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Triglyceride-glucose index as a predictor of cardiac adverse events in acute coronary syndrome patients undergoing percutaneous coronary intervention: role of diabetes

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Abstract

Background Triglyceride-glucose index (TyG), a surrogate marker of insulin resistance (IR), could be a potential prognostic marker in patients with acute coronary syndromes (ACS). We evaluated the effect of the TyG index on major adverse cardiac and cerebrovascular events (MACCE) in patients with ACS undergoing percutaneous coronary intervention (PCI).

Methods This registry-based cohort study was conducted at Tehran Heart Center from 2015 to 2021 and the median follow-up duration was 378 days. The primary outcome was MACCE and the secondary outcomes were MACCE components: all-cause mortality, myocardial infarction, stroke, target vessel revascularization, target lesion revascularization, and coronary artery bypass grafting. For comparison among TyG quartiles (Q), the log-rank test was used. Unadjusted and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were used to describe the association between TyG quartiles and MACCE. A subgroup of euglycemic patients was also evaluated.

Results A total of 13,542 patients were included. Patients in the fourth TyG quartile (Q4) were younger, had higher mean BMI, and higher prevalence of hypertension, diabetes, and dyslipidemia. The adjusted Cox model showed that a 1-unit increment of the TyG index was associated with a significantly higher risk of MACCE (aHR 1.18, 95% CI 1.08 to 1.30, $p < 0.001$). Among TyG quartiles, there was a higher MACCE incidence in Q4 compared to Q1 (aHR 1.29, 95% CI 1.08 to 1.53, $p = 0.005$). In the euglycemic subgroup of the population, there was no significant association between MACCE incidence and a 1-unit increase in TyG or among TyG quartiles.

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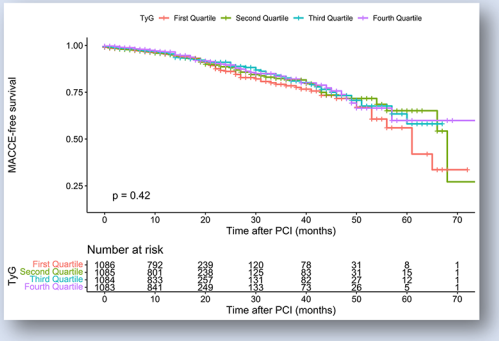
Conclusion Based on our findings, while higher TyG levels and quartiles were associated with higher rates of MACCE in ACS, there was no such effect in the euglycemic population. If confirmed in future studies, these results can be beneficial for clinicians to risk stratify these patients with an easy-to-use index and determine clinical plans based on their risk.

Graphical abstract

TyG index as a predictor of cardiac adverse events in ACS patients undergoing PCI: role of diabetes

Population: All patients with ACS that underwent PCI at Tehran Heart Center from 2015 to 2021
Statistical Methods: Cox Proportional Hazard Regression, Kaplan-Meier Methods

Adjusted HR (95% CI)	Quartile 1	Quartile 2	Quartile 3	Quartile 4
MACCE	Ref	1.066 [0.899 – 1.263]	1.002 [0.838 – 1.199]	**1.286 [1.080 – 1.532]**
All-cause mortality	Ref	0.967 [0.728 – 1.285]	0.827 [0.604 – 1.131]	1.094 [0.804 – 1.488]
MI	Ref	0.819 [0.606 – 1.106]	1.087 [0.813 – 1.453]	**1.341 [1.007 – 1.785]**
Stroke	Ref	1.751 [0.537 – 5.704]	1.607 [0.458 – 5.641]	1.654 [0.450 – 6.086]
CABG	Ref	1.195 [0.718 – 1.988]	0.872 [0.502 – 1.515]	1.380 [0.824 – 2.310]
Target Vessel Revascularization	Ref	1.345 [0.705 – 2.565]	1.223 [0.616 – 2.424]	1.432 [0.728 – 2.818]
Target Lesion Revascularization	Ref	**2.017 [1.160 – 3.508]**	1.389 [0.763 – 2.528]	1.422 [0.771 – 2.621]



Higher TyG levels and quartiles were associated with higher rates of MACCE in ACS.

Keywords Acute coronary syndrome, Percutaneous coronary intervention, Diabetes Mellitus, Insulin resistance, Prognosis, Triglyceride-glucose index

Introduction

Ischemic heart disease (IHD) is the most prevalent cause of mortality and morbidity among non-communicable diseases globally [1]. Acute coronary syndrome (ACS), including ST-elevation myocardial infarction (STEMI) and non-ST elevation ACS (nSTE-ACS), is responsible for an estimated 605,000 new heart attacks in the United States [2]. As patients with ACS have a greater risk for major adverse cardiac and cerebrovascular events (MACCE) than the general population [3], secondary prevention and identifying high-risk patients are of importance.

Diabetes, dyslipidemia, and obesity are established risk factors for adverse cardiac events after ACS [4, 5], highlighting the importance of lipid and glucose management in these patients [6]. In this regard, several lipid indices have been suggested to be associated with the prognosis of cardiovascular diseases [7–9]. Hyperglycemia increases the production of reactive oxidative species (ROS), which enhances the risk of vascular damage related to diabetes, ectopic angiotensinogen production, or inappropriate activation of the renin-angiotensin-aldosterone system [10, 11]. Moreover, insulin resistance (IR) to maintain glucose hemostasis leads to hyperinsulinemia and elevated oxidative stress [12]. Previous studies have shown the relationship between IR and adverse cardiovascular outcomes [11, 13]. The homeostasis model assessment for insulin resistance (HOMA-IR), composed of fasting insulin and fasting plasma glucose (FPG), has been used to assess IR. However, according to the interplay between IR and hyperlipidemia and as insulin levels are not routinely measured, the triglyceride-glucose index (TyG) has been proposed as an easy-to-measure marker for IR [14]. This index is composed of FPG and fasting triglycerides (TG) and has been shown to have associations with several non-communicable diseases [15–18].

The TyG index has been assessed as a marker of MACCE in several studies [19–21]. Studies evaluated the TyG index in a general population [20], diabetic patients [19], and non-diabetic patients [21]. Although they found promising results for TyG as a predictor of MACCE, the

exact role of diabetes as a confounder in evaluating the association between the TyG index and MACCE in ACS patients is unclear. In this study, we evaluated the prognostic value of the TyG index in predicting MACCE in ACS patients who underwent percutaneous coronary intervention (PCI). Moreover, the euglycemic subgroup of the ACS patients was evaluated separately to identify the possible confounding role of diabetes. The results of our study could be a guide for clinicians to stratify the risk of these critical patients by the use of an easy-to-dose index calculated from the routinely measured TG and FPG in patients.

Methods

Study design and population

Our study was a registry-based cohort study of patients with ACS undergoing PCI at Tehran Heart Center from 2015 to 2021 with a median follow-up duration of 378 days (interquartile range [IQR] 313 to 589 days). Patients with the presentation of ACS, based on the latest guidelines, had the eligibility to enter the study, including ST-elevation myocardial infarction (STEMI) and non-ST elevation ACS (nSTE-ACS). Those without data on FPG and TG or with a lack of follow-up data were excluded. The ethics committee of Tehran University of Medical Sciences approved this study with the registration number of IR.TUMS.MEDICINE.REC.1402.434. Moreover, due to the retrospective nature of this study, the need for obtaining informed consent was waived by the ethics committee.

Definitions and outcomes

Several demographic features, clinical history, laboratory features, and PCI features were collected [22]. Demographic features included age, sex, body mass index (BMI), and waist circumference (WC). Clinical history comprised of the history of hypertension, diabetes, dyslipidemia, atrial fibrillation, heart failure, valvular heart disease, peripheral vascular disease, previous PCI, previous coronary artery bypass grafting (CABG), stroke, STEMI, NSTEMI, unstable angina (UA), and stable angina (SA). Chronic lung disease, smoking status, opium use, and family history of cardiac diseases were also measured. Laboratory features were serum TG, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose (FPG), creatinine, and hemoglobin. Left ventricular ejection fraction (LVEF) was recorded using transthoracic echocardiography. Finally, PCI features included the length of the target lesion, ACS type (STEMI, NSTE-ACS), pre-procedure TIMI flow, vessel severity (single-vessel disease, two-vessel disease, three-vessel disease), ACC/AHA category of the target lesion, and PCI location. The TyG index was calculated as:

$$TyG = \ln\left(TG\left(\frac{mg}{dL}\right) \times \frac{FPG\left(\frac{mg}{dL}\right)}{2}\right)$$

The primary outcome in this study was a composite of MACCE that includes all-cause mortality, MI, stroke, target vessel revascularization (TVR), target lesion revascularization (TLR), and CABG as used in previous studies conducted at Tehran Heart Center [23]. TLR was defined as repeat PCI within the index procedure stent or 5 mm edge. In our study, TVR cases were those for whom repeat PCI was performed in the target vessel but in another site than the target lesion Secondary outcomes were each of these components of MACCE.

Statistical analysis

For reporting continuous data, mean and standard deviations (mean ± SD) were used, and categorical variables were reported as numbers (percentages) in each group. The Chi-square test and analysis of variance (ANOVA) were used to compare the variables among TyG quartiles (Qs).

For modeling freedom from events over time, the Kaplan-Meier method was used, while for comparison of outcomes among TyG quartiles, the log-rank test was implemented. The impact of TyG quartiles was assessed in the total population as well as the euglycemic subgroup of patients. Euglycemia was defined as FPG < 100 mg/dL, HbA1c < 5.7%, and no history of diabetes. The association between TyG quartiles and MACCE and its components was investigated through the calculation of unadjusted and adjusted Cox proportional hazard ratios (HRs) and their 95% confidence intervals (CIs) and three models were designed. Model 1 was unadjusted, model 2 was adjusted for age and sex, and model 3 (i.e. fully adjusted) was adjusted for age, sex, LVEF, hypertension, BMI, WC, LDL-C, HDL-C, creatinine, hemoglobin, family history of cardiac disease, cigarette smoking, opium consumption, type of ACS (STEMI, NSTEMI, or UA), and past medical histories of congestive heart failure, valvular heart disease, cerebrovascular disease, cardiopulmonary resuscitation (CPR), chronic lung disease, peripheral vascular disease, previous CABG, previous PCI, atrial fibrillation, STEMI, NSTEMI, UA, and SA. All statistical analyses were performed using R version 4.2.3 and packages *"survival"* and *"survminer"* under a two-sided P of 0.05 for statistical significance.

Results

Baseline characteristics

A total of 13,542 patients who presented with ACS and underwent PCI were included. Patients were assigned to four groups according to Qs of baseline TyG: TyG ≤ 8.54 (Q1), 8.55 ≤ TyG ≤ 8.93 (Q2), 8.94 ≤ TyG ≤ 9.39 (Q3), and

TyG > 9.39 (Q4). Baseline characteristics including demographics, comorbidities, past medical histories, laboratory tests, and PCI characteristics according to Qs of the TyG index are available in Table 1.

Patients in Q4 were younger and the male percentage was lower compared to Q1. Moreover, they had higher mean BMI, higher mean WC, and higher prevalence of hypertension, diabetes, and dyslipidemia compared to Q1. Past medical histories of HF, valvular heart disease, peripheral heart disease, previous CABG, and CVA were comparable between four Qs ($P > 0.05$). Moreover, no significant difference between the Qs of the TyG index was found in the pre-procedure stenosis percentage, ACC/AHA category, and PCI location of the target lesion ($P > 0.05$).

TyG and MACCE in ACS population

A 1-unit increment of TyG showed a significantly higher risk of MACCE in unadjusted (HR 1.09, 95% CI 1.01 to 1.18, $P = 0.034$), age- and sex-adjusted (HR 1.19, 95% CI 1.10 to 1.29, $P < 0.001$), and fully-adjusted (HR 1.18, 95% CI 1.08 to 1.30, $P < 0.001$) models (Table 2). After evaluating the same association between TyG and individual MACCE components, a 1-unit increment of TyG was significantly associated with a higher risk of MI (HR 1.34, 95% CI 1.15 to 1.55, $P < 0.001$), while TyG increments were not associated with TVR, TLR, CABG, stroke, and all-cause mortality (Supplementary Table 1).

The Kaplan-Meier plot illustrating MACCE-free survival based on months after PCI in Qs of the TyG index is shown in Fig. 1. The log-rank test comparing Qs of the TyG was significant ($P = 0.005$). There was higher MACCE incidence in Q4 compared to Q1 (fully-adjusted HR 1.29, 95% CI 1.08 to 1.53, $P = 0.005$), while comparable HRs were found for Q2 or Q3 vs. Q1($P > 0.05$) (Table 2). The adjusted models for components of MACCE between Q4 and Q1 were significant for MI (fully-adjusted HR 1.34, 95% CI 1.01 to 1.78, $P = 0.044$), while other components showed comparable MACCE occurrence (Supplementary Table 1). Kaplan-Meier plots and log-rank test P values comparing the TyG Qs in the occurrence of each MACCE component are available in Supplementary Figs. 1–6.

TyG index and MACCE in the euglycemic subgroup of the ACS population

After excluding patients with prediabetes or diabetes, 4,338 euglycemic patients were evaluated. Table 3 shows the association between the TyG and MACCE in the euglycemic subgroup. According to TyG Qs, patients were assigned to four groups: TyG index ≤ 8.28 (Q1), 8.29 ≤ TyG ≤ 8.60 (Q2), 8.61 ≤ TyG ≤ 8.94 (Q3), and TyG > 8.94 (Q4). The Kaplan-Meier plot comparing MACCE-free survival in this subgroup is shown in Fig. 2. The log-rank test showed no significant difference between TyG Qs in the occurrence of MACCE ($P = 0.420$). In the non-adjusted and age- and sex-adjusted models, we found comparable MACCE occurrence between TyG Qs, summarized in Table 3 (all $P > 0.05$). Finally, a 1-unit increment of TyG was not significantly associated with MACCE occurrence (fully-adjusted HR 1.06, 95% CI 0.82 to 1.38, $P = 0.662$).

Discussion

In this large registry-based cohort study on over 13,000 participants with ACS, significant association was demonstrated between the TyG index and incident MACCE. This association was observed with a roughly 8.9% increased risk of MACCE occurrence in the total population by a 1-unit increase in TyG. This association was more pronounced once the regression model was adjusted for prespecified covariates. Moreover, the incident MACCE in the TyG index Q4 was significantly higher than in the Tyg index Q1. Among the MACCE components, TyG index increment was significantly associated with increased incident MI, whereas no such associations were found for other MACCE components. Despite what was observed in the total population, in the sub-population of over 4000 euglycemic participants, no significant association was shown between TyG index increase and incident MACCE. The findings show evidence that the TyG index can potentially be a predictor for MACCE incidence in the ACS population, although it seems like this association is not observed in the euglycemic ACS population. This was one of the largest studies conducted on the effect of TyG as a novel predictor of adverse events, especially in diabetic patients.

Several novel indices and scores have been introduced for the prediction of adverse events in patients with ACS undergoing PCI. Some of these are highly related to the inflammatory status in these patients while others are as easy to measure as a simple complete blood cell count routinely performed for all of the patients [24–26]. In terms of the effects of diabetes, previously, we showed that while diabetes is associated with an increased risk of adverse events, prediabetes condition does not add significant hazards [27]. Considering the complex association between diabetes and ACS prognosis, a simple marker able to show insulin resistance could be a hands-on tool for the determination of prognosis in these patients. In contrast with HOMA-IR which needs measurement of serum insulin levels and is quite unavailable in low resource areas, the TyG index is one of the novel indices shown to have high values in the determination of cardiovascular disease prognosis [28–31].

The results of our study are supported by multiple previous studies. A systematic review and meta-analysis in 2023 was conducted on studies reporting an association

Table 1 Baseline characteristics of the total population according to quartiles of TyG index

	Q1 (≤ 8.54) (*N* = 3386)	Q2 (8.55–8.93) (*N* = 3385)	Q3 (8.94–9.39) (*N* = 3385)	Q4 (> 9.39) (*N* = 3386)	*P*
TyG index	8.2 ± 0.3	8.7 ± 0.1	9.1 ± 0.1	9.9 ± 0.4	< 0.001
Age (years)	65.3 ± 11.4	62.8 ± 11.1	61.9 ± 10.6	60.6 ± 10.3	< 0.001
Sex (Male)	2699 (79.7)	2592 (76.6)	2380 (70.3)	2158 (63.7)	< 0.001
BMI (kg/m^2)	26.8 ± 4.3	28.1 ± 4.3	28.8 ± 4.5	29.3 ± 4.5	< 0.001
Waist circumference (cm)	97.3 ± 10.4	100.0 ± 10.5	101.3 ± 10.4	102.5 ± 10.2	< 0.001
Hypertension	1644 (48.6)	1740 (51.4)	1864 (55.1)	2012 (59.4)	< 0.001
Diabetes	548 (16.2)	882 (26.0)	1488 (44.0)	2513 (74.2)	< 0.001
Cigarette smoking	1487 (43.9)	1441 (42.6)	1345 (39.7)	1307 (38.6)	< 0.001
Dyslipidemia	1103 (32.6)	1611 (47.6)	2505 (74.0)	3039 (89.8)	< 0.001
Heart failure	103 (3.0)	90 (2.6)	77 (2.3)	97 (2.9)	0.242
Atrial fibrillation	41 (1.2)	20 (0.6)	25 (0.7)	18 (0.5)	0.006
Valvular heart disease	74 (2.2)	57 (1.7)	56 (1.6)	48 (1.4)	0.102
Peripheral vascular disease	7 (0.2)	14 (0.4)	9 (0.3)	12 (0.4)	0.428
Chronic lung disease	76 (2.2)	86 (2.5)	92 (2.7)	55 (1.6)	0.015
Previous PCI	560 (16.5)	563 (16.6)	569 (16.8)	639 (18.9)	0.032
Previous CABG	304 (9.0)	331 (9.8)	332 (9.8)	347 (10.2)	0.356
History of CVA	114 (3.4)	96 (2.8)	93 (2.7)	126 (3.7)	0.072
Family history of CAD	616 (18.2)	638 (18.8)	682 (20.2)	716 (21.1)	0.011
Opium consumption	633 (18.7)	550 (16.2)	502 (14.8)	419 (12.4)	< 0.001
History of STEMI	188 (5.6)	195 (5.8)	189 (5.6)	190 (5.6)	0.983
History of NSTEMI	461 (13.6)	445 (13.1)	443 (13.1)	457 (13.5)	0.899
History of UA	1108 (32.7)	1220 (36.0)	1272 (37.6)	1196 (35.3)	< 0.001
History of SA	73 (2.2)	60 (1.8)	73 (2.2)	69 (2.0)	0.643
LVEF (%)	45.2 ± 9.2	45.8 ± 9.0	46.3 ± 9.0	45.5 ± 9.2	< 0.001
Total cholesterol (mg/dL)	140.4 ± 35.2	152.2 ± 38.4	163.3 ± 40.3	175.5 ± 47.2	< 0.001
TG (mg/dL)	80.1 ± 21.0	120.5 ± 24.6	161.2 ± 42.4	259.4 ± 142.7	< 0.001
LDL-C (mg/dL)	86.9 ± 31.3	96.1 ± 33.4	103.9 ± 35.6	106.4 ± 36.1	< 0.001
HDL-C (mg/dL)	41.2 ± 10.4	38.8 ± 9.3	38.1 ± 8.8	37.6 ± 9.9	< 0.001
TG/HDL-C	2.1 ± 0.8	3.3 ± 1.1	4.5 ± 1.7	7.5 ± 5.4	< 0.001
FPG (mg/dL)	97.8 ± 19.4	108.6 ± 25.3	125.9 ± 41.8	182.0 ± 74.0	< 0.001
Creatinine (mg/dL)	1.01 ± 0.58	1.00 ± 0.40	0.99 ± 0.51	0.98 ± 0.41	0.083
Hemoglobin (g/dL)	14.6 ± 1.8	14.8 ± 1.8	14.7 ± 1.8	14.7 ± 1.9	0.001
Lesion length (mm)	25.5 ± 12.4	25.9 ± 13.5	25.8 ± 12.6	26.4 ± 13.5	0.023
Pre-procedure stenosis (%)	91.7 ± 9.0	91.5 ± 9.4	91.9 ± 8.8	91.7 ± 8.6	0.372
ACS type					
STEMI	1311 (38.7)	1211 (35.8)	1162 (34.3)	1186 (35.0)	0.001
NSTEMI	610 (18.0)	610 (18.0)	597 (17.6)	652 (19.2)	
UA	1465 (43.3)	1564 (46.2)	1626 (48.0)	1548 (45.7)	
Pre-procedure TIMI flow					
0	927 (27.4)	916 (27.1)	892 (26.4)	856 (25.3)	0.037
1	115 (3.4)	150 (4.4)	134 (4.0)	156 (4.6)	
2	458 (13.5)	420 (12.4)	494 (14.6)	483 (14.3)	
3	1886 (55.7)	1898 (56.1)	1865 (55.1)	1891 (55.8)	
Vessel severity					
Single vessel	1313 (38.8)	1268 (37.4)	1225 (36.2)	1110 (32.8)	< 0.001
Two vessels	1144 (33.8)	1124 (33.2)	1169 (34.5)	1224 (36.1)	
Three vessels	922 (27.2)	984 (29.1)	985 (29.1)	1046 (30.9)	
ACC/AHA category					
A	7 (0.2)	5 (0.1)	3 (0.1)	6 (0.2)	0.136
B1	573 (16.9)	634 (18.7)	634 (18.7)	623 (18.4)	
B2	507 (15.0)	492 (14.5)	457 (13.5)	435 (12.8)	
C	2297 (67.9)	2254 (66.6)	2290 (67.7)	2322 (68.6)	

Table 1 (continued)

	Q1 (≤ 8.54) (*N* = 3386)	Q2 (8.55–8.93) (*N* = 3385)	Q3 (8.94–9.39) (*N* = 3385)	Q4 (> 9.39) (*N* = 3386)	*P*
PCI location					
Ostial	383 (11.3)	375 (11.1)	367 (10.8)	364 (10.8)	0.227
Proximal	1214 (35.8)	1283 (37.9)	1235 (36.5)	1185 (35.0)	
Non-Proximal	1789 (52.8)	1727 (51.0)	1783 (52.7)	1837 (54.2)	

TyG: triglyceride-glucose index, BMI: body mass index, PCI: percutaneous coronary intervention, CABG: coronary artery bypass grafting, CVA: cerebrovascular accident, STEMI: ST-elevated myocardial infarction, NSTEMI: non-ST-elevated myocardial infarction, UA: unstable angina, SA: stable angina, LVEF: left ventricular ejection fraction, TG, triglycerides, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, FPG: fasting plasma glucose, MI: myocardial infarction, ACS: acute coronary syndrome, TIMI: thrombolysis in myocardial infarction, ACC/AHA: American College of Cardiology/American Heart Association

Table 2 Risk of MACCE in the total population across unadjusted and adjusted models

	Model 1[a]		Model 2[b]		Model 3[c]	
	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*
Per 1-unit increment	1.089 [1.006–1.179]	0.034	1.188 [1.095–1.289]	< 0.001	1.184 [1.078–1.300]	< 0.001
Q1 (≤ 8.54)	Ref	Ref	Ref	Ref	Ref	Ref
Q2 (8.54–8.93)	0.977 [0.837–1.141]	0.768	1.046 [0.895–1.222]	0.575	1.066 [0.899–1.263]	0.464
Q3 (8.94–9.39)	0.892 [0.762–1.044]	0.154	0.990 [0.844–1.160]	0.896	1.002 [0.838–1.199]	0.978
Q4 (> 9.39)	1.167 [1.007–1.353]	0.040	1.359 [1.167–1.582]	< 0.001	1.286 [1.080–1.532]	0.005

[a] Model 1: Unadjusted

[b] Model 2: Adjusted with age and sex

[c] Model 3: Adjusted with age, sex, left ventricular ejection fraction, hypertension, body mass index, waist circumference, LDL-C, HDL-C, creatinine, hemoglobin, family history of CAD, cigarette smoking, opium, type of ACS (STEMI, NSTEMI, or UA), and past medical histories of congestive heart failure, valvular heart disease, cerebrovascular disease, CPR, previous CABG, previous PCI, atrial fibrillation, STEMI, NSTEMI, UA, and SA

MACCE: major adverse cardiac and cerebrovascular events, HR: hazard ratio, CI: confidence interval, Ref: reference

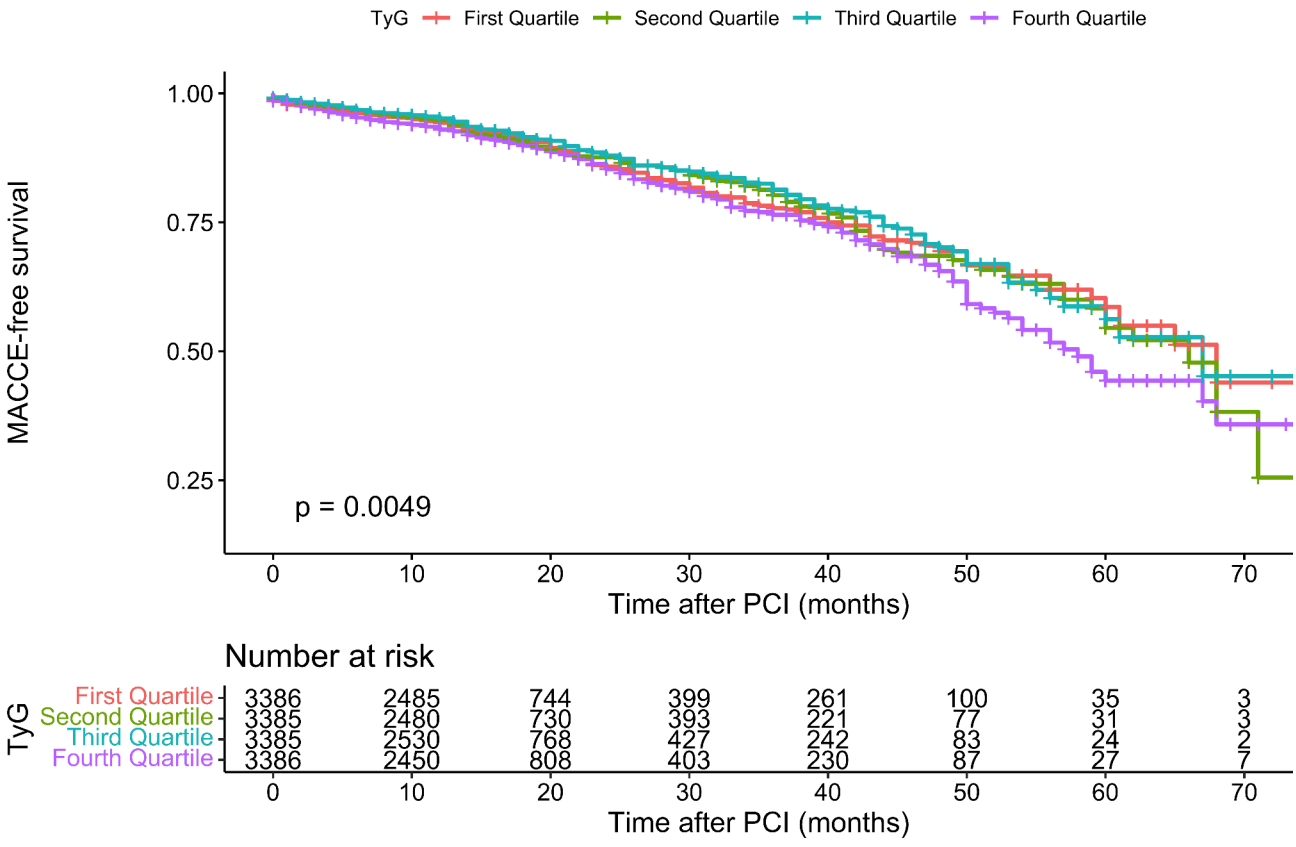


Fig. 1 Kaplan Meier graph for comparing major adverse cardiac and cerebrovascular events between quartiles of the TyG index in the overall ACS population

Table 3 Risk of MACCE in the euglycemic population across unadjusted and adjusted models

	Model 1[a]		Model 2[b]		Model 3[c]	
	HR [95% CI]	*P*	HR [95% CI]	*P*	HR [95% CI]	*P*
Per 1-unit increment	0.843 [0.682–1.043]	0.116	0.918 [0.736–1.146]	0.451	1.060 [0.815–1.379]	0.662
Q1 (≤ 8.28)	Ref	Ref	Ref	Ref	Ref	Ref
Q2 (8.28–8.60)	0.884 [0.661–1.181]	0.404	0.918 [0.686–1.229]	0.567	1.029 [0.748–1.417]	0.859
Q3 (8.61–8.94)	0.834 [0.622–1.120]	0.228	0.902 [0.669–1.217]	0.499	0.917 [0.650–1.295]	0.623
Q4 (> 8.94)	0.785 [0.582–1.060]	0.114	0.869 [0.638–1.185]	0.375	1.063 [0.745–1.517]	0.735

[a] Model 1: Unadjusted

[b] Model 2: Adjusted with age and sex

[c] Model 3: Adjusted with age, sex, left ventricular ejection fraction, hypertension, body mass index, waist circumference, LDL-C, HDL-C, creatinine, hemoglobin, family history of CAD, cigarette smoking, opium, type of ACS (STEMI, NSTEMI, or UA), and past medical histories of congestive heart failure, valvular heart disease, cerebrovascular disease, CPR, previous CABG, previous PCI, atrial fibrillation, STEMI, NSTEMI, UA, and SA

MACCE: major adverse cardiac and cerebrovascular events, HR: hazard ratio, CI: confidence interval, Ref: reference

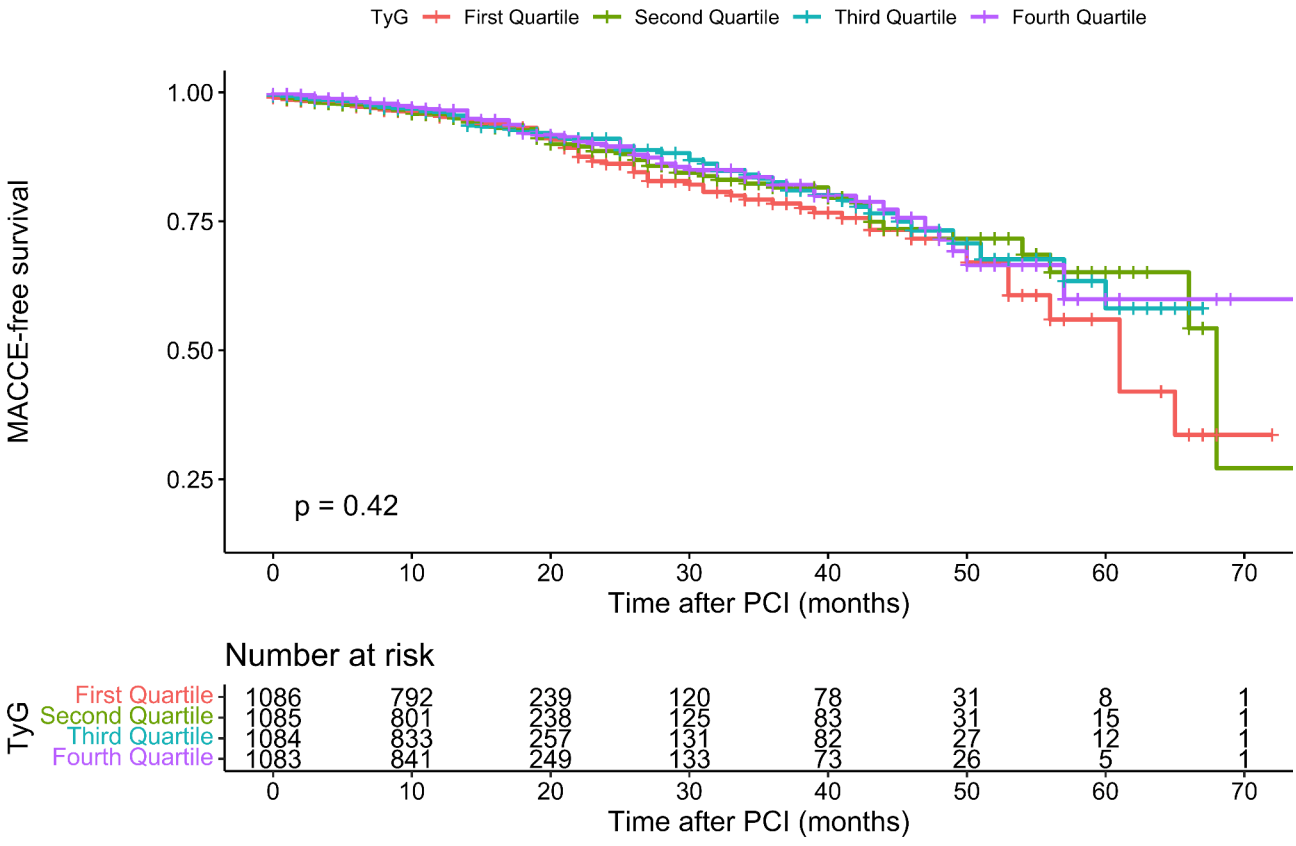


Fig. 2 Kaplan Meier graph for comparing major adverse cardiac and cerebrovascular events between quartiles of the TyG index in the euglycemic subgroup of the ACS population

between the TyG index and MACCE in patients with coronary artery disease [30]. In a subset of their study, they included 13 studies comparing MACCE events in groups of high and low TyG index in ACS patients. Of the 13 included studies: in 12 studies patients underwent PCI and only one of the studies was a prospective cohort study on 776 patients with type-2 diabetes and ACS undergoing PCI [32]; the rest of the included studies were retrospective cohorts, the largest sample size among which was 9285 [33]. The meta-analysis showed a significantly higher risk of MACCE occurrence in high TyG versus low TyG (HR: 2.09, 95% CI 1.68–2.62). Furthermore, they did the exact meta-analysis on 5 studies reporting the TyG index as a continuous variable, the result of which indicated a significantly higher incident MACCE by TyG increment (HR: 2.28, 95% CI 1.44–3.63) [30]. The results of this meta-analysis study are highly compatible with what we reported. Likewise, a recent 2022 retrospective cohort study on 1694 patients with ACS undergoing PCI showed similar results as ours [20]. They indicated that the risk of MACCE significantly increased with the increased baseline TyG index.

Interestingly, they demonstrated an even stronger prediction value for incident MACCE for the mean TyG index, i.e., the average TyG value for the patients calculated at follow-up visits [20].

We observed no significant association between the TyG index and the incidence of MACCE in euglycemic patients with ACS receiving PCI. In line with our results, a 2021 retrospective study in Poland on 1340 patients without diabetes and with acute myocardial infarction undergoing emergency PCI showed that the TyG index was not a significant predictor of MACCE [34]. Conversely, in a 2021 retrospective study in China on 1510 patients without diabetes and with NSTE-ACS undergoing elective PCI, the TyG index was found to be a significant predictor of MACCE [35]. It seems possible that the ACS type and being diagnosed with diabetes play pivotal roles in determining a predictor role for the TyG index in ACS patients receiving PCI. There is a need for assessment of the prognostic impact of TyG, as a surrogate marker of IR, in patients without diabetes in larger studies to confirm our findings. However, for now, it is evident that the clinical applications of TyG might be much more prominent in diabetic patients, and in real-life clinical practice, cardiologists should predict a higher rate of adverse events in diabetic patients with higher insulin resistance.

Strengths and limitations

To our knowledge, our study has the largest sample size among studies investigating the TyG index in participants with ACS undergoing PCI. Although this is a single-center study, thus potentially prone to selection bias, our center is a tertiary referral center with patients referred from all over Iran. Our study is limited due to its observational nature, making it unable to draw any conclusion on the causality between the TyG index and MACCE. Moreover, this is a retrospective cohort study conducted on a prospective registry in which the confounding effect and recall bias cannot be ruled out entirely. This study is limited as it has used the baseline TyG index and other covariates and has not included the follow-up values in the study design. In addition, as the baseline variables and outcomes were conducted by different clinicians at different times, heterogeneity affects the validity of our findings. Finally, there might be some other confounders such as inflammatory markers and socioeconomic status that were not measured in our study.

Conclusions

In our registry comprising over 13,000 participants with ACS, an increased TyG index was shown to be significantly associated with the higher incidence of MACCE. In addition, the TyG Q4 compared to Q1, was accompanied by a significantly higher risk for developing MACCE. Given that in the euglycemic ACS population, no such associations were observed, future studies are warranted to support this evidence. Overall, we demonstrated evidence of the TyG index as a biomarker of MACCE risk prediction in prediabetic and diabetic patients. Prospective studies with large sample sizes are required to confirm our findings and elaborate on the role of diabetes in this association.

Supplementary Information

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Supplementary Material 1

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Author contributions
AK, AHB: study conception/data analysis/drafting the manuscript/revision; YP, AR, TM, AA, SSK, IM: drafting the manuscript/revision; MM, AV, FM, KN, MKA, AH, JRN: drafting and critical revision of the manuscript; KH, AVH: study conception/drafting the manuscript/critical revision of the manuscript. All authors read and approved the final manuscript.

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Data availability
The data used in this study will be made available upon reasonable request from the corresponding author.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
The study proposal (IR.TUMS.MEDICINE.REC.1402.434) received approval from the ethics committee at the Tehran University of Medical Sciences. The need for informed consent was waived by the ethics committee due to retrospective nature of this study.

Consent to publish
Not applicable.

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