Predictive Effect of Triglyceride-Glucose Index on Clinical Events In Patients With Type 2 Diabetes Mellitus and Acute Myocardial Infarction: Results From an Observational Cohort Study In China

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Original investigation

Keywords: Insulin resistance (IR), triglyceride-glucose index (TyG index), type 2 diabetes mellitus (T2DM) , acute myocardial infarction (AMI), major adverse cardiac and cerebral events (MACCEs)

Posted Date: December 1st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-115412/v1

Version of Record: A version of this preprint was published on February 11th, 2021. See the published version at https://doi.org/10.1186/s12933-021-01236-3.

Abstract

Background: Triglyceride glucose (TyG) index is considered a reliable alternative marker of insulin resistance and an independent predictor of cardiovascular outcomes. However, the prognostic value of TyG index in patients with type 2 diabetes mellitus (T_2DM) and acute myocardial infarction (AMI) remains unclear.

Methods: A total of 1932 consecutive patients with T_2DM and AMI were enrolled in this study. Patients were divided into tertiles according to their TyG index levels. The incidences of major adverse cardiac and cerebral events (MACCEs), including all-cause death, non-fatal MI, non-fatal stroke, cardiac rehospitalization and revascularization, were recorded. The TyG index was calculated as the ln [fasting triglycerides (mg/dL) ×fasting plasma glucose (mg/dL)/2].

Results: Kaplan-Meier curves showed that the incidences of cardiac rehospitalization (p=0.001), revascularization (p<0.001) and composite MACCEs (p=0.027) increased with TyG index tertiles. Multivariable Cox regression models revealed that the TyG index was positively associated with all-cause death, cardiovascular death, cardiac rehospitalization, revascularization and composite MACCEs. The addition of TyG index to a baseline risk model had an incremental effect on the predictive value for composite MACCEs [AUC: 0.663 vs. 0.708, p<0.001].

Conclusions: The TyG index was significantly associated with MACCEs, suggesting that the TyG index may be a valid marker for risk stratification and prognosis in patients with T_2DM and AMI.

Trial registration: retrospectively registered

Background

Acute myocardial infarction (AMI) has been recognized as the leading cause of morbidity and mortality of cardiovascular diseases(CVDs) worldwide[1]. The World Bank estimated that the number of individuals with MI in China will increase to 23 million by 2030[2]. What's more, some AMI patients remain at high risk for recurrent cardiovascular events(CVEs) despite the use of current guideline-recommended treatment. This risk is particularly high among patients with type 2 diabetes mellitus (T_2DM), accounting for approximately 37% of AMI cases in China, and is classified as extreme-risk group for recurrent CVEs[3]. Studies have shown that T_2DM is significantly correlated with more complex coronary lesions and worse prognosis in AMI patients[4, 5].Therefore, early identification of the residual risk factors of AMI patients with T_2DM is crucial for better clinical management to reduce future CVEs.

Insulin resistance (IR), a crucial mediator of metabolic disorders, not only contributes to the pathogenesis of CVDs, but also correlates with adverse CV outcomes[6–8]. Although the hyperinsulinemic-euglycemic clamp is the gold-standard test for IR assessment[9], it is not commonly used in clinical settings and large population studies due to the complex testing process[10]. Given that IR is significantly associated with

the chronic increase in plasma glucose and triglycerides(TGs)[11], researchers hypothesized that the combination of plasma glucose and TGs might predict IR. Triglyceride glucose (TyG) index, which combines fasting plasma glucose (FPG) and TGs levels, has been shown to be significantly correlated with IR measured by the hyperinsulinaemic-euglycaemic clamp test[12] and even performed better than homeostasis model assessment of IR (HOMA-IR)[13]. The TyG index was regarded as a reproducible, reliable, and valid surrogate marker of IR[12, 14, 15]. Numerous studies have indicated that the TyG index was significantly correlated with the occurrence of CVDs and poor CV prognosis[16–25]. However, no previous study has exclusively investigated the predictive value of the TyG index for adverse CVEs in AMI patients with T_2DM. Our study was to fill this knowledge gap.

Methods

Study population

Study subjects were identified from the Cardiovascular Center of Beijing Friendship Hospital Database (CBD) Bank. The patient flowchart is presented in Fig. 1. A total of 5169 consecutive patients were diagnosed with AMI and underwent coronary angiography from January 2013 to August 2020. Of the 5169 patients, 3237 were excluded according to the exclusion criteria, which were 1) without T_2DM, 2) with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 or chronic dialysis, severe hepatic dysfunction, acute infection, malignant tumor, suspected familial hypertriglyceridemia [plasma TG ≥ 5.65 mmol/L], 3) with cardiogenic shock, prior coronary artery bypass graft (CABG), severe valvulopathy or congenital heart disease requiring cardiac surgery, 4) lack of clinical or follow-up data. Finally, 1932 patients were included in this analysis. The patients were divided into tertiles according to their TyG index levels (TyG index < 8.94 group, n = 644; 8.94 ≤ TyG index < 9.56 group, n = 644; TyG index ≥ 9.56 group, n = 644). All patients were followed up till October 31, 2020 with a median follow up of 26.8 (IQR: 12.4, 50.7) months.

Data Collections And Definitions

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 TGs 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 TGs (mg/dL) × FPG (mg/dL) /2][12]. Patients' demographics, medical history, laboratory test results, echocardiographic, and angiographic evaluation results were collected and verified using an electronic medical recording system. The outcomes from MACCEs were collected and recorded during clinical follow-up visits.

Criteria for T_2DM include: 1) previously diagnosed T_2DM under treatment of antidiabetic medication; 2) the typical symptoms of DM with a FPG ≥ 7.0 mmol/L, and/or random blood glucose(RBG) ≥ 11.1 mmol/L, and/or 2-h plasma glucose level after oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L[26]. AMI, including non-ST-segment elevation myocardial infarction(NSTEMI) and ST-elevation myocardial infarction(STEMI), 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, non-fatal MI, non-fatal stroke, cardiac rehospitalization (admission because of angina or heart failure), and revascularization. CV death was defined as fatal stroke and MI, sudden death, and other cardiac death. All-cause death was defined as the incidence of CV death or non-CV death. Non-fatal 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. Cardiac rehospitalization refers to rehospitalization for angina pectoris or heart failure. Any coronary revascularization was defined as a revascularization of the target vessel or non-target vessels.

Statistical Analyses

Continuous variables were presented as mean ± standard deviation (SD) or median (IQR). Comparisons between the 3 groups were analyzed by Student's *t*-test or Mann-Whitney U-test. Categorical variables were expressed as number and percentage and compared using the Pearson chi-square test or Fisher's exact test. The cumulative incidence of MACCEs was estimated by Kaplan-Meier curves, and the groups were compared using the log-rank test. A multivariable Cox regression analysis was performed in order to determine whether TyG index was an independent predictor for MACCEs, and to identify other predictors of MACCEs. Baseline variables that were significantly correlated with MACCEs by univariate analysis and clinically relevant were entered into the multivariate model. Also, intercorrelations among variables were taken into consideration in the multivariate analysis. The receiver operating characteristic (ROC) curve analysis was used to evaluate the incremental effect of the TyG index beyond baseline risk model for MACCEs. All analyses were two-tailed and P value < 0.05 was considered statistically significant. Data were analyzed using IBM SPSS statistics 24.

Results

Baseline characteristics of patients

Patient characteristics were listed in **Table 1**. The study patients had an average age of 65.4 ± 12.0 years and 1324 (68.5%) patients were male. The mean levels of TyG index of the three groups were 8.54 ± 0.32, 9.24 ± 0.18 and 10.09 ± 0.46, respectively.

There were significant differences (p < 0.05) among the three groups in terms of

Table 1. Baseline clinical characteristics of patients stratified by the optimal cutoff point of TyG index.

Variable	TyG < 8.94	8.94 ≤ TyG < 9.56	TyG ≥ 9.56	P value
	n = 644	n = 644	n = 644	
TyG index	8.54 ± 0.32	9.24 ± 0.18	10.09 ± 0.46	< 0.001
Age, years	69.1 ± 10.8	65.2 ± 11.4	61.8 ± 12.6	< 0.001
Male gender	469(72.8)	422(65.5)	433(67.2)	0.013
BMI, kg/m^2	25.0 ± 3.5	26.0 ± 3.4	26.4 ± 3.6	< 0.001
SBP, mmHg	130.4 ± 21.1	129.6 ± 21.6	132.6 ± 23.9	0.088
DBP, mmHg	72.5 ± 11.8	73.8 ± 12.8	75.2 ± 13.1	0.002
Medical history				
Current/ex-Smoker	358(55.6)	368(57.1)	376(58.4)	0.597
Duration of diabetes, years	8.0(1.0,14.0)	5.0(1.0,10.0)	6.0(1.0,11.0)	0.058
CKD	39(6.1)	36(5.6)	38(5.9)	0.936
stroke	149(23.1)	144(22.4)	103(16.0)	0.002
Hypertension	486(75.5)	490(76.1)	474(73.6)	0.563
Dyslipidemia	305(47.4)	317(49.2)	309(48.0)	0.793
Previous MI	88(13.7)	68(10.6)	62(9.6)	0.056
Past PCI	121(18.8)	98(15.2)	102(15.8)	0.184
Medication used before admission				

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; CKD, chronic kidney disease; MI, myocardial infarction;

PCI, percutaneous coronary intervention; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; WBC, white blood cell; Hs-CRP, hypersensitive C-reactive protein; RBG, random blood glucose; 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; NSTEMI, Non-ST-segment elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending; CABG, coronary artery bypass graft.

Table 1. Baseline clinical characteristics of patients stratified by the optimal cutoff point of TyG index.

Antiplatelet agent	196(30.4)	209(32.5)	213(33.1)	0.569
ACEI/ARB	215(33.4)	196(30.4)	179(27.8)	0.093
Beta-blocker	90(14.0)	102(15.8)	99(15.4)	0.623
Statins	146(22.7)	141(21.9)	117(18.2)	0.105
Laboratory values				
WBC, 10^9/L	7.5(5.9,9.1)	8.1(6.5,10.2)	8.9(7.0,10.8)	< 0.001
Hemoglobin, g/L	127.5 ± 19.4	132.9 ± 19.3	136.6 ± 20.2	< 0.001
Hs-CRP, mg/L	9.5(4.7,12.1)	9.8(5.5,12.3)	10.0(6.2,12.5)	< 0.001
RBG at admission, mmol/L	9.0(7.0,11.8)	11.3(8.7,14.4)	13.3(10.0,16.4)	< 0.001
FPG, mmol/L	6.6 ± 1.8	8.6 ± 2.6	11.1 ± 3.6	< 0.001
HbA1c, %	7.1 ± 1.3	7.7 ± 1.6	8.5 ± 1.7	< 0.001
Albumin, g/L	35.1 ± 3.0	36.1 ± 3.3	36.9 ± 3.1	< 0.001
Creatinine, umol/L	83.0(70.1,99.1)	78.2(66.9,94.0)	81.0(68.0,96.0)	0.004
eGFR, ml/min/1.73 m^2	77.8(60.0,95.7)	84.9(65.1,98.6)	84.0(63.7,101.5)	< 0.001
TC, mmol/L	3.9 ± 0.9	4.4 ± 1.0	5.0 ± 1.2	< 0.001

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; CKD, chronic kidney disease; MI, myocardial infarction;

PCI, percutaneous coronary intervention; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; WBC, white blood cell; Hs-CRP, hypersensitive C-reactive protein; RBG, random blood glucose; 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; NSTEMI, Non-ST-segment elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending; CABG, coronary artery bypass graft.

Table 1. Baseline clinical characteristics of patients stratified by the optimal cutoff point of TyG index.				
TGs, mmol/L	1.0 ± 0.3	1.6 ± 0.5	3.3 ± 2.1	< 0.001
LDL-C, mmol/L	2.2 ± 0.7	2.6 ± 0.7	2.9 ± 0.8	< 0.001
HDL-C, mmol/L	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.2	< 0.001
Initial diagnosis				
NSTEMI	384(59.6)	343(53.3)	315(48.9)	0.001
STEMI	260(40.4)	301(46.7)	329(51.1)	
Echocardiography				
LVEF	56.8 ± 10.8	57.6 ± 10.4	57.9 ± 9.7	0.354
Angiography findings				
LM/three-vessel	455(70.7)	467(72.5)	447(69.4)	0.467
Proximal LAD	296(46.0)	327(50.8)	325(50.5)	0.154
In-hospital treatment				
PCI/CABG	474(73.6)	503(78.1)	524(81.4)	0.004
Antiplatelet agent	614(95.3)	619(96.1)	621(96.4)	0.594
ACEI/ARB	428(66.5)	417(64.8)	446(69.3)	0.223
Beta-blocker	465(72.2)	474(73.6)	495(76.9)	0.146
Statin	560(87.0)	568(88.2)	545(84.6)	0.161
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; CKD, chronic kidney disease; MI, myocardial infarction;				
PCI, percutaneous coronary intervention; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; WBC, white blood cell; Hs-CRP, hypersensitive C-reactive protein; RBG, random blood glucose; 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; NSTEMI, Non-ST-segment elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending; CABG, coronary artery bypass graft.				

age, sex, body mass index (BMI), diastolic blood pressure (DBP), previous stroke, white cell count (WBC), hypersensitive C-reactive protein (hs-CRP), hemoglobin, FPG, RBG at admission, glycated hemoglobin (HbA1c), albumin,creatinine, eGFR, total cholesterol (TC),TGs, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), initial diagnosis(NSTEMI/STEMI) and in-hospital treatment[percutaneous coronary intervention (PCI)/CABG]. No significant difference was found in the other indicators.

Tyg Index Predicted The Occurrence Of Macces

During the median of 26.8-month follow-up, MACCEs occurred in 735 (38.0%) patients [all-cause death: 292 (15.1%); CV death: 233 (12.1%); non-fatal MI: 161 (8.3%); non-fatal stroke: 76 (3.9%); cardiac rehospitalization: 354 (18.3%); revascularization: 226 (11.7%)]. As shown in Fig. 2, Kaplan-Meier curves showed

that the cumulative incidences of cardiac rehospitalization($p = 0.001$), revascularization ($p < 0.001$) and composite MACCEs($p = 0.027$) increased with higher tertiles of the TyG index. Table 2 showed the events rates and Cox proportional hazard analysis for MACCEs. Rates of CV death, non-fatal MI, cardiac rehospitalization, revascularization and composite MACCEs increased progressively with a higher TyG index. On unadjusted Cox modeling, only the rates of cardiac rehospitalization, revascularization and composite MACCEs rose significantly with elevated TyG index levels (all $p < 0.05$). Notably, after adjusting for age, BMI and other potential confounding factors, multivariate-adjusted hazard ratio (HR) increased with rising TyG index levels for all-cause death, CV death, cardiac rehospitalization, revascularization and composite MACCEs (all $p < 0.05$).

Table 2
Multivariable Cox regression analysis of MACCE.

	%(Events)	Unadjusted HR(95% CI)	p value	Adjusted HR(95% CI)	p value
All cause death					
TyG < 8.94	15.4%(99)	Ref.	-/-	Ref.	-/-
8.94 ≤ TyG < 9.56	15.7% (101)	0.99(0.76,1.32)	0.996	1.40(1.05,1.86)	0.022
TyG ≥ 9.56	14.3%(92)	0.92(0.70,1.23)	0.587	1.69(1.25,2.29)	0.001
CV death					
TyG < 8.94	10.7%(69)	Ref.	-/-	Ref.	-/-
8.94 ≤ TyG < 9.56	12.6%(81)	1.15(0.83,1.59)	0.393	1.56(1.12,2.18)	0.009
TyG ≥ 9.56	12.9%(83)	1.20(0.87,1.65)	0.262	2.10(1.50,2.94)	< 0.001
Non-fatal MI					
TyG < 8.94	7.6%(49)	Ref.	-/-	Ref.	-/-
8.94 ≤ TyG < 9.56	7.8%(50)	1.01(0.68,1.50)	0.954	1.09(0.73,1.64)	0.670
TyG ≥ 9.56	9.6%(62)	1.30(0.90,1.89)	0.167	1.47(0.98,2.20)	0.064
Non-fatal stroke					
TyG < 8.94	4.3%(28)	Ref.	-/-	Ref.	-/-
8.94 ≤ TyG < 9.56	3.6%(23)	0.78(0.45,1.36)	0.385	0.83(0.47,1.47)	0.516
TyG ≥ 9.56	3.9%(25)	0.87(0.51,1.49)	0.610	1.06(0.59,1.90)	0.849
Cardiac rehospitalization					
TyG < 8.94	14.9%(96)	Ref.	-/-	Ref.	-/-
8.94 ≤ TyG < 9.56	17.4% (112)	1.15(0.87,1.51)	0.323	1.14(0.86,1.50)	0.374

Adjusted factors included TyG index, age, BMI, history of stroke and PCI, antiplatelet agent used before admission, WBC, hemoglobin, albumin, eGFR, LVEF, angiography findings(LM/three-disease and proximal LAD) and in-hospital treatment(PCI/CABG, antiplatelet agent, ACEI/ARB,beta-blocker and statins).

TyG, triglyceride-glucose index; CV, cardiovascular; MI, myocardial infarction; MACCE, major adverse cardiac and cerebral event; BMI, body mass index; PCI, percutaneous coronary intervention; WBC,white blood cell; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending; CABG, coronary artery bypass graft; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; HR, hazard ratio; CI, confidence interval.

	%(Events)	Unadjusted HR(95% CI)	p value	Adjusted HR(95% CI)	p value
TyG ≥ 9.56	22.7% (146)	1.59(1.23,2.06)	< 0.001	1.59(1.21,2.09)	0.001
Revascularization					
TyG < 8.94	8.9%(57)	Ref.	-/-	Ref.	-/-
8.94 ≤ TyG < 9.56	10.7%(69)	1.18(0.83,1.67)	0.359	1.04(0.72,1.49)	0.846
TyG ≥ 9.56	15.5% (100)	1.82(1.32,2.52)	< 0.001	1.55(1.09,2.20)	0.015
Composite MACCE					
TyG < 8.94	34.8% (224)	Ref.	-/-	Ref.	-/-
8.94 ≤ TyG < 9.56	37.6% (242)	1.06(0.88,1.27)	0.531	1.15(0.95,1.39)	0.145
TyG ≥ 9.56	41.8% (269)	1.26(1.05,1.50)	0.011	1.52(1.26,1.84)	< 0.001

Adjusted factors included TyG index, age, BMI, history of stroke and PCI, antiplatelet agent used before admission, WBC, hemoglobin, albumin, eGFR, LVEF, angiography findings(LM/three-disease and proximal LAD) and in-hospital treatment(PCI/CABG, antiplatelet agent, ACEI/ARB,beta-blocker and statins).

TyG, triglyceride-glucose index; CV, cardiovascular; MI, myocardial infarction; MACCE, major adverse cardiac and cerebral event; BMI, body mass index; PCI, percutaneous coronary intervention; WBC,white blood cell; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending; CABG, coronary artery bypass graft; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; HR, hazard ratio; CI, confidence interval.

Univariate and multivariate Cox proportional hazards regression analyses and predictors for composite MACCEs were presented in Table 3. In the univariate analysis, the predictor associated with MACCEs occurrence were TyG index, age,

Table 3
Independent predictors of composite MACCE.

	Univariate		Multivariate	
	HR(95%CI)	*p* value	Adjusted HR(95%CI)	*p* value
TyG index				
TyG < 8.94	Reference		Reference	
8.94 ≤ TyG < 9.56	1.06(0.88,1.27)	0.531	1.15(0.95,1.39)	0.145
TyG ≥ 9.56	1.26(1.05,1.50)	0.011	1.52(1.26,1.84)	< 0.001
Age, y	1.03(1.01,1.04)	< 0.001	1.02(1.01,1.03)	0.008
Male gender	1.04(0.88.1.20)	0.642		
BMI, kg/m^2	1.02(1.01,1.04)	0.046	1.01(0.99,1.03)	0.412
SBP, mmHg	1.01(0.99,1.02)	0.546		
DBP, mmHg	0.99(0.98,1.00)	0.461		
Medical history				
Current/ex-Smoker	0.93(0.80,1.07)	0.302		
CKD	1.85(1.43,2.40)	< 0.001		
Stroke	1.59(1.35,1.87)	< 0.001	1.33(1.12,1.59)	0.001
Hypertension	1.17(0.98,1.39)	0.075		
Dyslipidemia	1.04(0.90,1.21)	0.558		
Previous MI	1.15 (0.91,1.44)	0.243	1.15(0.93,1.42)	0.199
Past PCI	1.25(1.04,1.50)	0.020		
Medication used before admission				

Correlation analysis showed that FPG, RBG at admission and TyG index had a high correlation (p < 0.001). CKD, creatinine and eGFR had a high correlation (p < 0.001). In addition, WBC and hs-CRP had a high correlation (p < 0.001). Therefore, FPG, RBG at admission, CKD, creatinine and hs-CRP were not included in the multivariate model.

TyG, triglyceride-glucose index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; WBC, white blood cell; Hs-CRP, hypersensitive C-reactive protein; RBG, random blood glucose; 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; CABG, coronary artery bypass graft.

	Univariate		Multivariate	
Antiplatelet agent	1.25(1.08,1.46)	0.004	1.11(0.95,1.30)	0.176
ACEI/ARB	1.09(0.94,1.28)	0.261		
Beta-blocker	1.20 (0.98,1.45)	0.074		
Statins	1.15(0.96,1.38)	0.120		
Laboratory values				
WBC,10^9/L	1.04(1.02,1.05)	< 0.001	1.03(1.02,1.05)	< 0.001
Hemoglobin, g/L	0.98(0.97,0.99)	< 0.001	0.99(0.98,1.01)	0.678
Hs-CRP, mg/L	1.02(1.01,1.03)	< 0.001		
RBG at admission, mmol/L	1.02(1.01,1.03)	0.042		
FPG, mmol/L	1.05(1.03, 1.08)	< 0.001		
HbA1c, %	1.04(0.99,1.09)	0.066		
Albumin, g/L	0.97(0.95,0.99)	0.004	0.99(0.98,1.02)	0.934
Creatinine, umol/L	1.02(1.01,1.03)	< 0.001		
eGFR, ml/min/1.73 m^2	0.98(0.96,0.99)	< 0.001	0.98(0.97,0.99)	0.003
TC, mmol/L	1.01(0.95,1.09)	0.673		
TG, mmol/L	1.02(0.97,1.08)	0.333		
LDL-C, mmol/L	1.01(0.92,1.11)	0.821		
HDL-C, mmol/L	0.94(0.70,1.27)	0.705		
Echocardiography				
LVEF,%	0.97(0.96,0.98)	< 0.001	0.98(0.97,0.99)	< 0.001

Correlation analysis showed that FPG, RBG at admission and TyG index had a high correlation ($p < 0.001$). CKD, creatinine and eGFR had a high correlation ($p < 0.001$). In addition, WBC and hs-CRP had a high correlation ($p < 0.001$). Therefore, FPG, RBG at admission, CKD, creatinine and hs-CRP were not included in the multivariate model.

TyG, triglyceride-glucose index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; WBC, white blood cell; Hs-CRP, hypersensitive C-reactive protein; RBG, random blood glucose; 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; CABG, coronary artery bypass graft.

	Univariate		Multivariate	
Angiography findings				
LM/three-disease	1.39(1.19,1.62)	< 0.001	1.18(0.94,1.45)	0.145
Proximal LAD	1.38(1.20,1.60)	< 0.001	1.14(0.96,1.33)	0.129
In-hospital treatment				
PCI/CABG	0.52(0.45,0.61)	< 0.001	0.60(0.48,0.75)	< 0.001
Antiplatelet agent	0.67(0.49,0.94)	0.018	0.61(0.42,0.88)	0.009
ACEI/ARB	0.77(0.66,0.89)	0.001	0.89(0.76,1.04)	0.153
Beta-blocker	0.75(0.64,0.88)	< 0.001	0.83(0.70,0.99)	0.035
Statins	0.56(0.47,0.68)	< 0.001	0.63(0.51,0.78)	< 0.001
Correlation analysis showed that FPG, RBG at admission and TyG index had a high correlation ($p < 0.001$). CKD, creatinine and eGFR had a high correlation ($p < 0.001$). In addition, WBC and hs-CRP had a high correlation ($p < 0.001$). Therefore, FPG, RBG at admission, CKD, creatinine and hs-CRP were not included in the multivariate model.				
TyG, triglyceride-glucose index; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CKD, chronic kidney disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; WBC, white blood cell; Hs-CRP, hypersensitive C-reactive protein; RBG, random blood glucose; 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; CABG, coronary artery bypass graft.				

BMI, duration of diabetes, chronic kidney disease (CKD), previous stroke, past PCI, antiplatelet agent used before admission, WBC, hs-CRP, hemoglobin, FPG, RBG at admission, albumin,creatinine, eGFR, left ventricular ejection fraction (LVEF), angiography[left main coronary artery(LM)/three-disease, proximal left anterior descending (LAD)] and in-hospital treatment[PCI/CABG, antiplatelet agent, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), beta-blocker and statins]. FPG, RBG at admission and TyG index had a high correlation ($p < 0.001$). In addition, CKD and creatinine were significantly correlated with eGFR ($p < 0.001$), and hs-CRP was significantly correlated with WBC ($p < 0.001$). Therefore, FPG, RBG at admission, CKD, creatinine and hs-CRP were not included in the multivariate model. After adjusting for age, BMI and other confounding factors, multivariate Cox proportional hazards regression analysis showed that TyG index, age, previous stroke, WBC, eGFR, LVEF and in-hospital treatment(PCI/CABG, antiplatelet agent, beta-blocker and statins) independently predicted the occurrence of MACCEs in patients with AMI and T_2DM.

Incremental effect of TyG index on predictive value for MACCEs

Figure 3 **and** Table 4 showed the analysis results of the covariate adjusted model, including, age, sex, BMI, smoker, history of PCI and stroke, duration of diabetes, antiplatelet agent used before admission,

eGFR, hs-CRP, hemoglobin, LVEF, angiography findings(LM/three-disease and proximal LAD) and in-hospital treatment(PCI/CABG, antiplatelet agent, beta-blocker and statins). After including the covariates, the TGs, HbA1c, FPG and TyG index all significantly predicted MACCEs[AUC values of 0.666 for TG, 0.669 for HbA1c, 0.670 for FPG, and 0.708 for TyG index, all $p < 0.001$]. The addition of TyG index had a significant incremental effect on the AUC obtained from baseline risk model, which indicated that the TyG index may be a useful marker for risk stratification and prognosis in patients with AMI and T_2DM.

Table 4
Prematching receiver operating characteristic curve analysis of TG, HbA1c, FPG and TyG index adjusted by covariates for the prediction of composite MACCE.

	AUC	P value	95% CI
Covariates	0.663	< 0.001	0.638 to 0.688
TG + covariates	0.666	< 0.001	0.641 to 0.691
HbA1c + covariates	0.669	< 0.001	0.644 to 0.694
FPG + covariates	0.670	< 0.001	0.645 to 0.695
TyG + covariates	0.708	< 0.001	0.684 to 0.732
The covariates included age, male gender, BMI, smoker, history of PCI and stroke, duration of diabetes, antiplatelet agent used before admission, eGFR, hs-CRP, hemoglobin, LVEF, angiography findings(LM/three-disease and proximal LAD) and in-hospital treatment(PCI/CABG, antiplatelet agent, beta-blocker and statins).			
MACCE, major adverse cardiac and cerebral event; TG, triglyceride; HbA1c, glycosylated hemoglobin A1c; FPG, fasting plasma glucose; TyG, triglyceride-glucose index; BMI, body mass index; PCI, percutaneous coronary intervention; eGFR, estimated glomerular filtration rate; hs-CRP, hypersensitive C-reactive protein; LVEF, left ventricular ejection fraction; LM, left main coronary artery; LAD, left anterior descending; CABG, coronary artery bypass graft; AUC, area under the curve.			

Discussion

To the best of our knowledge, this is the first study to explore the association

between the TyG index and MACCEs in AMI patients with T_2DM. Our main findings include: (1) the incidences of MACCEs significantly increased with the increase of TyG index (cardiac rehospitalization, revascularization, and composite MACCEs), and (2) the TyG index was an independent predictor of MACCEs(all-cause death, CV death, cardiac rehospitalization, revascularization, and composite MACCEs), and (3) the addition of TyG index to a baseline risk model had an incremental effect on the predictive value for composite MACCEs, and(4) age, previous stroke, WBC, eGFR, LVEF and in-hospital treatment(PCI/CABG, antiplatelet agent, beta-blocker and statins) can also independently predicted the occurrence of MACCEs in patients with AMI and T_2DM. According to this study, we confirmed that the TyG index was positively associated with increased MACCEs. Most importantly, this study suggested

that a simple method of estimating IR may optimize the risk stratification of recurrent cardiovascular risk in AMI patients with T_2DM.

IR is defined as a decrease in the efficiency of insulin in promoting glucose uptake and utilization, which is an indicator of abnormal metabolism. IR promotes the progression of CVDs by inducing glucose metabolism imbalance, altering systemic lipid metabolism, and causing endothelial dysfunction[11]. Several clinical studies found that IR was an important risk factor for CVDs and poor clinical outcomes[6,27–29]. At present, the traditional methods of IR detection mainly include the hyperinsulinemic-euglycemic clamp and the HOMA-IR. However, due to the complexity and high cost of the detection process, the above two methods

cannot be applied to clinical practice on a large scale. In order to solve this clinical problem, researchers have done a lot of studies on TyG index and found that

it was a reliable surrogate marker of IR[12, 15],which can be widely used in clinical practice.

Numerous studies have robustly proved that TyG index is closely related to an increased risk of vascular disease. Shi et al. demonstrated that the TyG index was positively correlated with the incidence of ischemic stroke[30, 31]. Irace et al. found that the TyG-Index was significantly associated with carotid atherosclerosis[18]. Zhao et al. reported that an elevated TyG index was associated with a higher risk of arterial stiffness and nephric microvascular damage[32]. The findings of Park et al. and Lee et al. showed that elevated TyG index can predict the progression of coronary artery calcification[16] and coronary artery stenosis[19], respectively. Thus, we believed that the TyG index might be used to predict various vascular diseases, and it is an index worthy of in-depth study.

As for the predictive effect of TyG index on CVDs, researchers have done a lot of works. Sánchez-Íñigo et al. suggested that a higher level of TyG index was significantly associated with an increased risk of developing CVDs independent of confounding factors, and the TyG index might be used to early identify the high-risk CVEs in healthy individuals[33]. Da Silva et al. demonstrated that the TyG index was positively associated with a higher prevalence of symptomatic coronary artery disease(CAD) in patients underwent secondary care for CVD[20]. Mao et al. firstly confirmed that the TyG index was positively associated with SYNTAX score and major adverse cardiovascular events (MACEs) in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) population[22]. Additionally, a cohort study including 1092 STEMI patients who underwent PCI indicated that the incidences of composite MACCEs and all-cause death within 30 days, 6 months and 1 year were higher among those with highest level of TyG index (TyG index ≥ 9.608), and that the TyG index ≥ 9.608 was independently associated with an increased risk of MACCEs within 1 year [HR(95% CI): 1.53 (1.0 1,2.06), p = 0 003][21]. Considering that nearly one-third of ACS patients are combined with T_2DM, and these patients are characterized by more complex coronary lesions, higher incidence of recurrent CVEs, and worse prognosis. Relevant studies about the TyG index in predicting CVEs in patients with ACS complicated with T_2DM have been published

in succession. Wang et al. followed up 2,531 ACS patients with T_2DM for 3 years and found that the incidence of MACEs increased with the increase of TyG index, the TyG index was an independent predictor of MACEs, and the optimal TyG index cut-off for predicting MACEs was 9.323[24]. A study by Ma et al. of 776 patients with T_2DM and ACS who underwent PCI also showed that the TyG index was significantly associated with adverse CV outcomes, including all-cause mortality, non-fatal stroke, non-fatal MI and unplanned repeat revascularization[23]. In addition, a study including 798 patients with T_2DM and NSTE-ACS undergoing PCI reported that 1-unit increase of TyG index was independently associated with higher risk of primary endpoint (a composite of all-cause death, non-fatal MI and ischemia-driven revascularization)[HR: 3.208 per 1-unit increase, 95% CI: 2.40–4.29, $p < 0.001$], and the addition of TyG index to a baseline risk model had an incremental effect on the predictive value for adverse prognosis [AUC: baseline risk model, 0.800 vs. baseline risk model + TyG index, 0.856, $p < 0.001$] [25]. However, the predictive effects of the TyG index on MACCEs in patients with AMI combined with T_2DM, are still unclear.

In this study, we investigated the prognostic value of the TyG index in patients with AMI combined with T_2DM for the first time. In addition, to better understand the predictive power of TyG index for different CVEs, we analyzed the correlation between TyG index and each type of MACCEs (including all-cause death, CV death, non-fatal MI, non-fatal stroke, revascularization, and cardiac rehospitalization). In the current study, all-cause mortality and CV mortality did not significantly increase with the increase of TyG index. We attributed this “anomalous” result to the significant different baseline characteristics between the 3 groups. In this study, patients in the

highest TyG index tertiles were significantly younger, showed lower percent of male,

lower percent of previous stroke, higher levels of hemoglobin, albumin and eGFR. In addition, the proportion of patients receiving PCI/CABG during hospitalization was highest in the group with the highest TyG index. Because of these protective factors, the all-cause mortality and CV mortality in the TyG index ≥ 9.56 group was not significantly higher than those in the other 2 groups. Although there was no significant difference in the incidence of all-cause death and CV death between the 3 groups before adjusting for confounding factors, multivariate Cox regression analysis found that the elevated TyG index level was an independent predictor of all-cause death and CV death after adjusting for age, BMI and other confounding factors.

In addition, our study also found that, compared with TGs, HbA1c and FPG, adding TyG index to the baseline risk model had a significantly incremental effect on the predictive value for composite MACCEs[AUC: covariates, 0.663 vs. covariates + TyG index, 0. 708, $p < 0.001$]. A similar statistical analysis was performed by Zhao et al., whose AUC value [AUC: covariates, 0.800 vs. covariates + TyG index, 0.856, $p < 0.001$] was higher than that of our study[25]. We think it may be related to the differences in sample size(798 patients vs. 1932 patients), study subjects(T_2DM patients with NSTE-ACS who underwent PCI vs. T_2DM patients with AMI), and endpoint events[(a composite of all-cause death, non-fatal MI and ischemia-driven revascularization) vs. (a composite of all-cause death, non-fatal MI, non-fatal stroke,

cardiac rehospitalization, and revascularization)]. Even so, we can come to a similar conclusion that TyG index improved the ability to predict adverse CVEs in clinical practice. We assert that the use of TyG index for early risk stratification of AMI patients with T_2DM is crucial for better clinical management to prevent future CVEs.

Our study had several limitations. First, this was a single-center study although including a large sample size; thus, generalization of the findings should be cautious. Second, laboratory parameters were only measured once after hospital admission, which could cause potential bias due to measurement error. Third, this was a retrospective observational study. The information on the levels of TyG index during follow-up was limited. Prospective cohort studies are required to confirm our findings.

Conclusions

In conclusion, the current study firstly demonstrated that elevated TyG index level was a strong independent predictor of MACCEs in patients with AMI and T_2DM. In addition, the addition of TyG index to a baseline risk model had an incremental effect on the predictive value for MACCEs

Abbreviations

TyG: triglyceride-glucose; AMI: acute myocardial infarction; T_2DM: type 2 diabetes mellitus; MACCEs: major adverse cardiovascular and cerebrovascular

events; IR: insulin resistance; CVDs: cardiovascular diseases; CVEs: cardiovascular events; TGs: triglycerides; FPG: fasting plasma glucose; HOMA-IR: the homeostasis model assessment of insulin resistance; CBD: Cardiovascular Center of Beijing Friendship Hospital Database; eGFR: estimated glomerular filtration rate; CABG: coronary artery bypass graft; RBG: random blood glucose; OGTT: oral glucose tolerance test; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; ROC: receiver operating characteristic; BMI: body mass index; DBP: diastolic blood pressure; WBC: white blood cell; Hs-CRP, hypersensitive C-reactive protein; HbA1c, glycated hemoglobin; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; PCI: percutaneous coronary intervention; HR: hazard ratio; CKD: chronic kidney disease; LVEF: left ventricular ejection fraction; LM: left main coronary artery; LAD, left anterior descending; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CAD: coronary artery disease; MACEs: major adverse cardiovascular events; NSTE-ACS: Non-ST-segment elevation acute coronary syndrome.

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

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.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81670315) and Beijing Key Clinical Subject Program.

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 revised manuscript. WPL designed study and performed statistical analysis. HWL provided funding support, designed study and reviewed manuscript. All authors read and approved the final manuscript.

Acknowledgements

We gratefully acknowledge the contributions of all staffs who work on the CBD Bank.

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Figures

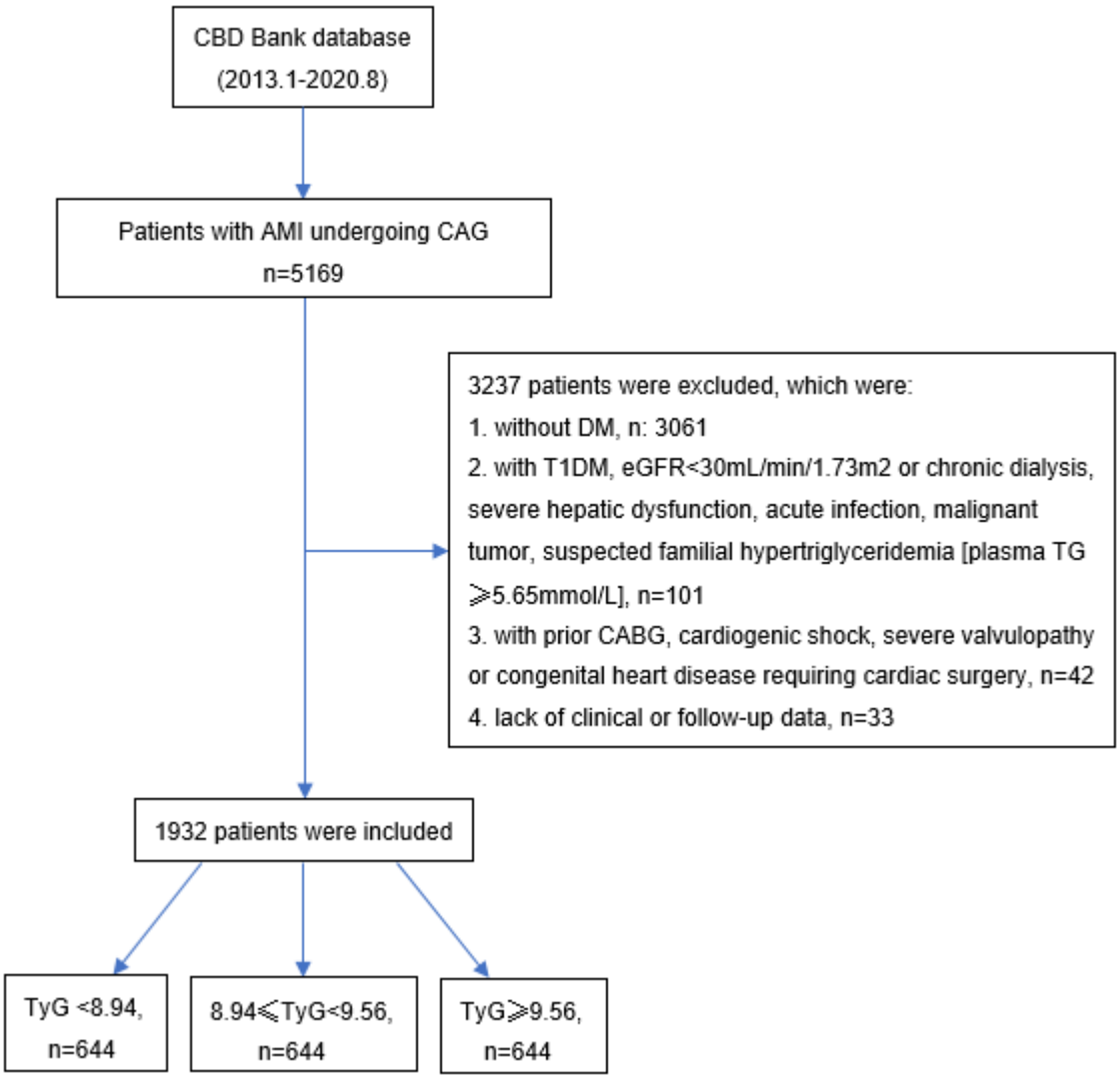
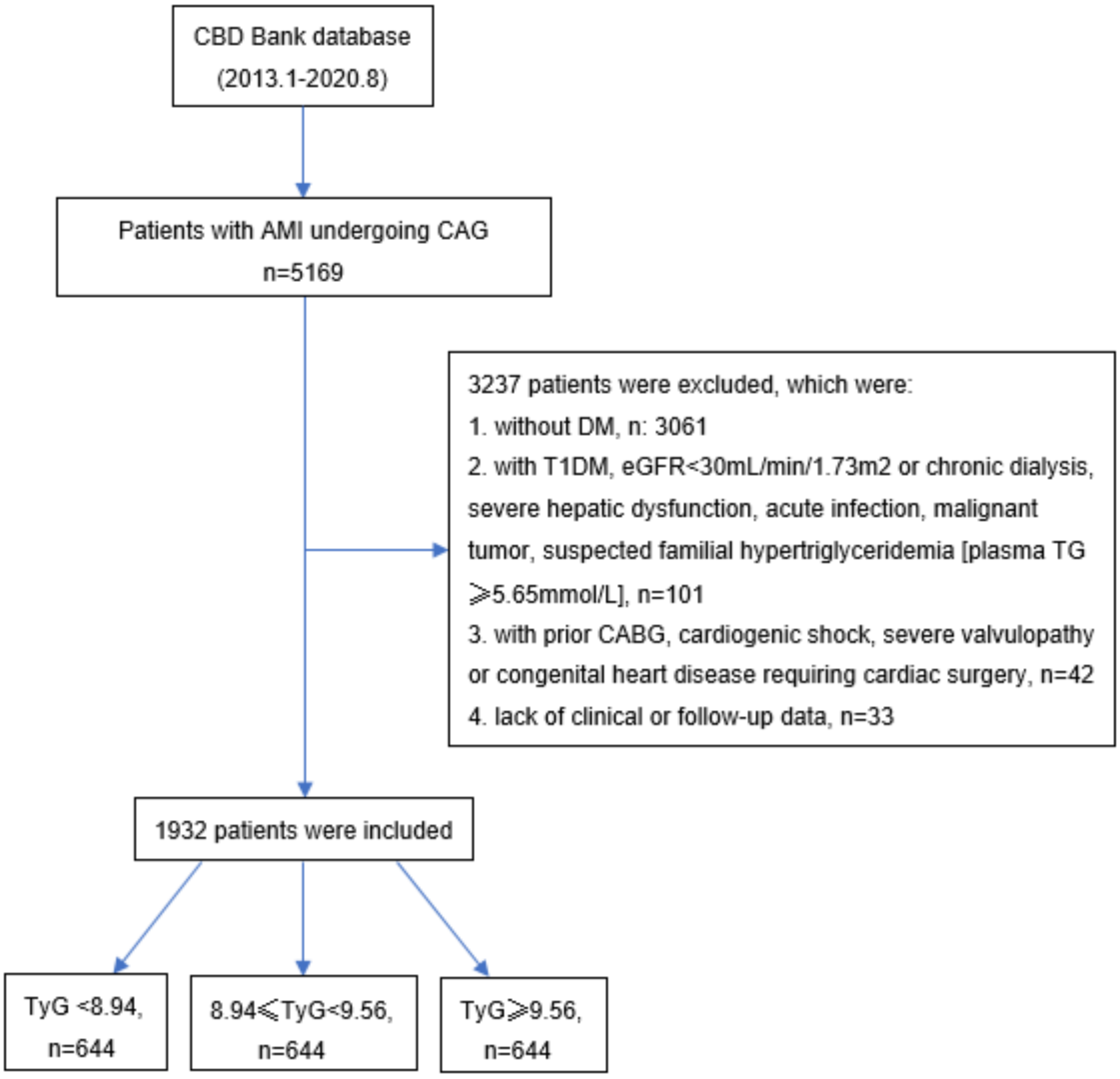


Figure 1

The flow chart of study subject enrollment. CBD, Cardiovascular Center of Beijing Friendship Hospital Database; AMI, acute myocardial infarction; CAG, coronary angiography; DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; eGFR, estimated glomerular filtration rate; TG, triglyceride; CABG, coronary artery bypass graft; TyG, triglyceride-glucose index.



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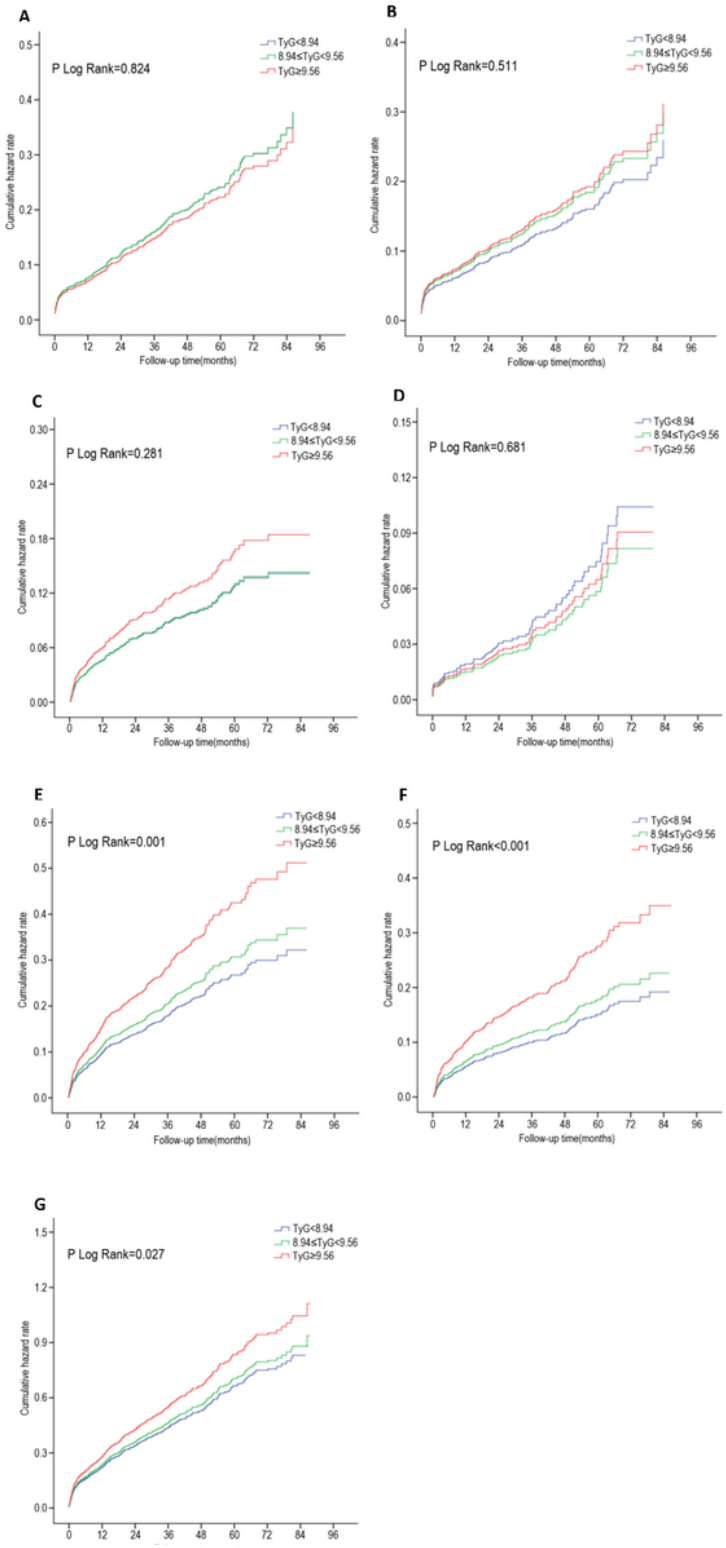
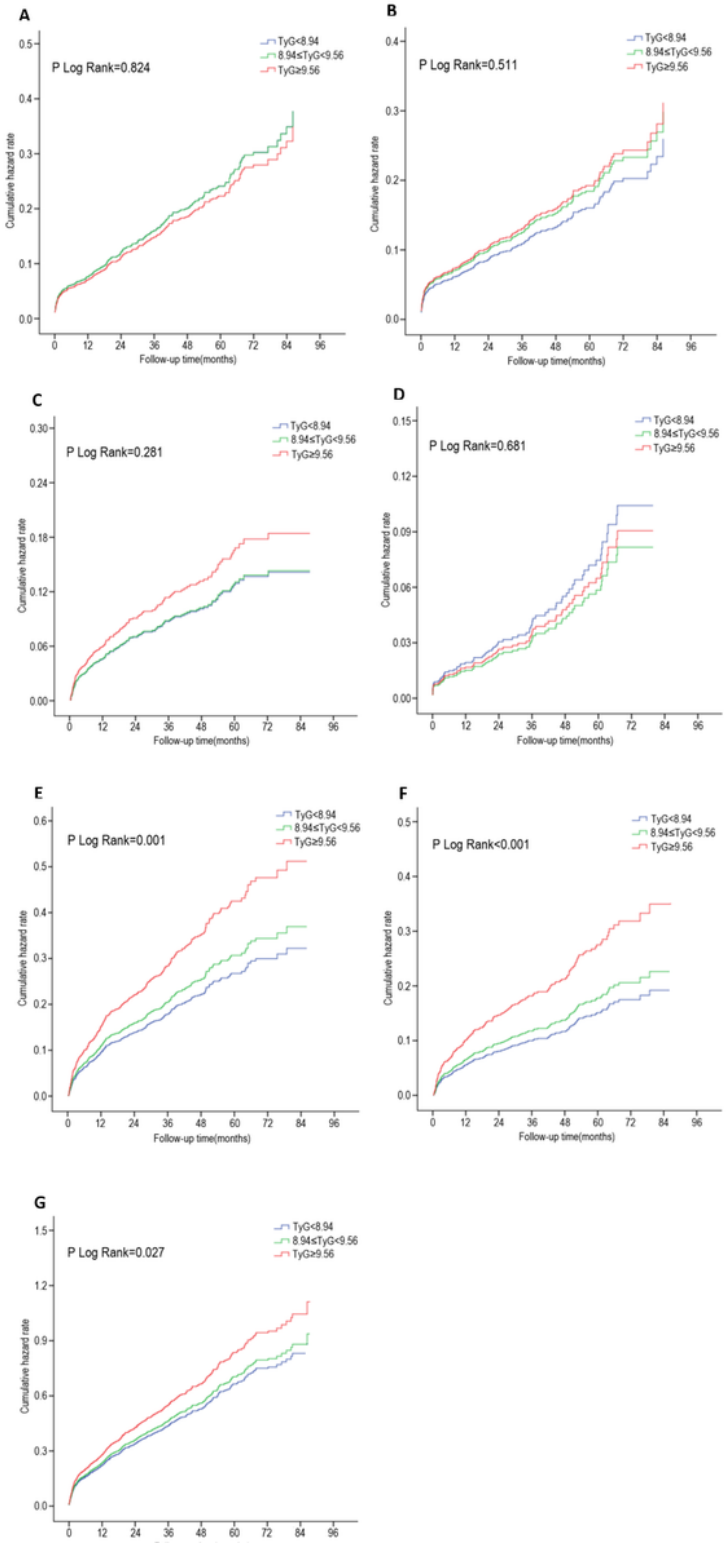


Figure 2

Kaplan-Meier curves for all-cause death(A), CV death(B), non-fatal MI(C), non-fatal stroke(D), cardiac rehospitalization(E), revascularization(F) and composite MACCEs(G) of the TyG<8.94 group(blue line) , the 8.94≤TyG<9.56 group(green line) and the TyG≥9.56 group(red line). TyG, triglyceride-glucose index; CV, cardiovascular; MI, myocardial infarction; MACCEs, major adverse cardiac and cerebral event.



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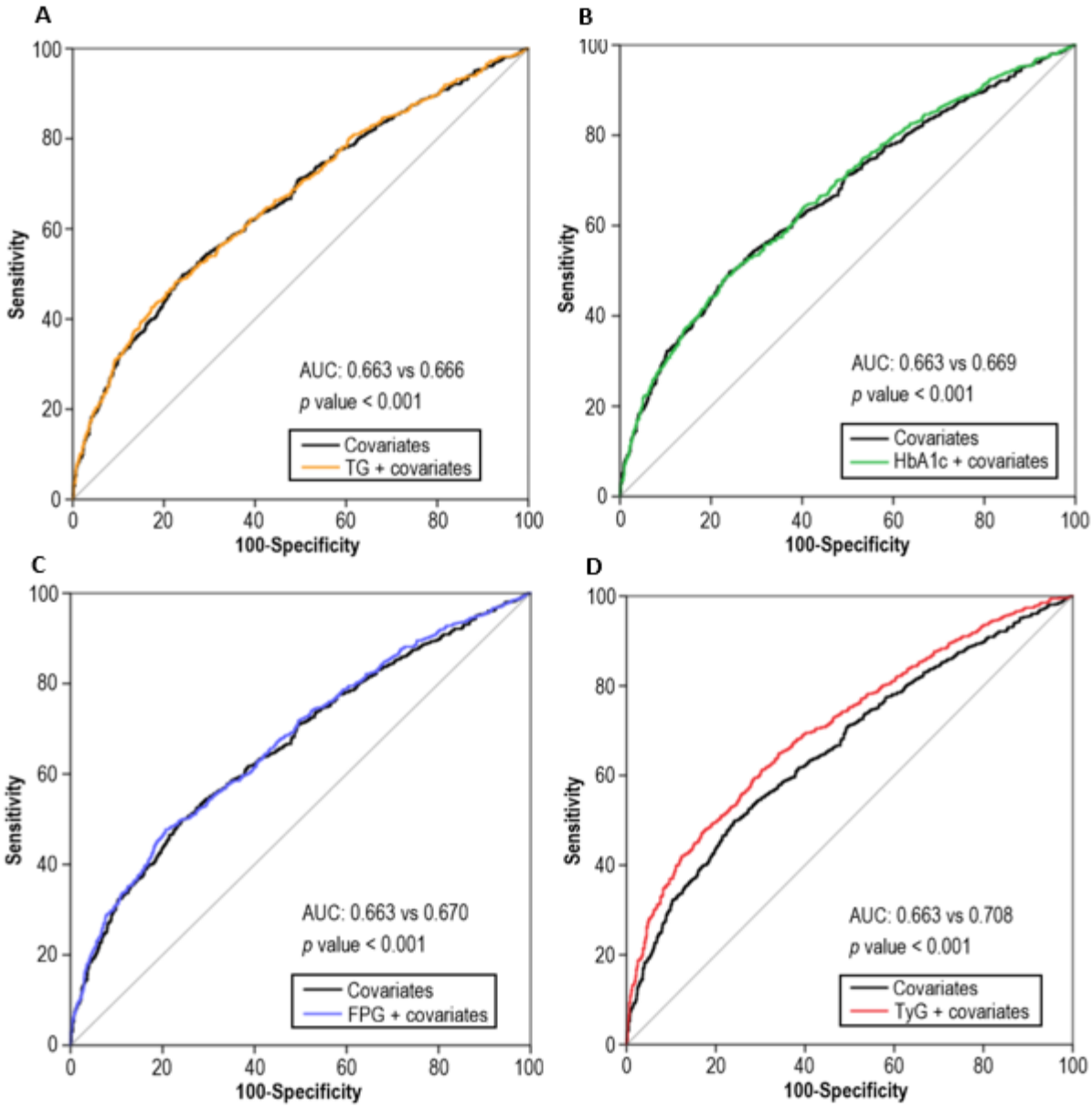
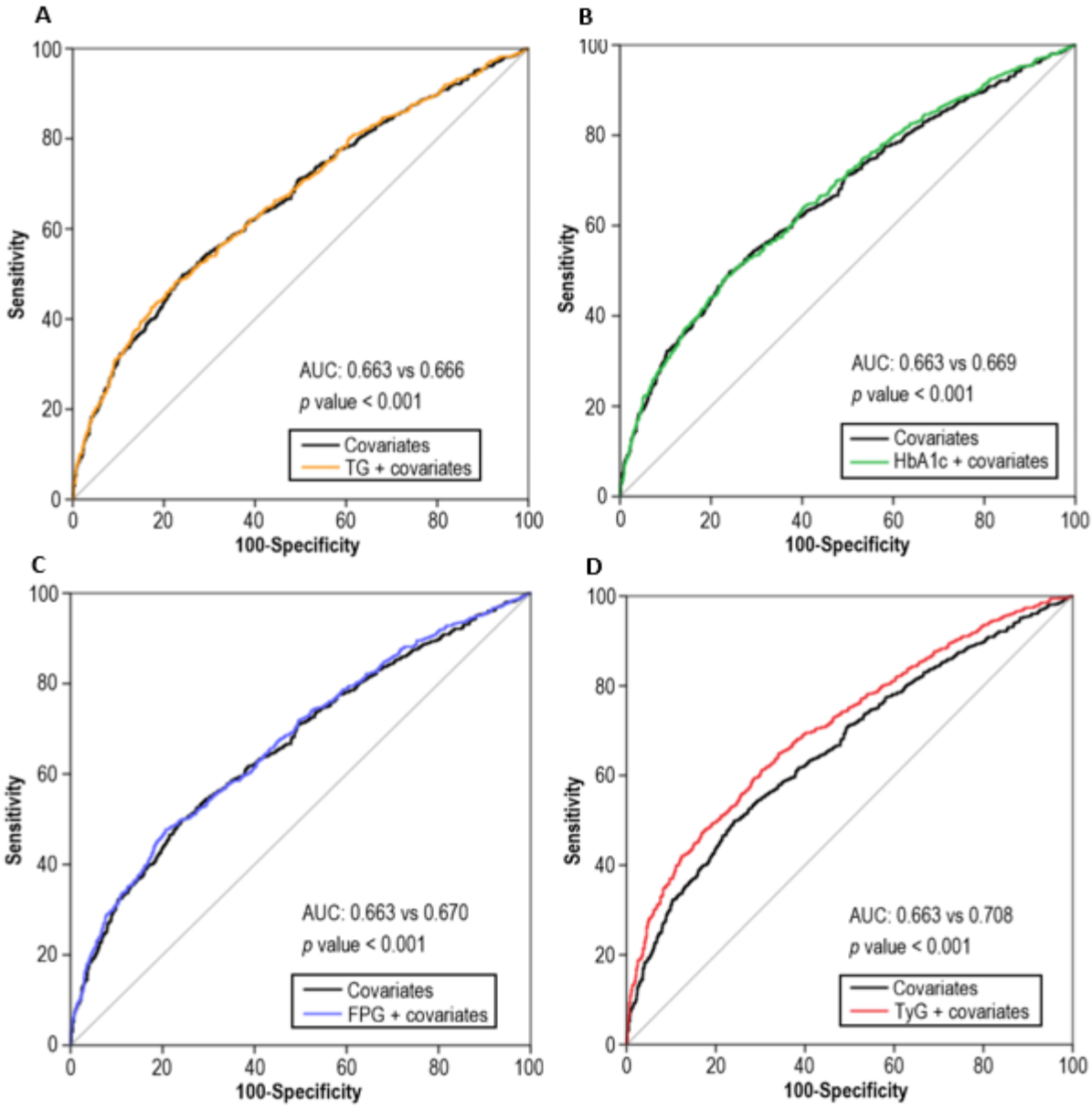


Figure 3

Prematching receiver operating characteristic curve including covariates for the prediction of composite MACCE by TG(A), HbA1c(B), FPG(C) and TyG index(D). MACCE, major adverse cardiac and cerebral event; TG, triglyceride; HbA1c, glycosylated hemoglobin A1c; FPG, fasting plasma glucose; TyG, triglyceride-glucose index; AUC, area under the curve.



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