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Triglyceride-Glucose Index as a Surrogate Marker of Insulin Resistance for Predicting Cardiovascular Outcomes in Nondiabetic Patients with Non-ST-Segment Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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Aim: The triglyceride-glucose index (TyG index) is proposed as a surrogate parameter for insulin resistance (IR) and, when elevated, is related to increased cardiovascular risks. Whether the TyG index is of great value in predicting adverse prognosis for individuals diagnosed with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), who received elective percutaneous coronary intervention (PCI), and without recognized diabetes remains unclear.

Methods: Overall, 1,510 subjects diagnosed with NSTE-ACS, who received elective PCI, and without recognized diabetes were enrolled in the current study. All participants received a routine follow-up after discharge. The TyG index was obtained from the following equation: napierian logarithmic (ln) [fasting triglyceride (TG, mg/dL) × fasting blood glucose (FBG, mg/dL)/2]. Adverse cardiovascular events included all-cause death, nonfatal myocardial infarction (MI), nonfatal ischemic stroke, and ischemia-driven revascularization, composite of which was defined as the primary endpoint.

Results: Overall, 316 (20.9%) endpoint events were documented during a 48-month follow-up. Despite adjusting for confounding variates, the TyG index remains to be a significant risk predictor for the primary endpoint, with a hazard ratio (HR) [95% confidence interval (CI)] of 2.433 (1.853–3.196) ($P<0.001$). A significant enhancement on the predictive performance for the primary endpoint emerged when adding the TyG index into a baseline model [area under the receiver-operating characteristic (ROC) curve (AUC), 0.835 for baseline model vs. 0.853 for baseline model + TyG index, $P<0.001$; net reclassification improvement (NRI), 0.194, $P<0.001$; integrated discrimination improvement (IDI), 0.023, $P=0.007$].

Conclusions: The TyG index is an independent risk predictor for adverse cardiovascular events in nondiabetic subjects diagnosed with NSTE-ACS and who received elective PCI. Further prospective studies are needed to verify these findings.

Key words: Triglyceride-glucose index, Non-ST-segment elevation acute coronary syndrome, Percutaneous coronary intervention, Adverse cardiovascular events

1. Introduction

Acute coronary syndrome (ACS), the most severe manifestation of atherosclerotic cardiovascular disease, has been extensively known as one of the most important issues that lead to a heavy socioeconomic

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burden. In recent years, significant improvement on the prognosis of patients with ACS has been realized since the extensive development and application of evidence-based strategies including optimal medical therapy and advanced revascularization techniques; however, the recurrence rate of cardiovascular events remains high in patients who experienced ACS[1, 2]. Therefore, identifying the residual risk factors for this specific high-risk cohort and then further developing novel treatment targets and customizing specific strategies concurring with risk levels are of great clinical significance.

Insulin resistance (IR) has been identified as not only the major pathogenesis of diabetes but also an important risk factor for the incidence and prognosis of cardiovascular disease[3-7]. Despite the hyperinsulinemic-euglycemic clamp and homeostasis model assessment of IR (HOMA-IR) having been generally recognized as the accurate and reliable methods to evaluate IR, disadvantages like time consumption, intricacy, and expensiveness make them difficult to be generalized in clinical practice. A novel parameter named triglyceride-glucose index (TyG index), simply determined by fasting triglyceride (TG) and fasting blood glucose (FBG), was proposed as a surrogate marker of IR with high correlation to HOMA-IR and hyperinsulinemic-euglycemic clamp[8-12]. It has been revealed that TyG index evaluation can provide useful information for predicting diabetes and identifying prediabetic status[13-17]. Furthermore, the TyG index was also proved to be significantly associated with the incidence of cardiovascular disease and adverse prognosis in patients with or without diabetes[18-21].

To our knowledge, the prognostic value of the TyG index has not been fully investigated among nondiabetic patients diagnosed with non-ST-segment elevation ACS (NSTE-ACS) and received elective percutaneous coronary intervention (PCI). The current study, thus, was designed to (1) ascertain the underlying prognostic impact of the TyG index, (2) identify the improvement ability of the TyG index on risk stratification beyond recognized cardiovascular risk factors, and (3) compare the discriminative performance of the TyG index and lipid- or glucose-related parameters for predicting adverse prognosis in nondiabetic participants with NSTE-ACS and who received elective PCI.

2. Aim

The current study aims to investigate the predictive value of the TyG index for adverse cardiovascular events in patients diagnosed with NSTE-ACS, who received elective PCI, and without recognized diabetes.

3. Methods

3.1. Study Participants

The present study is a single-center, observational, retrospective cohort study among patients without diabetes who were diagnosed with NSTE-ACS and treated with elective PCI at Beijing Anzhen Hospital in 2015. Patients with a prior definite diagnosis of diabetes or with a newly diagnosed diabetes at admission, criteria of which were referred to guidelines from the American Diabetes Association[22], were considered to have diabetes. Patients who were diagnosed with unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) at admission were considered to have NSTE-ACS, detailed definitions of which were consistent with relative guidelines[23]. Other inclusion and exclusion criteria were listed in detail in the flowchart **(Fig. 1)**. Overall, 1510 participants were finally enrolled for the present analyses after strictly following the enrollment criteria.

3.2. Clinical and Laboratory Information

Data including age, gender, height, weight, personal history (smoking, drinking), past medical history [hypertension, dyslipidemia, myocardial infarction (MI), PCI, stroke, and peripheral artery disease (PAD)], family history [family history of coronary artery disease (CAD)], systolic/diastolic blood pressure (SBP/DBP), heart rate, medication at admission and discharge, and laboratory examinations were collected from the medical information record system from Beijing Anzhen Hospital. Body mass index (BMI) was defined as weight (kg) / [height (m)]^2. Hypertension was defined as patients with previously diagnosed hypertension, receiving long-term antihypertensive treatments, or with more than two measurements of SBP/DBP ≥ 140/90 mmHg during hospitalization. Stroke was defined as a previously experienced cerebral infarction or transient ischemic attack. Patients with arterial lesions of ≥ 50% stenosis involving the arteries other than coronaries accompanied with relevant symptoms and signs (e.g., intermittent claudication, reduced or absent pulsation) were identified as having PAD. Laboratory parameters were analyzed by standard techniques in the central laboratory of the hospital using venous samples taken after overnight fasting (>8 h) before the baseline coronary procedure. The TG, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were measured by standard enzymatic methods, and the low-density lipoprotein cholesterol (LDL-C) was

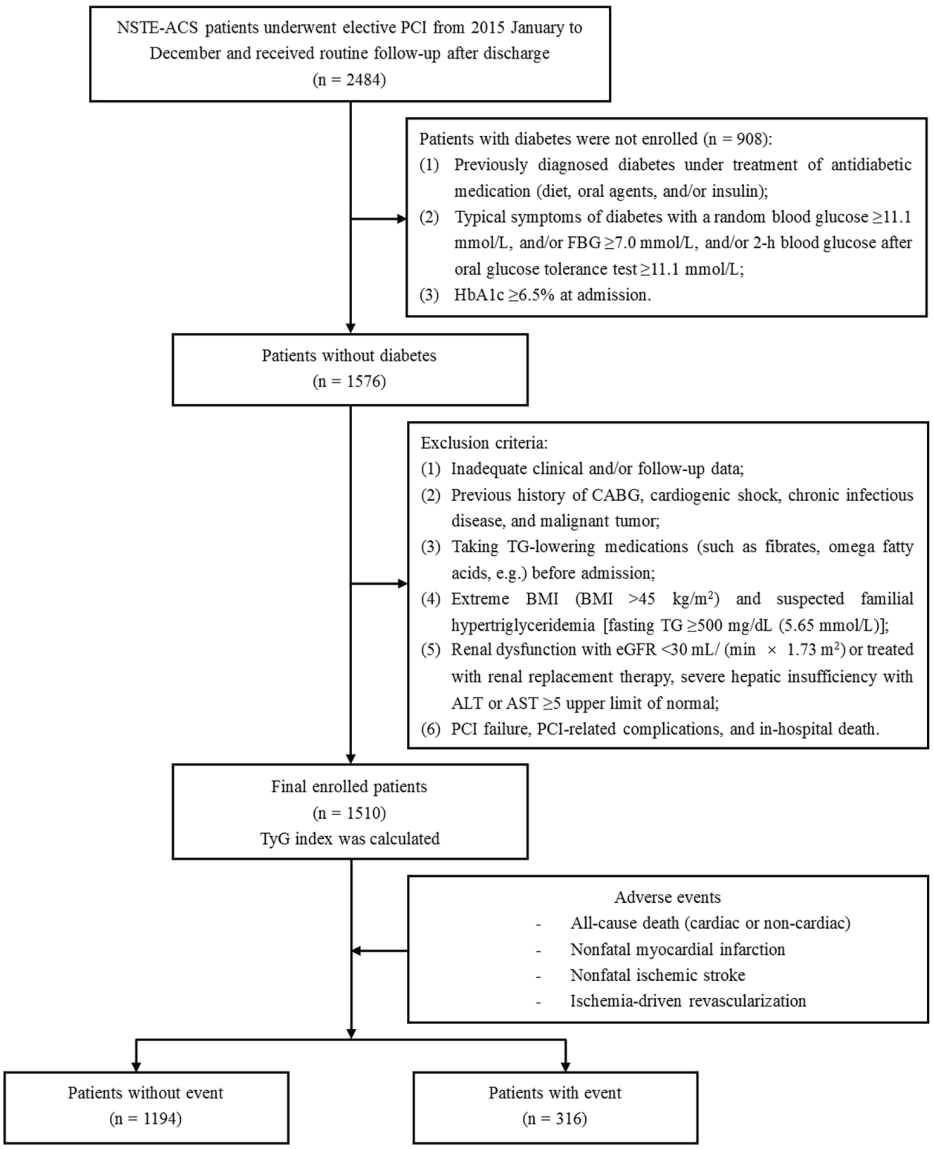

Fig. 1. Flowchart of the study population enrollment

NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; CABG, coronary artery bypass grafting; TG, triglyceride; BMI, body mass index; eGFR, estimated glomerular filtration rate; ALT, alanine transaminase; AST, aspartate transaminase; TyG, triglyceride-glucose.

determined by the homogeneous direct method. The FBG was determined by enzymatic hexokinase technique. The non-high-density lipoprotein cholesterol (non-HDL-C) was calculated by subtracting HDL-C from TC, and the remnant-like particle cholesterol (RLP-C) was calculated by subtracting LDL-C and HDL-C from TC[24]. The TyG index was quantified by the established formula: napierian logarithmic (ln) [fasting TG (mg/dL) × FBG (mg/dL)/2][8]. Patients with previously diagnosed dyslipidemia receiving long-term lipid-lowering treatments, or fasting TG of >150 mg/dL, TC of >200 mg/dL, LDL-C of >130 mg/dL, and/or HDL-C of <40 mg/dL at admission were considered to have dyslipidemia. The estimated glomerular filtration rate (eGFR) was calculated using the formula proposed by the Modification of Diet in Renal Disease Study Group[25].

3.3. Coronary Procedure

Coronary angiogram was interpreted and documented by at least two specialists who majored in interventional cardiology. The characteristics of coronary

artery lesions were defined according to the ACC/AHA guidelines for coronary lesion classification[26]. The in-stent restenosis was defined as the stenosis with an extent of ≥ 50% and occurring within a range of 5 mm proximal and distal to the stent[27]. The synergy between PCI with taxus and cardiac surgery (SYNTAX) score, which has been extensively used for evaluating the complexity of coronary artery lesions, was quantified using the calculator on the official website (www.syntaxscore.com). Coronary procedure was processed according to the current practice guidelines in China[28]. Patients whose all coronary artery lesions occurred in vessels ≥ 1.5 mm in diameter with ≥ 50% stenosis and who received successful interventional process (≤ 20% residual stenosis) were defined as reaching complete revascularization.

3.4. Follow-Up and Endpoint Events

Every patient was routinely followed up for 48 months after discharge. The information about prognosis was acquired by interviewing the patients and/or their family members on the phone and was verified by reviewing corresponding medical records provided by them. The primary endpoint was defined as the composite of adverse events including all-cause death, nonfatal MI, nonfatal ischemic stroke, and ischemia-driven revascularization. All-cause death was defined as death caused by any reason. MI was defined as the existence of myocardial injury detected by elevated cardiac troponin higher than the upper reference limit accompanied with myocardial ischemia indicated by ischemic symptoms and/or ischemia-related imaging manifestations. Ischemic stroke was defined as cerebral infarction with symptoms of neurological impairment that can be explained by ischemic lesions evidenced by the imageological examination. Ischemia-driven revascularization was adjudicated by the occurrence of repeat revascularization, including interventional or surgical procedure due to myocardial ischemia implicated by ischemic symptoms, and/or electrocardiographic changes, and/or other functional imaging results. Only the first event was chosen to perform the current analysis if more than one endpoint event was documented during the follow-up.

3.5. Statistical Analysis

Continuous variates with normal or non-normal distribution were expressed as mean ± standard deviation or median with interquartile range. Categorical variates were displayed as number and proportion. The study population was stratified into two groups based on whether there was a primary endpoint event. Disparities between groups were detected and analyzed by *t*-test or Mann-Whitney *U* test for normally or non-normally distributed continuous variates and Chi-square test or Fisher's exact test for categorical variates. Pearson's or Spearman's rank test was applied to investigate the extent to which the TyG index was correlated to recognized risk factors. The Kaplan–Meier analysis was performed to describe the cumulative event rates per the TyG index medians, and the log-rank test was employed to examine the discrepancies between Kaplan–Meier estimates of the two groups. The univariate Cox proportional hazards analysis was performed to preliminarily identify the potential determinants for the primary endpoint. To examine the independent performance of the TyG index for predicting the primary endpoint, variates that were identified as prognostic determinants in univariate analysis ($P<0.05$) and/or had plausible clinical significance were selected to construct four multivariate models. Details of the four multivariate models were described as follows: Model 1 was adjusted for age, gender, BMI, smoking history, hypertension, dyslipidemia, previous history of MI, PCI, stroke, and PAD; Model 2 was adjusted for variates in Model 1 and diagnosis, TC, HDL-C, eGFR, glycosylated hemoglobin A1c (HbA1c), and left ventricular ejection fraction (LVEF); Model 3 was adjusted for variates in Model 2 and left main artery (LM) disease, three-vessel disease, chronic total occlusion, diffuse lesion, in-stent restenosis, SYNTAX score, treatment of LM, left circumflex artery (LCX), right coronary artery (RCA), drug-eluting stent (DES) implantation, drug-coated balloon (DCB) application, complete revascularization, and number of stents; and Model 4 was adjusted for variates in Model 3 and dual antiplatelet therapy (DAPT) at admission, statins at admission, and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) at discharge. The TyG index was examined as a categorical or continuous variate, and the results were displayed with hazard ratio (HR) and 95% confidence interval (CI). Moreover, a restricted cubic spline curve adjusted for Model 4 was established to illustrate the dose-response relationship of the TyG index with the risk of the primary endpoint. The likelihood ratio test was used to verify the nonlinearity hypothesis. Further stratified analysis according to age, gender, BMI, smoking history, hypertension, diagnosis, HbA1c, HDL-C, LDL-C, and statins at admission was conducted to identify the consistency of the predictive value of the TyG index for the primary endpoint. The stratified analysis was adjusted for variates included in Model 4, except those applied for stratification. To investigate the incremental effects of the TyG index on

the discriminative performance beyond the baseline model, including recognized cardiovascular risk factors, the area under the receiver-operating characteristic (ROC) curves (AUCs) were obtained and compared by the DeLong's test. Then, the incremental effects of the TyG index for prognostic prediction were further examined by the net reclassification improvement (NRI) and integrated discrimination improvement (IDI), with the baseline model as reference. Statistical analyses were tested using SPSS 26.0 (IBM Corp, IL, USA), the R Project (version 3.6.3), and MedCalc 19.1 (Ostend, Belgium). A two-sided $P<0.05$ was taken for evaluating statistical significance.

4. Results

4.1. Baseline Characteristic of the Study Population

The baseline characteristics of the study population were displayed in **Table 1**. The current study finally enrolled 1510 participants, with a mean age of 59.7 ± 9.3 years and a male proportion of 73.7% (n=1,113). Patients were stratified into two groups according to the occurrence of the primary endpoint events. In comparison with those without, patients with an endpoint event exhibited significantly higher TyG index (8.7 ± 0.5 vs. 8.9 ± 0.5, $P<0.001$). Patients who experienced an endpoint event exhibited higher age, higher prevalence of hypertension, dyslipidemia, and previous history of MI, PCI, stroke, and PAD. The proportions of DAPT, P2Y12 inhibitors, and statins treatment at admission and ACEI/ARB treatment at discharge were significantly higher in participants with an endpoint event. Regarding laboratory results, patients with an endpoint event showed elevated TG, RLP-C, TG-to-HDL-C ratio (TG/HDL-C), creatinine, FBG, HbA1c, and high-sensitivity C-reactive protein (hs-CRP) but decreased HDL-C and eGFR. The LVEF was also significantly lower in those with an endpoint event. With respect to angiographic data, patients who developed an endpoint event displayed higher percentages of LM disease, three-vessel disease, chronic total occlusion, diffuse lesion, and in-stent restenosis. Correspondingly, the SYNTAX score was expressed to be higher in those with an endpoint event. As for procedural information, in patients with an endpoint event, more target vessels of LM, LCX, and RCA were treated; more DCBs were used; and more stents were implanted; however, lower proportions of DES implantation and complete revascularization were found.

The results of the correlation analysis revealed that the TyG index exhibited significant correlations with multiple recognized cardiovascular risk factors. Positive correlations were found between the TyG index and BMI, TG, TC, LDL-C, non-HDL-C, RLP-C, FBG, HbA1c, uric acid, hs-CRP, and SYNTAX score, while negative correlations were found between the TyG index, and age and HDL-C **(Table 2)**.

4.2. Predictive Implications of the TyG Index for Cardiovascular Events

During the 48-month follow-up, 316 (20.9%) cases of the primary endpoint event were recorded, including 19 (1.3%) cases of all-cause death [17 (1.1%) cases of cardiac death], 65 (4.3%) cases of nonfatal MI, 27 (1.8%) cases of nonfatal ischemic stroke, and 205 (13.6%) cases of ischemia-driven revascularization. Compared to those with lower TyG index median, patients with higher median showed increased incidence of the primary endpoint (26.9% vs. 14.9%, $P<0.001$), nonfatal MI (5.7% vs. 2.9%, $P=0.008$), and ischemia-driven revascularization (17.9% vs. 9.3%, $P<0.001$). However, the incidence of all-cause death, cardiac death, and nonfatal ischemic stroke did not differ between the two groups **(Supplemental Table 1)**.

Kaplan–Meier analysis manifested that the cumulative incidence of the primary endpoint significantly increased with the higher median of the TyG index (**Fig. 2A**, log-rank $P<0.001$). As for each component of the primary endpoint, an increased cumulative incidence of nonfatal MI (**Fig. 2D**, log-rank $P=0.007$) and ischemia-driven revascularization (**Fig. 2F**, log-rank $P<0.001$) were presented in patients with higher TyG index median. No significant differences were found in the cumulative incidence of all-cause death (**Fig. 2B**, log-rank $P=0.822$), cardiac death (**Fig. 2C**, log-rank $P=0.470$), and nonfatal ischemic stroke (**Fig. 2E**, log-rank $P=0.329$). To investigate the potential impact of HDL-C on the predictive value of TyG index, the population was further divided into four groups according to the median of TyG index and HDL-C (TyG index/HDL-C): Low/High, Low/Low, High/High, and High/Low. Patients with higher TyG index exhibited a consistently higher incidence of the primary endpoint and ischemia-driven revascularization, despite of the level of HDL-C. However, the difference in the incidence of nonfatal MI across the median of TyG index was not significant in patients with lower median of HDL-C **(Supplemental Fig. 1)**.

The results of the univariate Cox proportional hazards analysis conducted to identify the potential risk predictors for the primary endpoint were shown in **Supplemental Table 2**. Then, four multivariate

Table 1. Baseline clinical characteristics of patients with and without an adverse event

	Total population (n=1,510)	Without event (n=1,194)	With event (n=316)	P-value
Age, years	59.7±9.3	58.9±9.1	62.8±9.2	<0.001
Gender, male, *n* (%)	1,113 (73.7)	890 (74.5)	223 (70.6)	0.154
BMI, kg/m^2	25.8±3.1	25.7±3.1	26.0±3.2	0.091
Heart rate, bpm	68.6±10.0	68.6±10.0	68.7±9.7	0.917
SBP, mmHg	129.5±16.0	129.3±15.6	130.1±17.6	0.450
DBP, mmHg	77.1±9.6	77.3±9.4	76.2±10.1	0.074
Smoking history, *n* (%)	892 (59.1)	706 (59.1)	186 (58.9)	0.931
Drinking history, *n* (%)	352 (23.3)	287 (24.0)	65 (20.6)	0.195
Family history of CAD, *n* (%)	143 (9.5)	111 (9.3)	32 (10.1)	0.654
Medical history, *n* (%)				
Hypertension	863 (57.2)	661 (55.4)	202 (63.9)	0.006
Dyslipidemia	1,276 (84.5)	991 (83.0)	285 (90.2)	0.002
Previous MI	309 (20.5)	192 (16.1)	117 (37.0)	<0.001
Previous PCI	231 (15.3)	155 (13.0)	76 (24.1)	<0.001
Previous stroke	155 (10.3)	93 (7.8)	62 (19.6)	<0.001
Previous PAD	187 (12.4)	121 (10.1)	66 (20.9)	<0.001
Laboratory results				
TG, mg/dL	145.9±74.7	140.9±73.2	164.7±77.6	<0.001
TC, mg/dL	162.6±39.9	162.0±40.6	164.8±37.2	0.263
LDL-C, mg/dL	98.9±34.2	98.6±34.8	99.8±31.6	0.567
HDL-C, mg/dL	38.8±9.1	39.1±9.3	37.7±8.0	0.006
hs-CRP, mg/L	1.2 (0.5, 2.8)	1.1 (0.5, 2.7)	1.3 (0.6, 3.1)	0.041
Creatinine, μmol/L	77.2±16.2	76.6±15.8	79.2±17.3	0.011
eGFR, mL/ (min×1.73 m^2)	92.0±18.8	93.1±18.6	87.9±19.4	<0.001
Uric acid, μmol/L	353.5±82.0	353.3±82.5	353.9±80.4	0.913
FBG, mg/dL	95.8±10.9	95.2±10.5	97.8±11.9	0.001
HbA1c, %	5.6±0.4	5.6±0.4	5.7±0.4	<0.001
non-HDL-C, mg/dL	123.8±38.4	122.9±39.0	127.2±35.9	0.079
RLP-C, mg/dL	24.9±11.7	24.3±11.5	27.3±12.0	<0.001
TG/HDL-C	4.1±2.6	4.0±2.6	4.7±2.7	<0.001
TyG index	8.7±0.5	8.7±0.5	8.9±0.5	<0.001
LVEF, %	64.0±6.8	64.6±6.2	62.0±8.3	<0.001
Initial diagnosis, *n* (%)				0.388
UA	1,271 (84.2)	1,010 (84.6)	261 (82.6)	
NSTEMI	239 (15.8)	184 (15.4)	55 (17.4)	
Medication at admission, *n* (%)				
ACEI/ARB	304 (20.1)	231 (19.3)	73 (23.1)	0.139
DAPT	440 (29.1)	329 (27.6)	111 (35.1)	0.008
Aspirin	793 (52.5)	612 (51.3)	181 (57.3)	0.057
P2Y12 inhibitors	473 (31.3)	353 (29.6)	120 (38.0)	0.004
β-Blocker	339 (22.5)	256 (21.4)	83 (26.3)	0.068
Statins	474 (31.4)	360 (30.2)	114 (36.1)	0.044

(Cont. Table 1)

	Total population (n=1,510)	Without event (n=1,194)	With event (n=316)	P-value
Medication at discharge, *n* (%)				
ACEI/ARB	984 (65.2)	750 (62.8)	234 (74.1)	<0.001
DAPT	1,510 (100.0)	1,194 (100.0)	316 (100.0)	-
Aspirin	1,510 (100.0)	1,194 (100.0)	316 (100.0)	-
P2Y12 inhibitors	1,510 (100.0)	1,194 (100.0)	316 (100.0)	-
β-Blocker	1,351 (89.5)	1,069 (89.5)	282 (89.2)	0.881
Statins	1,469 (97.3)	1,158 (97.0)	311 (98.4)	0.163
Angiographic data				
LM disease, *n* (%)	59 (3.9)	36 (3.0)	23 (7.3)	0.001
Three-vessel disease, *n* (%)	344 (22.8)	200 (16.8)	144 (45.6)	<0.001
Chronic total occlusion, *n* (%)	182 (12.1)	100 (8.4)	82 (25.9)	<0.001
Diffuse lesion, n (%)	322 (21.3)	225 (18.8)	97 (30.7)	<0.001
In-stent restenosis, n (%)	67 (4.4)	37 (3.1)	30 (9.5)	<0.001
SYNTAX score	9.9±5.3	8.9±4.6	13.7±5.7	<0.001
Procedural information				
Target vessel territory, *n* (%)				
LM	35 (2.3)	21 (1.8)	14 (4.4)	0.005
LAD	993 (65.8)	780 (65.3)	213 (67.4)	0.489
LCX	469 (31.1)	353 (29.6)	116 (36.7)	0.015
RCA	580 (38.4)	419 (35.1)	161 (50.9)	<0.001
DES implantation, *n* (%)	1,466 (97.1)	1,171 (98.1)	295 (93.4)	<0.001
DCB application, *n* (%)	49 (3.2)	26 (2.2)	23 (7.3)	<0.001
Complete revascularization, *n* (%)	949 (62.8)	797 (66.8)	152 (48.1)	<0.001
Number of stents	1.9±1.2	1.8±1.1	2.3±1.6	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; non-HDL-C, non-high-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; TG/HDL-C, triglyceride-to-high-density lipoprotein cholesterol ratio; TyG, triglyceride-glucose; LVEF, left ventricular ejection fraction; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; LM, left main artery; SYNTAX, synergy between PCI with taxus and cardiac surgery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stent; DCB, drug-coated balloon.

Table 2. Correlations between the TyG index and recognized cardiovascular risk factors

	Correlation coefficient	P-value		Correlation coefficient	P-value
Age	−0.187	<0.001	RLP-C	0.715	<0.001
Gender	0.015	0.555	FBG	0.316	<0.001
BMI	0.266	<0.001	HbA1c	0.130	<0.001
TG	0.928	<0.001	Uric acid	0.254	<0.001
TC	0.296	<0.001	eGFR	−0.029	0.267
LDL-C	0.188	<0.001	hs-CRP	0.168	<0.001
HDL-C	−0.329	<0.001	LVEF	−0.034	0.189
non-HDL-C	0.385	<0.001	SYNTAX score	0.052	0.043

BMI, body mass index; TG, triglyceride; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin A1c; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; SYNTAX, synergy between PCI with taxus and cardiac surgery.

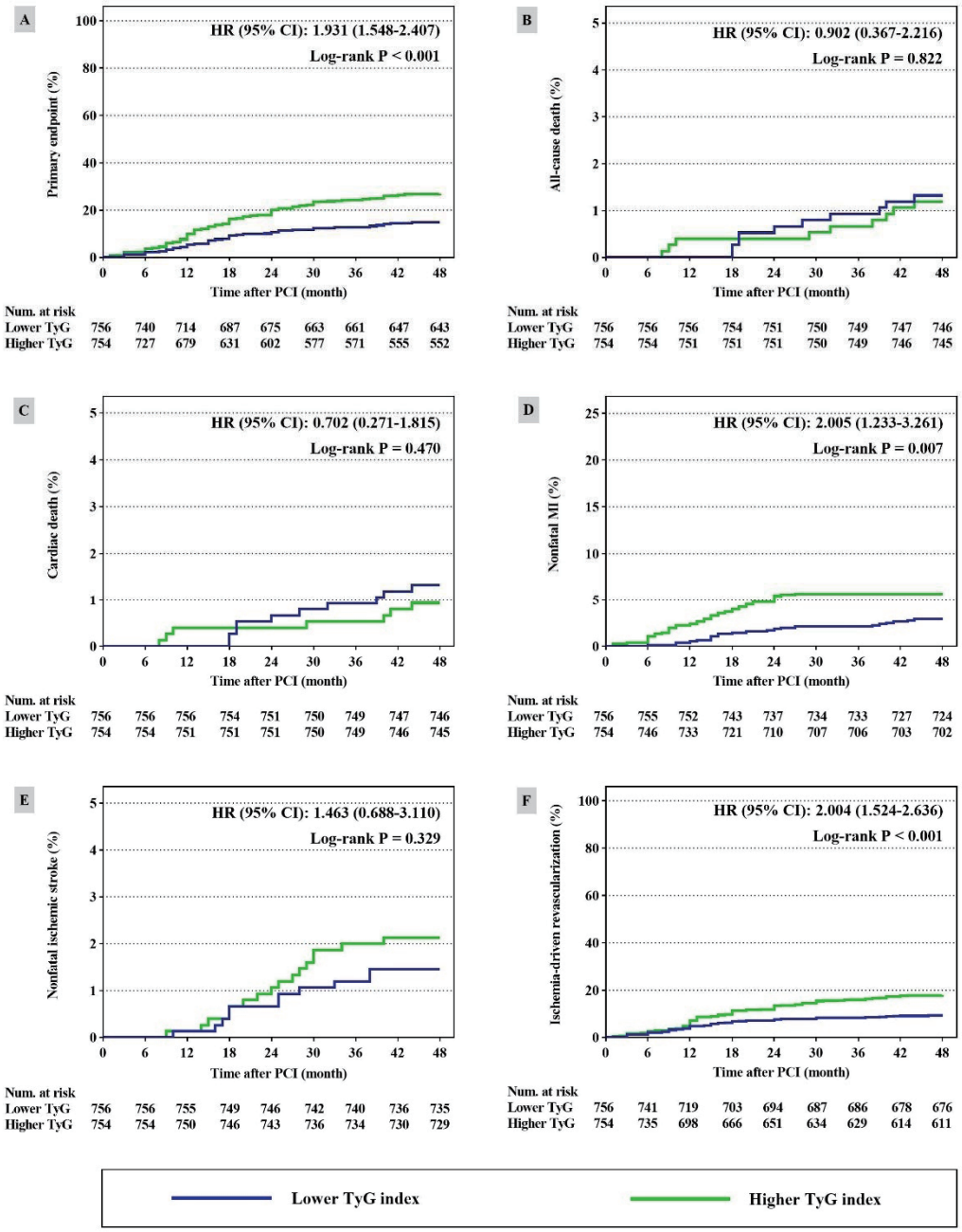

Fig. 2. Kaplan–Meier analysis for endpoint events according to the median of the TyG index

(A) Kaplan–Meier analysis for primary endpoint; (B) Kaplan–Meier analysis for all-cause death; (C) Kaplan–Meier analysis for cardiac death; (D) Kaplan–Meier analysis for nonfatal MI; (E) Kaplan–Meier analysis for nonfatal ischemic stroke; (F) Kaplan–Meier analysis for ischemia-driven revascularization.
TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval; PCI, percutaneous coronary intervention; MI, myocardial infarction.

models (Model 1–4 as described above) were constructed to investigate the predictive performance of the TyG index for the primary endpoint, variates of which were chosen based on the results from univariate analysis ($P<0.05$) and/or clinical significance. After the adjustment of variates in the four models, a higher level of the TyG index was consistent to have significant predictive potential for the primary endpoint, whether taking it as a categorical or continuous variate **(Table 3)**. When

Table 3. Predictive value of the TyG index for the primary endpoint in different Cox proportional hazards models

	TyG index as a categorical variate*			TyG index as a continuous variate**		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Crude model	1.931	1.534-2.431	<0.001	1.961	1.579-2.435	<0.001
Model 1	1.923	1.503-2.461	<0.001	2.221	1.739-2.838	<0.001
Model 2	1.763	1.363-2.282	<0.001	2.025	1.560-2.630	<0.001
Model 3	2.052	1.577-2.671	<0.001	2.414	1.840-3.168	<0.001
Model 4	2.087	1.600-2.722	<0.001	2.433	1.853-3.196	<0.001

Model 1: adjusted for age, gender, BMI, smoking history, hypertension, dyslipidemia, previous history of MI, PCI, stroke, and PAD.
Model 2: adjusted for variates in Model 1 and diagnosis, TC, HDL-C, eGFR, HbA1c, and LVEF.
Model 3: adjusted for variates in Model 2 and LM disease, three-vessel disease, chronic total occlusion, diffuse lesion, in-stent restenosis, SYNTAX score, treatment of LM, LCX, RCA, DES implantation, DCB application, complete revascularization, and number of stents.
Model 4: adjusted for variates in Model 3 and DAPT at admission, statins at admission, and ACEI/ARB at discharge.
*The HR was examined regarding the lower TyG index as reference (stratified by the median of the TyG index).
**The HR was examined by per 1-unit increase of the TyG index.
TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval.

Table 4. Predictive value of the TyG index for the primary endpoint and each component in univariate and multivariate analysis

	Univariate analysis			Multivariate analysis***		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
TyG index as a categorical variate*						
Primary endpoint	1.931	1.534-2.431	<0.001	2.087	1.600-2.722	<0.001
All-cause death	0.902	0.366-2.219	0.822	0.561	0.126-2.499	0.448
Nonfatal MI	2.005	1.200-3.352	0.008	1.966	1.091-3.545	0.025
Nonfatal ischemic stroke	1.463	0.679-3.152	0.332	1.305	0.521-3.269	0.570
Ischemia-driven revascularization	2.005	1.502-2.675	<0.001	2.292	1.635-3.213	<0.001
TyG index as a continuous variate**						
Primary endpoint	1.961	1.579-2.435	<0.001	2.433	1.853-3.196	<0.001
All-cause death	0.745	0.306-1.811	0.516	0.601	0.116-3.111	0.544
Nonfatal MI	2.725	1.681-4.416	<0.001	3.541	1.909-6.566	<0.001
Nonfatal ischemic stroke	1.513	0.723-3.164	0.272	1.864	0.689-5.045	0.220
Ischemia-driven revascularization	1.843	1.410-2.409	<0.001	2.290	1.628-3.221	<0.001

*The HR was examined regarding the lower TyG index as reference (stratified by the median of the TyG index).
**The HR was examined by per 1-unit increase of the TyG index.
***The multivariate analysis was performed by using Model 4 (adjusted for age, gender, BMI, smoking history, hypertension, dyslipidemia, previous history of MI, PCI, stroke and PAD, diagnosis, TC, HDL-C, eGFR, HbA1c, LVEF, LM disease, three-vessel disease, chronic total occlusion, diffuse lesion, in-stent restenosis, SYNTAX score, treatment of LM, LCX, RCA, DES implantation, DCB application, complete revascularization, and number of stents, DAPT at admission, statins at admission, and ACEI/ARB at discharge).
TyG, triglyceride-glucose; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.

investigating the prognostic impact of the TyG index on each component of the primary endpoint, the TyG index was shown to be significantly associated with the risk of nonfatal MI and ischemia-driven revascularization, as opposed to the risk of all-cause death and nonfatal stroke (Table 4), which was consistent with the Kaplan–Meier analysis results.

The dose-response relationship between the level of the TyG index and the risk of the primary endpoint after adjustment of variates included in Model 4 was elaborated by plotting a restricted cubic spline curve (Fig. 3). The log-transformed HR for the primary endpoint displayed a logarithmic rise with the increase of the TyG index. Therefore, the TyG index will present a linear relationship with the risk of the primary endpoint after taking a mathematical transformation. Furthermore, a significant *P*-value (< 0.001) was found when testing the nonlinear relationship, which confirmed the linear relationship illustrated by the restricted cubic spline curve.

The prognostic impact of the TyG index for the primary endpoint was further validated by stratifying the study population into multiple subgroups (Fig. 4). Despite stratifying the study population according to

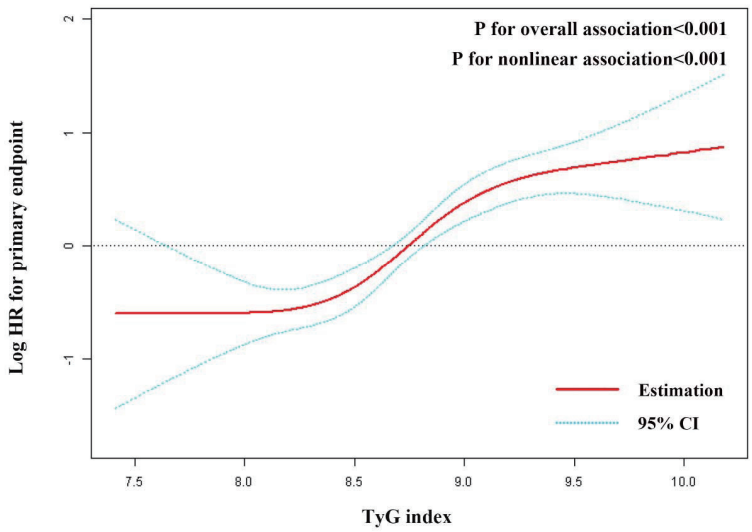

Fig. 3. Restricted cubic spline curve for the risk of the primary endpoint according to the TyG index

The HR was examined by per 1-unit increase of the TyG index.
The analysis was performed by adjusting for Model 4 (age, gender, BMI, smoking history, hypertension, dyslipidemia, previous history of MI, PCI, stroke and PAD, diagnosis, TC, HDL-C, eGFR, HbA1c, LVEF, LM disease, three-vessel disease, chronic total occlusion, diffuse lesion, in-stent restenosis, SYNTAX score, treatment of LM, LCX, RCA, DES implantation, DCB application, complete revascularization, and number of stents, DAPT at admission, statins at admission, and ACEI/ARB at discharge).
TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval.

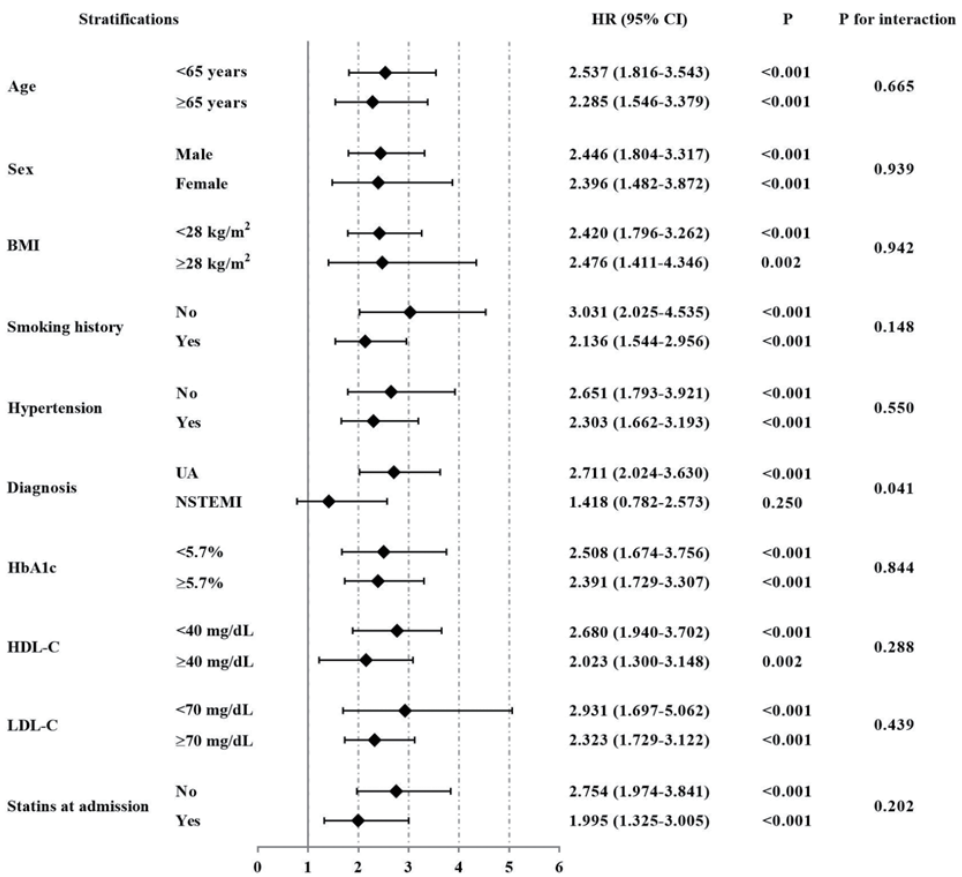

Fig. 4. Stratified analysis for the impact of the TyG index on the risk of the primary endpoint

The HR was examined by per 1-unit increase of the TyG index.
The analysis was performed by adjusting for Model 4 (age, gender, BMI, smoking history, hypertension, dyslipidemia, previous history of MI, PCI, stroke and PAD, diagnosis, TC, HDL-C, eGFR, HbA1c, LVEF, LM disease, three-vessel disease, chronic total occlusion, diffuse lesion, in-stent restenosis, SYNTAX score, treatment of LM, LCX, RCA, DES implantation, DCB application, complete revascularization, and number of stents, DAPT at admission, statins at admission, and ACEI/ARB at discharge).
BMI, body mass index; UA, unstable angina; NSTEMI, non-ST-segment elevation myocardial infarction; HbA1c, glycosylated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.

Table 5. The incremental ability of the TyG index and other parameters for risk discrimination beyond the baseline model

	ROC analysis		NRI		IDI	
	AUC (95% CI)	*P*-value	Estimation (95% CI)	*P*-value	Estimation (95% CI)	*P*-value
Baseline model*	0.835 (0.811-0.859)	Reference	-	Reference	-	Reference
+ HbA1c	0.835 (0.812-0.859)	0.717	−0.005 (−0.063-0.081)	0.791	0.001 (0.000-0.004)	0.146
+ FBG	0.837 (0.813-0.860)	0.363	0.126 (0.048-0.187)	0.007	0.006 (−0.001-0.019)	0.133
+ TG	0.849 (0.827-0.871)	<0.001	0.171 (0.086-0.234)	0.007	0.015 (0.003-0.032)	0.020
+ non-HDL-C	0.836 (0.812-0.860)	0.494	0.077 (−0.108-0.157)	0.206	0.002 (−0.001-0.009)	0.359
+ RLP-C	0.843 (0.820-0.867)	0.013	0.122 (0.054-0.210)	0.007	0.013 (0.001-0.029)	0.027
+ TG/HDL-C	0.845 (0.822-0.867)	0.005	0.175 (0.075-0.240)	<0.001	0.012 (0.001-0.026)	0.020
+ TyG index	0.853 (0.832-0.875)	<0.001	0.194 (0.122-0.271)	<0.001	0.023 (0.005-0.050)	0.007

*The baseline model includes age, gender, smoking history, hypertension, dyslipidemia, previous history of MI, PCI, stroke and PAD, eGFR, LVEF, LM disease, three-vessel disease, SYNTAX score, number of stents, statins at discharge and ACEI/ARB at discharge.
HbA1c, glycosylated hemoglobin A1c; FBG, fasting blood glucose; TG, triglyceride; non-HDL-C, non-high-density lipoprotein cholesterol; RLP-C, remnant-like particle cholesterol; TG/HDL-C, triglyceride-to-high-density lipoprotein cholesterol ratio; TyG, triglyceride-glucose; ROC, receiver-operating characteristic; AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; CI, confidence interval.

age (<65 or ≥ 65 years), gender (male or female), BMI (<28 or ≥ 28 kg/m^2), smoking history (yes or no), hypertension (with or without), HbA1c (<5.7% or ≥ 5.7%), HDL-C (<40 or ≥ 40 mg/dL), LDL-C (<70 or ≥ 70 mg/dL), and statins treatment at admission (with or without), the predictive performance of the TyG index for the primary endpoint remained consistent. However, when stratified by the diagnosis, the TyG index failed to be a significant risk predictor for the primary endpoint in patients diagnosed with NSTEMI, not as it was in those diagnosed with UA [HR (95% CI), 1.418 (0.782–2.573) for NSTEMI, *P*=0.250 vs. 2.711 (2.024–3.630) for UA, *P*<0.001; *P* for interaction=0.041].

4.3. Incremental Effect of the TyG Index on the Predictive Value of Baseline Model

The addition of the TyG index significantly increased the ability of risk prediction beyond the baseline model adjusted for recognized cardiovascular risk factors consisting of age, gender, smoking history, hypertension, dyslipidemia, previous history of MI, PCI, stroke and PAD, eGFR, LVEF, LM disease, three-vessel disease, SYNTAX score, number of stents, statins at discharge, and ACEI/ARB at discharge (Table 5). Compared with other parameters, adding the TyG index into the baseline model displayed the most significant enhancement on AUC for predicting the primary endpoint (AUCs: baseline model 0.835 vs. +TyG index 0.853, *P*<0.001; baseline model 0.835 vs. +TG/HDL-C 0.845, *P*=0.005; baseline model 0.835 vs. +RLP-C 0.843, *P*=0.013; baseline model 0.835 vs. +non-HDL-C 0.836, *P*=0.494; baseline model 0.835 vs. +TG 0.849, *P*<0.001; baseline model 0.835 vs. +FBG 0.837, *P*=0.363; baseline model 0.835 vs. +HbA1c 0.835, *P*=0.717). Moreover, the most significant improvements on risk reclassification and discrimination were found after the addition of the TyG index into the baseline model, with a NRI of 0.194 (*P*<0.001) and an IDI of 0.023 (*P*=0.007), in comparison with the addition of TG/HDL-C (NRI, 0.175, *P*<0.001; IDI, 0.012, *P*=0.020), RLP-C (NRI, 0.122, *P*=0.007; IDI, 0.013, *P*=0.027), non-HDL-C (NRI, 0.077, *P*=0.206; IDI, 0.002, *P*=0.359), TG (NRI, 0.171, *P*=0.007; IDI, 0.015, *P*=0.020), FBG (NRI, 0.126, *P*=0.007; IDI, 0.006, *P*=0.133), and HbA1c (NRI, −0.005, *P*=0.791; IDI, 0.001, *P*=0.146).

5. Discussion

The current study evaluated the performance of the TyG index for predicting adverse cardiovascular events in nondiabetic patients diagnosed with NSTE-ACS and who received elective PCI, results of which were summarized as follows: (1) the TyG index was closely correlated with multiple cardiovascular risk factors; (2) the increased level of the TyG index was significantly related to a higher risk of adverse cardiovascular events, even after adjusting for confounding factors; and, (3) compared with other lipid- or glucose-related parameters, adding the TyG index into the baseline model that included recognized cardiovascular risk factors exhibited the most significant incremental effect on risk discrimination for predicting adverse cardiovascular events.

IR, which is characterized by changes in physiological functions including reduced efficiency of

insulin in facilitating glucose utilization and hyperinsulinemia that resulted from compensatory oversecretion of insulin, can induce the imbalance and dysregulation in glucose and lipid metabolism and then lead to type 2 diabetes mellitus (T2DM) and metabolic syndrome. IR has been demonstrated to be significantly associated with atherosclerotic plaque formation and cardiac dysfunction[29], supporting the results revealed by previous studies that IR plays a critical role in the occurrence of cardiovascular disease[3-5]. Moreover, for patients who have ever had cardiovascular disease, IR has been also proved to be significantly related to clinical prognosis[6, 7]. Therefore, for individuals at risk or with a definite diagnosis of cardiovascular disease, quantitative assessment of the extent of IR can provide additional information on risk stratification. It has been demonstrated that the hyperinsulinemic-euglycemic clamp is the gold standard technique for evaluating IR[30]. However, the disadvantages of hyperinsulinemic-euglycemic clamp, including time consumption, expensiveness, and operational complexity, make it relatively hard to be extensively put into clinical application. The HOMA-IR, which is another well-established method for assessing IR and is determined by fasting insulin and glucose concentrations[30], has also been considered relatively unsuitable for comprehensive clinical application as the fasting insulin is not a parameter that is commonly measured in regular laboratory examinations, especially for individuals without confirmed diabetes. As an alternative marker of IR calculated from fasting TG and glucose, the TyG index has been proposed and shown to be highly correlated with the hyperinsulinemic-euglycemic clamp and HOMA-IR[8-12]. The TyG index is easy to calculate and does not require specific techniques and uncommon parameters; thus, it is conducive to clinical application. It has been even revealed that the TyG index performs better than HOMA-IR on evaluating IR and predicting atherosclerosis[31, 32].

The significant association between the TyG index and the incidence of diabetes and prediabetic status has been demonstrated by previous studies[13-17], implicating the considerable potential of the TyG index on early identification of individuals who were predisposed to diabetes and prediabetes. Former studies even showed that the TyG index represents a better performance in predicting the future onset of diabetes compared with other predictors like FBG and weight gain[33, 34]. Moreover, results from previous studies have confirmed the significant association of the TyG index with the incidence of cardiovascular disease, independent of diabetes and other cardiovascular risk factors[18-21, 35-37], suggesting that evaluating the TyG index is helpful for early identification of individuals who are susceptible to cardiovascular disease. On the other hand, for those who have already suffered a cardiovascular disease, the TyG index also plays an important role in the prediction of adverse prognosis. Certain studies have verified that the TyG index is significantly associated with recurrent adverse cardiovascular events in patients with a definite diagnosis of stable CAD, whether in diabetic status or not[38, 39]. As for patients diagnosed with ACS, there are also studies demonstrating the significant performance of the TyG index for predicting recurrent adverse cardiovascular events, either in those with or without a recognized diabetes[40-42]. To sum up, assessing the TyG index can provide helpful information involving risk stratification and treatment individualization for patients with cardiovascular diseases or those at high cardiovascular risk since the diagnostic and prognostic impacts of it have been widely illustrated.

However, no existing studies have focused on impacts of the TyG index on clinical outcomes in nondiabetic patients diagnosed with NSTE-ACS and who received PCI treatment. The current study, which expanded the prognostic importance of the TyG index on risk stratification to a specific population that was diagnosed with NSTE-ACS, treated with elective PCI, and without recognized diabetes, greatly agrees and complements previous researches. Further stratified analyses in the present study consistently revealed a similar prognostic implication for the TyG index. Of note, even in patients taking statins at admission, which might have a confounding effect on TG levels, increased TyG index remained to be an independent predictor for the primary endpoint. In the subclass diagnosed with NSTEMI, no significant association between the TyG index and the risk of primary endpoint was found; this may be due to the remarkably small number of participants who were diagnosed with NSTEMI [239 (15.8%)]. The results of the present study, both in univariate and multivariate analyses, showed that the TyG index failed to be a significant predictor of all-cause death and nonfatal ischemic stroke, reasons for which can largely attribute to the fact that the incidence of all-cause death and nonfatal ischemic stroke is relatively low [all-cause death, 19 (1.3%) cases; nonfatal ischemic stroke, 27 (1.8%)]. The relatively low incidence makes it hard to precisely evaluate the predictive value of the TyG index for all-cause death and nonfatal ischemic stroke.

Despite an important association between the TyG index and adverse cardiovascular events having been elucidated by the present study, it is worth to

note that the differences in the mean value of the TyG index between patients with and without an endpoint event are exactly small (8.9 ± 0.5 vs. 8.7 ± 0.5). The possible reasons are speculated as follows. Firstly, the TyG index is a computed parameter obtained from a ln transformation. Therefore, the holistic range of the TyG index is relatively small. Additionally, all enrolled participants in the present study are patients without recognized diabetes, which makes the TG and FBG concentrations (especially the FBG), the determinants of the TyG index, remain a relatively smaller variation across the whole population. Another issue that deserves attention is the strong correlation of the TyG index with TG (correlation coefficient, 0.928) and weaker correlation with FBG (correlation coefficient, 0.316). Part of this may be due to the fact that FBG has a significantly less fluctuating range than TG in nondiabetic population. The significantly high correlation between the TyG index and TG makes it difficult to determine that the TyG index itself plays a clinical significance rather than TG. After taking the TyG index, TG, and FBG into the baseline model, respectively, we found that the TyG index exhibited more significant incremental effect on the performance of risk prediction and stratification than TG and FBG, indicating that the TyG index provides more information on the prediction of recurrent cardiovascular events beyond TG and FBG.

The close association between the TyG index and cardiovascular disease may be partly ascribed to the following mechanisms. Firstly, as determined by FBG and TG, which were proved to be well correlated to IR level from the liver and adipose cells, respectively [43], the TyG index, thus, can comprehensively reflect the extent of IR from the whole organism. IR has been extensively proved to be significantly associated with inflammatory responses, endothelial dysfunction, clotting imbalance, oxidative stress, poor myocardial reperfusion, microcirculatory dysfunction, plaque vulnerability, and cardiovascular remodeling[29, 44-46], all of which mediate the occurrence and poor prognosis of cardiovascular disease. Is it worth to emphasize that the correlation between the TyG index and hs-CRP was also elucidated in the current study. Secondly, the TyG index has been evidenced to be prominently correlated with recognized cardiovascular risk factors like hypertension[47, 48], disturbance of glucose metabolism[13-17, 33, 34], reduced renal function estimated by eGFR[49], elevated serum uric acid[50], and metabolic obesity[51]. The significant association of the TyG index with cardiovascular risk factors was also revealed by the present study. Furthermore, it has been illustrated that the TyG index is significantly associated with the progression of coronary artery calcification[52, 53] and arterial stiffness evaluated by pulse wave velocity[54, 55], both of which were indicators for the progression of cardiovascular disease.

Former studies have extensively illustrated that IR plays a critical role in risk prediction and stratification for patients with CAD; however, studies targeting at whether incorporating IR evaluation and intervention into long-term management strategies will bring clinical benefits to patients with CAD remains inadequate. Previous studies have revealed that whole-grain diet can significantly mitigate the extent of IR and decrease the level of inflammatory markers[56, 57]. However, a meta-analysis including nine randomized studies suggested that whole-grain consumption has a neutral impact on improving cardiovascular outcomes and ameliorating recognized cardiovascular risk factors[58]. Pioglitazone, one of the insulin-sensitizing agents, has been demonstrated to have positive effects on reducing the risk of recurrent cardiovascular events mediated by increasing insulin sensitivity, regardless of the existence of diabetes or not at baseline[59]. Further prospective and well-designed studies investigating whether interventions specific to IR have a favorable effect on the improvement of prognosis are needed to be proceeded.

The present study elucidated the significant relationship between the TyG index and adverse cardiovascular events in a specific cohort of nondiabetic subjects diagnosed with NSTE-ACS and who received elective PCI, suggesting that the TyG index is a useful tool for risk stratification beyond the recognized cardiovascular risk factors. This study has a large sample size and a relatively long follow-up period and, more importantly, is the first to identify the predictive performance of the TyG index for adverse prognosis in this specific population. However, several limitations should be acknowledged. Firstly, as a single-center, retrospective, observational study, the power of the study is relatively weak. Secondly, multiple-time monitoring of the TyG index after discharge, which may provide more information, were inadequate in the database and, thus cannot be analyzed. Thirdly, the dosage of statins, as well as other lipid-lowering therapies, except for statins, was not specified, which may influence the study results. Fourthly, comparisons between the TyG index and hyperinsulinemic-euglycemic clamp or HOMA-IR cannot be conducted due to insufficient information. Lastly, the enrolled patients are from China; therefore, the results should be carefully interpreted and extended to other ethnicities.

6. Conclusions

The increased level of the TyG index is a significant predictor for adverse cardiovascular events in nondiabetic patients diagnosed with NSTE-ACS and who received elective PCI. As a surrogate marker of IR, the TyG index exhibits a significant enhancement on the discriminative ability for predicting adverse cardiovascular events on the basis of recognized cardiovascular risk factors. Furthermore, to investigate whether interventions targeting at the TyG index have the potential to promote clinical prognosis, conducting randomized studies is needed.

Abbreviations

ACS, acute coronary syndrome; IR, insulin resistance; HOMA-IR, homeostasis model assessment of insulin resistance; TyG, triglyceride-glucose; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; DBP, diastolic blood pressure; PAD, peripheral artery disease; TG, triglyceride; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; BMI, body mass index; eGFR, estimated glomerular filtration rate; SYNTAX, the synergy between PCI with taxus and cardiac surgery; LM, left main artery; HbA1c, glycosylated hemoglobin A1c; DAPT, dual antiplatelet therapy; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; RLP-C, remnant-like particle cholesterol; LVEF, left ventricular ejection fraction; LCX, left circumflex artery; RCA, right coronary artery; DCB, drug-coated balloon; DES, drug-eluting stent; non-HDL-C, non-high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; NSTEMI, non-ST-segment elevation myocardial infarction; UA, unstable angina; CI, confidence interval; AUC, area under the curve; TG/HDL-C, triglyceride-to-high-density lipoprotein cholesterol ratio; NRI, net reclassification improvement; IDI, integrated discrimination improvement; CAD, coronary artery disease; T2DM, type 2 diabetes mellitus.

Declarations

Ethics Approval and Consent to Participate

Given the retrospective nature of the current study, the requirement for informed consent was waived. The study protocol was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

QZ and TYZ made substantial contributions to study design, data collection, data analysis, and manuscript writing. YJZ made substantial contributions to study design and intellectual direction. YJC, YM, YKX, JQY made contributions to data collection and analysis. All authors read and approved the final manuscript.

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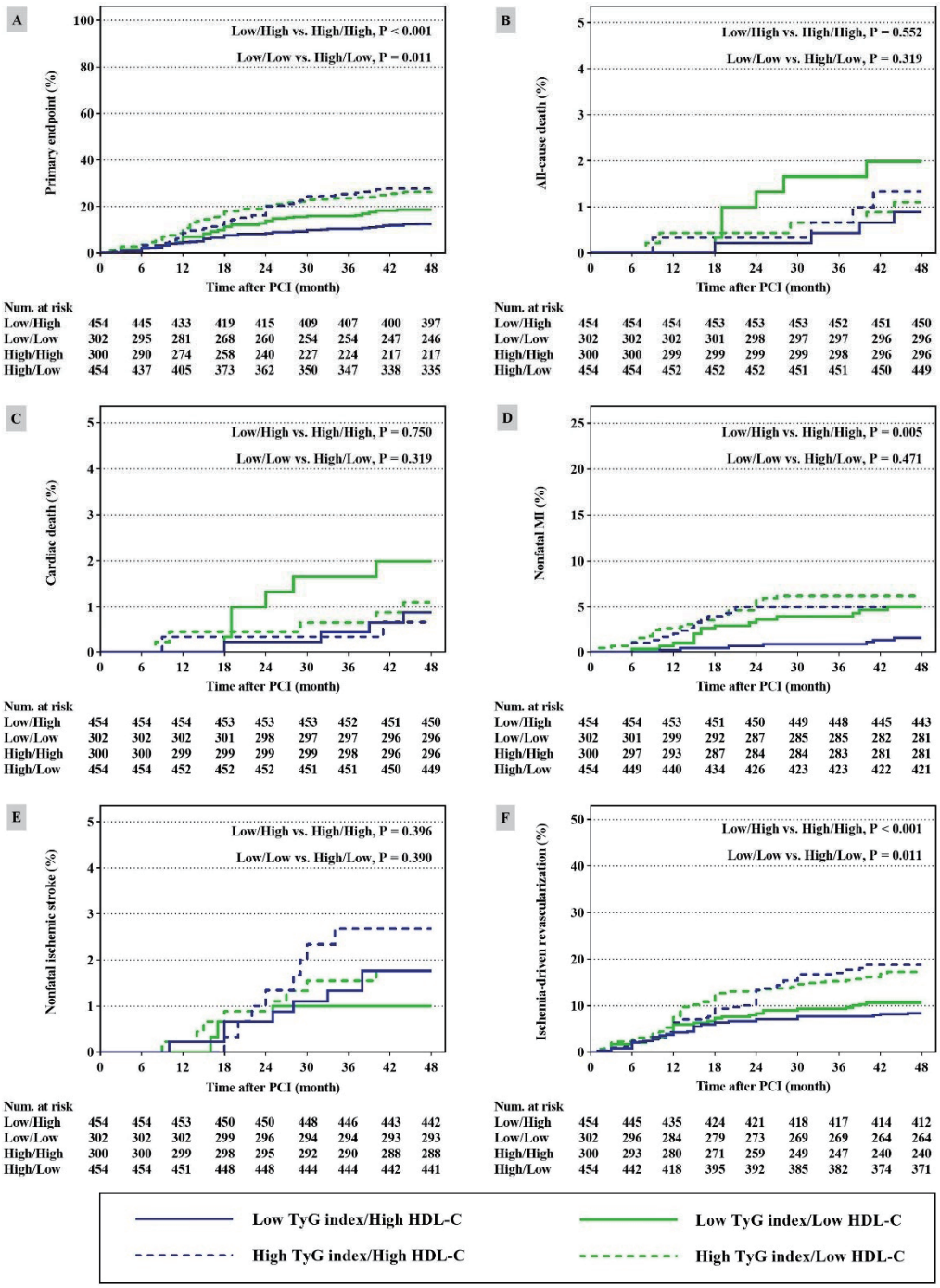
Supplemental Table 1. The primary endpoint event rate according to the median of TyG index

	Total population (n = 1,510)	Lower TyG index (≤ 8.72; n = 756)	Higher TyG index (> 8.72; n = 754)	P-value
Primary endpoint, n (%)	316 (20.9)	113 (14.9)	203 (26.9)	< 0.001
All-cause death, n (%)	19 (1.3)	10 (1.3)	9 (1.2)	0.822
Cardiac death, n (%)	17 (1.1)	10 (1.3)	7 (0.9)	0.468
Nonfatal MI, n (%)	65 (4.3)	22 (2.9)	43 (5.7)	0.008
Nonfatal ischemic stroke, n (%)	27 (1.8)	11 (1.5)	16 (2.1)	0.328
Ischemia-driven revascularization, n (%)	205 (13.6)	70 (9.3)	135 (17.9)	< 0.001

The lower and higher TyG index groups were stratified by the median of TyG index.
TyG, triglyceride-glucose; MI, myocardial infarction.



Supplemental Fig. 1. Kaplan–Meier analysis for endpoint events according to the median of the TyG index and HDL-C

(A) Kaplan–Meier analysis for primary endpoint; (B) Kaplan–Meier analysis for all-cause death; (C) Kaplan–Meier analysis for cardiac death; (D) Kaplan–Meier analysis for nonfatal MI; (E) Kaplan–Meier analysis for nonfatal ischemic stroke; (F) Kaplan–Meier analysis for ischemia-driven revascularization.

PCI, percutaneous coronary intervention; MI, myocardial infarction; TyG, triglyceride-glucose; HDL-C, high-density lipoprotein cholesterol.

Supplemental Table 2. Univariate Cox proportional hazards analysis for the primary endpoint

	Univariate analysis		
	HR	95% CI	*P* value
Age, per 10 years	1.535	1.351-1.744	<0.001
Gender, female	1.197	0.940-1.525	0.145
BMI, per 1 kg/m^2	1.031	0.996-1.067	0.088
Heart rate, per 10 bpm	1.010	0.905-1.127	0.862
SBP, per 10 mmHg	1.025	0.956-1.098	0.489
DBP, per 10 mmHg	0.893	0.795-1.003	0.057
Smoking history	1.000	0.800-1.252	0.998
Drinking history	0.836	0.637-1.099	0.199
Family history of CAD	1.101	0.764-1.586	0.607
Hypertension	1.356	1.078-1.706	0.009
Dyslipidemia	1.788	1.234-2.590	0.002
Previous MI	2.656	2.113-3.338	<0.001
Previous PCI	1.896	1.465-2.455	<0.001
Previous stroke	2.402	1.819-3.171	<0.001
Previous PAD	2.065	1.574-2.709	<0.001
Diagnosis, NSTEMI	1.161	0.868-1.553	0.315
TC, per 10 mg/dL	1.016	0.989-1.044	0.240
LDL-C, per 10 mg/dL	1.010	0.979-1.042	0.531
HDL-C, per 10 mg/dL	0.846	0.745-0.961	0.010
hs-CRP, per 1 mg/L	1.009	0.992-1.026	0.313
eGFR, per 10 mL/ (min × 1.73 m^2)	0.875	0.824-0.930	<0.001
HbA1c, per 1%	2.322	1.728-3.121	<0.001
LVEF, per 10%	0.632	0.552-0.725	<0.001
ACEI/ARB at admission	1.233	0.949-1.602	0.117
DAPT at admission	1.375	1.091-1.732	0.007
Statins at admission	1.280	1.017-1.610	0.035
ACEI/ARB at discharge	1.581	1.229-2.033	<0.001
Statins at discharge	1.821	0.753-4.406	0.184
LM disease	2.241	1.466-3.426	<0.001
Three-vessel disease	3.446	2.760-4.301	<0.001
Chronic total occlusion	3.226	2.507-4.150	<0.001
Diffuse lesion	1.767	1.391-2.244	<0.001
In-stent restenosis	2.699	1.853-3.933	<0.001
SYNTAX score, per 1-unit	1.143	1.123-1.163	<0.001
LM treatment	2.218	1.298-3.791	0.004
LAD treatment	1.074	0.849-1.358	0.553
LCX treatment	1.333	1.061-1.676	0.014
RCA treatment	1.777	1.425-2.216	<0.001
DES implantation	0.298	0.191-0.464	<0.001
DCB application	3.249	2.125-4.968	<0.001
Complete revascularization	0.496	0.398-0.619	<0.001
Number of stents, per 1 stent	1.278	1.185-1.377	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PAD, peripheral artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin A1c; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DAPT, dual antiplatelet therapy; LM, left main artery; SYNTAX, synergy between PCI with taxus and cardiac surgery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; DES, drug-eluting stent; DCB, drug-coated balloon.