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Original Research

Predictive Value of the Triglyceride–Glucose (TyG) Index and Modified TyG Index Combined With Cardiopulmonary Exercise Testing Parameters for Major Adverse Cardiovascular Events

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Abstract

Background: The triglyceride–glucose (TyG) index, a convenient alternative marker of insulin resistance (IR), has been shown to correlate with cardiovascular disease risk and to demonstrate robust predictive capacity for cardiovascular outcomes. However, because the TyG index relies solely on biomarkers, this metric does not capture critical functional states, including cardiopulmonary reserve. In contrast, cardiopulmonary exercise testing (CPET) is an established, objective, and quantitative functional assessment tool for evaluating cardiorespiratory fitness in patients undergoing percutaneous coronary intervention (PCI) and provides prognostic value for risk stratification. Therefore, this study aimed to develop the modified TyG indices by combining the TyG index with CPET parameters and to compare their predictive performance for major adverse cardiovascular events (MACEs) with that of the original TyG index. **Methods:** Cox proportional hazards regression was used to analyze associations and predictive capacity based on hazard ratio (HR) and Harrell's C-index. Mediation analysis was performed to quantify mediation effects. **Results:** The study enrolled 8803 patients with acute coronary syndrome (ACS) who underwent CPET after PCI. The mean participant age was 57.39 ± 8.97 years, and 2032 participants (23.1%) were female. Over a median follow-up of 5.0 years, 1548 MACEs occurred (17.6%). For each index, including the TyG index and its modified versions (peak oxygen uptake (VO_2)/kg_TyG, anaerobic threshold (AT) VO_2/kg_TyG, and peak O_2 pulse_TyG), participants were independently divided into tertiles (T1–T3) to evaluate their respective associations with MACEs. Compared with the lowest tertile, the highest tertile was associated with the following HRs for MACEs: TyG, 1.268 (95% confidence interval (CI), 1.108–1.500); peak oxygen uptake per kilogram (peak VO_2/kg)_TyG, 0.796 (95% CI, 0.694–0.912); peak O_2 pulse_TyG, 0.820 (95% CI, 0.713–0.942); AT VO_2/kg_TyG, 0.850 (95% CI, 0.747–0.967). The C-index values for peak VO_2/kg_TyG and AT VO_2/kg_TyG in predicting MACEs were higher than those of the TyG index. Mediation analysis further clarified these relationships: peak VO_2/kg mediated 13.8% of the association between the TyG index and MACEs, whereas TyG accounted for only 3.8% of the association between peak VO_2/kg and MACEs. **Conclusion:** Peak VO_2/kg_TyG showed significantly improved predictive accuracy for risk of MACE stratification in patients with ACS compared with the traditional TyG index.

Keywords: cardiac rehabilitation; cardiopulmonary exercise testing; insulin resistance

1. Introduction

Insulin resistance, one of important pathophysiological mechanisms underlying the development and progression of atherosclerotic cardiovascular disease (ASCVD), demonstrates significant clinical value in cardiovascular risk stratification [1,2]. While the hyperinsulinemic-euglycemic clamp (HIEC) remains the gold standard for assessing insulin resistance (IR) [3], its clinical utility is constrained by procedural complexity and high costs. In recent years, the triglyceride-glucose (TyG) index has emerged as a reliable alternative marker for IR in large-scale epidemiological studies, owing to its accessibility and reproducibility [4]. Previous research has shown the TyG index correlates with subclinical atherosclerosis markers such as carotid intima-media thickness (CIMT) and independently predicts cardiovascular risks such as acute coronary syndrome [5,6]. Despite its established prognostic value, the TyG index is a static biochemical marker. It only reflects basal glucolipid metabolism and cannot capture dynamic functional dimensions. These include an individual's cardiopulmonary reserve, exercise tolerance, and hemodynamic response to physiological stress. Such functional dimensions may be critical for comprehensive risk assessment in patients after percutaneous coronary intervention (PCI) [7].

Cardiopulmonary exercise testing (CPET) is an objective method for quantifying cardiopulmonary function. In post-PCI patients, key CPET parameters such as peak oxygen uptake per kilogram (peak VO_2/kg), anaerobic thresh-

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old volume of oxygen per kilogram (anaerobic threshold (AT) VO_2/kg), and peak oxygen pulse (peak O_2 pulse) have been established as independent predictors of cardiovascular mortality and adverse outcomes, providing incremental prognostic value beyond traditional risk factors. By monitoring gas exchange, electrocardiogram (ECG), and hemodynamic responses during exercise, CPET aids cardiovascular disease management through diagnosis, prognosis assessment, and treatment monitoring. Furthermore, it accurately identifies exercise-induced myocardial ischemia, malignant arrhythmias, and abnormal hemodynamic responses, emphasizing its clinical significance in cardiovascular medicine [8,9,10].

Based on the above rationale, the purpose of the present study is to develop an optimized TyG index through integration of CPET parameters. The study aimed to compare the predictive performance of the conventional versus modified TyG indices for major adverse cardiovascular events (MACE). These findings may provide novel evidence for refining cardiovascular risk stratification models.

2. Methods

2.1 Study Design and Population

This retrospective cohort study enrolled patients who underwent CPET at the General Hospital of Northern Theater Command from March, 2016 to May, 2019. Inclusion criteria were Patients diagnosed with acute coronary syndrome (ACS) who successfully underwent PCI. Clinically stable patients who are able to tolerate and complete standard cardiopulmonary exercise testing. Exclusion criteria comprised: Presence of co-existing conditions such as hereditary cardiomyopathy, severe valvular heart disease, end-stage renal disease, or active malignancy. Acute or active medical conditions that could interfere with cardiopulmonary function assessment, including (but not limited to) uncontrolled severe infection within the past 4 weeks, acute pulmonary embolism, or a stroke within the preceding 3 months. In present study, the timing of CPET was stratified according to the patient's clinical presentation. For the majority of patients, CPET was performed during their post-PCI hospitalization. However, for those presenting with acute myocardial infarction (AMI), testing was safely deferred to 1 to 3 months post-PCI. At the time of assessment, all participants were required to be clinically stable and capable of completing a symptom-limited incremental exercise test [11]. The study protocol was approved by the Ethics Committee of General Hospital of Northern Theater Command [Y (2025)444]. A waiver of informed consent was granted due to the retrospective nature of the study and anonymized data processing. This study adhered to the principles of the Declaration of Helsinki.

2.2 Data Collection and Definitions

Baseline clinical characteristics included age, sex, body mass index (BMI), smoking history, alcohol consumption, and comorbidities (e.g., hypertension, diabetes mellitus, prior AMI). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, or current use of antihypertensive therapy. Diabetes mellitus was diagnosed based on fasting blood glucose ≥7.0 mmol/L, 2-hour postprandial blood glucose ≥11.1 mmol/L, glycated hemoglobin (HbA1c) ≥6.5%, or a confirmed diagnosis of diabetes with active treatment. Fasting venous blood samples (after ≥8 hours of fasting) collected closest to the CPET date (typically within one week before or after CPET) were analyzed for fasting triglyceride (TG, mg/dL) and fasting plasma glucose (FPG, mg/dL).

CPET was performed following a standardized symptom-limited incremental protocol using SCHILLER bicycle ergometers (SCHILLER AG, Baar, Zug, Switzerland). Before each test, the gas analyzers and flow sensors were calibrated with reference gases (16% O_2, 5% CO_2) and a 3-liter calibration syringe, respectively. Static lung function was assessed prior to exercise and used to verify system accuracy. Following a 2 to 3 minute rest period, participants performed unloaded cycling at 60 revolutions per minute. Subsequently, the workload was progressively increased in increments corresponding to 10% of each participant's estimated exercise capacity (calculated from age, height, and weight). Exercise was continued until one or more of the following termination criteria were met, consistent with American Heart Association recommendations: (1) achievement of volitional exhaustion (rating of perceived exertion ≥18 on the Borg 6-20 scale); (2) a plateau in oxygen uptake despite increasing workload; (3) respiratory exchange ratio ≥1.10; (4) attainment of age-predicted maximal heart rate; (5) significant ST-segment depression (>2 mm) or elevation; (6) sustained ventricular arrhythmias or progressive atrioventricular block; (7) a drop in systolic blood pressure >20 mmHg despite increasing workload; or (8) patient request to stop due to intolerable symptoms (angina, dyspnea, or leg fatigue). Key CPET parameters were recorded as follows: (1) Peak VO_2/kg (mL/kg/min): the highest oxygen uptake averaged over 30 seconds during the final stage of exercise, normalized to body weight. (2) AT VO_2/kg (mL/kg/min): determined by the V-slope method, wherein the inflection point at which the VCO_2 vs. VO_2 slope transitions from <1.0 to >1.0 was identified. This was confirmed by ventilatory equivalent analysis (systematic increase in VE/VO_2 without a concurrent increase in VE/VCO_2). All AT determinations were independently performed by two experienced technicians blinded to patient outcomes; discrepancies were resolved by a third senior reviewer. (3) Peak O_2 pulse (mL/beat): calculated as peak VO_2 (mL/min) divided by peak heart rate (bpm). All tests were administered by trained rehabilitation technicians under standardized protocols [11,12]. In addition, MACE was defined as a composite endpoint consisting of the following individual components: Cardiovascular death; Non-fatal myocardial infarction; Ischemia-driven

revascularization (including repeat percutaneous coronary intervention or coronary artery bypass grafting); Stroke (ischemic or hemorrhagic) in the present study [13].

2.3 Model Specification

Three statistical models were constructed for this study. Model 1 was unadjusted. Model 2 was adjusted for age and sex. Given that age and sex are fundamental, unmodifiable cardiovascular risk variables, they were routinely adjusted as covariates in studies assessing the prognostic value of the TyG index [14,15]. Furthermore, given the natural decline in cardiorespiratory fitness with age and the generally superior core CPET metrics in males compared to females, adjustment for age and sex is an essential step to minimize relevant confounding bias [16,17]. In addition to age and sex, Model 3 was adjusted for age, sex, smoking status, drinking status, hypertension, diabetes, estimated glomerular filtration rate (eGFR), low-density lipoprotein cholesterol (LDL-C), left ventricular ejection fraction (LVEF), high-sensitivity C-reactive protein (HsCRP), BMI, and high-density lipoprotein cholesterol (HDL-C). These variables were included to control for potential confounding from traditional cardiovascular risk factors.

2.4 Index Calculation

The TyG index was calculated using the formula [4]:

$$\mathrm{TyG} = \ln([\text{fastingtriglycerides (TG,mg/dL)} \times \text{glucose (mg/dL)} /2])$$

The modified TyG indices were calculated as follows:

$$\text{peak } O_2\text{pulse_TyG} = \text{peak } O_2\text{pulse/TyG index}$$

$$\text{peak}VO_2/\text{kg_TyG} = \text{peak}VO_2/\text{kg/TyG index}$$

$$ATVO_2/\text{kg_TyG} = ATVO_2/\text{kg/TyG index}$$

The TyG index and the modified TyG indices were grouped into tertiles as follows:

TyG (index), tertile 1: <8.51, tertile 2: 8.51–9.04, tertile 3: >9.04

peak VO_2/kg_TyG (mL/kg/min), tertile 1: <1.54, tertile 2: 1.54–1.95, tertile 3: >1.95

peak O_2 pulse_TyG (mL/beat), tertile 1: <0.95, tertile 2: 0.95–1.20, tertile 3: >1.20

AT VO_2/kg_TyG (mL/kg/min), tertile 1: <1.12, tertile 2: 1.12–1.34, tertile 3: >1.34

2.5 Statistical Analysis

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as number (percentage). Baseline characteristics were summarized according to tertiles of the TyG index. Spearman's rank correlation coefficients were used to evaluate associations between the TyG index and its modified indices (peak O_2 pulse_ TyG, peak VO_2/kg_TyG, AT VO_2/kg_ TyG). Multivariable-adjusted Cox proportional hazards regression models were employed to assess the associations of the TyG index and its modified indices with cardiovascular outcomes, generating hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was validated using Schoenfeld residual tests, with no significant violations identified. Restricted cubic spline models (with knots at the 10th, 50th, and 90th percentiles) were applied to explore dose-response relationships, using the median value of each index as the reference. The predictive performance of the TyG index and its modified indices for MACE was evaluated using time-dependent Harrell's C-index and area under the curve (AUC) values. We performed mediation analysis to examine both direct and indirect associations between the TyG index and MACE through CPET parameters. In this analytical framework, elevated TyG index values served as the predictor variable (X), reduced CPET parameters functioned as the mediator variable (M), and MACE occurrence represented the outcome variable (Y). Additionally, the study conducted a complementary mediation analysis to evaluate whether CPET parameters mediated the relationship between TyG index and MACE events. All statistical analyses were conducted using R software (version 4.4.3, R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Characteristics of the Study Population

A total of 8803 participants (6771 male and 2032 female) were included in this study. The mean age was 57.39 ± 8.97 years. Over a median follow-up of 5.0 years, 1548 MACEs occurred (17.6%). Significant differences were found in age, smoking status, drinking status, hypertension, diabetes, body mass index (BMI), fasting plasma glucose (FPG), high-sensitivity C-reactive protein (hsCRP), triglycerides (TG), high-density lipoprotein (HDL), left ventricular ejection fraction (LVEF), white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), serum uric acid (SUA), and platelet (PLT). Other variables showed no statistically significant differences (Table 1). TyG was not strongly correlated with the modified TyG indices, and the Spearman's coefficients for peak VO_2/kg_TyG, peak O_2 pulse_TyG, and AT VO_2 /kg_TyG were 0.18, 0.31, and 0.25, respectively (Fig. 1).

Table 1. Characteristics of 8803 participants according to baseline TyG levels.

	Overall	Baseline TyG index			*p* value
		Tertile 1	Tertile 2	Tertile 3	
Participants, No.	8, 803	2, 935	2, 934	2, 934	
Age, years, mean (SD)	57.39 ± 8.97	58.43 ± 8.77	57.53 ± 8.81	56.21 ± 9.17	<0.001*
Sex, Male, n (%)	6771 (76.92%)	2274 (77.5%)	2235 (76.2%)	2262 (77.1%)	0.477
Smoking status, n (%)					
Never	4201 (47.72%)	1467 (50%)	1432 (48.8%)	1302 (44.4%)	<0.001*
Former	1451 (16.48%)	515 (17.5%)	460 (15.7%)	476 (16.2%)	
Current	3151 (35.79%)	953 (32.5%)	1042 (35.5%)	1156 (39.4%)	
Drinking status, n (%)					
Never	6566 (74.59%)	2183 (74.4%)	2203 (75.1%)	2180 (74.3%)	0.029*
Former	588 (6.68%)	229 (7.8%)	178 (6.1%)	181 (6.2%)	
Current	1649 (18.73%)	523 (17.8%)	553 (18.8%)	573 (19.5%)	
Hypertension, n (%)	5028 (57.12%)	1545 (52.6%)	1713 (58.4%)	1770 (60.3%)	<0.001*
Diabetes, n (%)	2283 (25.93%)	429 (14.6%)	607 (20.7%)	1247 (42.5%)	<0.001*
BMI, kg/m^2					<0.001*
Continuous	25.52 ± 3.43	24.78 ± 3.39	25.58 ± 3.34	26.21 ± 3.39	
<24.0	2816 (31.99%)	1224 (41.7%)	870 (29.7%)	722 (24.6%)	
24.0 ≤ BMI < 28	4171 (47.38%)	1268 (43.2%)	1461 (49.8%)	1442 (49.1%)	
≥28.0	1816 (20.63%)	443 (15.1%)	603 (20.6%)	770 (26.2%)	
Lipid-lowering drugs, n (%)	8345 (94.80%)	2766 (94.24%)	2773 (94.51%)	2806 (95.64%)	0.038*
LDL-C mg/dL, mean (SD)	81.02 ± 29.65	72.02 ± 25.69	83.32 ± 29.08	87.71 ± 31.66	<0.001*
FPG, mg/dL, mean (SD)	116.63 ± 44.45	94.98 ± 16.39	108.51 ± 27.62	146.39 ± 58.96	<0.001*
hsCRP, mg/L, median (IQR)	1.20 (0.50–3.10)	0.80 (0.40–2.40)	1.2 (0.50–3.10)	1.60 (0.70–3.80)	<0.001*
TG, mg/dL, median (IQR)	119.54 (86.33–169.13)	77.9 (64.6–91.2)	125.0 (107.0–146.0)	196.0 (155.0–254.0)	<0.001*
HDL-C, mg/dL, mean (SD)	41.43 ± 9.40	43.07 ± 9.72	40.86 ± 8.59	40.37 ± 9.63	<0.001*
CK, U/L median (IQR)	89 (65–118)	90 (66–118)	89 (65–118)	89 (64–119)	0.175
LVEF, %, mean (SD)	61.36 ± 5.97	61.63 ± 5.87	61.27 ± 6.03	61.17 ± 5.99	0.009*
WBC, ×10^9/L, mean (SD)	8.03 ± 2.68	7.68 ± 2.65	8.12 ± 2.70	8.28 ± 2.67	<0.001*
RBC, ×10^{12}/L, mean (SD)	4.53 ± 0.46	4.47 ± 0.44	4.54 ± 0.45	4.59 ± 0.47	<0.001*
Hb, mean, g/L (SD)	139.52 ± 13.64	138.27 ± 13.33	139.68 ± 13.48	140.61 ± 14.00	<0.001*
SCr, μmol/L, mean (SD)	70.25 ± 21.30	69.52 ± 15.07	70.77 ± 28.11	70.45 ± 18.53	0.066
SUA, μmol/L, mean (SD)	350.32 ± 88.42	335.61 ± 80.59	353.60 ± 88.63	361.74 ± 93.57	<0.001*
PLT, ×10^9/L, mean (SD)	221.95 ± 54.51	215.10 ± 54.54	224.99 ± 53.33	225.76 ± 55.02	<0.001*

Data are presented as mean ± SD for normally distributed continuous variables, median (interquartile range (IQR)) for skewed continuous variables, and n (%) for categorical variables. Statistical analysis: Differences among groups were compared using One-way ANOVA for normally distributed variables. Kruskal-Wallis H test was used for skewed variables. Chi-square test was used for categorical variables.

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CK, creatine kinase; FPG, fasting plasma glucose; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; PLT, platelet; RBC, red blood cell; SCr, serum creatinine; SUA, serum uric acid; TG, triglyceride; TyG, triglyceride-glucose index; WBC, white blood cell; Lipid-lowering drugs, including statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i).

* Indicates a statistically significant difference among the three groups ($p < 0.05$).

3.2 Associations of TyG and Modified TyG Indices With MACE.

In the model 2 (age and sex were adjusted), participants in the highest tertile (tertile 3) of the TyG index had a significantly increased risk of MACE (HR 1.145, 95% CI 1.012–1.294, $p = 0.031$). In contrast, the highest tertiles (tertile 3) of the modified TyG indices were associated with a dose-dependent reduction in MACE risk compared to the lowest tertile (tertile 1): peak VO_2/kg_TyG: HR 0.828, 95% CI 0.726–0.944, $p = 0.005$; peak O_2 pulse_TyG: HR 0.831, 95% CI 0.724–0.953, $p = 0.008$; AT VO_2/kg_TyG: HR 0.878, 95% CI 0.774–0.995, $p = 0.042$. In the model 3 (age, sex, smoking status, drinking status, hypertension, diabetes, eGFR, LDL-C, LVEF, HsCRP, BMI and HDL-C were adjusted), compared with tertile 1, the adjusted HRs (95% CIs) for MACE in tertile 3 were: TyG: 1.268 (1.108–

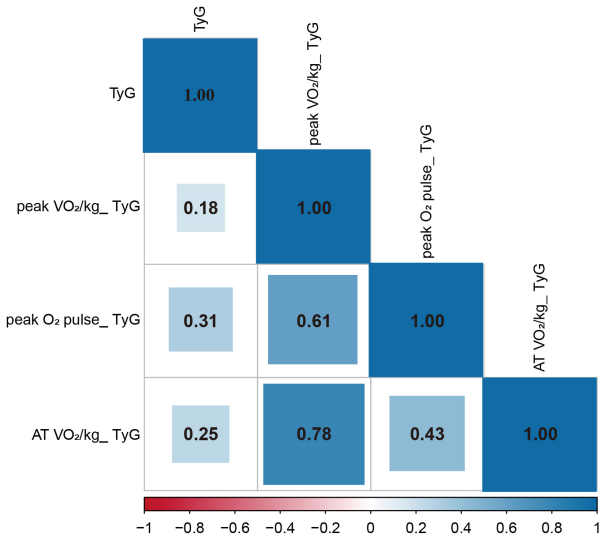


Fig. 1. Spearman's correlation of TyG and modified indices. Abbreviations: TyG, triglyceride-glucose index; peak VO_2/kg, peak oxygen uptake per kilogram; peak O_2 pulse, peak oxygen pulse; AT VO_2/kg, anaerobic threshold volume of oxygen per kilogram. Color intensity represents the strength and direction of the Spearman correlation coefficients. The strength of the correlation between two variables is represented by the color at the intersection.

1.500), $p < 0.001$; peak VO_2/kg_TyG: 0.796 (0.694–0.912), $p = 0.001$; peak O_2 pulse_TyG: 0.820 (0.713–0.942), $p = 0.005$; AT VO_2/kg_TyG: 0.850 (0.747–0.967), $p = 0.014$ (Table 2).

Restricted cubic spline analyses were performed to examine the shape of the dose-response relationships. For all four indices, tests for nonlinearity were not significant (all p for nonlinearity > 0.05), suggesting that the associations did not deviate from linearity. The restricted cubic spline curves are provided in **Supplementary Fig. 1**.

3.3 Predictive Capacity Comparison

The study calculated time-dependent Harrell's C-indices for four TyG-related parameters: TyG, peak VO_2/kg_TyG, peak O_2 pulse_TyG and AT VO_2/kg_TyG. These indices showed significant predictive value for MACE (Fig. 2). The C-index values (95% CI) were: 0.565 (0.563–0.568) for TyG; 0.579 (0.577–0.581) for peak VO_2/kg_TyG; 0.565 (0.563–0.567) for peak O_2 pulse_TyG; and 0.569 (0.568–0.571) for AT VO_2/kg_TyG. The C-index of peak VO_2/kg_TyG was significantly higher than that of the TyG index ($p < 0.05$), confirming its superior discriminative performance for MACE. The time-dependent AUC indicated that the TyG index and its modified indices (including peak VO_2/kg_TyG, peak O_2 pulse_TyG, and AT VO_2/kg_TyG) consistently exhibited significant predictive value for MACE throughout the follow-up period (Fig. 3).

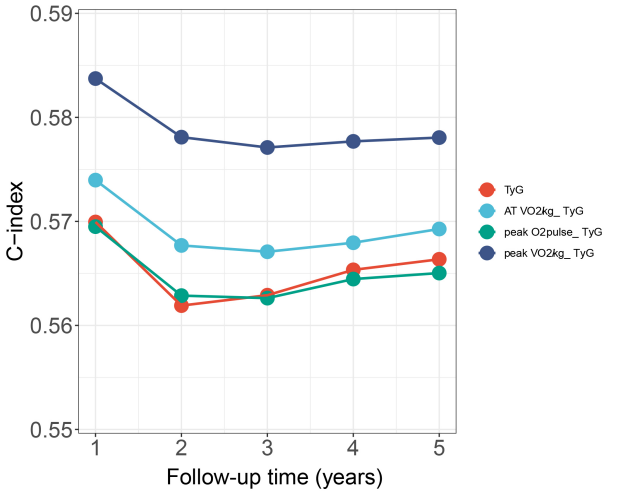


Fig. 2. C-index values of TyG and modified indices for MACE. Abbreviations: TyG, triglyceride-glucose index; peak VO_2/kg, peak oxygen uptake per kilogram; peak O_2 pulse, peak oxygen pulse; AT VO_2/kg, anaerobic threshold volume of oxygen per kilogram; C-index, concordance index.

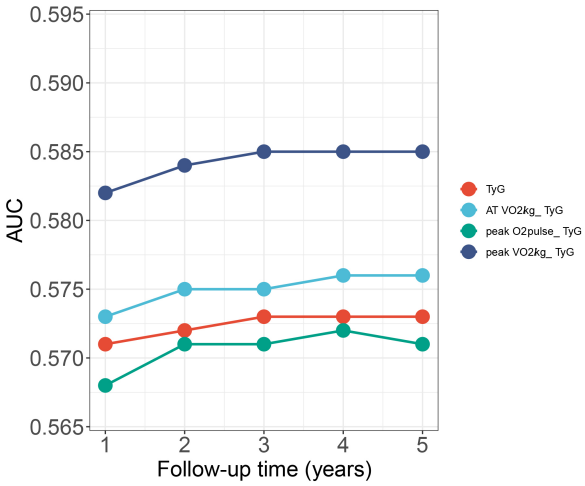


Fig. 3. AUCs value of TyG and modified indices for MACE. TyG, triglyceride-glucose index; peak VO_2/kg, peak oxygen uptake per kilogram; peak O_2 pulse, peak oxygen pulse; AT VO_2/kg, anaerobic threshold volume of oxygen per kilogram; AUC, area under curve.

3.4 Stratified Analysis

Subgroup Analysis Stratified by Peak VO_2/kg, participants were stratified by median peak VO_2/kg. Among those with above-median peak VO_2/kg, a higher TyG index (above median) was associated with an increased risk of MACE (HR: 1.199, 95% CI: 1.027–1.400, $p = 0.022$). Similarly, in the group with below-median peak VO_2/kg, a higher TyG index (above median) also significantly increased the risk of MACE (HR: 1.162, 95% CI: 1.007–1.341, $p = 0.040$) (Table 3).

Table 2. Associations of TyG index and modified TyG index with major adverse cardiovascular events .

Index	Tertile 1	Tertile 2			Tertile 3		
		HR	95% CI	*p* value	HR	95% CI	*p* value
TyG							
Model 1	Ref	1.147	1.011–1.301	0.033*	1.155	1.022–1.305	0.021#
Model 2		1.150	1.013–1.304	0.030*	1.145	1.012–1.294	0.031#
Model 3		1.213	1.067–1.379	0.003*	1.268	1.108–1.500	<0.001#
peak VO_2/kg_TyG	Ref						
Model 1		0.868	0.772–0.976	0.018*	0.841	0.741–0.955	0.007#
Model 2		0.865	0.768–0.974	0.016*	0.828	0.726–0.944	0.005#
Model 3		0.846	0.750–0.955	0.006*	0.796	0.694–0.912	0.001#
peak O_2 pulse_ TyG	Ref						
Model 1		0.943	0.836–1.063	0.337	0.854	0.755–0.967	0.013#
Model 2		0.932	0.819–1.060	0.283	0.831	0.724–0.953	0.008#
Model 3		0.949	0.834–1.081	0.432	0.820	0.713–0.942	0.005#
AT VO_2/kg_ TyG	Ref						
Model 1		0.972	0.864–1.094	0.641	0.872	0.771–0.987	0.031#
Model 2		0.977	0.867–1.100	0.700	0.878	0.774–0.995	0.042#
Model 3		0.958	0.849–1.081	0.487	0.850	0.747–0.967	0.014#

Abbreviations: HR, hazard ratio; CI, confidence interval; TyG, triglyceride-glucose index; Peak VO_2/kg, peak oxygen uptake per kilogram; Peak O_2 pulse, peak oxygen pulse; AT VO_2/kg, anaerobic threshold volume of oxygen per kilogram.

* Indicates a statistically significant difference between tertile 1 and tertile 2 ($p < 0.05$).

# Indicates a statistically significant difference between tertile 1 and tertile 3 ($p < 0.05$).

Model 1: unadjusted; Model 2: age and sex were adjusted; Model 3: age, sex, smoking status, drinking status, hypertension, diabetes, estimated glomerular filtration rate (eGFR), LDL-C, LVEF, hsCRP, BMI and high-density lipoprotein cholesterol (HDL-C) were adjusted.

Subgroup Analysis Stratified by TyG Index, stratification was performed by the TyG index. Participants with a below-median TyG index and low peak VO_2/kg (below median) had a significantly higher risk of MACE (HR: 1.186, 95% CI: 1.016–1.384, $p = 0.030$). However, among those with an above-median TyG index, low peak VO_2/kg was not significantly associated with an increased risk of MACE (HR: 1.142, 95% CI: 0.984–1.327, $p = 0.081$) (Table 3).

3.5 Mediation Analysis

In the model 3 (age, sex, smoking status, drinking status, hypertension, diabetes, eGFR, LDL-C, LVEF, HsCRP, BMI and HDL-C were adjusted) with the TyG index as the independent variable, the average causal mediation effect (ACME) was 0.00244 (95% CI 0.00133–0.00375; $p < 0.001$). The average direct effect (ADE) was 0.01523 ($p = 0.036$). Consequently, the proportion of the total effect mediated was 13.80% ($p = 0.016$). When peak VO_2/kg was included as the independent variable, the ACME was–0.00018 (95% CI –0.00038–0.00002; $p = 0.036$), while the ADE was –0.00461 ($p < 0.001$). Thus, the mediated proportion was 3.79% ($p = 0.036$) (Fig. 4).

4. Discussion

This study integrated the TyG index with key CPET parameters to develop novel modified TyG indices. We subsequently evaluated and compared the predictive value for MACE of the traditional TyG index versus these novel indices. Although the TyG index and the modified indices showed only weak-to-moderate correlations, all were found to be independent predictors of MACE. Notably, for MACE risk stratification, peak VO_2/kg_TyG and AT VO_2/kg_TyG showed significantly superior predictive accuracy compared to the traditional TyG index, with the peak VO_2/kg_TyG index performing the best. Moreover, mediation analysis revealed that peak VO_2/kg partially mediated the association between the TyG index and MACE.

The TyG index has been extensively validated as an independent predictor of cardiovascular outcomes. For instance, the large retrospective cohort study by Mavraganis et al. [6] confirmed that elevated TyG was an independent predictor of all-cause and cardiovascular mortality. This was further supported by a meta-analysis that synthesized data from multiple studies and confirmed significant associations between the TyG index and the risks of cardiovascular events, all-cause mortality, and cardiovascular-specific mortality [18]. In this regard, our findings regarding the predictive value of the traditional TyG index align with the established body of evidence.

In recent years, CPET has emerged as the gold-standard, non-invasive method for comprehensively assessing cardiorespiratory fitness, gas exchange efficiency, and

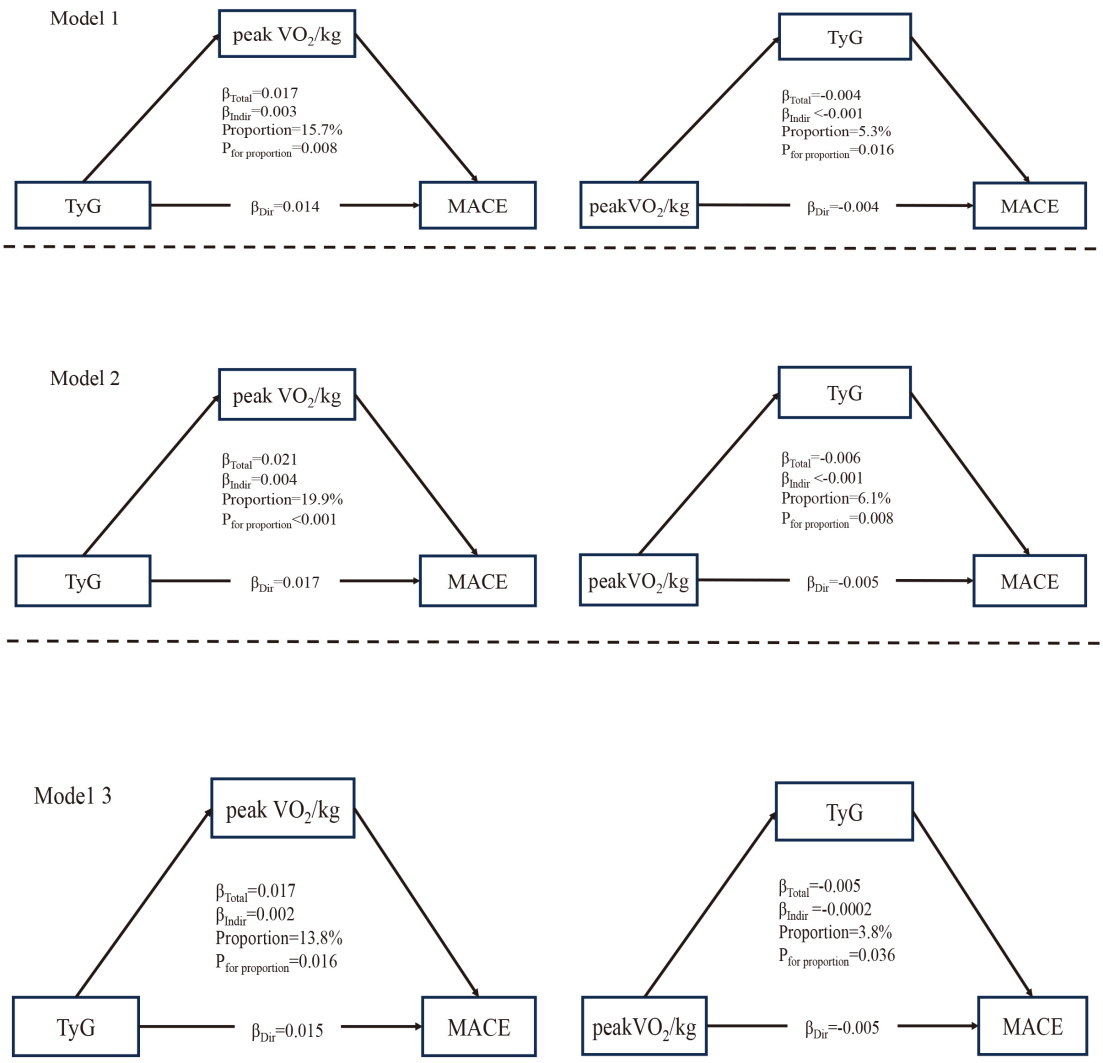


Fig. 4. Reciprocal mediation between the TyG index and peak VO_2/kg on the risk of MACE. Abbreviations: TyG, triglyceride-glucose index; peak VO_2/kg, peak oxygen uptake per kilogram; MACE, major adverse cardiovascular events.

exercise tolerance, thus providing established benchmarks for evaluating cardiovascular functional reserve [19]. In the present study, we integrated the TyG index (reflecting basal metabolic state) with key CPET parameters (representing dynamic cardiorespiratory response) to construct novel modified TyG indices. Peak VO_2/kg, peak O_2 pulse, and AT VO_2/kg serve as key indicators of cardiorespiratory fitness [20]. These parameters directly quantify the overall efficiency of oxygen transport and utilization dynamics under exercise stress [20]. Although physiological interplay exists between cardiorespiratory function and the glucolipid metabolic dysregulation reflected by the TyG index, these systems occupy distinct physiological domains: the former governs the delivery and utilization of energy substrates, while the latter primarily regulates their metabolism [21,22]. Consistent with this conceptual distinction, the present study found only weak correlations between the TyG index and the modified TyG indices. This key finding indicates the modified TyG indices do not merely amplify or replicate the metabolic information contained within the original index. Instead, their structure incorporates a novel dimension of cardiorespiratory reserve, thereby creating a more comprehensive and integrative risk assessment tool.

The present study confirmed that both the TyG index and the modified TyG indices were independent predictors of the long-term risk of MACE. Notably, with regard to predictive performance, both peak VO_2/kg_TyG and AT VO_2/kg_TyG significantly outperformed the TyG index, with peak VO_2/kg_TyG showing the greatest superiority.

The underlying mechanism for the superior predictive capacity of modified TyG indices is primarily attributed to the rich pathophysiological information captured by peak VO_2/kg. Specifically, peak VO_2/kg is a comprehensive indicator of overall cardiopulmonary function, assessing not only the patient's maximum cardiac pumping capacity and

Table 3. Stratified Associations of the TyG Index and Peak VO_2/kg With MACE.

	HR	95% CI	*p* value
Subgroup Analysis Stratified by Peak VO_2/kg			
peak VO_2/kg > median			
TyG < median	-	-	
TyG > median	1.199	1.027–1.400	0.022*
peak VO_2/kg < median			
TyG < median	-	-	
TyG > median	1.162	1.007–1.341	0.040*
Subgroup Analysis Stratified by TyG Index			
TyG < median			
peak VO_2/kg > median	-	-	
peak VO_2/kg < median	1.186	1.016–1.384	0.030#
TyG > median			
peak VO_2/kg > median	-	-	
peak VO_2/kg < median	1.142	0.984–1.327	0.081

Abbreviations: Hazard ratios (HR) and 95% confidence intervals (CI) were derived from Cox proportional hazards models. Median values were used as cut-off points for both the TyG index and peak VO_2/kg < median.

* Indicates a statistically significant difference ($p < 0.05$) compared to the TyG < median reference group within the same aerobic capacity stratum.

# Indicates a statistically significant difference ($p < 0.05$) compared to the peak VO_2/kg > median reference group within the same TyG index stratum.

TyG, triglyceride-glucose index; peak VO_2/kg, peak oxygen uptake per kilogram; MACE, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval.

Subgroup Analysis Stratified by Peak VO_2/kg: Association between TyG and MACE across peak VO_2/kg groups; Subgroup Analysis Stratified by TyG Index: association between peak VO_2/kg and MACE across TyG groups.

functional reserve, but also providing an integrated assessment of cardiovascular disease severity [23,24,25]. Moreover, robust clinical evidence confirms a clear association between peak VO_2/kg levels and all-cause mortality, while improvement in peak VO_2/kg is indicative of enhanced cardiac function and is associated with a corresponding reduction in adverse clinical outcomes [26,27,28,29,30]. The high clinical predictive value of peak VO_2/kg and its reflection of the integrated health status of the cardiovascular system explains why its incorporation into the TyG index significantly increases the model's predictive capacity for MACE risk.

Mediation analysis confirmed that peak VO_2/kg partially mediated the association between the TyG index and MACE. Moreover, the indirect effect remained significant after comprehensive adjustment for traditional risk factors, cardiac function, and inflammatory markers. This finding indicates that a significant portion of the cardiovascular risk conveyed by insulin resistance operates through its detrimental impact on cardiorespiratory fitness. The reverse mediation pathway (peak VO_2/kg → TyG → MACE) showed a substantially smaller indirect effect. Although nominally significant in the fully adjusted model, the magnitude of this reverse pathway was considerably less than that of the primary pathway. This supports the interpretation that the dominant direction is from metabolic disturbance to functional decline, rather than the reverse. The modest reverse mediation may reflect the known bidirectional relationship between exercise capacity and metabolic health, but the asymmetry in effect sizes reinforces the proposed "metabolic → functional → events" sequence.

This directional pathway is biologically plausible. Insulin resistance impairs the PI3K/Akt/eNOS signaling pathway, reducing the bioavailability of endothelial nitric oxide and limiting vasodilation during exercise. Concurrently, it forces the myocardium toward excessive fatty acid oxidation, leading to inefficient ATP production and accumulation of lipotoxic intermediates (e.g., ceramides), thereby compromising the cardiac contractile reserve [31,32]. Collectively, these vascular and myocardial effects reduce oxygen delivery and utilization, manifesting as lower peak VO_2/kg. In turn, the reduced cardiopulmonary fitness, a strong independent predictor of cardiovascular mortality [33], partially conveys the metabolic risk into clinical events. This sequence of "metabolic disturbance → functional decline → adverse events" provides a biological framework for our mediation findings. The remaining direct effect of TyG likely reflects non-hemodynamic pathways such as accelerated atherogenesis and a prothrombotic state. The reverse mediation pathway was notably modest, supporting the unidirectionality of metabolic insult to functional impairment.

This study provides a novel MACE predictor for post-PCI patients. The peak VO_2/kg_TyG index also guides clinical practice. It stratifies cardiac rehabilitation (CR) intensity. A low index identifies a high-risk composite phenotype. These patients have severe metabolic and functional impairments. They require intensified, center-based CR. This requires strict supervision and metabolic monitoring. Conversely, a high index indicates a low-risk status. Home-based CR is safe and sufficient for them. This framework optimizes limited hospital CR resources. However, these clinical recommendations are currently observational. Prospective trials must validate this stratified management. Basic research must also confirm the underlying mechanisms.

5. Limitations

Several limitations of this study should be acknowledged. First, the retrospective design inherently carries risks of selection and information bias, despite the application of rigorous inclusion/exclusion criteria and thorough data cleaning. Second, the absence of prospective controls and interventions precludes establishing a causal relationship between the TyG index and MACE. Third, although adjustments were made for multiple known cardiovascular risk factors, the influence of unmeasured confounders such as inflammatory states, medication adherence, and lifestyle factors cannot be entirely excluded. Fourth, although patients received individualized exercise prescriptions based on their CPET results and underwent structured telephone follow-ups to monitor physical activity, they were not enrolled in a formal, center-based supervised cardiac rehabilitation program. Because post-discharge exercise was primarily self-reported during these calls, granular metrics such as exact training volume and intensity could not be reliably quantified. Consequently, the specific influence of varying exercise levels on CPET performance and MACE outcomes could not be statistically assessed, representing an unmeasured confounder. Future prospective studies with detailed, objective documentation of exercise adherence are needed to address this gap. Fifth, another limitation lies in the dependence of CPET parameters on patient cooperation and the consistency of test administration. Despite all tests being conducted by experienced technicians under standardized protocols, CPET results may still be affected by subjective effort and exercise tolerance. At last, the near-universal use of guideline-directed medical therapy in this post-PCI cohort precluded adjustment for individual medication effects, and we cannot exclude the possibility of residual confounding related to differences in drug classes, dosages, or adherence.

6. Conclusions

The TyG index and the modified TyG indices presented significantly independent associations with MACE in the study population. Peak VO_2/kg_TyG presented significantly higher predictive accuracy for MACE risk stratification compared with the TyG index. In addition, peak VO_2/kg significantly mediates the association between the TyG index and MACE. Clinically, the peak VO_2/kg_TyG index stratifies cardiac rehabilitation. A low index identifies high-risk patients. They require intensive, center-based rehabilitation. A high index indicates home-based care is sufficient.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to confidentiality restrictions but can be made available by the corresponding authors upon reasonable request.

Author Contributions

YLH and QYZ conceived the study concept and designed the study. SCN, NS, JW, YXW, CLW, YZ, LP, and SYW conducted the research, oversaw the cardiac rehabilitation program, and were responsible for data acquisition and curation. SCN and XBM performed the statistical analysis, with XBM handling validation and visualization. YCL, JZ, and QYZ provided critical interpretation of the data. SCN drafted the manuscript, and all authors (YLH, QYZ, YCL, JZ, JW, YXW, CLW, YZ, LP, SYW, NS, XBM, and SCN) contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript, participated sufficiently in the work, and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of General Hospital of Northern Theater Command (approval [Y (2025)444]). A waiver of informed consent was granted due to the retrospective nature of the study and anonymized data processing. This study adhered to the principles of the Declaration of Helsinki.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/RCM52259.

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