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Triglyceride-Glucose Index Predicts Adverse Events in Patients with Acute Coronary Syndrome: A Meta-Analysis of Cohort Studies

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Key words

triglyceride-glucose index, insulin resistance, acute coronary syndrome, major adverse cardiovascular events, meta-analysis

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ABSTRACT

The triglyceride-glucose (TyG) index, a recently proposed indicator for insulin resistance, has been related with cardiovascular risks. We aimed to summarize the association between TvG index and incidence of major adverse cardiovascular events (MACEs) in patients with acute coronary syndrome (ACS). Cohort studies demonstrating the association between TyG index and incidence of MACEs in ACS patients with multivariate adjusted analyses were identified by search of PubMed, Embase, and Web of Science databases. A random-effekt model incorporating the heterogeneity was applied to pool the results. Eight cohort studies with 19 611 participants were included. Results showed that compared to those with the lowest category of TyG index, ACS patients with the highest category of TyG index were independently associated with higher risk of MACEs [risk ratio (RR): 1.94, 95% confidence interval (CI): 1.47-2.56, $I^2 = 85\%$, p < 0.001). Subgroup analyses showed consistent results in patients with ST-segment elevated myocardial infarction or non-ST segment elevated ACS, in patients with or without diabetes, and in patients after percutaneous coronary intervention. Results were consistent in studies with TyG index analyzed as continuous variable (RR for per standard deviation increment of TyG index: 1.59, 95% CI: 1.38-1.83, $I^2 = 24\%$, p < 0.001). In conclusion, higher TyG index may be independently associated with higher incidence of MACEs in patients with ACS.

Introduction

Acute coronary syndrome (ACS) is a category of clinically severe coronary artery disease (CAD) characterized by the acute rupture of vulnerable atherosclerotic plaques and subsequent total occlusion of the coronary arteries [1,2]. Clinically, ACS could be further classified as ST segment elevated myocardial infarction (STEMI) and non-ST segment elevated ACS (NSTE-ACS) [1]. Despite of continuing advances in the treatment of ACS, particularly of the revascularization therapy such as percutaneous coronary intervention (PCI), patients with ACS remain of poor prognosis [3,4]. Accordingly, identification of predictors for prognosis in ACS patients has becoming more and more important for improving the risk strati-

fication of the patients and development of novel treatment strategies [5, 6].

Accumulating evidence from experimental and epidemiological studies suggests that insulin resistance plays key roles in the pathogenesis and progression of CAD in both the diabetic and non-diabetic patients [7,8]. However, previous studies evaluating the potential prognostic role of insulin resistance in ACS patients are rare, possibly due to the lack of reliable and convenient surrogate indicator of insulin resistance [9]. Indeed, the "gold standard" indicator of insulin sensitivity is the hyperinsulinemic-euglycemic clamp test [10], while the application of the index is limited by the time consuming and expensive nature of the method [11]. Recent-

ly, the triglyceride-glucose (TyG) index, which is derived from fasting blood glucose and triglyceride, is suggested as a reliable and easily obtained indicator of insulin resistance [12]. A higher TyG index has been associated with the risk of CAD in general population [13, 14]. Besides, TyG index has also been related with the severity of coronary calcification [15, 16]. However, the association between TyG index and the incidence of major adverse cardiovascular events (MACEs) in patients with ACS remains not fully determined [17–24]. Therefore, in this study, we aimed to summarize the potential independent association between TyG index and subsequent incidence of MACEs in ACS patients by performing a meta-analysis of previous published cohort studies. Besides, influences of subtype of ACS and diabetic status of the patients on the above association were also explored in subgroup analyses.

Materials and Methods

The MOOSE (Meta-analysis of Observational Studies in Epidemiology) [25] Statement and Cochrane's Handbook [26] were followed in the design, performing and reporting of the meta-analysis.

Literature search

Electronic databases including PubMed, Embase, and Web of Science were searched with the combination of the following terms: (1) "TyG index" OR "triglyceride-glucose index" OR "triglyceride and glucose index" OR "triglyceride glucose index" OR "triacylglycerol glucose index"; and (2) "coronary artery disease" OR "angina" OR "myocardial infarction" OR "acute coronary syndrome" OR "percutaneous coronary intervention" OR "major adverse cardiovascular events" OR "CAD" OR "STEMI" OR "NSTEMI" OR "ACS" OR "AMI" OR "PCI". Filters of human were applied and only studies published in English or Chinese were considered. References lists of related original and review articles were manually searched for potential eligible studies. The final literature search was performed on January 18, 2021.

Study selection

Studies that fulfilled all of the following criteria were included: (1) cohort studies published as full-length articles; (2) included patients with ACS at baseline; (3) evaluated the association between TyG index and the incidence of MACEs during follow-up; and (4) reported the relative risk for the association after adjustment of potential confounding factors. TyG index was calculated as In[TG (mg/dl) × FPG (mg/dl)/2] [27]. The definition of MACEs was in accordance with the included studies, which was defined as composite outcomes of all-cause death, non-fatal myocardial infarction, non-fatal stroke, revascularization, and cardiac rehospitalization. Cross-sectional studies, reviews, preclinical studies, and studies irrelevant to the aim of the meta-analysis were excluded.

Data extracting and quality evaluation

Literature search, data extraction, and quality assessment of the included studies were performed by 2 authors independently according to the predefined criteria. Discrepancies were resolved by consensus. The extracted data were: (1) name of first author, publication year, and country; (2) study design characteristics; (3) patient characteristics, including the diagnosis, sample size, age, sex,

and proportions of patients with diabetes; (4) patterns for TyG index analysis; (5) follow-up durations; (6) numbers of patients with subsequent incidence of MACEs; and (7) confounding factors adjusted in the multivariate analyses. The quality of each study was evaluated using the Newcastle-Ottawa Scale [28]. This scale judges the quality of cohort studies with 3 domains: selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest. The quality score of NOS ranges from 1 to 9 stars in total.

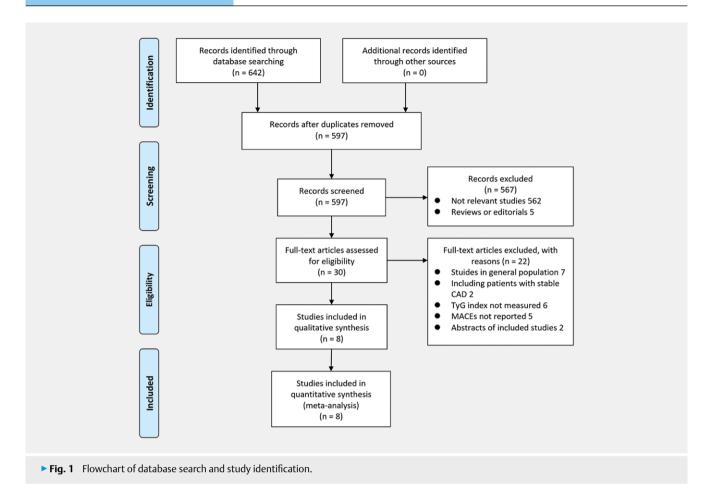
Statistical analyses

Risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were applied as the general measure for the association between TyG index and risk of MACEs in ACS patients. For studies with TyG index analyzed as categorized variables, RRs of MACEs for participants with the highest TyG index level compared to those with the lowest TyG index level were extracted. For studies with TyG index analyzed as continuous variables, RRs of MACEs incidence per 1-standard deviation (SD) increment of TyG index was extracted. Data of RRs and their stand errors (SEs) were calculated from 95% CIs or p-values, and were logarithmically transformed for the stabilization of the variance and normalization of the distribution [26]. To indicate a potential independent association between TyG index and subsequent incidence of MACEs in patients with ACS, only RR data with the most adequately adjusted model of multivariate analysis was extracted and combined. The Cochrane's Q test was used to evaluate the heterogeneity among the include cohort studies, as well as the estimation of I^2 statistic [29]. If $I^2 > 50\%$, a significant heterogeneity was considered. We used a random-effekt model to synthesize the RR data because this model is considered as a more generalized method which could incorporate the potential heterogeneity among the included studies [26]. Sensitivity analyses, which exclude one individual study at a time, were performed to test the stability of the results [30]. Predefined subgroup analyses were performed to evaluate the influences of subtype of ACS and diabetic status of the patients on the association. Further meta-analysis restricted to patients with after PCI was also performed. A p-value < 0.05 indicates statistical significance. The potential publication bias was assessed by visual inspection of the funnel plots for symmetry, as well as the Egger's regression asymmetry test [31]. RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and STATA (Version 12.0) software were used to perform the meta-analysis and statistics.

Results

Literature search

▶ Figure 1 shows the process of database search. Briefly, 597 articles were obtained via initial literature search of the databases after excluding of the duplications. Among them, 567 were excluded through screening of the titles and abstracts for irrelevance. Subsequently, 30 articles underwent full-text review. Of these, 22 were further excluded for the reasons listed in ▶ Fig. 1. Finally, 8 cohort studies were obtained for the meta-analysis [17–24].



Study characteristics and quality evaluation

Eight cohort studies including 19 611 participants were included in the meta-analysis. The detailed study characteristics were shown in **Table 1**. All of the available studies were performed in China. Two of them were prospective [18, 20], and the remaining 6 were retrospective [17, 19, 21-24]. The sample sizes of the included studies varied between 438 and 9285. Mean ages of the included patients with ACS varied from 59 to 67 years. All of the included studies provided data of TyG index analyzed as a categorized variable, while 4 studies also analyzed as a continuous variable [20, 21, 23, 24]. With a follow-up duration of 1~3 years, 2762 patients had subsequent MACEs. Age, sex, BMI, smoking status, blood pressure, serum total cholesterol or low-density lipoprotein cholesterol, diabetic status, features of coronary lesions, revascularization therapy, and concurrent medications were adjusted to a varying degree when the association between TyG index and MACEs were studied. The NOS scores of the included studies were 8~9. indicating good study quality (► Table 2).

TyG index and the incidence of MACEs

ACS patients with the highest category of TyG index were independently associated with higher risk of MACEs (RR: 1.94, 95 % CI: 1.47–2.56, I² = 85 %, p < 0.001; ► Fig. 2a). Consistent results were obtained for meta-analysis with TyG index analyzed as continuous variables (4 studies [20, 21, 23, 24], RR for 1-SD increment of TyG index: 1.59, 95 % CI: 1.38–1.83, I² = 24 %, p < 0.001; ► Fig. 2b). Re-

sults of sensitivity analyses by excluding one study at a time showed similar results. For meta-analysis of studies with TyG index analyzed as categorized variables, subgroup analyses showed consistent results in patients with STEMI or NSTE-ACS, and in patients with or without diabetes (both p for subgroup difference > 0.05; ► Fig. 3a,b). Meta-analysis restricted to patients after PCI also showed similar results (RR: 2.14, 95 % CI: 1.66–2.75, I² = 73 %, p < 0.001; ► Fig. 3c).

Publication bias

The funnel plots regarding the meta-analysis with TyG index analyzed as a categorized variable were shown in \triangleright Fig. 4. The funnel plots were symmetry on visual inspection, suggesting low risk of publication bias. Egger's regression tests showed consistent results (p = 0.197). Publication bias for the meta-analysis with TyG index analyzed as a continuous variable was difficult to estimate since limited studies were included.

Discussion

In this meta-analysis of relevant cohort studies, we found that higher TyG index was independently associated with increased incidence of subsequent MACEs in patients with ACS. Consistent results were obtained for meta-analyses of studies of TyG index analyzed as categorized variables and continuous variables. Besides, sensitivity analyses by omitting one study at a time confirmed the

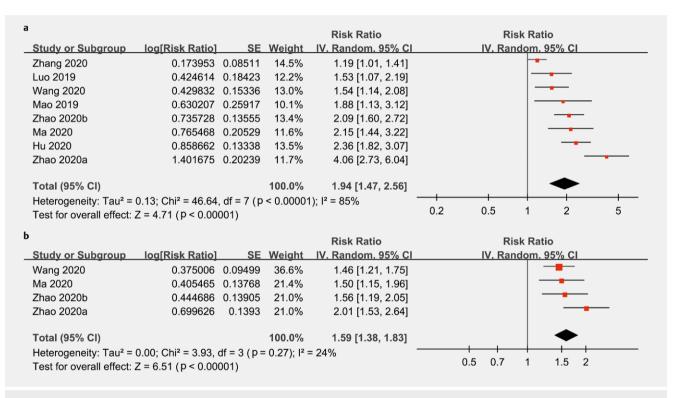
► **Table 1** Characteristics of the included studies.

NOS		∞	6	6	∞	∞	∞	∞	∞
Variables adjusted		Age, sex, BMI, SBP, DBP, Killip Class, smoking, HDL-C, LDL-C, Gensini score, and LVEF	Age, sex, BMI, hypertension, DM, smoking, HDL-C, LDL-C, UA, eGFR, BNP, and hs-CRP	Age, sex, BMI, DBP, HDL-C, current smoking, HbA1c, PAD, CKD, previous MI, previous PCI, CAD severity, and insulin use	Age, sex, smoker, previous MI, previous CABG, BMI, LVEF, left main disease, multi-vessel disease, HbA1c, hs-CRP, statin, and insulin use	Age, sex, BMI, smoker, hypertension, previous MI, previous stroke, previous revascularization, non-HDL-C, lipid-lowering medications and antidiabetes medication use	Age, sex, BMI, SBP, DBP, smoking, drinking, duration of diabetes, dyslipidemia, prior MI, PCI, stroke, PAD, TC, HDL-C, eGFR, HbA1c, LVEF, SYNTAX score, lipid-lowering medications and antidiabetes medication use	Age, sex, BMI, smoking, hypertension, dyslipidemia, previous history of MI, PCI, stroke, and PAD, TC, HDL-C, eGFR, HbA1c, LVEF, SYNTAX score, statin use, and use of ACEI/ARB	Age, sex, DM, hypertension, previous MI, hemoglobin, albumin, eGFR, TG, LVEF and multi-vessel/LM lesions
No. of patients with MACEs		375	78	188	289	480	180	316	856
Follow-up duration	years	1.0	1.0	2.5	3.0	1.5	3.0	4.0	2.8
TyG analysis		Q4:Q1	Median	T3:T1, and continuous	T3:T1, and continuous	T3:T1	ROC analysis determined, and continuous	Median, and continuous	Median
2	%	100	76.3	100	57.2	100	100	100	06
DM	%	24.7	32.6	100	100	43.9	100	0	38.7
Male	%	79.1	67.4	72.2	55.9	75.3	68.3	73.7	75.6
Mean age	years	62.4	62.5	61.0	66.3	59.9	6.09	59.7	63.3
Number of patients	Number of patients		438	776	2531	9285	798	1510	3181
Patient character- istics		Patients with STEMI undergoing PCI	Patients with NSTE- ACS	T2DM patients with ACS undergoing PCI	T2DM patients with ACS	Patients with ACS undergoing PCI	T2DM patients with NSTE-ACS undergoing PCI	Non-DM patients with NSTE-ACS undergoing PCI	Patients with STEMI or NSTEMI
Design		RC	PC	PC	RC	RC	RC	RC	RC
Country		China	China	China	China	China	China	China	China
Study [Ref.]		Luo 2019 [17]	Mao 2019 [18]	Ma 2020 [20]	Wang 2020 [21]	Hu 2020 [19]	Zhao 2020a [23]	Zhao 2020b [24]	Zhang 2020 [22]

eGFR: Estimated glomerular filtrating rate; HbA1c: Glycosylated hemoglobin; PAD: Peripheral artery disease; CAD: Coronary artery disease; CKD: Chronic kidney disease; MI: Myocardial infarction; CABC: Coronary NSTEMI: Non-ST-segment elevation myocardial infarction; Q: Quartile; Trefrile; ROC: Receiver operating characteristics; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; BNP: B-type natriuretic peptide; hs-CRP: High-sensitivity C-reactive protein; UA: Uric acid; Newcastle-Ottawa Scale; T2DM: Type 2 diabetes mellitus; ACS: Acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTE-ACS: Non-5T-segment elevation acute coronary syndrome; PC: Prospective cohort; RC: Retrospective cohort; DM: Diabetes mellitus; PCI: Percutaneous coronary intervention; TyG index: Triglyceride-glucose index; MACEs: Major adverse cardiovascular events; NOS: artery bypass graft; TC: Total cholesterol; TG: Triglyceride; ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; LM: Left main artery.

▶ Table 2 Details of study quality evaluation via the Newcastle-Ottawa Scale.

Study	Represent- ativeness of the exposed cohort	Selection of the non- exposed cohort	Ascertain- ment of exposure	Outcome not present at baseline	Control for age	Control for other confound- ing factors	Assess- ment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Luo 2019	0	1	1	1	1	1	1	1	1	8
Mao 2019	1	1	1	1	1	1	1	1	1	9
Ma 2020	1	1	1	1	1	1	1	1	1	9
Wang 2020	0	1	1	1	1	1	1	1	1	8
Hu 2020	0	1	1	1	1	1	1	1	1	8
Zhao 2020a	0	1	1	1	1	1	1	1	1	8
Zhao 2020b	0	1	1	1	1	1	1	1	1	8
Zhang 2020	0	1	1	1	1	1	1	1	1	8

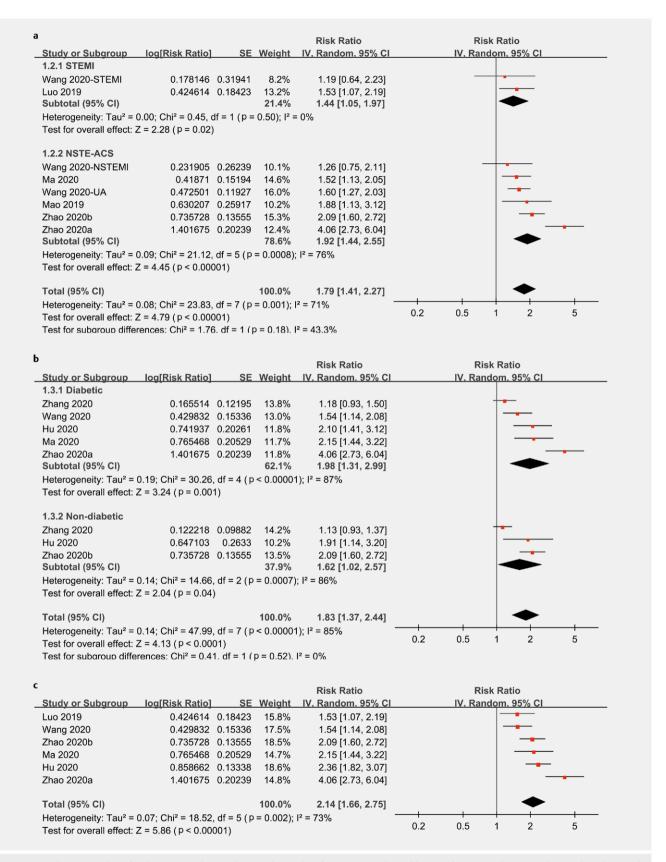


▶ Fig. 2 Forest plots for the meta-analysis of the association between TyG index and risk of subsequent MACEs in ACS patients; a: meta-analysis with TyG index analyzed as categorized variables; and b: meta-analysis with TyG index analyzed as continuous variables.

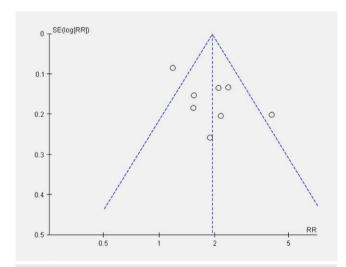
robustness of the results. In addition, further subgroup analyses showed consistent results in patients with STEMI or NSTE-ACS, with or without diabetes, and in those after PCI. Collectively, these findings suggested that higher TyG index may be an independent predictor of MACEs in patients with ACS.

To the best of our knowledge, this is the first meta-analysis which summarized the association between TyG index and risk of MACEs in ACS patients. Our study has several strengths. First, only cohort studies were included, which avoided the potential bias inherited in the cross-sectional studies, such as patient selection bias

and recall bias. In addition, only studies with multivariate analyses were included, which enabled us to indicate a potential independent association between TyG index and subsequent risk of MACEs. Moreover, consistent results were obtained for meta-analyses with TyG index analyzed categorized or continuous variables, and for sensitivity and subgroup analyses, which all suggested the robustness and stability of the results. Taken together, these findings support that insulin resistance as evaluated by TyG index could be a prognostic factor for patients with ACS. These findings were consistent with the results of previous studies, which showed that a



▶ Fig. 3 Subgroup analyses for the meta-analysis with TyG index analyzed as categorized variables; a: subgroup analysis according to the subtype of ACS; b: subgroup analysis according to the diabetic status of the patients; and c: meta-analysis limited to patients after PCI.



▶ Fig. 4 Funnel plots for the publication bias underlying the meta-analysis with TyG index analyzed as categorized variables.

higher TyG index was related with the severity of coronary lesions in patients with CAD [12]. An early study including 2840 participants who underwent coronary computed tomography angiography showed that the TyG index was independently associated with the presence and severity of CAD due to an increased risk for calcified or mixed plaque [32]. Moreover, subsequent follow-up study showed that TyG index is an independent predictor of coronary artery calcification progression in adult Koreans [16]. Besides, in patients with NSTE-ACS, higher TyG index was independently related to severer coronary lesions as evidenced by higher SYNTAX score [18]. These findings may partly explain the potential association between higher TyG index and increased risk of subsequent MACEs in ACS patients. Pathophysiologically, insulin resistance has been associated with low-grade but persistent inflammatory response [33], which has been associated with the rupture of atherosclerotic plagues in ACS [34]. Besides, higher TyG index has also be related to endothelial dysfunction and impaired autonomic function [35, 36], which were both considered as predictors of poor clinical outcomes in ACS patients [37]. Future studies are needed to determine the exact molecular mechanisms underlying the potential association between TyG index and risk of MACEs in ACS patients.

Measuring insulin resistance with TyG index was easy, inexpensive, and fast based on routine blood biochemical tests. Besides, TyG index was shown to with a high sensitivity (96.5%) and specificity (85.0%) for evaluation of insulin resistance compared to the hyperinsulinemic-euglycemic clamp test [38]. In addition, TyG index was shown to be better than homeostatic model assessment for measuring insulin resistance (HOMA-IR) [39], which supported the use of TyG index as a potential component for risk stratification of ACS patients. Future studies are needed to determine the predictive efficacy of adding TyG index to established risk scores in ACS patients. Comparisons for the predictive efficacies between TyG index and HOMA-IR for MACEs in patients with ACS are also important for real-world clinical practice, and future studies are also warranted.

This meta-analysis also has some limitations. Firstly, limited studies were available for the meta-analysis, all performed in China, and significant heterogeneity was detected. The influences of other study characteristics on the outcome should be further investigated, such as the ethnicity and treatments for ACS. Moreover, it remains unknown if the association between TyG index and risk of MACEs was linear. Besides, the optimal cutoff value of TyG index as a prognostic factor for ACS patients could not been determined based on the results of current meta-analysis and previous studies. Studies are needed in the future to address this issue. Also, although studies with multivariate analyses were included, residual confounding factors may still exist which may affekt the association between TyG index and MACEs in ACS patients. Particularly, difference in dietary and nutritional factors, and use of glycemic and lipids-lowering medications may affekt TyG index, which may further influence the association between TyG index and subsequent incidence of MACEs [40]. However, we were unable to determine the potential influences of these factors on the association between TyG index and MACEs since these variables were rarely reported among the included studies. Finally, TyG index was measured for once among the included studies. The stability of the index, changes of TyG index during the hospitalization and after discharge and their associations with subsequent incidence of MACEs in ACS patients remain to be determined.

In conclusion, current evidence from cohort studies suggests that higher TyG index may be an independent predictor of subsequent risk of MACEs in patients with ACS. Since measuring insulin resistance with TyG index was reliable, easy, fast, and inexpensive, future studies are needed to determine whether incorporation of TyG index into current ACS risk stratification scores could improve their predictive efficacies.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Notice

This article was changed according to the erratum on September 28, 2021.

Erratum

There was a misspelling in the title of the above mentioned article, the correct title is: Triglyceride-Glucose Index Predicts Adverse Events in Patients with Acute Coronary Syndrome: A Meta-Analysis of Cohort Studies.