

Association of the C-Reactive Protein-Triglyceride Glucose Index with Coronary Severity and Incident Heart Failure in Newly Diagnosed Coronary Artery Disease

Weijie Zhang

The First Affiliated Hospital, Fujian Medical University

Wanjie Chen

The First Affiliated Hospital, Fujian Medical University

Xin Yan

The First Affiliated Hospital, Fujian Medical University

Shuwei Weng

The First Affiliated Hospital, Fujian Medical University

Yishu Chen

The First Affiliated Hospital, Fujian Medical University

Qiong Su

The First Affiliated Hospital, Fujian Medical University

Hailin Zhang

The First Affiliated Hospital, Fujian Medical University

Dajun Chai

dajunchai-fy@fjmu.edu.cn

The First Affiliated Hospital, Fujian Medical University

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Abstract

Background

Chronic inflammation and metabolic dysregulation are key contributors to coronary artery disease (CAD) progression. The C-reactive protein–triglyceride glucose (CTI) index integrates these pathways, but its association with coronary lesion severity and incident heart failure (HF) in patients with newly diagnosed CAD remains unclear.

Methods

This single-center retrospective cohort included 813 consecutive patients with angiography-confirmed, newly diagnosed CAD between January 2020 and June 2025; patients with pre-existing HF or prior HF hospitalization were excluded. Coronary lesion severity was quantified by the Gensini score. CTI was calculated as $0.412 \times \ln(\text{CRP [mg/L]}) + \ln(\text{TG [mg/dL]} \times \text{FPG [mg/dL]}/2)$. The primary outcome was new-onset clinical HF during follow-up. Restricted cubic spline (RCS) analysis with four knots examined the CTI–Gensini association. Multivariable Cox models with sequential adjustment estimated HRs and 95% CIs. Sensitivity analyses excluded STEMI and HF events within 12 months, used complete-case analysis, and applied LASSO-Cox and Firth penalized regression. Time-dependent ROC, subgroup, and exploratory mediation analyses were also performed.

Results

Over a median follow-up of 37 months, 64 patients (7.9%) developed HF. HF-free survival decreased across CTI tertiles (log-rank $P < 0.001$). RCS analysis revealed a non-linear CTI–Gensini association (P for non-linearity < 0.05). After adjustment, each one-unit increase in CTI was associated with a higher HF risk (HR = 2.117, 95% CI 1.498–2.991, $P < 0.001$), and the association persisted after further adjustment for ejection fraction (HR = 2.057, 95% CI 1.334–3.173). CTI showed good discrimination at 12, 24, and 36 months (AUC 0.791, 0.802, and 0.796), comparable to CRP and superior to the TyG index at 24 and 36 months. Subgroup analyses showed no significant effect modification. Exploratory mediation analysis suggested partial mediation by the Gensini score (30.4%) and E/e' ratio (17.7%). Sensitivity analyses confirmed the robustness of the association.

Conclusion

In patients with newly diagnosed CAD, CTI was associated with coronary lesion severity and incident HF after adjustment for confounders. Because CTI is derived from routine laboratory measurements at negligible additional cost, further prospective evaluation of its role in risk stratification is warranted.

Trial registration

ChiCTR2100044802 (registered on 27 March 2021).

Introduction

CAD remains one of the leading causes of morbidity and mortality worldwide, placing a substantial burden on healthcare systems [1]. Although revascularization techniques and pharmacological therapies have improved substantially in recent years, many patients with CAD still develop adverse cardiac remodeling that can progress to ischemic cardiomyopathy and heart failure (HF) [2, 3]. Timely identification of high-risk patients at the time of diagnosis is therefore clinically important for guiding early intervention and improving long-term outcomes.

The pathogenesis of CAD involves intricate interactions among multiple biological pathways, with chronic inflammation and insulin resistance recognized as two central drivers of atherosclerosis initiation and progression [4, 5]. C-reactive protein (CRP), a classic marker of systemic inflammation, not only reflects the overall inflammatory burden but also directly contributes to endothelial dysfunction and plaque instability [6]. Disturbances of glucose and lipid metabolism, characterized by elevated fasting plasma glucose (FPG) and triglycerides (TG), further increase the risk of cardiovascular events by inducing oxidative stress, impairing vascular function, and accelerating atherosclerosis [7, 8]. Previous research indicates that inflammation and insulin resistance do not operate independently; instead, they reinforce one another through complex crosstalk, creating a vicious cycle of meta-inflammation that promotes CAD progression [9].

In conventional clinical practice, these risk markers are usually assessed separately. Accumulating evidence, however, suggests that integrating information from multiple pathological pathways may provide more comprehensive prognostic insights [10]. Based on this concept, several composite biomarkers have been developed, including the triglyceride-glucose (TyG) index and the systemic immune-inflammation index (SII), both of which have shown higher discriminative value for cardiovascular events than individual indicators [11, 12]. Building on this framework, Ruan et al. proposed the C-reactive protein–triglyceride-glucose (CTI) index, which combines information on inflammation, glucose metabolism, and lipid metabolism into a single composite measure designed to capture the body's metabolic-inflammatory state more comprehensively [13].

The cardiovascular relevance of CTI has recently attracted increasing attention. Zhang et al. reported that each one-unit increase in CTI was associated with a 44% higher risk of cardiovascular disease in the CHARLS cohort [14]. Sun et al., using NHANES data, found that higher CTI was associated with increased incidence and mortality of cardiovascular disease [15], and Xu et al. showed that CTI was useful for detecting prevalent coronary heart disease [16]. More recently, Cheng et al. reported an association between CTI and heart failure in the general US population [17]. Across these populations, CTI consistently added prognostic information beyond either component alone.

However, these studies were mostly conducted in general or community-based populations, and whether CTI is associated with outcomes specifically in patients with newly diagnosed CAD, who represent a particularly high-risk group, remains unclear. In addition, although the relationship between CTI and composite cardiovascular endpoints has been explored, its association with heart failure as a distinct

outcome has not been examined specifically in patients with newly diagnosed CAD, despite HF being a major complication after CAD diagnosis [18]. It also remains unclear whether CTI is associated with both coronary anatomical severity and incident HF, and whether cardiac remodeling contributes to this pathway. To address these questions, the present study aimed to evaluate the association of CTI with coronary lesion severity (Gensini score), incident HF, and potential mediating pathways involving cardiac structure and function in patients with angiography-confirmed, newly diagnosed CAD.

Methods

Study Design and participants

This single-center, retrospective, hospital-based study included consecutive patients who presented to the First Affiliated Hospital of Fujian Medical University between January 2020 and June 2025 with chest pain or tightness and who received a first-time diagnosis of CAD confirmed by coronary angiography. Newly diagnosed CAD was defined as angiographically confirmed de novo CAD without a prior history of myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or obstructive CAD on previous coronary angiography.

The final analytical cohort comprised 813 patients. Inclusion criteria were: (1) aged ≥ 18 years; and (2) angiographically confirmed CAD, defined as $\geq 50\%$ luminal diameter stenosis in at least one major epicardial coronary artery. Exclusion criteria were: (1) pre-existing HF (including HF with reduced, mildly reduced, or preserved ejection fraction) or prior HF hospitalization; (2) a history of MI, PCI, CABG, or obstructive CAD on prior coronary angiography; (3) moderate or severe valvular heart disease, hypertrophic cardiomyopathy, or dilated cardiomyopathy; (4) acute infection or autoimmune disease at enrollment, active hepatitis, cirrhosis, or malignancy within the preceding 5 years; (5) severe renal insufficiency (estimated glomerular filtration rate < 30 mL/min/1.73 m² or receiving dialysis); (6) pregnancy or lactation; and (7) missing key baseline or follow-up data.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Fujian Medical University (Approval No. MRCTA, ECFAH of FMU [2021]072). Owing to the retrospective design, the requirement for written informed consent was waived; all identifiable patient information was de-identified to protect privacy. The study was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2100044802) on 27 March 2021.

Data Collection and CTI Calculation

Baseline data and medical histories at the time of admission were retrieved from the electronic medical record system, covering the following four categories: (1) demographic and lifestyle characteristics, including age, gender, smoking status, and alcohol consumption; (2) anthropometric measurements, including height, weight, waist circumference, hip circumference, body mass index (BMI), and 24-hour

mean systolic blood pressure (SBP); (3) medical history and medications, including hypertension, diabetes, dyslipidemia, and related cardiovascular medications (including antihypertensive, lipid-lowering, and antidiabetic agents); and (4) laboratory tests and echocardiographic data. Fasting venous blood samples were collected from all patients on the morning after admission (within 24 h of admission). An automated clinical chemistry analyzer (ADVIA 2400, Siemens, Munich, Germany) was used to measure alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine (Crea), uric acid (UA), fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); eGFR was calculated using the CKD-EPI equation. An automated hematology analyzer (ADVIA 2120i, Siemens, Munich, Germany) was used to measure neutrophil count and hemoglobin (Hb). CRP was measured using an immunoturbidimetric assay (detection limit 0.1 mg/L); values below the detection limit ($n = 3$) were assigned 0.1 mg/L for CTI calculation. TG (mmol/L) and FPG (mmol/L) were converted to mg/dL using conversion factors of 88.57 and 18.00, respectively. CTI was calculated as $0.412 \times \ln(\text{CRP [mg/L]}) + \ln(\text{TG [mg/dL]} \times \text{FPG [mg/dL]}/2)$.

Assessment of Coronary Artery Disease Severity

All enrolled patients underwent coronary angiography, with the transradial approach preferred. In patients presenting with acute coronary syndrome, angiography was performed on an emergency basis or after hemodynamic stabilization. Judkins or Amplatz catheters were selected at the operator's discretion according to the anatomical characteristics of the aortic root. Two senior interventional cardiologists, blinded to the patients' clinical and laboratory data, independently reviewed the angiographic findings and quantified coronary lesion severity using the Gensini scoring system; the score was derived from the initial diagnostic angiogram obtained before any percutaneous coronary intervention. The intraclass correlation coefficient (ICC) for interobserver agreement was > 0.90 .

Echocardiography

All patients underwent standard transthoracic echocardiography during hospitalization. Examinations were performed by experienced sonographers using a Philips iE Elite diagnostic ultrasound system (Philips Investment Ltd, Shanghai, China) equipped with an S5-1 phased-array probe (frequency range, 1.0–5.0 MHz). Patients were examined in the left lateral decubitus position with simultaneous electrocardiographic monitoring, and all measurements were averaged over three consecutive cardiac cycles.

In the parasternal left ventricular long-axis view, the aortic root diameter (AOD) and left atrial anteroposterior diameter (LAD) were measured at end-systole, whereas left ventricular end-diastolic diameter (LVDd), left ventricular end-systolic diameter (LVDs), interventricular septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT) were measured at end-diastole (all linear dimensions in cm). Left ventricular end-diastolic volume (LVVd), end-systolic volume (LVVs), and ejection

fraction (EF) were derived using the biplane Simpson method, with the left ventricular endocardial contour traced in the apical four-chamber and two-chamber views.

In the apical four-chamber view, the pulsed-wave Doppler sample volume was placed at the level of the mitral valve tips to record the early diastolic peak flow velocity (E wave). Tissue Doppler imaging was then used to place the sample volume at the septal mitral annulus to measure the early diastolic myocardial velocity (e'). The E/e' ratio was calculated as a non-invasive index of left ventricular filling pressure.

To evaluate intra- and interobserver variability, 10% of patients were randomly selected for reproducibility testing. The intraclass correlation coefficients for three consecutive measurements by the same operator and for measurements obtained independently by two operators were all > 0.90 , confirming the reliability of the echocardiographic measurements.

Follow-up and Outcome Definitions

After discharge, patients were followed up through regular outpatient visits, electronic medical record reviews, and structured telephone interviews. The study cutoff date was December 2025, ensuring a minimum follow-up of 6 months for all patients. Follow-up duration was calculated from the date of admission to the date of the outcome event, the date of last known contact, or the study cutoff date, whichever occurred first. Patients without an endpoint event were censored at their last contact date. Patients who died before the development of HF were censored at the time of death; given the small number of such events, standard Cox regression was considered appropriate. All potential endpoint events were independently adjudicated by an endpoint committee of two trained clinicians who were blinded to patient management, based on medical records and examination results.

The primary endpoint was new-onset clinical HF during follow-up, excluding HF events occurring during the index hospitalization. HF was defined as meeting at least one of the following criteria: (1) HF hospitalization: unplanned hospitalization for new or worsening HF symptoms (NYHA class III–IV) requiring intensified HF therapy; or (2) emergency visit: intravenous diuretics or vasoactive agents administered for acute HF in the emergency department or outpatient clinic.

Secondary endpoints comprised other major adverse cardiovascular and cerebrovascular events (MACCE), including: (1) all-cause death; (2) unplanned revascularization, defined as repeat percutaneous coronary intervention or coronary artery bypass grafting for myocardial ischemia attributable to the target vessel or new lesions; and (3) stroke, defined as acute cerebral infarction or cerebral hemorrhage confirmed by neuroimaging with corresponding neurological deficits.

Statistical Analysis

Normality of continuous variables was tested using the Kolmogorov–Smirnov (K–S) test. Normally distributed variables were expressed as mean $\pm$ standard deviation (SD) and compared between groups

using analysis of variance (ANOVA). Non-normally distributed variables were presented as median (interquartile range [IQR]) and compared using the Kruskal–Wallis test. Categorical variables were expressed as frequencies (percentages) and compared using the chi-square test. Multicollinearity among independent variables was assessed using the variance inflation factor (VIF) before multivariable modeling; variables with $VIF \geq 5$ were excluded. Missing data were limited to anthropometric variables: height (45/813, 5.5%), weight (45/813, 5.5%), waist circumference (48/813, 5.9%), and hip circumference (48/813, 5.9%); no variable exceeded 20% missingness. Missing data were handled using multiple imputation by chained equations (MICE), with the imputation model including all baseline variables, the Gensini score, CTI, follow-up time, and the HF outcome indicator. Twenty imputed datasets were generated, and estimates were pooled using Rubin's rules; convergence was assessed by inspecting trace plots.

Spearman rank correlation analysis was initially used to examine the association between CTI and the Gensini score. Given the potentially non-linear nature of this relationship, restricted cubic spline (RCS) models with four knots placed at the 5th, 35th, 65th, and 95th percentiles of the CTI distribution were fitted, with CTI as the predictor and the Gensini score as the dependent variable. Three RCS models were constructed. Model 1 was unadjusted; Model 2 was adjusted for demographic factors (age and gender); Model 3 was further adjusted for clinical and metabolic risk factors, including hypertension, diabetes, dyslipidemia, aspirin use, diuretic use, SGLT2 inhibitor use, EF, LVDd, AST, Crea, HDL-C, and LDL-C. Covariates were selected based on clinical relevance and variables associated with the Gensini score in univariate linear regression analyses ($P < 0.01$). Non-linearity was tested by comparing the linear and spline models using an F-test.

To evaluate the association between CTI and new-onset HF, univariate and multivariable Cox proportional hazards models were used to estimate HRs and 95% CIs. Covariates were selected based on clinical relevance and prior literature. Model 1 was unadjusted; Model 2 was adjusted for age and gender; Model 3a was further adjusted for ACS type (STEMI, NSTEMI, UA, stable angina), BMI, eGFR, hypertension, and diabetes; Model 3b additionally adjusted for EF to examine the influence of baseline cardiac function on the CTI–HF association. Five sensitivity analyses were performed: (1) excluding patients with STEMI; (2) excluding HF events occurring within the first 12 months of follow-up to address potential reverse causation; (3) complete-case analysis excluding patients with missing anthropometric data; (4) LASSO-Cox regression for variable selection followed by standard Cox regression; and (5) Firth's penalized Cox regression to reduce potential small-sample bias. All sensitivity analyses were adjusted for the same covariates as Model 3a.

Subgroup analyses were performed to evaluate the stability and potential heterogeneity of the associations. For the CTI–Gensini association, patients were stratified by age (< 60 vs. ≥ 60 years), gender, hypertension, diabetes, dyslipidemia, EF ($< 50\%$ vs. $\geq 50\%$), diuretic use, LVDd (≤ 4.76 vs. >4.76 cm), HDL-C (≤ 1.00 vs. >1.00 mmol/L), IVST (≤ 1.02 vs. >1.02 cm), AST (≤ 24.00 vs. >24.00 U/L), creatinine (≤ 74.20 vs. >74.20 $\mu\text{mol/L}$), antiplatelet use, SGLT2 inhibitor use, and LDL-C (≤ 2.81 vs. >2.81 mmol/L); within each stratum, linear regression models were fitted using the same covariates as the

fully adjusted model, with the stratification variable excluded, and interaction P values were calculated using the F-test. For the CTI–HF association, patients were stratified by age (< 60 years vs. ≥60 years), gender, history of hypertension, history of diabetes, disease type (STEMI, NSTEMI, unstable angina, stable angina), BMI (< 18.5, 18.5–23.9, ≥ 24 kg/m²), and eGFR (< 90.2 vs. ≥90.2 mL/min/1.73 m²); within each stratum, Cox regression analyses were performed using the same covariates as the fully adjusted model (Model 3a), with the stratification variable excluded. The number of events in each stratum is reported, and subgroup findings are considered exploratory. Interaction P values were calculated using the likelihood ratio test; conclusions regarding effect modification were based on interaction P values rather than within-stratum significance.

To explore potential mediating pathways in an exploratory framework, mediation analysis was performed using the same covariates as Model 3a. Candidate mediators included cardiac structure and function indicators (EF, LVDs, LVVs, E/e', LVDd, LVVd, LAD, IVST, LVPWT, AOD), Gensini score, neutrophil count, Hb, UA, SBP, ALT, and AST. For each mediator, linear regression was used to assess the association between CTI and the mediator (path a), and Cox regression was used to assess the association between the mediator and HF, additionally adjusting for CTI and the Model 3a covariates (path b). The total effect was defined as the CTI coefficient in Model 3a; the direct effect was defined as the CTI coefficient after adding the mediator; and the indirect effect was calculated as the difference between the total and direct effects. Bootstrap (1000 resamples) percentile 95% confidence intervals were calculated for indirect effects and mediated proportions. Because the mediators were measured at baseline and multiple mediators were examined, all mediation results were considered exploratory.

Time-dependent receiver operating characteristic (ROC) analyses were performed using the timeROC package with inverse probability of censoring weighting to estimate areas under the curve (AUCs) at 12, 24, and 36 months, with 95% CIs derived from influence-function-based standard errors. Pairwise AUC comparisons between CTI, CRP, and the TyG index were tested using the timeROC::compare procedure. The incremental time-dependent AUC of CTI over a baseline clinical model (age, gender, ACS type, BMI, eGFR, hypertension, and diabetes) was assessed using the riskRegression::Score function. Category-based net reclassification improvement (NRI) with cutoffs of 5% and 10%, integrated discrimination improvement (IDI), and continuous NRI at 24 and 36 months were calculated using the nricens and survIDINRI packages with 1000 perturbations. Calibration at 36 months was evaluated by comparing deciles of predicted risk with Kaplan-Meier observed cumulative incidence, and decision curve analysis was used to assess the net benefit of CTI-based risk stratification across threshold probabilities. All statistical analyses were performed using R software (version 4.5.2) and IBM SPSS Statistics (version 26.0). All hypothesis tests were two-sided, and P < 0.05 was considered statistically significant.

Results

Patient Baseline Characteristics

A total of 813 patients were included and divided into three groups according to CTI tertiles: T1 ($7.010 \leq \text{CTI} < 9.079$), T2 ($9.079 \leq \text{CTI} < 9.778$), and T3 ($9.778 \leq \text{CTI} < 12.781$). The median age of the overall cohort was 64.0 years, and 79.6% of patients were male. Baseline characteristics of the three groups are summarized in Table 1.

Significant differences in multiple demographic and clinical characteristics were observed across the groups. Compared with the T1 group, patients in the T3 group were younger ($P = 0.028$) but had higher body weight, BMI, and waist circumference (all $P < 0.05$), indicating that higher CTI levels were associated with greater obesity-related anthropometric indices. The proportions of patients with diabetes and dyslipidemia increased progressively across CTI tertiles (both $P < 0.05$). The use of aspirin, beta-blockers, diuretics, SGLT2 inhibitors, and PCI was significantly more frequent in the T3 group than in the T1 group (all $P < 0.001$), whereas CCB use tended to decrease across tertiles ($P = 0.055$). Notably, the distribution of disease types differed significantly among the groups ($P < 0.001$): STEMI accounted for the highest proportion in the T3 group (43.5%), whereas stable angina (SA) was most common in the T1 group (49.8%).

With respect to echocardiographic parameters, patients with higher CTI levels exhibited worse cardiac structure and function. Compared with the T1 group, the T3 group had larger LAD, LVDd, LVDs, IVST, LVVs, and LVVd, as well as lower EF (all $P < 0.001$). The E/e' ratio also increased with higher CTI tertiles ($P < 0.001$), suggesting elevated left ventricular filling pressure.

Laboratory results showed a clear dose-response relationship between CTI tertiles and most biomarkers. Inflammatory markers (CRP and neutrophil count) were significantly higher in the T3 group (both $P < 0.001$), and FPG increased with higher CTI tertiles ($P < 0.001$). In the lipid profile, TG levels increased progressively across groups, whereas HDL-C levels decreased (all $P < 0.05$). ALT and AST levels were highest in the T3 group (both $P < 0.001$).

Table 1
Patient demographics and baseline characteristics

Age, years	Overall N = 813	T1 N = 271	T2 N = 271	T3 N = 271	P
	64.00 (56.00, 70.00)	65.00 (57.00, 70.00)	64.00 (57.00, 70.00)	62.00 (54.50, 69.00)	0.028
Gender					0.011
Male	647.0 (79.6%)	201.0 (74.2%)	217.0 (80.1%)	229.0 (84.5%)	
Female	166.0 (20.4%)	70.0 (25.8%)	54.0 (19.9%)	42.0 (15.5%)	
Height, cm	167.00 (160.00, 171.00)	166.00 (160.00, 170.00)	168.00 (160.00, 171.00)	168.00 (162.00, 171.00)	0.232
Weight, kg	67.92 ± 10.53	66.11 ± 11.63	67.99 ± 9.57	69.64 ± 10.03	< 0.001
BMI, kg/m²	24.46 (22.79, 26.63)	23.95 (21.79, 26.30)	24.61 (22.88, 26.58)	24.79 (23.11, 26.84)	< 0.001
Waist, cm	88.50 (83.30, 93.60)	87.40 (80.70, 93.10)	89.20 (84.30, 94.00)	89.00 (84.30, 93.70)	0.004
Hip, cm	91.39 ± 6.87	91.16 ± 7.28	91.62 ± 6.41	91.41 ± 6.91	0.739
Hypertension	538.0 (66.2%)	185.0 (68.3%)	181.0 (66.8%)	172.0 (63.5%)	0.482
SBP, mmHg	122.00 (111.00, 133.00)	120.00 (111.00, 131.00)	123.00 (114.00, 135.00)	121.00 (108.00, 136.00)	0.131
Diabetes	357.0 (43.9%)	78.0 (28.8%)	120.0 (44.3%)	159.0 (58.7%)	< 0.001
Dyslipidemia	281.0 (34.6%)	80.0 (29.5%)	93.0 (34.3%)	108.0 (39.9%)	0.041
Metformin	148.0 (18.2%)	40.0 (14.8%)	46.0 (17.0%)	62.0 (22.9%)	0.041
Statins	791.0 (97.3%)	263.0 (97.0%)	264.0 (97.4%)	264.0 (97.4%)	0.954
Aspirin	768.0 (94.5%)	244.0 (90.0%)	259.0 (95.6%)	265.0 (97.8%)	< 0.001
CCB	294.0 (36.2%)	109.0 (40.2%)	102.0 (37.6%)	83.0 (30.6%)	0.055
ACEI	106.0 (13.0%)	29.0 (10.7%)	31.0 (11.4%)	46.0 (17.0%)	0.060
ARB	214.0 (26.3%)	81.0 (29.9%)	75.0 (27.7%)	58.0 (21.4%)	0.067
Beta-blockers	558.0 (68.6%)	155.0 (57.2%)	198.0 (73.1%)	205.0 (75.6%)	< 0.001

Age, years	Overall N = 813	T1 N = 271	T2 N = 271	T3 N = 271	P
	64.00 (56.00, 70.00)	65.00 (57.00, 70.00)	64.00 (57.00, 70.00)	62.00 (54.50, 69.00)	0.028
Diuretic	144.0 (17.7%)	26.0 (9.6%)	37.0 (13.7%)	81.0 (29.9%)	< 0.001
SGLT2i	108.0 (13.3%)	19.0 (7.0%)	38.0 (14.0%)	51.0 (18.8%)	< 0.001
Smoking	448.0 (55.1%)	138.0 (50.9%)	158.0 (58.3%)	152.0 (56.1%)	0.208
Drinking	142.0 (17.5%)	52.0 (19.2%)	47.0 (17.3%)	43.0 (15.9%)	0.594
PCI	657.0 (80.8%)	162.0 (59.8%)	238.0 (87.8%)	257.0 (94.8%)	< 0.001
Disease types					< 0.001
STEMI	201.0 (24.7%)	29.0 (10.7%)	54.0 (19.9%)	118.0 (43.5%)	
NSTEMI	192.0 (23.6%)	45.0 (16.6%)	70.0 (25.8%)	77.0 (28.4%)	
Unstable angina	175.0 (21.5%)	62.0 (22.9%)	66.0 (24.4%)	47.0 (17.3%)	
SA	245.0 (30.1%)	135.0 (49.8%)	81.0 (29.9%)	29.0 (10.7%)	
Gensini Score	38.50 (18.50, 67.00)	18.00 (9.50, 36.00)	38.00 (22.00, 60.00)	62.00 (40.00, 92.00)	< 0.001
AOD, cm	3.43 (3.20, 3.66)	3.39 (3.19, 3.66)	3.39 (3.19, 3.65)	3.49 (3.23, 3.69)	0.107
LAD, cm	3.80 (3.47, 4.05)	3.64 (3.40, 3.96)	3.79 (3.45, 4.05)	3.87 (3.59, 4.16)	< 0.001
LVDD cm	4.76 (4.46, 5.07)	4.73 (4.35, 4.99)	4.69 (4.40, 4.96)	4.83 (4.53, 5.18)	< 0.001
LVDs, cm	3.05 (2.82, 3.39)	2.95 (2.69, 3.25)	3.01 (2.78, 3.26)	3.25 (2.90, 3.74)	< 0.001
IVST, cm	1.02 (0.93, 1.14)	0.99 (0.90, 1.10)	1.01 (0.93, 1.15)	1.08 (0.97, 1.19)	< 0.001
LVPW, cm	0.90 (0.83, 0.97)	0.87 (0.82, 0.94)	0.89 (0.83, 0.96)	0.93 (0.85, 1.03)	< 0.001
LVVs, ml	36.43 (30.07, 47.09)	33.59 (26.77, 42.52)	35.29 (29.03, 43.49)	42.52 (32.20, 59.63)	< 0.001
LVVD, ml	105.44 (90.52, 122.12)	103.88 (85.36, 118.23)	101.84 (87.69, 116.05)	109.08 (93.90, 128.36)	< 0.001

Age, years	Overall N = 813	T1 N = 271	T2 N = 271	T3 N = 271	P
	64.00 (56.00, 70.00)	65.00 (57.00, 70.00)	64.00 (57.00, 70.00)	62.00 (54.50, 69.00)	0.028
EF, %	64.79 (58.54, 69.09)	66.69 (62.45, 70.82)	65.22 (59.68, 69.23)	60.82 (50.16, 66.62)	< 0.001
E/e'	10.67 (8.75, 13.33)	9.82 (8.00, 12.15)	10.40 (9.00, 12.67)	12.15 (9.43, 15.50)	< 0.001
CRP, mg/L	3.47 (1.48, 10.90)	1.46 (0.56, 2.61)	3.92 (2.05, 8.50)	12.00 (4.89, 33.91)	< 0.001
Neut, ×10 ⁹ /L	4.94 (3.83, 6.64)	4.20 (3.43, 5.47)	4.93 (3.83, 6.89)	5.82 (4.56, 7.72)	< 0.001
Hb, g/L	138.00 (126.00, 148.00)	137.00 (125.00, 146.00)	138.00 (126.00, 148.00)	139.00 (126.00, 148.00)	0.281
FPG, mmol/L	5.26 (4.57, 6.41)	4.73 (4.36, 5.35)	5.37 (4.67, 6.34)	5.97 (5.05, 8.66)	< 0.001
Crea, μmol/L	74.20 (64.00, 87.00)	74.00 (62.00, 84.10)	75.00 (64.00, 87.00)	74.70 (64.60, 88.00)	0.197
Urea, mmol/L	5.14 (4.33, 6.25)	5.08 (4.29, 6.11)	5.03 (4.21, 6.16)	5.34 (4.39, 6.59)	0.114
UA, μmol/L	344.80 (287.00, 406.30)	328.20 (276.00, 382.00)	353.00 (296.30, 420.00)	357.70 (291.70, 418.50)	< 0.001
ALT, U/L	23.00 (16.00, 36.00)	20.00 (14.00, 28.00)	23.00 (16.00, 37.00)	26.00 (17.00, 45.00)	< 0.001
AST, U/L	24.00 (18.00, 43.00)	22.00 (17.00, 29.00)	24.00 (19.00, 40.00)	32.00 (19.00, 73.00)	< 0.001
TC, mmol/L	4.24 (3.54, 4.91)	4.12 (3.52, 4.85)	4.29 (3.57, 4.91)	4.34 (3.55, 5.03)	0.089
TG, mmol/L	1.48 (1.08, 2.02)	1.11 (0.86, 1.50)	1.58 (1.19, 2.04)	1.83 (1.37, 2.97)	< 0.001
HDL-C, mmol/L	1.00 (0.86, 1.16)	1.10 (0.96, 1.25)	0.97 (0.85, 1.11)	0.93 (0.80, 1.09)	< 0.001
LDL-C, mmol/L	2.81 (2.15, 3.50)	2.76 (2.15, 3.47)	2.88 (2.16, 3.64)	2.81 (2.10, 3.47)	0.347
eGFR, ml/min/1.73m ²	90.20 (78.29, 98.57)	90.40 (78.57, 98.14)	89.70 (78.03, 98.21)	90.23 (78.12, 100.36)	0.781
Categorical variables (such as smoking history, drinking history, medication history, etc.) only display the frequency (percentage) of 'Yes'.					

Association Between CTI and Coronary Artery Lesion Severity

Spearman rank correlation analysis revealed a moderate positive correlation between CTI and the Gensini score ($p = 0.574$, $P < 0.001$; Fig. 1). To characterize the dose-response relationship further, restricted cubic spline (RCS) regression models with four knots were constructed with sequential adjustment: Model 1 (unadjusted), Model 2 (adjusted for age and gender), and Model 3 (further adjusted for clinical comorbidities, medication history, echocardiographic parameters, and laboratory parameters) (Table 2).

In all three models, RCS analysis revealed a significant non-linear association between CTI and the Gensini score (P for non-linearity <0.05 ; Fig. 2), indicating that the relationship was not adequately described by a linear trend. The explanatory capacity of the models increased progressively with the addition of covariates, with adjusted R^2 rising from 0.279 (Model 1) to 0.291 (Model 2) and 0.349 (Model 3). After full adjustment, the overall association between CTI and the Gensini score remained statistically significant ($P < 0.001$).

To illustrate the clinical significance of this non-linear relationship, predicted Gensini scores were estimated from Model 3 (Table 3) with all other covariates held at their median values (continuous variables) or most common categories (categorical variables) (Table 4). The predicted Gensini score increased from 24.13 at CTI = 8 to 35.28, 45.74, and 58.06 at CTI = 9, 9.44 (the median), and 10, respectively, with the steepest increase occurring between CTI values of approximately 9 and 10. Beyond this range, the increase gradually attenuated, with predicted scores of 68.42 at CTI = 11 and 76.74 at CTI = 12.

Table 2
Restricted Cubic Spline Models of CTI and Gensini score

Model	Knots	R ²	Adjusted R ²	AIC	BIC	P for overall	P for non-linear
Model 1	4	0.282	0.279	7790.0	7813.5	< 0.001	< 0.001
Model 2	4	0.296	0.291	7777.9	7810.8	< 0.001	< 0.001
Model 3	4	0.363	0.349	7721.7	7815.7	< 0.001	< 0.05
Model 1: CTI only; Model 2: CTI + Age + Gender; Model 3: Full model with all covariates. Note: Model 3 refers to the fully adjusted CTI–Gensini model and should be distinguished from the HF models (Model 3a/3b).							

Table 3
Regression Coefficients of the RCS Model 3

Category	Variable	β (SE)	95% CI	t-value	P-value
	Intercept	-44.548(39.657)	[-122.393, 33.296]	-1.12	0.262
CTI (RCS terms)	CTI	6.909(4.271)	[-1.474, 15.293]	1.62	0.106
CTI (RCS terms)	CTI'	29.788(10.845)	[8.499, 51.078]	2.75	< 0.01
CTI (RCS terms)	CTI''	-146.39(50.775)	[-246.059, -46.722]	-2.88	< 0.01
Demographics	Age	-4.590(2.876)	[-0.018, 0.372]	1.78	0.075
Demographics	Gender=Female	-3.787(2.817)	[-10.236, 1.055]	-1.6	0.111
Clinical conditions	Diabetes = Yes	0.638(2.216)	[-3.711, 4.988]	0.29	0.773
Clinical conditions	Dyslipidemia = Yes	1.261(2.120)	[-2.901, 5.424]	0.59	0.552
Clinical conditions	Hypertension = Yes	-1.081(2.238)	[-5.474, 3.311]	-0.48	0.629
Treatments	Aspirin = Yes	4.814(4.352)	[-3.729, 13.357]	1.11	0.269
Treatments	Diuretic = Yes	4.887(2.954)	[-0.911, 10.686]	1.65	0.098
Treatments	SGLT2i = Yes	-3.964(3.110)	[-10.068, 2.140]	-1.27	0.203
Echocardiography	EF	-0.701(0.126)	[-0.948, -0.455]	-5.58	< 0.001
Echocardiography	IVST	11.356(5.425)	[0.707, 22.006]	2.09	< 0.05
Echocardiography	LVDd	4.652(2.235)	[0.264, 9.039]	2.08	< 0.05
Laboratory	AST	-0.033(0.018)	[-0.069, 0.003]	-1.8	0.073
Laboratory	Crea	0.098(0.058)	[-0.015, 0.211]	1.7	0.090
Laboratory	HDL_C	-4.386(4.059)	[-12.354, 3.581]	-1.08	0.280
Laboratory	LDL_C	2.453(0.983)	[0.524, 4.383]	2.5	< 0.05

Table 4
Predicted Gensini Score by CTI Level (RCS Model 3)

CTI	Predicted Gensini	95% CI
8.00	24.13	18.22–30.03
9.00	35.28	30.32–40.25
9.44 (median)	45.74	41.11–50.38
10.00	58.06	52.64–63.48
11.00	68.42	60.82–76.01
12.00	76.74	63.08–90.40

Subgroup Analyses for the Association Between CTI and Gensini Score

To explore the stability and potential heterogeneity of the association between CTI and the Gensini score, subgroup analyses were performed (Fig. 3). The positive association between CTI and the Gensini score was consistently observed across all subgroups (all $P < 0.05$). A significant interaction was detected for diabetes (P for interaction = 0.027), with a stronger association in patients without diabetes ($\beta = 18.651$, 95% CI 15.045–22.258, $P < 0.001$) than in those with diabetes ($\beta = 13.650$, 95% CI 9.457–17.843, $P < 0.001$). Borderline effect modification was observed for gender and LVDd (both P for interaction = 0.070); the association tended to be stronger in male patients ($\beta = 17.304$, 95% CI 14.208–20.399, $P < 0.001$) than in female patients ($\beta = 10.507$, 95% CI 4.779–16.235, $P < 0.001$), and in patients with LVDd > 4.76 cm ($\beta = 20.437$, 95% CI 16.354–24.519, $P < 0.001$) than in those with LVDd ≤ 4.76 cm ($\beta = 12.422$, 95% CI 8.857–15.987, $P < 0.001$). No significant effect modification was observed for the remaining subgroup variables (all P for interaction > 0.05), consistent with the robustness of the main findings; these subgroup results should be interpreted as exploratory.

Association Between CTI and HF Risk

A total of 813 patients were included in this study, with a median follow-up of 37 months. During follow-up, 64 HF events (7.9%) and 39 other MACCE (4.8%) were documented, including 25 unplanned revascularizations (3.1%), 12 all-cause deaths (1.5%), and 2 strokes (0.2%). Kaplan-Meier survival curves illustrated progressively decreasing HF-free survival across CTI tertiles (log-rank $P < 0.001$; Fig. 4). HF events occurred in 1 (0.4%), 14 (5.2%), and 49 (18.1%) patients in T1, T2, and T3, respectively, and the corresponding 36-month HF-free survival probabilities were 99.5%, 94.6%, and 79.8%. Cox regression analysis (Table 5) demonstrated a significant positive association between CTI and HF risk. In the unadjusted model (Model 1), each one-unit increase in CTI was associated with a 192.9% increase in HF risk (HR = 2.929, 95% CI 2.276–3.768, $P < 0.001$). After adjustment for age and gender (Model 2), the association slightly strengthened (HR = 3.002, 95% CI 2.326–3.875, $P < 0.001$). In the model further adjusted for ACS type, BMI, eGFR, hypertension, and diabetes (Model 3a), CTI remained significantly

associated with HF risk (HR = 2.117, 95% CI 1.498–2.991, P < 0.001). After additional adjustment for EF (Model 3b), the association was slightly attenuated but remained significant (HR = 2.057, 95% CI 1.334–3.173, P = 0.001); however, the exploratory mediation analysis did not support a statistically significant indirect effect through EF. In Model 3b, EF was significantly and inversely associated with HF risk (HR = 0.871, 95% CI 0.850–0.892, P < 0.001; Table 6), indicating that each one-unit increase in EF was associated with a 12.9% reduction in HF risk.

Table 5
Cox Regression Analysis of CTI and Heart Failure Risk

Model	Hazard Ratio	95% CI	P Value
Model 1 (Unadjusted)	2.929	2.276–3.768	< 0.001
Model 2 (+ Age+Gender)	3.002	2.326–3.875	< 0.001
Model 3a (+ ACS+BMI+eGFR + HTN+DM)	2.117	1.498–2.991	< 0.001
Model 3b (+ EF)	2.057	1.334–3.173	0.001

Table 6
Fully Adjusted Cox Regression Model for Heart Failure Risk

Variable	HR_SE	CI95	Z	P
Model 3a (+ ACS+BMI+eGFR + HTN+DM)				
CTI	2.117 (0.176)	1.498–2.991	4.252	< 0.001
Age	0.998 (0.998)	0.971–1.026	-0.157	0.875
GenderFemale	1.244 (1.244)	0.648–2.390	0.656	0.512
Disease_TypesNSTEMI	0.306 (0.306)	0.163–0.577	-3.665	< 0.001
Disease_TypesUA	0.156 (0.156)	0.060–0.402	-3.837	< 0.001
Disease_TypesSA	0.031 (0.031)	0.004–0.232	-3.386	< 0.001
BMI	0.900 (0.900)	0.818–0.990	-2.162	0.031
eGFR	0.990 (0.990)	0.975–1.006	-1.231	0.218
HypertensionYes	1.054 (1.054)	0.604–1.840	0.187	0.852
DiabetesYes	2.088 (2.088)	1.139–3.826	2.382	0.017
Model 3b (+ EF)				
CTI	2.057 (2.057)	1.334–3.173	3.263	0.001
Age	0.992 (0.992)	0.968–1.016	-0.684	0.494
GenderFemale	2.373 (2.373)	1.204–4.678	2.496	0.013
Disease_TypesNSTEMI	0.501 (0.501)	0.245–1.025	-1.893	0.058
Disease_TypesUA	0.558 (0.558)	0.210–1.487	-1.166	0.244
Disease_TypesSA	0.227 (0.227)	0.029–1.768	-1.417	0.157
BMI	0.914 (0.914)	0.820–1.020	-1.603	0.109
eGFR	0.993 (0.993)	0.976–1.010	-0.824	0.410
HypertensionYes	1.614 (1.614)	0.918–2.836	1.664	0.096
DiabetesYes	1.340 (1.340)	0.702–2.559	0.888	0.375
EF	0.871 (0.871)	0.850–0.892	-11.129	< 0.001

Sensitivity Analysis

Sensitivity analyses confirmed the robustness of the CTI–HF association (Table 7). After excluding patients with STEMI, CTI remained significantly associated with HF risk (HR = 2.062, 95% CI 1.209–3.516, P = 0.008). Exclusion of HF events occurring within the first 12 months of follow-up yielded

consistent results (HR = 2.047, 95% CI 1.424–2.942, $P < 0.001$). Complete-case analysis restricted to 726 patients with complete anthropometric data showed a significant association (HR = 2.355, 95% CI 1.604–3.457, $P < 0.001$). LASSO-Cox regression selected CTI, and the refitted model yielded an HR of 2.117 (95% CI 1.506–2.978, $P < 0.001$). Firth’s penalized Cox regression confirmed the association (HR = 2.113, 95% CI 1.493–2.976, $P < 0.001$). The consistency of these results across the five sensitivity analyses argues against the association being driven solely by ACS severity, reverse causation, missing data, or model overfitting.

Table 7
Sensitivity Analyses of the CTI–HF Association

Analysis	N	HF events	CTI HR (95% CI)	P
Main Model 3a	813	64	2.117 (1.498–2.991)	< 0.001
Excluding STEMI	612	19	2.062 (1.209–3.516)	0.008
Excluding early HF (< 12 mo)	806	57	2.047 (1.424–2.942)	< 0.001
Complete-case	726	56	2.355 (1.604–3.457)	< 0.001
LASSO-Cox	813	64	2.117 (1.506–2.978)	< 0.001
Firth penalized Cox	813	64	2.113 (1.493–2.976)	< 0.001

Model Performance Evaluation

Time-dependent receiver operating characteristic (ROC) curve analysis was used to evaluate the predictive performance of CTI for HF and to compare it with CRP and the TyG index (Fig. 5). CTI showed moderate-to-good discrimination, with AUCs of 0.791 (95% CI 0.635–0.948), 0.802 (95% CI 0.735–0.870), and 0.796 (95% CI 0.745–0.847) at 12, 24, and 36 months, respectively. These values were comparable to those of CRP (0.775 [0.576–0.974], 0.786 [0.694–0.879], and 0.793 [0.731–0.856]) and higher than those of the TyG index at 24 and 36 months (0.677 [0.474–0.880], 0.639 [0.541–0.737], and 0.619 [0.545–0.693]). Pairwise comparisons showed no statistically significant difference between CTI and CRP at any time point ($P = 0.838$, 0.667 , and 0.933 , respectively), whereas CTI was superior to the TyG index at 24 and 36 months ($P = 0.0005$ and $P < 0.001$). Adding CTI to the baseline clinical model increased the time-dependent AUC by 1.5 ($P = 0.343$), 2.3 ($P = 0.035$), and 1.5 ($P = 0.052$) percentage points at 12, 24, and 36 months, respectively.

At 24 months, the IDI (0.029, 95% CI 0.003–0.072, $P = 0.026$) and continuous NRI (0.275, 95% CI 0.001–0.425, $P = 0.046$) favored the CTI-containing model, whereas the category NRI (0.206, 95% CI –0.052 to 0.308) was not significant. At 36 months, the IDI (0.045, 95% CI 0.011–0.088, $P = 0.018$) and continuous NRI (0.267, 95% CI 0.056–0.375, $P = 0.022$) also favored the CTI-containing model, while the category NRI (0.119, 95% CI –0.039 to 0.191) was not significant. CTI did not significantly improve discrimination or reclassification over models containing CRP, either by replacing CRP (24-month IDI –0.010, $P = 0.711$;

36-month IDI 0.001, $P = 0.959$) or by adding CTI to a CRP-containing model (24-month IDI 0.012, $P = 0.254$). Calibration plots showed that predicted 36-month HF risks were broadly consistent with observed Kaplan-Meier cumulative incidences across risk deciles, with the closest agreement for the Base + CTI model; the CTI model modestly underestimated risk in several high-risk deciles, whereas the CRP model showed the largest deviations, overestimating risk in lower-risk deciles and underestimating risk in the highest-risk decile (predicted 21.8% vs observed 33.7%) (Fig. 6). Decision curve analysis indicated that the Base + CTI and CTI models provided positive net benefit over clinically relevant threshold probabilities (approximately 5%–20%), with Base + CTI maintaining positive net benefit up to a 30% threshold; the TyG model provided negligible net benefit at thresholds above 15%, and the treat-all strategy yielded negative net benefit beyond approximately a 10% threshold (Fig. 7).

Subgroup Analyses for the Association Between CTI and HF

To further evaluate the consistency of the association between CTI and HF risk across patients with different clinical characteristics, subgroup analyses and interaction tests were performed using the same covariates as the fully adjusted model (Model 3a), with the stratification variable excluded (Fig. 8). No significant effect modification was detected for age (P for interaction = 0.663), gender ($P = 0.587$), hypertension ($P = 0.324$), diabetes ($P = 0.129$), disease type ($P = 0.550$), BMI ($P = 0.591$), or eGFR ($P = 0.287$), indicating that the CTI–HF association was broadly consistent across subgroups. In strata with limited numbers of events, estimates had wide confidence intervals and should be interpreted as exploratory (e.g., female patients: HR = 2.147, 95% CI 0.992–4.646; 12 events). Stratum-specific estimates were not estimable in strata with fewer than five events (e.g., stable angina: 1 event; BMI < 18.5: 0 events).

Mediation Analysis

To explore potential mediating pathways, exploratory mediation analysis was performed for each candidate mediator (Fig. 9). Only the Gensini score (indirect effect = 0.228, bootstrap 95% CI 0.081–0.445; mediated proportion 30.4%, bootstrap 95% CI 10.3%–68.1%) and the E/e' ratio (indirect effect = 0.133, bootstrap 95% CI 0.008–0.264; mediated proportion 17.7%, bootstrap 95% CI 1.0%–38.1%) showed statistically significant indirect effects. No significant indirect effects were observed for EF, LVDs, LVVs, LVDd, LVVd, LAD, IVST, LVPWT, AOD, neutrophil count, Hb, UA, SBP, ALT, or AST (all bootstrap 95% CIs contained zero). Given the cross-sectional measurement of baseline mediators and the exploratory nature of this analysis, these results should be interpreted with caution.

Discussion

In this single-center retrospective cohort of 813 patients with newly diagnosed coronary artery disease (CAD), we examined whether the C-reactive protein–triglyceride glucose (CTI) index was associated with coronary lesion severity and incident heart failure (HF), whether the association was consistent across patient subgroups, and whether it could be partly explained by baseline cardiac and metabolic measures.

Over a median follow-up of 37 months, 64 patients (7.9%) developed new-onset HF. CTI was non-linearly and positively associated with the Gensini score, and each one-unit increase in CTI was associated with a more than twofold higher risk of HF after adjustment for age, gender, disease type, BMI, eGFR, hypertension, and diabetes (Model 3a: HR 2.117, 95% CI 1.498–2.991). Subgroup analyses showed no significant effect modification, and exploratory mediation analysis suggested that coronary severity and the E/e' ratio may partly account for the association. These findings extend earlier work on the TyG index and CTI in community-based populations [11, 12, 14–16] by suggesting that a composite marker of inflammatory and metabolic burden may be informative for HF risk in patients already diagnosed with CAD.

The non-linear relationship between CTI and the Gensini score is consistent with the view that the contribution of metabolic-inflammatory stress to coronary atherosclerosis is not uniform across the range of CTI. Although CRP and the TyG index have each been associated with coronary lesion burden [19, 20], combining them into a single index may capture the synergistic effects of insulin resistance and inflammation on plaque progression. In our data, the CTI–Gensini relationship accelerated beyond a certain level of CTI, a pattern that parallels the concept of meta-inflammation, in which insulin resistance and inflammatory signaling mutually reinforce one another [9, 21, 22]. This concept is also reflected in the observation that HDL functionality, rather than HDL-C alone, modulates cardiometabolic risk [23], consistent with the broader metabolic-immune crosstalk underlying cardiovascular disease [24]. This synergistic amplification may explain why the incremental impact of worsening metabolic-inflammatory status on coronary atherosclerosis appears to accelerate beyond a threshold. The interaction with diabetes status ($P = 0.027$) also deserves attention: the association was stronger among patients without diabetes, possibly because in patients with diabetes, coexisting metabolic and vascular abnormalities dilute the relative contribution of any single marker. Given the borderline interactions for gender and LVDd (both $P = 0.070$), these subgroup differences should be regarded as exploratory.

The association between CTI and incident HF remained significant after comprehensive adjustment (Model 3a: HR 2.117, 95% CI 1.498–2.991), in line with previous reports linking CTI to cardiovascular outcomes and HF in general populations [14–16, 18]. The use of LVEF in classifying HF [25] and the central role of insulin resistance in systemic metabolic dysfunction [26] further support the clinical relevance of this association. Our cohort differs from community-based samples in that all participants had angiographically confirmed CAD, a population in which metabolic-inflammatory burden may help identify individuals at particularly high risk of subsequent HF. Nevertheless, because ACS type was unequally distributed across CTI tertiles, part of this association may reflect the severity of the index event rather than a purely chronic metabolic effect. Sensitivity analyses restricted to non-STEMI patients were consistent with the main findings, but residual confounding by infarct size, periprocedural myocardial injury, and completeness of revascularization cannot be entirely excluded. CTI has also been associated with new-onset atrial fibrillation after STEMI [27], and its inflammatory component parallels the established relationship between CRP and cardiovascular risk [28]. Consistent with this interpretation, our fully adjusted HR (2.117 per unit) was larger than the 44% higher cardiovascular risk

per unit increase reported in a community cohort [14], which may reflect the higher baseline risk of patients with established CAD.

In subgroup analyses, no significant effect modification was found for age, gender, hypertension, diabetes, disease type, BMI, or eGFR (all P for interaction > 0.05), suggesting that the CTI–HF association was largely consistent across clinically relevant strata. Several stratum-specific estimates were unstable because of small event numbers—for example, only 12 events occurred in women, one in patients with stable angina, and none in patients with BMI < 18.5 —and these results should be interpreted with caution. The consistency of the association across subgroups therefore favors viewing CTI as a broadly applicable prognostic marker.

With respect to discrimination, CTI achieved moderate-to-good accuracy for incident HF (AUC 0.79–0.80 at 12, 24, and 36 months), performed similarly to CRP, and outperformed the TyG index at 24 and 36 months. Its incremental value over a clinical baseline model was modest, and adding CTI did not meaningfully improve discrimination or reclassification beyond models that already contained CRP, suggesting that much of its predictive information is carried by the inflammatory component. Calibration was acceptable, particularly for the clinical model including CTI, and decision curve analysis showed positive net benefit over clinically relevant threshold probabilities. These results temper the claim that CTI clearly outperforms its components; the practical value of CTI may lie more in its availability as a single, low-cost index than in large gains in risk discrimination [13, 14, 16].

To explore potential pathways, we conducted an exploratory mediation analysis in which each candidate mediator was examined separately, with all models adjusted for the Model 3a covariates (age, gender, disease type, BMI, eGFR, hypertension, and diabetes). Only the Gensini score (mediated proportion 30.4%, bootstrap 95% CI 10.3%–68.1%) and the E/e' ratio (17.7%, bootstrap 95% CI 1.0%–38.1%) showed statistically significant indirect effects; no significant indirect effects were observed for EF, left ventricular remodeling indices, or inflammatory and hepatic markers. Although these findings are biologically plausible—coronary severity and left ventricular filling pressure are recognized determinants of HF, and impaired myocardial energy metabolism [29, 30], CRP-mediated clearance of injured cells [31], mitochondrial dysfunction [32], immune-inflammatory processes [33, 34], and the liver-heart axis [35, 36] have each been implicated in the pathogenesis of HF, with inflammation considered central to HF with preserved ejection fraction [37]—the cross-sectional measurement of mediators precludes conclusions about causality. In particular, the absence of significant indirect effects through EF and remodeling indices suggests that these measures may partly reflect baseline cardiac damage or confounding rather than true mediating pathways. CRP also retains prognostic value among individuals without conventional risk factors [38]. Longitudinal data are needed to clarify the temporal order of these associations.

From a clinical perspective, CTI could help identify patients with a high inflammatory-metabolic burden who might warrant closer follow-up after a new diagnosis of CAD, particularly when comprehensive biomarker assessment is not routinely available. The index is derived from standard laboratory tests and

adds minimal additional cost. Sex-specific patterns of cardiometabolic risk [39] and the cumulative burden of insulin resistance [40] may further inform risk assessment. However, CTI is not a directly modifiable target, and its clinical utility for guiding treatment decisions remains unproven; prospective studies with repeated measurements of CTI and its components are needed before it can be considered for routine use.

This study has several limitations. First, its single-center retrospective design limits causal inference and may introduce selection bias, and external validation in other populations is required. Second, the CTI–HF association may be partly confounded by the severity of the presenting ACS; cardiac troponin, NT-proBNP, GRACE and SYNTAX scores, medication adherence, and completeness of revascularization were not available for adjustment. Third, death was treated as a censoring event rather than as a competing risk in the primary analysis. Fourth, missing data were handled by multiple imputation, and the robustness of the results to imputation assumptions should be assessed further. Fifth, the predictive analyses were conducted in a single cohort without external validation, and the modest incremental value of CTI over CRP-containing models limits any claim of added clinical benefit. Finally, the mediation analyses were based on baseline measurements and should be regarded as exploratory.

Despite these limitations, this is, to our knowledge, the first study to evaluate CTI in relation to both coronary anatomical severity and incident HF in patients with newly diagnosed CAD. The detailed echocardiographic and laboratory data allowed us to adjust for a broad set of confounders and to explore potential mediators in a systematic manner. Future multicenter prospective studies with comprehensive adjustment for ACS severity, cardiac biomarkers, and competing risks are needed to confirm these findings and to assess whether CTI-guided follow-up improves outcomes.

Conclusion

In patients with newly diagnosed CAD, CTI was associated with coronary lesion severity and incident HF after adjustment for confounders. CTI showed discrimination comparable to CRP and superior to the TyG index, with only modest incremental value beyond clinical models containing CRP. CTI may help identify patients with a higher inflammatory-metabolic burden who need closer follow-up, although its value as a risk-stratification tool still needs confirmation in prospective cohorts.

Abbreviations

ACEI Angiotensin-converting enzyme inhibitor

ALT Alanine aminotransferase

AOD Aortic diameter

ARB Angiotensin receptor blocker

AST Aspartate aminotransferase

BMI	Body mass index
CAD	Coronary artery disease
CCB	Calcium channel blocker
Crea	Creatinine
CRP	C-reactive protein
CTI	C-reactive protein–triglyceride glucose index
eGFR	Estimated glomerular filtration rate
EF	Ejection fraction
E/e'	Ratio of early diastolic peak flow velocity (E) to early diastolic myocardial peak velocity (e')
FPG	Fasting plasma glucose
Hb	Hemoglobin
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HR	Hazard ratio
IQR	Interquartile range
IVST	Interventricular septal thickness
LAD	Left atrial anteroposterior diameter
LDL-C	Low-density lipoprotein cholesterol
LVDd	Left ventricular end-diastolic diameter
LVDs	Left ventricular end-systolic diameter
LVVd	Left ventricular end-diastolic volume
LVVs	Left ventricular end-systolic volume
LVPWT	Left ventricular posterior wall thickness
MACCE	Major adverse cardiovascular and cerebrovascular events

MICE	Multiple imputation by chained equations
NAFLD	Non-alcoholic fatty liver disease
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
SA	Stable angina
SBP	Systolic blood pressure
SGLT2	Sodium-glucose cotransporter 2
SII	Systemic immune-inflammation index
STEMI	ST-segment elevation myocardial infarction
TC	Total cholesterol
TG	Triglycerides
TyG	Triglyceride-glucose index
UA	Uric acid

Declarations

Authorship contributions

Weijie Zhang: Conceptualization, Formal analysis, Writing original draft. Wanjie Chen, Shuwei Weng: Data curation. Xin Yan, Yishu Chen: Resources. Qiong Su, Hailin Zhang: Investigation, Visualization. Dajun Chai: Supervision, Funding acquisition, Writing review & editing.

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Data availability

The datasets used and/or analysed during the current study are not publicly available because they contain potentially identifying patient information and were collected under institutional ethics approval. De-identified data may be made available from the corresponding author on reasonable request, subject to institutional review board approval.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the First Affiliated Hospital of Fujian Medical University (Approval No : MRCTA, ECFAH of FMU [2021]072). Owing to the retrospective nature of the study, the committee waived the requirement for written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹ The Higher Educational Key Laboratory for Cardiovascular Disease of Fujian Province; Clinical Research Center for Metabolic Heart Disease of Fujian Province; The First Affiliated Hospital, Fujian Medical University, Fuzhou 350005, China.

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Figures

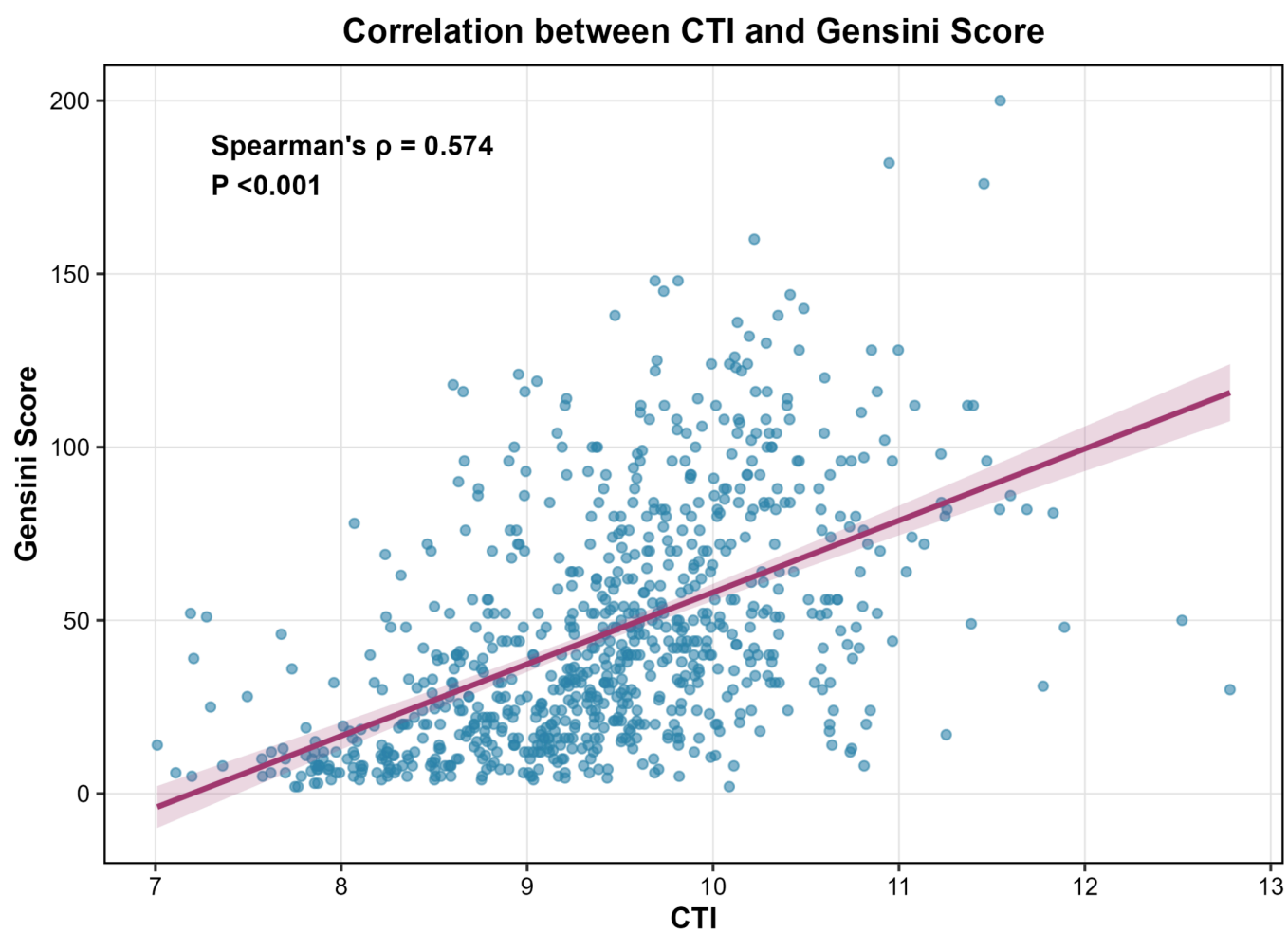


Figure 1

Spearman correlation analysis between CTI and Gensini score

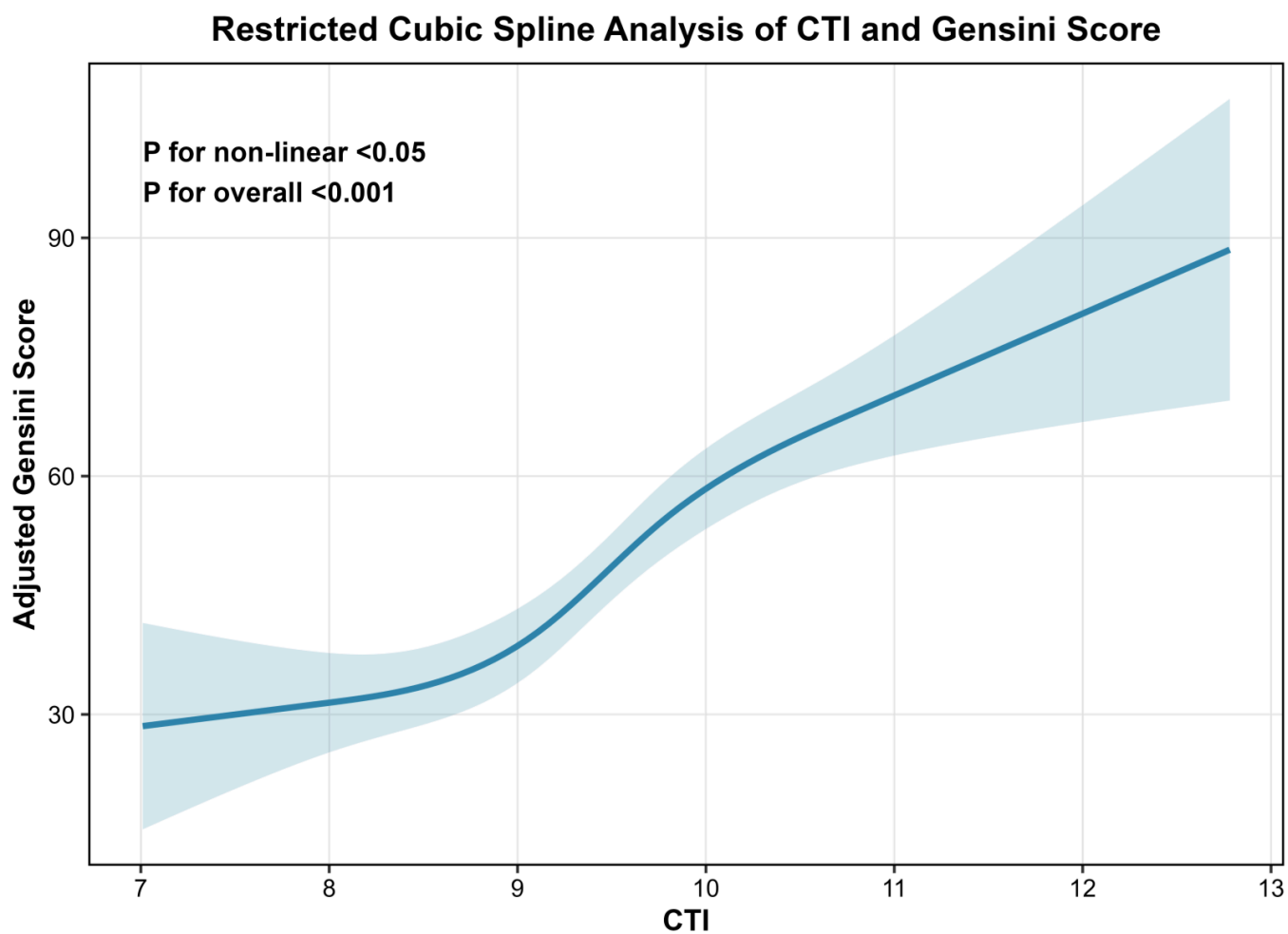


Figure 2

Restricted cubic spline analysis of the association between CTI and Gensini Score in Model 3

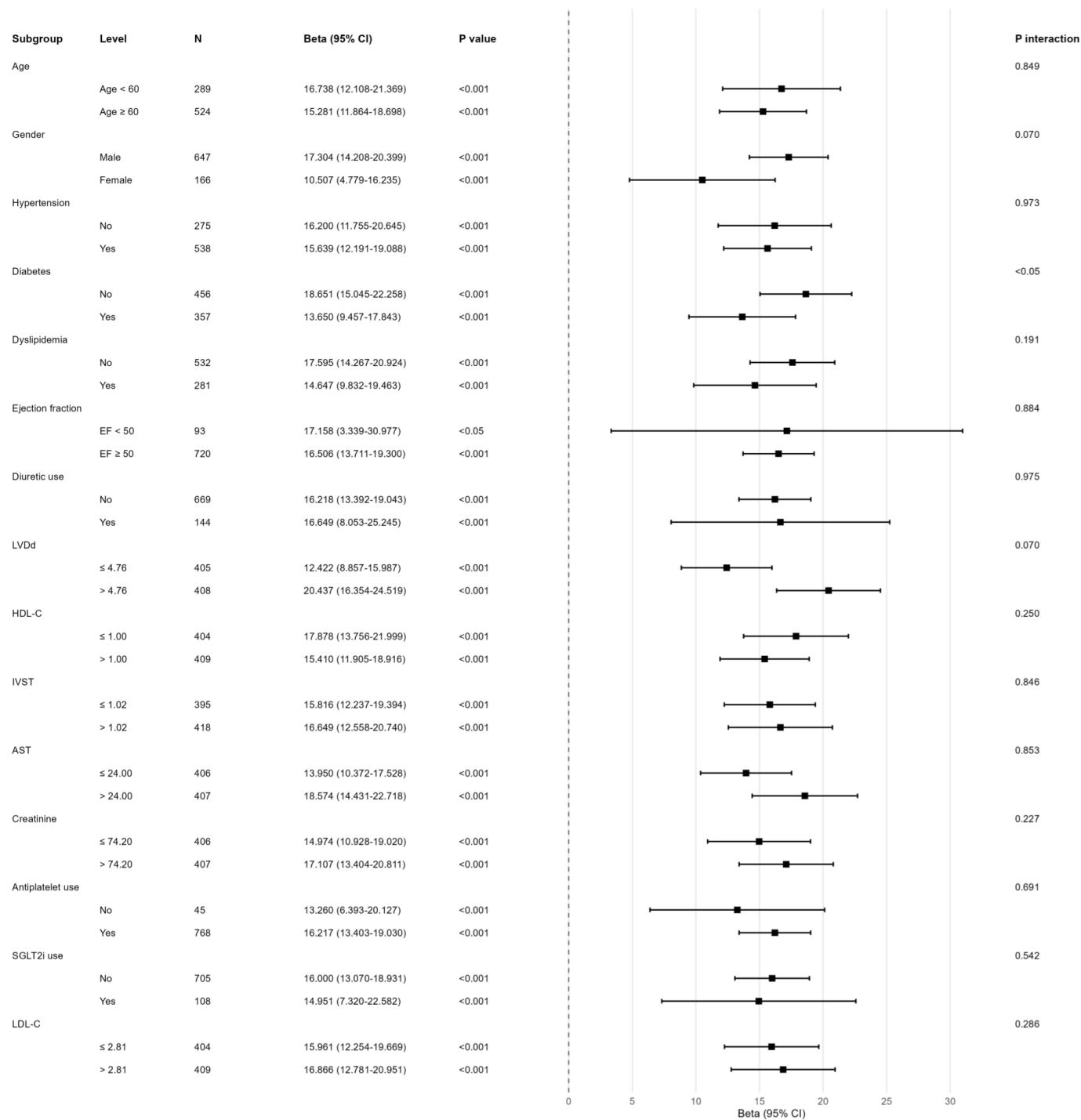


Figure 3

Subgroup Analyses for the Association Between CTI and Gensini Score

Kaplan-Meier Curves for Heart Failure by CTI Tertile

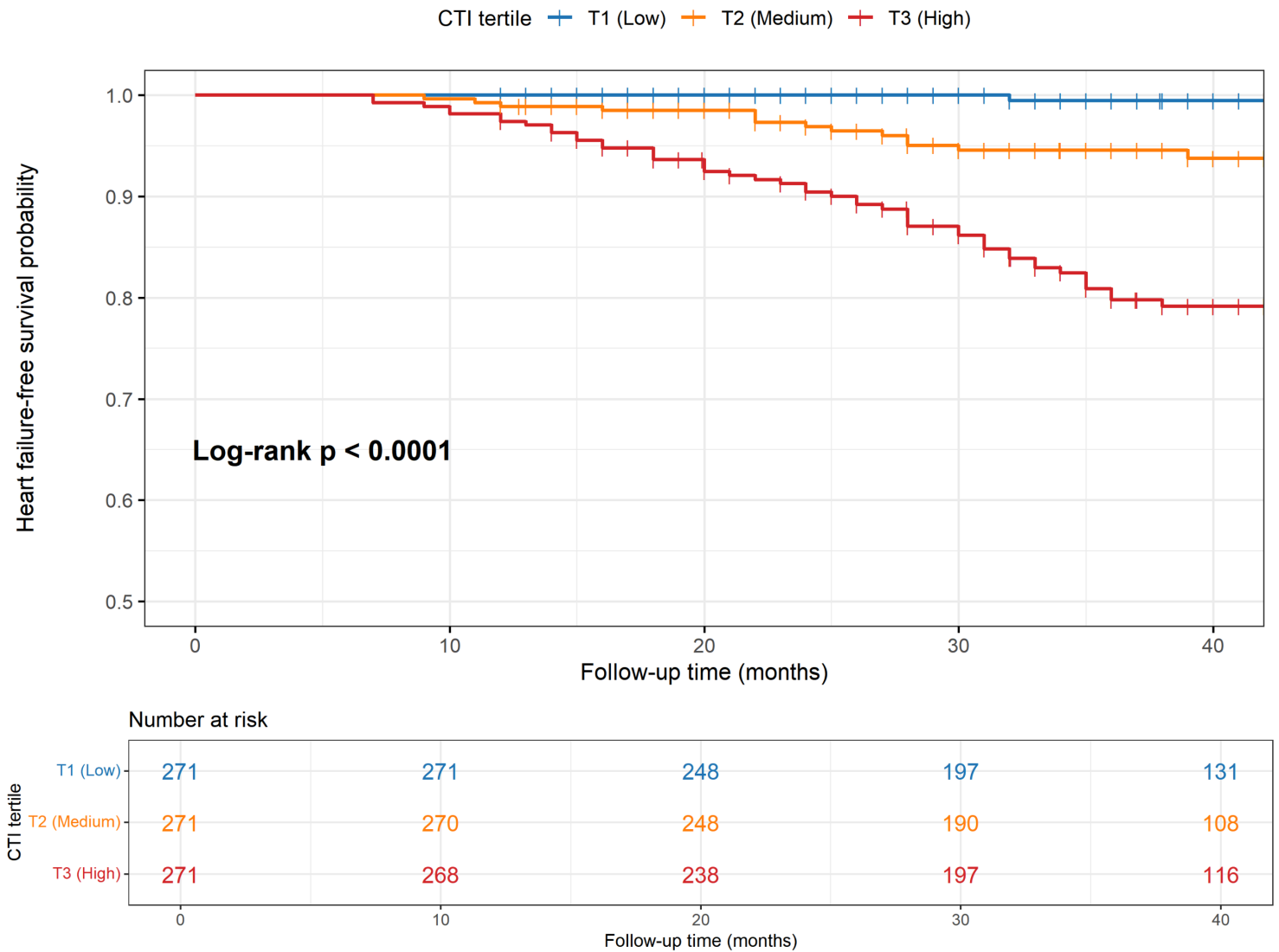


Figure 4

Kaplan-Meier curves of HF-free survival based on the tertiles of the CTI index

Time-dependent ROC curves of CTI, CRP, and TyG index for predicting heart failure at 12, 24, and 36 months

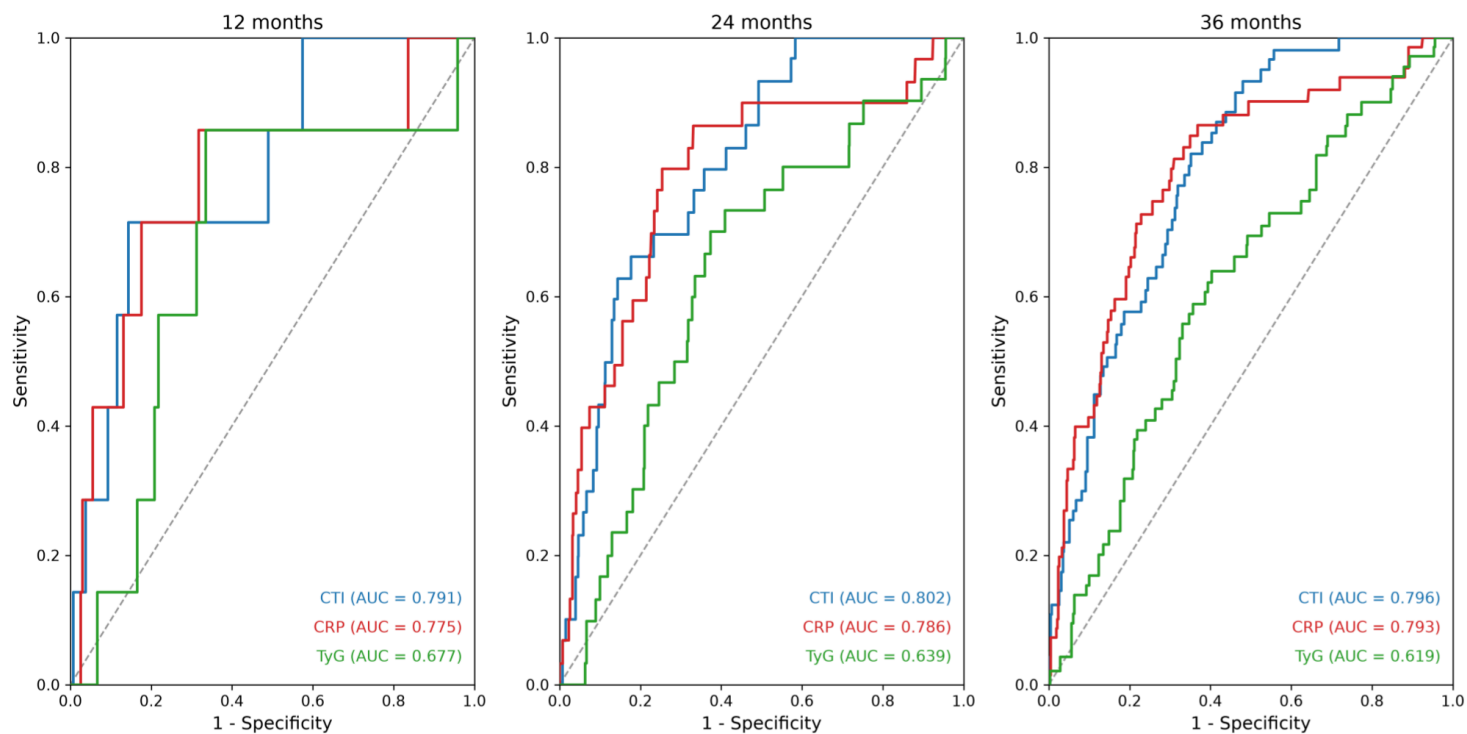


Figure 5

ROC curves of CTI, CRP, and TyG index for predicting heart failure at 12, 24, and 36 months

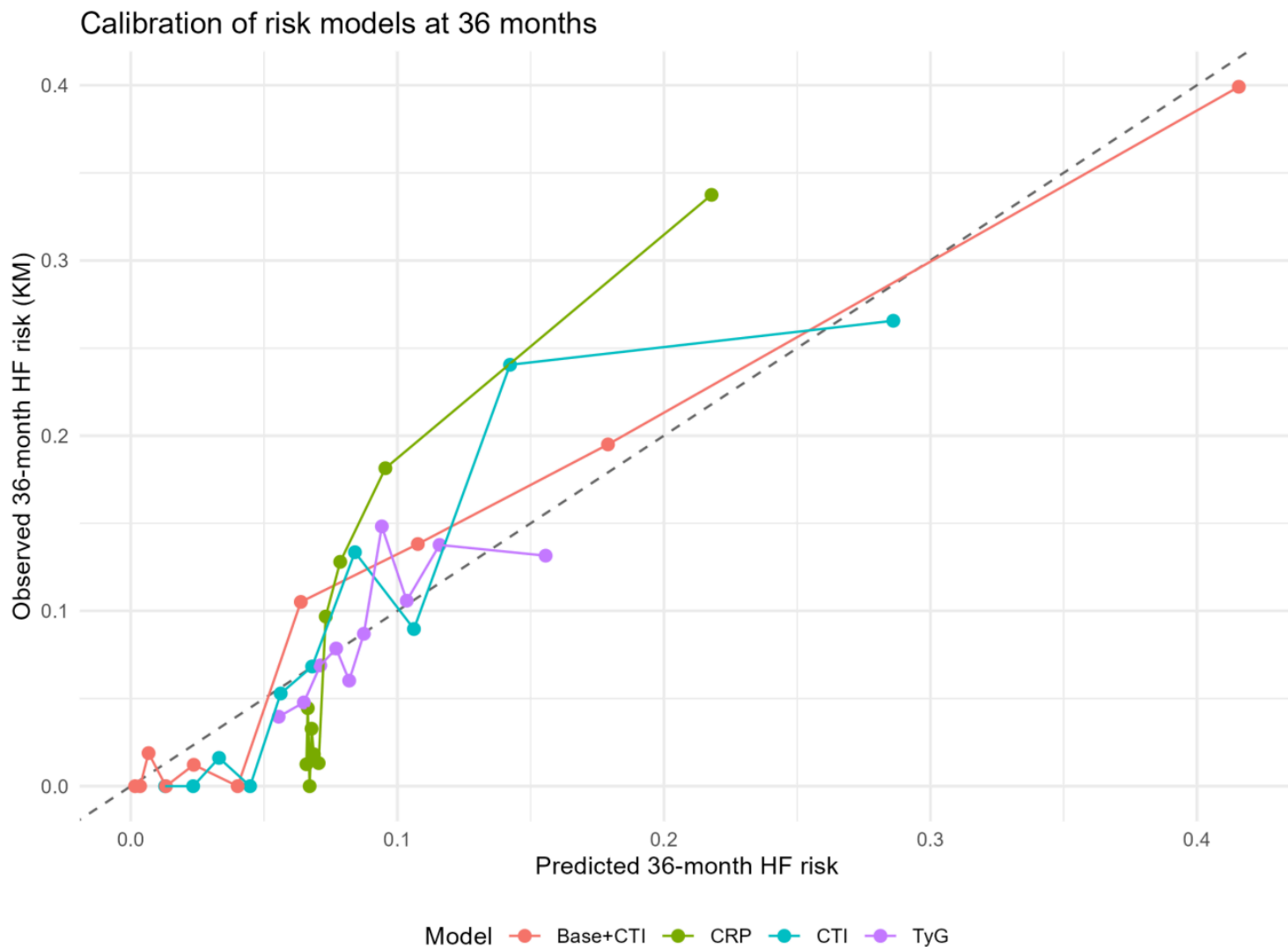


Figure 6

Calibration plots of the 36-month HF risk models. Predicted risk is plotted against observed Kaplan-Meier cumulative incidence across deciles.

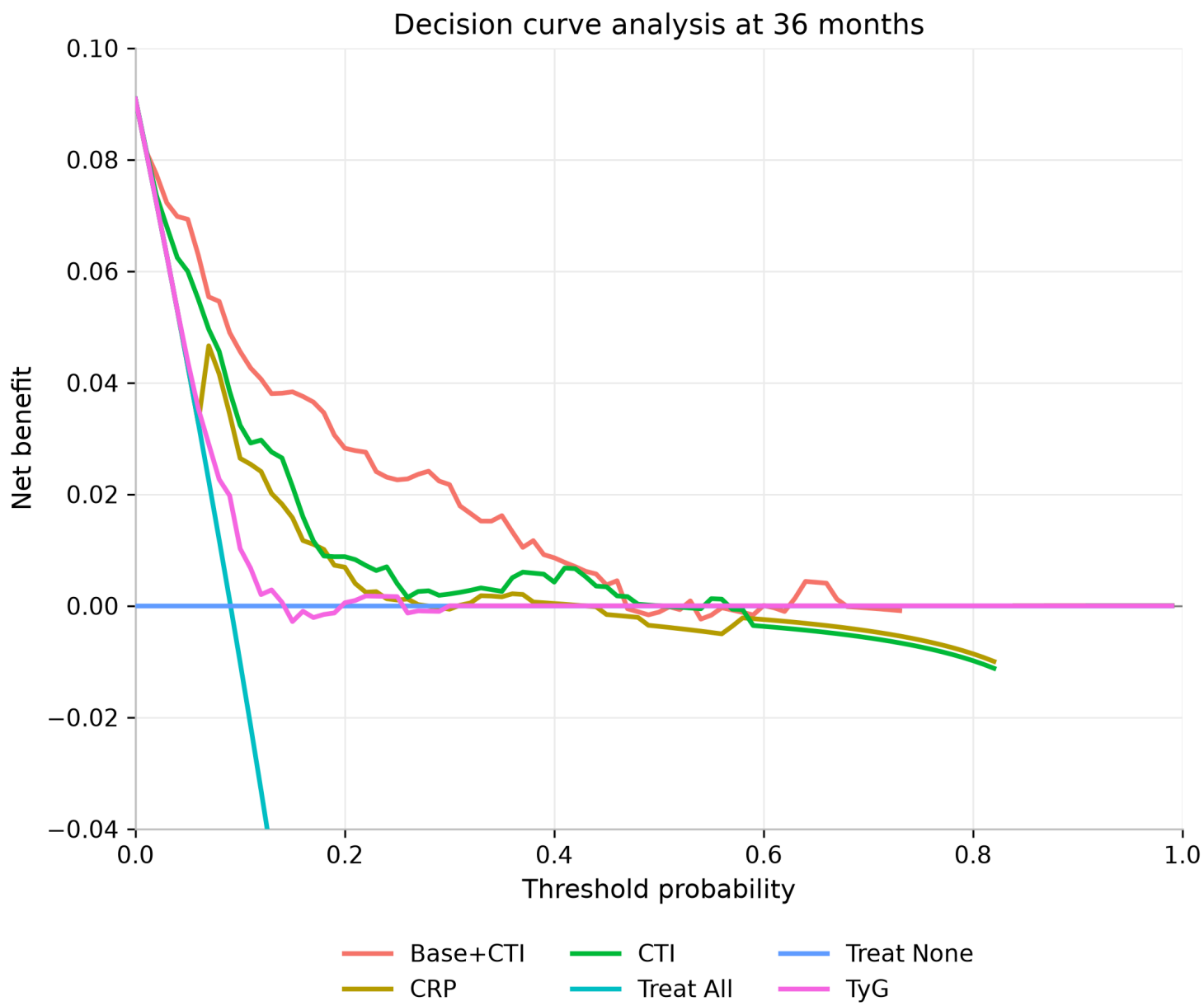


Figure 7

Decision curve analysis for 36-month HF risk. Net benefit is plotted across threshold probabilities for CTI-, CRP-, TyG-, and clinical model-based strategies.

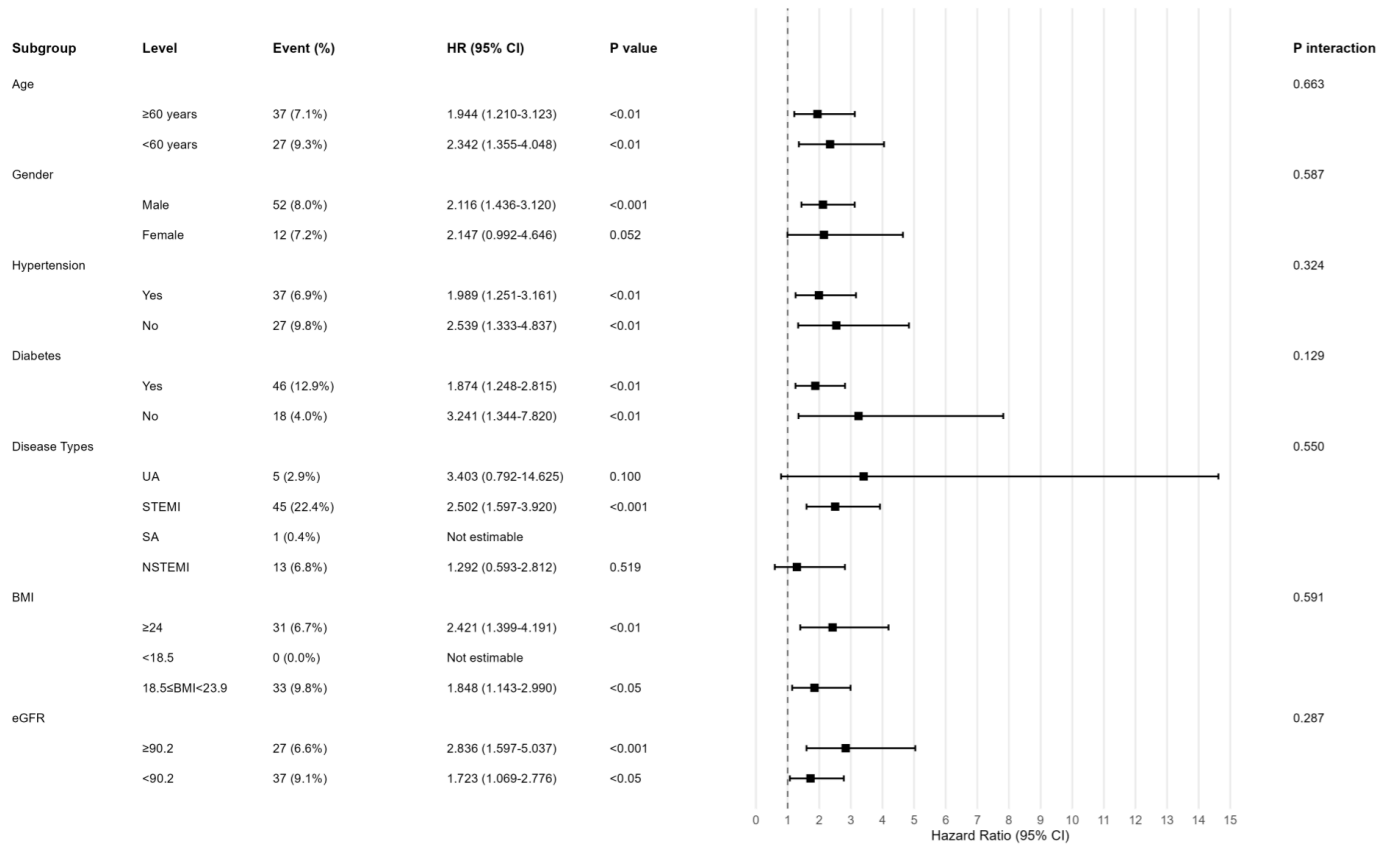
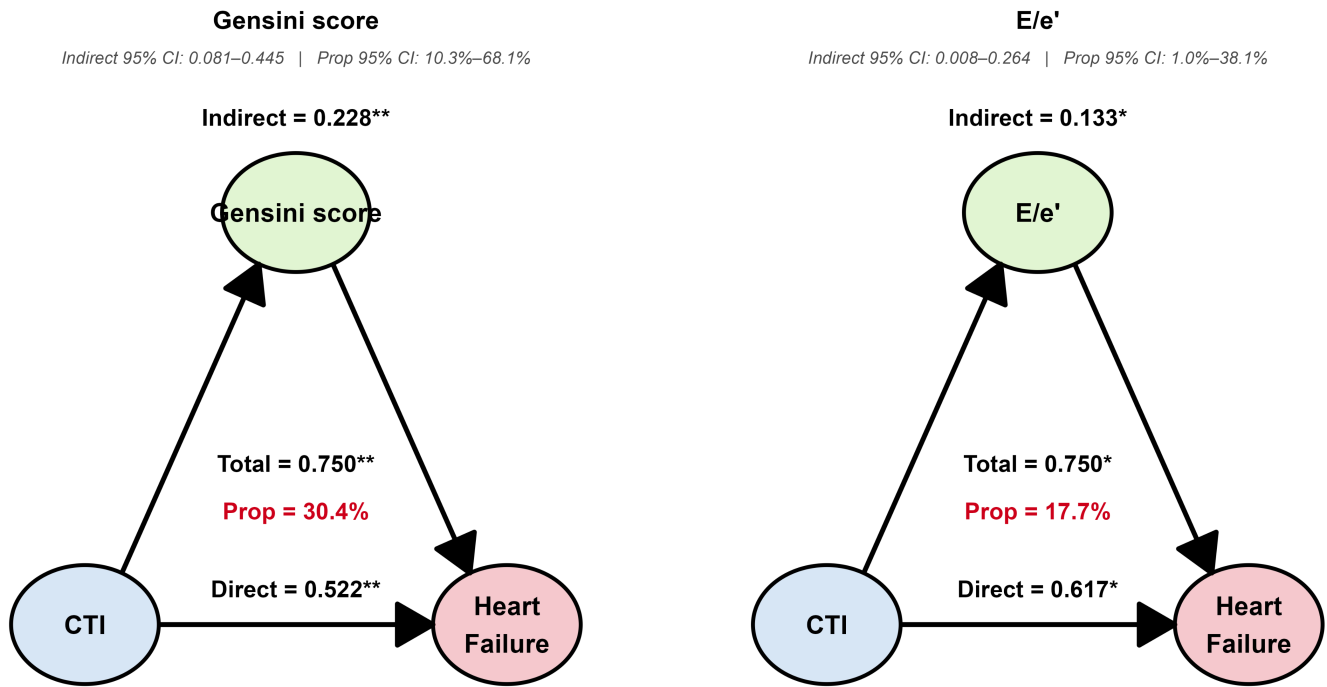


Figure 8

Subgroup Analyses for the Association Between CTI and HF. HRs (95% CIs), event counts, and interaction P values are shown.

Mediation Analysis: CTI → Mediator → Heart Failure (Model 3a)



Adjusted for age, sex, disease type, BMI, eGFR, hypertension, and diabetes | Bootstrap 95% CIs | * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 9

Exploratory mediation analysis of the CTI–HF association. Indirect effects and mediated proportions with bootstrap 95% CIs are shown.