Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

# Triglyceride–Glucose Index as a Predictor of Major Adverse Cardiovascular Events in Post-PCI Patients Diagnosed with In-Stent Restenosis

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**Background:** The triglyceride–glucose index (TyG) is a reliable indicator for predicting the prognosis of patients with coronary heart disease (CAD) after percutaneous coronary intervention (PCI). However, its influence on patients with in-stent restenosis (ISR) is unclear. This study was designed to evaluate the association between the TyG index and the occurrence of major adverse cardiovascular events (MACEs) after PCI in patients with ISR.

**Methods:** This retrospective study included 1654 patients who underwent PCI between 2016 and 2022 at Nanjing First Hospital. Patients were stratified into three groups based on the quantile level of the TyG index. The TyG index was determined as Ln (triglycerides [mg/dL] × fasting plasma glucose [mg/dL]/2).

**Results:** Individuals with the highest TyG index showed an increased risk of MACEs compared to those with the lowest level of the TyG index (HR 1.60; 95% CI 1.11–2.30; P = 0.01). When analyzing the TyG index as a continuous variable, each standard deviation increase was associated with an HR of 1.51 (95% CI: 1.11–2.05; P = 0.01). For the male subgroup and the diabetes subgroup, this trend was even more pronounced (HR 1.269; 95% CI 1.055–1.527; P = 0.011; HR 1.385; 95% CI 1.125–1.706; P = 0.002). Additionally, the landmark analysis showed that patients with the highest level of TyG had an increased risk of MACEs 6 months after the PCI (P = 0.019).

**Conclusion:** Elevated TyG index is associated with increased risk of adverse cardiovascular events in patients with ISR, and the extent of increase in the risk is more significant in male patients with diabetes.

**Keywords:** triglyceride–glucose index, percutaneous coronary intervention, in-stent restenosis

## Introduction

Percutaneous coronary intervention (PCI) is a prevalent therapeutic approach for coronary artery disease (CAD) and has been used extensively worldwide.[1] Stent implantation, a major treatment method, is performed to support narrow arteries, restoring blood flow and subsequently improving physiological function.[2] As a common stent failure event,[3] although the incidence of in-stent restenosis (ISR) has decreased with the advent of new-generation drug-eluting stents (DES), the occurrence of in-stent restenosis (ISR) and the need for target lesion revascularization (TLR) after PCI still increases with an annual growth rate of 1% to 2%.[4] Additionally, the probability of restenosis exceeds that of primary lesions, reaching up to 30%, particularly in patients without a clear etiology.[5–7] Identifying factors that increase the risk of major cardiovascular adverse events (MACEs) in patients with ISR is crucial for risk classification and future management of health.

Previous studies have shown that irrespective of BMI, IR elevates the risk of cardiovascular adverse events.[8,9] Traditional methods for assessing IR, such as the hypoglycemic-hyperinsulinemic clamp test, although is widely regarded

Received: 22 March 2024
Accepted: 18 June 2024
Published: 23 July 2024

as the gold standard, is cumbersome and expensive. For several decades, the triglyceride-glucose (TyG) index has been recognized as a reliable and cost-effective alternative for diagnosing IR.[10] Zhu et al reported that elevated TyG index was associated with increased risk of adverse cardiovascular events in patients with primary coronary lesions.[11] This study aims to assess the potential prognostic value of TyG index in post-PCI patients who are diagnosed with ISR.

# Methods

## Study Population

This study retrospectively included post-PCI patients who were diagnosed with DES-ISR at Nanjing First Hospital between January 2016 and December 2022. The exclusion criteria for patients were as follows: 1) received intravascular-imaging guidance, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT). 2) inability to interpret angiographic images owing to poor imaging quality. 3) refusal of re-PCI treatment or transfer for coronary artery bypass surgery after diagnosing DES-ISR.

Patients were stratified into three groups based on the tertile of the TyG index (Lowest/Median/Highest): T1 (<8.50), T2 (8.50 ≤ TyG index <9.01), and T3 (≥9.01).

Following local standards of diagnosis and treatment, the patients received standardized care and clinical health management during and post-re-PCI.[12] Additionally, they were provided with medication and lifestyle guidance upon discharge. Patients were treated with dual antiplatelet therapy (DAPT) including aspirin 100 mg/d + clopidogrel 75 mg/d or ticagrelor 90 mg bid and switched to aspirin single antiplatelet therapy 12 months post-PCI. All participants provided informed consent, either in written or oral form. The detailed process for the inclusion and exclusion of patients is illustrated in Figure 1.

## Data Collection and Definition

The data were collected from the electronic health systems from databases at Nanjing First Hospital during hospitalization, including age, sex, body mass index (BMI), disease history, laboratory test results, angiography characteristics, and discharge medication. The TyG index was determined as Ln (triglycerides [mg/dL] × fasting plasma glucose [mg/dL]/2).[10] Diabetes was defined as a history of diagnosed diabetes mellitus, receiving hypoglycemic drugs, or presenting typical symptoms of diabetes with the level of fasting plasma glucose (FBG)>7 mmol/L or an HbA1c≥6.5% (ie meeting any one of these criteria).[11] In-stent restenosis (ISR) was defined as the presence of significant diameter stenosis (≥50%) at the segment inside the stent or involving its 5-mm edges, which is consistent with previous studies.[13]

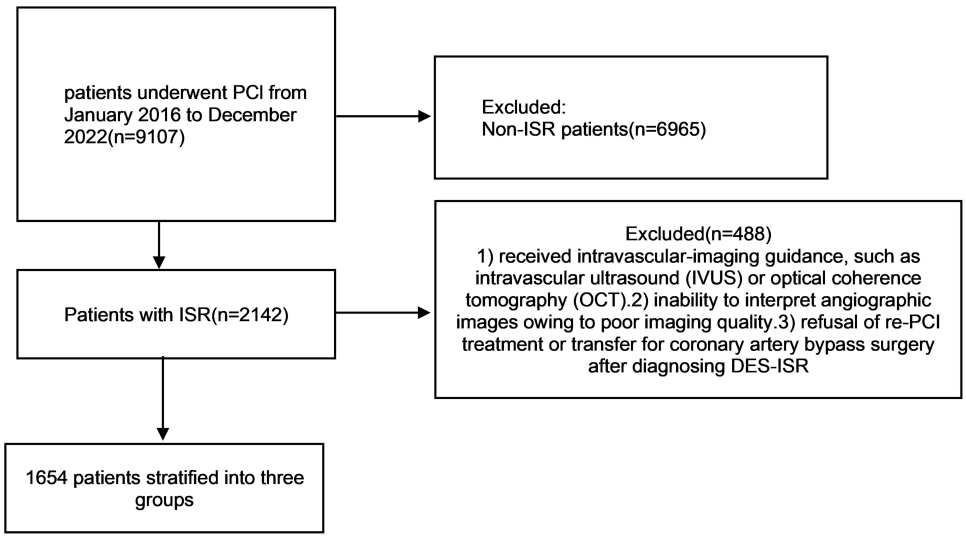


**Figure 1** Flow chart of this study.

## Endpoint Definition and Follow-Up

The primary endpoint of this study was a composite of major cardiovascular adverse events (MACEs), including all-cause death, myocardial infarction (MI), TLR/TVR (target lesion/vessel revascularization), stroke, and heart failure (HF). Patients received regular follow-up by letters, phone or re-hospitalization at 3–6 month intervals. This work is conducted using an independent follow-up term consisting of well-trained researchers who were ignorant of the aim of this research.

## Statistical Analysis

Continuous variables with a normal distribution were calculated using the mean ± standard deviation, others were calculated using the median and interquartile range (IQR). Subtype variables are presented as numerical values accompanied by corresponding percentages (%). The chi-square test was used to compare subtype variables, ANOVA was used to analyze normally distributed continuous variables, and the Kruskal–Wallis test was used for skewed continuous variables. Kaplan–Meier survival analysis and long-rank tests were performed for patients with different levels of the TyG index.

Additionally, Cox regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of the TyG index at the risk of MACEs. In the final adjusted model, age, BMI, LDL-C, TG, Lp(a), gender, smoking, STEMI, hypertension, β-block, ACEI/ARB were included. All the statistical analyses were performed using R (software version 4.3.1), with P value <0.05 considered to indicate statistical significance.

# Results

## Baseline Characteristics

The study included a total of 1654 patients diagnosed with ISR. Based on the tertile of the TyG index, the patients were further divided into three groups (Table 1). The mean age of the individuals was 66.74±10.44 years, and 1261 (76.24%) patients were male. The occurrence of hypertension, diabetes, and smoking were 72.61%, 41.66%, and 27.09%. The

**Table 1** Baseline Characteristics of Patients with ISR

| Variables | Total (n = 1654) | T1 (n = 557) | T2 (n = 552) | T3 (n = 545) | *P*-Value |
|---|---|---|---|---|---|
| **(A)** | | | | | |
| Age | 66.74 ± 10.44 | 67.88 ± 10.80 | 66.45 ± 10.39 | 65.87 ± 10.03 | 0.004 |
| Gender, n (%) | | | | | <0.001 |
| Female | 393 (23.76) | 111 (19.93) | 122 (22.10) | 160 (29.36) | |
| Male | 1261 (76.24) | 446 (80.07) | 430 (77.90) | 385 (70.64) | |
| BMI | 24.96 ± 3.31 | 23.96 ± 3.18 | 25.10 ± 3.12 | 25.85 ± 3.33 | <0.001 |
| Disease history, n (%) | | | | | |
| Hypertension, n (%) | 1201 (72.61) | 371 (66.61) | 407 (73.73) | 423 (77.61) | <0.001 |
| Diabetes mellitus, n (%) | 689 (41.66) | 145 (26.03) | 201 (36.41) | 343 (62.94) | <0.001 |
| Smoking, n (%) | | | | | 0.297 |
| Non-smoking | 889 (53.75) | 293 (52.60) | 294 (53.26) | 302 (55.41) | |
| Current smoking | 448 (27.09) | 149 (26.75) | 144 (26.09) | 155 (28.44) | |
| Previous smoking | 317 (19.17) | 115 (20.65) | 114 (20.65) | 88 (16.15) | |
| STEMI, n (%) | 264 (15.96) | 66 (11.85) | 82 (14.86) | 116 (21.28) | <0.001 |

(*Continued*)

**Table 1** (Continued).

| Variables | Total (n = 1654) | T1 (n = 557) | T2 (n = 552) | T3 (n = 545) | *P*-Value |
|---|---|---|---|---|---|
| Laboratory tests | | | | | |
| LDL-C, mmol/L | 1.94 ± 0.81 | 1.67 ± 0.65 | 1.97 ± 0.82 | 2.19 ± 0.87 | <0.001 |
| ALT, U/L | 25.86 ± 19.67 | 23.54 ± 16.81 | 26.23 ± 20.47 | 27.86 ± 21.29 | 0.001 |
| TYG index, mmol/L | 8.79 ± 0.65 | 8.12 ± 0.30 | 8.75 ± 0.14 | 9.52 ± 0.45 | <0.001 |
| FBG, mmol/L | 6.37 ± 2.28 | 5.10 ± 1.01 | 6.02 ± 1.44 | 8.03 ± 2.86 | <0.001 |
| TC, mmol/L | 3.54 ± 1.00 | 3.15 ± 0.77 | 3.49 ± 0.93 | 3.98 ± 1.10 | <0.001 |
| TG, mmol/L | 1.58 ± 1.06 | 0.88 ± 0.23 | 1.38 ± 0.31 | 2.49 ± 1.37 | <0.001 |
| CKMB, U/L | 16.42 ± 26.17 | 15.88 ± 21.89 | 15.15 ± 24.32 | 18.26 ± 31.41 | 0.120 |
| Lp(a), mg/L | 268.00 (109.25–370.00) | 268.00 (117.00–367.00) | 271.00 (111.00–376.25) | 261.00 (100.00–370.00) | 0.801 |
| HDL-C, mmol/L | 0.95 (0.82–1.11) | 1.04 (0.89–1.21) | 0.94 (0.82–1.08) | 0.89 (0.77–1.01) | <0.001 |
| Medications at discharge | | | | | |
| DAPT, n (%) | 1588 (96.01) | 540 (96.95) | 530 (96.01) | 518 (95.05) | 0.272 |
| Statin, n (%) | 1624 (98.19) | 547 (98.20) | 541 (98.01) | 536 (98.35) | 0.913 |
| β-block, n (%) | 937 (56.65) | 245 (43.99) | 345 (62.50) | 347 (63.67) | <0.001 |
| ACEI/ARB, n (%) | 642 (38.81) | 178 (31.96) | 207 (37.50) | 257 (47.16) | <0.001 |
| **(B)** | | | | | |
| Angiography, n (%) | | | | | |
| Target vessels | | | | | 0.811 |
| LAD | 890 (53.81) | 298 (53.50) | 310 (56.16) | 282 (51.74) | |
| LCX | 214 (12.94) | 69 (12.39) | 72 (13.04) | 73 (13.39) | |
| RCA | 468 (28.3) | 162 (29.08) | 143 (25.91) | 163 (29.91) | |
| Treatment, n (%) | | | | | 0.443 |
| DES | 960 (58.04) | 309 (55.48) | 318 (57.61) | 333 (61.10) | |
| DCB | 436 (26.36) | 150 (26.93) | 150 (27.17) | 136 (24.95) | |
| PTCA | 174 (10.52) | 70 (12.57) | 54 (9.78) | 50 (9.17) | |
| DES+DCB | 84 (5.08) | 28 (5.03) | 30 (5.43) | 26 (4.77) | |

**Abbreviations**: ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CKMB, Creatine Kinase-MB; DCB, drug-coated balloon; DES, drug-eluting stent; FBG, fasting blood glucose; HDL-C, high-density lipoprotein-C; LAD, left anterior descending artery; LCX, left circumflex artery; LDL-C, low-density lipoprotein-C; Lp(a), Lipoprotein(a); PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; TC, total cholesterol; TG, triglycerides. TyG, triglyceride-glucose.

incidence of all conditions, except smoking, significantly increased with increasing TyG index. Patients with the highest level of TyG index were significantly younger (P = 0.004), and had hypertension and diabetes more regularly (*P* all <0.001). Furthermore, the distribution of target lesion vessels and treatment strategies were comparable among individuals with different levels of TyG index. Detailed information on baseline characteristics was described in Table 1.

## The Association Between the TyG Index and the Occurrence of Major Cardiovascular Adverse Events After PCI

Cox regression analysis was used to explore the relationship between the TyG index and post-PCI MACEs (Table 2). According to the unadjusted model, Individuals with the highest level of TyG index had an increased risk of MACEs compared to others (HR = 1.30; 95% CI: 1.02–1.67; P = 0.03). Additionally, consistent results were observed when the TyG index was analyzed as a continuous variable (HR = 1.18; 95% CI: 1.01–1.38; P = 0.03). When analyzing the TyG index as a continuous variable, each standard deviation increase was associated with an HR of 1.51 (95% CI: 1.11–2.05; P = 0.01).

Among patients with different levels of the TyG index, there was a marginally significant discrepancy in the risk of MACEs (P = 0.053) (Figure 2). The further landmark analysis revealed that individuals with elevated levels of TyG index had a significantly increased risk of MACEs starting from 6 months after PCI (P = 0.019) (Figure 3).

## Subgroup Analysis

In subgroup analysis, the associations between the risk of experiencing MACEs and the TyG index were evaluated (Figure 4). The results indicated that the TyG index was significantly associated with the risk of post-PCI MACEs in male (HR 1.269; 95% CI 1.055–1.527; P = 0.011) and diabetic patients (HR 1.385; 95% CI 1.125–1.706; P = 0.002). As depicted in Figure 5, among individuals with diabetes, the MACEs group had a significantly higher TyG index than the non-MACEs group (P = 0.001).

# Discussion

This study first analyzed the association between the TyG index and the risk of post-PCI MACEs in patients diagnosed with ISR. We found elevated TyG index is associated with increased risk of major adverse cardiovascular events in patients with ISR, and the extent of increase in the risk is more significant in male patients with diabetes.

Previous study based on primary coronary artery disease (CAD) by Zhu et al investigated the association between the TyG index and the incidence of ISR in patients underwent PCI.[10,11] Our previous study revealed that elevated TyG index may lead to coronary revealed a significant correlation between the TyG index and the risk of MACEs. Thus, it is noted that the TyG index impacts the occurrence, development and prognosis of ISR.

Insulin resistance and disturbances in glucose metabolism led to oxidative stress, inflammation, and dysfunctional immune modulation and then exacerbates the development of arteriosclerosis and promotes the formation of plaques.[14–17] As a common stent failure event, ISR may be triggered by inflammation, which is induced by insulin resistance and following disturbances in glucose metabolism. In the context of atherosclerosis, the mitogen-activated protein kinase signaling pathway can facilitate its development, and IR is known to activate this pathway. It is also implicated in causing

**Table 2** The Association Between the TyG Index and the Occurrence of Major Cardiovascular Adverse Events (MACEs) After PCI

| | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | **HR** | **95%CI** | ***P*-value** | **HR** | **95%CI** | ***P*-value** | **HR** | **95%CI** | ***P*-value** |
| TyG index | 1.18 | 1.01–1.38 | 0.03 | 1.22 | 1.04–1.44 | 0.02 | 1.51 | 1.11–2.05 | 0.01 |
| TyG tertiles | | | | | | | | | |
| T1 | Ref | | | Ref | | | Ref | | |
| $T_2$ | 1.00 | 0.77–1.31 | 0.98 | 1.05 | 0.80–1.37 | 0.75 | 1.11 | 0.81–1.53 | 0.51 |
| $T_3$ | 1.30 | 1.02–1.67 | 0.03 | 1.36 | 1.04–1.77 | 0.02 | 1.60 | 1.11–2.30 | 0.01 |

**Notes**: Model 1: unadjusted. Model 2: adjusted for age, BMI, gender, LDL-C. Model 3: adjusted for age, BMI, LDL-C, TG, Lp(a), gender, smoking, STEMI, hypertension, β-block, ACEI/ARB.

**Abbreviations**: CI, confidence interval; HR, hazard ratio; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; Lp(a), Lipoprotein(a); TyG, triglyceride-glucose ; LDL-C, low-density lipoprotein-C; STEMI, ST-segment elevation myocardial infarction.

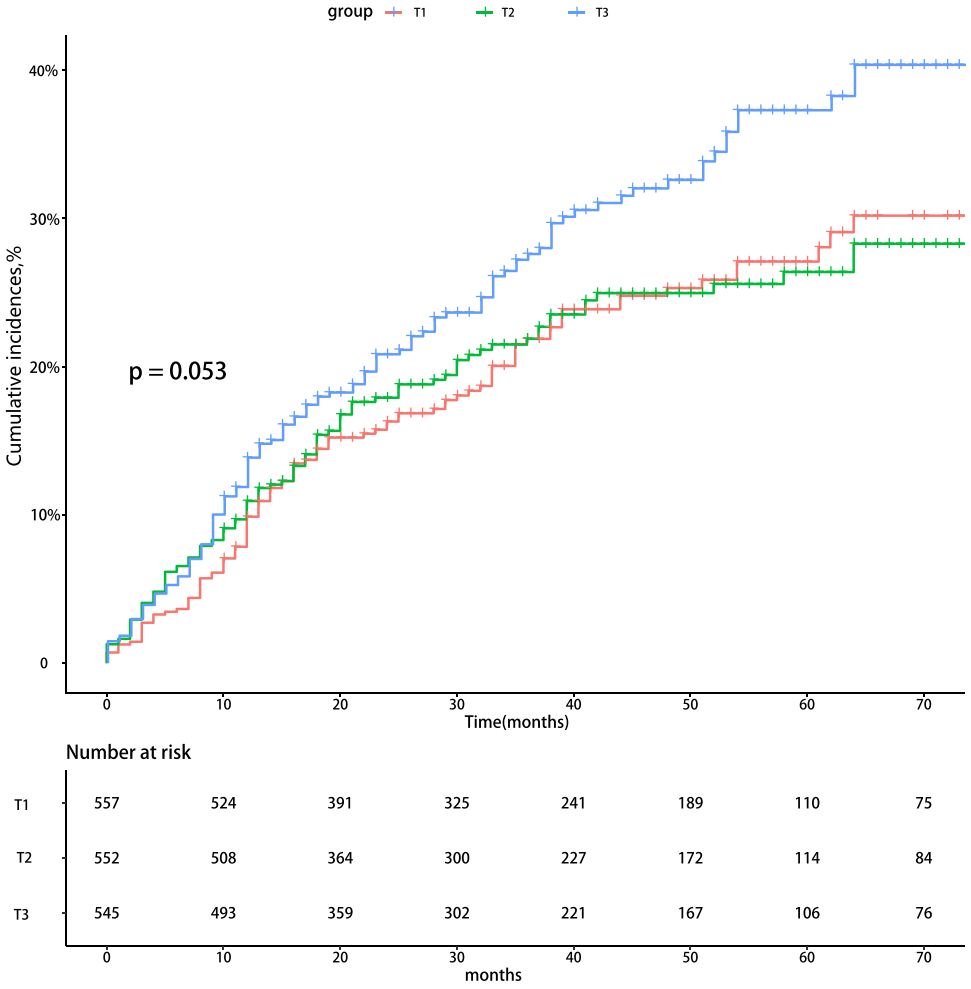


**Figure 2** Kaplan–Meier curve for MACEs.

endothelial dysfunction and excessive proliferation of vascular smooth muscle cells,[18–20] accelerating the generation of neointimal hyperplasia (NIH), which serves as a restenosis substrate within the stent. Additionally, in patients with ISR, IR-induced impaired endothelial function may trigger neotenic atherosclerosis, leading to plaque rupture and impaired blood flow dynamics.[18–21] Previous study revealed that elevated TyG index may lead to coronary slow flow, and this abnormal blood flow dynamic may worsen the prognosis.[21]

ISR ranks among the most common long-term complications following stent implantation. The prognosis varied among different pathological patterns and tissue characteristics.[22] For example, diffuse ISR tends to result in the occurrence of earlier and more severe MACEs.[23] Furthermore, studies have shown a correlation between the adverse prognosis of ISR and various metabolic factors and metabolic disorders.[24] Patients with this etiology have an increased risk of experiencing MACEs or greater disease severity than patients with the primary disease.[25] Considering that, we thought future research should analysis the potential association between the TyG index and dynamic morphologies and component changes in atherosclerosis to clarify the predictive value of the TyG index profoundly by intravascular imaging (OCT&IVUS).

Subgroup analysis indicated that the extent of increase in the risk of MACEs is more significant in male patients with diabetes, which is consistent with previous study.[26–28] Conversely, Wu et al found that the TyG index was an independent predictor of MACEs for non-diabetic patients who underwent coronary artery bypass grafting (CABG) and significantly enhanced the accuracy of existing risk-predictive model.[29] As a physiological response to acute syndrome, there may be an abnormal elevation of blood glucose level owing to the existence of stress-induced hyperglycemia (SIH) and the level

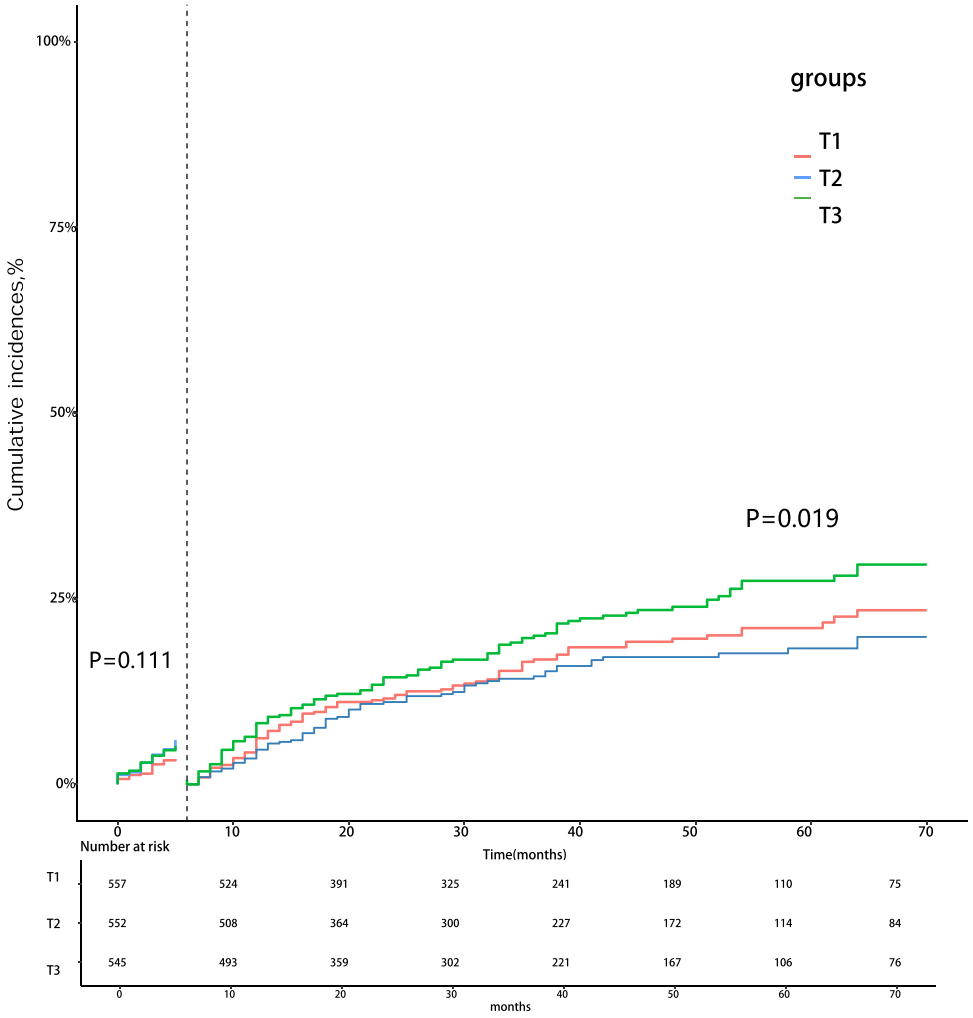


**Figure 3** Landmark analysis of the cumulative incidence of MACEs base on the duration of follow-up.

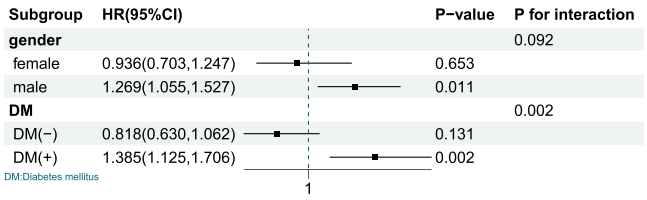


**Figure 4** Subgroup analysis.

of TyG may be influenced.[30–32] Confounding factors such as SIH may influence the predictive ability of the TyG index, and relevant study which combined the elimination of collinear factors with following subgroup analysis based on diabetes was absent.

Previous research has identified that integrating the TyG index into the GRACE risk score could improve the prognostic predictive capability for patients who underwent PCI (18, 30). Although further research was needed, we thought our research clarified the predictive value of the TyG index and provided useful information for the management of prognosis in patients diagnosed with ISR.

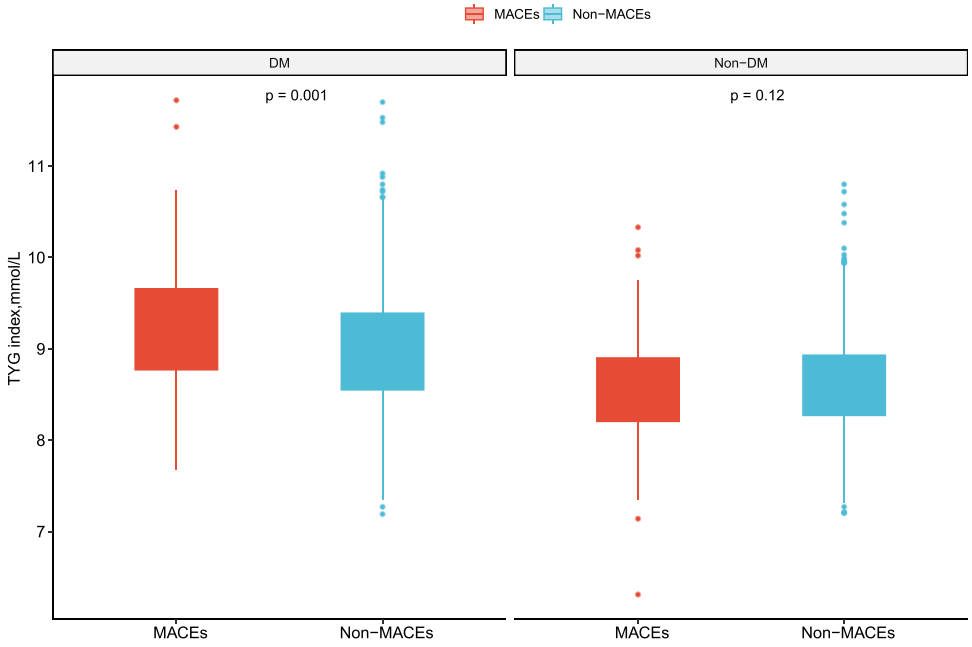


**Figure 5** Comparison of the TyG index level between the MACEs and non-MACEs groups in patients with DM.
**Abbreviation**: DM, diabetes mellitus.

## Strengths and Limitations of the Study

The strength of this study lies in the inclusion of a sufficiently large sample population, specifically for in-stent restenosis. However, there were still some limitations. Firstly, it was a single-center retrospective study therefore could not determine the causality between the TyG index and DES-IS. Secondly, limited information was available about the changes in patients' TyG index levels among the duration of follow-up, suggesting that future research is needed to explore the utility of dynamic monitoring of the TyG index or cumulative TyG index.

## Conclusion

Elevated TyG index is associated with increased risk of adverse cardiovascular events in patients with ISR, and the extent of increase in the risk is more significant in male patients with diabetes.

## Data Sharing Statement

Applicants could apply by visiting the official website of the hospital and accessing relevant data after approval by the committee.

## Ethics Approval and Consent to Participate

The Ethics Review Committee of Nanjing First Hospital approved this study. As a retrospective study, follow-up was conducted through telephone, letters or rehospitalization, with verbal consent from the ethics committee.

## Acknowledgments

Yi-fei Wang and Xiao-han Kong are co-first authors for this study. Huimin Tao and Li Tao shared a second authorship. This paper has been updated to a preprint server as a preprint. Link: https://www.researchgate.net/publication/377642728).

## Funding

There is no funding to report.

## Disclosure

The authors report no conflicts of interest in this work.

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