286.5)	215.0 (182.0, 262.0)	236.5 (190.0, 288.0)	214.0 (148.0, 306.0)	0.10
WBC,10^9/L	11.1 (8.6, 15.2)	9.3 (7.2, 12.0)	11.8 (9.1, 15.8)	13.8 (10.0, 18.9)	< 0.001
Anion gap, mmol/L	15.0 (13.0, 17.0)	15.0 (13.0, 17.0)	15.0 (13.0, 17.0)	16.0 (14.0, 19.0)	0.020
Creatinine, mg/dL	1.0 (0.8, 1.4)	0.9 (0.8, 1.1)	0.9 (0.7, 1.3)	1.2 (0.9, 2.0)	< 0.001
Glucose, mg/dL	119.3 (104.0, 155.5)	106.5 (96.5, 118.5)	123.2 (106.0, 154.6)	135.6 (118.4, 184.0)	< 0.001
TG, mg/dL	119.5 (81.0, 159.0)	87.0 (65.0, 126.0)	115.0 (83.0, 149.0)	156.0 (117.0, 214.0)	< 0.001
CRP, mg/L	26.2 (4.7, 109.1)	3.1 (1.2, 6.5)	27.8 (10.8, 54.5)	162.0 (91.6, 221.0)	< 0.001
TyG index	8.9 (8.5, 9.3)	8.5 (8.1, 8.8)	8.9 (8.5, 9.2)	9.4 (9.0, 9.7)	< 0.001
Comorbidities					

[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

CTI, C-reactive protein-triglyceride glucose index, GCS, Glasgow Coma Scale; APS III, Acute Physiology Score; LODS, logistic organ dysfunction system; OASIS, oxford acute severity of illness score; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; HR, heart rate; MBP, mean blood pressure; RR, respiratory rate; Temp, temperature; SpO2, percutaneous oxygen saturation; RBC, red blood cell; Hb, hemoglobin; PT, platelet; WBC, white blood cell; TG, triglycerides; CRP,C-reactive peptide; TyG, triglyceride-glucose index; CCI, Charlson comorbidity index; OMI, Old myocardial infarction; CHF, chronic heart failure; CPD, chronic pulmonary disease; ACS, acute coronary syndrome; CHF, chronic heart failure; CPD, chronic pulmonary disease; DM, diabetes mellitus; HP, hypertension; AF: atrial fibrillation; AKI, acute kidney injury; ACEI, angiotensin converting enzyme inhibitors; CRR, continuous renal replacement therapy; MV, mechanical ventilation

Characteristic	Overall	CTI			p-value[2]
	N = 476[1]	Low	Medium	High	
		N = 159[1]	N = 158[1]	N = 159[1]	
CCI	6.0 (4.0, 8.0)	5.0 (4.0, 7.0)	6.0 (4.0, 8.0)	7.0 (4.0, 8.0)	0.005
ACS, n (%)	58 (12%)	9 (5.7%)	17 (11%)	32 (20%)	< 0.001
CHF, n (%)	107 (22%)	21 (13%)	33 (21%)	53 (33%)	< 0.001
CPD, n (%)	61 (13%)	15 (9.4%)	23 (15%)	23 (14%)	0.3
DM, n (%)	149 (31%)	26 (16%)	60 (38%)	63 (40%)	< 0.001
HP, n (%)	232 (49%)	85 (53%)	86 (54%)	61 (38%)	0.006
AF, n (%)	145 (30%)	47 (30%)	45 (28%)	53 (33%)	0.6
AKI, n (%)	355 (75%)	102 (64%)	116 (73%)	137 (86%)	< 0.001
Sepsis	220 (46%)	32 (20%)	68 (43%)	120 (75%)	< 0.001
Treatments					
Vasopressin, n (%)	25 (5.3%)	0 (0%)	6 (3.8%)	19 (12%)	< 0.001
Statin, n (%)	342 (72%)	121 (76%)	116 (73%)	105 (66%)	0.12
Antiplatelet, n (%)	380 (80%)	134 (84%)	128 (81%)	118 (74%)	0.074
ACEI, n (%)	237 (50%)	65 (41%)	90 (57%)	82 (52%)	0.014
Thrombectomy, n (%)	58 (12%)	28 (18%)	22 (14%)	8 (5.0%)	0.002
MV, n (%)	178 (37%)	23 (14%)	64 (41%)	91 (57%)	< 0.001
Outcomes					
3-month mortality	101 (21%)	23 (14%)	29 (18%)	49 (31%)	< 0.001
1-year mortality	133 (28%)	29 (18%)	41 (26%)	63 (40%)	< 0.001

[1]Median (Q1, Q3); n (%)

[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

CTI, C-reactive protein-triglyceride glucose index, GCS, Glasgow Coma Scale; APS III, Acute Physiology Score; LODS, logistic organ dysfunction system; OASIS, oxford acute severity of illness score; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; HR, heart rate; MBP, mean blood pressure; RR, respiratory rate; Temp, temperature; SpO2, percutaneous oxygen saturation; RBC, red blood cell; Hb, hemoglobin; PT, platelet; WBC, white blood cell; TG, triglycerides; CRP,C-reactive peptide; TyG, triglyceride-glucose index; CCI, Charlson comorbidity index; OMI, Old myocardial infarction; CHF, chronic heart failure; CPD, chronic pulmonary disease; ACS, acute coronary syndrome; CHF, chronic heart failure; CPD, chronic pulmonary disease; DM, diabetes mellitus; HP, hypertension; AF: atrial fibrillation; AKI, acute kidney injury; ACEI, angiotensin converting enzyme inhibitors; CRR, continuous renal replacement therapy; MV, mechanical ventilation

When analyzed by CTI tertile (Low: med = 5.1 [4.7–5.4]; Medium: med = 6.1 [5.8–6.4]; High: med = 7.0 [6.8–7.3]), stepwise increases were seen across most markers of illness severity: significantly higher APS III, LODS, OASIS, SIRS, SOFA scores, HR, and RR accompanied higher CTI (all $P < 0.05$). Lower MBP, RBC, and Hb characterized higher tertiles (all $P < 0.05$), whereas WBC, creatinine, TG, CRP, and TyG index rose progressively. Comorbidities (ACS, CHF, DM, AKI, sepsis) and interventions like vasopressors/MV became more prevalent with increasing CTI, though thrombectomy rates decreased (all $P < 0.05$). Age, gender, race, and statin usage showed no significant inter-tertile differences (all $P > 0.05$). Crucially, both 3-month and 1-year mortality escalated significantly across ascending CTI tertiles.

Clinical outcomes

Kaplan-Meier survival curves demonstrated significant divergence across CTI tertiles (log-rank test $P < 0.01$; Fig. 2). Restricted cubic spline analyses confirmed a predominantly linear association between continuous CTI and both 3-month mortality (overall $P = 0.001$; non-linear component $P = 0.757$; Fig. 3A) and 1-year mortality (overall $P = 0.001$; non-linear component $P = 0.721$; Fig. 3B).

In Cox proportional hazards models adjusting progressively for confounders (Table 2), each unit increase in continuous CTI predicted significantly higher 3-month mortality: Model 1 (HR 1.56; 95% CI 1.24–1.96; $P < 0.001$), Model 2 (HR 1.61; 95% CI 1.27–2.04; $P < 0.001$), and Model 3 (HR 1.37; 95% CI 1.06–1.78; $P = 0.017$). Treating CTI as an ordered categorical exposure confirmed a graded relationship with mortality risk (P for trend < 0.05). Most compellingly, assignment to the highest versus lowest CTI tertile conferred adjusted hazard ratios of 2.29 (95% CI 1.39–3.76; $P = 0.001$) in Model 1, 2.43 (95% CI 1.48–4.01; $P < 0.001$) in Model 2, and 1.84 (95% CI 1.07–3.17; $P = 0.027$) in Model 3 for 3-month mortality. The prognostic value extended to 1-year survival benchmarks.

Table 2
Cox Proportional Hazards Models of CTI and All-Cause Mortality

Outcomes	Model 1			Model 2			Model 3		
	HR (95% CI)	P-value	P for tend	HR (95% CI)	P-value	P for tend	HR (95% CI)	P-value	P for tend
3-Month Mortality									
Continuous	1.56(1.24–1.96)	< 0.001		1.61(1.27–2.04)	< 0.001		1.37 (1.06–1.78)	0.017	
Categorical			< 0.001			< 0.001			0.023
Low	Reference			Reference			Reference		
Medium	1.29(0.75–2.24)	0.4		1.28(0.74–2.22)	0.4		1.17(0.67–2.03)	0.6	
High	2.29(1.39–3.76)	0.001		2.43(1.48–4.01)	< 0.001		1.84(1.07–3.17)	0.027	
1-Year Mortality									
Continuous	1.62(1.33–1.98)	< 0.001		1.70(1.37–2.09)	< 0.001		1.42(1.13–1.79)	0.003	
Categorical			< 0.001			< 0.001			0.007
Low	Reference			Reference			Reference		
Medium	1.47(0.92–2.37)	0.11		1.46(0.91–2.36)	0.12		1.31(0.81–2.12)	0.3	
High	2.44(1.57–3.79)	< 0.001		2.62(1.68–4.07)	< 0.001		1.92(1.19–3.10)	0.008	

HR: hazard ratio; CI: confidence interval.

Model 1: unadjusted; Model 2: adjusted age, gender, race; Model 3: adjusted age, gender,race, SOFA, ACS, CHF, AF, HP, Statin

Subgroup analysis

Subgroup analyses were conducted to explore the CTI–mortality relationship across the following strata: age (< 70 vs. ≥70 years), sex, race, Glasgow Coma Scale score (3–12 vs. 13–15), comorbidities (acute coronary syndrome, diabetes mellitus, congestive heart failure, and hypertension), and clinical conditions (sepsis and mechanical ventilation requirement). For 3-month mortality, a statistically significant interaction emerged between CTI and sepsis status (P for interaction < 0.05). (Fig. 4). For 1-year mortality, significant interactions emerged with ACS, CHF, sepsis, and MV (all P for interaction < 0.05) (Fig. 5).

Comparison of Predictive Efficacy Between CTI and TyG Indices

Direct comparison revealed superior predictive performance of CTI over TyG for both 3-month and 1-year mortality. At 3 months, CTI demonstrated a significantly higher AUC than TyG (0.627 vs. 0.563; p = 0.018; Fig. 6A). Similarly, for 1-year mortality prediction, CTI showed markedly better discrimination with an AUC of 0.644 compared to TyG's 0.546 (p < 0.001; Fig. 6B).

Sensitivity analysis

To validate robustness against missing data mechanisms, sensitivity analyses were conducted using four advanced multiple imputation approaches: PMM, mean substitution, CART, and RF. Post Model 3 adjustment, results were consistent across methods, yielding a pooled HR for 3-month mortality of 1.37 (95% CI 1.06–1.78) (**Supplementary Fig. 1**).

Discussion

From the MIMIC-IV database, 476 critically ill patients with ischemic stroke were ultimately included to evaluate the relationship between CTI and survival endpoints, including all-cause mortality at 3 months and mortality at 1 year. The prognostic association of CTI with all-cause mortality was examined within distinct patient stratifications, including those presenting with acute coronary syndrome, chronic cardiac decompensation, systemic inflammatory response to infection, and invasive respiratory support dependence. Elevated CTI was significantly associated with reduced overall survival at 3 months and 1 year, exhibiting a clear dose-response relationship. Furthermore, CTI was superior to the TyG index alone in predicting both 3-month all-cause mortality and 1-year mortality.

CTI is a composite index incorporating insulin resistance (TyG index) and inflammatory response (CRP). Prior investigations have linked CTI to both the development and fatality of myocardial infarction. Moreover, CTI has been associated with ischemic stroke. Multiple investigations have linked sustained CTI elevation to heightened stroke susceptibility among middle-aged and older adults, with chronic exposure conferring a markedly increased cerebrovascular risk profile [26] [27]. Yet the prognostic relevance of CTI following ischemic stroke—especially in critically ill presentations—remains indeterminate.

The TyG index, calculated from fasting glucose and triglyceride levels, serves as a reliable indicator of insulin resistance. Extensive observational data demonstrate robust links between heightened TyG index levels and unfavorable clinical endpoints, encompassing mortality, functional disability, and new-onset ischemic stroke. In a cohort of severe ischemic stroke patients, Weimin Cai et al[8] identified a significant correlation between the TyG index and all-cause mortality; Jiasheng Hou et al.[28] demonstrated that the TyG index serves as an independent risk factor for all-cause mortality in non-diabetic patients; a separate investigation identified the TyG index as an independent determinant of adverse stroke outcomes[9]. Additionally, studies by Jiang Y et al.[6] and Wang A et al.[5] established the association between the TyG index and stroke risk. Moreover, a prospective cohort study by Wang et al.[29] demonstrated that cumulative TyG exposure over time provides additional predictive value for ischemic stroke. Notably, our findings indicate that the TyG index alone exhibits limited predictive ability for mortality (AUC < 0.57); however, the incorporation of CRP (i.e., CTI) substantially enhances its predictive performance. This finding suggests that the integration of an inflammatory marker (CRP) with the TyG index significantly improves predictive accuracy compared with the TyG index alone in critically ill stroke patients.

CRP is a well-established biomarker of systemic inflammation; atherosclerotic plaque initiation, progression, and destabilization are each linked to heightened CRP concentrations[30]. Given the involvement of these processes in ischemic stroke pathogenesis, CRP can be considered an important parameter for assessing disease progression. Studies have demonstrated that high-sensitivity CRP (hs-CRP) can modify the predictive value of other biomarkers for ischemic stroke prognosis[31]. However, CRP levels may also be elevated due to concurrent infections or stress responses, thereby attenuating its independent predictive capacity. CTI, as a combined indicator integrating the TyG index and CRP, bridges metabolic and inflammatory dimensions. CTI has demonstrated significant associations with cerebrovascular event risk among middle-aged and older adult populations, with sustained elevations in this composite biomarker indicating substantially heightened stroke susceptibility.[27]. The present investigation revealed that CTI exhibits enhanced prognostic accuracy for 90-day and 12-month survival probabilities relative to the TyG index in isolation. The pathophysiological pathways linking CTI to mortality among critically ill patients with ischemic stroke remain incompletely characterized; nonetheless, a bidirectional interplay between insulin resistance and inflammatory responses is well documented. Insulin resistance promotes the production of pro-inflammatory factors, while elevated CRP further contributes to vascular endothelial cell damage and oxidative stress[14][15][32], thereby perpetuating a vicious cycle that promotes ischemic stroke development and progression.

The findings of the current investigation indicate that CTI maintains a robust statistical association with fatal outcomes among intensive care unit admissions presenting with cerebral ischemia, outperforming the TyG index in prognostic discrimination, which consequently offers physicians an alternative evaluative instrument for anticipating patient trajectories. Second, this composite index integrates both metabolic and inflammatory indicators, highlighting that clinical management should encompass not only the control of blood lipids and glucose but also the monitoring of metabolic and inflammatory marker dynamics. Third, CTI is simple, rapid, and cost-effective to calculate, as the three required components—triglycerides, fasting blood glucose, and Both constituent biomarkers of the CTI, namely fasting triglycerides and C-reactive protein, are standard components of routine admission laboratory panels, permitting expedited recognition of individuals at elevated mortality risk and thereby streamlining therapeutic strategizing at the bedside. Additionally, the present investigation incorporated robustness checks and comprehensive covariate adjustment strategies to strengthen the internal validity and reproducibility of the observed associations. Empirical evidence from this analysis establishes a significant correlation between CTI and fatal outcomes among intensive care unit patients with ischemic cerebrovascular pathology, with this composite indicator demonstrating enhanced prognostic accuracy relative to the triglyceride-glucose index alone, thereby furnishing healthcare providers with a supplementary evaluative resource for clinical outcome prediction. Second, this composite index integrates both metabolic and inflammatory indicators, highlighting that clinical management should encompass not only the control of blood lipids and glucose but also the monitoring of metabolic and inflammatory marker dynamics. Third, CTI offers a straightforward, expeditious, and economical calculation method, given that its three constituent parameters—triglycerides, fasting glucose, and C-reactive protein—are standard components of admission laboratory panels, thereby permitting prompt risk stratification for mortality and supporting informed clinical decisions. Moreover, the present investigation utilized robustness testing and meticulous control for potential confounders to bolster the trustworthiness and dependability of the results.

This study has several limitations. First, the study population was derived exclusively from the MIMIC-IV database, which comprises predominantly American patients, and was limited to critically ill ischemic stroke

patients without comparison to other populations. Future prospective, large-scale, multi-ethnic studies are warranted to validate the association between CTI and ischemic stroke prognosis across diverse populations. Second, the retrospective design precludes definitive causal inference; although covariate adjustment was performed for age, sex, race, and SOFA score, residual confounding from unmeasured variables likely persists. Third, CTI was calculated solely at admission, and dynamic changes during the ICU stay and their relationship with prognosis were not examined. Future studies investigating the longitudinal trajectory of CTI and its prognostic implications are warranted. Fourth, the pathophysiological mechanisms linking CTI to ischemic stroke outcomes remain incompletely characterized; mechanistic studies are warranted to clarify these pathways and identify therapeutic targets aimed at modulating inflammation and insulin resistance, ultimately enabling earlier detection and intervention.

Conclusion

In conclusion, this study demonstrates that the C-Reactive Protein-Triglyceride-Glucose Index (CTI) independently predicts 3-month all-cause mortality and 1-year mortality in critically ill ischemic stroke patients, with superior predictive performance relative to the conventional TyG index. CTI demonstrates considerable potential as an easily obtainable instrument for risk categorization and personalized therapeutic decision-making among severely ill individuals presenting with cerebrovascular accidents. Future longitudinal investigations are warranted to substantiate its translational utility in clinical practice.

Declarations

Ethical approval and consent to participate

The study was performed according to the guidelines of the Helsinki Declaration. The use of the MIMIC-IV database was approved by the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The data is publicly available (in the MIMIC-IV database), therefore, the ethical approval statement and the requirement for informed consent were waived for this study.

Consent for publication

All authors of the manuscript agreed to its publication.

Competing interests

The authors declare that they have no competing interests.

Clinical trial number

Not applicable.

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Author Contribution

HS ,AL and HG conceived the study and participated in the design of the study. HS and HG collected the data, MQ, JG and KY analyzed and interpreted the data. HS, AL,HG and MQ drafted and edited the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The raw clinical data analyzed in this study were extracted from the publicly available Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.0) database (https://physionet.org/content/mimiciv/). MIMIC-IV contains de-identified patient ICU data from Beth Israel Deaconess Medical Center (2008–2022) and is accessible to qualified researchers after completing human research protection training and obtaining access authorization. The processed analytic datasets and statistical codes generated in the present study are available from the corresponding author (Aihua Liu, email: liuaihuadoctor@163.com) upon reasonable request. Restrictions apply to raw individual-level clinical data due to the HIPAA privacy regulations of the MIMIC-IV database, which prohibits full public deposition of original patient-level data.

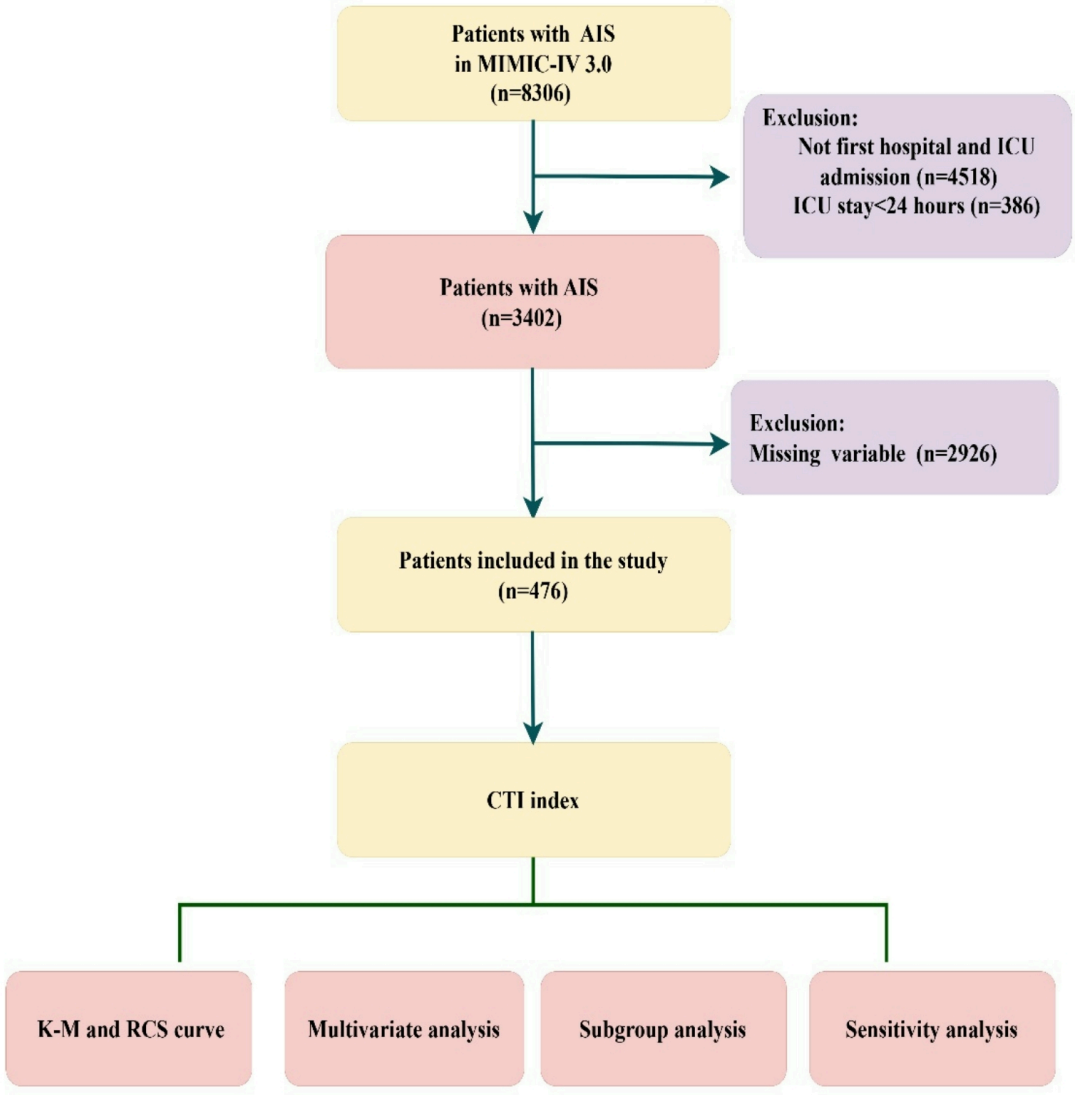
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Figures



CTI, C-reactive protein-triglyceride glucose index

Figure 1

Flow chart for patient selection in this study. AIC, Acute ischemic stroke; MIMIC-IV, medical information mart for intensive care database; RCS, restricted cubic spline, K-M, Kaplan-Meier; RCS, restricted cubic spline.

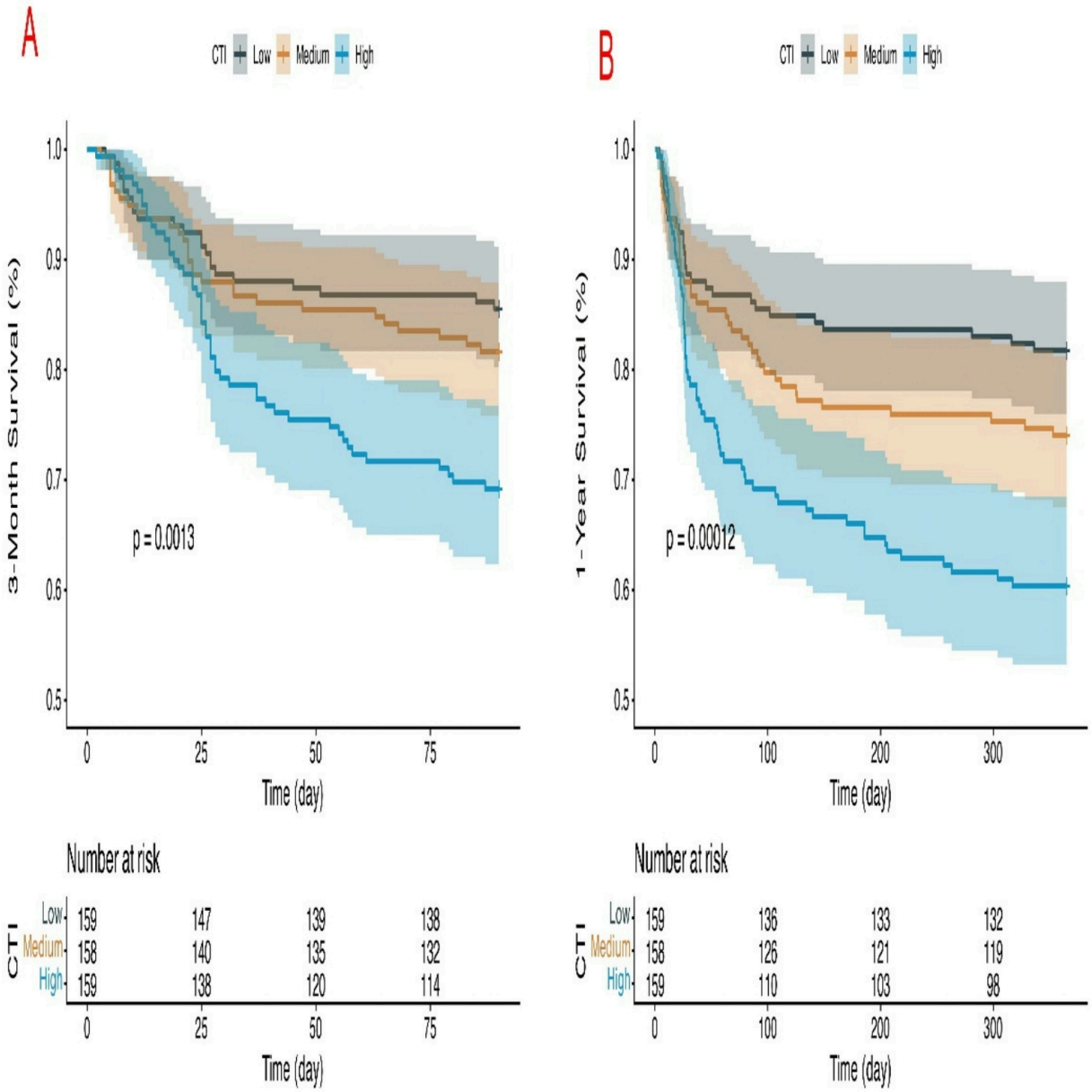


Figure 2

Kaplan–Meier Estimates of 3-Month (A) and 1-Year (B) Mortality across CTI groups.

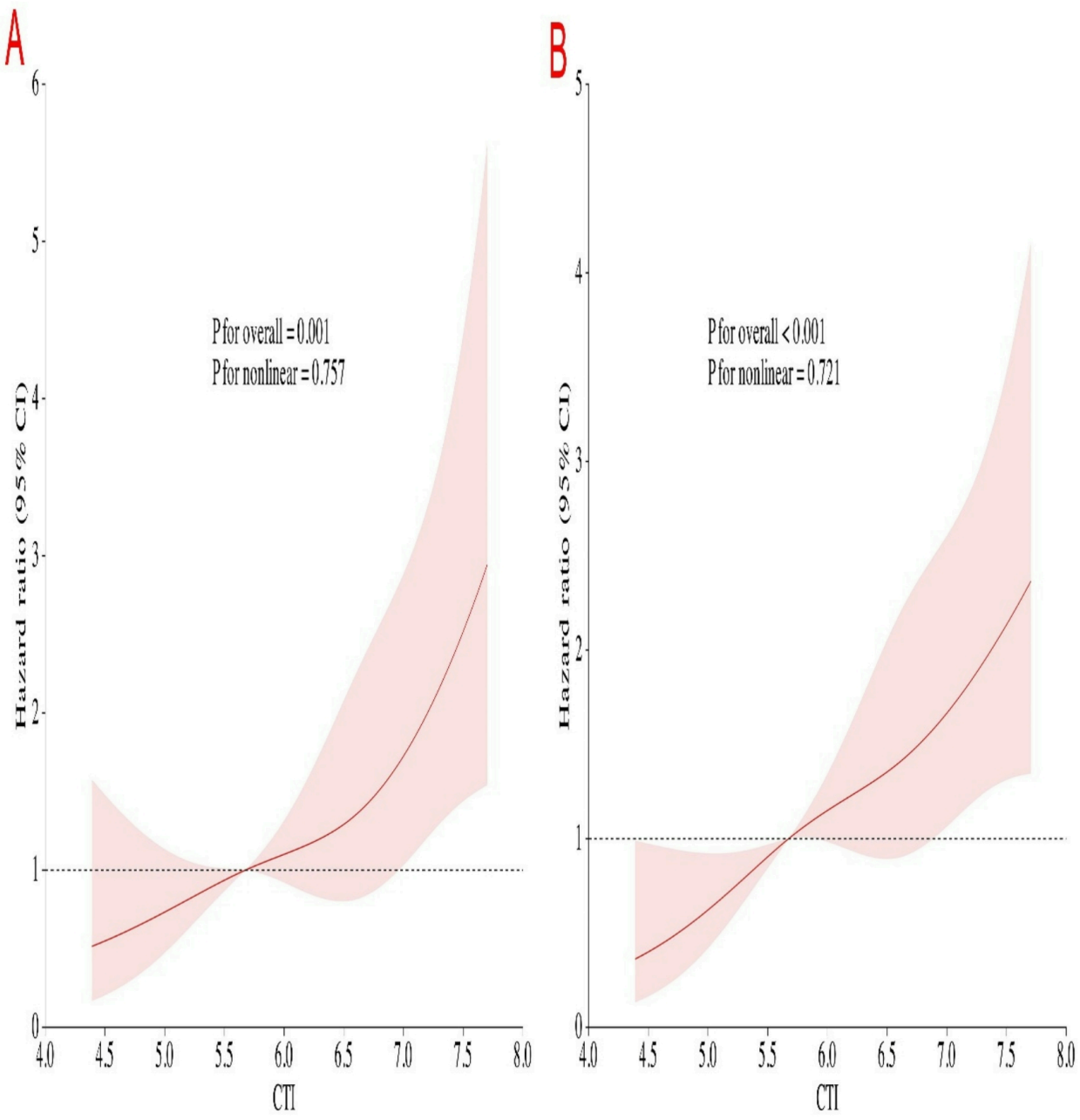


Figure 3

Restricted Cubic Spline Analysis of CTI and risk of all-cause mortality at 3 months (A) and 1 year (B)

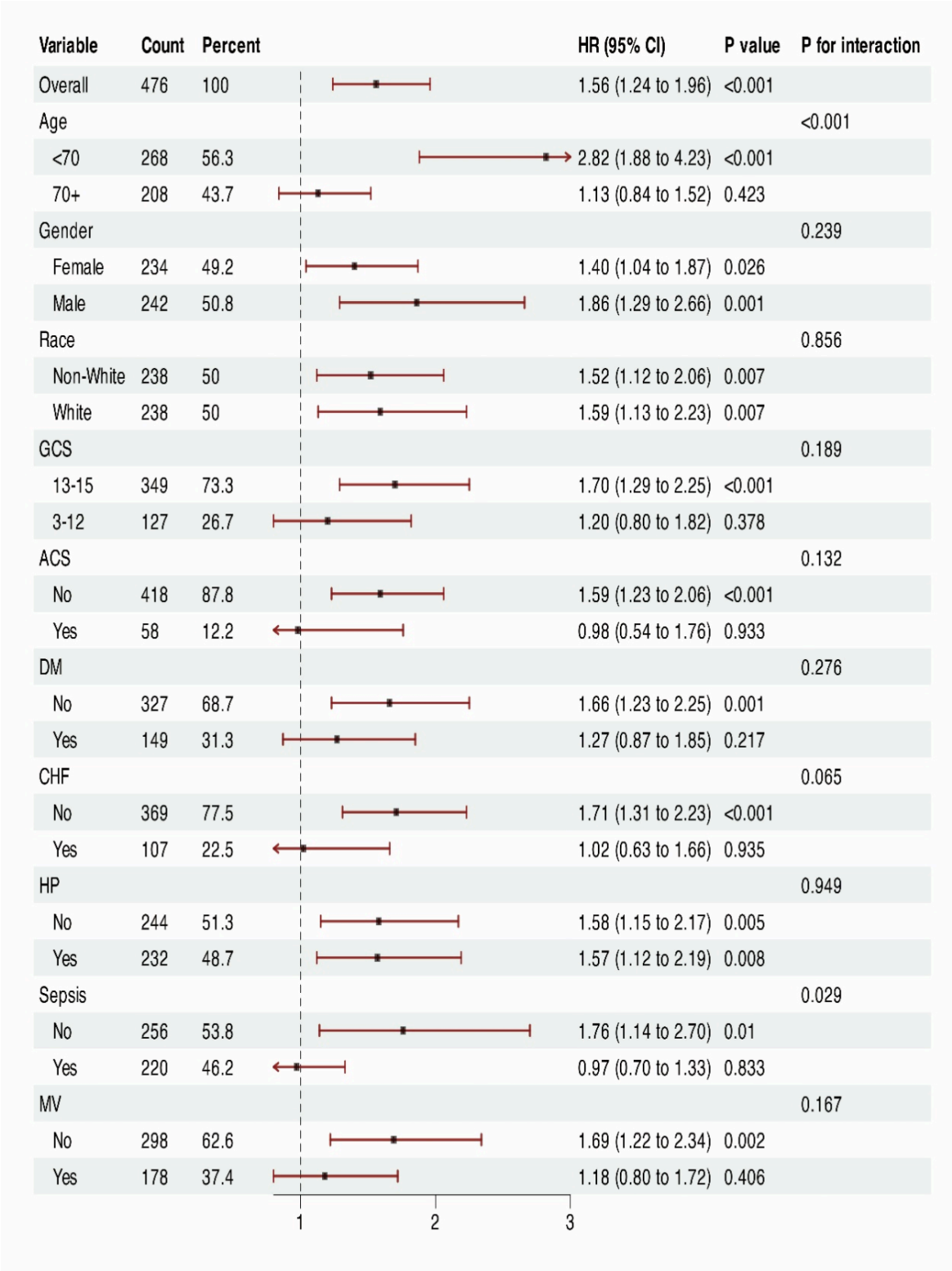


Figure 4

Subgroup analysis of the relationship between CTI and 3-month mortality. CTI, C-reactive protein-triglyceride glucose index; GCS, Glasgow Coma Scale; ACS, acute coronary syndrome; DM, Diabetes mellitus; CHF, chronic heart failure; HP, hypertension; MV, mechanic ventilation

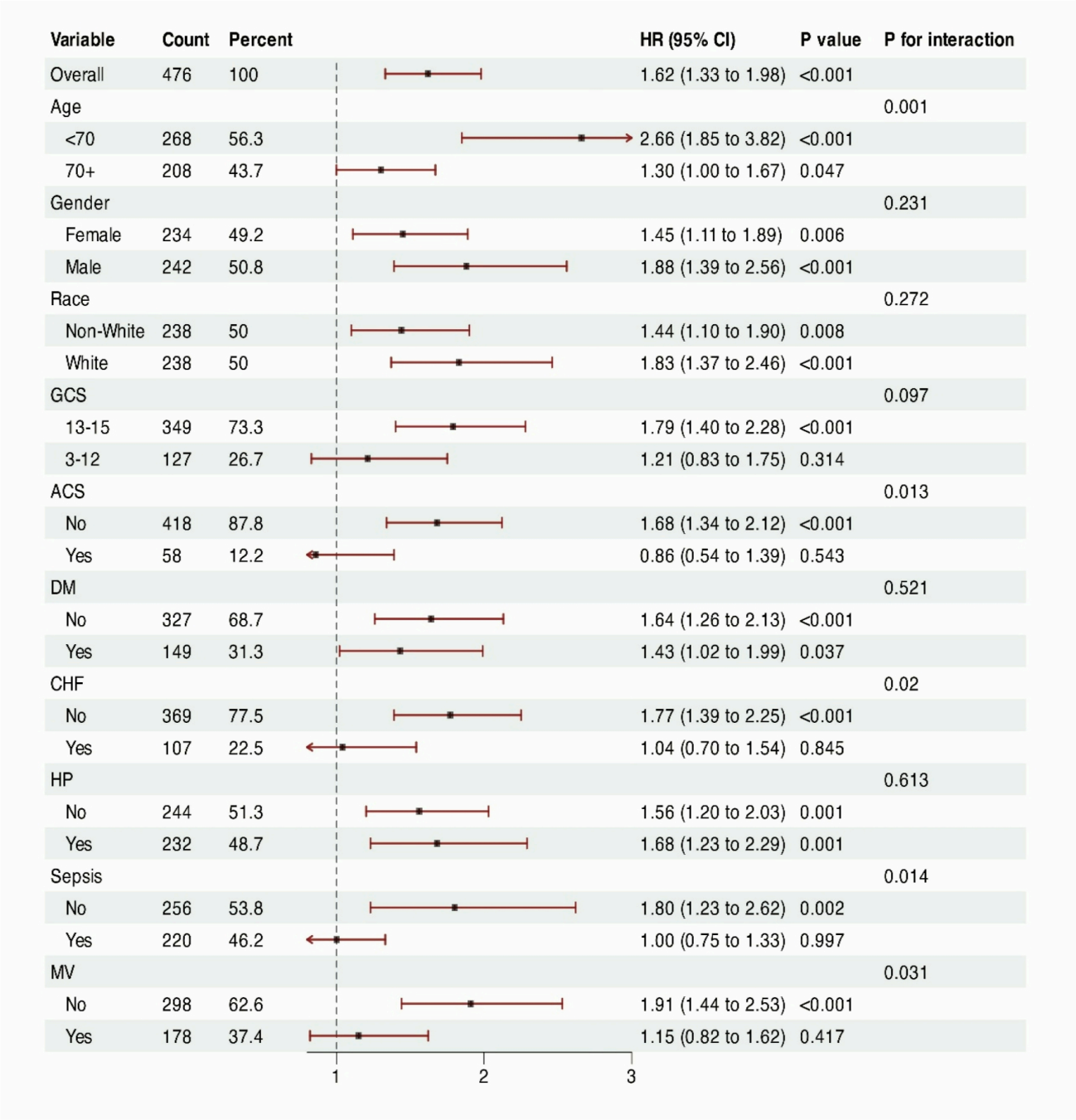


Figure 5

Subgroup analysis of the relationship between CTI and 1-year mortality. CTI, C-reactive protein-triglyceride glucose index; GCS, Glasgow Coma Scale; ACS, acute coronary syndrome; DM, Diabetes mellitus; CHF, chronic heart failure; HP, hypertension; MV, mechanic ventilation

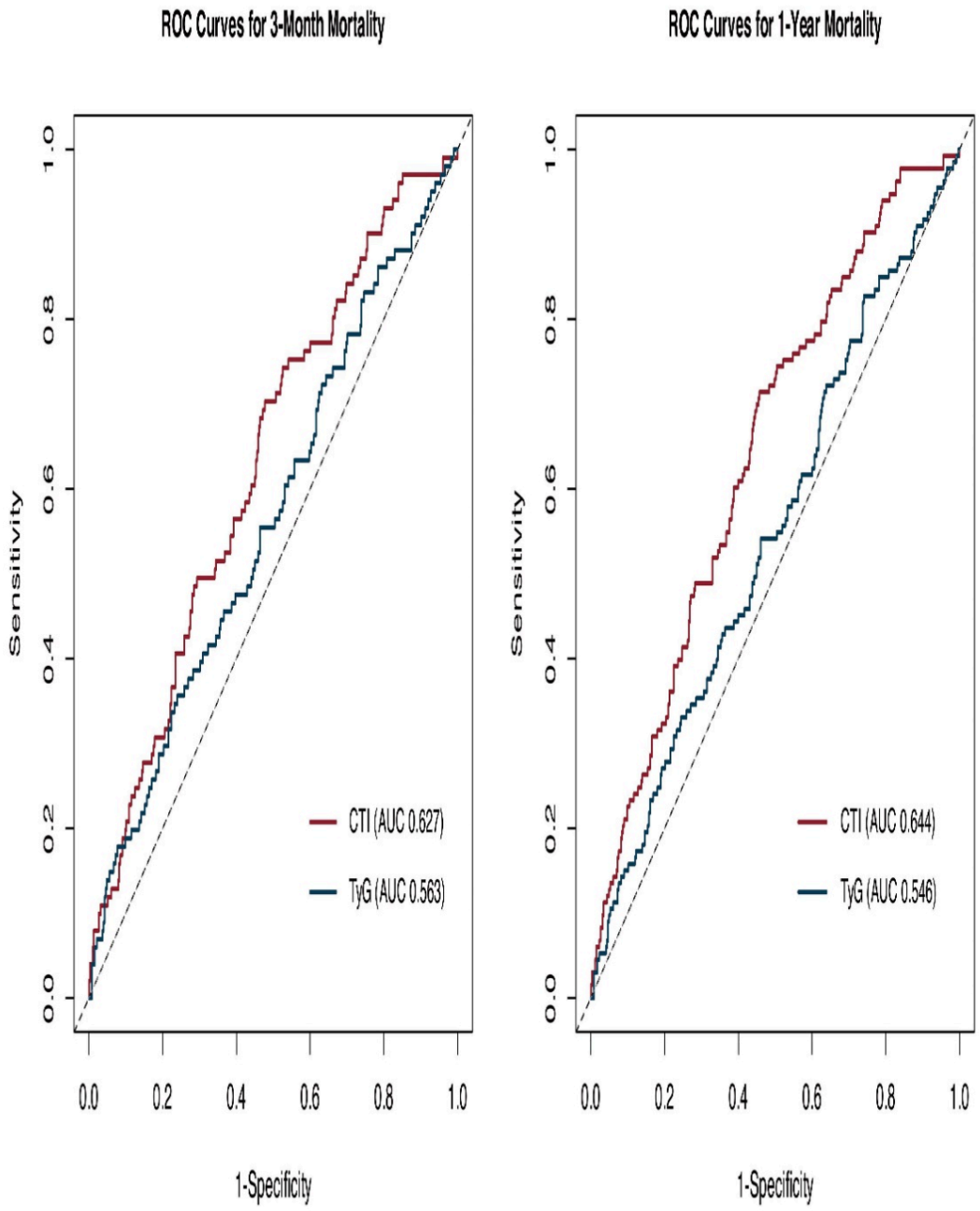


Figure 6

ROC Comparison of CTI and TyG for 3-Month (A) and 1-Year (B) Mortality