Original Article Open Access

Association between Triglyceride-glucose index and coronary artery in-stent restenosis: A case-control study in an Iranian patient population

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Received: 2025-10-29
Accepted: 2026-04-15

How to cite this article:
Kolahi Ahari R, Eftekhar R, Sahranavard T, Najjari M, Karami S, Shabani N, Safavishamloo M, Soleimani A, Ferns G, Moohebati M, Saffar Soflaei S, Ghayour-Mobarhan M. **Association between Triglyceride-glucose index and coronary artery in-stent restenosis: A case-control study in an Iranian patient population.** ARYA Atheroscler. 2026; 22(3): 53-66.

DOI:
https://doi.org/10.48305/arya.2026.45619.3101

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Abstract

BACKGROUND: The Triglyceride-glucose (TyG) index, a useful surrogate marker of insulin resistance (IR), is associated with cardiovascular disease (CVD). However, the correlation between the TyG index and coronary in-stent restenosis (ISR) remains unknown.

METHODS: A total of 325 subjects who underwent coronary angiography due to acute coronary syndrome (ACS) ≥ 1 month after stent implantation were included in this retrospective case-control study from December 2014 to April 2017. Based on ISR status (≥ 50% stenosis), 111 patients were assigned to the ISR group and 214 to the non-ISR (NISR) group. Baseline characteristics and biochemical data were gathered. Logistic regression (LR) analysis was used to evaluate the predictive value of the TyG index for ISR with different models. $P < 0.05$ was considered statistically significant.

RESULTS: The TyG index was significantly higher among patients with ISR compared with NISR patients (8.84 ± 0.85 vs. 8.61 ± 0.63; P = 0.010). The TyG index remained an independent predictor for ISR in all multivariable LR analysis models, with the fully adjusted model demonstrating the strongest relation (OR = 2.239; 95% CI: 1.325–3.782; P = 0.003). Furthermore, the risks for ISR were almost 5-fold greater in patients in the highest TyG quartile than in those in the lowest quartile (95% CI: 1.718–14.454; P = 0.003).

CONCLUSION: An elevated TyG index is independently linked with ISR. Consequently, the TyG index acts as a simple and pivotal marker for identifying patients at higher risk of ISR and for evaluating adverse cardiovascular outcomes.

Keywords: Triglyceride-Glucose Index; Coronary In-Stent Restenosis; Stent; Acute Coronary Syndrome

Introduction

Coronary artery disease (CAD) results from atherosclerosis, characterized by the thickening of the inner arterial lining and the narrowing of the arterial lumen[1]. In 2019, CAD was responsible for approximately 9 million deaths globally[2]. In Iran, around 50% of annual deaths are attributed to CAD[3]. Despite the availability of various treatment options for CAD, it remains a significant cause of morbidity and mortality on a global scale[4]. Two primary approaches have been developed to address atherosclerosis: pharmacological interventions and device-based strategies (DBS)[5]. One such DBS approach is stent implantation, which entails the insertion of a metal stent into the narrowed arteries. Among the therapeutic methods for treating atherosclerosis are bare metal stents (BMS) and drug-eluting stents (DES)[6]. In-stent restenosis (ISR) refers to the occurrence of restricted blood flow following stent placement[7,8]. Coronary ISR denotes the loss of the stented lumen that arises after percutaneous coronary intervention (PCI) or percutaneous transluminal stenting (PTAS), necessitating revascularization. The factors contributing to this phenomenon are not completely understood[9]. The clinical incidence of ISR following BMS implantation has been documented to range from 20% to 30%, while the application of DES can decrease the incidence of ISR by 5% to 10%[10]. Numerous factors have been identified as predisposing individuals to ISR, including insulin resistance (IR) strategies, which can be assessed using the homeostasis model assessment of insulin resistance (HOMA-IR), triglyceride-glucose (TyG) criteria, high-sensitivity C-reactive protein (hs-CRP), stent type, and the number of stents used[11–13].

The TyG index was first introduced in 2008 as a valuable measure of IR. It has been noted that the TyG index serves as an appropriate indicator for developing nations where laboratory testing for IR is not readily available. Prior research indicates that elevated TyG levels correlate with cardiovascular disease (CVD)[10]. Most studies on this subject focus on the Chinese demographic, which may limit the applicability of findings to other ethnic groups[13–15]. Additionally, the evidence regarding the relationship between the TyG index and CVD remains inconsistent[16–18]. In this study, we sought to determine the connection between the TyG index and coronary ISR in an Iranian adult cohort exhibiting coronary symptoms after stent placement.

Methods

Study population

This evaluation was carried out in Mashhad city, located in northeastern Iran, from December 2014 to April 2017. A total of 325 participants with a history of coronary stent implantation more than 1 month, who were later referred for angiography due to ACS occurring at least 1 month post-surgery, were included in the study. The exclusion criteria were as follows: (1) age < 18 years; (2) participants who underwent primary PCI within the first month following angioplasty; (3) a diagnosis of myocardial infarction (MI); (4) restenosis resulting from conditions such as active cancer, thrombosis, and autoimmune disorders; and (5) lack of baseline measurements necessary for calculating the TyG index. According to angiographic findings, 111 subjects with ≥ 50% in-stent stenosis were categorized as the ISR group, while 214 subjects with < 50% stenosis were categorized as the NISR group[19]. The flow chart depicting the study subjects and the final analysis plan is illustrated in Figure 1.

Data collection

Demographic, clinical, and laboratory parameters of the participants were gathered. All blood samples were obtained after a 14-hour fasting period and were centrifuged for 15 minutes at 1000 g to isolate the serum. The sera were preserved at -80°C before analysis. Serum hs-CRP was assessed using a BT-3000 autoanalyzer and Biosystems Assay kit. Additional biomedical data were evaluated using the same autoanalyzer and Pars Azmoon kits. The Friedewald formula was employed to compute low-density lipoprotein cholesterol (LDL-C). Echocardiography, specifically the Simpson's two-plane method,

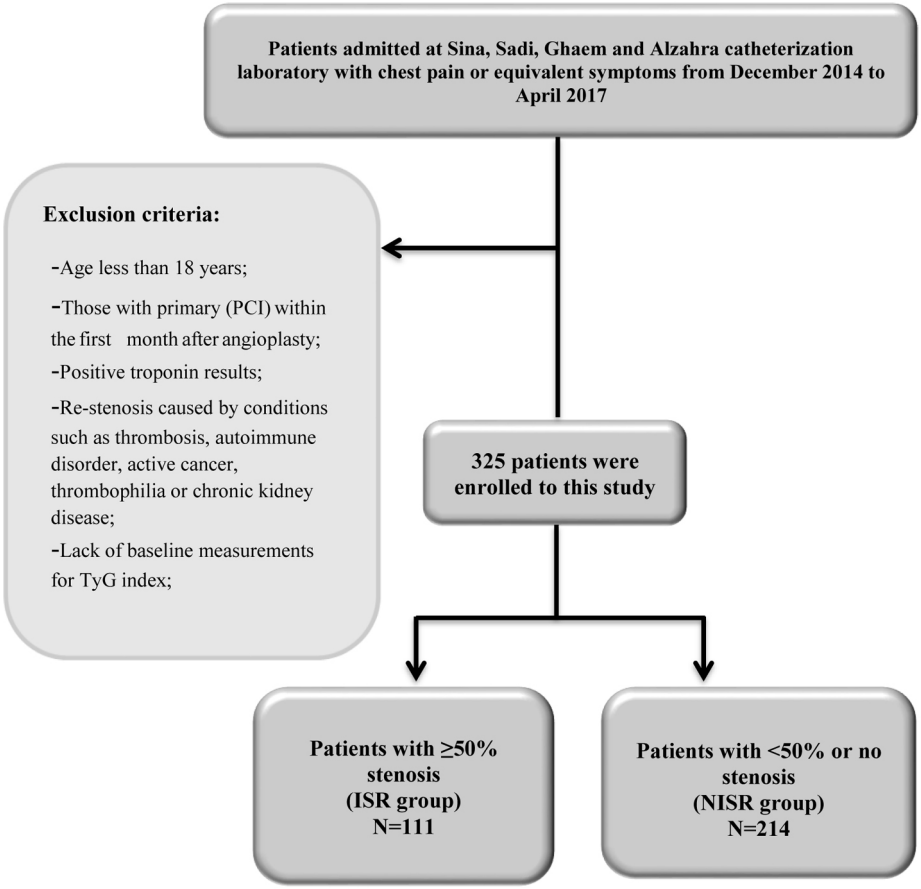

Figure 1. The flowchart of present study

was used to determine left ventricular ejection fraction (LVEF).

Definitions

Dyslipidemia was characterized by total cholesterol (TC) ≥ 200 mg/dL, LDL-C > 130 mg/dL, triglycerides (TG) > 150 mg/dL, and high-density lipoprotein cholesterol (HDL-C) < 50 mg/dL for women or HDL-C < 40 mg/dL for men.

Hypertension (HTN) was defined as a history of hypertension with the use of antihypertensive medication or recurrent blood pressure readings ≥ 140/90 mmHg.

Diabetes mellitus (DM) was identified as fasting blood glucose (FBG) ≥ 126 mg/dL or the use of glucose-lowering agents.

Body mass index (BMI) was calculated by dividing weight (kg) by height (m^2).

The TyG index was assessed as ln [fasting TG (mg/dL) x FSG (mg/dL)/2][20].

Statistical analysis

The distribution of continuous and categorical variables was characterized by the mean ± standard deviation (SD) and frequency (%), respectively. Given that TG and hs-CRP exhibited a skewed distribution, they were represented by the median along with the interquartile range (IQR). To compare the variables, Student's t-test, chi-square test, the Mann-Whitney U test, and the Kruskal-Wallis test were utilized. LR analysis was conducted to examine the relationship between the TyG index and ISR through multiple analytical models. The receiver operating characteristic (ROC) curve analysis was performed using MedCalc software to determine the discriminative cut-point for detecting ISR. Statistical analysis was executed using SPSS 26.0 (Chicago, Illinois, USA). P < 0.05 was considered statistically significant.

Table 1. Baseline and clinical characteristics of the study population

Characteristics		NISR (n= 214)	ISR (n= 111)	P-value*
Male n(%)		146 (68.20 %)	81 (73 %)	0.370
Age (year)		61.96±8.94	60.70±8.80	0.230
Smoking status n(%)		39 (18.20 %)	13 (12.30 %)	0.133
Diabetes n(%)		67 (31.80 %)	63 (57.30 %)	**<0.001**
HTN n(%)		131 (61.50%)	61 (55%)	0.250
Dyslipidemia n(%)		111 (52.40%)	67 (60.90%)	0.142
Statin n(%)		195 (93.80%)	102 (97.10%)	0.199
Aspirin n(%)		197 (95.20%)	103 (97.20%)	0.400
Clopidogrel n(%)		173 (84.40%)	95 (93.10%)	**0.015**
NSAID n(%)		3 (1.50%)	5 (4.80%)	0.340
Corticosteroids n(%)		5 (2.50%)	0 (0%)	0.190
β blocker n(%)		33 (15.40%)	18 (16.20%)	0.850
ARB n(%)		62 (29%)	30 (27%)	0.710
ACE inhibitor n(%)		13 (6.10%)	10 (9%)	0.350
CCB (%)		19 (8.90%)	4 (3.60%)	0.070
Insulin n(%)		21 (9.80%)	17 (15.30%)	0.140
Stent type n(%)	BM	52 (36.60%)	41 (60.30%)	**0.010**
	DE	90 (63.40%)	27 (39.70%)	
Stent number n(%)	1	169 (82.80%)	77 (71.30%)	**0.017**
	>1	35 (17.20%)	31 (28.70)	
SBP (mmHg) (Mean±SD)		125.88±16.71	122.98±12.27	0.150
DBP (mmHg) (Mean±SD)		77.50±9.15	78.27±7.88	0.480
BMI (Mean±SD)		29.66±29.44	26.83±3.54	0.180
LVEF (Mean±SD)		51.46±10.52	50.72±8.75	0.590
FSG (mg/dl) (Mean±SD)		108.64±56.19	127.11±70.92	**0.010**
hs-CRP (mg/dl) (Median [Q1-Q3])		2.30 [1.30-4.19]	3.46 [1.79-7.80]	**0.005**
TC (mg/dl) (Mean±SD)		149.43±40.05	155.74±41.94	0.210
TG (mg/dl) (Median [Q1-Q3])		111.50 [79.75-148.75]	127 [79.75-149.25]	**0.039**
HDL-C (mg/dl) (Mean±SD)		35.78±10.61	35.16±8.33	0.580
LDL-C (mg/dl) (Mean±SD)		89.07±32.45	89.90±31.36	0.830

Abbreviations: ACE Inhibitor: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; BM: bare metal; BMI: body mass index; CCB: calcium channel blocker; DBP: diastolic blood pressure; DE: drug eluting; FSG: fasting serum sugar; HDL-C: high- density lipoprotein cholesterol; hs-CRP: high sensitivity C reactive protein; HTN: Hypertension; ISR: in-stent restenosis; LDL-C: low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; NSAID: Nonsteroidal anti-inflammatory drug; SBP: Systolic Blood Pressure; TC: Total Cholesterol; TG: Triglyceride.

*P-value less than 0.05 was considered significant. Significant p-values are shown in bold.

Results

Basic features

Among the 325 patients, 214 were allocated to the NISR group, whereas 111 were included in the ISR group. Notable differences were identified between the ISR and NISR groups regarding DM (P < 0.001), clopidogrel administration (P = 0.015), FSG concentrations (P = 0.010), hs-CRP levels (P = 0.005), and triglyceride concentrations (P = 0.039). Moreover, the TyG index was significantly higher in the ISR group compared to the NISR group (P = 0.010). Furthermore, the type of stent used (P = 0.010) and the quantity of stents applied (P = 0.017) also demonstrated significant disparities between the two groups. The ISR group that utilized BMS stents exhibited a usage rate approximately 50% greater than that of the DES group (see Table 1). As shown in Figure 2A, the prevalence of ISR in the TyG quartiles was significantly different (P = 0.021). Also, the prevalence of ISR in the fourth quartile was higher than in the other quartiles (47.6% vs. 30%, 32.9%, 25.4%). Figure 2B shows the median TyG index was significantly higher in the ISR group than the NISR group (ISR: 8.75 vs. NISR: 8.58; P = 0.032).

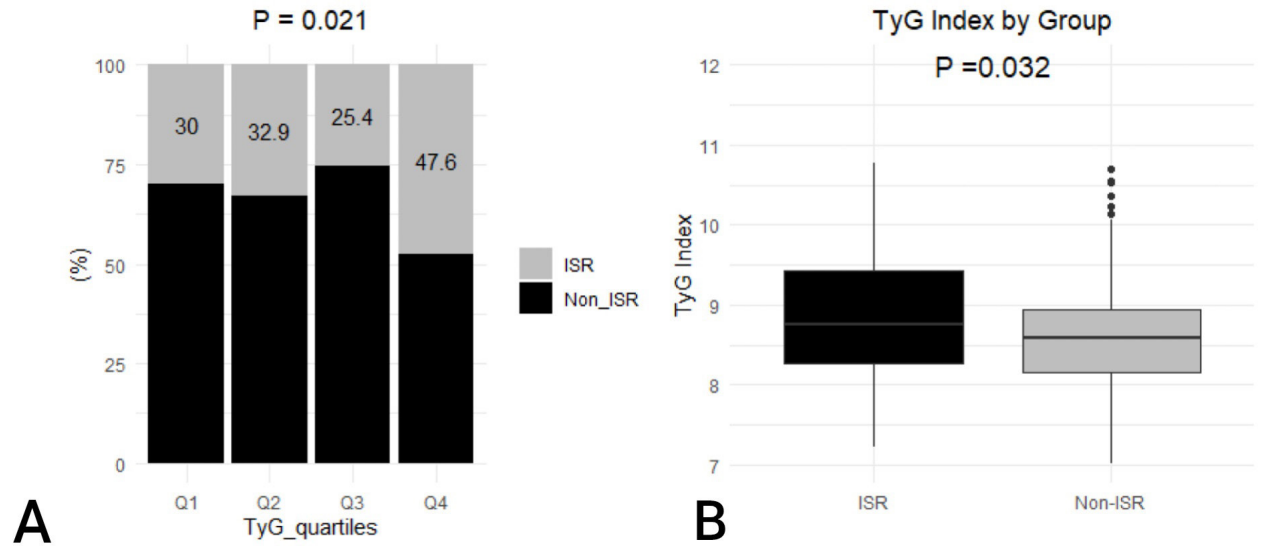

Figure 2. **(A)** Relationship between TyG quartiles and ISR prevalence and **(B)** comparison of TyG index distribution in ISR and Non-ISR groups

Table 2. Correlation between TyG index and other cardio-metabolic risk factors

Variable	Correlation coefficient (r)	P-value**
Age	0.005	0.905
TC	0.341	**<0.01**
LDL-C	0.121	**0.006**
HDL-C	-0.086	0.051
SBP	0.051	0.284
DBP	0.134	**0.005**

Abbreviations: TyG: triglyceride-glucose index; TC: total cholesterol; HDL-C: high-density lipoprotein-C; LDL-C: low-density lipoprotein-C; SBP: systolic blood pressure; DBP diastolic blood pressure.
**Correlation is significant at the 0.01 level (2-tailed). Significant p-values are shown in bold.

TyG Index and Its Correlation with Cardiometabolic Risk Factors

As shown in Table 2, the TyG index was positively correlated with TC (r = 0.341, P < 0.010), LDL-C (r = 0.121, P = 0.006), and diastolic blood pressure (DBP) (r = 0.134, P = 0.005). These results indicate that age, BMI, blood pressure, and lipid profile may influence both the TyG index and ISR, and they were therefore included as covariates in the adjusted models.

Asscociation betwwn TyG and ISR

LR analysis was utilized to investigate the association between the TyG index and ISR, while considering various confounding factors (Table 3). Model 1 evaluated the connection between the TyG index and ISR after controlling for the confounding effect of sex and age. In this model, the TyG index, regarded as a continuous variable, was recognized as an independent risk factor (RF) for ISR (OR = 1.561; 95% CI: 1.113–2.194; P < 0.001). Model 2 assessed the relationship after accounting for the variables in Model 1, in addition to the number of stents and the type of stent utilized. In this context, the TyG index continued to be acknowledged as an independent RF for ISR (OR = 1.631; 95% CI: 1.153–2.309; P = 0.006). Model 3 examined the association after adjusting for Model 1 along with BMI, hypertension, and smoking status. In this model, the TyG index remained an independent RF for ISR (OR = 1.894; 95% CI: 1.283–2.796; P = 0.001). Model 4 analyzed the relationship of the TyG index with ISR after adjusting for Model 1, BMI,

Table 3. Odds ratio for ISR by TyG index after adjustment

	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Continuous TyG				
	1.56 (1.113-2.194)*	1.631 (1.153-2.309)**	1.894 (1.283-2.796)**	2.239 (1.325-3.782)**
Categorical TyG				
Q1	Ref.	Ref.	Ref.	Ref.
Q2	1.041 (0.504-2.151)	0.930 (0.441-1.961)	1.294 (0.581-2.880)	1.385 (0.480-3.993)
Q3	0.737 (0.348-1.567)	0.736 (0.343-1.580)	0.898 (0.386-2.090)	1.284 (0.427-3.860)
Q4	2.154 (1.096-4.232)*	2.382 (1.191-4.762)*	3.231 (1.502-6.950)**	4.983 (1.718-14.454)**

Abbreviations: TyG: triglyceride-glucose index;
Model 1: Associations of TyG index with ISR after adjustment for sex and age
Model 2: Associations of TyG index with ISR after adjustment for sex and age and stent number and stent type
Model 3: Associations of TyG index with ISR after adjusting for age, sex, BMI, HTN and smoking status
Model 4: Associations of TyG index with ISR after adjusting for age, sex, BMI, HTN and smoking status, stent number and stent type
* P-value less than 0.05 are considered significant. Significant p-values are shown in bold.
** P value less than 0.01

hypertension, smoking status, stent number, and stent type. In this model, the TyG index continued to be an independent RF for ISR (OR = 2.239; 95% CI: 1.325–3.782; P = 0.003). When the TyG index was analyzed as a categorical variable, the highest quartile across all four models exhibited a significant and positive correlation with ISR when compared to the first quartile.

Subgroup analysis

Subgroup analysis was performed considering the TyG index as both a continuous and categorical variable. Figure 3 indicated that the prevalence of ISR was significantly different in the TyG quartiles for subgroups of age ≥ 61 years, female, non-current smoking, hypertensive, and BMI ≥ 25 subjects.

As shown in Figure 4, a significant positive association was observed between the TyG index and risk of ISR in the subgroups of age ≤ 61 years, female gender, hypertensive, non-current smoking, and BMI ≥ 25 subjects.

Predictive value of TyG criteria for ISR prevalence

We performed ROC analysis (Figure 5) to evaluate the ability of the TyG index to discriminate ISR and NISR groups within this retrospective case-control study. We emphasize that this analysis does not represent prospective diagnostic performance and should be interpreted as a descriptive measure of association between the TyG index and ISR within the selected sample. The area under the ROC curve (AUC) for the TyG index was 0.575 (95% CI: 0.517–0.633; P = 0.043), with a TyG cutoff > 9.3 yielding 31.4% sensitivity and 88.6% specificity.

Discussion

In this research, we assessed the relationship between the TyG index and ISR. We examined 325 participants with a history of coronary stenting who later underwent coronary angiography due to ACS. Our findings indicated that the TyG index was significantly elevated in the ISR group when compared to the NISR group. Additionally, we noted a significant positive correlation between the TyG index and various cardiometabolic RFs, such as TC, LDL-C, and DBP. Following adjustments for multiple co-factors in LR models, the link between the TyG index and ISR persisted.

A clear dose-response pattern was seen between TyG levels and ISR risk. Notably, the highest TyG quartile demonstrated a nearly

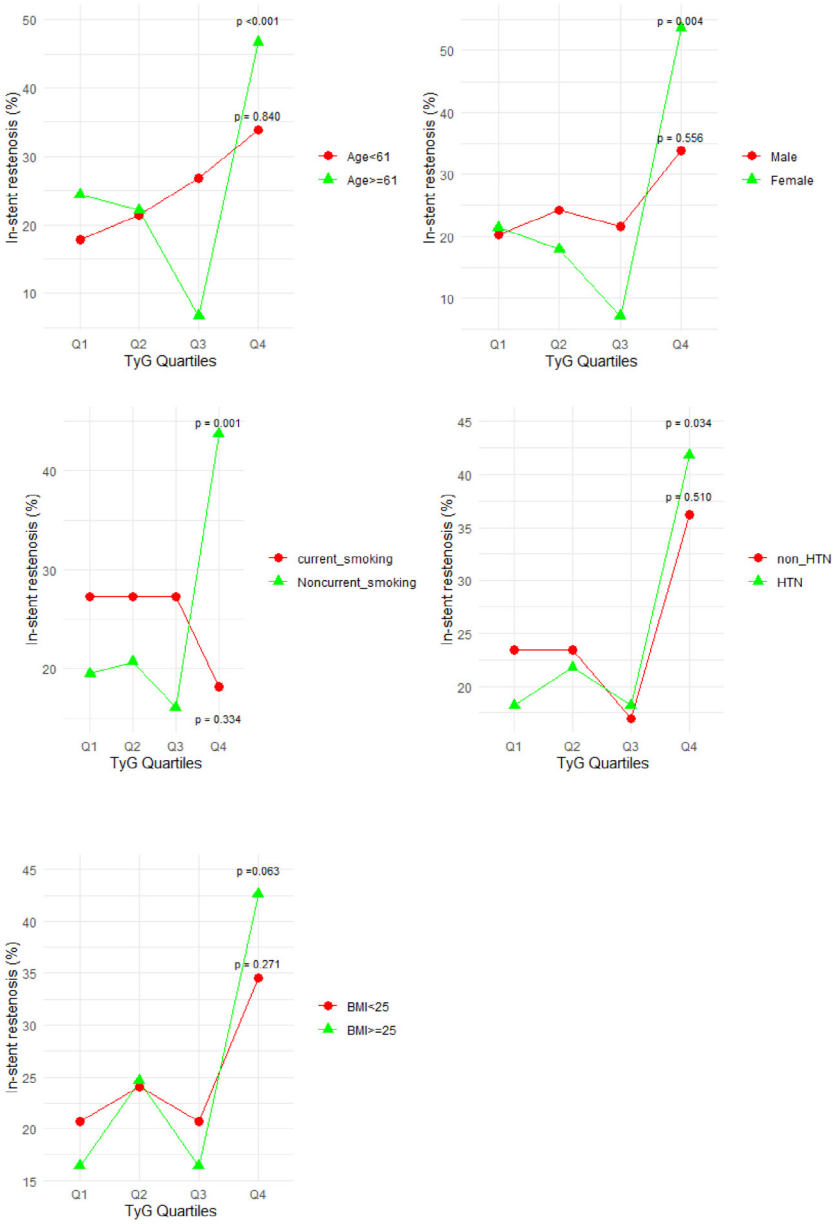

Figure 3. Subgroup line plots for the relationship between TyG quartiles and ISR prevalence

fivefold increased risk of ISR compared to patients in the lowest quartile. This dose-dependent association implies that higher degrees of IR may play an increasingly pivotal function in promoting neointimal hyperplasia and vascular injury after stent implantation[13,15,24]. These findings imply that this biomarker may serve as a valuable tool for evaluating the risk of ISR in patients with a history of stenting who experience ACS.

Despite notable advancements in reducing adverse outcomes following PCI, ISR remains a considerable complication, occurring in 3% to 20% of instances[23,25,26]. Research indicates that patients experiencing ISR are at an increased risk of adverse cardiac events and ACS during follow-up[27]. Consequently, the prompt identification of individuals predisposed to ISR is essential. The TyG index was initially proposed by Simental-Mendía et al. as a potential surrogate marker for IR, offering a comparison to HOMA-IR[28]. Elevated levels of the TyG index are linked to an increased risk of CVDs and related events[29]. In a cohort study involving 1092 patients with ST-segment

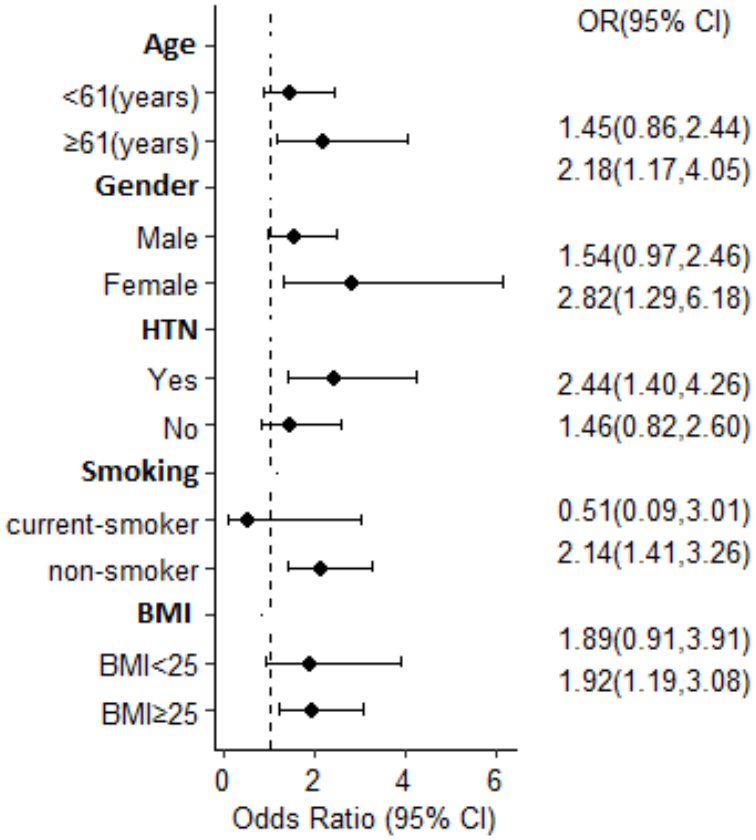

Figure 4. Adjusted subgroup forest plot for the association between the TyG index and ISR (adjusted for age, sex, BMI, HTN and smoking status). A significant positive association is observed between the TyG index and risk of ISR in the subgroups of age ≤61 years, female gender, hypertensive, non-current smoking and BMI ≥25 subjects

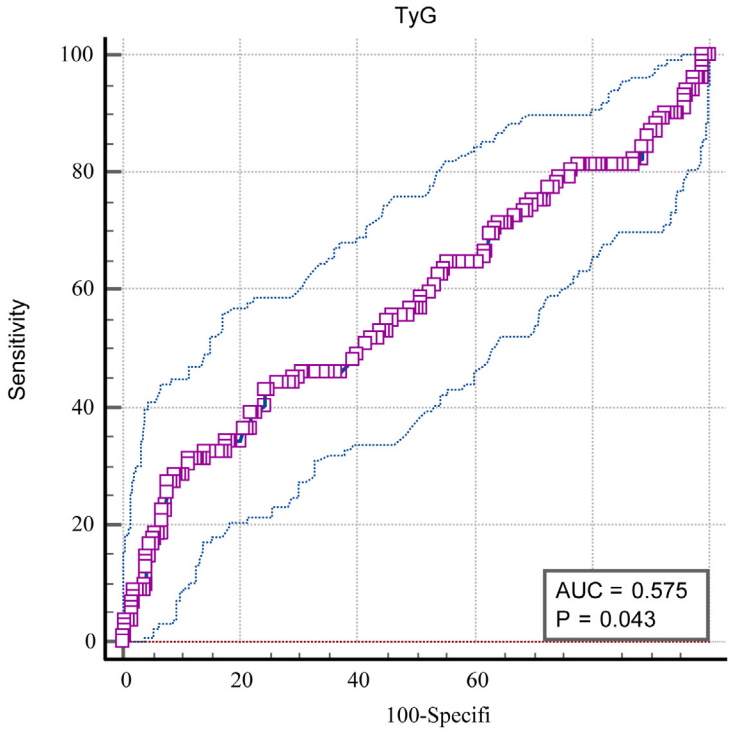

Figure 5. ROC curve analysis for TyG index and development of in-stent restenosis

elevation myocardial infarction (STEMI), Luo et al. identified a correlation between elevated TyG levels and unfavorable outcomes post-PCI[30]. Furthermore, Zhao et al. conducted a study with 2830 elderly participants, revealing that higher TyG levels were associated with an increased risk of renal microvascular injury and arterial stiffness[31]. Additionally, a study involving 1282 diabetic patients with CAD demonstrated that elevated TyG levels were significantly correlated with a heightened risk of adverse cardiovascular and cerebrovascular events, even after controlling for various confounding variables[32]. Notably, TyG levels were also linked to hospital readmissions and mortality due to CVD in diabetic patients suffering from heart failure[33].

Recently, a favorable correlation between the TyG score and ISR has been identified in patients with ACS[13], aligning with findings from other research[13,34,35]. Zhou and associates discovered that patients who successfully underwent DES-based PCI for ACS, specifically those exhibiting elevated TyG scores, had a significantly increased likelihood of experiencing DES-ISR[13]. According to reports of a prospective study, Guo and colleagues noted that a higher TyG score correlated with an elevated risk of long-term complications following PCI, including repeat revascularization and ISR[15]. Furthermore, a meta-analysis indicated a positive relationship between the TyG score (whether considered as a discrete or continuous variable) and atherosclerotic CVD[36].

Building upon the aforementioned findings, our research demonstrated that the TyG score exhibited a significant association with ISR, even after controlling for age, sex, BMI, hypertension, smoking status, the number of stents, and stent type across different models. Notably, no statistically significant increase in the risk of ISR was found in our quartile-based analysis for Q2 and Q3 TyG levels when compared with Q1. This may demonstrate a threshold effect where only notably high levels of TyG, as presented in Q4, will contribute to the progression of ISR. It is possible that metabolic dysfunctions may require a more advanced stage before exerting considerable vascular impact[37,38]. Moreover, akin to other studies[36,39], we identified positive correlations between the TyG index and cardiometabolic RFs. We propose that innovative therapeutic approaches aimed at lowering the TyG score could be viable in preventing ISR as a complication of PCI in the future.

Another significant finding of this research pertains to the influence of stent type. Our analysis revealed that ISR was markedly more prevalent among BMS compared to DES. This observation aligns with the conclusions drawn by Liang et al. The latest meta-analysis indicated that BMS were utilized in 60.9% of cases, with a notably higher incidence of ISR observed in these patients (73.1% versus 48.3%, P = 0.001)[14]. Additionally, another investigation noted that the ISR rate for DES was below 10%, whereas for BMS, it approached 25% at six months post-stenting[40]. Despite the established safety and effectiveness of DES in patients undergoing PCI, BMS remains prevalent in clinical settings. A primary factor contributing to this trend is the elevated risk of bleeding associated with the extended duration of dual antiplatelet therapy following DES[41,42]. Moreover, it has been observed that coronary arteries exhibit a quicker healing process after BMS implantation in comparison to DES implantation, which corroborates findings of an increased incidence of very late (> 1 year) in-stent thrombosis associated with DES[43,44].

Moreover, our research indicates that the quantity of stents exceeding one was markedly increased in the ISR group compared to controls. This finding aligns with the investigations conducted by Zhao et al.[23], Tang et al.[45], and Wan[46]. An increase in the number of stents correlates with a heightened risk of stent thrombosis[47,48], and the formation of thrombus contributes to stent restenosis[49]. Additionally, given that stents can inflict damage on the blood vessels themselves, a greater number of stents elevates the risk of vascular injury[50].

We observed that levels of hs-CRP were markedly higher in the ISR group in comparison

to the NISR group. This finding aligns with our earlier research conducted in 2019[51] as well as other investigations. A meta-analysis indicated that increased hs-CRP levels were linked to a greater risk of ISR and unfavorable outcomes in individuals with CAD who underwent stent implantation[52].

Inflammation is known to significantly influence both early and late complications associated with PCI, primarily due to arterial damage. Nevertheless, certain studies indicate that while hs-CRP levels are markedly elevated in individuals experiencing ISR, they do not serve as reliable predictors of restenosis[52,53]. Given that our research was not longitudinal in nature, additional studies are required to evaluate the predictive capacity of hs-CRP for ISR and to establish a causal link.

Diabetes has been identified as an independent predictor of restenosis risk[54,55]. As anticipated, our findings indicated that the ISR group exhibited a significantly higher prevalence of diabetes compared to the NISR group. This phenomenon may be linked to endothelial dysfunction and elevated levels of plasminogen activator inhibitor-1 (PAI-1) activity in individuals with diabetes, resulting in an increased likelihood of late in-stent thrombosis and subsequent PCI[56].

In our research, the sole medication that exhibited a significant difference between the ISR and NISR cohorts was clopidogrel. A notably higher number of ISR patients were utilizing clopidogrel in comparison to NISR patients. This discrepancy may be attributed to the fact that coronary symptoms manifested much earlier in ISR patients than in their NISR counterparts, particularly at the time clopidogrel was administered following PCI. Nevertheless, a study conducted by Kalyoncuoglu et al., which involved a smaller sample size (n = 124), did not reveal any statistical difference in clopidogrel usage between the ISR and NISR groups[26].

In the subgroup analyses, the correlation of the TyG index with ISR was particularly and consistently prominent in female patients, nonsmokers, those aged ≤ 61 years, patients with hypertension, and those with BMI ≥ 25 kg/m^2. These results may demonstrate greater metabolic susceptibility and inflammatory activation in these subgroups and that IR exerts a more harmful effect on vascular outcome under such clinical conditions[13,57].

Furthermore, a study involving 1608 individuals who underwent PCI, primarily with DES implantation, indicated that a diminished platelet response to clopidogrel was not linked to an elevated risk of restenosis[58].

Regarding the limitations, as this study was a case-control study, it demonstrated an association between the TyG index and ISR, rather than establishing a causal link. Consequently, additional longitudinal studies in this field are necessary. Furthermore, the findings of this research may not be applicable to other ethnic groups. Moreover, while the sample size was adequate, conducting further studies with larger cohorts could enhance the interpretation of the results. There is a need for multicenter and prospective studies to ascertain the predictive value of the TyG index in relation to the development of ISR as a complication of PCI.

Conclusion

This research demonstrated that the TyG index was markedly elevated in the ISR group in comparison to the NISR group. Furthermore, the TyG index was found to be independently linked to ISR in individuals with ACS following PCI, even after controlling for various confounding factors. This relationship underscores the clinical significance of the TyG index in evaluating adverse cardiovascular outcomes in patients who underwent coronary stent implantation and are experiencing ACS.

Acknowledgements

We wish to thank the participants of this study and colleagues at the Sina, Sadi, and Ghaem catheterization laboratories and technicians of the Isfahan Alzahra Genetics Laboratory. The authors also wish to thank Mashhad University of Medical Sciences (MUMS) for supporting this project.

Conflict of interests
The authors declare no conflict of interest.

Funding
There is no funding in this study.

Author's Contributions
Study Conception or Design: SSS; MJM
Data Acquisition: RE; MM; SSS
Data Analysis or Interpretation: RKA; RE; TS; NS; SSS
Manuscript Drafting: RKA; RE; MN; SK; MS; AS
Critical Manuscript Revision: GF

All authors have approved the final manuscript and are responsible for all aspects of the work.

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