Vascular Health and Risk Management

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ORIGINAL RESEARCH

A Combined Measure of the Triglyceride Glucose Index and Trimethylamine N-Oxide in Risk Stratification of ST-Segment Elevation Myocardial Infarction Patients with High-Risk Plaque Features Defined by Optical Coherence Tomography: A Substudy of the OCTAMI Registry Study

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Background and Aim: An elevated triglyceride-glucose (TyG) level is associated with increased risk of mortality in patients with CAD. Trimethylamine N-oxide (TMAO) has mechanistic links to atherosclerotic coronary artery disease (CAD) pathogenesis and is correlated with adverse outcomes. However, the incremental prognostic value of TMAO and TyG in the cohort of optical coherence tomography (OCT)-defined high-risk ST-segment elevation myocardial infarction (STEMI) patients is unknown.

Methods: We studied 274 consecutive aged ≥18 years patients with evidence of STEMI and detected on pre-intervention OCT imaging of culprit lesions between March 2017 and March 2019.

Outcomes: There were 22 (22.68%), 27 (27.84%), 26 (26.80%), and 22 (22.68%) patients in groups A-D, respectively. The baseline characteristics according to the level of TMAO and TyG showed that patients with higher level in both indicators were more likely to have higher triglycerides ($p < 0.001$), fasting glucose ($p < 0.001$) and higher incidence of diabetes ($p = 0.008$). The group with TMAO > median and TyG ≤ median was associated with higher rates of MACEs significantly ($p = 0.009$) in fully adjusted analyses. During a median follow-up of 2.027 years, 20 (20.6%) patients experienced MACEs. To evaluate the diagnostic value of the TyG index combined with TMAO, the area under the receiver operating characteristic curve for predicting MACEs after full adjustment was 0.815 (95% confidence interval, 0.723–0.887; sensitivity, 85.00%; specificity, 72.73%; cut-off level, 0.577). Among the group of patients with TMAO > median and TyG ≤ median, there was a significantly higher incidence of MACEs ($p=0.033$). A similar tendency was found in the cohort with hyperlipidemia ($p=0.016$) and diabetes mellitus ($p=0.036$).

Conclusion: This study demonstrated the usefulness of combined measures of the TyG index and TMAO in enhancing risk stratification in STEMI patients with OCT-defined high-risk plaque characteristics.

Trial Registration: This study was registered at ClinicalTrials.gov as NCT03593928.

Keywords: optical coherence tomography, triglyceride glucose index, trimethylamine N-oxide, high risk plaque feature, major adverse cardiovascular events, prospective study

Received: 16 November 2023
Accepted: 10 March 2024
Published: 29 March 2024

Introduction

Acute coronary syndrome (ACS) has been extensively proven to cause a heavy socio-economic burden, and it remains a high risk for major adverse cardiovascular events (MACEs) according to the current guidelines.[1–3] The triglyceride-glucose (TyG) index, derived from fasting blood glucose and fasting triglycerides (TGs), has been proposed as a surrogate biomarker for insulin resistance (IR).[4–6] Moreover, former clinical researches show a high correlation of the TyG index with the prevalence and prognosis of cardiovascular diseases, regardless of whether a patient has comorbidity of diabetes mellitus (DM).[7–10] Furthermore, trimethylamine N-oxide (TMAO), a gut microbiota-related metabolite, has been reported in epidemiological studies as a novel marker that correlates with MACEs risks.[11–13] Optical coherence tomography (OCT), a high-resolution intravascular imaging modality, enables detailed visualization of superficial plaque components and assessment of coronary plaque characteristics.[14,15] Additionally, OCT is capable of identifying high-risk plaques.[16–18] However, the incremental prognostic value and the clinical significance of TMAO and TyG in the cohort of optical coherence tomography (OCT)-defined high-risk ST-segment elevation myocardial infarction (STEMI) patients are unknown. Thus, we aim to determine the prognostic values of both the TyG index and TMAO level in high-risk patients enrolled in the OCTAMI (Optical Coherence Tomography Examination in Acute Myocardial Infarction) registry study.

Methods

Study Population

In the present study, a post hoc analysis of the OCTAMI (Optical Coherence Tomography Examination in Acute Myocardial Infarction) registry, in which prospectively and consecutively recruited 434 patients screened by OCT if they were hospitalized for STEMI underwent primary PCI between March 2017 and March 2019 at one of the top-ranked and largest PCI center in China.

For the purpose of this sub-study, we analyzed prognostic value of both TyG and TMAO among patients with OCT defined high-risk features. The present study is addressing the 2-year follow-up results. Furthermore, we excluded the poor imaging quality (N = 87), in-stent restenosis (N = 34), coronary spasm (N = 11), coronary embolism (N = 2), calcified nodule (N = 17), without follow-up data (N = 1) and absence of value of TMAO (N = 59). The inclusion criteria was patients meet at least three of the OCT criteria [including minimum lumen area (MLA) <3.5mm2, fibrous cap thickness (FCT) <75mm, lipid arc circumferential extension >180, and macrophage infiltration]. Finally, there are 97 patients was included the study.

The study protocol was conducted in accordance with the principles outlined in the Declaration of Helsinki and approved by the institutional review board committee and all patients have written informed consent (Fuwai Hospital OCTAMI Registry, clinical trials.gov: NCT03593928).

Definition

The definition of STEMI was followed by the established criteria.[19–22] Patients smoking status that do not meet standards of never smokers (never cigarettes in their life-time) or former light smokers (stopped smoking at least 15 years ago, with a total of ≤10 pack-years of smoking) are considered as current smoking.[23] CKD was defined as the abnormality of kidney structure or function for more than 3 months, and ESRD was the final common pathway for CKD.[20] Body mass index was calculated by dividing weight (kg) by the square of height (m2). Prior PCIs were identified by patients once they conducted the PCI (including percutaneous transluminal coronary angioplasty and stent implantation). According to the TyG index levels, patient data were divided into 3 tertiles: tertile 1: TyG ≤ 8.79; tertile 2: 8.79 ≤ 9.35; tertile 3: TyG>9.35. Furthermore, TMAO level was divided into 3 tertiles: TMAO ≤ 150 mg/L; tertile 2: 150 mg/L < TMAO ≤ 277 mg/L; tertile 3: TMAO > 277 mg/L.

Quantitative OCT Image Analysis and Calculating of TyG

OCT image analysis was performed by using an offline review work station of OCT (Ilumien Optis, St Jude Medical) in the core laboratory by three independent observers investigators (RZ.C., ZX.S, and JN.L.) who were double-blinded to

angiographic data, laboratory examinations, clinical presentations, and endpoint events of enrolled patients. They are in charge of screening suitability for culprit-plaque evaluation, analyzing the characteristics of plaque, clearing plaque morphology and measuring the index of microstructural including minimal lumen area, maximal lipid arc, minim*al* fibrous cap thickness, and the thickness of thin-cap fibroatheroma. When it comes to disagreements and inconsistency among the investigators, we resolved situation by the consensus. A culprit plaque was defined as segments centered on the culprit lesion and bilaterally extending to more than 5 mm of the normal vessel segment.[14,24] Based on established criteria,[14] calcifications[25] (Figure 1A), lipid plaque (Figure 1B), macrophage infiltration (Figure 1C),[26] rupture plaque (Figure 1D), erosion plaque (Figure 1E), Microvessels[23] (Figure 1F), White thrombi[8] (Figure 1G), Cholesterol crystal (Figure 1H) [25] are shown. The TyG index was assessed by the formula of ln [fasting TG (mg/dL)×FPG (mg/dL)/2].[4,27]

Endpoints and Follow-Up

Figure 2 summarizes the inclusion/exclusion study criteria. MACEs were defined as a composite of all-cause mortality, recurrence MI and ischemic cerebrovascular events and revascularization. Recurrence MI was diagnosed as positive cardiac troponins and the changes of typical electrocardiogram serial. A clinical follow-up was performed via direct interviews, telephone calls and hospital discharge records or clinical notes in the event (including all-cause death, MI recurrence, ischemic stroke and revascularization) well-trained physicians and nurses performed the clinical follow-up in the enrolled patients of OCTAMI registry (median time to follow-up: 740.44 days/2.03 years). The protocol of the follow-up was approved by obtaining permission from the Institutional Review Board of Fuwai Hospital and has been registered online (https://www.clinicaltrials.gov/ct2/show/NCT03593928 and term=NCT03593928&draw=2andrank=1). Well-trained physicians in charge of the follow-up primary endpoints, including MI recurrence, angina pectoris, all-cause

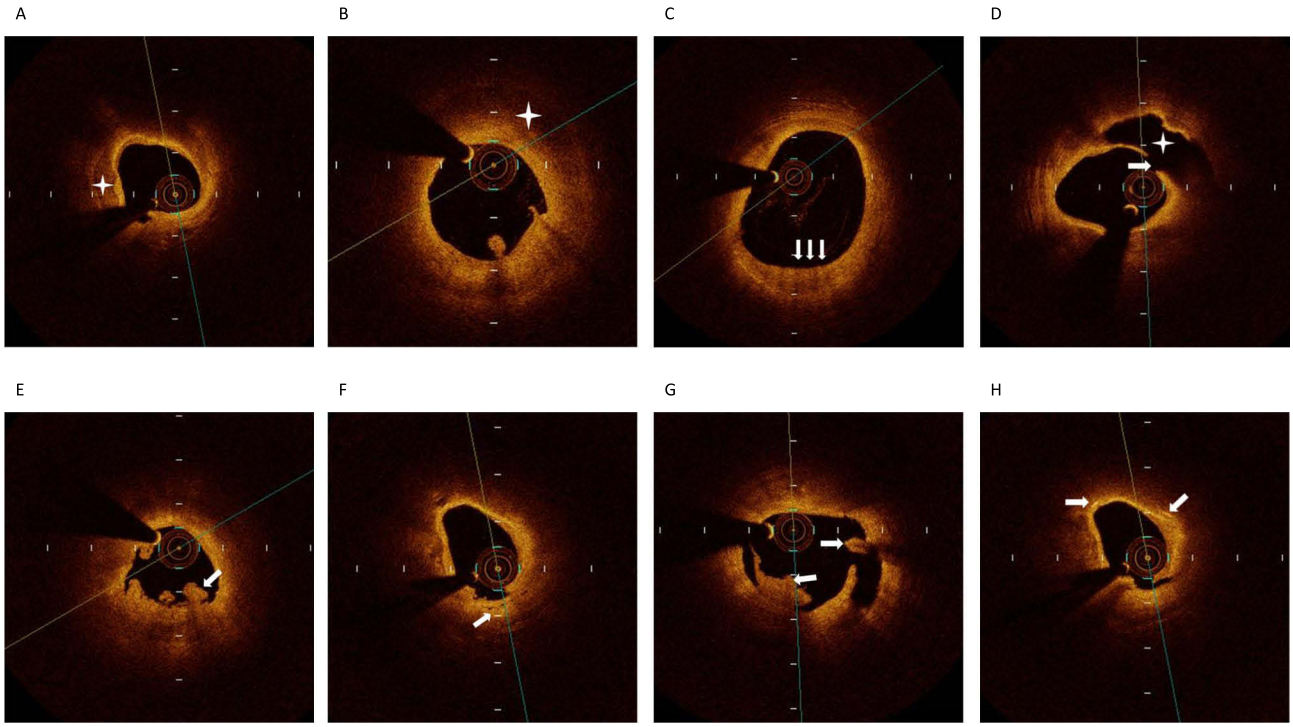

Figure 1 Representative cross-sectional optical coherence tomography images. (**A**) Calcification identified by the presence of a well-delineated, low-backscattering heterogeneous region (asterisk). (**B**) Lipid plaque (asterisk) most often appears as diffusely bordered, signal-poor regions with overlying signal-rich bands. (**C**) Macrophage infiltration (arrow) defined as a signal-rich, distinct or confluent punctate region of higher intensity than background speckle noise that generates remarkable backward shadowing (**D**) Plaque rupture identified by disruption of the fibrous cap and cavity formation (asterisk). The area where the plaque ruptures was marked by arrow. (**E**) Plaque erosion identified by the presence of attached thrombus (arrow) overlying an intact plaque. (**F**) Microvessels defined as tubule luminal structures that do not generate a signal, with no connection to the vessel lumen (arrow). (**G**) Red thrombus consists mainly of red blood cells; relevant OCT images are characterized as high-backscattering protrusions with signal free shadowing (arrow). White thrombi mainly consisted of white blood cells (WBCs) and platelets and were characterized as signal-rich, low-backscattering, billowing projections protruding into the lumen (arrow). (**H**) Cholesterol crystal (arrow) identified by linear, highly backscattering structures without remarkable backward shadowing.

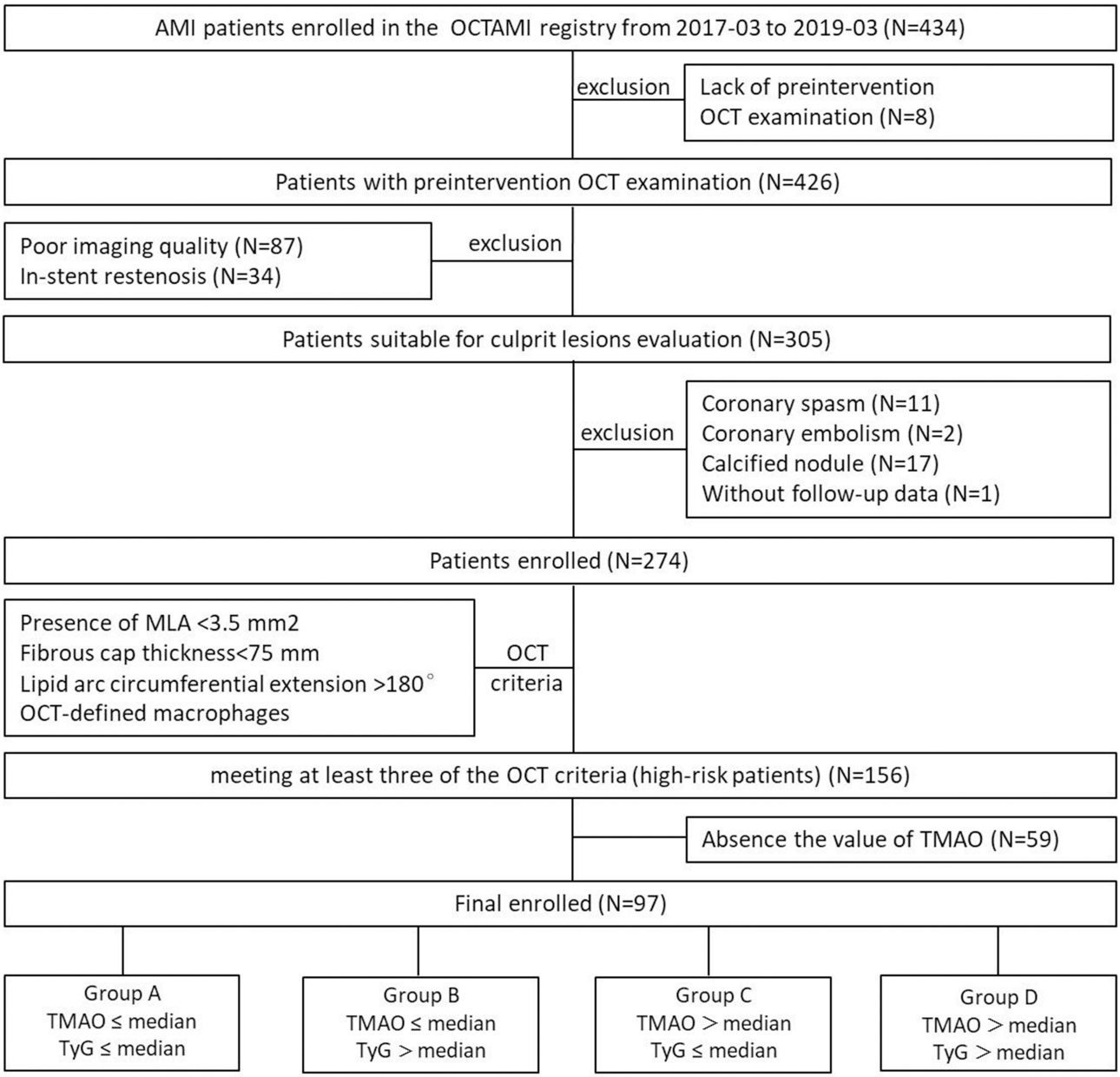

Figure 2 Study flow chart.

Abbreviations: OCTAMI, Optical Coherence Tomography Examination in Acute Myocardial Infarction; OCT optical coherence tomography, AMI acute myocardial infarction; MLA, minimal lumen area; TMAO, Trimethylamine N-Oxide; TyG, Triglyceride glucose index Exclusion criteria of conducting OCT were cardiac shock, serious liver dysfunction, allergy to contrast media, severe hepatic and renal insufficiency, congestive heart failure, contraindication to aspirin or ticagrelor and lesions with characteristics which raised the difficulty and risk in performing OCT (eg, heavily calcified vessels, chronic total occlusion and left main coronary artery diseases).

death, cardiac death, revascularization, heart failure, ischemic stroke, hemorrhagic apoplexy and bleeding events identified and extracted the primary endpoints from laboratory reports, hospital records, medical records, emergency records, and clinical notes which required to be sent to our centers. More than two professional physicians who were blinded to clinical and angiographic data confirmed the clinical endpoints.

Statistical Analysis

Data are presented as mean ± standard deviation (SD) or median (interquartile range) for continuous variables, and continuous data are presented as median (25th and 75th percentiles) in the case of non-normal or normal distribution. For baseline characteristics analysis, the statistical differences among four groups were tested with *t*-test or one-way ANOVA

for continuous variables and chi-square or Fisher test for categorical variables. The normal distribution of outcome variables was accessed using the Kolmogorov–Smirnov test. For baseline characteristic analysis, the statistical differences among groups were tested with *t*-test or one-way ANOVA for continuous variables and chi-square or Fisher test for categorical variables. We analyzed normal and non-normal distributed data using the independent sample *t*-test or Mann–Whitney *U*-test respectively between-group differences. Categorical data were presented as numbers (percentages) and were compared using the Fisher's exact test or Pearson's chi-squared (χ^2) test. We used the multivariable Cox proportional hazards regression models with adjustments for confounding factors to determine the prognostic value. Furthermore, to evaluate the incidence rate of MACEs among groups according to the group of the TyG index and TMAO, we constructed Kaplan–Meier survival curves. Discrepancy rates of cumulative events were compared using the Log rank test. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written. Statistical analyses were performed using SPSS (version 20.0; IBM Corp., Armonk, NY, USA), R Programming Language X64 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria), and MedCalc version 18.2.1 (MedCalc Software, Ostend, Belgium). Statistical significance was set at $P < 0.05$, and all P values were two-tailed.

Results

Patient Characteristics

Baseline characteristics of the 97 patients included in our study are shown in Table 1. The mean age was 57 years old, 80.4% were men, 62 (63.92%) had hypertension, while 32 (32.99%) were diabetic. Figure 1 has presented the representative cross-sectional optical coherence tomography images and 67 (69.07%), 67 (69.07%), and 25 (56.70%) patients had plaque ruptures, lipid-rich plaques, and calcifications, respectively. Furthermore, the prevalence of macrophages, microvessels, and cholesterol crystals were 92.78%, 20.62%, and 13.40%, respectively. The baseline characteristics according to the level of TMAO and TyG showed that patients with higher level in both indicators were more likely to have higher triglycerides ($p < 0.001$), fasting glucose ($p < 0.001$) and higher incidence of diabetes ($p = 0.008$). During the follow-up, some of the participants presented with MACE (20.67%), while a small subset of patients died (1.03%) or had recurrent MI (3.09%) and ischemic stroke (6.19%). The median values of concordance and discordance were 9.13 for the TyG index and 287.15 mg/L for the TMAO level, respectively (Table 1).

Comparison of Baseline Characteristics According to the TyG Index and TMAO Levels

According to the TyG index levels, we have divided the cohort into 4 groups: group A: TMAO ≤ median and TyG ≤ median; group B: TMAO ≤ median and TyG > median; group C: TMAO > median and TyG ≤ median; group C: TMAO > median and TyG > median. There were 22 (22.68%), 27 (27.84%), 26 (26.80%), 22 (22.68%) patients in group A, group B, group C, and group D, respectively. Patients in group C were older ($p<0.001$) and had higher ejection fraction ($p=0.011$), increased incidence of MACEs ($p=0.048$) and ischemic stroke ($p=0.034$). Meanwhile, patients in group D had a higher prevalence of hyperlipidemia ($p=0.030$), DM ($p=0.008$), plaque rupture ($p=0.001$), and lipid-rich plaques ($p<0.001$). Moreover, the characteristics of minimal fibrous cap thickness (FCT) were thinner among patients in group D ($p=0.006$) (Table 1).

Relationship Between Biomarkers and Parameters of OCT Characteristics

The TyG index was remained independently associated with the prevalence of thin-cap fibroatheroma (TCFA) ($p=0.043$) (Table 2). Moreover, the TMAO levels are correlated with parameters of plaque morphology (PE&PR) ($p=0.012$), lipid-rich plaque ($p=0.016$), mixed plaque ($p=0.003$), minimal FCT ($p=0.004$), and TCFA ($p=0.001$) significantly.

Relationship Between MACEs Stratified According to the TyG Index and TMAO Levels

Table 3 describes univariable and fully adjusted multivariable relationships between MACEs stratified according to the TyG index and TMAO levels in the overall population. On stratifying according to TMAO levels, a 42.8% increased risk

Table 1 Baseline Clinical and Optical Coherence Tomography Characteristics of the Study Population Among the High-Risk Cohort

Variables	Whole Cohort (N = 97)	Group A TMAO ≤ Median TyG ≤ Median (N = 22)	Group B TMAO ≤ Median TyG>Median (N = 27)	Group C TMAO> Median TyG ≤ Median (N = 26)	Group D TMAO> Median TyG>Median (N = 22)	P value	Statistics
Age (years)	57.2 ± 11.1	55.4 ± 11.0	51.0 ± 8.7	63.6 ± 9.8	59.0 ± 11.4	< 0.001*	7.237
Male [%(n)]	78 (80.4)	17 (77.3)	23 (85.2)	20 (76.9)	18 (81.8)	0.869	–
Heart rate(beats/min)	77.15 ± 13.96	76.36 ± 16.04	81.15 ± 14.99	75.40 ± 10.78	75.00 ± 13.54	0.366	1.069
SBP (mmHg)	120.90 ± 19.31	118.50 ± 18.03	121.52 ± 22.07	123.80 ± 17.23	119.23 ± 20.01	0.783	0.358
DBP(mmHg)	78.82 ± 13.20	79.95 ± 16.32	80.33 ± 14.55	77.28 ± 9.27	77.59 ± 12.39	0.795	0.342
EF at admission	56.0 (52.0, 60.0)	53.5 (46.8, 55.8)	56.0 (50.5, 60.0)	58.0 (55.0, 60.0)	57.5 (55.0, 60.0)	0.011*	5.059
Risk factors							
Hypertension[%(n)]	62 (63.92)	13 (59.09)	19 (70.37)	16 (61.54)	14 (63.64)	0.856	0.774
Hyperlipidemia[%(n)]	88 (90.72)	20 (90.91)	26 (96.3)	20 (76.92)	22 (100)	0.030*	–
Smoking[%(n)]	73 (75.26)	18 (81.82)	21 (77.78)	17 (65.38)	17 (77.27)	0.570	2.010
Diabetes mellitus	32 (32.99)	3 (13.64)	10 (37.04)	6 (23.08)	13 (59.09)	0.008*	11.863
Previous PCI[%(n)]	7 (7.22)	0 (0)	3 (11.11)	3 (11.54)	1 (4.55)	0.398	–
CKD[%(n)]	2 (2.13)	0 (0)	0 (0)	2 (8)	0 (0)	0.154	–
Laboratory examinations							
HDL (mg/dl)	1.04 ± 0.23	1.11 ± 0.22	1.00 ± 0.23	1.07 ± 0.22	0.97 ± 0.23	0.173	1.698
LDL (mg/dl)	2.94 ± 0.86	2.89 ± 0.90	3.16 ± 0.89	2.60 ± 0.74	3.11 ± 0.86	0.084	2.287
Triglycerides (mmol/L)	1.43 (0.88, 1.96)	1.20 (0.81, 1.51)	1.92 (1.63, 2.30)	0.82 (0.57, 1.25)	2.00 (1.45, 2.53)	< 0.001*	13.619
LPA (g/L)	113.00 (50.00, 311.30)	82.63 (51.50, 186.50)	104.50 (45.28, 326.80)	162.80 (77.75, 306.00)	129.30 (62.60, 306.50)	0.733	0.166
hs-CRP (mg/L)	4.94 (2.22, 9.19)	3.12 (1.71, 5.70)	6.58 (2.82, 10.52)	4.77 (2.30, 7.99)	7.50 (3.15, 10.77)	0.161	1.805
Crea (μmol/L)	76.38 (67.33, 87.28)	73.66 (66.54, 78.46)	72.39 (66.70, 86.92)	78.05 (68.90, 90.58)	81.34 (68.39, 89.15)	0.267	1.725
Fasting glucose (mmol/L)	7.53 (6.71, 9.86)	6.71 (6.14, 7.30)	9.18 (7.28, 10.23)	7.45 (6.52, 9.28)	12.39 (7.50, 14.88)	< 0.001*	13.201
TyG	9.13 ± 0.74	8.65 ± 0.40	9.64 ± 0.54	8.50 ± 0.45	9.75 ± 0.50	< 0.001*	1.983
TMAO (mg/L)	287.15 ± 252.35	143.14 ± 42.86	128.25 ± 59.87	450.85 ± 267.83	432.73 ± 299.79	< 0.001*	18.71
cTnI at baseline level (mmol/L)	2.4 ± 5.1	2.0 ± 4.2	3.5 ± 6.8	2.4 ± 5.4	1.4 ± 3.0	0.550	0.707
cTnI at peak level (mmol/L)	30.3 ± 26.2	31.1 ± 24.6	36.3 ± 30.0	27.5 ± 25.9	25.6 ± 23.5	0.488	0.816
NT-proBNP at baseline level (mmol/L)	426.6 ± 891.2	298.6 ± 443.6	204.9 ± 319.0	828.6 ± 1472.4	351.7 ± 663.7	0.053	2.655
NT-proBNP at peak level (mmol/L)	3430.5 ± 6266.3	4823.8 ± 9409.4	1830.7 ± 1973.9	4893.6 ± 7873.3	2271.3 ± 1722.6	0.170	1.71
Discharge medication regimen							
Statin[%(n)]	92 (94.85)	21 (95.45)	26 (96.3)	24 (92.31)	21 (95.45)	0.929	-
Aspirin[%(n)]	93 (95.88)	21 (95.45)	27 (100)	24 (92.31)	21 (95.45)	0.515	-
Clopidogrel[%(n)]	58 (59.79)	14 (63.64)	20 (74.07)	12 (46.15)	12 (54.55)	0.196	4.690
Ticagrelor[%(n)]	39 (40.21)	8 (36.36)	7 (25.93)	14 (53.85)	10 (45.45)	0.196	4.690
ACEI/ARB[%(n)]	74 (76.29)	16 (72.73)	20 (74.07)	21 (80.77)	17 (77.27)	0.913	0.523
Beta-Blockers[%(n)]	84 (86.60)	19 (86.36)	23 (85.19)	25 (96.15)	17 (77.27)	0.264	-
Type of ACC						0.437	-
A	1 (1.03)	0 (0)	1 (3.7)	0 (0)	0 (0)		
B1	8 (8.25)	0 (0)	2 (7.41)	3 (11.54)	3 (13.64)		

B2	10 (10.31)	2 (9.09)	5 (18.52)	2 (7.69)	1 (4.55)		
C	78 (80.41)	20 (90.91)	19 (70.37)	21 (80.77)	18 (81.82)		
Use of IABP	1 (1.03)	0 (0)	1 (3.7)	0 (0)	0 (0)	1.000	-
Optical coherence tomography characteristics							
Plaque morphology						0.001*	-
Plaque rupture[%(n)]	67 (69.07)	10 (45.45)	15 (55.56)	22 (84.62)	20 (90.91)		-
Plaque erosion[%(n)]	30 (30.93)	12 (54.55)	12 (44.44)	4 (15.38)	2 (9.09)		-
Lipid-rich plaque[%(n)]	67 (69.07)	10 (45.45)	15 (55.56)	22 (84.62)	20 (90.91)	0.001*	-
Fibrous plaque[%(n)]	15 (15.46)	2 (9.09)	8 (29.63)	3 (11.54)	2 (9.09)	0.159	-
Mixed plaque [%(n)]	17 (17.53)	11 (50)	5 (18.52)	1 (3.85)	0 (0)	< 0.001*	-
Healing plaque[%(n)]	25 (25.77)	6 (27.27)	9 (33.33)	4 (15.38)	6 (27.27)	0.508	-
Calcification[%(n)]	55 (56.70)	11 (50)	15 (55.56)	14 (53.85)	15 (68.18)	0.64	-
Micro-calcification[%(n)]	53 (54.64)	10 (45.45)	15 (55.56)	14 (53.85)	14 (63.64)	0.686	-
Macrophage[%(n)]	90 (92.78)	21 (95.45)	24 (88.89)	24 (92.31)	21 (95.45)	0.834	-
Microvessels[%(n)]	20 (20.62)	5 (22.73)	3 (11.11)	6 (23.08)	6 (27.27)	0.514	-
Cholesterol crystal[%(n)]	13 (13.40)	2 (9.09)	2 (7.41)	5 (19.23)	4 (18.18)	0.561	-
Thrombus[%(n)]	96 (98.97)	22 (100)	26 (96.3)	26 (100)	22 (100)	1.000	-
Minimal FCT, um	70.00 (60.00, 90.00)	80.00 (70.00, 100.00)	80.00 (60.00, 100.00)	65.00 (60.00, 80.00)	60.00 (60.00, 67.50)	0.006*	-
Maximal lipid arc, °	360.00 (269.00, 360.00)	360.00 (270.00, 360.00)	360.00 (258.10, 360.00)	360.00 (277.50, 360.00)	360.00 (298.50, 360.00)	0.617	-
MLA, mm2	1.62 (1.35, 2.05)	1.56 (1.48, 2.21)	1.62 (1.34, 1.93)	1.77 (1.40, 2.27)	1.56 (1.32, 1.83)	0.657	-
TCFA, um	41 (42.27)	2 (9.09)	10 (37.04)	13 (50)	16 (72.73)	< 0.001	-
Endpoint events							
MACEs[%(n)]	20 (20.62)	2 (9.09)	3 (11.11)	10 (38.46)	5 (22.73)	0.048*	-
All caused mortality[%(n)]	1 (1.03)	0 (0)	1 (3.70)	0 (0)	0 (0)	1.000	-
Recurrence MI[%(n)]	3 (3.09)	0 (0)	0 (0)	2 (7.69)	1 (4.55)	0.401	-
Ischemic stroke[%(n)]	6 (6.19)	2 (9.09)	0 (0)	4 (15.38)	0 (0)	0.034*	-
Angina[%(n)]	8 (8.25)	2 (9.09)	0 (0)	2 (7.69)	4 (18.18)	0.123	-
Heart failure[%(n)]	3 (3.09)	1 (4.55)	1 (3.7)	1 (3.85)	0 (0)	1.000	-
Bleeding [%(n)]	38 (39.18)	6 (27.27)	11 (40.74)	13 (50)	8 (36.36)	0.442	-

Continuous data are presented as mean±standard deviation (SD) or median (25th, 75th percentiles). Categorical data are presented as number (%). degree;*P<0.05.

Abbreviations: DM, -diabetes mellitus; SBP, systolic blood pressure; DBP, diabetes blood pressure; PCI, percutaneous coronary intervention; CKD, chronic kidney disease; HDL, high density lipoprotein; LDL, low density lipoprotein; LPA, lipase activator; hs-CRP, high sensitive C-reactive protein; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; TnI, troponin; ACC, American College of Cardiology; MLA minimal lumen area; TCFA, thin-cap fibroatheroma; MACE, major adverse cardiovascular events; MI, myocardial infarction. TyG, triglyceride glucose; TMAO, trimethylamine N-oxide; T, tertiles.

https://doi.org/10.2147/VHRM.S443742

Table 2 Correlation Between Biomarkers and Optical Coherence Tomography Characteristics

	TyG		TMAO	
	R	***P* value**	**R**	***P* value**
Plaque morphology(PE&PR)	0.103	0.315	0.253	0.012*
Lipid-rich plaque	0.075	0.463	0.243	0.016*
Fibrous plaque	0.005	0.960	−0.055	0.593
Mixed plaque	−0.105	0.307	−0.298	0.003*
Healing plaque	0.085	0.406	−0.180	0.077
Calcification	0.005	0.961	−0.057	0.578
Micro-calcification	0.011	0.911	−0.113	0.063
Macrophage	0.043	0.676	0.092	0.158
Microvessels	−0.015	0.884	0.117	0.253
Cholesterol crystal	0.128	0.212	0.132	0.198
Thrombus	0.016	0.878	0.074	0.471
Minimal FCT, um	−0.127	0.215	−0.288	0.004*
Maximal lipid arc, °	0.015	0.885	0.079	0.444
MLA, mm2	−0.042	0.681	−0.087	0.395
TCFA, um	0.206	0.043*	0.339	0.001*

Notes: degree;*P<0.05.
Abbreviations: as in Table 1PE, plaque erosion; PR, plaque rupture; FCT, fibrous cap thickness; MLA, minimal lumen area; TCFA, thin-cap fibroatheroma; TyG, triglyceride glucose; TMAO, trimethylamine N-oxide.

Table 3 Associations Between MACEs Stratified According to TyG Index and TMAO Tertiles Among High Risk OCT-Defined Patients

Population	**Kaplan-Meier Estimate, No. / Total No. (%)**	**N (Mean+SD)**	**Crude HR**	**MACE, Crude P value**	**MACE, Adjusted HR a**	**MACE, Adjusted P value**
Overall TMAO per SD	NA	NA	1.428	0.020*	1.530	0.113
T1	4 (20.0%)	32 (103.74 ± 36.01)	1 [Reference]	NA	1 [Reference]	NA
T2	6 (30.0%)	32 (217.62 ± 31.59)	1.600	0.467	1.678	0.491
T3	10 (50.0%)	33 (532.42 ± 297.17)	2.770	0.085	4.748	0.048*
Overall TyG per SD	NA	NA	0.836	0.445	1.057	0.895
T1	8 (40.0%)	32 (8.36 ± 0.37)	1 [Reference]	NA	1 [Reference]	NA
T2	5 (25.0%)	32 (9.13 ± 0.17)	0.581	0.341	1.151	0.849
T3	7 (35.0%)	33 (9.89 ± 0.52)	0.812	0.688	1.439	0.645

Notes: [a], Adjusted variables, gender, age, history of hypertension, history of hyperlipidemia, platelet, creatinine, fasting Glucose, glycated hemoglobin, total cholesterol, low density lipoprotein, high density lipoprotein, Statin, history of diabetes mellitus, the use of insulin, C-reaction protein.*P<0.05.
Abbreviations: HR, hazard ratio; CI, confidential interval; MACE, major adverse cardiovascular events (cardiovascular death, myocardial infarction, or stroke); NA, not applicable; T, tertiles; TyG, triglyceride glucose index.

of MACEs in the crude model was observed per standard deviation (SD) increase in the TMAO (HR = 1.428, p = 0.020). Furthermore, a 53% increased risk of MACEs was observed per SD increase in the TMAO among the fully adjusted model (HR = 1.530, p = 0.113). Patients in Tertile 3 (mean ± SD, 532.42 ± 297.17 mg/L) gained significantly higher risk for MACEs (hazard ratio [HR]: 4.748, *p*=0.048), while MACEs risk of patients in Tertile 2 did not show a significant difference (HR: 1.679, *p*=0.491). In addition, per SD level increase of the TyG index was associated with a 5.7% increase in MACEs risk (HR: 1.057, p = 0.895) among the fully adjusted model. Compared to Tertile 1 of the TyG index, patients in Tertile 3 were associated with a 43.9% increase in MACEs risk in the fully adjusted model. The survival curves for TyG and TMAO are shown in Figure 3.

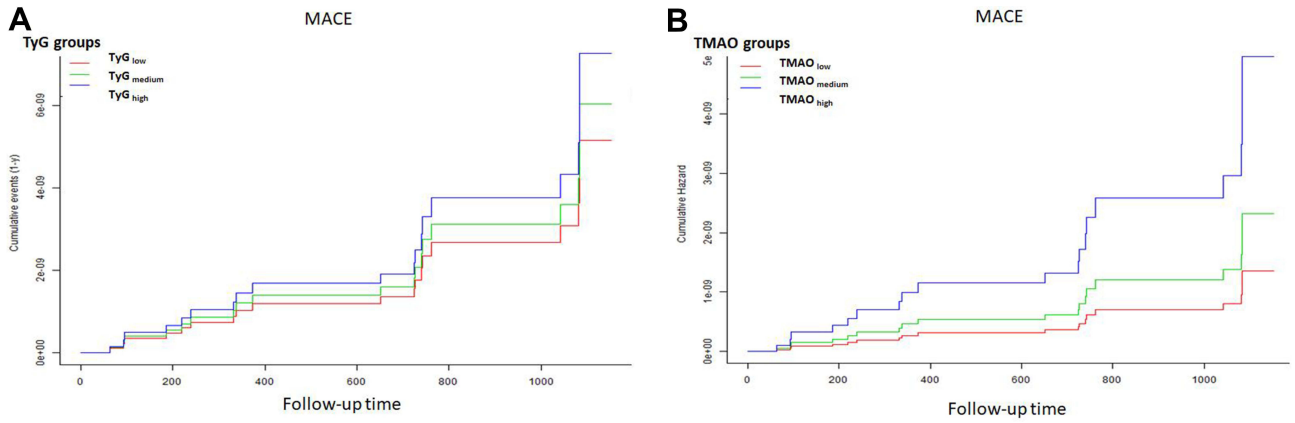

Figure 3 Survival curves for predicting MACEs according to the tertiles of TyG or TMAO. (**A**) performed survival curves for predicting MACEs according to the tertiles of TyG (**A**) and (**B**) performed survival curves for predicting MACEs according to the tertiles of TMAO (**B**).

Outcomes According to the TyG Index and TMAO Plasma Levels

During a median follow-up of 2.03 years (25th to 75th percentiles range: 1.97–2.97), 20 (20.62%) patients experienced MACEs. In univariable analysis, group C, D, and B were associated with 4.97 (HR = 4.972, 95% confidence interval (CI): 1.089–22.703, P-value = 0.038), 2.58 (HR = 2.581, 95% CI: 0.499–13.350, P-value=0.038), and 1.21-fold (HR = 1.206, 95% CI: 0.201–7.231, P-value = 0.837) increase in MACEs compared with group A, respectively (Table 4). After adjusting for several variables in different models, including sex, age, hypertension, hyperlipidemia, DM,

Table 4 Univariable and Multivariable Analyses of the Impact of TyG and TMAO on MACE

Analysis	Group	HR	95% CI	*P* value
Unadjusted	TMAO ≤ median and TyG ≤ median	Ref	–	–
	TMAO ≤ median and TyG>median	1.206	0.201,7.231	0.837
	TMAO>median and TyG ≤ median	4.972	1.089,22.703	0.038*
	TMAO>median and TyG>median	2.581	0.499,13.350	0.258
Model I:	TMAO ≤ median and TyG ≤ median	Ref	–	–
	TMAO ≤ median and TyG>median	1.421	0.233,8.687	0.703
	TMAO>median and TyG ≤ median	4.558	0.964,21.565	0.056
	TMAO>median and TyG>median	2.449	0.462,12.565	0.293
Model II:	TMAO ≤ median and TyG ≤ median	Ref	–	–
	TMAO ≤ median and TyG>median	1.249	0.195,8.011	0.814
	TMAO>median and TyG ≤ median	5.518	1.143,26.654	0.034*
	TMAO>median and TyG>median	2.248	0.389,12.990	0.365
Model III:	TMAO ≤ median and TyG ≤ median	Ref	–	–
	TMAO ≤ median and TyG>median	1.552	0.193,12.514	0.680
	TMAO>median and TyG ≤ median	8.839	1.719,45.451	0.009*
	TMAO>median and TyG>median	4.905	0.735,32.709	0.100
Model IV:	TMAO ≤ median and TyG ≤ median	Ref	–	–
	TMAO ≤ median and TyG>median	2.569	0.236,28.000	0.439
	TMAO>median and TyG ≤ median	11.392	1.836,70.707	0.009*
	TMAO>median and TyG>median	4.362	0.627,30.354	0.137

Notes: Adjust I model adjusts for sex and age; Adjust II model adjusts for adjust I plus ejection fraction, smoke, hypertension, hyperlipidemia, diabetes mellitus and killip classification; Adjust III model adjusts for adjust II + creatinine, heart rate and C-reactive protein. *P<0.05.

Abbreviations: TyG, triglyceride glucose, TMAO, trimethylamine N-oxide.

creatine kinase, C-reactive protein, TGs, and glucose, group C remained independently associated with an increased risk of MACEs. In contrast, no trend was observed in other groups compared with group A (Table 4). Notably, the incidence of MACEs was higher in group A (TMAO > median and TyG ≤ median) than in the other groups (p=0.033) significantly (Figure 4A). Similarly, patients in group A had an increased risk of MACEs compared to other groups with hyperlipidemia (p=0.016) (Figure 4B) or DM (p=0.036) (Figure 4C). However, there is no significant difference between the four groups among patients with hypertension (Figure 4D). We conducted the Receiver operating characteristic curve of TyG combined with plaque characteristics for predicting MACEs (Figure 5). The area under the ROC curve was 0.815 (95% CI, 0.723–0.887). The cut-off threshold (Youden index) was 0.5773 to generate the maximum sensitivity and specificity in predicting MACEs. The corresponding sensitivity and specificity were 85.00% and 72.73%, respectively.

Discussion

In the present study, we retrospectively investigated the prognostic significance of the TyG index and TMAO levels to MACEs in patients with high-risk plaque characteristics defined by OCT, then treated with PCI. The main findings of the present study were: 1) In fully adjusted analyses, the TMAO > median and TyG ≤ median group were significantly associated with higher rates of MACEs (p=0.009). 2) The area under the receiver operating characteristic curve for predicting MACEs constructed to evaluate the diagnostic value of the TyG index combined with TMAO after full adjustment was 0.815. 3) Kaplan–Meier curves were generated for the cumulative incidence of MACEs stratified by the groupings of the TyG index and TMAO levels. Among the group of patients with TMAO > median and TyG ≤ median, there was a significantly higher incidence of MACEs (p=0.033).

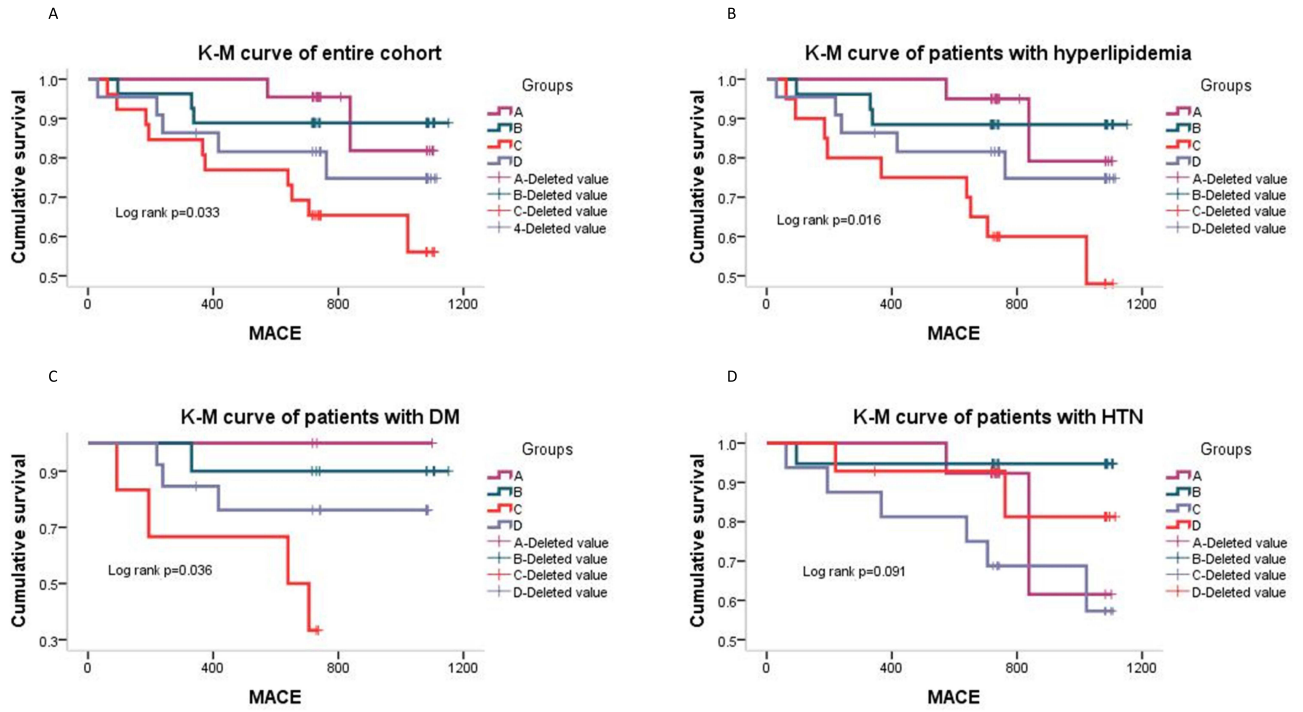

Figure 4 Kaplan–Meier curves showing cumulative MACE rates for up to median 2.03 years stratified by the level of TyG and TMAO characteristic among patients with high risk plaque characteristic. (**A**) Kaplan–Meier curves showing cumulative MACE rates stratified by the level of TyG and TMAO among total cohort of patients with high risk plaque characteristic. (**B**) Kaplan–Meier curves showing cumulative MACE rates stratified by the level of TyG and TMAO among hyperlipidemia cohort of patients with high risk plaque characteristic (**C**) Kaplan–Meier curves showing cumulative MACE rates stratified by the level of TyG and TMAO among DM cohort of patients with high risk plaque characteristic. (**D**) Kaplan–Meier curves showing cumulative MACE rates stratified by the level of TyG and TMAO among hypertension cohort of patients with high risk plaque characteristic. Group (**A**) TMAO ≤ median and TyG ≤ median; Group (**B**) TMAO ≤ median and TyG>median; Group (**C**) TMAO>median and TyG ≤ median; Group (**D**) TMAO>median and TyG>median.

Abbreviations: MACE, major adverse cardiovascular events; K-M curve, Kaplan–Meier curves.

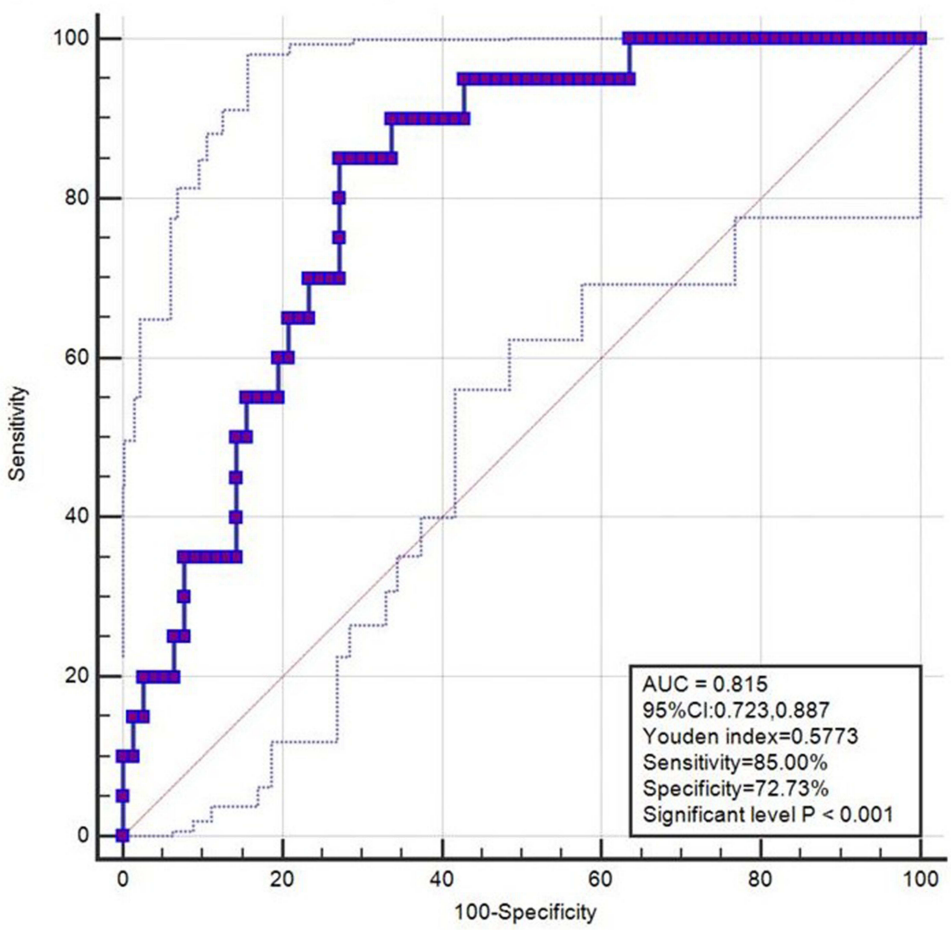

Figure 5 Receiver operating characteristic curve of triglyceride glucose index combined with plaque characteristics for predicting MACES. Adjusted variables including gender, age, status of smoking, hypertension, hyperlipidemia, diabetes mellitus, history of PCI, Killip classification, creatinine, low density lipoprotein.
Abbreviations: MACEs, major adverse cardiovascular events; AUC, areas under the ROC curve; CI, 95% confidence interval.

The TyG Index and Coronary Artery Disease

There has been an increasing interest for using blood biomarkers to enhance risk stratification and clinical decision-making in several cardiovascular diseases. Previous studies have demonstrated and considered the TyG index an early predictor for individuals at high risk of developing DM and pre-DM. Several clinical literatures have been shown to be useful for risk stratification in patients with STEMI. TMAO and TyG are the two most commonly measured biomarkers for this purpose, and they represent different responses to those associated with cardiac atherogenic. In addition, the increased TyG index is prominently correlated with an increased risk of developing cardiovascular disease; thus, it helps identify people susceptible to cardiovascular disease.[28–30] Ma et al[31] evaluated the prognostic impact of the TyG index and incremental effect of risk stratification in a relatively longer follow-up among cohorts with non-ST-segment elevation acute coronary syndromes who underwent PCI and reported that the TyG index was an independent predictor of adverse clinical outcomes. Our previous results[32] showed that the middle tertile of TyG was significantly associated with greater rates of MACEs in patients with plaque rupture in fully adjusted analyses. Moreover, the results indicated a significantly higher HR for MACEs in patients in the middle tertile of TyG than in those in the low tertile of TyG after full additional adjustment (HR, 5.45; 95% CI, 1.10–27.09; p=0.038). Furthermore, being in the high tertile of TyG independently and significantly increased the risk of major bleeding events among patients with pulmonary embolism (HR, 2.50; 95% CI, 1.11–5.65; p=0.028). These data, including our current findings, support that increasing the TyG index contributes to the higher incidence of MACEs. Additionally, these may suggest IR as a target in novel interventions for coronary heart disease prevention.

TMAO Levels and Coronary Artery Disease

There is a growing appreciation that the gut microbes play an important role in overall host metabolism. TMAO is atherogenic,[11,33] while plasma TMAO levels can predict future CVD prevalence and MACEs, owing to the increased number of diseased coronary vessels and enhanced coronary artery atherosclerotic burden in patients with elevated TMAO levels.[12,34] One study provided evidence on the relation of increased TMAO level to enhanced prothrombotic effect in patients.[35] Similarly, we found that assessment of a high level of TMAO and low TyG index over a median follow-up of 2.03 years has a higher incidence of MACEs. Wang et al reported that blocking the production of trimethylamine might prevent the formation of atherosclerotic lesions. Thus, the gut microbial TMAO as a therapeutic target for atherosclerosis may be a novel intervention for coronary heart disease prevention.[36]

By contrast, decreasing plasma TMAO levels can reduce the risk of MACEs.[37] Therefore, as recommended by current dietary guidelines, lifestyle intervention[38] and modification of diet,[12] such as reducing red meat intake,[39] are important for modulating the gut microbiome and circulating TMAO levels. Subsequently, these could improve carotid intima-media thickness and reduce the incidence of MACEs.[40]

Prognostic Value of the Combination of the TyG Index and TMAO Levels on IR and the Gut Microbiota

In the present study, the two biomarkers were complementary in terms of prognostication. The incidence of MACEs was significantly higher in the group with TMAO > median, TyG ≤ median/TMAO > median, and TyG > median compared to other groups (p=0.033). Moreover, several human and animal experiments have confirmed that IR is closely associated with the gut microbiome.[41,42] Germ-free mice infected with the gut microbiota content of conventionally raised mice presented with an increase in body weight and fat content, correlated with IR and glucose intolerance.[43] Furthermore, intestinal microbiota transplantation to germ-free mice enhanced IR-associated adiposity, which may indicate a cause–effect relationship between IR and microbiota.[44]

Various hypotheses have explained the mechanism of the association. A hypothesis indicated that the intestinal bacteria of ob/ob mice are capable of removing more energy from the diet,[45] which may result in enzymes produced by such bacteria that are efficient in dietary nutrient degradation. Meanwhile, most of the reported mechanisms propose that enzyme-produced bacteria may significantly influence the link between microbiota and insulin sensitivity.[46] Moreover, the lipopolysaccharide from the intestinal flora bacteria can induce a chronic subclinical inflammatory process that leads to IR.[47] Furthermore, a variety of inflammatory mediators, including branch-chain amino acids, are produced by intestinal microflora. Therefore, dysbiosis of the gut microbiota can increase intestinal mucosal permeability. These concepts may introduce new therapeutic avenues for the gut and gut microbiota-promoting metabolic inflammation, disorders, and their comorbidities.

Strength and Limitation

Our study for the first time assessed the relations of TyG combined with TAMO and subsequent risk of coronary heart disease among patients with high-risk plaque characteristics defined by OCT. However, several potential limitations warrant consideration. Firstly, it was a single-center study that was restricted to a selected group and the time of follow-up might not be long enough. Thus, further multi-center studies are needed to verify the findings of the present study. Furthermore, our study did not assess the timing or trajectories of the changes of TyG and TAMO. Therefore, there might be unmeasured exogenous or endogenous confounding factors; there also might be residual confounding factors for CHD incidence. Finally, compared with the OCTAMI registry study, which focuses on cardiovascular studies, other glucose-related variables were not assessed in this study.

Conclusion

This study demonstrated the usefulness of combined measures of the TyG index and TMAO in enhancing risk stratification in STEMI patients with OCT-defined high-risk plaque characteristics. Further studies with a larger number of patients are needed to confirm these results.

Data Sharing Statement

The datasets used and/or analyzed are available from the corresponding author (Hongbing Yan) on reasonable request.

Ethics Approval and Consent to Participate

It is from the ethics committee of the department of Cardiology, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College, China.

Acknowledgments

The authors gratefully acknowledge all individuals who participated in this study.

The abstract of this paper was presented at the Conference name Organizing Committee of China Heart Congress (CHC) 2021 in conjunction with the 6th China Vascular Congress (CVC) as conference proceedings. The abstract was published in ZHONGGUO XUNHUAN ZAZHI CHINESE CIRCULATION JOURNAL (ISSN 1000-3614 CN 11-2212/R1).

Author Contributions

All authors have made a significant contribution to the work reported, including conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors have drafted or written, or substantially revised or critically reviewed the article. All authors have agreed on the journal to which the article will be submitted. All authors have reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All authors have agreed to take responsibility and be accountable for the contents of the article.

Funding

This study was supported by Shenzhen Key Medical Discipline Construction Fund (number: SZXK001), the Fund of "Sanming" Project of Medicine in Shenzhen (number: SZSM201911017), the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (2016-I2M-1–009), National Natural Science Funds (number: 81970308). CAMS Innovation Fund for Medical Sciences (2023-I2M-C&T-B-069).

Disclosure

The authors report no conflicts of interest in this work.

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