Cardiovascular Diabetology

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Multiple triglyceride-derived metabolic indices and incident cardiovascular outcomes in patients with type 2 diabetes and coronary heart disease

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Abstract

Background Triglyceride (TG) and its related metabolic indices are recognized as important biomarker gauging cardiovascular diseases. This study aimed to explore the association between multiple TG-derived metabolic indices including the atherogenic index of plasma (AIP), triglyceride-glucose (TyG) index, triglyceride glucose-body mass index (TyG-BMI) and cardiovascular outcomes to identify valuable predictors for cardiovascular prognosis in patients with type 2 diabetes (T2DM) and coronary heart disease (CHD).

Methods Data of 1034 patients with T2DM and CHD from China-Japan Friendship Hospital between January 2019 and March 2022 were collected and analyzed. Multivariate Cox proportional hazards models and restricted cubic spline (RCS) analysis were conducted to examine the associations between AIP, TyG index, TyG-BMI and major adverse cardiac and cerebrovascular events (MACCEs). The area under the receiver operating characteristic (ROC) curve (AUC) was used to screen the most valuable predictor. Kaplan-Meier curve analysis was employed to examine the relationship between the predictor and prognosis. The goodness-of-fit of models was evaluated using the calibration curve and χ^2 likelihood ratio test. Subgroup analysis and interaction test were performed to control for confounding factors.

Results The overall incidence of MACCEs was 31.04% during a median of 13.3 months of follow-up. The results showed that AIP, TyG index and TyG-BMI were all positively correlated with the risk of MACCEs in patients with T2DM and CHD ($P < 0.05$). Furthermore, ROC (AUC = 0.899) suggested that AIP had the strongest ability to predict the risk of MACCEs, and the highest AIP values enhanced the risk by 83.5% in the population. RCS model demonstrated that AIP was nonlinearly associated with the incident cardiovascular outcomes (P for nonlinear = 0.0118). The Kaplan-Meier analysis for MACCEs grouped by the AIP tertiles indicated that the probability of cumulative incidences of MACCEs was significantly higher in patients with a higher AIP (all Log rank $P < 0.001$). Meanwhile, the calibration curve demonstrated an excellent goodness-of-fit of the multivariate model ($\chi^2 = 13.210$, $P = 0.105$). Subgroup analysis revealed that the trend of positive association of AIP with cardiovascular risk was similar across subgroups except in non-hypertensive individuals.

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Conclusion Our study, for the first time, may provide valuable information that multiple TG-derived metabolic indices play a crucial role in the risk of MACCEs and it is recommended to monitor the AIP for lipid management in patients with established T2DM and CHD.

Keywords Coronary heart disease, Type 2 diabetes, Major adverse cardiac and cerebrovascular events, Atherogenic index of plasma, Triglyceride-glucose index, Triglyceride glucose-body mass index

Introduction

Ischemic heart disease is still the leading cause of human death, ranking first in the global disease burden according to the latest Global Burden of Disease Study [1]. Coronary heart disease (CHD) is a significant challenge facing global public health, affecting 244.11 million individuals worldwide [2, 3]. Currently, diabetes mellitus is affecting 529 million people worldwide and type 2 diabetes (T2DM) accounts for 96% of all those cases, and more than 1.31 billion people are projected to suffer from diabetes by 2050 [4]. The relationship between T2DM and CHD has been well-established yet. Data from a study [5] of 318,083 participants screened from the Swedish National Diabetes Registry determined that T2DM has been linked to an early onset of CHD and in middle-aged adults the risk of developing CHD is 2–4 times greater in subjects with T2DM than in those without T2DM. Furthermore, the simultaneity of T2DM with CHD raises the risk of mortality by up to 80% compared to the ratio observed across individuals without CHD [6], thus worsening the prognosis for this population. Therefore, early identification of individuals at high cardiovascular risk in patients with T2DM and CHD may contribute to improving prognosis.

Insulin resistance (IR) serves as the primary pathological mechanism of metabolic syndrome, which is ubiquitous in most diabetic patients and strongly related to major adverse cardiac and cerebrovascular events (MACCEs), bringing a huge burden to public health [7]. Pathophysiological studies have shown that IR promotes an inflammatory state, vascular endothelial dysfunction and dyslipidemia, which may be the main mechanisms of CHD progression [8]. Triglyceride (TG) and its related metabolic indices, all recognized as surrogates of IR, have been demonstrated to be relevant to clinical prognosis of patients with cardiovascular diseases [9].The atherogenic index of plasma (AIP), calculated as a logarithmically converted ratio of TG to high-density lipoprotein cholesterol (HDL-C), has been used to identify atherogenic dyslipidaemia and IR based on a positive association with cholesterol esterification rates, lipoprotein particle size, and remnant lipoproteinaemia [10–12]. A multi-center retrospective cohort study [13] involving 15,421 prediabetic subjects revealed that AIP was negatively correlated with the reversion from prediabetes to normoglycemia and played a crucial role in the risk assessment of prediabetes progression. In addition to the plasma lipid profile, dysglycemia and overweight/obesity also have been recognized as key predictors for incident cardiovascular outcomes in patients with T2DM [14–16]. Recently, diverse affordable tools that combine multiple risk factors have been identified as meaningful biomarkers for predicting cardiovascular prognosis, such as the triglyceride-glucose (TyG) index, triglyceride glucose-body mass index (TyG-BMI). The TyG index and TyG-BMI, as simple and reliable surrogate predictors for gauging IR, are closely associated with the progression of various cardiovascular events [17, 18]. Recent studies have confirmed the positive association of the incidence of MACCEs with the TyG index in patients with T2DM [19, 20]. Nevertheless, information on the association of TyG-BMI with incident cardiovascular outcomes in patients with T2DM and CHD was not well understood. Additionally, there is still a lack of evidence on which TG-derived metabolic indices may serve as a predictive predictor of MACCEs in patients with T2DM and CHD.

The purpose of the study first was to determine the association between TyG-BMI and MACCEs. Furthermore, we sought to compare the values of AIP, the TyG index and TyG-BMI in predicting MACCEs and to identify valuable predictors for incident cardiovascular outcomes in patients with T2DM and CHD through accessible real-world data.

Materials and methods

Study design and participants

The present study is a large single-center observational cohort study that mainly occurred in China-Japan Friendship Hospital. Admission data of consecutive patients with T2DM and CHD were enrolled and assessed from China-Japan Friendship Hospital from January 2019 to March 2022. All eligible patients ranged from 18 to 80 years fulfilled the diagnostic criteria for T2DM and CHD. The definition of T2DM complied with the current guideline of the American Diabetes Association [21]: (1) glycated hemoglobin A1c (HbA1c) ≥ 6.5% (48 mmol/mol) or fasting plasma glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L) or 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test. In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results obtained at the same time (e.g., HbA1c and FPG) or at two different time points; (2) In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

Random is any time of the day without regard to time since previous meal. CHD was defined as having at least one of the following conditions [22]: (1) percutaneous coronary angiography or computed tomographic angiography examination showed that at least one coronary artery trunk or primary branch had≥50% stenosis; (2) typical exertional angina symptoms with positive stress test (electrocardiogram stress test, stress echocardiography or nuclide myocardial stress imaging); (3) previously diagnosed myocardial infarction or unstable angina pectoris.

Among the 9316 patients, 1034 patients were enrolled in the present study finally after exclusion of patients with prior coronary artery bypass grafting, suspected familial hypertriglyceridemia [plasma TG≥500 mg/dL (5.65 mmol/L) or more than one first-degree relative with TG≥500 mg/dL], >30% missing baseline-related data, severe complications such as cardiogenic shock, advanced cancer, severe hepatic and renal dysfunction, severe hematological and endocrine system diseases. Fourteen patients were also excluded because of missing follow-up data when more than three separate attempts to contact them (Fig. 1). All patients were followed up at the first year after discharge. The study was implemented in accordance with the Declaration of Helsinki. The need for informed consent was waived by the institutional review board due to its retrospective nature and information related to patient identity was concealed.

Data collection

Patients' clinical information including demographic information, clinical characteristics, laboratory indicators, echocardiography and peripheral arterial disease features were collected at admission from the Hospital Information System. Demographic characteristics encompassed age, gender, baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate (HR), smoking and drinking history. Clinical characteristics comprised hypertensive and diabetic medical histories, familial cardiovascular diseases (FCVDs), diabetes, old myocardial infarction (OMI), stroke, dyslipidemia as well as the states of medical treatments. Medical treatments embraced antiplatelet, antihypertensive, antidiabetic and antilipidemic agents. Venous blood samples were collected after overnight fasting prior to angiography, and laboratory tests consisting of neutrophil (Neu), lymphocyte (Lym), platelets (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (TC), TG, low density lipoprotein cholesterol (LDL-C), HDL-C, lipoprotein (a) [Lp (a)], homocysteine (HCY), hypersensitive C-reactive protein (Hs-CRP), serum creatinine (Scr), FPG and HbA1c were performed under standardized instructions and assaying system. Echocardiography features consisting of left atrial diameter (LAD), left ventricular end-diastolic diameter (LVDd), interventricular septal thickness (IVST), left ventricular posterior wall thickness (PWT), and left ventricular ejection fraction (LVEF) were analyzed and recorded by two independent echocardiographers. The angiographic data was obtained from the cardiac catheterization laboratory records. Peripheral arterial disease indicators included brachial-ankle pulse wave velocity (baPWV), ankle-brachial index (ABI) and brachial artery flow-mediated vasodilatation (FMD) value.

TG-derived metabolic indices

The TG-derived metabolic indices in the study included AIP, the TyG index and TyG-BMI, and the formulas for calculating these indices were as follows:

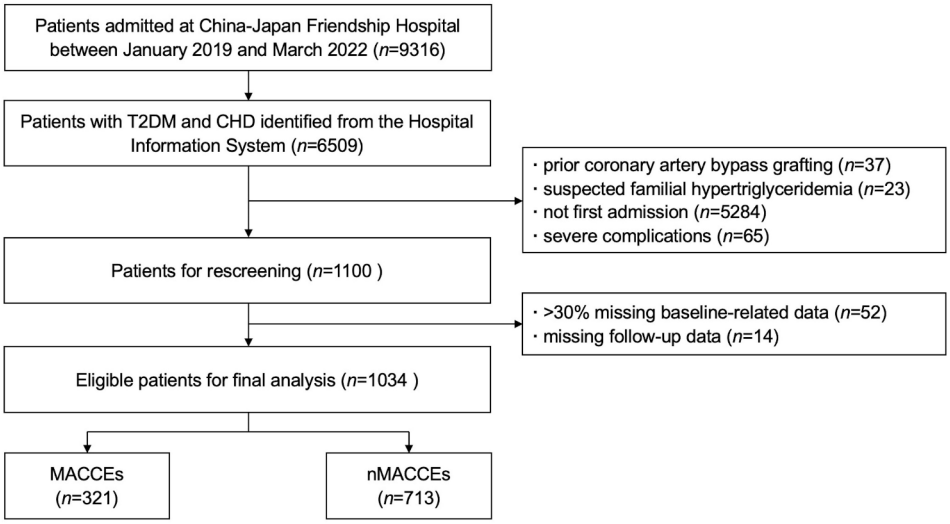

Fig. 1 Flow diagram of patient selection. T2DM, type 2 diabetes; CHD, coronary heart disease; MACCEs, major adverse cardiac and cerebrovascular events

(1) AIP = Lg [TG (mmol/L)/HDL-C (mmol/L)] [11];
(2) TyG index = Ln [fasting TG (mg/dL) × FPG (mg/dL)/2] [23];
(3) TyG-BMI = TyG index × BMI (kg/m^2) [24].

Endpoints and definitions

Trained investigators used standardized questionnaires to gather data from prior inpatient and outpatient medical records. The primary outcome was regarded as a combination of cardiac death, non-fatal myocardial infarction, unplanned revascularization, and stroke. Secondary endpoints included in-stent restenosis and unplanned rehospitalization. MACCEs were considered the first occurrence of an event during each patient's follow-up.

The total MACCEs was defined as follows: (1) cardiac death, including fatal events caused by coronary artery disease or myocardial infarction; (2) non-fatal myocardial infarction, referring to myocardial necrosis but no death, accompanied by ischemia symptoms, abnormal myocardial markers, ST segment changes or pathological Q wave changes; (3) unplanned revascularization, which means that the patient underwent revascularization again due to unexpected internal cardiac causes; (4) stroke, including cerebral infarction, cerebral hemorrhage and subarachnoid hemorrhage; (5) in-stent restenosis, which was defined as 50% or more of the target vessel stenosis within 5 mm from the edge of the stent or both ends of the stent after percutaneous coronary intervention as shown by coronary angiography; and (6) unplanned rehospitalization for cardiac causes (unstable angina pectoris, acute exacerbation of chronic heart failure, etc.).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)], and the *t*-test or the Mann-Whitney *U* test was selected for hypothesis testing for those with normal and skewed distributions, respectively. Categorical variables were summarized as percentage-based figures and compared by the Chi-Square test.

Multivariate Cox proportional hazards models were used to examine the associations between TG-derived metabolic indices and MACCEs, and the results were expressed with hazard ratio (HR) and 95% confidence interval (CI) values. The area under the receiver operating characteristic (ROC) curve (AUC) was used to screen the most valuable predictor, and the Restricted cubic spline (RCS) analysis was conducted to identify the nonlinear relationship between the predictor and MACCEs. Meanwhile, the potential cut-off point was calculated. The cumulative incidence of endpoints was assessed through the Kaplan-Meier method and compared between groups using the log-rank test. Moreover, we established three regression models by adjusting different indicators to control for confounding biases. In addition to the Model 1 without any adjustments for confounders, two other models were fitted. In Model 2, age, BMI, HR, OMI, dyslipidemia and FCVDs were modified. Model 3 was a fully adjusted model that took gender, age, BMI, HR, OMI, dyslipidemia, hypertension, FCVDs, echocardiography and PAD features into account. The selection of indicators was driven both theoretically and statistically. Indicators theoretically related to the endpoints, including age, gender and hypertension, were fixed in the model. Meanwhile, indicators with statistically significant in the baseline characteristics analysis also were considered to construct the model. Furthermore, we assessed the goodness-of-fit of the fully adjusted model using calibration curve and χ^2 likelihood ratio test. The decision curve analysis (DCA) and clinical impact curve (CIC) were also applied to comprehensively evaluate the predictive accuracy and clinical value of the model. Finally, we conducted subgroup analysis and interaction test based on age, gender, BMI, history of hypertension and OMI, and FCVDs.

Statistical analyses were performed using IBM-SPSS (version 26.0, Chicago, IL, USA) and R (version 4.1.2, Vienna, Austria). A two-sides $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

Among the 1034 patients enrolled, the average age was 65 years, 72.14% of patients were male, 79.98% of patients had hypertension, 78.63% of patients had a history of dyslipidemia, and 31.33% of patients had FCVDs. Of these, 321 patients (31.04%) developed MACCEs after a median follow-up of 13.3 months. Table 1 summarizes baseline characteristics of included patients by MACCEs.

Between patients who developed MACCEs and patients who did not, no significant difference was observed in their medical treatments and coronary lesions severity. Similarly, compared with the nMACCEs group, some traditional risk factors for cardiovascular diseases, including old age, overweight/obesity and higher levels of HR, were also more prevalent in patients with MACCEs in our study. Meanwhile, patients who suffered MACCEs had higher levels of AIP, TyG index and TyG-BMI. Patients with adverse events were more likely to have the medical history of OMI, dyslipidemia and FCVDs, and elevated concentration of TG, LDL-C, HDL-C, Lp (a), HCY, Hs-CRP, FPG and HbA1c. Severer peripheral arterial diseases and worse cardiac function also appeared in subjects suffered MACCEs.

Table 1 Baseline characteristics of included patients by MACCEs

Variables	All ($n=1034$)	MACCEs ($n=321$)	nMACCEs ($n=713$)	*P* value
Demographics				
Male (n, %)	746 (72.14)	230 (71.65)	516 (72.37)	0.822
Age (years)	65 (57, 71)	69 (61, 72)	62 (56, 71)	< 0.001
BMI (kg/m^2)	25.18 (23.44, 27.77)	26.3 (24.22, 28.65)	24.57 (23.24, 26.93)	< 0.001
SBP (mmHg)	135 (120, 148)	139 (120, 150)	133 (121, 147)	0.056
DBP (mmHg)	77 (67, 85)	72 (66, 85)	77 (68, 85)	0.099
HR (bpm)	74 (68, 81)	77 (70, 82)	73 (68, 80)	< 0.001
Medical history (n, %)				
Smoking	458 (44.29)	133 (41.43)	325 (45.58)	0.224
Drinking	238 (23.02)	77 (23.99)	161 (22.58)	0.632
Hypertension	827 (79.98)	262 (81.62)	565 (79.24)	0.402
Stroke	218 (21.08)	69 (21.5)	149 (20.9)	0.869
OMI	214 (20.7)	111 (34.58)	103 (14.45)	< 0.001
Dyslipidemia	813 (78.63)	269 (83.8)	544 (76.3)	0.007
FCVDs	324 (31.33)	140 (43.61)	184 (25.81)	< 0.001
Coronary lesions (n, %)				
One-vessel disease	793 (76.69)	249 (77.57)	544 (76.3)	0.691
Two-vessel disease	196 (18.96)	60 (18.69)	136 (19.07)	0.932
Multi-vessel disease	45 (4.35)	12 (3.74)	33 (4.63)	0.622
Medical treatments (n, %)				
Antiplatelet agents	1022 (98.84)	316 (98.44)	706 (99.02)	0.531
Statins	1007 (97.39)	314 (97.82)	693 (97.19)	0.676
ACEI/ARB	653 (63.15)	194 (60.44)	459 (64.38)	0.237
β-blockers	807 (78.05)	248 (77.26)	559 (78.4)	0.685
CCB	408 (39.46)	126 (39.25)	282 (39.55)	0.945
Nitrates	339 (32.79)	106 (33.02)	233 (32.68)	0.943
OHAs	722 (69.83)	236 (73.52)	486 (68.16)	0.092
Insulin	299 (28.92)	102 (31.78)	197 (27.63)	0.182
Laboratory results				
Neu (10^9/L)	4.13 (3.33, 5.1)	4.23 (3.22, 5.11)	4.11 (3.36, 5.09)	0.905
Lym (10^9/L)	1.77 (1.39, 2.25)	1.72 (1.34, 2.18)	1.77 (1.4, 2.31)	0.177
PLT (10^9/L)	207 (165, 249)	208 (165, 248)	205 (164, 252)	0.727
ALT (U/L)	20 (14, 28)	19 (12, 28)	20 (14, 28)	0.054
AST (U/L)	18 (15, 25)	18 (14, 23)	18 (15, 26)	0.457
TC (mmol/L)	3.82 (3.07, 4.6)	3.82 (3.01, 4.78)	3.77 (3.17, 4.58)	0.530
TG (mmol/L)	1.44 (1.1, 1.96)	1.61 (1.23, 2.04)	1.32 (1.08, 1.82)	< 0.001
LDL-C (mmol/L)	2.29 (1.79, 2.84)	2.41 (1.75, 3.17)	2.28 (1.8, 2.8)	0.027
HDL-C (mmol/L)	0.96 (0.81, 1.14)	0.93 (0.73, 1.14)	0.97 (0.83, 1.14)	0.018
Lp (a) (mg/L)	92.19 (39.5, 227.47)	144.6 (49.36, 285.21)	82.91 (34.48, 199.47)	< 0.001
HCY (μmol/L)	13.49 (10.87, 17.12)	15.65 (13.28, 19.35)	12.7 (10.55, 16.21)	< 0.001
Hs-CRP (mg/L)	2.49 (1.16, 4.81)	4.81 (2.33, 6.94)	1.78 (0.94, 4.81)	< 0.001
Scr (μmol/L)	74.2 (61, 84.15)	75.45 (61.5, 84.05)	73.9 (61, 84.5)	0.112
FPG (mmol/L)	6.72 (5.74, 7.91)	6.83 (5.86, 8.3)	6.6 (5.65, 7.85)	0.019
HbA1c (%)	7.1 (6.4, 8.1)	7.5 (6.6, 8.7)	6.8 (6.2, 7.9)	< 0.001
PAD indicators				
baPWV (m/s)	17.4 (15.42, 22.12)	22.39 (20.17, 24.65)	16 (15, 18.8)	< 0.001
ABI	1.06 (0.92, 1.17)	0.9 (0.76, 1.01)	1.14 (1.01, 1.19)	< 0.001
FMD (%)	6.8 (6, 7.9)	6 (5.6, 6.3)	7.2 (6.4, 8.55)	< 0.001
Echocardiography measurements				
LAD (mm)	38 (36, 40)	39 (38, 43)	37 (35, 39)	< 0.001
LVEF (%)	65 (60, 69)	63 (55, 68)	66 (62, 70)	< 0.001
LVDd (mm)	50 (48, 54)	53 (50, 56)	50 (47, 53)	< 0.001
IVST (mm)	10 (9, 11)	11 (10, 12)	10 (9, 11)	< 0.001

Table 1 (continued)

Variables	All ($n=1034$)	MACCEs ($n=321$)	nMACCEs ($n=713$)	*P* value
PWT (mm)	9 (8, 10)	10 (9, 10)	9 (8, 10)	< 0.001
TG-derived metabolic indices				
AIP	0.17 (0.03, 0.33)	0.23 (0.09, 0.37)	0.14 (0.01, 0.3)	< 0.001
TyG index	8.97 (8.61, 9.35)	9.13 (8.8, 9.41)	8.88 (8.58, 9.31)	< 0.001
TyG-BMI	227.79 (206.65, 250.27)	240.1 (215.32, 260.53)	224.36 (204.46, 244.99)	< 0.001

MACCEs, major adverse cardiac and cerebrovascular events; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; OMI, old myocardial infarction; FCVDs, familial cardiovascular diseases; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; OHAs, Oral hypoglycemic agents; Neu, neutrophil; Lym, lymphocyte; PLT, platelets; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Lp (a), lipoprotein (a); HCY, homocysteine; Hs-CRP, hypersensitive C-reactive protein; Scr, serum creatinine; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; PAD, peripheral arterial disease; baPWV, brachial-ankle pulse wave velocity; ABI, ankle-brachial index; FMD, brachial artery flow-mediated vasodilatation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; LVDd, left ventricular end-diastolic diameter; IVST, interventricular septal thickness; PWT, left ventricular posterior wall thickness; AIP, atherogenic index of plasma; TyG, triglyceride-glucose; TyG-BMI, triglyceride glucose-body mass index.

Table 2 The association between TG-derived metabolic indices and MACCEs

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
AIP	1.801 (1.203 ~ 2.697)	0.004	2.220 (1.455 ~ 3.387)	< 0.001	1.835 (1.188 ~ 2.834)	0.006
TyG index	1.284 (1.076 ~ 1.532)	0.006	1.356 (1.128 ~ 1.630)	0.001	1.267 (1.042 ~ 1.539)	0.017
TyG-BMI	1.011 (1.008 ~ 1.014)	< 0.001	1.012 (1.005 ~ 1.019)	0.001	1.010 (1.002 ~ 1.017)	0.010

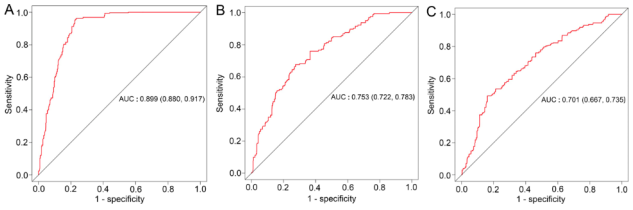

Fig. 2 Predictive power of TG-derived metabolic indices for MACCEs in patients with T2DM and CHD. The area under the receiver operating characteristic curve of **A** AIP, **B** TyG index, and **C** TyG-BMI

Association between TG-derived metabolic indices and MACCEs

Table 2 describes the results of the multivariate Cox proportional hazards regression analysis, indicating a potential association between TG-derived metabolic indices and MACCEs. The unadjusted model 1 showed that AIP, TyG index and TyG-BMI were all positively correlated with the risk of MACCEs in patients with T2DM and CHD ($P<0.05$). After adjusting for age, BMI, HR, OMI, dyslipidemia and FCVDs in model 2, the three TG-derived metabolic indices as continuous variables were also independently related to the endpoints ($P<0.05$). The risks of the primary outcome were 2.220-fold higher (HR 2.220, 95% *CI* 1.455 ~ 3.387, $P<0.001$), 1.356-fold higher (HR 1.356, 95% *CI* 1.128 ~ 1.630, $P=0.001$) and 1.012-fold higher (HR 1.012, 95% *CI* 1.005 ~ 1.019, $P=0.001$) for every unit increase in AIP, TyG index and TyG-BMI, respectively. After further adjusting for gender, age, BMI, HR, OMI, dyslipidemia, hypertension, FCVDs, echocardiography and PAD features in model 3, the three TG-derived metabolic indices still remained independently associated with the risk of MACCEs ($P<0.05$).

In addition, AUC was calculated to evaluate the discrimination ability of the three TG-derived metabolic indices. The findings suggested that AIP, TyG index and TyG-BMI may all play an important role in risk prediction. Thereinto, AIP had the strongest ability to predict the risk of MACCEs with an AUC of 0.899 (0.880, 0.917), indicating that it may be a valuable predictor of incident cardiovascular outcomes in patients with T2DM and CHD.

AIP, atherogenic index of plasma; TyG, triglyceride-glucose; TyG-BMI, triglyceride glucose-body mass index; HR, hazard ratio; CI, confidence interval; Model 1, Unadjusted; Model 2, Adjusted for age, BMI, HR, OMI, dyslipidemia and FCVDs; Model 3, Adjusted for gender, age, BMI, HR, OMI, dyslipidemia, hypertension, FCVDs, echocardiography and PAD features.

The relationship between AIP and MACCEs

Multivariate RCS analysis was conducted to determine whether there was a potential nonlinear association between AIP and MACCEs in patients with T2DM and CHD. As shown in Fig. 3, RCS model indicated that AIP was nonlinearly correlated with the risk of MACCEs (P for nonlinear = 0.0118). When the AIP was 0.17, the risk of MACCEs was differentiated, and the HR value of AIP was near 1. When the AIP was greater than 0.17, it was significantly positively associated with the risk of MACCEs (HR 2.197, 95% *CI* 1.204 ~ 4.008, $P=0.010$). Moreover, we defined three categories of included patients based on the tertiles of AIP: T1 (AIP < 0.082, $n=344$), T2 ($0.082 \le$ AIP < 0.266, $n=344$), and T3 (AIP ≥ 0.266, $n=346$). The Kaplan-Meier analysis for MACCEs grouped by the AIP tertiles indicated that the probability

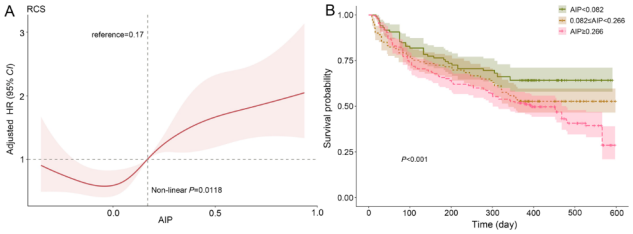

Fig. 3 The relationship between AIP and MACCEs. **A** Multivariate RCS regression analysis for the nonlinear association between AIP and MACCEs. **B** Kaplan-Meier analysis results illustrated the survival probability of the risk of MACCEs in various groups divided by the AIP tertiles. AIP, atherogenic index of plasma; HR, hazard ratio; CI, confidence interval

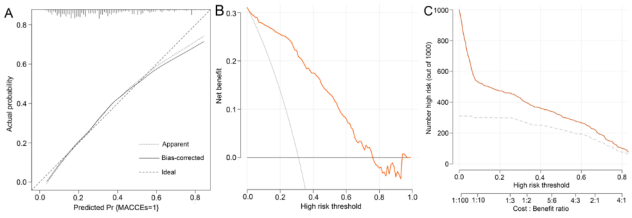

Fig. 4 Performance evaluation of AIP for predicting MACCEs. After adjustment for confounding factors, predictive power of AIP for cardiovascular outcomes was examined using (**A**) calibration curve, **B** decision curve analysis (DCA), and **C** clinical impact curve (CIC) analysis; MACCEs, major adverse cardiac and cerebrovascular events

of cumulative incidences of MACCEs was significantly higher in patients with a higher AIP than in those with a lower AIP (all Log rank $P<0.001$).

Furthermore, multivariate Cox proportional hazards regression analysis was performed to demonstrate the relationship between different AIP groups and MACCEs (Table 3). We documented a significant association of elevated AIP with a higher risk of MACCEs without adjusting for any confounding factors (P for trend <0.001). After adjusting for age, BMI, HR, OMI, dyslipidemia and FCVDs in model 2, significant association was recorded only in T3 group (HR 2.699, 95% *CI* 2.028 ~ 3.591, $P<0.001$). After adjustment all potential confounders, AIP still remained independently related to the endpoints in both T2 and T3 groups ($P<0.05$). Besides, taking the T1 in as a reference, the risks of MACCEs were 2.699-fold higher (HR 2.699, 95% *CI* 2.028 ~ 3.591, $P<0.001$) and 3.051-fold higher (HR 3.051, 95% *CI* 2.298 ~ 4.050, $P<0.001$) in T3 groups of Model 2 and Model 3, respectively. The trend analyses from T1 to T3 for the three models were all statistically significant (all P for trend <0.001).

Predictive ability test

As shown in Fig. 4, the calibration curve, DCA and CIC were conducted to comprehensively identify the predictive ability of AIP for MACCEs. After adjustment for confounding factors, the calibration curve demonstrated an excellent goodness-of-fit of the multivariate model using the χ^2 likelihood ratio test ($\chi^2=13.210$, $P=0.105$). Moreover, DCA and CIC analysis were performed to examine the clinical utility of the model, revealing a favorable overall net benefit and clinical impact within most reasonable threshold probability of the model.

Subgroup analysis

Subgroup analyses were further conducted to determine the association between AIP and the risk of MACCEs stratified by age, gender, BMI, history of hypertension and OMI, and FCVDs (Table 4). We found that AIP was positively associated with the risk of MACCEs in different subgroups, and the trend of cardiovascular risk was similar across subgroups. Among patients without hypertension, the impact of AIP tertiles did not appear substantially different on cardiovascular risk ($P>0.05$). Moreover, the results indicated no significant interaction between subgroups and AIP on the risk of MACCEs (all P for interaction <0.05).

Discussion

This study determined the relationship between multiple TG-derived metabolic indices and incident cardiovascular outcomes in patients with T2DM and CHD in China. Notably, using RCS and ROC analysis, AIP was identified to be a better predictor of cardiovascular outcomes than other TG-derived metabolic indices in patients with T2DM and CHD. According to multivariate Cox proportional hazards models, the results confirmed that the elevated AIP level was associated with a greater prevalence of cardiovascular events in patients with T2DM and CHD, and this relationship also remained significant

Table 3 The relationship between different AIP groups and MACCEs

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
AIP tertiles						
T1	1 (reference)		1 (reference)		1 (reference)	
T2	1.529 (1.134 ~ 2.061)	0.005	1.308 (0.963 ~ 1.777)	0.086	1.453 (1.073 ~ 1.969)	0.016
T3	2.769 (2.104 ~ 3.644)	< 0.001	2.699 (2.028 ~ 3.591)	< 0.001	3.051 (2.298 ~ 4.050)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

AIP, atherogenic index of plasma; T1, tertile 1; T2, tertile 2; T3, tertile 3; HR, hazard ratio; CI, confidence interval; Model 1, Unadjusted; Model 2, Adjusted for age, BMI, HR, OMI, dyslipidemia and FCVDs; Model 3, Adjusted for gender, age, BMI, HR, OMI, dyslipidemia, hypertension, FCVDs, echocardiography and PAD features.

Table 4 Association between AIP and MACCEs in different subgroups

Variables	Case	AIP tertiles [HR (95% CI)]			*P* for trend	*P* for interaction
		T1	T2	T3		
Age (years)						
< 65	507	1 (reference)	2.062 (1.103 ~ 3.855)	2.465 (1.342 ~ 4.526)	< 0.001	0.398
≥ 65	527	1 (reference)	1.193 (0.821 ~ 1.734)	2.876 (2.055 ~ 4.023)	< 0.001	
Gender						
Male	746	1 (reference)	1.132 (0.780 ~ 1.642)	2.774 (1.969 ~ 3.906)	< 0.001	0.585
Female	288	1 (reference)	1.678 (0.919 ~ 3.062)	2.418 (1.363 ~ 4.289)	0.001	
BMI (kg/m^2)						
< 24	357	1 (reference)	0.911 (0.505 ~ 1.643)	2.525 (1.453 ~ 4.388)	0.033	0.075
≥ 24	677	1 (reference)	1.569 (1.087 ~ 2.266)	2.881 (2.052 ~ 4.045)	< 0.001	
Hypertension						
Yes	827	1 (reference)	1.172 (0.828 ~ 1.658)	2.751 (2.014 ~ 3.759)	< 0.001	0.504
No	207	1 (reference)	1.767 (0.873 ~ 3.574)	1.946 (0.920 ~ 4.118)	0.015	
OMI						
Yes	214	1 (reference)	1.009 (0.588 ~ 1.731)	2.126 (1.278 ~ 3.537)	0.006	0.365
No	820	1 (reference)	1.689 (1.148 ~ 2.483)	3.519 (2.450 ~ 5.054)	< 0.001	
FCVDs						
Yes	324	1 (reference)	1.261 (0.759 ~ 2.095)	2.273 (1.439 ~ 3.588)	< 0.001	0.077
No	710	1 (reference)	2.062 (1.103 ~ 3.855)	2.465 (1.342 ~ 4.526)	< 0.001	

MACCEs, major adverse cardiac and cerebrovascular events; AIP, atherogenic index of plasma; BMI, body mass index; OMI, old myocardial infarction; FCVDs, familial cardiovascular diseases; T1, tertile 1; T2, tertile 2; T3, tertile 3; HR, hazard ratio; CI, confidence interval.

even after adjustment for all confounding factors, with the highest AIP value increasing the risk by 83.5% in the population. Additionally, the multivariate model had an excellent goodness-of-fit based on the results of calibration curve and χ^2 likelihood ratio test. DCA and CIC analysis also suggested a favorable overall net benefit and clinical impact of the multivariate model. Our study confirmed the prognostic value of TG-derived metabolic indices for incident cardiovascular outcomes in patients with T2DM and CHD, especially the predictive power of AIP was more prominent. Most importantly, this study revealed a simple method of evaluating IR and optimizing the risk stratification of incident cardiovascular outcomes in patients with T2DM and CHD.

IR is postulated to be the principal characteristic of metabolic syndrome which is also defined as a precursor to the development of T2DM and CHD [25, 26]. Elevated TG levels have been suggested as a surrogate marker of IR [27, 28]. Data from a cross-sectional study [29] of 258 nondiabetic and overweight volunteers revealed that TG and TG/HDL-C were the most valuable metabolic markers in identifying individuals with IR. Excessive visceral fat in patients with IR may increase the flow of free fatty acids to the liver, thus promoting very low-density lipoproteins secretion and resulting in hypertriglyceridemia [30]. TG-derived metabolic indicators may also be used as surrogate indices for IR to further improve the prognostic value of isolated TG for incident cardiovascular outcomes in patients with T2DM and CHD [31].

Compared with patients without MACCEs, patients with MACCEs tended to have more cardiovascular risk factors, including hyperlipidemia. Although there was no significant difference in statin use between the two groups, other it was possible that other metabolism-related indicators such as comorbidities may have contributed to the development of MACCEs. The mechanism of atherosclerosis is complex, and epidemiological studies suggest that the internationally recognized risk factors for CHD include dyslipidaemia and diabetes [32]. In T2DM, atherosclerosis has the same mechanism such as dyslipidaemia and inflammation may also cause damage to cardiovascular organs [33]. However, patients with T2DM also have a unique mechanism of atherosclerosis, for example, increased Lp(a) confers greater risk for additional adverse events when TC and LDL-C are elevated especially for patients with T2DM [34]. Under the combined influence of dyslipidaemia and dysglycemia in T2DM patients, the coronary lesions are more severe, and the prognosis is worse [35]. Furthermore, it is well known that LDL-C is the major risk factor for atherosclerosis and incident cardiovascular outcomes [32, 36]. However, several recent meta-analyses have shown that the residual risk of MACCEs remains high even in patients whose LDL-C levels meet the treatment targets after statin therapy [37, 38]. More importantly, AIP was considered to be a more promising predictor of atherosclerosis than LDL-C level and could be used in addition to the traditional risk factors [12, 39]. Here we reported that the prognosis of the high AIP group was significantly worse than that of the low AIP group in patients with T2DM and CHD, and the difference was mainly due to MACCEs, including cardiac death, non-fatal myocardial

infarction, unplanned revascularization, stroke, in-stent restenosis and unplanned rehospitalization. In brief, we speculated that AIP was most probably a reflection of atherosclerosis, the potential cause of cardiovascular diseases that may lead to stroke and acute coronary syndrome. Consequently, standardized lipid and glucose managements after PCI are of great significance for the prognosis of diabetic patients.

Previous studies have confirmed that high TG level and low HDL-C are characteristic of dyslipidemia in the metabolic syndrome and are significantly associated with poor prognosis [40, 41]. Elevated TG/ HDL-C ratio has been proposed to be associated with incident cardiovascular outcomes in hyperglycemic populations with established CHD [42]. AIP is a log-transformation of the TG/ HDL-C ratio, which has been used to assess changes in atherogenic lipoprotein profiles induced by IR reduction therapy and has been confirmed to outperform TG/ HDL-C in characterizing treatment effects [43]. In the present study, TG-derived metabolic indices were found to have favorable predictive power in predicting MACCEs in patients with T2DM and CHD, especially the predictive ability of AIP was more outstanding. Similarly, AIP has been found to exhibit a correlation with cardiovascular risk using a large-scale population dataset involving 514,866 participants from the NHIS-HEALS study [44]. Previous studies supported that the mean values of AIP ranged from −0.24 to 0.55 in the general population [45]. Our study extended the results of previous reports that patients with T2DM have higher AIP levels compared to the general population. We found that monitoring AIP levels for lipid management in diabetic patients after PCI was recommended, with the target threshold set at 0.17, as the baseline AIP value of 0.17 was identified as the optimal cut-off point for incident cardiovascular outcomes risk prediction in patents with T2DM and CHD. Consistent with our findings, a multicenter retrospective cohort study of 15,421 participants [13] demonstrated that maintaining AIP below 0.17 was also vital to decrease the risk of diabetes for those with prediabetes. Furthermore, an observational cohort study of 2,356 patients [46] showed that the prognosis of diabetic patients with high levels of the AIP included more MACCEs and was not affected by LDL-C levels, and it was recommended to monitor the AIP for lipid management in diabetic patients after percutaneous coronary intervention and ensure that the AIP was not higher than 0.318. Substantial studies [47, 48] have also confirmed that AIP was more suggestive among lipid parameters to reflect the risk of T2DM, and AIP also might be a strong biomarker that could be used to predict the risk of cardiovascular events in patients with T2DM. Similarly, our study also suggested the outstanding ability of AIP in predicting prognosis. The risk of MACCEs were significantly increased in patients with elevated AIP levels. Overall, AIP is an independent indicator of lipid status in diabetic patients, and we believe that our findings may provide new insights into the risk management in patients with T2DM and CHD.

Additionally, the study population was subcategorized based on demographic and clinical parameters, and AIP had consistent effects in predicting patient outcomes in different subgroups. Our results supported that these associations may be broadly generalizable to different populations. Besides, consistent with previous studies, we found that the other two TG-derived metabolic indices (TyG index and TyG-BMI) also played an essential role in predicting prognosis in patients with T2DM and CHD. A retrospectively study [20] highlighted the potential of the TyG index as a predictor of recurrent revascularization and suggested that the incorporation of the TyG index into risk prediction models was likely to be beneficial for risk stratification and improve prognosis in patients with T2DM and CHD. TyG-BMI may help to identify high-risk individuals and develop clinical strategies to prevent cardiovascular diseases in diabetic population [31].

However, several limitations of the present study should be addressed. First, this study was a single-center observational study, patients' clinical information was collected from the Hospital Information System, although the sample size was large, there were still unforeseeable confounding factors affecting the results. Second, we only recorded lipid levels after statin use, without continuous monitoring after percutaneous coronary intervention. Repeated measurements of the AIP during follow-up may be of further value in predicting MACCEs. Third, other TG-derived metabolic indices, such as visceral adiposity index and lipid accumulation products, were not analyzed because waist circumference was not routinely measured in our cardiovascular center. Moreover, the present results were found in Chinese population and should be discreetly generalizable to other ethnic groups.

Conclusion

Overall, this study has shown the potential predictive power of TG-derived metabolic indices in identifying patients at risk of developing MACCEs. Furthermore, AIP identified as positively associated with MACCEs development in patients with T2DM and CHD, exhibits an independent link with incident cardiovascular outcomes and has provided a valuable model to be used in clinical practice. The findings suggest that monitoring AIP is expected to discover individuals at high risk of MACCEs, providing novel prevention strategy for the clinical management in patients with T2DM and CHD.

Abbreviations

AIP	Atherogenic index of plasma
TyG	Triglyceride-glucose
TyG-BMI	Triglyceride glucose-body mass index
T2DM	Type 2 diabetes
CHD	Coronary heart disease
PCI	Percutaneous coronary intervention
MACCEs	Major adverse cardiac and cerebrovascular events
IR	Insulin resistance
RCS	Restricted cubic spline
ROC	Receiver operating characteristic curve
AUC	Area under curve
DCA	Decision curve analysis
CIC	Clinical impact curve
BMI	Body mass index
OMI	Old myocardial infarction
FCVDs	Familial cardiovascular diseases
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blocker
TC	Total cholesterol
TG	Triglyceride
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
FPG	Fasting plasma glucose
HbA1c	Glycated hemoglobin A1c
PAD	Peripheral arterial disease
baPWV	Brachial-ankle pulse wave velocity
ABI	Ankle-brachial index
FMD	Brachial artery flow-mediated vasodilatation
LAD	Left atrial diameter
LVEF	Left ventricular ejection fraction
LVDd	Left ventricular end-diastolic diameter
PWT	Left ventricular posterior wall thickness

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Author contributions
JL and ST defined the study theme and methods. ST, LY and LH performed the data collection, data analyses and wrote the original manuscript. ST, TX, and DY were responsible for the database establishment. XH and CM checked the data. ST, LY and JL contributed to interpreted the results. All authors made critical revision of the manuscript for important intellectual content and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki. Information related to patient identity was concealed, thus ethics approval and consent for participation is not applicable for this study.

Consent for publication
All authors have consent for publication.

Competing interests
The authors declare no competing interests.

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