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Evaluation and comparison of inflammatory and insulin resistance indicators on recurrent cardiovascular events in patients undergoing percutaneous coronary intervention: a single center retrospective observational study

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Abstract

Background The aim of this study was to evaluate and compare the usefulness of the C-reactive protein (CRP)-triglyceride glucose (TyG) index (CTI) and other insulin resistance (IR) or inflammatory indexes for predicting recurrent cardiovascular events in percutaneous coronary intervention (PCI)—treated patients. In addition, the mediating effects of systemic inflammation, represented by high-sensitive CRP (hs-CRP), on TyG index-associated adverse cardiovascular events across different subgroups were also evaluated.

Methods The formula for calculating the CTI was 0.412 × ln [high-sensitivity CRP (mg/L)] + ln [triglyceride (mg/dl) × fasting glucose (mg/dl)/2]. The primary endpoint was defined as the incidence of major adverse cerebrovascular and cardiovascular events (MACCEs), including cardiovascular death, nonfatal acute myocardial infarction (AMI), nonfatal ischemic stroke and repeat coronary revascularization.

Results Among the 2383 PCI-treated patients, 413 experienced MACCEs during a median of 34 months follow-up. Correlation analysis showed CTI was significantly associated with cardiometabolic factors. The CTI was the strongest predictor for MACCEs (adjusted HR 1.85, 95% CI 1.44–2.38) among the inflammatory and IR indicators. CTI had an incremental effect on the predictive ability of the prognostic model for MACCEs (NRI: 0.220, $p < 0.001$; IDI: 0.009, $p < 0.001$). Subgroup analysis revealed that the prognostic value of the CTI remained significant across all subgroups (all $p < 0.05$) whereas the predictive abilities of other IR or inflammatory indicators were more or less influenced by the metabolic abnormalities. Finally, mediation analysis revealed that the effects of systemic inflammation on TyG index—associated MACCEs were more prominent in patients with metabolic disorders.

Conclusions CTI was a practical indicator for evaluating cardiometabolic diseases. Among the IR and inflammatory indicators, CTI was the most promising index for predicting recurrent cardiovascular risks in PCI-treated patients. TyG

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index—associated cardiovascular risks were partially mediated by systemic inflammation in patients with metabolic abnormalities.

Keywords Percutaneous coronary intervention, C-reactive protein-triglyceride glucose index, Insulin resistance, Systemic inflammation, Mediation analysis

Introduction

Owing to the ageing population and the increasing prevalence of cardiometabolic risk factors, cardiovascular deaths have become the leading cause of mortality, accounting for more than 40% of deaths in China [1]. Despite the intensified pharmacological strategies and technological innovations in PCI, relatively high rates of adverse cardiovascular outcomes can still be foreseen in many patients, especially for those with multiple cardiometabolic complications, an issue commonly ascribed to the residual cardiovascular risk. As the global incidence of cardiometabolic factors has increased, the prevalence of associated cardiovascular diseases has also increased, presenting enormous challenges in cardiovascular disease and mortality prevention [2].

Insulin resistance (IR), defined as a decrease in sensitivity and responsiveness to the metabolic action of insulin, played a detrimental role in the development of coronary artery disease (CAD) [3]. Recent clinical trials targeting IR among individuals with cardiovascular diseases or high cardiovascular risks have produced positive results [4–9]. The TyG index, calculated as ln [triglyceride (mg/dl) × fasting blood glucose (mg/dl)/2], has emerged as a practical tool in clinical practice for evaluating IR because of its easy availability and convenience for use. Previous studies have evaluated the prognostic value of the TyG index for adverse outcomes in patients with various cardiovascular disease phenotypes [10–12]. However, these studies only emphasized the deteriorative role of IR in the progression of cardiovascular diseases while neglecting the fact that systemic inflammation may contribute to this process with a synergetic or mediating effect. Inflammation initiates the process of atherosclerosis through the dysregulation of endothelial dysfunction, from promoting cholesterol uptake, oxidation and accumulation to erosion and rupture of plaques as a consequence of acute ischemic syndrome [13]. In large-scale cohort studies, inflammation has been shown to be an independent predictor for incident heart failure, myocardial infarction, stroke and sudden cardiac death even in patients with low low-density lipoprotein (LDL) levels [14]. A synergetic effect was found between the TyG index and hs-CRP for predicting adverse cardiovascular outcomes in diabetic patients, suggesting inflammation as a potential target for reducing cardiovascular risk in diabetic patients and that IR and systemic inflammation are causally linked to the progression of cardiovascular diseases [15]. However, whether the mediating effect of systemic inflammation on TyG index-associated adverse events could also be applied to patients with no obvious metabolic dysfunction remained largely unknown. Recently, a more comprehensive indicator, CTI, has been validated as a useful tool for predicting the prognosis of patients with cancer [16], but its potential application in patients with cardiovascular diseases was currently unknown. Hence, the aim of this study was to evaluate and compare the usefulness of the CTI and other IR or inflammatory indicators for predicting recurrent cardiovascular events in PCI-treated patients. In addition, the mediating effects of systemic inflammation on TyG—associated recurrent cardiovascular events were also evaluated.

Methods

Study design and population

The enrolled population came from the study of the efficacy and safety of Genetic and platelet Function testing for guiding Antiplatelet Therapy after percutaneous coronary intervention (GF-APT) registry (ChiCTR2100047090). Considering the dynamic changes of inflammation levels over the early phase in unstable patients and more than half of the participants presented with acute coronary syndrome, we selected individuals with repeat biochemical measurements at a median of 2 months follow-up for analysis to better represent the long-term inflammatory and metabolic burdens after PCI treatment. Finally, 2383 PCI-treated patients with serial biochemical measurements were recruited for this single-center, retrospective observational study. This study was performed in accordance with the principles of the Declaration of Helsinki, and all patients provided informed consent before discharge. The exclusion criteria were as follows: (1) failure to complete at least 12 months of follow-up; (2) major adverse clinical events within 3 months after the PCI procedure; (3) end-stage renal dysfunction or treatment with renal replacement therapy, or serious liver dysfunction; (4) acute or chronic infectious diseases, malignant tumors, immune system disorders or treatment with anti-inflammatory medication; and (5) suspected familial hypertriglyceridemia (triglyceride ≥ 5.65 mmol/L). A detailed flow chart of the enrolled participants was provided in Fig. 1.

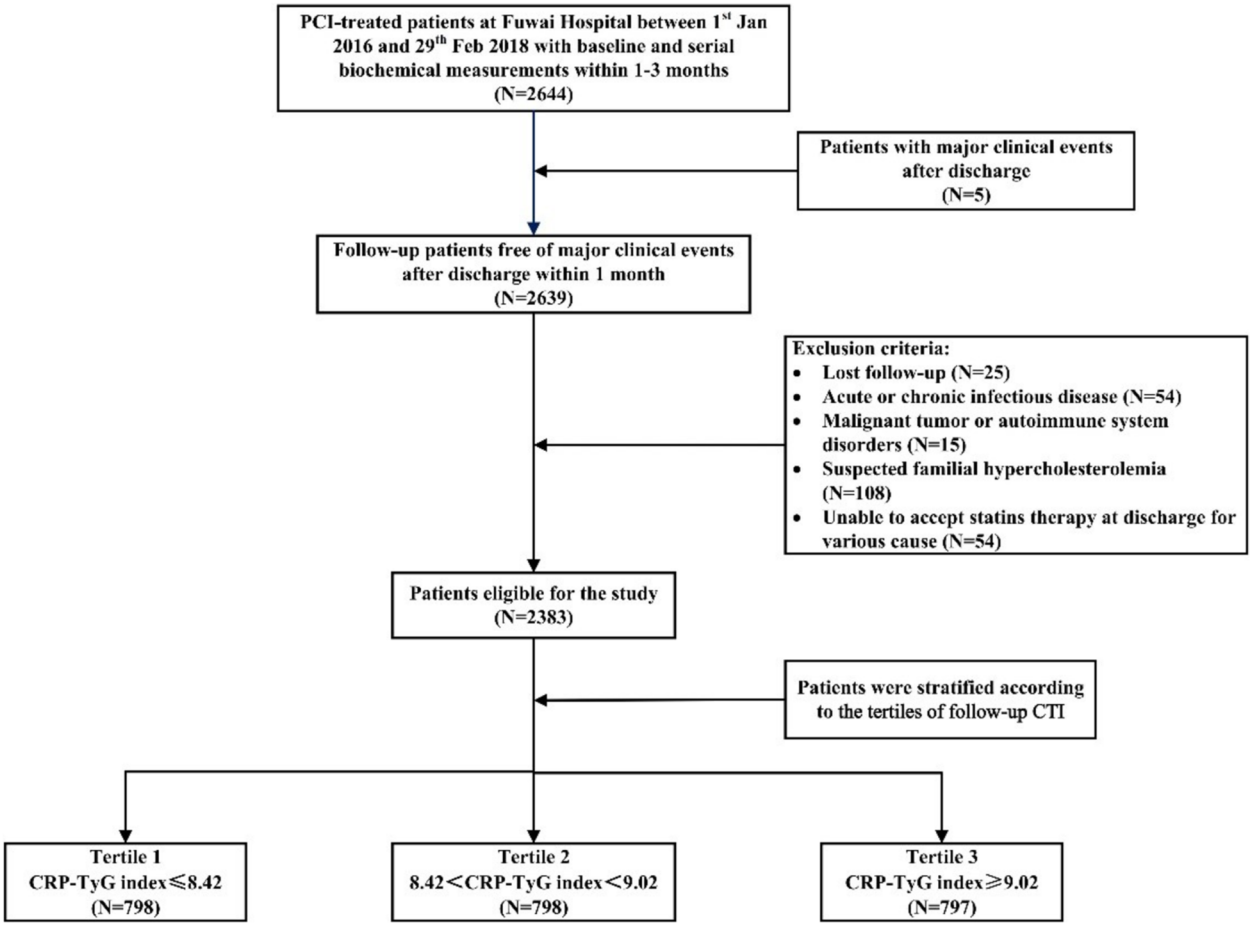

Fig. 1 Flow diagram of patient selection

Clinical and laboratory data collection

Demographic data such as age, sex, height, weight, previous medical history and medication at discharge were obtained through a review of medical records, which was approved by Beijing Fuwai Hospital. Body mass index (BMI) was calculated as weight (kg)/[height (m)]^2. The TyG index was quantified via the following formula: ln [triglyceride(mg/dL) × fasting glucose (mg/dL)/2]. Considering that hs-CRP is a useful indicator for predicting the prognosis of ASCVD patients in previous cohort studies, we used the hs-CRP level to calculate the CTI. The value of the CTI was defined as the TyG index + 0.412 × ln [hs-CRP (mg/L)]. The formula for calculating the NLR was the neutrophil to lymphocyte ratio and the TG/HDL-C ratio was calculated as triglyceride to HDL-C ratio. The diagnosis of diabetes mellitus was based on having a previous diagnosis and receiving treatment with glucose-lowering medication or was made following the recommendations of the American Diabetes Association [17]. Hypertension was defined by the recommendations of the European Society of Hypertension, an office systolic blood pressure value ≥140 mmHg, a diastolic blood pressure value ≥90 mmHg or the use of antihypertensive drugs in the past 2 weeks [18]. Dyslipidemia was characterized by increased total cholesterol, LDL-C or triglyceride levels or decreased high-density lipoprotein cholesterol levels according to the third report of the National Cholesterol Education Program [19]. AMI was defined as increased cardiac troponin levels with ischemic symptoms or ischemic changes on electrocardiogram or imaging evidence of recent loss of viable myocardium or new regional wall motion abnormalities that are not related to the procedure [20].

Coronary procedure

The coronary angiography and PCI procedures were performed by at least two experienced cardiologists whose expertise were interventional cardiology. The coronary procedure was performed according to current practice guidelines. The characteristics of coronary artery lesions are defined on the basis of the ACC/AHA guidelines for coronary lesion classification [21]. Multivessel disease is

defined as a ≥50% diameter stenosis occurring in 2 or more vessels. The calculation of SYNTAX and residual SYNTAX scores was based on the SYNTAX calculator (available at http://www.syntaxscore.com). If one or more PCIs were performed, the latest SYNTAX or residual SYNTAX score was incorporated into the final analysis.

Follow-up and endpoint events

All participants accepted guideline-recommended medical therapy for coronary artery disease at discharge, unless there were some contradictions or inability to endure the side effects. All enrolled participants were followed up for at least 12 months or until the time of a major adverse clinical event. Follow-up was performed by telephone interviewers via standardized questionnaires at 6 and 12 months after PCI and the follow-up were recorded during clinical visits via the hospital medical record system. The primary endpoint of this study was the occurrence of MACCEs after PCI during follow-up, defined as a composite of cardiovascular death, nonfatal AMI, nonfatal ischemic stroke and repeat unplanned coronary revascularization. Ischemic stroke was defined as cerebral infarction with symptoms of neurological impairment that can be explained by imaging examinations.

Statistical analysis

To better understand the characteristics of the PCI-treated populations, patients were categorized into three groups according to the CTI tertiles. Descriptive variables are expressed as the means ± standard deviations or medians with interquartile ranges for normally or nonnormally distributed continuous variables. Categorical variables are presented as frequencies and percentages. Differences among the three groups were compared by one-way analysis of variance or the Kruskal–Wallis H test for normally or nonnormally distributed variables. Restricted cubic spline (RCS) analysis was applied to determine the relationships between the inflammatory and IR indicators and the primary endpoint. Univariate Cox proportional hazards analysis was performed to preliminarily explore the risk factors associated with MACCEs. We further constructed multivariate Cox proportional hazards models to evaluate the prognostic value of the TyG index, the CTI, the NLR and the TG/HDL-C for MACCEs and the results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Receiver operating characteristic curve (ROC) analysis was performed to investigate the discriminative performance of these indicators for predicting MACCEs, and decision curve analysis (DCA) was conducted to compare the predictive value of the TyG index, the CTI, the NLR and the TG/HDL-C for MACCEs. The incremental predictive values of the inflammatory and IR indicators were comprehensively examined by the NRI and IDI when these indicators were added to the prognostic model. In addition, we also performed a mediation analysis to explore whether the mediating effect of systemic inflammation on IR-associated MACCEs was affected by metabolic abnormalities. Furthermore, subgroup and interaction analyses were performed to identify whether the relationships between the CTI or other indicators and MACCEs varied under different cardiometabolic status. Statistical analyses were conducted via SPSS 26.0 (IBM SPSS statistics) and R language (version 4.2.3).

Results

Baseline characteristics

Among these participants, 413 experienced MACCEs during a median of 34 months of follow-up. The baseline characteristics of the study population stratified by the CTI value are summarized in Table 1. The average age of the participants was 58.5 years, and 76.5% of the participants in this cohort were male. Compared with the T1 tertile group, the T3 tertile group had greater rates of MACCEs (12.8% vs. 23.6%, $p<0.001$), and cardiometabolic risk factors, such as higher rates of diabetes mellitus (26.7% vs. 51.9%, $p<0.001$) and hypertension (57.0% vs. 71.3%, $p<0.001$) and higher BMI values (25.1 ± 3.23 vs. 26.7 ± 3.54, $p<0.001$). No differences were found between the rates of previous coronary revascularization, myocardial infarction and stroke (all $p>0.05$). In term of anatomical characteristics, the proportions of individuals with multivessel diseases were greater in the T3 tertile group (66.8% vs. 77.3%, $p=0.002$). Additionally, compared with patients with low CTI values, patients in the T3 group also had higher SYNTAX and residual SYNTAX scores (all $p<0.05$). Multivariate logistic regression analysis revealed that a high CTI (CTI ≥ 9.02) value was positively associated with diabetes mellitus (OR 1.89, 95% CI: 1.52–2.36, $p<0.001$), BMI (OR 1.08, 95% CI: 1.04–1.11, $p<0.001$), white blood count (OR 1.31, 95% CI: 1.24–1.39, $p<0.001$), LDL-C (OR 2.52, 95% CI: 2.12–3.00, $p<0.001$), multivessel disease (OR 1.29, 95% CI: 1.01–1.63, $p<0.001$), and discharge insulin medication (OR 1.98, 95% CI: 1.30–3.00, $p=0.001$) and was negatively associated with female sex (OR 0.39, 95% CI: 0.31–0.50, $p<0.001$), and HDL-C value (OR 0.06, 95% CI: 0.04–0.10, $p<0.001$) (Supplementary file: Table S1).

Associations of inflammatory and IR indicators with MACCE risk

During the follow-up, there were significant differences in the risks of MACCEs across the CTI tertiles ($p<0.001$) (Table 1). RCS analysis was used to explore the relationships of the inflammatory and IR indicators and MACCEs

Table 1 Baseline characteristics of PCI-treated participants divided by the CTI value

	Overall (*n* = 2383)	T1 (*n* = 798)	T2 (*n* = 798)	T3 (*n* = 787)	*p* value
Demographic data					
Age (years)	58.5 ± 10.32	58.6 ± 10.61	58.8 ± 10.34	58.1 ± 10.01	0.392
Male sex, *n* (%)	1823 (76.5%)	639 (80.1%)	601 (75.3%)	583 (74.1%)	**0.004**
BMI (kg/m^2)	25.9 ± 3.41	25.1 ± 3.23	25.8 ± 3.23	26.7 ± 3.54	**<0.001**
Comorbidities					
Hypertension, *n* (%)	1526 (64.0%)	455 (57.0%)	510 (63.9%)	561 (71.3%)	**<0.001**
Diabetes mellitus, *n* (%)	860 (36.1%)	213 (26.7%)	241 (30.2%)	406 (51.9%)	**<0.001**
Hyperlipidemia, *n* (%)	2175 (91.3%)	722 (90.5%)	721 (90.4%)	732 (93.0%)	0.531
Current Smokers, *n* (%)	1425 (60.0%)	451 (56.5%)	488 (61.1%)	486 (61.8%)	0.096
Previous revascularization, *n* (%)	450 (18.9%)	140 (17.5%)	164 (20.6%)	146 (18.6%)	0.282
Previous myocardial infarction, *n* (%)	309 (13.0%)	102 (12.8%)	100 (12.5%)	107 (13.6%)	0.864
Previous Stroke, *n* (%)	249 (10.4%)	88 (11.0%)	81 (10.2%)	80 (10.2%)	0.780
Index presentation					0.155
SAP, *n* (%)	753 (31.6%)	260 (32.6%)	259 (32.5%)	329 (41.8%)	
NSTE-ACS, *n* (%)	964 (40.6%)	316 (40.0%)	342 (42.9%)	306 (38.9%)	
STEMI, *n* (%)	438 (18.4%)	142 (17.8%)	144 (18.0%)	152 (19.3%)	
Laboratory measurements					
White blood count (10^9/L)	6.6 ± 1.82	6.0 ± 1.64	6.6 ± 1.79	7.2 ± 1.84	**<0.001**
Neutrophil (10^9/L)	4.2 ± 1.31	3.7 ± 1.15	4.2 ± 1.27	4.6 ± 1.35	**<0.001**
Lymphocyte (10^9/L)	1.9 ± 0.59	1.8 ± 0.54	1.9 ± 0.61	2.0 ± 0.61	**<0.001**
Hemoglobin (g/dL)	13.7 ± 3.03	13.6 ± 3.27	13.6 ± 3.18	13.9 ± 2.58	0.155
Creatinine (mmol/L)	82.1 ± 17.17	81.4 ± 16.17	82.1 ± 16.07	82.9 ± 19.12	0.235
Fasting glucose (mmol/L)	5.6 (5.1–6.5)	5.3 (4.9–5.8)	5.5 (5.1–6.3)	6.1 (5.4–7.7)	**<0.001**
Triglyceride (mmol/L)	1.4 ± 0.73	1.0 ± 0.33	1.3 ± 0.41	2.0 ± 0.88	**<0.001**
Total cholesterol (mmol/L)	3.4 ± 0.74	3.2 ± 0.64	3.4 ± 0.71	3.7 ± 0.79	**<0.001**
HDL-C (mmol/L)	1.1 ± 0.28	1.2 ± 0.30	1.1 ± 0.27	1.0 ± 0.24	**<0.001**
LDL-C (mmol/L)	1.9 ± 0.60	1.7 ± 0.50	1.9 ± 0.58	2.0 ± 0.66	**<0.001**
TG/HDL-C	1.4 ± 0.99	0.9 ± 0.40	1.3 ± 0.53	2.2 ± 1.28	**<0.001**
Hs-CRP (mg/L)	1.1 (0.6–2.0)	0.5 (0.2–0.8)	1.2 (0.7–1.7)	2.1 (1.3–4.1)	**<0.001**
TyG index	8.7 ± 0.52	8.3 ± 0.33	8.7 ± 0.30	9.2 ± 0.46	**<0.001**
NLR	2.4 ± 1.34	2.2 ± 1.07	2.4 ± 1.47	2.5 ± 1.42	**<0.001**
LVEF (%)	61.1 ± 7.54	61.6 ± 6.66	61.1 ± 8.00	60.7 ± 7.89	0.104
Medications at discharge					
Antiplatelet medication, *n* (%)					**0.011**
Aspirin + Clopidogrel, *n* (%)	1850 (77.6%)	644 (27.9%)	612 (76.7%)	594 (75.5%)	
Intensified statins medication, *n* (%)	492 (20.6%)	164 (20.6%)	168 (21.1%)	160 (20.3%)	0.884
β-blockers, *n* (%)	2060 (86.4%)	669 (83.8%)	678 (85.0%)	713 (90.6%)	**0.003**
Angiotensin blockade, *n* (%)	1354 (56.8%)	401 (50.3%)	477 (59.8%)	476 (60.5%)	**<0.001**
Insulin, *n* (%)	181 (7.6%)	41 (5.1%)	39 (4.9%)	101 (12.8%)	**<0.001**
Procedural characteristics					
Target vessel during PCI, *n* (%)					
LMCA, *n* (%)	131 (5.5%)	37 (4.6%)	49 (6.1%)	45 (5.7%)	0.401
LAD, *n* (%)	1392 (58.4%)	486 (60.9%)	461 (57.8%)	445 (56.5%)	0.117
LCX, *n* (%)	599 (25.1%)	192 (24.1%)	192 (24.1%)	215 (27.3%)	0.303
RCA, *n* (%)	840 (35.2%)	262 (32.8%)	284 (35.6%)	294 (37.4%)	0.219
Others, *n* (%)	8 (0.3%)	4 (0.5%)	1 (0.1%)	3 (0.4%)	0.416
Multivessel or LMCA disease, *n* (%)	1711 (71.8%)	533 (66.8%)	570 (71.4%)	608 (77.3%)	**<0.001**
AHA/ACC lesion: type B2/C, *n* (%)	1732 (72.7%)	570 (71.4%)	584 (73.2%)	578 (73.4%)	0.731

Table 1 (continued)

	Overall (*n* = 2383)	T1 (*n* = 798)	T2 (*n* = 798)	T3 (*n* = 787)	*p* value
Stent length	29 (18–46)	30 (18–49)	28 (18–45)	28 (18–46)	0.432
SYNTAX score	10 (6–16)	9 (6–15)	10 (6–16)	11 (7–17)	**0.002**
Residual SYNTAX score	2 (0–5)	1 (0–5)	2 (0–5)	2 (0–5)	**0.001**
MACCEs	413 (17.3%)	102 (12.8%)	125 (15.7%)	186 (23.6%)	**<0.001**
Cardiovascular death, *n* (%)	4 (1.7%)	0 (0.0%)	1 (0.1%)	3 (0.4%)	0.134
Non-fatal AMI, *n* (%)	75 (3.1%)	11 (1.4%)	27 (3.4%)	37 (4.7%)	**<0.001**
Repeat coronary revascularization, *n* (%)	367 (15.4%)	94 (11.8%)	113 (14.2%)	160 (20.3%)	**< 0.001**
Stroke, *n* (%)	11 (0.5%)	2 (0.3%)	3 (0.4%)	6 (0.8%)	0.115

The data are expressed as the means ± SD, median with interquartile ranges or *n* (%); Statistically significant differences between groups were highlighted in bold ($p < 0.05$)

PCI percutaneous coronary intervention, *TyG index* triglyceride glucose index, *Hs-CRP* high-sensitivity C-reactive protein, *CTI* CRP-TyG index, *BMI* body mass index, *SAP* stable angina pectoris, *NSTEACS* non-ST-segment elevation acute coronary syndrome, *STEMI* ST-segment elevation myocardial infarction, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *TG/HDL-C* TG-HDL-C ratio, *NLR* neutrophil to lymphocyte ratio, *LVEF* left ventricular ejection fraction, *LMCA* left main coronary artery, *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *RCA* right coronary artery, *MACCEs* major adverse cardiac and cerebrovascular events, *AMI* acute myocardial infarction

in PCI-treated patients. Nonlinear relationships between the CTI, TyG index, TG/HDL-C ratio, NLR and the risk of MACCEs were observed (p for nonlinearity <0.001) (Fig. 2). When adjusted for known covariates, patients in the highest inflammatory and IR indicator tertile (except for the NLR) presented significantly higher rates of

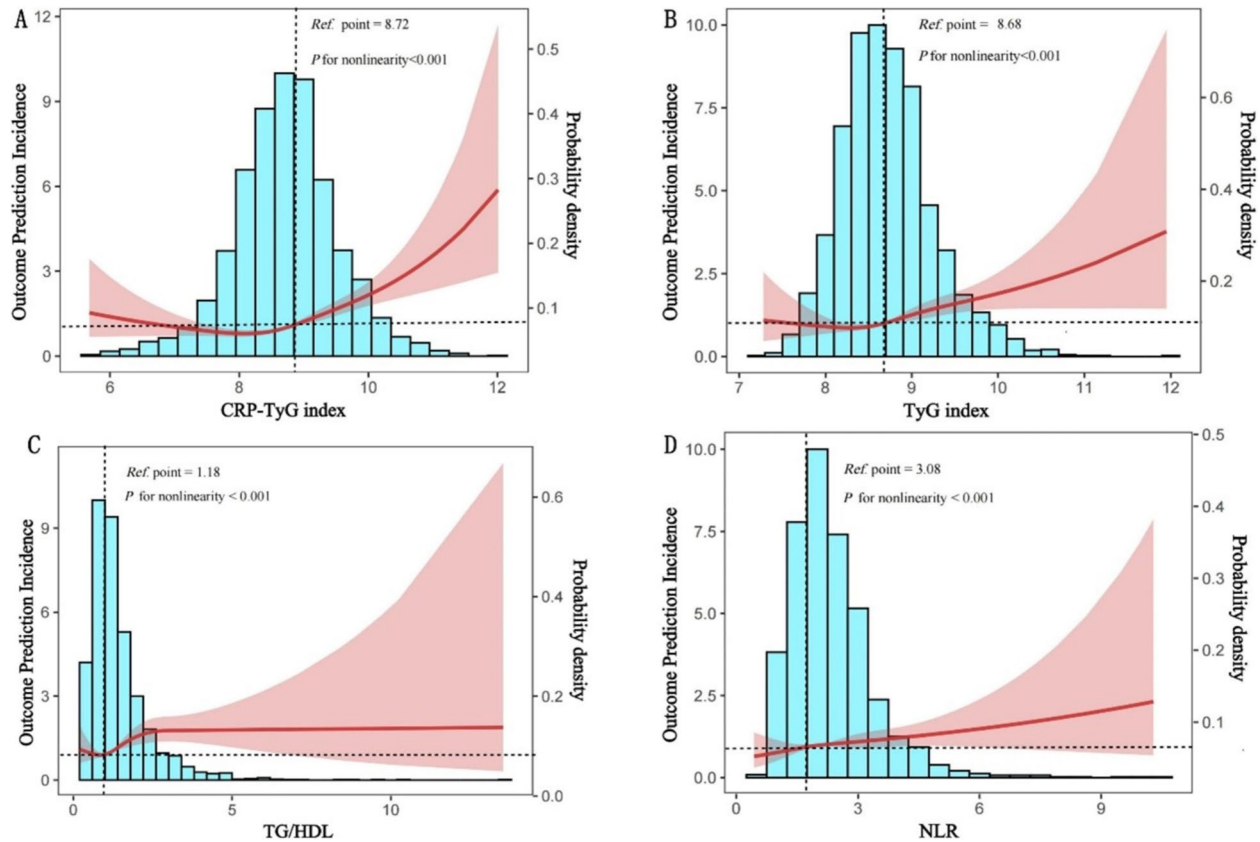

Fig. 2 Distribution and restricted cubic spline curves for the associations between the CTI (**A**), TyG index (**B**), TG/HDL-C (**C**) and NLR (**D**) and the incidence of MACCEs among PCI-treated patients

MACCEs (Supplementary file: Table S2; Fig. 3), nonfatal AMI (Supplementary file: Figure S1) and unplanned coronary revascularization (Supplementary file: Figure S2) than those in the lowest tertile. Compared with the lowest NLR tertile, the highest NLR tertile was only significantly associated with the risks of in-stent restenosis (T3: HR 1.80, 95% CI 1.05–3.06, $p=0.032$) (Supplementary file: Figure S3). The stratified analysis results obtained via univariate and multivariate Cox proportional hazards models to show the associations of the CTI, TyG index, TG/HDL-C ratio and NLR with the elevated risk of clinical endpoints were presented in Table 2. The inflammatory and IR indicators, except for the NLR tertiles, remained independently associated with the occurrence of MACCEs after adjusting for known confounding factors (CTI T3: HR 1.85, 95% CI 1.44–2.38, $p<0.001$; TyG index T3: HR 1.53, 95% CI 1.19–1.98, $p=0.001$; TG/HDL-C ratio T3: HR 1.55, 95% CI 1.22–1.97, $p<0.001$; NLR T3: HR 1.27, 95% CI 1.00–1.62, $p=0.051$).

Comparison of the predictive ability of the inflammatory and IR indicators for MACCEs

ROC analysis and DCA were performed to comprehensively determine the predictive value of the inflammatory and IR indicators for MACCEs (Fig. 4A, B). As shown in Fig. 4A, the area under the curve (AUC) of the CTI for predicting MACCEs was the highest among the inflammatory and IR indicators (CTI 0.592 vs. TyG index 0.563, TG/HDL-C 0.570, NLR 0.542, $p<0.001$). In addition, DCA was conducted to assess the clinical utility of

MACCEs

CRP-TyG index (CTI)	*Forest plot*	Events	Total	Event rate	Unadjusted HR (95%CI)	adjusted HR (95%CI)	*P* value
							<0.001
T1 (CTI ≤ 8.42)		103	798	12.91%	*Ref.*	*Ref.*	-
T2 (8.42 <CTI <9.02)		125	798	15.66%	*1.19 (0.91-1.54)*	*1.11 (0.86-1.45)*	0.427
T3 (CTI ≥9.02)		185	787	23.51%	*2.06 (1.62-2.62)*	*1.85 (1.44-2.38)*	<0.001
TyG index		**Events**	**Total**	**Event rate**	**Unadjusted HR (95%CI)**	**adjusted HR (95%CI)**	***P* value**
							0.002
T1 (TyG ≤ 8.47)		109	795	13.7%	Ref.	Ref.	-
T2 (8.47 <TyG <8.90)		134	794	16.9%	1.24 (0.96-1.59)	1.15 (0.89-1.48)	<0.001
T3 (TyG ≥8.90)		170	794	21.4%	1.71 (1.35-2.18)	1.53 (1.19-1.98)	<0.001
TG/HDL		**Events**	**Total**	**Event rate**	**Unadjusted HR (95%CI)**	**adjusted HR (95%CI)**	***P* value**
							<0.001
T1 (TG/HDL ≤ 0.94)		115	795	14.5%	Ref.	Ref.	-
T2 (0.94 <TG/HDL <1.48)		117	794	14.7%	0.99 (0.77-1.28)	0.99 (0.76-1.28)	0.94
T3 (TG/HDL ≥1.48)		181	794	22.8%	1.68 (1.33-2.12)	1.55 (1.22-1.97)	<0.001
Neutrophil to lymphocyte ratio (NLR)		**Events**	**Total**	**Event rate**	**Unadjusted HR (95%CI)**	**adjusted HR (95%CI)**	***P* value**
							0.145
T1 (NLR ≤ 1.85)		119	795	15.0%	Ref.	Ref.	-
T2 (1.85 <NLR <2.57)		141	794	17.7%	1.17 (0.92-1.50)	1.14 (0.89-1.45)	0.306
T3 (NLR ≥2.57)		153	794	19.3%	1.33 (1.05-1.69)	1.27 (1.00-1.62)	0.051

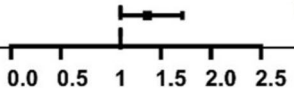

Fig. 3 Forest plot of the usefulness of the CTI, TyG index, TG/HDL-C ratio and NLR for predicting MACCE risk among PCI-treated patients

Table 2 Prognostic value of the CTI, TyG index, TG/HDL-C ratio and NLR for the risk of MACCEs among PCI-treated patients

MACCEs	HR (95% CI)							
	Unadjusted	*p* value	Model 1	*p* value	Model 2	*p* value	Model 3	*p* value
CTI tertile		**<0.001**		**<0.001**		**<0.001**		**<0.001**
T1 (CTI ≤ 8.42)	Ref		Ref		Ref		Ref	
T2 (8.42 < CTI < 9.02)	1.19 (0.91–1.54)	0.199	1.13 (0.87–1.47)	0.349	1.14 (0.88–1.48)	0.338	1.11 (0.86–1.45)	0.427
T3 (CTI ≥ 9.02)	2.06 (1.62–2.62)	**<0.001**	1.81 (1.41–2.32)	**<0.001**	1.84 (1.43–2.37)	**<0.001**	1.85 (1.44–2.38)	**<0.001**
TyG tertile		**<0.001**		**0.005**		**0.007**		**0.002**
T1 (CTI ≤ 8.47)	Ref		Ref		Ref		Ref	
T2 (8.47 < CTI < 8.90)	1.24 (0.96–1.59)	0.102	1.17 (0.91–1.51)	0.221	1.15 (0.89–1.48)	0.286	1.15 (0.89–1.48)	0.284
T3 (CTI ≥ 8.90)	1.71 (1.35–2.18)	**<0.001**	1.51 (1.17–1.94)	**0.001**	1.48 (1.15–1.91)	**0.002**	1.53 (1.19–1.98)	**0.001**
TG/HDL-C tertile		**<0.001**		**<0.001**		**<0.001**		**<0.001**
T1 (CTI ≤ 0.94)	Ref		Ref		Ref		Ref	
T2 (0.94 < CTI < 1.48)	0.99 (0.77–1.28)	0.954	0.96 (0.74–1.25)	0.778	0.97 (0.75–1.25)	0.802	0.99 (0.76–1.28)	0.940
T3 (CTI ≥ 1.48)	1.68 (1.33–2.12)	**<0.001**	1.50 (1.18–1.91)	**0.001**	1.51 (1.19–1.92)	**0.001**	1.55 (1.22–1.97)	**<0.001**
NLR tertile		0.067		0.101		0.143		0.145
T1 (CTI ≤ 1.85)	Ref		Ref		Ref		Ref	
T2 (1.85 < CTI < 2.57)	1.17 (0.92–1.50)	0.207	1.14 (0.89–1.46)	0.291	1.12 (0.88–1.43)	0.359	1.14 (0.89–1.45)	0.306
T3 (CTI ≥ 2.57)	1.33 (1.05–1.69)	**0.020**	1.30 (1.02–1.65)	**0.033**	1.27 (1.00–1.62)	0.050	1.27 (1.00–1.62)	0.051

Stratified analysis was performed via the log-rank test and backwards stepwise selection methods in Cox proportional hazard regression models. Statistically significant differences were highlighted in bold ($p < 0.05$)

Model 1: adjusted for hypertension, diabetes mellitus, body mass index and smoking status

Model 2: adjusted for Model 1, previous history of coronary revascularization and myocardial infarction

Model 3: adjusted for Model 2, multivessel/LMCA diseases, stent length, SYNTAX score and residual SYNTAX score

CTI CRP-TyG index, *TyG index* triglyceride glucose index, *TG/HDL-C* triglyceride to high density lipoprotein cholesterol ratio, *NLR* neutrophil to lymphocyte ratio, *MACCE* major adverse cardiovascular and cerebrovascular event, *HR* hazard ratio, *CI* confidence interval, *LMCA* left main coronary artery

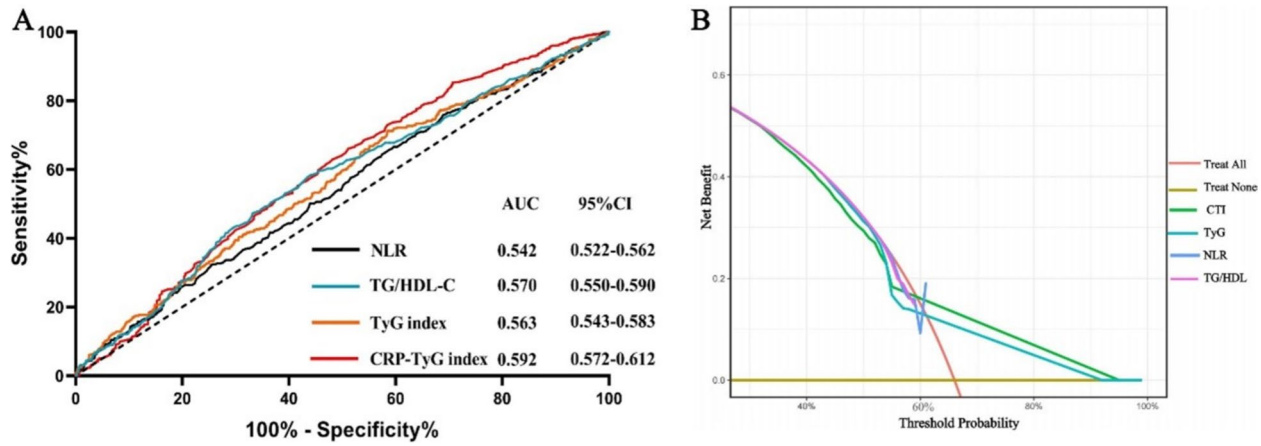

Fig. 4 Performance evaluation of the CTI, TyG index, TG/HDL-C and NLR for discriminating MACCEs. The predictive ability of various indices was determined via the ROC analysis (**A**) and DCA (**B**)

the CTI, and the results suggested that the CTI had better overall net benefit and clinical impact than the TyG index, TG/HDL-C ratio and NLR did (Fig. 4B). Analysis was also performed to evaluate whether the incorporation of the inflammatory and IR indicators into the prognostic model would increase the predictive ability for MACCEs. The prognostic model included hypertension, diabetes mellitus, body mass index, current smoker, previous history of coronary revascularization, myocardial infarction, multivessel diseases, stent length, SYNTAX score and residual SYNTAX score. As is shown in Table 3, the most significant increase in risk reclassification and discrimination was found after the inclusion of the CTI into the prognostic model, with an NRI of 0.220

Table 3 The discriminative value of the CTI, TyG index, TG/HDL-C ratio and NLR for the risk of MACCEs among PCI-treated patients

	ROC analysis			IDI (continuous)			NRI		
	AUC	95% CI	*p* values	Estimation	95% CI	*p* values	Estimation	95% CI	*p* values
Baseline model	0.694	0.675–0.712		Ref	Ref		Ref	Ref	
Baseline model + CTI	0.701	0.682–0.720	0.174	0.009	0.005–0.014	**<0.001**	0.220	0.115–0.326	**<0.001**
Baseline model + TyG index	0.697	0.678–0.715	0.406	0.004	0–0.007	**0.020**	0.166	0.060–0.272	**0.022**
Baseline model + TG/HDL-C	0.696	0.677–0.715	0.281	0.002	0–0.005	**0.049**	0.159	0.055–0.263	**0.003**
Baseline model + NLR	0.695	0.676–0.714	0.483	0.004	−0.001 to 0.008	0.074	0.058	−0.046 to 0.162	0.277

The baseline model was adjusted for hypertension status, diabetes mellitus status, body mass index, current smoking status, previous history of coronary revascularization, myocardial infarction, multivessel/LMCA diseases, stent length, SYNTAX score and residual SYNTAX score; Statistically significant differences were highlighted in bold ($p < 0.05$)

CTI CRP-TyG index, *TyG index* triglyceride glucose index, *TG/HDL-C* triglyceride to high density lipoprotein cholesterol ratio, *NLR* neutrophil to lymphocyte ratio, *MACCE* major adverse cardiovascular and cerebrovascular event, *PCI* percutaneous coronary intervention, *ROC* receiver operating characteristic, *IDI* integrated discrimination index, *NRI* net discrimination index, *AUC* area under the curve, *CI* confidence interval

($p < 0.001$), and a continuous IDI of 0.009 ($p < 0.001$) (Table 3).

Subgroup analysis of the prognostic effect of high CTI values on MACCEs

We performed subgroup analysis to confirm whether the association of increased CTI with the risk of adverse outcomes remained the same when patients were grouped by diabetes mellitus, hypertension, current smoker, obesity, elder age, sex and multivessel disease (Fig. 5). Compared with those with low CTI values (CTI < 9.02), subjects with high CTI value (CTI ≥ 9.02) had worse prognosis across all subgroups ($p < 0.05$) while the prognostic values of other indicators were attenuated in patients with metabolic disorders (Additional file: Figures S4–S6).

Mediating effect of systemic inflammation on IR-associated MACCEs

The mediating effects of hs-CRP on TyG index-associated MACCEs stratified by diabetes mellitus, hypertension, high BMI, age and sex were shown in Table 4. Overall, hs-CRP significantly mediated 15.5% of TyG index-associated MACCEs. Subgroup analysis revealed that hs-CRP mediated a greater proportion of TyG index-associated MACCEs in patients with diabetes mellitus (yes: 24.4% vs. no: 0.8%), hypertension (yes: 16.2% vs. no: 5.03%), overweight (BMI ≥ 25: 16.2% vs. BMI < 25: 5.03%) and a younger age (age < 65: 19.3% vs. age ≥ 65: 7.07%). No significant difference in the mediating effect of hs-CRP on TyG index-associated MACCEs between female and male subgroups (male: 10.97% vs. female: 11.07%). The mediating proportion of hs-CRP on the risk of TyG index-associated MACCEs in patients with diabetes mellitus (Fig. 6A), higher BMI values (Fig. 6B) and hypertension (Fig. 6C) is shown in Fig. 6.

Discussion

The main strengths of this study were as follows: (1) this was the first study focusing on the potential use of the CTI for the risk stratification and prediction of MACCEs among PCI-treated patients, and we demonstrated that the CTI was a practical indicator used for assessing prognosis and evaluating cardiometabolic risk. (2) In addition, we compared the predictive ability of the CTI for MACCEs with other IR or inflammatory indicators and revealed that the CTI was a more valuable metric for identifying high-risk patients after PCI treatment. (3) Subgroup analysis revealed that the predictive value of the CTI for adverse cardiovascular outcomes remained stable, whereas the predictive abilities of other indicators were affected by the metabolic status. (4) Last, the mediating effects of systemic inflammation on TyG index—associated MACCEs were more prominent in patients with metabolic disorders.

The CTI value is mainly determined by two critical components: systemic inflammation, represented by the hs-CRP level, and IR, represented by the TyG index. Inflammation and IR are both important components of residual risk for cardiovascular diseases and confer an increased risk of AMI and heart failure [22–25]. Strong correlations were detected between an elevated CTI value and cardiometabolic factors (Additional file: Table S1), indicating that IR and inflammation jointly contributed to the initiation and progression of cardiometabolic diseases. One plausible explanation for this association could be that the cholesterol efflux capacity of HDL-C was impaired among individuals with IR [26], whereas the HDL-C efflux capacity exerts anti-inflammatory effects by suppressing the accumulation of cholesterol esters in macrophages, thus inhibiting inflammasome activation [27]. Significant association between the CTI and obesity indicated that there is an interplay among obesity, IR and inflammation. A cross-sectional study

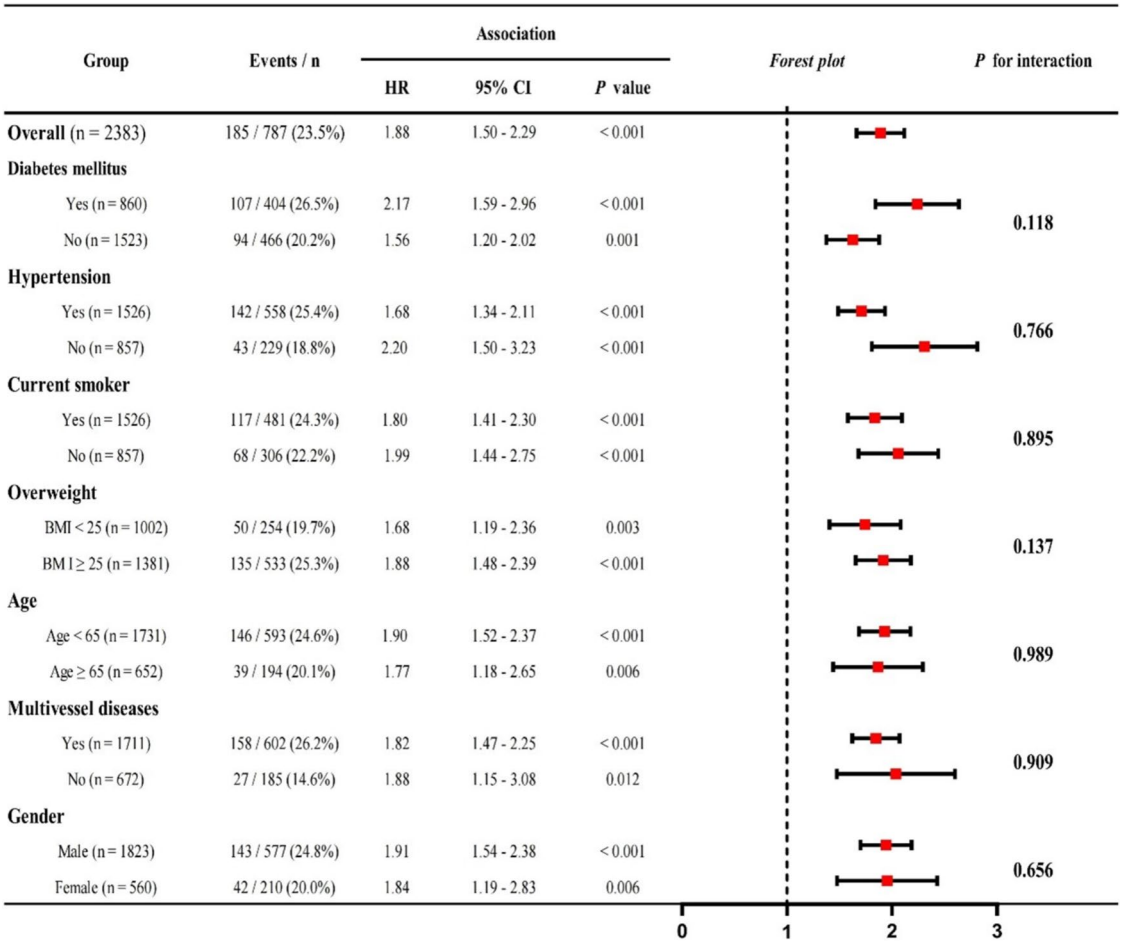

Fig. 5 Subgroup analysis of the prognostic value of a high CTI (≥9.02) for the risk of MACCEs

from Korea revealed a synergistic effect of inflammation and BMI on IR in nondiabetic adults and their combined effects on IR were greater than the sum of the separate effects [28]. Increased fat distribution of adipose tissue led to an altered secretion pattern of proinflammatory cytokines and decreased insulin sensitivity [29]. In addition to the association between the CTI and metabolic risk factors, we also found that patients with multivessel diseases tended to have higher CTI values. Karrowni et al. reported an independent association between IR and multivessel CAD after adjusting for demographic and metabolic factors in nondiabetic patients surviving AMI, suggesting the atherogenic effect of IR was independent of glucose metabolism [30]. Li et al. reported that the TyG index was positively correlated with coronary inflammation levels, as measured by peri-coronary adipose tissue attenuation ($r=0.016$, $p<0.001$) and further revealed that coronary inflammation mediated 31.66% of the association between the TyG index and multivessel CAD, stressing the importance of controlling inflammation in multivessel disease patients with IR [31]. Sex difference in CTI values was also noted in the present study. The reasons could be that women are more insulin sensitive than men and the differences in the immune response and sex hormones lead to increased inflammatory reactions in men [32, 33].

Among the inflammatory and IR indices, the CTI, TyG, and TG/HDL-C tertiles were significantly associated with the occurrence of MACCEs after adjusting for confounding covariates, whereas the NLR tertiles were not (p for trend = 0.145) (Fig. 3). As surrogate markers for IR, the increased TyG index and TG/HDL-C value for a worse prognosis prompt attention in the surveillance of IR in the management of CVD patients. Studies evaluating the effects of IR on cardiovascular events have substantiated the TyG index and TG/HDL-C as potential IR surrogate markers for predicting heart failure, AMI and cardiovascular death in cardiovascular patients [10–12, 34–36]. While the correlations between NLR and increased cardiovascular risks have also been studied previously [37, 38],

Table 4 Decomposition of the total association between TyG index and the risk of MACCEs into direct and indirect associations mediated by hs-CRP in different subgroups

Model	Associations					Proportion mediated (%)
	Indirect HR (95% CI)	Direct HR (95 CI)	ACME	ADE	Total effect	
Overall ($n=2383$)	1.12 (1.09–1.16)	1.50 (1.26–1.79)	0.010	0.052	0.062	15.50
Diabetes mellitus						
Yes ($n=860$)	1.47 (1.14–1.89)	1.62 (1.26–2.09)	0.020	0.060	0.079	24.40
No ($n=1523$)	1.37 (1.03–1.83)	1.36 (1.02–1.81)	0.001	0.038	0.039	0.80
Hypertension						
Yes ($n=1526$)	1.37 (0.94–1.99)	1.55 (1.26–1.90)	0.013	0.069	0.082	16.20
No ($n=857$)	1.34 (0.93–1.94)	1.36 (1.02–1.81)	0.001	0.022	0.023	5.03
Overweight						
BMI < 25 ($n=1002$)	1.32 (0.96–1.82)	1.34 (0.97–1.85)	0.001	0.049	0.050	2.04
BMI ≥ 25 ($n=1381$)	1.50 (1.22–1.86)	1.60 (1.29–1.98)	0.017	0.048	0.067	26.90
Age						
Age < 65 ($n=1731$)	1.41 (1.15–1.72)	1.49 (1.22–1.83)	0.012	0.048	0.060	19.30
Age ≥ 65 ($n=652$)	1.37 (1.03–1.83)	1.36 (1.02–1.81)	0.005	0.062	0.067	7.07
Gender						
Male ($n=1823$)	1.55 (1.27–1.89)	1.59 (1.30–1.94)	0.008	0.061	0.069	10.97
Female ($n=560$)	1.39 (0.94–2.05)	1.55 (1.05–2.29)	0.008	0.064	0.071	11.07

ACME average causal mediation effect, *ADE* average direct effect, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index

we found a weaker association in PCI-treated patients. The timing of NLR measurement could explain the difference. In the present study, we included the measurement of NLR during follow-up for analysis to better represent the long-term inflammatory burden after PCI, which was different from the study conducted by He et al. [37]. The weakened association could be partially attributed to the anti-inflammatory effect of statins at discharge and dynamic changes in the inflammatory response after PCI treatment. In addition, our study also revealed that the CTI had greater predictive ability than the single IR or inflammatory surrogates, suggesting that the CTI could be a better cardiometabolic indicator for evaluating long-term cardiovascular risk in advanced CAD patients. Subgroup analysis was further conducted to explore whether the prognostic values of IR and inflammatory indices for MACCEs were affected by the metabolic disorders and to evaluate whether there is an interactive effect. Weakened correlations were found between IR indicators and cardiovascular outcomes in patients without metabolic disorders while higher CTI value was still associated with a worse prognosis across all subgroups ($p<0.05$), indicating the generalizability of the CTI for cardiovascular risk prediction and stratification. Our findings also revealed a significant difference in the mediating effect of hs-CRP on the TyG—associated cardiovascular outcomes, providing insights into the complex association between CAD and metabolic process through which inflammation worsens the prognosis. Li et al. demonstrated a partial mediating effect of systemic inflammation on the association of IR with adverse cardiovascular events in diabetic chronic coronary syndrome patients [15], which was consistent with our findings. Furthermore, we also found no obvious mediating effect of hs-CRP on TyG-associated MACCEs in patients with no obvious metabolic abnormalities, implying that the effect of IR on prognosis was more likely to be triggered by direct effects in these patients. Hence, attention should be given to assessing inflammation in cardiovascular disease patients with multiple metabolic dysfunctions, as inflammation may represent a potential target for preventing recurrent event.

Clinical implications

To the best of our knowledge, this was the first study to explore the associations between high CTI values and cardiometabolic indicators, suggesting the potential of the CTI for evaluating metabolic disorders and CAD complexity. The comparison of the prognostic value of the CTI with other IR or inflammatory surrogates across different subgroups indicated the generalizability of CTI for identifying high-risk patients and predicting future cardiovascular events after PCI treatment. Lastly, the mediating effect of systemic inflammation on IR—associated cardiovascular outcomes in CAD patients with multiple metabolic disorders also demonstrated that prevention strategies reducing both systemic inflammation

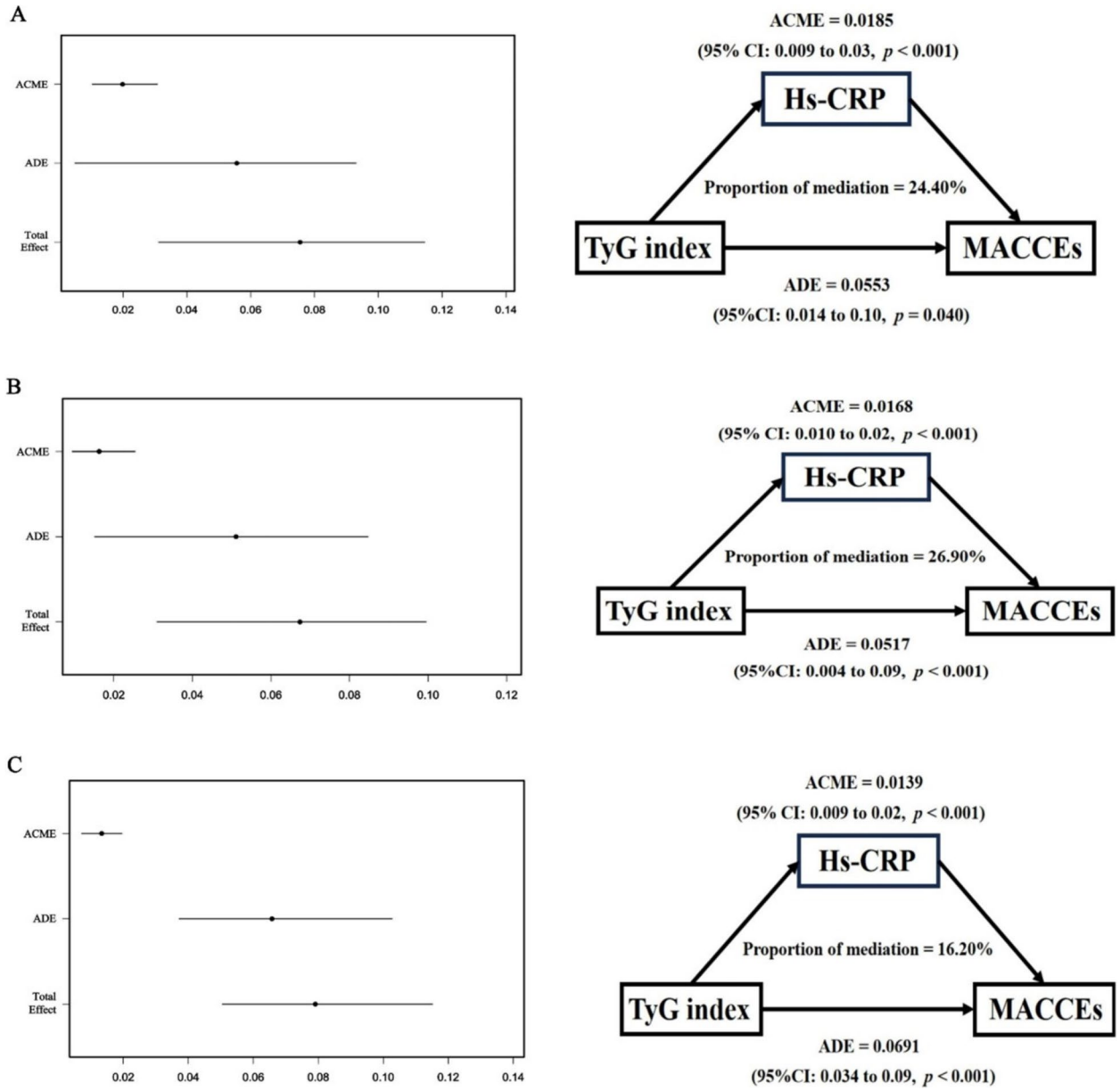

Fig. 6 Mediating proportion of hs-CRP in the TyG index associated with MACCEs in patients with diabetes mellitus (**A**), higher BMI values (**B**) and hypertension (**C**)

and IR may exceed the expected benefits by targeting these factors separately.

Limitations

Several limitations should be acknowledged. First, this was a single-center observational retrospective cohort study, so potential selection bias invariably existed. Second, the sample size was relatively small, so the exact cutoff value of the CTI and the generalizability of the conclusions still needs to be further confirmed in a larger multi-ethic study. Third, the cardiovascular death and stroke rates were relatively low during the follow-up, which may limit the statistical analysis and make it difficult to find a connection with the IR and inflammatory indicators. Finally, although these indicators were measured during follow-up to assess long-term IR and the inflammatory burden after PCI, dynamic measurements of IR or inflammation were still needed to explore their associations with cardiovascular outcomes.

Conclusions

CTI was a practical indicator for evaluating cardiometabolic diseases. Among the IR and inflammatory indicators, CTI was the most promising index for predicting recurrent cardiovascular risks in PCI-treated patients. TyG index-associated cardiovascular risks were partially mediated by systemic inflammation in patients with metabolic abnormalities.

Abbreviations

IR	Insulin resistance
CRP	C-reactive protein
TyG index	Triglyceride glucose index
CTI	C-reactive protein-triglyceride glucose index
MACCE	Major adverse cerebrovascular and cardiovascular event
PCI	Percutaneous coronary intervention
AMI	Acute myocardial infarction
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High density lipoprotein cholesterol
NLR	Neutrophil to lymphocyte ratio
TG/HDL-C	Triglyceride to HDL-C ratio
ROC	Receiver operating characteristic
AUC	Area under the curve
NRI	Net reclassification improvement
IDI	Integrated discrimination improvement
BMI	Body mass index
CAD	Coronary artery disease
DCA	Decision curve analysis
RCS	Restricted cubic spline
HOMA-IR	Homeostasis model assessment-IR

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01687-8.

Additional file 1.

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Not applicable.

Author contributions

A.G. and B.P. concepted and designed the study. A.G. and Y.N.G. analyzed and interpreted the data. A.G. wrote the main manuscript. Z.Q.Y and Z.F.L prepared the figures 1–6 and tables 1–4. T.T.G and H.Q. prepared the supplementary files. T.T.G. and H.Q. revised the manuscript critically for important intellectual content. All authors reviewed the manuscript.

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Availability of data and materials

The datasets and materials mentioned above are available from the authors upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Fuwai Hospital (No. 2021-1063). The need to obtain informed consent from the participants was waived by the Ethics Committee.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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