Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Associations Between the Atherogenic Index of Plasma and Triglyceride-Glucose Index With Coronary Microvascular Dysfunction in Hypertensive Patients

Xiaodong Cui[1,2], Mingyang Li[1,2], Anran Jing[1,2], Yan Zhang[3], Liuying Zheng[2], Ting Li[2], Tianxu Hao[1,2], Jiachun Lang[1,2], Zhihao Guo[1,2,4], Hongliang Cong[1,2], Yingyi Zhang[1,2]

[1]Clinical School of Thoracic, Tianjin Medical University, Tianjin, People's Republic of China; [2]Department of Cardiology, Tianjin Chest Hospital, Tianjin, People's Republic of China; [3]Tianjin Union Medical Center, Tianjin Medical University, Tianjin, 300122, People's Republic of China; [4]Department of Cardiology, Cangzhou Center Hospital, Cangzhou, Hebei Province, People's Republic of China

Correspondence: Hongliang Cong, Department of Cardiology, Tianjin Chest Hospital, 261 Tai'erzhuang Road, Jinnan District, Tianjin, 300222, People's Republic of China, Tel +86-22-88185003, Email hongliangcong@126.com; Yingyi Zhang, Department of Cardiology, Tianjin Chest Hospital, 261 Tai'erzhuang Road, Jinnan District, Tianjin, 300222, People's Republic of China, +86-22-88185003, Email zyyzh2010@126.com

Background: The triglyceride-glucose (TyG) index is a reliable marker of insulin resistance, and the atherogenic index of plasma (AIP) reflects atherosclerosis. However, the relationship between these biomarkers—particularly AIP—and coronary microvascular dysfunction (CMD) in hypertensive patients has not been systematically studied. This study investigates the association between TyG, AIP, and CMD in hypertensive individuals.

Methods: We included 155 hypertensive patients with coronary anatomy confirmed by coronary angiography (CAG) or computed tomography angiography (CTA) within six months of SPECT imaging. CMD was diagnosed with a summed stress score (SSS) ≥4 and a summed difference score (SDS) ≥2. Patients were stratified into tertiles by TyG index and AIP. Logistic regression, adjusted for traditional cardiovascular risk factors, was used to explore the relationship with CMD. The predictive value of TyG and AIP was assessed using receiver operating characteristic (ROC) curves, and decision curve analysis (DCA) evaluated their clinical benefit.

Results: Logistic regression revealed that both TyG and AIP were independently associated with coronary artery disease (CAD) ($P<0.05$ for both). The area under the ROC curve (AUC) for TyG, AIP, and their combined predictive capacity for CMD was 0.744, 0.707, and 0.748, respectively ($P<0.001$ for all). The optimal cutoff values for TyG and AIP were 7.012 and 0.5175, respectively. Combining both biomarkers enhanced clinical decision-making and patient benefit.

Conclusion: Higher levels of TyG and AIP are significantly associated with an increased risk of CMD in hypertensive patients. Both biomarkers exhibit strong predictive value, with AIP showing greater specificity and TyG higher sensitivity. Their combined use can improve clinical decision-making and patient outcomes.

Keywords: triglyceride-glucose index, atherogenic index of plasma, coronary microvascular dysfunction, hypertension

Introduction

Hypertension represents a major global health burden and remains one of the foremost cardiovascular risk factors. Hypertension-mediated organ damage (HMOD) is frequently observed in individuals with severe or long-standing hypertension, and even in those with modest elevations in blood pressure, including asymptomatic individuals with elevated blood pressure levels.[1] Notably, the presence of HMOD is associated with a 2- to 3-fold increased cardiovascular risk across all categories of blood pressure above normal or optimal levels.[2] Coronary microvascular disease (CMD), which involves dysfunction and structural impairment of the coronary microcirculation, is a well-established complication of hypertension.[3,4] Other contributing factors, including metabolic syndrome, diabetes, and dyslipidemia,

Received: 17 December 2024
Accepted: 24 March 2025
Published: 8 April 2025

exacerbate the development of CMD in hypertensive patients. Consequently, a significant proportion of individuals with hypertension are affected by CMD.[5,6] Early identification of high-risk subgroups within this population is critical for effective prevention and improved clinical outcomes.

Dyslipidemia has been implicated in exacerbating coronary endothelial and microvascular dysfunction.[7] The atherogenic index of plasma (AIP), first proposed by Dobiásová and Frohlich in 2001, is calculated as the negative logarithm of the ratio of triglycerides (TG) to high-density lipoprotein cholesterol (HDL-C).[8] AIP not only reflects the lipid profile but also correlates with the pathogenesis of atherosclerosis, coronary plaque formation, acute coronary thrombosis, and chronic coronary occlusion.[7,9,10] Epidemiological evidence supports AIP as a significant predictor of hypertension, diabetes, obesity, and other components of metabolic syndrome, with a direct association to an elevated risk of cardiovascular events.[11] Recent studies have further suggested that dyslipidemia may be linked to coronary slow flow, implicating AIP in the development of CMD.[12–15] However, while AIP has been linked to CMD in various populations, the specific relationship between AIP and CMD in hypertensive patients remains insufficiently explored. Our study specifically addresses this gap, focusing on hypertensive individuals who are at higher risk for CMD and cardiovascular events, thereby providing valuable insights for this high-risk subgroup.

Insulin resistance (IR), a hallmark of type 2 diabetes mellitus (T2DM), is recognized as a pivotal contributor to CMD.[16,17] Defined by diminished insulin sensitivity, IR necessitates elevated insulin levels to achieve normal physiological responses, and it is a well-established risk factor for CMD, influencing both its initiation and progression.[18,19] Despite its critical role in the pathogenesis of CMD, challenges in the clinical detection of IR, coupled with the limited number of studies specifically examining its role in CMD, highlight the need for further investigation. The triglyceride-glucose (TyG) index, derived from fasting blood glucose (FBG) and fasting triglycerides (TG), has emerged as a reliable surrogate marker for IR.[20,21] Several studies have demonstrated that an elevated TyG index correlates with the presence and poor prognosis of various cardiovascular conditions, including carotid atherosclerosis, coronary artery disease, arterial stiffness, and coronary microvascular dysfunction.[22–25] Furthermore, recent studies suggest that the TyG index may independently predict coronary slow flow, further implicating it in the pathogenesis of CMD.[26] However, while the TyG index has been explored in relation to cardiovascular conditions, its specific role in CMD among hypertensive patients remains to be fully elucidated. This study addresses this gap by investigating both the TyG index and AIP in hypertensive patients with CMD, offering a dual biomarker approach to better understand the complex interplay between these indices in CMD development.

This study aims to investigate the associations between the TyG index, AIP, and CMD in hypertensive patients, with a focus on their combined predictive value for CMD risk. By examining both biomarkers in a hypertensive population, we seek to provide a more comprehensive understanding of their roles in CMD and to explore their potential utility for early detection and clinical decision-making.

Methods

Ethical Considerations

This study was conducted at Tianjin Chest Hospital in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Institutional Review Board of Tianjin Chest Hospital. Given the retrospective design of the study, the requirement for informed consent was waived by the review board. However, measures were taken to protect participants' privacy, and it was confirmed that the data were anonymized or maintained with confidentiality.

Study Design

We conducted a retrospective cohort study involving 346 hypertensive patients who underwent myocardial single-photon emission computed tomography (SPECT) imaging at Tianjin Chest Hospital between September 17, 2021, and November 1, 2023. The inclusion criteria were: (1) age $\geq$ 18 years and $\leq$ 80 years; (2) completion of coronary angiography (CAG) or coronary computed tomography angiography (CTA) within 6 months before or after the SPECT examination. Exclusion criteria included: (1) malignancy, infectious diseases, severe hepatic or renal dysfunction,

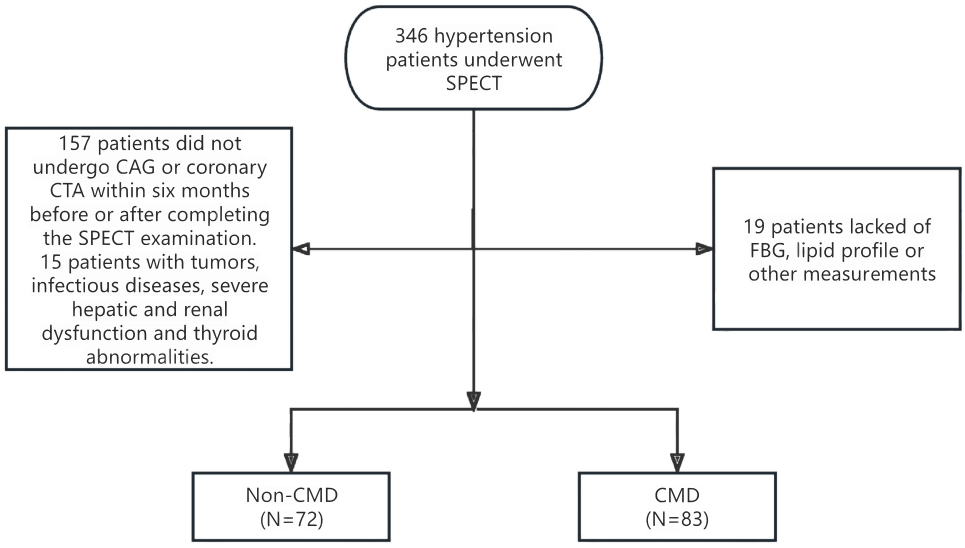

Figure 1 Flow chart of subject recruitment.
Abbreviations: CAG coronary angiography; CTA coronary computed tomography angiography; CMD coronary microvascular dysfunction; FBG, fasting plasma glucose.

or thyroid disorders; (2) incomplete laboratory data, including fasting blood glucose (FBG) or other relevant measurements (Figure 1). A total of 155 patients met the inclusion criteria, of whom 83 were diagnosed with coronary microvascular disease (CMD) and 72 were not (Figure 1). Based on predefined diagnostic criteria for CMD, the patients were divided into two groups: the CMD group (n = 83) and the non-CMD group (n = 72).

Data Collection

Patient data were extracted from the hospital's electronic medical records, including demographic characteristics, clinical histories, laboratory results, and relevant imaging reports. Demographic variables included age, sex, and smoking history. Clinical histories included diabetes, coronary artery disease (CAD), heart failure (HF), atrial fibrillation, family history of cardiovascular disease, and current medication use, including antihypertensive, antidiabetic, lipid-lowering, and antiplatelet drugs. Blood samples were collected by trained medical personnel following an overnight fast. Laboratory parameters measured included red blood cell count (RBC), microalbuminuria (MAU), estimated glomerular filtration rate (eGFR), uric acid (UA), serum creatinine (Cr), homocysteine (HCY), D-dimer, brain natriuretic peptide (BNP), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), FBG, glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high-sensitivity C-reactive protein (hs-CRP), and high-sensitivity troponin T (hs-TNT). Echocardiogram, CAG, and CTA data were obtained from the corresponding reports.

Evaluation of Coronary Microvascular Function

SPECT images were independently interpreted by two experienced cardiologists, both blinded to the patients' clinical characteristics. Using QPS software (Cedars-Sinai Medical Center, LA, CA), standardized myocardial segmentation of 17 regions and a 5-point scoring system were applied to assess the extent and severity of perfusion defects (0 = normal, 4 = no tracer uptake).[27] The summed stress score (SSS) represented the total score for defects observed in the stress images, the summed rest score (SRS) represented the total score for defects in the rest images, and the summed difference score (SDS) was the sum of the differences between the corresponding stress and rest scores. SSS, SRS, and SDS values were recorded as the mean of upright and supine image scores. A perfusion defect was considered abnormal if SSS $\geq$ 4 and SDS $\geq$ 2, which indicates ischemia in a single coronary artery region without $\geq$50% coronary stenosis.[28,29]

Definitions and Grouping

Diabetes was diagnosed based on the following criteria: (1) HbA1c $\geq$ 6.5%; (2) random blood glucose $\geq$ 11.1 mmol/L; (3) FBG $\geq$ 7.0 mmol/L; or (4) 2-hour plasma glucose $\geq$ 11.1 mmol/L in an oral glucose tolerance test.[20] Hypertension was

defined as a resting systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, or the use of antihypertensive medications. CAD was defined by ≥50% luminal stenosis in the main coronary artery.[30] CMD was diagnosed according to previously established criteria: SSS ≥ 4, SDS ≥ 2, and ischemic regions with coronary stenosis <50%. The atherogenic index of plasma (AIP) was calculated using the formula: lg (TG [mg/dL] / HDL-C [mg/dL]).[8] The triglyceride-glucose (TyG) index was calculated as ln((TG [mg/dL] × FPG [mg/dL]) / 2).[20]

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) for normally distributed data or as median (interquartile range [IQR]) for non-normally distributed data. Between-group comparisons were performed using the independent *t*-test or analysis of variance (ANOVA) for normally distributed variables and the Mann–Whitney *U*-test or Kruskal–Wallis test for non-normally distributed variables. Categorical variables are presented as frequencies and percentages, with comparisons between groups conducted using Pearson's chi-square (χ^2) test or Fisher's exact test as appropriate. Logistic regression models were employed to examine the association between the TyG index and AIP (independent variables) and CMD (dependent variable), with odds ratios (ORs) and 95% confidence intervals (CIs) calculated. The TyG index was divided into three groups based on tertiles, and three models were constructed to explore the interaction between the TyG index and CMD: Model 1 (unadjusted); Model 2 (adjusted for age and sex); and Model 3 (adjusted for age, sex, coronary artery disease [CAD], left ventricular [LV] volume, left ventricular ejection fraction [LVEF], LDL, MAU, D-dimer, HDL, lipid-lowering drugs, antiplatelet drugs, and antidiabetic medications).

Similarly, AIP was categorized into tertiles, and three models were developed to evaluate the relationship between AIP and CMD, considering significant covariates: Model 1 (unadjusted); Model 2 (adjusted for age and sex); and Model 3 (adjusted for additional covariates including CAD, LV, LVEF, LDL, MAU, D-dimer, HbA1c, lipid-lowering drugs, antiplatelet drugs, and antidiabetic medications).

Receiver operating characteristic (ROC) curve analysis was used to assess the predictive performance of the TyG index and AIP for CMD, with area under the curve (AUC) values and corresponding 95% CIs reported. The optimal cut-off values for TyG and AIP were determined using the maximum Youden index, calculated as sensitivity + specificity − 1. Decision curve analysis (DCA) was employed to evaluate the clinical utility of the TyG index and AIP in decision-making. All statistical analyses were performed using SPSS 25.0 (IBM, USA) and R (version 4.2.0, R) statistical software. A two-tailed P value < 0.05 was considered statistically significant.

Results

Clinical Characteristics of CMD and Non-CMD Groups

The study included 155 participants, of whom 83 were newly diagnosed with coronary microvascular dysfunction (CMD) and 72 served as controls without CMD (Table 1). The mean age of the cohort was 64.0 years (interquartile range [IQR], 54.5–70.0), with 56.77% (88/155) of the participants being male. Statistically significant differences between the CMD and non-CMD groups were observed in terms of coronary artery disease (CAD), left ventricular (LV) function, left ventricular ejection fraction (LVEF), microalbuminuria (MAU), D-dimer levels, the use of lipid-lowering medications, antiplatelet therapy, antihyperglycemic treatment, triglyceride levels (TG), high-density lipoprotein cholesterol (HDL-C), the triglyceride-glucose (TyG) index, the atherogenic index of plasma (AIP), and fasting blood glucose (P < 0.05).

Association Between the TyG Index and CMD

The TyG index was stratified into three tertiles: I (TyG ≤ 6.814), II (6.814 < TyG ≤ 7.148), and III (TyG > 7.148). Multivariable logistic regression analysis, adjusted for conventional cardiovascular risk factors and medical treatments, revealed a significant association between the TyG index and CMD (P = 0.001; Table 2). As a continuous variable, the TyG index was significantly associated with CMD (odds ratio [OR] = 1.25; 95% confidence interval [CI], 1.10–1.43; P = 0.001). Furthermore, in the categorical analysis, individuals in the highest tertile (III) exhibited a 5.91-fold increased risk of CMD compared to those in the lowest tertile (I) (95% CI, 1.81–19.27; P < 0.005), after adjusting for confounders.

Table 1 Baseline Characteristics of the Study Population

Variables	Total (n = 155)	CMD (n =83)	NON-CMD (n = 72)	*P*
Age, years	64.00 (54.50, 70.00)	64.00 (56.00, 70.00)	64.00 (53.75, 70.25)	0.539
Male, n(%)	88 (57.56.77)	47 (56.63)	41 (56.94)	0.968
CAD, n(%)	87 (56.13)	55 (66.27)	32 (44.44)	0.006
Smoking, n(%)	51 (32.90)	27 (32.53)	24 (33.33)	0.915
Family, n(%)	13 (8.39)	6 (7.23)	7 (9.72)	0.576
HF, n(%)	45 (29.22)	23 (28.05)	22 (30.56)	0.733
Diabetes, n(%)	57 (36.77)	35 (42.17)	22 (30.56)	0.135
Atrial fibrillation, n(%)	16 (10.32)	10 (12.05)	6 (8.33)	0.448
LA, mm	38.00 (36.00, 43.00)	40.00 (36.00, 44.75)	38.00 (35.00, 40.00)	0.087
LV, mm	50.00 (47.00, 54.00)	53.00 (48.25, 56.00)	49.00 (47.00, 52.00)	0.005
LVEF, %	61.00 (56.00, 63.00)	60.00 (54.00, 62.00)	61.00 (58.00, 63.00)	0.030
Laboratory findings				
hs-Tn, ng/mL	0.01 (0.01, 0.02)	0.01 (0.01, 0.02)	0.01 (0.01, 0.01)	0.273
RBC	4.52 ± 0.50	4.50 ± 0.48	4.54 ± 0.52	0.611
MAU	12.09 (8.09, 25.18)	15.12 (9.59, 36.34)	9.33 (7.14, 15.20)	0.001
eGFR	89.07 (78.34, 97.75)	88.48 (75.74, 95.68)	92.07 (84.13, 98.76)	0.063
D-dimer	0.22 (0.17, 0.35)	0.23 (0.19, 0.40)	0.20 (0.14, 0.32)	0.004
Creatinine, umol/l	74.00 (61.00, 84.50)	75.00 (61.00, 86.50)	73.50 (61.00, 83.00)	0.433
UA, μmol/L	320.00 (266.00, 381.50)	337.00 (266.50, 386.00)	295.50 (262.50, 375.25)	0.303
TC, mmol/L	6.78 ± 34.31	3.96 ± 0.98	10.03 ± 50.32	0.273
TG, mmol/L	1.38 (1.17, 1.81)	1.55 (1.32, 1.98)	1.31 (1.07, 1.53)	<0.001
LDL, mmol/L	2.62 ± 0.93	2.56 ± 0.88	2.68 ± 0.98	0.403
HDL, mmol/L	1.03 (0.86, 1.22)	0.97 (0.85, 1.15)	1.10 (0.92, 1.29)	0.002
BNP, pg/mL	25.89 (13.27, 90.16)	31.75 (13.18, 131.15)	25.15 (13.59, 80.06)	0.260
HCY, μmol/L	11.35 (9.31, 14.12)	11.29 (9.29, 14.39)	11.46 (9.31, 13.87)	0.874
FBG, mmol/L	5.34 (4.83, 6.27)	5.66 (4.96, 6.88)	5.04 (4.78, 5.59)	<0.001
HbA1c, %	6.10 (5.60, 6.77)	6.20 (5.70, 7.10)	5.80 (5.50, 6.30)	0.003
hs-CRP, mg/L	0.86 (0.54, 1.78)	0.96 (0.55, 2.54)	0.78 (0.54, 1.59)	0.568
TyG index	7.14 (6.96, 7.44)	7.24 (7.08, 7.55)	6.98 (6.77, 7.19)	<0.001
AIP	0.51 ± 0.20	0.58 ± 0.20	0.43 ± 0.17	<0.001
Medicine				
antiPLT, n(%)	91 (58.71)	59 (71.08)	32 (44.44)	<0.001
Statins, n(%)	128 (82.58)	74 (89.16)	54 (75.00)	0.020
ACEI /ARB, n(%)	42 (27.10)	25 (30.12)	17 (23.61)	0.363
ARNI, n(%)	122 (78.71)	61 (73.49)	61 (84.72)	0.089
Beta blocker, n(%)	104 (67.10)	57 (68.67)	47 (65.28)	0.653
CCBs, n(%)	57 (36.77)	34 (40.96)	23 (31.94)	0.245
Anticoagulation, n(%)	17 (10.97)	9 (10.84)	8 (11.11)	0.958
MRAs, n(%)	16 (13.3)	12 (18.2)	4 (7.4)	0.084
OADs, n(%)	58 (37.42)	37 (44.58)	21 (29.17)	0.048

Notes: Data are expressed as mean ± SD, medians with interquartile ranges or percentage.

Abbreviations: CAD, coronary artery disease; HF, heart failure; LA, left atrium volume; LV, left ventricular volume; LVEF, left ventricle ejection fraction; RBC, red blood cell count; MAU, microalbuminuria; eGFR, estimated glomerular filtration rate; UA, uric acid; Cr, serum creatinine; HCY, homocysteine; D, dimer; BNP, brain natriuretic peptide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; hs-TNT, high-sensitivity troponin T TyG triglyceride-glucose; AIP, atherogenic index of plasma antiPLT; ACEI / ARB, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; CCBs, Calcium Channel Blockers; MRAs, Mineralocorticoid receptor antagonists; OADs, Oral Antidiabetic Drugs.

Association Between AIP and CMD

Similarly, the AIP was categorized into three tertiles: I (AIP ≤ 0.427), II (0.427 < AIP ≤ 0.574), and III (AIP > 0.574). Following multivariable adjustment, AIP was significantly associated with CMD (P = 0.002; Table 3). When treated as a continuous variable, AIP showed a robust correlation with CMD (OR = 1.62; 95% CI, 1.19–2.21; P = 0.002).

Table 2 Association Between the TyG Index and CMD

Variables	Model1		Model2		Model3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
TyG	1.28(1.14 ~ 1.44)	<0.001	1.27(1.13~1.43)	<0.001	1.25(1.10~1.43)	0.001
I	Reference		Reference		Reference	
II	6.32 (2.67 ~ 14.95)	<0.001	6.16 (2.58 ~ 14.73)	<0.001	7.56 (2.42 ~ 23.60)	<0.001
III	7.80 (3.22 ~ 18.88)	<0.001	8.05 (3.29 ~ 19.68)	<0.001	5.91 (1.81 ~ 19.27)	0.003
P-trend	1.32 (1.17 ~ 1.49)	<0.001	1.32 (1.17 ~ 1.50)	<0.001	1.28 (1.09 ~ 1.50)	0.002

Notes: Model1: Crude. Model2: Adjust: Sex, Age. Model3: Adjust: Sex, Age, D-dimer, LDL-C, MAU, HDL, LV, LVEF, CAD, antidiabetic drugs, antilipidemic drugs, antiplatelet drugs.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Table 3 Association Between the AIP and CMD

Variables	Model1		Model2		Model3	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
AIP	1.72(1.33 ~ 2.24)	<0.001	1.70(1.31 ~ 2.22)	<0.001	1.62(1.19 ~ 2.21)	0.002
1	Reference		Reference		Reference	
2	2.24 (1.01 ~ 4.95)	0.046	2.13 (0.96 ~ 4.75)	0.064	5.72 (1.78 ~ 18.33)	0.003
3	5.85 (2.48 ~ 13.78)	<0.001	5.95 (2.49 ~ 14.24)	<0.001	6.00 (1.59 ~ 22.66)	0.008
P-trend	1.59 (1.27 ~ 1.99)	<0.001	1.59 (1.27 ~ 2.00)	<0.001	1.68 (1.19 ~ 2.37)	0.003

Notes: Model1: unadjusted. Model2: Adjusted: Sex, Age. Model3: Adjusted: Sex, Age, D-dimer, LDL-C, HbAlc, MAU, LV, LVEF, CAD, antidiabetic drugs, antilipidemic drugs, antiplatelet drugs.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Moreover, in the categorical analysis, individuals in the highest tertile (III) were found to have a 1.68-fold higher risk of CMD than those in the lowest tertile (I) (95% CI, 1.19–2.37; P = 0.003).

Predictive Value of TyG Index and AIP for Coronary Microvascular Dysfunction

The RCS curve analysis demonstrated a nonlinear positive correlation between AIP and CMD (nonlinear P = 0.019; Figure 2A), as well as between TyG and CMD (nonlinear P = 0.005; Figure 2B). The predictive performance of the TyG index and AIP for CMD was further evaluated using ROC curve analysis (Figure 3). The area under the curve (AUC) for TyG, AIP, and their combined use in predicting CMD were 0.744, 0.707, and 0.748, respectively (P<0.001 for all;

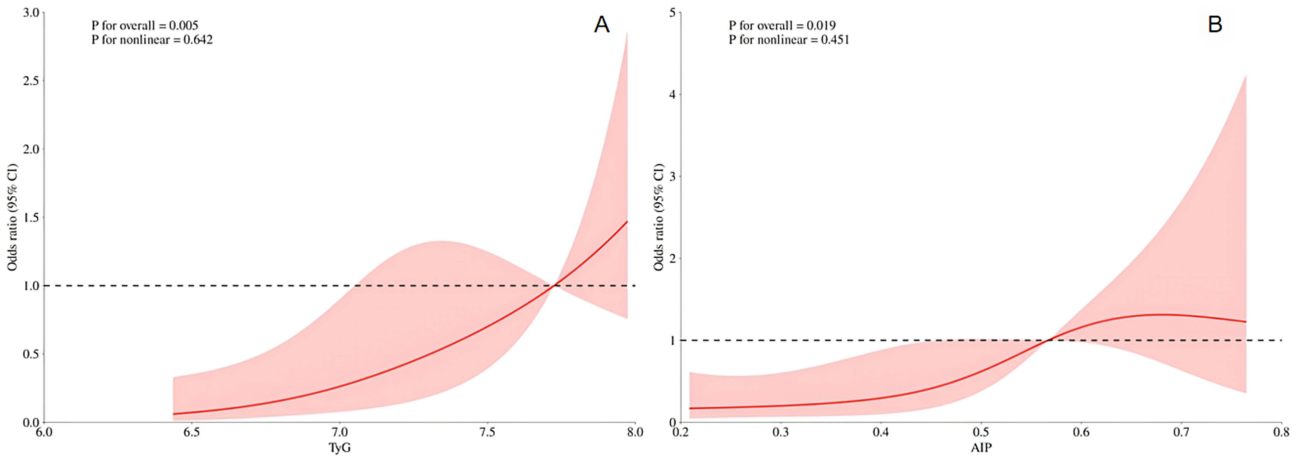

Figure 2 Restricted cubic spline curves for the association of TyG index (**A**) andAIP (**B**) with the risk of CMD in the adjusted model. Adjusted for Sex, Age, D-dimer, LDL-C, HbAlc, MAU, LV, LVEF, CAD, antidiabetic drugs, antilipidemic drugs, antiplatelet drugs.
Abbreviations: TyG triglyceride-glucose, AIP atherogenic index of plasma.

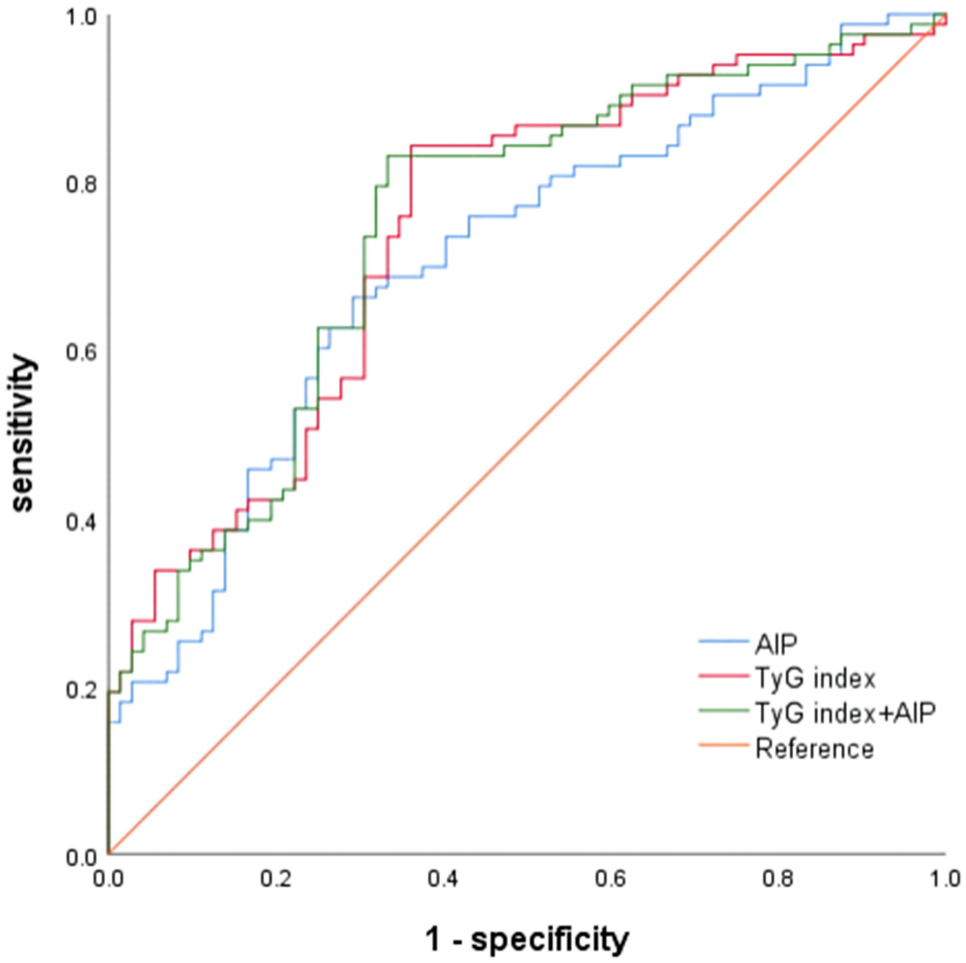

Figure 3 ROC curve for TyG index, AIP and their combination in predicting CMD. Optimal cut-off: TyG Index: 7.012; AIP: 0.5175. AUC TyG index: 0.744 (0.666–0.821), AUC AIP: 0.707 (0.625–0.788); AUC combine: 0.748 (0.670–0.826).
Abbreviations: ROC receiver operating characteristic, AUC an area under the curve, TyG triglyceride-glucose, AIP atherogenic index of plasma.

Table 4). The optimal cutoff values for the TyG index and AIP were 7.012 (Youden index = 0.482, sensitivity = 0.843, specificity = 0.639) and 0.5175 (Youden index = 0.371, sensitivity = 0.663, specificity = 0.708), respectively. The combined use of TyG and AIP for predicting CMD yielded a sensitivity of 0.831 and specificity of 0.667. Incorporating both the TyG index and AIP into clinical decision-making processes significantly enhanced net patient benefit (Figure 4).

Table 4 ROC Curve for TyG Index, AIP and Their Combination in Predicting CMD

	AUC	Optimal cut-off value	Sensitivity %	Specificity %	95% CI	P value
TyG	0.744	7.012	84.30	63.90	0.666–0.821	<0.001
AIP	0.707	0.5175	66.30	66.70	0.625–0.788	<0.001
TyG+AIP	0.748		83.10	66.70	0.670–0.826	<0.001

Abbreviations: TyG, index triglyceride-glucose, AIP, atherogenic index of plasma; ROC, receiver operating characteristic; AUC, an area under the cure; CI, confidential intervals.

https://doi.org/10.2147/DMSO.S510851

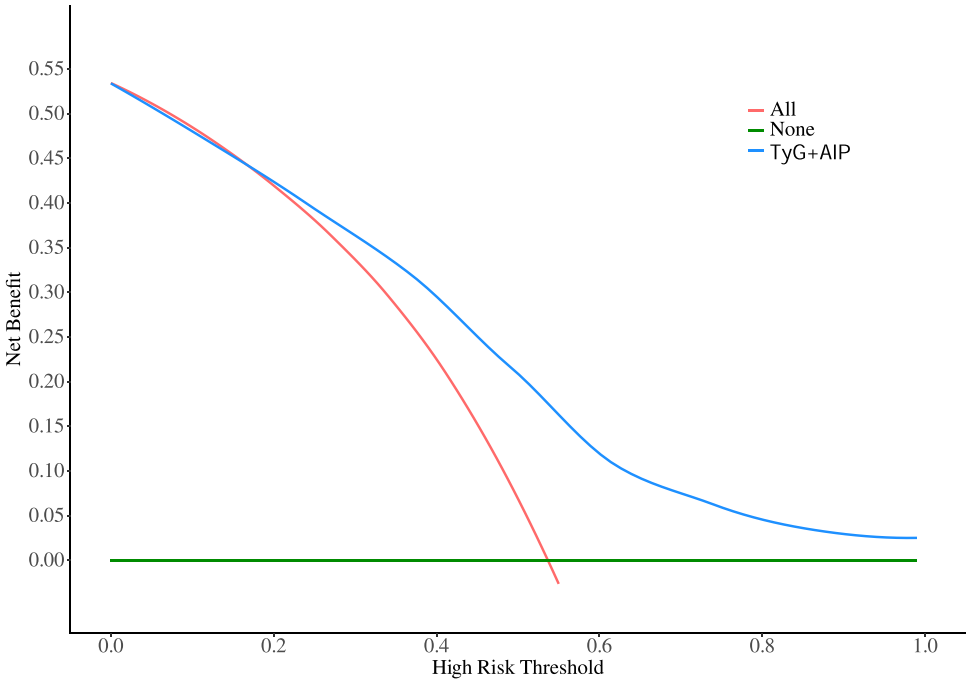

Figure 4 DCA curve for the combined prediction of CMD by the TyG index and AIP.DCA Decision Curve Analysis. Adjusted for Sex, Age, D-dimer, LDL-C, HbAlc, MAU, LV, LVEF, CAD, antidiabetic drugs, antilipidemic drugs, antiplatelet drugs.

Discussion

This study represents the first investigation specifically focusing on the hypertensive population, examining the association between the Atherogenic Index of Plasma (AIP) and Coronary Microvascular Dysfunction (CMD). Additionally, it is the first comprehensive investigation to explore the concurrent roles of both AIP and the Triglyceride-Glucose (TyG) index in relation to CMD. The key findings of this study include:

1. **CMD patients exhibited significantly higher AIP and TyG indices compared to those without CMD within the hypertensive cohort.**
2. **Both AIP and TyG indices were identified as independent risk factors for CMD in hypertensive patients, even after adjusting for multiple confounding variables.**
3. **AIP and TyG indices emerged as promising biomarkers for CMD prediction, with AIP demonstrating superior specificity and TyG exhibiting enhanced sensitivity.**

CMD represents a group of disorders affecting the structure and function of the coronary microcirculation, commonly observed in patients with cardiovascular risk factors, and is associated with an increased risk of adverse cardiovascular events. In recent years, CMD has garnered increasing attention due to its significant deleterious effects on both short- and long-term cardiovascular health. Rajai et al highlighted that CMD is strongly linked to the development of cancer in patients with non-obstructive coronary artery disease.[31] Additionally, several studies have demonstrated that patients with CMD are more likely to experience cognitive impairments.[32] These observations underscore the broader systemic implications of CMD beyond traditional cardiovascular outcomes.

Hypertension and CMD

Hypertension is a well-established risk factor for CMD and one of its primary etiological causes. Chronic hypertension induces a systemic pro-inflammatory state that contributes to endothelial dysfunction, particularly within the coronary microcirculation.[33] Many hypertensive patients may exhibit underlying microvascular dysfunction, which underscores the importance of investigating CMD specifically within this population. The pathophysiology of CMD is multifactorial

and involves a combination of structural and functional alterations in the coronary microvascular bed. These alterations may include microvascular spasm, endothelial dysfunction, excessive sympathetic nervous activity, and hormonal or psychological influences.[34,35] Dyslipidemia, insulin resistance, and lipotoxicity are considered critical pathophysiological drivers, all of which contribute to increased oxidative stress, the release of pro-inflammatory mediators, and further disruption of microvascular function.[3]

Our study specifically focused on analyzing the relationship between lipid and glucose metabolism and CMD in hypertensive individuals, providing novel insights into the mechanisms linking these metabolic disturbances with microvascular dysfunction.

Dyslipidemia and CMD

Dyslipidemia remains a cornerstone cardiovascular risk factor and a primary driver of atherosclerosis. Due to the complex interactions of lipoprotein metabolism, the Atherogenic Index of Plasma (AIP)—which integrates triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C)—has emerged as a valuable marker for assessing atherosclerotic risk. Although AIP is widely utilized for cardiovascular disease screening and risk stratification, studies linking it to CMD specifically have been limited. Dyslipidemia is known to contribute to the development of CMD,[3] and recent investigations have suggested a link between AIP and myocardial metabolic disorders.[36] One study identified an association between dyslipidemia and slow coronary flow, a clinical manifestation indicative of microvascular abnormalities.[12]

Our study is the first to establish AIP as a significant independent risk factor for CMD in hypertensive individuals. After adjusting for confounding variables, AIP remained a robust predictor of CMD. These findings underscore the clinical importance of addressing dyslipidemia in hypertensive patients as part of a strategy to prevent or mitigate CMD. Interestingly, while AIP demonstrated higher specificity, it had lower sensitivity compared to the TyG index. Although the direct causal relationship between AIP and CMD remains unclear, these findings suggest that further investigation is warranted to explore the underlying mechanisms.

Insulin Resistance and CMD

Insulin resistance (IR) is a key feature of metabolic dysfunction and a well-established risk factor for cardiovascular diseases, including CMD.[18,19,37] IR can impair endothelial nitric oxide synthase (eNOS) activity, reducing the protective effects of nitric oxide (NO) and contributing to microvascular dysfunction.[38] Furthermore, hyperinsulinemia, a hallmark of IR, elevates free fatty acids, reactive oxygen species (ROS), and disrupts lipid metabolism, thereby increasing oxidative stress and promoting the release of pro-inflammatory cytokines, all of which exacerbate CMD development.[18]

Although previous studies have linked IR to CMD, the clinical detection of IR remains challenging due to the cost, complexity, and biases associated with standard diagnostic methods. The TyG index, which combines fasting blood glucose (FBG) and fasting triglycerides (TG), has emerged as a reliable and convenient surrogate marker for IR.[20–22] High TyG index levels are associated with a range of cardiovascular conditions, including symptomatic coronary artery disease, arterial stiffness, and coronary artery calcification. Moreover, the TyG index has been linked to various microvascular diseases, including kidney dysfunction, microalbuminuria, and slow coronary flow.[26,39–41] Our study found that CMD patients had significantly higher TyG indices than non-CMD patients in the hypertensive population, and the TyG index was independently associated with CMD. These results support the hypothesis that IR may indirectly contribute to the development of CMD, suggesting that targeting IR could offer a therapeutic strategy to prevent CMD in hypertensive individuals. However, the direct causal relationship between the TyG index and CMD remains unclear and warrants further research.

Comparison Between AIP and TyG Index

Although several studies have explored the link between the TyG index and CMD in patients with chronic coronary syndrome,[16] to our knowledge, this is the first study to compare the roles of both the Atherogenic Index of Plasma (AIP) and the TyG index in relation to CMD. Our findings indicate that both AIP and TyG indices exhibit comparable predictive performance for CMD, with the TyG index showing superior sensitivity and the AIP demonstrating enhanced

specificity. In clinical practice, the integration of both indices may offer complementary advantages, with each index contributing unique strengths in detecting CMD.

Given the findings from this study, both TyG and AIP indices emerge as promising biomarkers for identifying individuals at high risk for CMD. Their combination may improve the accuracy of risk stratification and facilitate more targeted therapeutic interventions or preventative measures for hypertensive patients.

Study Limitations

This study is subject to several limitations. First, the retrospective nature and single-center design, combined with a relatively small sample size, limit the ability to establish a definitive causal relationship between the elevated TyG index and the occurrence of CMD. Larger-scale, multicenter, prospective studies are needed to validate these findings. Second, while SPECT is a widely used and relatively quantitative imaging technique, the interpretation of results is inherently subjective and may introduce variability. Third, the potential impact of prolonged use of antihypertensive, antidiabetic, and lipid-lowering medications on lipid and glucose measurements, as well as on the incidence of CMD, could introduce bias. Fourth, the absence of body mass index (BMI) data represents a notable limitation, as BMI is a known confounding factor in both metabolic disorders and CMD. Finally, given that this study was conducted within a Chinese population, there may be selection bias, and the findings may not be directly generalizable to other ethnic groups. Future research should aim to address these limitations to improve the robustness and generalizability of the results.

Conclusion

This study provides novel evidence that elevated AIP and TyG indices are significantly associated with the risk of coronary microvascular disease (CMD) in hypertensive patients, with both biomarkers showing critical clinical value for early prevention and risk stratification of CMD. AIP exhibits higher specificity, while TyG shows superior sensitivity. The integration of both biomarkers in clinical decision-making can enhance patient management by providing more personalized interventions for CMD. Given that hypertension is a major risk factor for CMD, it is recommended to include TyG and AIP in routine assessment tools to help identify high-risk patients early and implement interventions. Furthermore, for hypertensive patients with CMD, comprehensive treatment, including blood pressure control and the management of lipid and glucose metabolism disorders, should be considered to slow CMD progression. Future multi-center, large-scale prospective studies are needed to further validate the effectiveness of TyG and AIP, explore their underlying mechanisms, and assess their potential applications in different populations.

Abbreviations

CAD, coronary artery disease; HF, heart failure; LA, left atrium volume; LV, left ventricular volume; LVEF, left ventricle ejection fraction; RBC, red blood cell count; MAU, microalbuminuria; eGFR estimated glomerular filtration rate; UA uric acid; Cr serum creatinine; HCY homocysteine; D-dimer; BNP, brain natriuretic peptide; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; TC, total cholesterol; TG, triglycerides; hs-CRP, high-sensitivity C-reactive protein; and hs-TNT, high-sensitivity troponin T TyG triglyceride-glucose; AIP, atherogenic index of plasma; antiPLT, ACEI /ARB angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers; ARNI, Angiotensin Receptor-Neprilysin Inhibitor; CCBs, Calcium Channel Blockers; MRAs, Mineralocorticoid receptor antagonists; OADs, Oral Antidiabetic Drugs.

Data Sharing Statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author/s.

Ethics Statement

The studies involving human participants were reviewed and approved by the Tianjin Chest Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Consent for Publication

The manuscript was approved by all authors for publication.

Funding

This study was funded by Tianjin Key Medical Discipline (Specialty) Construction Project (TJYXZDXK-055B).

Disclosure

The authors declare that they have no competing interests.

References

1. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. *Nat Rev Cardiol*. 2021;18(11):785–802. doi:10.1038/s41569-021-00559-8
2. Vasan RS, Song RJ, Xanthakis V, et al. Hypertension-mediated organ damage: prevalence, correlates, and prognosis in the community. *Hypertension*. 2022;79(3):505–515. doi:10.1161/HYPERTENSIONAHA.121.18502
3. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(21):2625–2641. doi:10.1016/j.jacc.2018.09.042
4. Chen C, Wei J, AlBadri A, Zarrini P, Bairey Merz CN. Coronary microvascular dysfunction - epidemiology, pathogenesis, prognosis, diagnosis, risk factors and therapy. *Circ J*. 2016;81(1):3–11. doi:10.1253/circj.CJ-16-1002
5. Labazi H, Trask AJ. Coronary microvascular disease as an early culprit in the pathophysiology of diabetes and metabolic syndrome. *Pharmacol Res*. 2017;123:114–121. doi:10.1016/j.phrs.2017.07.004
6. Horton WB, Barrett EJ. Microvascular dysfunction in diabetes mellitus and cardiometabolic disease. *Endocr Rev*. 2021;42(1):29–55. doi:10.1210/endrev/bnaa025
7. Liu T, Liu J, Wu Z, Lv Y, Li W. Predictive value of the atherogenic index of plasma for chronic total occlusion before coronary angiography. *Clin Cardiol*. 2021;44(4):518–525. doi:10.1002/clc.23565
8. Dobiásová M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)). *Clin Biochem*. 2001;34(7):583–588. doi:10.1016/s0009-9120(01)00263-6
9. Wang L, Chen F, Xiaoqi C, Yujun C, Zijie L. Atherogenic index of plasma is an independent risk factor for coronary artery disease and a higher SYNTAX score. *Angiology*. 2021;72(2):181–186. doi:10.1177/0003319720949804
10. Nam JS, Kim MK, Nam JY, et al. Association between atherogenic index of plasma and coronary artery calcification progression in Korean adults. *Lipids Health Dis*. 2020;19(1):157. doi:10.1186/s12944-020-01317-4
11. Fu L, Zhou Y, Sun J, et al. Atherogenic index of plasma is associated with major adverse cardiovascular events in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2021;20(1):201. doi:10.1186/s12933-021-01393-5
12. Toprak K, Karataş M, Kaplangoray M, et al. Comparison of the effect of non-HDL-C/HDL-C ratio on coronary slow flow with other non-traditional lipid markers. *Acta Cardiol Sin*. 2024;40(4):388–401. doi:10.6515/ACS.202407_40(4).20240419A
13. Yuan Y, Shi J, Sun W, Kong X. The positive association between the atherogenic index of plasma and the risk of new-onset hypertension: a nationwide cohort study in China. *Clin Exp Hypertens*. 2024;46(1):2303999. doi:10.1080/10641963.2024.2303999
14. Li YW, Kao TW, Chang PK, Chen WL, Wu LW. Atherogenic index of plasma as predictors for metabolic syndrome, hypertension and diabetes mellitus in Taiwan citizens: a 9-year longitudinal study. *Sci Rep*. 2021;11(1):9900. doi:10.1038/s41598-021-89307-z
15. Zhang X, Zhang X, Li X, Feng J, Chen X. Association of metabolic syndrome with atherogenic index of plasma in an urban Chinese population: a 15-year prospective study. *Nutr Metab Cardiovasc Dis*. 2019;29(11):1214–1219. doi:10.1016/j.numecd.2019.07.006
16. Zhang W, Liu L, Chen H, et al. Association between the triglyceride-glucose index and the presence and prognosis of coronary microvascular dysfunction in patients with chronic coronary syndrome. *Cardiovasc Diabetol*. 2023;22(1):113. doi:10.1186/s12933-023-01846-z
17. 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. doi:10.1186/s12933-018-0762-4
18. Konst RE, Guzik TJ, Kaski JC, Maas A, Elias-Smale SE. The pathogenic role of coronary microvascular dysfunction in the setting of other cardiac or systemic conditions. *Cardiovasc Res*. 2020;116(4):817–828. doi:10.1093/cvr/cvaa009
19. Takei Y, Tomiyama H, Tanaka N, Yamashina A, Chikamori T. Association between insulin resistance, oxidative stress, sympathetic activity and coronary microvascular function in patients with early stage impaired glucose metabolism. *Circ J*. 2022;86(5):866–873. doi:10.1253/circj.CJ-21-0549
20. Du T, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol*. 2014;13:146. doi:10.1186/s12933-014-0146-3
21. Navarro-González D, Sánchez-íñigo L, Pastrana-Delgado J, Fernández-Montero A, Martinez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: the vascular-metabolic CUN cohort. *Prev Med*. 2016;86:99–105. doi:10.1016/j.ypmed.2016.01.022
22. Tao LC, Xu JN, Wang TT, Hua F, Li JJ. Triglyceride-glucose index as a marker in cardiovascular diseases: landscape and limitations. *Cardiovasc Diabetol*. 2022;21(1):68. doi:10.1186/s12933-022-01511-x

23. Neglia D, Aimo A, Lorenzoni V, Caselli C, Gimelli A. Triglyceride-glucose index predicts outcome in patients with chronic coronary syndrome independently of other risk factors and myocardial ischaemia. *Eur Heart J Open*. 2021;1(1):oeab004. doi:10.1093/ehjopen/oeab004
24. Wu Z, Liu L, Wang W, et al. Triglyceride-glucose index in the prediction of adverse cardiovascular events in patients with premature coronary artery disease: a retrospective cohort study. *Cardiovasc Diabetol*. 2022;21(1):142. doi:10.1186/s12933-022-01576-8
25. Li Y, He S, Wu Z, et al. The predictive value of the triglyceride-glucose index for cardiovascular events in patients with coronary chronic total occlusion. *Cardiovasc Diabetol*. 2022;21(1):149. doi:10.1186/s12933-022-01588-4
26. Buber I, Nar R, Kaya D, Senol H, Adali MK, Nar G. Assessment of triglyceride/glucose index with respect to coronary slow flow. *Bratisl Lek Listy*. 2022;123(8):585–588. doi:10.4149/BLL_2022_095
27. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ. ASNC imaging guidelines for SPECT nuclear cardiology procedures: stress, protocols, and tracers. *J Nucl Cardiol*. 2016;23(3):606–639. doi:10.1007/s12350-015-0387-x
28. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. *Circulation*. 1998;97(6):535–543. doi:10.1161/01.CIR.97.6.535
29. Sharir T, Germano G, Kang X, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. *J Nucl Med*. 2001;42(6):831–837.
30. Wang X, Xu W, Song Q, et al. Association between the triglyceride-glucose index and severity of coronary artery disease. *Cardiovasc Diabetol*. 2022;21(1):168. doi:10.1186/s12933-022-01606-5
31. Rajai N, Ahmad A, Toya T, et al. Coronary microvascular dysfunction is an independent predictor of developing cancer in patients with non-obstructive coronary artery disease. *Eur J Prev Cardiol*. 2023;30(3):209–216. doi:10.1093/eurjpc/zwac184
32. Mejia-Renteria H, Travieso A, Matías-Guiu JA, et al. Coronary microvascular dysfunction is associated with impaired cognitive function: the cerebral-coronary connection study (C3 study). *Eur Heart J*. 2023;44(2):113–125. doi:10.1093/eurheartj/ehac521
33. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol*. 2013;62(4):263–271. doi:10.1016/j.jacc.2013.02.092
34. Masi S, Rizzoni D, Taddei S, et al. Assessment and pathophysiology of microvascular disease: recent progress and clinical implications. *Eur Heart J*. 2021;42(26):2590–2604. doi:10.1093/eurheartj/ehaa857
35. Suda A, Takahashi J, Hao K, et al. Coronary functional abnormalities in patients with angina and nonobstructive coronary artery disease. *J Am Coll Cardiol*. 2019;74(19):2350–2360. doi:10.1016/j.jacc.2019.08.1056
36. Huang X, Wen S, Huang Y, Huang Z. Gender differences in the association between changes in the atherogenic index of plasma and cardiometabolic diseases: a cohort study. *Lipids Health Dis*. 2024;23(1):135. doi:10.1186/s12944-024-02117-w
37. Laakso M. Is insulin resistance a feature of or a primary risk factor for cardiovascular disease. *Curr Diab Rep*. 2015;15(12):105. doi:10.1007/s11892-015-0684-4
38. Inoguchi T, Li P, Umeda F, et al. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C--dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes*. 2000;49(11):1939–1945. doi:10.2337/diabetes.49.11.1939
39. Potier L, Chequer R, Roussel R, et al. Relationship between cardiac microvascular dysfunction measured with 82Rubidium-PET and albuminuria in patients with diabetes mellitus. *Cardiovasc Diabetol*. 2018;17(1):11. doi:10.1186/s12933-017-0652-1
40. Zhao S, Yu S, Chi C, et al. Association between macro- and microvascular damage and the triglyceride glucose index in community-dwelling elderly individuals: the Northern Shanghai study. *Cardiovasc Diabetol*. 2019;18(1):95. doi:10.1186/s12933-019-0898-x
41. Chiu H, Tsai HJ, Huang JC, et al. Associations between triglyceride-glucose index and micro- and macro-angiopathies in type 2 diabetes mellitus. *Nutrients*. 2020;12(2):328. doi:10.3390/nu12020328