## RESEARCH

BMC Cardiovascular Disorders

**Open Access** 

# Association of triglyceride-glucose index and neutrophil-to-lymphocyte ratio with coronary artery disease



Bing Zhang<sup>1</sup>, Aihong Peng<sup>1</sup>, Shu Li<sup>2</sup>, Fei Li<sup>1</sup>, Jing Wan<sup>1\*</sup> and Jinping Lu<sup>3\*</sup>

## Abstract

**Objective** The present study aimed to investigate the association of triglyceride-glucose (TyG) index and neutrophilto-lymphocyte ratio (NLR) with coronary artery disease (CAD), and evaluate the cumulative value of TyG index and NLR in identifying CAD, as well as the severity of CAD.

**Methods** This retrospective study enrolled 2867 patients who underwent coronary angiography (CAG) for the first time between January 2013 and June 2022 in Zhongnan Hospital of Wuhan University. There were 2109 patients with CAD and 758 patients without CAD. The CAD patients were divided into two groups based on the median of Gensini score (mild stenosis CAD group: Gensini score < 26 points; severe stenosis CAD group: Gensini score  $\geq$  26 points). To further evaluate the cumulative value of TyG index and NLR in identifying CAD and CAD severity, all patients were classified into four groups based on median of TyG index and NLR: (1) the control group: patients with low-TyG and low-NLR; (2) isolated high-NLR group: patients with low-TyG and high-NLR group: patients with high-TyG and low-NLR; (4) high-TyG combined with high-NLR group: patients with high-TyG and high- NLR.

**Results** Multivariate logistic regression analysis showed that both the TyG index and NLR were independent risk factors for CAD, and they were also independent risk factors for severe stenosis in CAD (P < 0.05). Compared with the low-TyG and low- NLR group, patients in high-TyG and high- NLR group had a 1.418 times higher odds ratio (OR) of having CAD and a 1.692 times higher OR of having severe stenosis in CAD in the multivariable logistic regression model. It is worth noting that the OR values of the high-TyG and high- NLR group were higher than those of the isolated high-NLR group and the isolated high-TyG group. The ROC analysis showed that the combination of the TyG index and NLR was superior to TyG index or NLR in predicting CAD and CAD severity.

**Conclusion** Compared to TyG index or NLR, the combination of the TyG index and NLR is beneficial to improve the diagnostic accuracy of CAD and CAD severity.

Keywords Coronary artery disease, Triglyceride-glucose index, Neutrophil-to-lymphocyte ratio

\*Correspondence: Jing Wan wanjing\_zn@163.com Jinping Lu lujp1024@whu.edu.cn <sup>1</sup>Department of Cardiology, Zhongnan Hospital of Wuhan University, No 169 Donghu Road, Wuchang District, Wuhan 430071, Hubei Province, China

<sup>2</sup>Department of Critical Care Medicine, Zhongnan Hospital of Wuhan University, No 169 Donghu Road, Wuchang District, Wuhan 430071, Hubei Province, China

<sup>3</sup>Department of General Practice, Zhongnan Hospital of Wuhan University, No 169 Donghu Road, Wuchang District, Wuhan 430071, Hubei Province, China



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicate otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

## Introduction

Coronary artery disease (CAD) is a chronic cardiovascular disease caused by coronary atherosclerosis. Due to population aging, urbanization, and unhealthy lifestyle, the incidence and mortality of CAD are increasing, which has become a serious public health problem [1, 2]. Inflammation and insulin resistance (IR) play important roles in the occurrence and development of atherosclerosis [3–6]. Inflammation is also closely related to IR [7]. On the one hand, chronic inflammation is a key pathological mechanism of IR [8]. Chronic inflammation can impair normal lipid accumulation, adipose tissue function, mitochondrial function, and cause endoplasmic reticulum stress, which lead to IR. On the other hand, some studies have shown that IR can exacerbate chronic inflammation [9]. While it is unclear which comes first, IR or inflammation, it is clear that there is a vicious cycle between inflammation and IR.

Recent studies have confirmed that the triglycerideglucose (TyG) index is a reliable index for evaluating IR [10, 11]. Neutrophil-to-lymphocyte ratio (NLR) as a marker of inflammation, can reflect the degree of systemic inflammation. Both TyG index and NLR are associated with atherosclerosis. However, the cumulative value of TyG index and NLR in predicting CAD and CAD severity is still uncertain. This study aimed to further evaluate the value of the combination of the TyG index and NLR.

## **Patients and methods**

#### **Study population**

This study population comprised 2867 patients who underwent coronary angiography (CAG) for the first time and hospitalized in the Department of Cardiology, Zhongnan Hospital of Wuhan University from January 2013 to June 2022. Exclusion criteria: (1) congenital heart disease, old myocardial infarction, heart failure, valvular heart disease and other cardiac history; (2) previous coronary intervention or coronary artery bypass grafting; (3) infectious diseases, hematological diseases, malignant tumors, thyroid diseases, severe hepatic or renal dysfunction; (4) autoimmune diseases or being treated with hormones or immunosuppressants; (5) surgical operation or severe trauma within 3 months. This study conformed with the declaration of Helsinki and was approved by the Ethics Committee of Zhongnan Hospital.

## Data collection and laboratory determination

Personal information such as age, sex, smoking history, and medical history, such as a history of surgery, hypertension, diabetes, infectious diseases and other diseases were obtained from the medical records. All patients were required to fast overnight and then venous blood samples were collected the next day early morning. Subsequently, laboratory parameters, such as neutrophil (NE) counts, lymphocyte (LY) counts, fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured in the Department of Clinical Laboratory in our hospital. TyG index and NLR were calculated as follows: TyG=ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2]; NLR = [neutrophil counts (×10<sup>9</sup>/L)/lymphocyte counts (×10<sup>9</sup>/L)].

## Coronary angiography and groups

CAG was performed by at least two experienced cardiovascular interventional experts based on the Judkin method through the radial or femoral artery. The severity of CAD was assessed using the Gensini scoring system. Based on the result of CAG, all patients were divided into CAD group and non-CAD group. Then, we divided the patients with CAD into two groups according to the median of Gensini score as follows: mild stenosis CAD group: Gensini score <26 points; severe stenosis CAD group: Gensini score ≥26 points.

### Dichotomy of TyG index and NLR

We defined high-TyG level as TyG index  $\geq$  8.78, high-NLR level as NLR  $\geq$  2.46, based on the median of all patients in this study. All patients were classified into four groups according to their level of TyG index and NLR: (1) the control group: without high-TyG and without high-NLR level; (2) isolated high-NLR group: with high-NLR but without high-TyG level; (3) isolated high-TyG group: with high-TyG but without high-NLR level; and (4) high-TyG combined with high-NLR group: with both high-TyG and high-NLR levels.

#### Statistical analysis

Data analysis was performed by SPSS 26.0 software (IBM Corp, Armonk, New York, USA). Categorical variables were described as counts and percentages. Continuous variables with normal distribution were described as the mean±standard deviation, whereas variables with non-normal distribution were described as median and interquartile range (25-75%). The Chi-square test was used for categorical variables and the Student's t-test, Mann–Whitney test or Kruskal–Wallis test was used for continuous variables. Bonferroni correction was used for multiple comparisons. Logistic regression analysis was applied to identify the risk factors for CAD and severe stenosis in CAD. The receiver operating characteristic (ROC) curve analysis was performed to evaluate the cumulative value of the combination of the TyG index and NLR in predicting CAD and CAD severity. A twotailed p-value of < 0.05 was considered significant.

Table 1 Baseline characteristics of the study patients

Characteristics	non-CAD	CAD group	t/x2	Р	
	group	(n=2109)	Value	Value	
	(n=758)				
Male (n,%)	397 (52.4)	1467 (69.6)	72.392	< 0.001	
Age (years)	$59.50 \pm 9.91$	$62.66 \pm 10.05$	-7.452	< 0.001	
Smoking (n, %)	185 (24.4)	789 (37.4)	42.041	< 0.001	
Hypertension (n, %)	390 (51.5)	1363 (64.6)	40.749	< 0.001	
Diabetes (n, %)	103 (13.6)	599 (28.4)	66.177	< 0.001	
NE counts (×10 <sup>9</sup> /L)	$3.72 \pm 1.46$	$4.72 \pm 3.09$	-8.586	< 0.001	
LY counts (×10 <sup>9</sup> /L)	$1.71 \pm 0.60$	$1.61 \pm 0.59$	4.057	< 0.001	
TC (mmol/L)	$4.45 \pm 0.98$	4.36±1.11	1.953	0.051	
TG (mmol/L)	$1.67 \pm 1.18$	$1.82 \pm 1.51$	-3.842	< 0.001	
HDL-C (mmol/L)	$1.18 \pm 0.31$	$1.07 \pm 0.27$	9.834	< 0.001	
LDL-C (mmol/L)	$2.69 \pm 0.85$	$2.69 \pm 0.92$	0.165	0.869	
FPG (mmol/L)	$5.82 \pm 1.98$	$6.22 \pm 2.21$	-4.357	< 0.001	
TyG index	$8.76 \pm 0.64$	$8.87 \pm 0.64$	-4.057	< 0.001	
NLR	$2.43 \pm 1.51$	$3.46 \pm 3.14$	-8.687	< 0.001	

Abbreviations: CAD, coronary artery disease; NE, neutrophil; LY, lymphocyte; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; TyG, triglyceride-glucose; NLR, neutrophil-to-lymphocyte ratio

## Results

### **Baseline characteristics**

Table 1 shows the baseline characteristics of patients with CAD and patients without CAD. Compared with the non-CAD group, the patients in CAD group tended to be older and male and had higher NE counts, TG, FPG, TyG index, NLR values but lower LY counts and HDL-C values (all P<0.05). Moreover, patients in the CAD group

tended to have a history of smoking, hypertension and diabetes (all P < 0.05).

Table 2 shows the baseline characteristics of patients stratified by TyG index and NLR level. Compared with the control group, the percentages of CAD and severe stenosis in CAD in the other three groups were higher (P<0.05), especially in the high-TyG combined with high-NLR group.

## Analysis of the risk factors for CAD

Multivariate logistic regression analysis was performed for variables with significantly associated with CAD (P<0.05) in univariate logistic regression. After adjusting for confounding factors (gender, age, smoking, hypertension and diabetes), the TyG index (odds ratio [OR] 1.250, 95% confidence interval [CI] 1.077–1.452) and NLR (OR 1.299, 95% CI 1.222–1.381) as continuous variables were independent risk factors for CAD (all P<0.05).

Table 3 shows the combined value of TyG index with NLR level for predicting CAD. Patients with isolated high-NLR level (OR 1.400, 95% CI 1.238–1.583), isolated high-TyG (OR 1.366, 95% CI 1.251–1.492), and high-TyG combined with high-NLR (OR 1.418, 95% CI 1.119–1.797) were independently associated with CAD after adjusting for conventional confounders.

# Diagnostic ability of TyG, NLR, and their combination in predicting CAD

As shown in Fig. 1, the area under the receiver operating characteristic (ROC) curve (AUC) of TyG, NLR, TyG

Tab	le 2	Baseline c	haracteristics o	f patients	stratified	by Ty	G and	NLR	evel
-----	------	------------	------------------	------------	------------	-------	-------	-----	------

Characteristics	low-TyG index		high-TyG index		Over-
	low-NLR (n = 690)	high-NLR (n = 744)	low-NLR (n = 737)	high-NLR (n = 696)	all P Value
Male (n,%)	404 (58.6)	518 (69.6) <sup>a</sup>	452 (61.3)	490 (70.4) <sup>a</sup>	< 0.001
Age (years)	59.81 ± 9.59	$64.07 \pm 10.04^{a}$	$61.20 \pm 9.70$	$62.08 \pm 10.10^{a}$	< 0.001
Smoking (n, %)	214 (31.0)	251 (33.7)	238 (32.3)	271 (38.9) <sup>a</sup>	0.010
Hypertension (n, %)	377 (54.6)	443 (59.5)	465 (63.1) <sup>a</sup>	468 (67.2) <sup>a</sup>	< 0.001
Diabetes (n, %)	115 (16.7)	121 (16.3)	233 (31.6) <sup>a</sup>	233 (33.5) <sup>a</sup>	< 0.001
TC (mmol/L)	4.17±0.97	$4.07 \pm 0.99$	$4.70 \pm 1.11^{a}$	$4.60 \pm 1.10^{a}$	< 0.001
TG (mmol/L)	$1.00 \pm 0.52$	$0.99 \pm 0.50$	$2.81 \pm 1.82^{a}$	$2.50 \pm 1.92^{a}$	< 0.001
HDL-C (mmol/L)	1.19±0.29	1.16±0.29	$1.03 \pm 0.27^{a}$	$1.02 \pm 0.23^{a}$	< 0.001
LDL-C (mmol/L)	$2.57 \pm 0.89$	$2.53 \pm 0.87$	$2.83 \pm 0.93^{a}$	$2.83 \pm 0.90^{a}$	< 0.001
FPG (mmol/L)	5.19±0.82	$5.47 \pm 1.05$	$6.60 \pm 2.42^{a}$	$7.20 \pm 2.91^{a}$	< 0.001
Gensini score	19.0 (10.0, 27.0)	22.6 (16.0, 36.8) <sup>a</sup>	24.0 (13.0, 32.8) <sup>a</sup>	28.0 (19.6, 42.0) <sup>a</sup>	< 0.001
CAD (n,%)	428 (62.0)	581 (78.1) <sup>a</sup>	522 (70.8) <sup>a</sup>	578 (83.0) <sup>a</sup>	< 0.001
CAD severity					
Mild stenosis (n,%)	269 (39.0)	322 (43.3)	252 (34.2)	211 (30.3) <sup>a</sup>	< 0.001
Severe stenosis (n,%)	159 (22.9)	259 (34.8) <sup>a</sup>	270 (36.6) <sup>a</sup>	367 (52.7) <sup>a</sup>	< 0.001

Abbreviations: CAD, coronary artery disease; TyG, triglyceride-glucose; NLR, neutrophil-to-lymphocyte ratio; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose

Overall P value was for the test of difference among the four group

a, significantly different from low-TyG index+low-NLR group (the Bonferroni correction was applied)

 Table 3
 Multivariate-adjusted OR and 95% CI for CAD

Groups	OR (95%CI) <sup>a</sup>	Р	
		Value	
low-TyG and low-NLR	1.00 (Reference)		
low-TyG and high-NLR	1.400 (1.238–1.583)	< 0.001	
high-TyG and low-NLR	1.366 (1.251–1.492)	< 0.001	
high-TyG and high-NLR	1.418 (1.119–1.797)	0.004	

Abbreviations: CAD, coronary artery disease; TyG, triglyceride-glucose; NLR, neutrophil-to-lymphocyte ratio; OR: odds ratio; CI: confidence interval

a, adjustment for age, gender, smoking, hypertension, diabetes, TC, TG, HDL-C, LDL-C



Fig. 1 ROC diagram of TyG, NLR, and their combination in predicting CAD

combined with NLR for predicting CAD were 0.671 (95% CI 0.648–0.694), 0.630 (95% CI 0.608–0.652), 0.707 (95% CI 0.685–0.728), respectively. Thus, the combination of the TyG index and NLR was superior to TyG index or NLR in predicting CAD.

Abbreviations: CAD, coronary artery disease; TyG, triglyceride-glucose; NLR, neutrophil-to-lymphocyte ratio; ROC: receiver operating characteristic; AUC: area under the receiver operating characteristic; FPR: false positive rate; TPR: true positive rate.

#### Baseline characteristics according to CAD severity

Table 4 shows baseline characteristics of patients in different groups according to the severity of CAD. Compared with the mild stenosis CAD group, the severe stenosis CAD group had higher TyG index and NLR values (all P < 0.05).

Characteristics	Mild	Severe	X <sup>2</sup> /t/Z	Р
	stenosis	stenosis		Value
	(n = 1054)	(n=1055)		
Male (n,%)	707 (67.1)	760 (72.0)	6.126	0.013
Age (years)	$62.26\pm9.98$	$63.06 \pm 10.10$	-1.822	0.069
Smoking (n, %)	379 (36.0)	410 (38.9)	1.899	0.168
Hypertension (n, %)	625 (59.3)	738 (70.0)	26.183	< 0.001
Diabetes (n, %)	253 (24.0)	346 (32.8)	20.044	< 0.001
NE counts (×10 <sup>9</sup> /L)	$4.30 \pm 1.98$	$5.14 \pm 3.85$	-6.309	< 0.001
LY counts (×10 <sup>9</sup> /L)	1.61±0.57	$1.61 \pm 0.62$	-0.189	0.850
TC (mmol/L)	$4.13\pm0.95$	$4.60 \pm 1.21$	-9.808	< 0.001
TG (mmol/L)	1.61±1.23	$2.04 \pm 1.72$	-6.571	< 0.001
HDL-C (mmol/L)	$1.09 \pm 0.28$	$1.05 \pm 0.25$	4.074	< 0.001
LDL-C (mmol/L)	$2.48 \pm 0.80$	$2.89 \pm 0.99$	-10.566	< 0.001
FPG (mmol/L)	$5.97 \pm 2.02$	$6.46 \pm 2.36$	-5.200	< 0.001
TyG index	$8.75 \pm 0.58$	$8.99 \pm 0.67$	-8.896	< 0.001
NLR	$3.06 \pm 2.23$	3.87±2.81	-5.923	< 0.001
Gensini score	18.3 (13.0,22.0)	40.5 (30.5,70.0)	-39.763	< 0.001

Table 4 Baseline characteristics of CAD patients according to

Abbreviations: CAD, coronary artery disease; TyG, triglyceride-glucose; NLR, neutrophil-to-lymphocyte ratio; NE, neutrophil; LY, lymphocyte; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose

**Table 5**Multivariate-adjusted OR and 95% CI for severe stenosisCAD

Groups	OR (95%CI) <sup>a</sup>	Р	
		Value	
low-TyG and low-NLR	1.00 (Reference)		
low-TyG and high-NLR	1.158 (1.017–1.319)	0.026	
high-TyG and low-NLR	1.393 (1.275–1.522)	< 0.001	
high-TyG and high-NLR	1.692 (1.296–2.211)	< 0.001	

Abbreviations: CAD, coronary artery disease; TyG, triglyceride-glucose; NLR, neutrophil-to-lymphocyte ratio; OR: odds ratio; CI: confidence interval a, adjustment for gender, smoking, hypertension, diabetes, TC, TG, HDL-C, LDL-C

#### Analysis of the risk factors for severe stenosis in CAD

The severity of CAD (mild or severe stenosis CAD) was used as dependent variable, multivariate logistic regression analysis was performed for variables with significantly associated with CAD severity (P < 0.05) in univariate logistic regression. The results showed that the TyG index (OR 1.811, 95% CI 1.561–2.102) and NLR (OR 1.129, 95% CI 1.088–1.172) as continuous variables were independent risk factors for severe stenosis in CAD (all P < 0.05).

Table 5 shows the combined value of TyG index with NLR level for predicting severe stenosis in CAD. Patients with isolated high-NLR level (OR 1.158, 95% CI 1.017–1.319), isolated high-TyG (OR 1.393, 95% CI

1.275–1.522), and high-TyG combined with high-NLR (OR 1.692, 95% CI 1.296–2.211) were independently associated with severe stenosis in CAD after adjusting for conventional confounders.

## Diagnostic ability of TyG, NLR, and their combination in predicting severe stenosis in CAD

As shown in Fig. 2, the AUC of TyG, NLR, TyG combined with NLR for predicting severe stenosis in CAD were 0.609 (95% CI 0.585–0.633), 0.567 (95% CI 0.542–0.591), 0.635 (95% CI 0.611–0.658), respectively. Thus, the combination of the TyG index and NLR was also superior to TyG index or NLR in predicting severe stenosis in CAD.

Abbreviations: CAD, coronary artery disease; TyG, triglyceride-glucose; NLR, neutrophil-to-lymphocyte ratio; ROC: receiver operating characteristic; AUC: area under the receiver operating characteristic; FPR: false positive rate; TPR: true positive rate.

## Discussion

CAD is the second leading cause of death in the Chinese population, and its prevalence and mortality are increasing year by year [2, 12]. Atherosclerosis is the main pathophysiological basis of CAD, and inflammation plays a pivotal role in the entire process of atherosclerosis [4, 13]. Neutrophils, the important inflammatory cells, have been regarded as important players in atherosclerosis-related inflammation [13]. A high level of circulating neutrophils can cause a hypercoagulable state by increasing blood viscosity, and lead to microvascular injury and reperfusion injury by interacting with platelets and vascular



Fig. 2 ROC diagram of TyG, NLR, and their combination in predicting severe stenosis CAD

endothelial cells [14]. It has been proved that neutrophil counts were related to the extent of atherosclerosis and were positively correlated with the sizes of atherosclerotic lesions [15, 16]. In contrast, lymphocytes, the immune regulatory cells, have antiatherosclerotic effects. Inflammatory mediators from lymphocytes have a modulatory effect on neutrophils and inflammatory process. Oxidative stress plays an important role in the pathological process of atherosclerosis. The number of lymphocyte counts will decrease when oxidative stress occurs. NLR is a new measure of system inflammation, which integrates neutrophils and lymphocytes. Unlike other inflammatory biomarkers, such as hsCRP and IL-6 which are not detected routinely, NLR is convenient and easy to obtain in daily clinical work. NLR has been proposed as a useful diagnostic and prognostic marker for CAD [17]. A meta-analysis of 17 studies involving 7017 patients with CAD showed that NLR was independently associated with CAD severity and confirmed the diagnostic power of NLR in predicting severe stenosis in CAD [18].

In addition to inflammation, IR is another factor that plays an important role in the development and progression of atherosclerosis [19]. IR has a strong relationship with atherosclerotic cardiovascular diseases, especially CAD [20-22]. IR refers to the decreased efficiency of insulin-mediated glucose uptaking and utilizating, that is, the sensitivity and responsiveness of insulin cells to insulin are reduced. IR cause glucose and lipid metabolism disorders, inflammatory reactions, thrombosis, endothelial dysfunction, which ultimately leads to atherosclerosis [21]. The traditional "gold standard" for evaluating insulin resistance is the hyperinsulinemic-euglycemic clamp test. However, it is difficult to apply the hyperinsulinemiceuglycemic clamp test in large-scale studies because it is expensive, time-consuming and difficult to perform. TyG index, which combines triglyceride and fasting blood glucose, can be used as a reliable surrogate index to assess IR [23]. A previous study showed that the TyG index had high sensitivity (96.5%) and specificity (85.0%) for detecting IR compared with the hyperinsulinemic-euglycemic clamp test [24]. Multiple studies have demonstrated that TyG index is associated with cardiovascular disease [25, 26]. At present, there are also studies focusing on the relationship between TyG index and CAD. Park et al. found that TyG index was an independent predictor of CAD in people without traditional cardiovascular risk factors [27]. In addition, a prospective study with more than 10 years of follow-up found that TyG index was associated with an increased risk of CAD, whether as a continuous or categorical variable [28]. Recently, two large sample retrospective studies in China showed that TyG index was associated with the severity of CAD and could be used as a predictor of CAD severity [29, 30].

Inflammation and IR are important predisposing factors for the development of atherosclerosis. Inflammation and IR are also intimately related in atherosclerosis. Under normal conditions, the binding of insulin to the insulin receptor stimulates tyrosine autophosphorylation of the receptor, which then phosphorylates adaptor proteins such as insulin receptor substrates (IRS). IRS can activate phosphatidylinositol 3-kinase and pyruvate dehydrogenase kinase 1 to transduce signals to protein kinase B and glucose transporter (GLUT). GLUT-4 vesicles are transported to the plasma membrane, which turn on glucose transport. Inflammatory mediator can impaire insulin signaling by several mechanisms and result in IR [7]. Inflammatory factors can also aggravate IR by inducing oxidative stress. Furthermore, inflammation was shown to be driven by IR and IR can increase the intensity of inflammation [31]. In summary, the relationship between inflammation and IR is bidirectional with each promoting the other, and eventually jointly contribute to atherosclerosis.

NLR and TyG index, as indicators of inflammation and IR, have become important predictors of CAD and adverse events. However, there is a lack of research on the combined value of TyG index and NLR in predicting CAD and CAD severity. Therefore, our study firstly investigated the combined value of TyG index and NLR in predicting CAD and CAD severity.

In this study, multivariate logistic regression analysis showed that TyG index and NLR were independent risk factors for CAD and severe stenosis in CAD (P<0.05), which was consistent with previous studies. Compared with the low-TyG and low-NLR group, patients with high-TyG and high-NLR group had a 1.418 times higher OR of having CAD and a 1.692 times higher OR of having severe stenosis in CAD in the multivariable logistic regression model. Notably, the OR values of the high-TyG and high-NLR group were higher than those of the isolated high-NLR group and the isolated high- TyG group. ROC curve analysis showed that the combination of the TyG index and NLR had a higher diagnostic efficiency for CAD and CAD severity than TyG index or NLR alone.

However, there are some limitations in our study. First, the most important limitations of the study is that it is a retrospective study. So, we can not prove a causal association of TyG index and NLR with CAD. Second, we only collected the data from a single hospital. Third, the participants were only inpatients in a Chinese hospital. Therefore, multi-center, large-sample, prospective studies are needed to further explore the association of TyG index and NLR with CAD.

#### Conclusions

In conclusion, this study found that both high-TyG and high-NLR level were independently associated with CAD and CAD severity. In addition,this is the first study to indicate that the combination of the TyG index and NLR was superior to TyG index or NLR in predicting CAD and severe stenosis in CAD.

#### Abbreviations

TyG	Triglyceride-glucose
NLR	Neutrophil-to-lymphocyte ratio
CAD	Coronary artery disease
CAG	Coronary angiography
IR	Insulin resistance
NE	Neutrophil
LY	Lymphocyte
FPG	Fasting plasma glucose
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
OR	Odds ratio
CI	Confdence interval
ROC	Receiver operating characteristic
AUC	Area under the receiver operating characteristic
FPR	False positive rate
TPR	True positive rate
IRS	Insulin receptor substrates

GLUT Glucose transporter

#### Acknowledgements

Not applicable.

#### Authors' contributions

BZ designed the study, performed the statistical analyses and drafted the manuscrip. AP, SL and FL collected the data. JW and JL revised the manuscript. All authors have reviewed and approved the final manuscript.

#### Funding

There is no funding to support the study.

#### **Data Availability**

The data used and analyzed to support the findings of this study are available from the corresponding author on reasonable request.

#### Declarations

#### Ethics approval and consent to participate

The study was approved by the ethics committee of Zhongnan Hospital of Wuhan University. The informed consent was obtained from all patients before enrollment.

#### **Consent for publication**

Not applicable.

#### Competing interests

The authors declare no competing interests.

#### Received: 30 May 2023 / Accepted: 17 October 2023 Published online: 01 November 2023

#### References

. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, et al. Heart Disease and

Stroke Statistics-2021 update: a Report from the American Heart Association. Circulation. 2021;143(8):e254–e743.

- China Cardiovascular Health and Disease Report. (Coronary Heart Disease). J Cardiovasc Pulmonary. 2021;41(12):1205–11.
- Russell Ross PS, Wash. Atherosclerosis is an inflammatory disease. N Engl J Med,1999,340(2):115–126 1999.
- Libby P. Inflammation during the life cycle of the atherosclerotic plaque. Cardiovasc Res. 2021;117(13):2525–36.
- Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and Atherosclerosis. Cell Metab. 2011;14(5):575–85.
- Theuma P, Fonseca VA. Inflammation, insulin resistance, and Atherosclerosis. Metab Syndr Relat Disord. 2004;2(2):105–.
- Zand H, Morshedzadeh N, Naghashian F. Signaling pathways linking inflammation to insulin resistance. Diabetes Metab Syndr. 2017;11(Suppl 1):307–s309.
- 8. Rehman K, Akash MSH. Mechanisms of inflammatory responses and develop-
- ment of insulin resistance: how are they interlinked? J Biomed Sci. 2016;23:18.Lele RD. Causation, prevention and reversal of vascular endothelial dysfunc-
- tion. J Assoc Phys India. 2007;55:643–51.
  Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, Jacques-Camarena O, Rodríguez-Morán M. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95(7):3347–51.
- 11. Du TT, Yuan G, Zhang MX, Zhou XR, Sun XX, Yu XF. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. Cardiovasc Diabetol. 2014;13:10.
- Zhou MG, Wang HD, Zhu J, Chen WQ, Wang LH, Liu SW, Li YC, Wang LJ, Liu YN, Yin P, et al. Cause-specific mortality for 240 causes in China during 1990–2013: a systematic subnational analysis for the global burden of Disease Study 2013. Lancet (London England). 2016;387(10015):251–72.
- Murphy AJ, Woollard KJ, Suhartoyo A, Stirzaker RA, Shaw J, Sviridov D, Chin-Dusting JP. Neutrophil activation is attenuated by high-density lipoprotein and apolipoprotein A-I in in vitro and in vivo models of inflammation. Arterioscler Thromb Vasc Biol. 2011;31(6):1333–41.
- Kawaguchi H, Mori T, Kawano T, Kono S, Sasaki J, Arakawa K. Band neutrophil count and the presence and severity of coronary Atherosclerosis. Am Heart J. 1996;132(1 Pt 1):9–12.
- Kostis JB, Turkevich D, Sharp J. Association between leukocyte count and the presence and extent of coronary Atherosclerosis as determined by coronary arteriography. Am J Cardiol. 1984;53(8):997–9.
- Drechsler M, Megens RT, van Zandvoort M, Weber C, Soehnlein O. Hyperlipidemia-triggered neutrophilia promotes early Atherosclerosis. Circulation. 2010;122(18):1837–45.
- Angkananard T, Anothaisintawee T, McEvoy M, Attia J, Thakkinstian A. Neutrophil lymphocyte ratio and Cardiovascular Disease Risk: a systematic review and Meta-analysis. Biomed Res Int. 2018;2018:2703518.
- Li X, Ji Y, Kang J, Fang N. Association between blood neutrophil-to-lymphocyte ratio and severity of coronary artery Disease: evidence from 17 observational studies involving 7017 cases. Med (Baltim). 2018;97(39):e12432.
- Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R. Insulin sensitivity and Atherosclerosis.

- 20. Chen WQ, Wang SK, Lv W, Pan YS. Causal associations of insulin resistance with coronary artery Disease and ischemic Stroke: a mendelian randomization analysis. BMJ Open Diab Res Care. 2020;8(1):9.
- 21. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of Cardiovascular Disease. Cardiovasc Diabetol. 2018;17(1):122.
- 22. Reaven G. Insulin resistance and coronary Heart Disease in nondiabetic individuals. Arterioscler Thromb Vasc Biol. 2012;32(8):1754–9.
- Kang B, Yang Y, Lee EY, Yang HK, Kim HS, Lim SY, Lee JH, Lee SS, Suh BK, Yoon KH. Triglycerides/glucose index is a useful surrogate marker of insulin resistance among adolescents. International journal of obesity (2005) 2017, 41(5):789–792.
- Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, Jacques-Camarena O, Rodriguez-Moran M. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab. 2010;95(7):3347–51.
- Li S, Guo B, Chen H, Shi Z, Li Y, Tian Q, Shi S. The role of the triglyceride (triacylglycerol) glucose index in the development of cardiovascular events: a retrospective cohort analysis. Sci Rep. 2019;9(1):7320.
- Mao Q, Zhou DL, Li YM, Wang YQ, Xu SC, Zhao XH. The triglyceride-glucose index predicts coronary artery Disease Severity and Cardiovascular outcomes in patients with Non-ST-Segment elevation Acute Coronary Syndrome. Dis Markers. 2019;2019:11.
- 27. Park GM, Cho YR, Won KB, Yang YJ, Park S, Ann SH, Kim YG, Park EJ, Kim SJ, Lee SG, et al. Triglyceride glucose index is a useful marker for predicting subclinical coronary artery Disease in the absence of traditional risk factors. Lipids Health Dis. 2020;19(1):7.
- Barzegar N, Tohidi M, Hasheminia M, Azizi F, Hadaegh F. The impact of triglyceride-glucose index on incident cardiovascular events during 16 years of follow-up: Tehran lipid and glucose study. Cardiovasc Diabetol. 2020;19(1):155.
- Wang X, Xu W, Song Q, Zhao Z, Meng X, Xia C, Xie Y, Yang C, Jin P, Wang F. Association between the triglyceride-glucose index and severity of coronary artery Disease. Cardiovasc Diabetol. 2022;21(1):168.
- 30. Su J, Li Z, Huang M, Wang Y, Yang T, Ma M, Ni T, Pan G, Lai Z, Li C, et al. Triglyceride glucose index for the detection of the severity of coronary artery Disease in different glucose metabolic states in patients with coronary Heart Disease: a RCSCD-TCM study in China. Cardiovasc Diabetol. 2022;21(1):96.
- Shimobayashi M, Albert V, Woelnerhanssen B, Frei IC, Weissenberger D, Meyer-Gerspach AC, Clement N, Moes S, Colombi M, Meier JA, et al. Insulin resistance causes inflammation in adipose tissue. J Clin Investig. 2018;128(4):1538–50.

### **Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.