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Original Article

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High Triglyceride-Glucose Index is Associated with Poor Cardiovascular Outcomes in Nondiabetic Patients with ACS with LDL-C below 1.8 mmol/L

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Aim: To evaluate the prognostic value of triglyceride-glucose (TyG) index in nondiabetic patients with acute coronary syndrome (ACS) with low-density lipoprotein cholesterol (LDL-C) below 1.8 mmol/L.

Methods: A total of 1655 nondiabetic patients with ACS with LDL-C below 1.8 mmol/L were included in the analysis. Patients were stratified into two groups. The incidence of acute myocardial infarction (AMI), infarct size in patients with AMI, and major adverse cardiac and cerebral event during a median of 35.6-month follow-up were determined and compared between the two groups. The TyG index was calculated using the following formula: ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2].

Results: Compared with the TyG index <8.33 group, the TyG index ≥ 8.33 group had a significantly higher incidence of AMI (21.2% vs. 15.2%, $p=0.014$) and larger infarct size in patients with AMI [the peak value of troponin I: 10.4 vs. 4.8 ng/ml, $p=0.003$; the peak value of Creatine kinase MB: 52.8 vs. 22.0 ng/ml, $p=0.006$; the peak value of myoglobin: 73.7 vs. 46.0 ng/ml, $p=0.038$]. Although there was no significant difference in mortality between the two groups, the incidence of revascularization of the TyG index ≥ 8.33 group was significantly higher than that of the TyG index <8.33 group (8.9% vs. 5.0%, $p=0.035$). A multivariable Cox regression revealed that the TyG index was positively associated with revascularization [hazard ratio, 1.67; 95% confidence interval, 1.02–2.75; $p=0.043$].

Conclusions: In nondiabetic patients with ACS with LDL-C below 1.8 mmol/L, a high TyG index level was associated with higher incidence of AMI, larger infarct size, and higher incidence of revascularization. A high TyG index level might be a valid predictor of subsequent revascularization.

Key words: Triglyceride-glucose (TyG) index, Insulin resistance (IR), Acute coronary syndrome (ACS), Major adverse cardiac and cerebral event (MACCE)

Background

Acute coronary syndrome (ACS) is the leading cause of morbidity and mortality from cardiovascular (CV) disease worldwide[1, 2]. Therefore, identifying patients at high risk of developing major adverse cardiac and cerebral event (MACCE) that may contribute to optimal management is crucial.

Insulin resistance (IR), a hallmark of metabolic syndrome (MetS), is not only associated with an increased risk of CV disease but also significantly correlated with a higher risk of MACCE[3, 4]. However, direct measurement of IR, including the hyperinsulinemic-euglycemic clamp and the homeostasis

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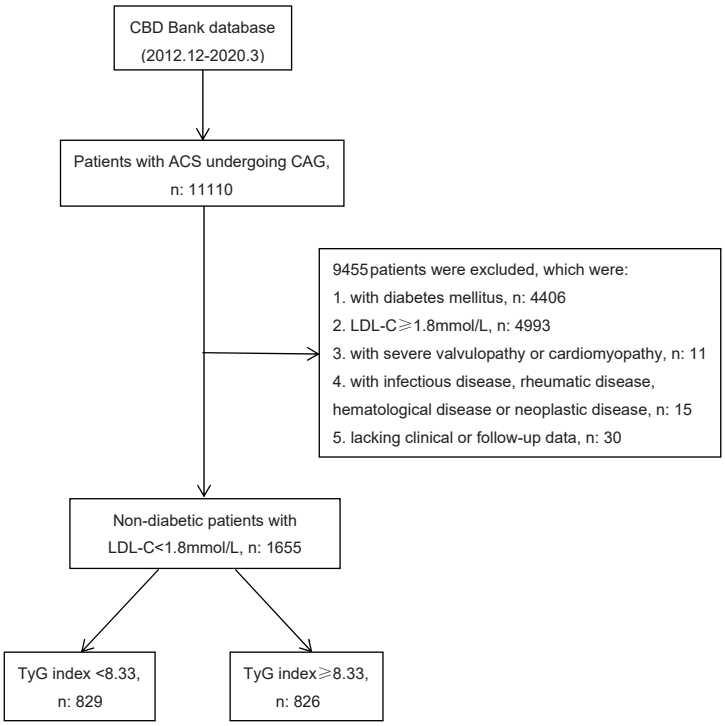

Fig. 1. The flowchart of study subject enrollment

CBD, Cardiovascular Center of Beijing Friendship Hospital Database; ACS, acute coronary syndrome; CAG, coronary angiography; LDL-C, low-density lipoprotein cholesterol; TyG, triglyceride-glucose index.

model assessment of IR (HOMA-IR), are too complex and expensive to be used in large-scale epidemiological studies and clinical practice[5]. Therefore, we urgently need a simple, accessible, and reliable index to quantitively evaluate IR.

High levels of triglyceride (TG) and fasting plasma glucose (FPG) are the important components of MetS. Recently, the triglyceride-glucose (TyG) index, which combines the TG and FPG levels, has been proved as a reliable surrogate marker of IR in clinical practice[6]. In addition, the TyG index has been found to be well correlated with coronary artery disease (CAD)[7-9]. Luo *et al.* firstly reported a positive correlation between the TyG index level and the incidence of MACCE in patients with ST-elevation myocardial infarction (STEMI) who underwent percutaneous coronary intervention (PCI)[10]. Mao *et al.* also found that in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS), the high TyG index group showed significantly increased risk of major adverse cardiac event (MACE) compared with the low TyG index group[11]. To the best of our knowledge, the relationship between the TyG index and CV outcomes in nondiabetic patients with ACS with LDL-C below 1.8 mmol/L remains unknown. Our study was to fill this knowledge gap. Here we aimed to investigate not only the relationship between the TyG index and patient characteristics during hospitalization but also the predictive value of the TyG index on CV outcomes.

Methods

Study Population

Patients' records in the Cardiovascular Center of Beijing Friendship Hospital Database Bank were screened. As shown in **Fig. 1**, the records of 11,110 patients with ACS undergoing coronary angiography from December 2012 to March 2020 in our center were screened. Of the 11,110 patients, 9455 were excluded according to the following exclusion criteria: 1) with diabetes mellitus; 2) with LDL-C ≥ 1.8 mmol/L; 3) with severe valvulopathy or cardiomyopathy; 4) with acute infectious disease, rheumatic disease, hematological disease, or neoplastic disease; and 5) lacking clinical or follow-up data. Finally, 1655 patients were included in this analysis. According to the median value of the TyG index level, 1655 patients were stratified into two groups: the TyG index < 8.33 group (n=829) and the TyG index ≥ 8.33 group (n=826). All patients were followed up until April 30, 2020, with a median follow-up of 35.6 (IQR, 13.2–

51.8) months.

Data Collection and Definition

The data collection process was approved by the Institutional Review Board of Beijing Friendship Hospital affiliated to Capital Medical University and was in accordance with the Declaration of Helsinki.

The concentrations of TG and FPG in the first fasting blood samples during the stay in the hospital, which were obtained after 12 h of fasting, were determined at the central laboratory of Beijing Friendship Hospital. The TyG index was calculated as ln [fasting TG (mg/dL) × FPG (mg/dL)/2] [12]. Patients' demographics, medical and medication history, laboratory test results, and echocardiographic and angiographic evaluation results were collected and verified using an electronic medical recording system. The outcomes from MACCE were collected and recorded during clinical follow-up visits.

MetS was defined when three or more of the following findings were present according to NCEP ATPIII criteria [13]: central obesity, high FPG, high TG, low high-density lipoprotein cholesterol(HDL-C), and high blood pressure. ACS contains unstable angina pectoris (UAP) and acute myocardial infarction (AMI). UAP was diagnosed in patients with unstable chest discomfort (rest, new onset, or worsening of angina) and without elevation of myocardial necrosis markers. AMI was defined as chest pain with new ST-segment changes and elevation of myocardial necrosis markers to at least twice of the upper limit of the normal range. MACCEs included all-cause death, nonfatal MI, nonfatal stroke, revascularization, and cardiac rehospitalization (admission because of angina or heart failure). All-cause death was defined as the incidence of cardiac or noncardiac death. CV death was defined as fatal myocardial infarction, fatal stroke, sudden death, and other CV deaths. Nonfatal stroke, including ischemic and hemorrhagic stroke, was defined as cerebral dysfunction caused by cerebral vascular obstruction or sudden rupture and was diagnosed based on signs of neurological dysfunction or evidence of brain imaging. Any coronary revascularization was defined as a revascularization of the target vessel or nontarget vessels. Cardiac rehospitalization refers to rehospitalization for angina pectoris or heart failure.

Statistical Analyses

Continuous variables are presented as mean ± standard deviation or median (IQR). Comparisons between the two study groups were analyzed using the Student's *t*-test or Mann-Whitney *U*-test. Categorical variables are expressed as number and percentage and compared using the Pearson chi-square test or Fisher's exact test. To control confounding factors, we performed propensity score matching (PSM). The cumulative incidence of MACCE was estimated by Kaplan-Meier survival curves. A multivariable Cox regression analysis was performed to identify independent predictors for MACCE. Baseline variables that were significantly correlated with outcomes by univariate analysis were used in the multivariate model. Correlation analysis among variables was also taken into consideration in multivariate analysis. All analyses were two-tailed, and a P value of <0.05 was considered statistically significant. Data were analyzed using the statistical analysis software IBM SPSS statistics 24.0.

Propensity Score Matching

PSM was used to reduce selection bias in this study. The matching process was conducted with a minimum-distance scoring method and a 1-to-1 match between the TyG index ≥ 8.33 group and the TyG index <8.33 group. In this study, propensity scores were calculated through a binary logistic regression model, including covariates of age, sex, body mass index (BMI), systolic blood pressure (SBP), hemoglobin (HGB), albumin, creatinine, glycated hemoglobin (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, history of smoking and stroke, previous medication history including beta-blocker and statins, and statins treatment during hospitalization. Ultimately, 505 TyG index ≥ 8.33 patients were individually 1:1 matched to 505 TyG index <8.33 controls using nearest available score matching. The statistical analysis software SPSS version 24.0 was used for the matching.

Results

Patient Characteristics

As shown in **Fig. 1**, of the 1655 eligible patients, 829 patients were in the TyG index <8.33 group and 826 patients were in the TyG index ≥ 8.33 group. Comparing with patients in the TyG index <8.33 group, patients in the TyG index ≥ 8.33 group showed a significantly higher BMI, were younger, had lower SBP, had a higher percent of smoker and MetS and lower percent of stroke, and were significantly more likely to receive beta-blocker or statins before hospital admission for ACS. In hospital medical and interventional treatments were similar between the two groups, except for the significantly higher number of patients treated with beta-blocker in the TyG index ≥ 8.33 group than in the TyG index <8.33 group during hospitalization. Laboratory values showed that

the TyG index ≥ 8.33 group had a significantly higher white cell count, HGB, FPG, HbA1c, albumin, creatinine, TG, and LDL-C than the TyG index < 8.33 group. The results of coronary angiography and echocardiography showed no significant difference between the two groups **(Table 1)**.

Propensity Score Matching

The propensity scores of 505 TyG index ≥ 8.33 patients were 1:1 matched to 505 TyG index <8.33 patients. There were no significant differences in baseline clinical characteristics and medical history between the PSM TyG index ≥ 8.33 and TyG index <8.33 groups, except that the PSM TyG index ≥ 8.33 group had a significantly higher FPG and TG and higher percent of MetS **(Table 1)**.

The TyG index ≥ 8.33 group had a significantly higher incidence of AMI at the admission than the TyG index <8.33 group (21.2% vs. 15.2%, $p=0.014$, **Fig. 2**). The peak levels of serum myoglobin (Myo), creatine kinase MB (CKMB), and cardiac troponin I (cTnI) were used to estimate infarct size. The peak levels of serum Myo, CKMB, and cTnI were significantly higher in the TyG index ≥ 8.33 group (pMyo: 73.7 vs. 46.0 ng/ml, $p=0.038$; pCKMB: 52.8 vs. 22.0 ng/ml, $p=0.006$; pTNI: 10.4 vs. 4.8 ng/ml, $p=0.003$, **Table 2**).

Subsequent MACCE and Mortality

During the median follow-up of 35.6 (IQR, 13.2–51.8) months, composite MACCE occurred in 28.2% of patients in the TyG index ≥ 8.33 group and 24.3% in the TyG index <8.33 group [hazard ratio (HR), 1.16; 95% confidence interval (CI), 0.96–1.40; $p=0.117$)]. All-cause death was observed in 3.6% of patients in the TyG index ≥ 8.33 group and 5.0% of patients in the TyG index <8.33 group (HR, 0.71; 95%CI, 0.45–1.14; $p=0.161$). CV death occurred in 2.7% of patients in the TyG index ≥ 8.33 group and 3.4% of patients in the TyG index <8.33 group (HR, 0.77; 95%CI, 0.44–1.35; $p=0.364$). Revascularization occurred in 8.6% of patients in the TyG index ≥ 8.33 group and 4.8% of patients in the TyG index <8.33 group (HR, 1.82; 95%CI, 1.23–2.69; $p=0.003$). Subsequent nonfatal MI, nonfatal stroke, and cardiac rehospitalization were not statistically different between the two groups **(Table 3)**.

After propensity score matching, composite MACCE occurred in 30.9% of patients in the PSM TyG index ≥ 8.33 group and 24.6% in the PSM TyG index <8.33 group (HR, 1.14; 95%CI, 0.90–1.44; $p=0.282$); all-cause death was observed in 4.4% of patients in the PSM TyG index ≥ 8.33 group and 3.8% in the PSM TyG index <8.33 group (HR, 1.01; 95%CI, 0.55–1.87; $p=0.976$); CV death was identified in 3.0% of patients in the PSM TyG index ≥ 8.33 group and 2.8% in the PSM TyG index <8.33 group (HR, 0.96; 95%CI, 0.46–2.00; $p=0.920$); revascularization occurred in 8.9% of patients in the PSM TyG index ≥ 8.33 group and 5.0% in the PSM TyG index <8.33 group (HR, 1.71; 95%CI, 1.04–2.81; $p=0.035$). Subsequent nonfatal MI, nonfatal stroke, and cardiac rehospitalization were not statistically different between the two groups **(Table 3)**.

The Kaplan-Meier curves show that the TyG index ≥ 8.33 group had a significantly higher cumulative rate of subsequent revascularization than the TyG index <8.33 group **(Fig. 3)**. The cumulative rate of all-cause death, CV death, nonfatal MI, nonfatal stroke, cardiac rehospitalization, and composite MACCE were not statistically different between the two groups.

Risk factors for Subsequent Revascularization

Univariate and multivariate analysis results and predictors for revascularization are presented in **Supplemental Table 1**. Univariate analysis revealed that the TyG index, FPG, multivessel/left main (LM) coronary artery lesions, and PCI/Coronary Artery Bypass Graft (CABG) treatment during hospitalization were risk factors for revascularization in patients with ACS (all, $p<0.05$). Correlation analysis displayed that the FPG and TyG indexes had a high correlation ($p<0.001$). Therefore, FPG were not included in the multivariate model. In addition, PCI/CABG treatment during hospitalization was significantly correlated with multivessel/LM coronary artery lesions ($p<0.001$). Therefore, PCI/CABG treatment during hospitalization was also not included in the multivariate model. After adjusting for confounding factors, multivariate analysis found that the TyG index [HR, 1.67; 95%CI, 1.02–2.75; $p=0.043$] and multivessel/LM coronary artery lesions [HR, 3.06; 95%CI, 1.23–7.62; $p=0.016$] were independent predictors of subsequent revascularization in patients with ACS.

Independent Association of the TyG Index with Subsequent Revascularization in Different Subgroups

As shown in **Fig. 4**, the independent predictive effect of the TyG index on subsequent revascularization was mainly reflected in the subgroups of male gender, age <65 years, BMI <25 kg/m^2, smoker, UAP group, estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m^2, HDL-C <1.01 mmol/L, and left ventricular ejection fraction (LVEF) ≥ 50%.

Table 1. Baseline clinical characteristics

Characteristics	Before PS match		*p* value	After PS match		*p* value
	TyG < 8.33 (*n*: 829)	TyG ≥ 8.33 (*n*: 826)		TyG < 8.33 (*n*: 505)	TyG ≥ 8.33 (*n*: 505)	
TyG index	8.0 ± 0.2	8.8 ± 0.7	< 0.001	8.0 ± 0.2	8.7 ± 0.4	< 0.001
Age, years	67.4 ± 10.2	63.9 ± 10.2	< 0.001	65.6 ± 10.5	65.9 ± 9.7	0.674
Male gender	604 (73.1)	619 (74.7)	0.474	364 (72.1)	371 (73.5)	0.621
BMI, kg/m^2	24.8 ± 3.6	26.0 ± 3.2	< 0.001	25.5 ± 3.6	25.6 ± 3.1	0.720
SBP, mmHg	129.2 ± 17.7	127.1 ± 17.8	0.013	128.2 ± 17.6	127.6 ± 17.7	0.599
DBP, mmHg	74.5 ± 11.5	74.6 ± 11.2	0.769	74.7 ± 11.7	74.3 ± 10.5	0.550
Heart rate, bpm	68.9 ± 12.8	68.8 ± 11.5	0.901	68.1 ± 12.3	68.8 ± 11.3	0.398
Medical history						
Current/ex-Smoker	445 (53.9)	491 (59.2)	0.028	276 (54.7)	286 (56.6)	0.526
Hypertension	586 (70.9)	615 (74.2)	0.139	357 (70.7)	37.6 (74.5)	0.180
Stroke	194 (23.5)	148 (17.9)	0.005	97 (19.2)	107 (21.2)	0.433
OMI	119 (14.4)	111 (13.4)	0.550	75 (14.9)	70 (13.9)	0.654
Previous PCI/CABG	298 (36.1)	295 (35.6)	0.835	199 (39.4)	171 (33.9)	0.067
MetS	148 (17.9)	378 (45.8)	< 0.001	107 (21.2)	177 (35.0)	< 0.001
Medication used before admission						
Antiplatelet agent	518 (62.7)	521 (62.8)	0.955	330 (65.3)	304 (60.2)	0.091
ACEI/ARB	299 (36.2)	329 (39.7)	0.144	183 (36.2)	204 (40.4)	0.174
Beta-blocker	213 (25.8)	275 (33.2)	0.001	149 (29.5)	138 (27.3)	0.443
CCB	297 (36.0)	314 (37.9)	0.418	184 (36.4)	189 (37.4)	0.744
Diuretics	42 (5.1)	57 (6.9)	0.124	25 (5.0)	26 (5.1)	0.886
Statins	348 (42.1)	397 (47.9)	0.019	233 (46.1)	224 (44.4)	0.569
Laboratory values						
WBC, 10^9/L	6.4 ± 2.0	6.9 ± 2.3	< 0.001	6.4 ± 1.9	6.6 ± 2.2	0.215
Neutrophil ratio, %	66.6 ± 9.0	65.8 ± 9.0	0.065	66.3 ± 8.9	66.1 ± 9.3	0.775
Hemoglobin, g/L	134.2 ± 15.1	137.6 ± 15.6	< 0.001	135.9 ± 15.1	135.8 ± 15.7	0.912
FPG, mmol/L	4.8 ± 0.6	5.4 ± 0.9	< 0.001	4.8 ± 0.5	5.4 ± 0.9	< 0.001
HbA1c, %	5.7 ± 0.4	5.8 ± 0.5	< 0.001	5.7 ± 0.5	5.6 ± 0.6	0.538
Albumin, g/L	39.9 ± 3.6	40.7 ± 3.7	< 0.001	40.4 ± 3.5	40.4 ± 3.9	0.926
Creatinine, umol/L	74.1 (65.2, 86.0)	76.0 (66.0, 88.6)	0.038	74.2 (64.9, 86.0)	75.3 (66.0, 88.0)	0.176
eGFR, ml/min/1.73 m^2	84.8 (70.9, 98.2)	85.3 (71.5, 98.2)	0.664	85.5 (72.5, 99.9)	83.3 (70.5, 96.0)	0.077
TC, mmol/L	3.1 ± 0.4	3.1 ± 0.4	0.102	3.1 ± 0.4	3.1 ± 0.4	0.611
TG, mmol/L	0.8 ± 0.2	1.6 ± 0.7	< 0.001	0.8 ± 0.2	1.4 ± 0.4	< 0.001
LDL-C, mmol/L	1.5 ± 0.1	1.6 ± 0.2	< 0.001	1.5 ± 0.2	1.5 ± 0.2	0.311
HDL-C, mmol/L	1.2 ± 0.3	1.0 ± 0.3	< 0.001	1.1 ± 0.3	1.1 ± 0.2	0.878
Echocardiography						
LVEF, %	63.9 ± 9.7	64.6 ± 8.4	0.094	63.9 ± 9.4	64.3 ± 8.7	0.554
Angiography findings						
Multi-vessel/LM	665 (80.5)	683 (82.4)	0.325	279 (55.2)	287 (56.8)	0.612
Proximal LAD	382 (46.2)	399 (48.1)	0.443	230 (45.5)	249 (49.3)	0.231
In-hospital treatment						
PCI/CABG	461 (55.8)	484 (58.4)	0.290	279 (55.2)	287 (56.8)	0.612
Antiplatelet agent	794 (96.1)	800 (96.5)	0.685	485 (96.0)	489 (96.8)	0.497
ACEI/ARB	415 (50.2)	418 (50.4)	0.942	250 (49.5)	253 (50.1)	0.850
Beta-blocker	534 (64.6)	579 (69.8)	0.024	347 (68.7)	336 (66.5)	0.459
CCB	297 (36.0)	316 (38.1)	0.363	184 (36.4)	191 (37.8)	0.648
Diuretics	72 (8.7)	71 (8.6)	0.912	39 (7.7)	41 (8.1)	0.816
Statins	742 (89.8)	754 (91.0)	0.438	454 (89.9)	458 (90.7)	0.671
Hospital stay, day	5 (4, 7)	5 (4, 7)	0.778	5 (4, 7)	6 (4, 7)	0.938

Dates are presented as mean ± SD, median (IQR) or number (%).

TyG, triglyceride-glucose index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; OMI, old myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MetS, metabolic syndrome; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB; calcium channel blocker; WBC, white blood cell; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending.

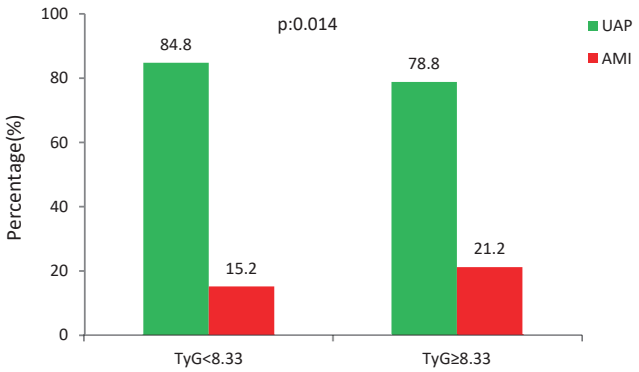

Fig. 2. Percentages of patients with UAP and AMI in the two groups
TyG, triglyceride-glucose index; UAP, unstable angina pectoris; AMI, acute myocardial infarction.

Table 2. The estimated infarction size in patients with AMI

The peak value of myocardial enzyme	Before PS match		*P* value	After PS match		*P* value
	TyG < 8.33 (*n*: 135)	TyG ≥ 8.33 (*n*: 168)		TyG < 8.33 (*n*: 77)	TyG ≥ 8.33 (*n*: 107)	
pMyo, ng/ml	51.5 (23.8, 143.8)	73.7 (26.8, 189.0)	0.123	46.0 (22.1, 136.5)	73.7 (27.7, 176.0)	0.038
pCK-MB, ng/ml	26.5 (5.9, 78.8)	54.1 (8.5, 156.0)	0.017	22.0 (6.0, 73.3)	52.8 (12.8, 153.0)	0.006
pTNI, ng/ml	5.5 (0.9, 18.8)	10.5 (1.7, 32.3)	0.008	4.8 (0.7, 16.1)	10.4 (2.4, 36.3)	0.003

Data are presented as IQR
AMI, acute myocardial infarction; TyG, triglyceride-glucose index; pMyo, The peak value of myoglobin; pCK-MB, The peak value of Creatine kinase MB; pTNI, The peak value of troponin I.

Table 3. Clinical events during long-term follow-up

	TyG < 8.33	TyG ≥ 8.33	HR (95%CI)	*p* value
Overall population				
Number	829	826		
Composite MACCE	201 (24.3)	234 (28.2)	1.16 (0.96,1.40)	0.117
All cause death	41 (5.0)	30 (3.6)	0.71 (0.45,1.14)	0.161
CV death	28 (3.4)	22 (2.7)	0.77 (0.44,1.35)	0.364
Non-fatal MI	21 (2.5)	25 (3.0)	1.15 (0.64,2.06)	0.635
Non-fatal stroke	17 (2.1)	21 (2.5)	1.19 (0.63,2.26)	0.596
Revascularization	40 (4.8)	71 (8.6)	1.82 (1.23,2.69)	0.003
Cardiac rehospitalization	158 (19.1)	186 (22.4)	1.16 (0.94,1.44)	0.168
Matched population				
Number	505	505		
Composite MACCE	124 (24.6)	156 (30.9)	1.14 (0.90,1.44)	0.282
All cause death	19 (3.8)	22 (4.4)	1.01 (0.55,1.87)	0.976
CV death	14 (2.8)	15 (3.0)	0.96 (0.46,2.00)	0.920
Non-fatal MI	9 (1.8)	16 (3.2)	1.56 (0.69,3.54)	0.288
Non-fatal stroke	9 (1.8)	16 (3.2)	1.53 (0.67,3.46)	0.312
Revascularization	25 (5.0)	45 (8.9)	1.71 (1.04,2.81)	0.035
Cardiac rehospitalization	101 (20.0)	121 (24.0)	1.07 (0.82,1.39)	0.629

Dates are presented as number (%) or median (IQR).
TyG, triglyceride-glucose index; MACCE, major adverse cardiac and cerebral event; CV, cardiovascular; MI, myocardial infarction; HR, hazard ratio; CI, confidence interval.

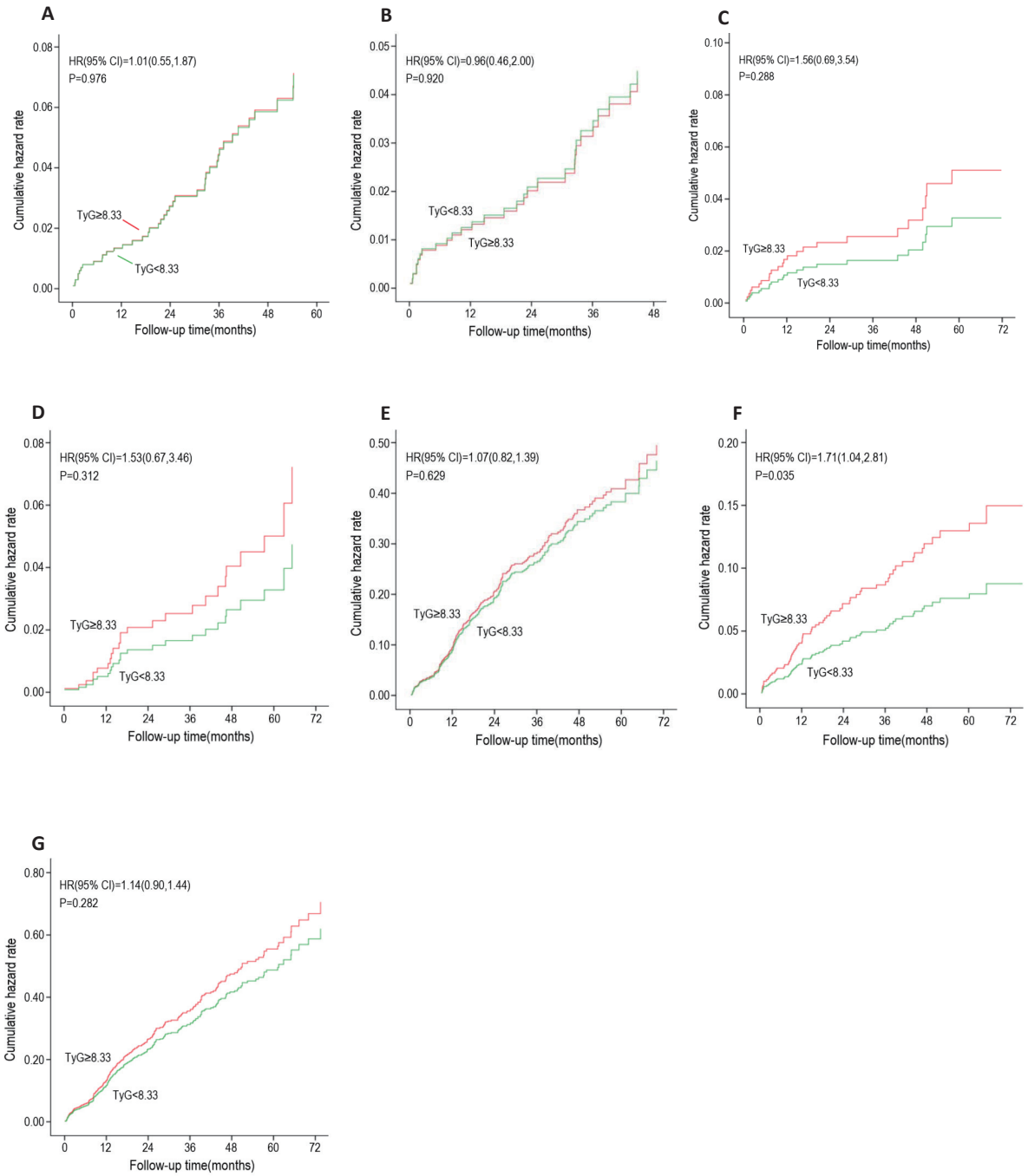

Fig. 3. Kaplan-Meier curves for all-cause death (A), CV death (B), nonfatal MI (C), nonfatal stroke (D), cardiac rehospitalization (E), revascularization (F), and composite MACCE (G) of the TyG <8.33 group (green line) versus the TyG ≥ 8.33 group (red line)

TyG, triglyceride-glucose index; CV, cardiovascular; MI, myocardial infarction; MACCE, major adverse cardiac and cerebral event; HR, hazard ratio; CI, confidence interval.

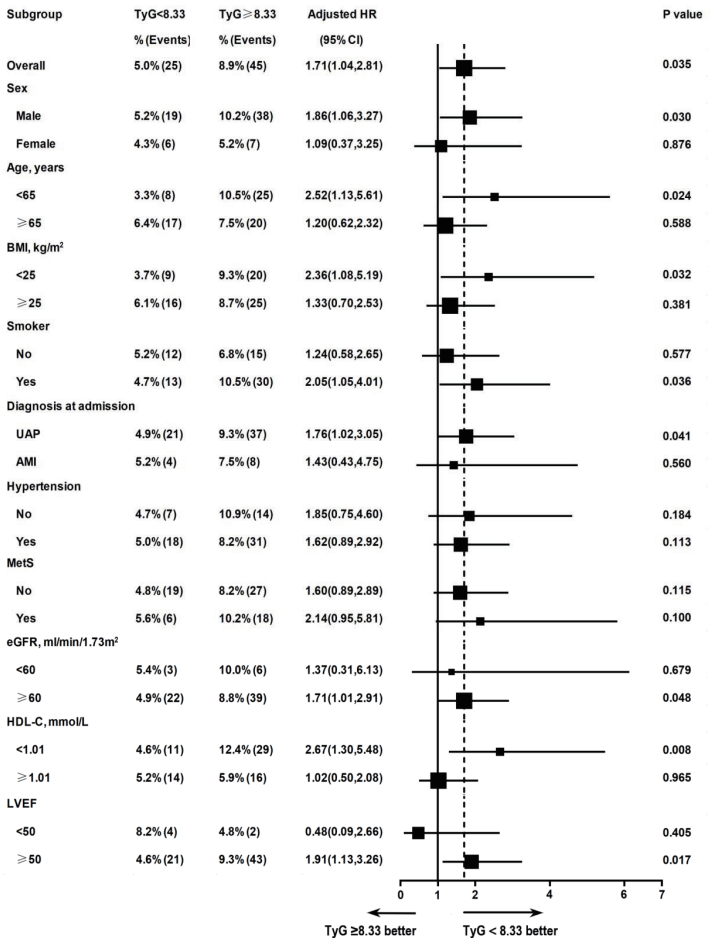

Fig. 4. Forest plot of revascularization according to different subgroups

The prespecified subgroups of interest in this analysis are sex, age, BMI, smoker, diagnosis at admission (UAP/AMI), hypertension, MetS, eGFR, HDL-C, and LVEF. The dashed vertical line represents the hazard ratio for the overall study population. The box sizes are proportional to the precision of the estimates (with larger boxes indicating a greater degree of precision). TyG, triglyceride-glucose index; BMI, body mass index; UAP, unstable angina pectoris; AMI, acute myocardial infarction; MetS, metabolic syndrome; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; LM, left main coronary artery; HR, hazard ratio; CI, confidence interval.

Discussion

To the best of our knowledge, the current study was the first to investigate whether the TyG index could be associated with patient characteristics during hospitalization and subsequent CV outcomes in nondiabetic patients with ACS with LDL-C below 1.8 mmol/L. Our main findings include the following: in nondiabetic patients with ACS with LDL-C below 1.8 mmol/L, (1) the high TyG index group had a significantly higher incidence of AMI and larger infarct size than the low TyG index group; (2) the incidence of subsequent revascularization of the high TyG index group was significantly higher than that of the low TyG index group; (3) the high TyG index was an independent predictor of subsequent revascularization; and (4) the independent predictive effect of TyG index on revascularization was mainly reflected in the subgroups of male gender, age <65 years, BMI <25 kg/m^2, smoker, UAP group, eGFR ≥ 60 ml/min/1.73 m^2, HDL-C <1.01 mmol/L, and LVEF $\geq 50\%$.

IR, a hallmark of MetS, is defined as a decrease in the efficiency of insulin in promoting glucose uptake and utilization. IR can induce glucose metabolism imbalance, which leads to chronic hyperglycemia and then in turn triggers oxidative stress and causes inflammatory responses. In addition, IR can alter systemic lipid metabolism, including increased TG levels, decreased HDL-C levels, increased small dense low-density lipoproteins, and

excessive postprandial lipemia. Moreover, IR can also cause endothelial dysfunction by decreasing nitric oxide production from endothelial cells and increasing procoagulant factor release. Therefore, it is easy to understand that IR has been proven to contribute to the progression of CV disease[14, 15] due to the above mechanisms. However, traditional measurement of IR, including the hyperinsulinemic-euglycemic clamp and HOMA-IR, are too complex and expensive to be used in clinical practice on a large scale. In recent years, researchers have tried to find a simpler and more valid surrogate marker of IR.

As is known to all, high levels of TG and FPG are the components of MetS. Recently, the TyG index, a composite indicator composed of TG and FPG, has been demonstrated as a reliable marker of IR[6, 12, 16] and has a high sensitivity and specificity for identifying MetS[17]. Previous studies reported that the TyG index is a simple, cost effective surrogate marker of IR compared to HOMA-IR[18, 19]. It was demonstrated that the TyG index was a useful predictor of type 2 diabetes mellitus (T_2DM)[20, 21], which contributed to CV disease risk. Studies have also shown an association of the TyG index with arterial stiffness[22, 23], stroke[24], carotid atherosclerosis[25], coronary artery calcification[7], and coronary artery stenosis[8]. Subsequently, several studies were conducted and found a positive relationship between the TyG index and CV disease. It has been reported that the TyG index may contribute to the early identification of apparently healthy individuals at high risk for CV events[26-28]. Jin *et al.* revealed that the TyG index was positively associated with CV event risk [HR, 1.36; 95%CI, 1.10–1.69; $p=0.005$] in patients with stable CAD[29]. The findings of Luo *et al.* showed that the TyG index was significantly associated with an increased risk of MACCE in patients with STEMI within 1 year after PCI [HR, 1.53; 95%CI, 1.01–2.06; $p=0.003$][10]. It was demonstrated that the TyG index was an independent predictor of MACE [HR, 1.88; 95%CI, 1.13–3.12; $p=0.015$] in patients with NSTE-ACS[11]. Jin *et al.* [30] and Su *et al.*[31] found that both TyG index and HbA1c could predict CV outcomes in patients with T_2DM, while the TyG index might be better. Unfortunately, no data is currently available with regard to the effects of TyG index on clinical outcomes in nondiabetic patients with ACS, especially those with LDL-C lower than 1.8 mmol/L. Recently, Alizargar *et al.* questioned the conclusion that the TyG index can be used to predict CV events in patients with CAD, considering that it might be influenced by diabetes and the hyperlipidemic state that led to CV disease[32]. Therefore, to avoid the mixed effects of diabetes and hyperlipidemia on CV events, we only analyzed nondiabetic patients with ACS and LDL-C below 1.8 mmol/L, which was the novelty of this study.

We found that higher TyG index levels had no significant effect on the incidence of all-cause death, CV death, and composite MACCE. However, our study indicated an association between higher TyG index levels and an increased risk of subsequent revascularization for the first time, and the TyG index might be a valid predictor of subsequent revascularization in nondiabetic patients with ACS with LDL-C below 1.8 mmol/L. This finding might be greatly of interest. A high TyG index level still has a significant impact on the risk of subsequent revascularization; after all, patients without diabetes and with LDL-C below 1.8 mmol/L seem to be a relatively low-risk group for CV events in follow-up. In addition, we found that the independent predictive effect of TyG index on subsequent revascularization was mainly reflected in the subgroups of male gender, age <65 years, BMI <25 kg/m^2, smoker, UAP group, eGFR ≥ 60 ml/min/1.73 m^2, HDL-C <1.01 mmol/L, and LVEF $\geq 50\%$. This finding implied that using the TyG index for early risk stratification in the above subgroups may have more important clinical significance. Notably, in the AMI subgroup, the cumulative hazard curve **(Supplemental Fig. 1)** showed that the curve of TyG ≥ 8.33 group was above the curve of TyG <8.33 group, and the two curves markedly diverged. However, the adjusted HR (95%CI) value was 1.43 (0.43–4.75), and the p value was not statistically significant, which may be related to the small sample size ($n=187$) in this group. In the future, we need to verify the predictive effect of the TyG index on revascularization in the AMI subgroup on the basis of large sample size.

Perhaps readers will have doubts about these findings. Why was the TyG index only associated with revascularization? This can be explained from the following two sides. First of all, Zhang *et al.* showed that the risk of incident T_2DM is increased with increasing TyG index[20-21]. In our study, patients in the higher TyG index group were more likely to develop diabetes during follow-up. This meant that they were more likely to develop multivessel CAD, which would inevitably lead to an increased incidence of revascularization. Unfortunately, we were unable to obtain blood samples from patients during follow-up to determine whether they had developed diabetes because the study was retrospective. In addition, Mao *et al.* found that the TyG index might be an independent predictor of CAD severity as evaluated by the SYNTAX Score[11]. This meant that the severity of coronary atherosclerotic lesions is more severe in

patients with higher TyG index levels. There is no doubt that the proportion of patients receiving revascularization in the high TyG index group will be significantly higher than that in the low TyG index group.

Although the mechanism underlying the association of the TyG index with the development of arteriosclerosis has not been elucidated, it may be linked to IR[33]. As mentioned before, several metabolic changes caused by IR can induce the development of arteriosclerosis. Moreover, IR accompanied by hyperglycemia and hypertriglyceridemia has been proved to be correlated with elevated plasminogen activator inhibitor-1 levels, leading to decreased fibrinolytic activity and increased thrombotic events[34, 35].

Luo *et al.*[10] and Mao *et al.*[11] demonstrated that the TyG index was an independent predictor of CV events in STEMI and NSTE-ACS population, respectively. The cutoff value of the former was TyG ≥ 9.608 and that of the latter was TyG ≥ 8.805. In this study, we found that a high TyG index level was an independent predictor of subsequent revascularization in nondiabetic patients with ACS with LDL-C < 1.8 mmol/L. We proposed the cutoff point of TyG ≥ 8.33, which was significantly lower than that in previous studies. The main reason is that patients with diabetes and hyperlipemia have been excluded in this study, whereas previous studies have not. Therefore, the cutoff value of the TyG index in this study might be lower than that in previous studies.

Limitations

The present study has several limitations. Firstly, this was a single-center study, the sample size might be not large enough, and the follow-up time might be not long enough; thus, generalization of the findings should be cautious. Secondly, laboratory parameters were only measured once after hospital admission, which could cause potential bias due to measurement error. Thirdly, this was a retrospective observational study. The information on the levels of the TyG index during follow-up was limited. Hence, prospective cohort studies with larger sample and longer follow-up time are required to confirm our findings.

Conclusions

In nondiabetic patients with ACS with LDL-C below 1.8 mmol/L, the high TyG index group had a significantly higher incidence of AMI and larger infarct size than the low TyG index group. In addition, the incidence of subsequent revascularization of the high TyG index group was significantly higher than that of the low TyG index group, and a high TyG index level was an independent predictor of subsequent revascularization.

List of Abbreviations

TyG: Triglyceride-glucose; IR: Insulin resistance; ACS: Acute coronary syndrome; LDL-C: Low-density lipoprotein cholesterol; AMI: Acute myocardial infarction; MACCE: Major adverse cardiac and cerebral event; cTNI: Cardiac troponin I; CKMB: Creatine kinase MB; Myo: Myoglobin; MetS: Metabolic syndrome; HOMA-IR: the Homeostasis model assessment of IR; TG: Triglyceride; FPG: Fasting plasma glucose; STEMI: ST-elevation myocardial infarction; PCI: Percutaneous coronary intervention; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; MACE: Major adverse cardiac event; UAP: Unstable angina pectoris; CV: Cardiovascular; PSM: Propensity score matching; BMI: Body mass index; SBP: Systolic blood pressure; HGB: Hemoglobin; HbA1c: Glycated hemoglobin; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LM: left main coronary artery; CABG: Coronary Artery Bypass Grafting; CAD: Coronary artery disease; T_2DM: Type 2 diabetes mellitus.

Declarations

Ethics approval and Consent to Participate

The study data collections were approved by the Institutional Review Board of Beijing Friendship Hospital affiliated to Capital Medical University, and written informed consent was obtained from all patients.

Consent for Publication

Consent to publish from the participant to report individual patient data: not

applicable (no patient identifier or personalized data shown).

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions

YZ performed study, statistical analysis and wrote manuscript. XSD, BH, QBL and HG participated in study data collection. HC contributed discussion and edited manuscript. XQZ designed study and revised manuscript. WPL designed study, performed statistical analysis and edited manuscript. HWL provided funding support, designed study and reviewed manuscript. All authors read and approved the final manuscript.

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Availability of Data and Materials

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

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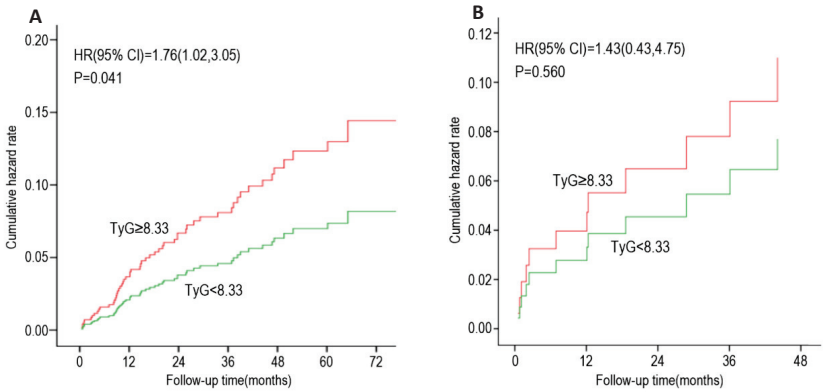
Supplemental Table 1. Multivariate COX regression analysis of revascularization

	Univariate		Multivariate	
	HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
TyG index ≥ 8.33	1.71 (1.04, 2.81)	0.035	1.67 (1.02, 2.75)	0.043
Age, y	1.01 (0.98, 1.03)	0.526		
Male gender	1.50 (0.82, 2.75)	0.187		
BMI, kg/m^2	1.05 (0.98, 1.13)	0.203		
SBP, mmHg	1.01 (0.99, 1.02)	0.126		
DBP, mmHg	1.01 (0.99, 1.03)	0.490		
Heart rate, bpm	0.99 (0.97, 1.02)	0.572		
Medical history				
Current/ex-Smoker	1.13 (0.70, 1.84)	0.613		
Hypertension	0.89 (0.53, 1.49)	0.655		
Stroke	0.82 (0.43, 1.56)	0.537		
OMI	1.61 (0.91, 2.85)	0.105		
Previous PCI/CABG	1.06 (0.65, 1.73)	0.820		
MetS	1.54 (0.91, 2.28)	0.153		
Medication used before admission				
Antiplatelet agent	0.85 (0.53, 1.38)	0.517		
ACEI/ARB	0.88 (0.54, 1.44)	0.609		
Beta-blocker	0.78 (0.45, 1.36)	0.383		
CCB	0.88 (0.54, 1.45)	0.620		
Diuretics	0.87 (0.28, 2.78)	0.819		
Statins	0.81 (0.50, 1.32)	0.403		
Laboratory values				
WBC, 10^9/L	0.93 (0.82, 1.06)	0.288		
Neutrophil ratio, %	0.99 (0.96, 1.01)	0.321		
Hemoglobin, g/L	0.99 (0.98, 1.02)	0.852		
FPG, mmol/L	1.31 (1.04, 1.65)	0.020		
HbA1c, %	1.52 (0.92, 2.50)	0.156		
Albumin, g/L	0.95 (0.90, 1.02)	0.139		
Creatinine, umol/L	1.01 (0.99, 1.02)	0.182		
eGFR, ml/min/1.73 m^2	0.99 (0.98, 1.01)	0.244		
TC, mmol/L	1.02 (0.55, 1.87)	0.953		
TG, mmol/L	1.44 (0.88, 2.35)	0.149		
LDL-C, mmol/L	2.02 (0.60, 6.80)	0.255		
HDL-C, mmol/L	0.51 (0.19, 1.41)	0.193		
Echocardiography				
LVEF, %	0.99 (0.97, 1.02)	0.631		
Angiography findings				
Mutil-vessel/LM	3.11 (1.25, 7.74)	0.015	3.06 (1.23, 7.62)	0.016
Proximal LAD	1.01 (0.63, 1.63)	0.956		
In-hospital treatment				
PCI/CABG	2.31 (1.35, 3.96)	0.002		
Antiplatelet agent	2.43 (0.34, 17.5)	0.379		
ACEI/ARB	0.82 (0.51, 1.31)	0.403		
Beta-blocker	1.17 (0.70, 1.97)	0.549		
CCB	0.85 (0.52, 1.40)	0.534		
Diuretics	0.82 (0.30, 2.25)	0.697		
Statins	0.87 (0.40, 1.91)	0.735		

Correlation analysis showed that FPG and TyG index ≥ 8.33 had a high correlation ($p<0.001$). In addition, PCI/CABG treatment during hospitalization was significantly correlated with multi-vessel/LM coronary artery lesions ($p<0.001$). Therefore, FPG and PCI/CABG treatment during hospitalization were not included in the multivariate model.



Supplemental Fig. 1. Cumulative hazard curves for revascularization of the TyG < 8.33 group(green line) versus the TyG ≥ 8.33 group(red line) in UAP (A) and AMI (B) subgroups

TyG, triglyceride-glucose index; UAP, unstable angina pectoris; AMI, acute myocardial infarction; HR, hazard ratio; CI, confidence interval.