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TRIGLYCERIDE TO HIGH-DENSITY LIPOPROTEIN RATIO AND THE RISK OF MAJOR ADVERSE CARDIOVASCULAR EVENTS IN A NON-DIABETIC GENERAL POPULATION

Objective This study aimed to investigate the role of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C)

ratio for the prediction of major adverse cardiovascular events (MACEs) in non-diabetic individuals.

Material and methods In total 88946 non-diabetic individuals were enrolled in the study. These individuals were divided into four groups according to the TG/HDL-C ratios. The clinical endpoints were composite MACEs

and their subtypes, myocardial infarction and stroke. Cox proportional hazards regression models and restricted cubic spline (RCS) analysis were conducted to explore the relationship between

the TG/HDL-C ratio and MACEs.

Results Multivariable Cox proportional hazards analyses showed that a higher TG/HDL-C ratio was associ-

ated with an elevated risk of MACEs. Kaplan–Meier survival curve showed that participants in higher quartiles of TG/HDL-C ratio had a higher cumulative incidence of composite MACEs (p<0.0001). In addition, RCS analysis indicated that the TG/HDL-C ratio and composite MACEs followed a non-

linear relationship (p<0.0001).

Conclusions The TG/HDL-C ratio can serve as a prognostic marker of MACEs in non-diabetic individuals.

Keywords Insulin resistance; major adverse cardiovascular events; non-diabetic individuals

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Introduction

Insulin resistance (IR) is a subnormal response of insulin-targeting cells to insulin at physiological levels. Recent studies indicated that IR is associated with a variety of metabolic and cellular activities that facilitate atherosclerosis and blood clotting [1]. These conditions may play critical roles in the development of major adverse cardiovascular events (MACEs) [2]. The triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio has been regarded as an alternative surrogate marker of IR [3]. Since IR is most commonly linked to diabetes mellitus [4], many studies have examined the role of the TG/HDL-C ratio in the prediction of MACEs for patients with diabetes mellitus [5–7]. However, the role of the TG/HDL-C ratio in MACEs prediction in a non-diabetic condition are unclear. Therefore, the current study aimed to investigate the TG/HDL-C ratio in MACEs prediction for non-diabetic individuals.

Material and methods Study subjects

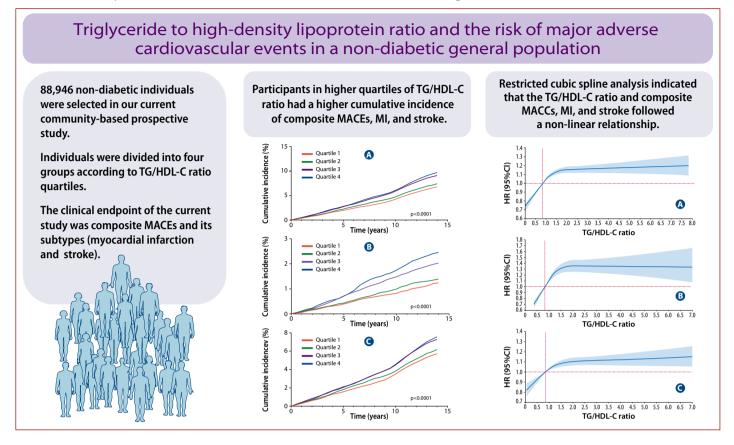
The subjects involved in the present research were extracted from the Kailuan study database. The Kailuan study is a prospective longitudinal cohort study that aimed to observe the mortality and mobility of cardiovascular diseases (CVD) in Tangshan city. The design of the Kailuan study has been thoroughly detailed in earlier publications [8,9].

A total of 101,510 individuals participated in the Kailuan study. The *inclusion criteria* in the current study were:

- 1) Individuals more than 18 yrs of age.
- 2) Sign an informed consent and cooperate with the physician. The *exclusion criteria* were:
- 1) Patients with diabetes mellitus, myocardial infarction (MI), stroke, cancer, and/or any other severe disease.
- 2) Individuals with incomplete lab results.



Central illustration. Triglyceride to High-Density Lipoprotein Ratio and the Risk of Major Adverse Cardiovascular Events in a Non-Diabetic General Population



According to these criteria, 9013 patients with diabetes mellitus, 90 patients with prior MI, 2201 patients with prior stroke, and 1260 individuals with incomplete lab results were excluded. Finally, 88,946 non-diabetic individuals were selected.

Data collection

Data on demographic characteristics, lifestyle factors, and medical history were gathered through the administration of a standardized questionnaire by personnel trained in data collection. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the height in meters. Blood pressure was measured in the seated position using a mercury sphygmomanometer, and the average of three readings for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded.

All blood samples were analyzed on the day of collection using an automated analyzer (Hitachi 747, Hitachi, Tokyo, Japan). The biochemical markers analyzed included fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein (hs-CRP).

Hypertension was defined as an SBP of 140 mmHg or higher, a DBP of 90 mmHg or higher, the use of antihypertensive medications, or a self-reported history of hypertension. Dyslipidemia was identified based on a history of self-reported use or prescription of lipid-lowering medications, or a TC level of 5.17 mmol/l or higher. High educational background refers to middle school and above. High income refers to 800 Yuan per month. High salt diet refers to more than 10 g salt intake per day. All medical examinations and laboratory tests were conducted for every individual biennially from July 2006 to December 2020.

Clinical endpoints and follow-up

The clinical endpoints of the current study were composite MACEs and its subtypes, MI and stroke. Follow-ups were conducted biennially and continued until the day of incident or Dec. 2021.

Statistical analyses

All statistical analyses were performed using SAS Analytics Software 9.4. Baseline characteristics are described as mean±standard deviation (mean±SD) for continuous and normally distributed variables, as median (interquartile range (IQR) for non-normally distributed variables, or as percentages (number, %) for categorical variables. Data from different quartiles were compared using a one-way analysis of variance (normally distributed variables), Kruskal-Wallis test (non-normally distributed variables), or chi-square test for cate-

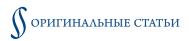
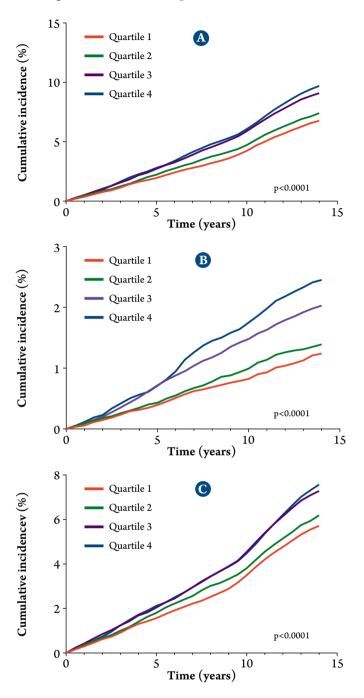


Figure 1. Cumulative incidence of MACEs according to TG/HDL-C ratio quartiles



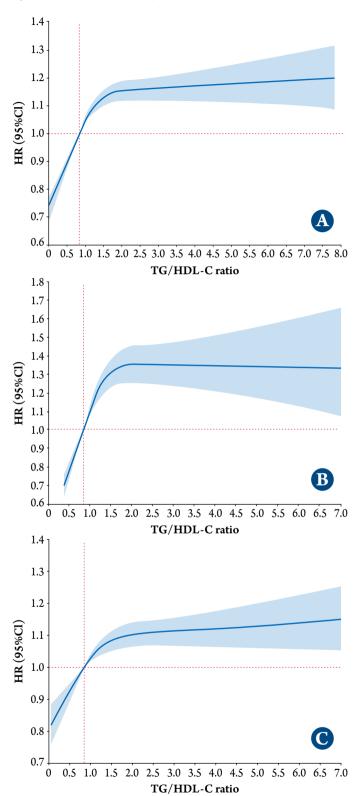
Panel A: Cumulative incidence of composite MACEs.

Panel B: Cumulative incidence of MI.

Panel C: Cumulative incidence of stroke.

gorical variables. Kaplan–Meier curves were performed to compare the cumulative effect of time on MACEs between different quartiles. Cox proportional hazards regression models were used to investigate the association between the levels of the TG/HDL-C ratio and MACEs. Restricted cubic spline analysis (RCS) was conducted to explore the dose-response relationship between the TG/HDL-C ratio and the risk of MACEs. Statistical significance was indicated as p<0.05.

Figure 2. Restricted cubic spline (RCS) analysis for MACEs



Panel A: RCS for composite MACEs.

Panel B: RCS for composite MI.

Panel C: RCS for stroke.

Results Baseline characteristics

The baseline characteristics of 88,946 individuals are shown in Table 1. All individuals were divided into four



Table 1. Baseline characteristics according TG/HDL-C ratios quartiles

Variables	Quartile 1 (n=22,237)	Quartile 2 (n=22,240)	Quartile 3 (n=22,232)	Quartile 4 (n=22,237)	p value
Age, yrs	51.2±13.4	51.1±12.9	51.5±12.5	50.7±11.8	<0.0001
Male	16,413 (73.81)	17,425 (78.35)	17,918 (80.60)	18,839 (84.72)	<0.0001
BMI, kg/m ²	23.38±3.23	24.53±3.29	25.44±3.34	26.32±3.34	<0.0001
SBP, mmHg	126.1±20.7	129.2±20.5	131.1±20.5	133.3±20.3	<0.0001
DBP, mmHg	80.4±11.3	82.6±11.4	83.9±11.6	85.6±11.8	<0.0001
TG/HDL-C ratio	0.41±0.10	0.69±0.08	1.04±0.14	2.40±2.18	<0.0001
FBG, mmol/l	4.97±0.67	5.06±0.67	5.13±0.69	5.17±0.72	<0.0001
TC, mmol/l	4.83±0.96	4.93±1.00	5.04±1.02	4.88±1.43	<0.0001
TG, mmol/l	0.70 (0.57-0.85)	1.07 (0.92–1.23)	1.46 (1.25–1.72)	2.63 (2.04–3.75)	<0.0001
HDL-C, mmol/l	1.78±0.44	1.58±0.34	1.46±0.33	1.36±0.35	<0.0001
LDL-C, mmol/l	2.20±0.93	2.39±0.85	2.43±0.89	2.33±0.93	<0.0001
hs-CRP, mg/l	0.61 (0.21–2.00)	0.72 (0.29–2.10)	0.86 (0.32–2.28)	1.00 (0.40-2.56)	<0.0001
Hypertension	7188 (32.32)	8929 (40.15)	9970 (44.85)	11,132 (50.06)	< 0.0001
Dyslipidemia	8146 (36.63)	9167 (41.22)	13,474 (60.61)	21,614 (97.20)	< 0.0001
Antihypertensive drugs	365 (1.64)	470 (2.11)	650 (2.92)	787 (3.54)	<0.0001
Antihyperlipidemic drugs	116 (0.52)	132 (0.59)	173 (0.78)	254 (1.14)	<0.0001
Smoking	7262 (32.66)	6942 (31.21)	7755 (34.88)	8688 (39.07)	<0.0001
Drinking	8480 (38.13)	7475 (33.61)	8297 (37.32)	9329 (41.95)	<0.0001
Snoring	7699 (34.62)	7169 (32.32)	8078 (36.34)	9194 (41.35)	<0.0001
High educational background	5056 (22.74)	4138 (18.61)	4339 (19.52)	4583 (20.61)	<0.0001
High income	3411 (15.34)	2857 (12.85)	3097 (13.93)	3281 (14.75)	<0.0001
High salt diet	2256 (10.15)	2067 (9.29)	2387 (10.74)	2711 (12.19)	<0.0001
Regular exercise	20,436 (91.90)	20,423 (91.83)	20,186 (90.80)	20,117 (90.47)	<0.0001

Data are mean ± SD, median (IQR), or number (percentage). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein.

equal subgroups according to the TG/HDL-C ratio quartiles: quartile 1 (\leq 0.56), quartile 2 (0.56–0.83), quartile 3 (0.83–1.32), quartile 4 (>1.32). Individuals in quartile 4 included more males and had higher BMI, blood pressure, FBG, and hs-CRP. In addition, individuals in quartile 4 had a higher proportion of smokers, drinkers, snorers, patients with hypertension and dyslipidemia, patients taking antihypertensive drugs and antihyperlipidemic drugs, and those consuming a high salt diet.

Association between TG/HDL-C ratio and risk of MACEs

During a median follow-up of 14 years, in total 6999 MACEs were recorded. Specifically, there were 1509 cases of new-onset MI and 5658 cases of new-onset stroke. Of note, 168 patients occurred of both MI and stroke. Kaplan–Meier survival curve showed that participants in higher quartiles of TG/HDL-C ratio had a higher cumulative incidence of composite MACEs, MI, and stroke compared with other groups over follow-up (log-rank test, p<0.0001) (Figure 1).

Multivariate Cox proportional hazards regression analysis showed that a higher TG/HDL-C ratio was not only associated with increased risk of composite MACEs but also with MI and stroke. Compared to quartile 1, the ha-

zard ratio (HR) and 95% confidence interval (CI) of composite MACEs in quartiles 2–4 were 1.015 (0.942–1.094), 1.169 (1.081–1.263), and 1.175 (1.061–1.301), respectively. The HR (95% CI) of MI in quartiles 2–4 were 1.049 (0.882–1.248), 1.461 (1.227–1.739), and 1.786 (1.435–2.223), respectively. The HR (95% CI) of stroke in quartiles 2–4 were 1.015 (0.938–1.098), 1.122 (1.048–1.223), and 1.184 (1.045–1.221), respectively (Table 2). RCS analysis indicated that TG/HDL-C ratio, composite MACEs, MI, and stroke followed non-linear relationships (Figure 2).

Discussion

In the current study, we demonstrated that individuals with higher TG/HDL-C ratio had a higher proportion of smokers, drinkers, snorers, and they tend to have a high salt diet. Indeed, it has demonstrated that excessive consumption of dietary salt can considerably modify the standard biochemical values of lipid parameters, such as the TG/HDL-C ratio [10]. In addition, cumulative incidences of stroke were higher than that of MI for quartile1–quartile 4, suggesting a higher risk of stroke than that of MI in the non-diabetic individuals. Furthermore, RCS showed that the TG/HDL-C ratio has a non-linear, typically positive, relationship with composite MACEs, MI, and stroke, indicating that

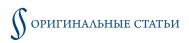


Table 2. Adjusted hazard ratios of MACEs according to TG/HDL-C ratio quartiles

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Composite MACEs	p value	HR	95% CI				
Composite MACEs							
Model 1							
Quartile 2	0.004	1.111	1.034-1.193				
Quartile 3	<0.0001	1.367	1.277-1.464				
Quartile 4	<0.0001	1.509	1.410-1.614				
Model 2							
Quartile 2	0.070	1.015	0.942-1.094				
Quartile 3	< 0.0001	1.169	1.081-1.263				
Quartile 4	0.0019	1.175	1.061-1.301				
MI							
Model 1							
Quartile 2	0.128	1.138	0.964-1.345				
Quartile 3	<0.0001	1.673	1.435-1.951				
Quartile 4	<0.0001	2.083	1.794-2.418				
Model 2							
Quartile 2	0.587	1.049	0.882-1.248				
Quartile 3	<0.0001	1.461	1.227-1.739				
Quartile 4	<0.0001	1.786	1.435-2.223				
Stroke							
Model 1							
Quartile 2	0.024	1.095	1.012-1.184				
Quartile 3	<0.0001	1.284	1.191-1.385				
Quartile 4	<0.0001	1.377	1.277-1.484				
Model 2							
Quartile 2	0.709	1.015	0.938-1.098				
Quartile 3	0.002	1.122	1.048-1.223				
Quartile 4	0.002	1.184	1.045-1.221				
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MACEs, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; HR, hazard ratio; CI, confidence level. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, body mass index, systolic blood pressure, fasting blood glucose, total cholesterol, low density lipoprotein cholesterol, high-sensitivity C-reactive protein, hypertension, dyslipidemia, antihypertensive drugs, antihyperlipidemic drugs, smoking, drinking, snoring, high educational background, high income, high salt diet, and regular exercise.

the risk of these events changes in a non-straight manner as the TG/HDL-C ratio rises.

The main finding of the current study is that an increased TG/HDL-C ratio is associated with an elevated risk of MACEs in non-diabetic individuals. Here, we demonstrated that a higher TG/HDL-C ratio is gradiently associated with an elevated risk of MACEs. Therefore, the TG/HDL-C ratio is clinically significant and may serve as a prognostic marker of MACEs in non-diabetic individuals. In a related study, Park et al. studied community-dwelling cohort of 16,455 Korean individuals who did not have diabetes. The clinical endpoint of the research was ischemic heart disease (IHD), which included angina pectoris and acute MI. Over a follow-up period of 50 months, 321 participants, representing 2.0% of the cohort, developed IHD.

The HRs for IHD in the second to fourth quartiles were 1.61, 1.85, and 2.29, respectively. Notably, women exhibited higher HRs for the risk of developing incident IHD in the fourth quartile, with HR values of 2.98 compared to men, and 1.80 overall [11]. Similarly, Guo et al. studied 1648 non-diabetic patients with acute MI. The participants were categorized into four groups based on the quartiles of the TG/HDL-C ratio. Although the in-hospital mortality rates in the fourth group with the highest TG/HDL-C ratio were greater than those in the other groups, these differences did not reach statistical significance. Furthermore, logistic regression analysis indicated a significant association between the TG/HDL-C ratio and in-hospital mortality among acute MI patients without diabetes, with an odds ratio (OR) of 1.167 [12].

Additionally, in alignment with our findings, Sultani et al. conducted a study involving 482 patients who underwent coronary angiography as part of a prospective cohort analysis. The patients were divided into two groups based on their baseline TG/HDL-C ratio, utilizing a cut-off point of 2.5 for the TG/HDL-C ratio. MACEs were defined as cardiac death, nonfatal MI, stroke, or coronary revascularization. The findings indicated that coronary artery disease was significantly more common in patients with a TG/HDL-C ratio of ≥ 2.5 (83.6% vs. 69.4%, p=0.03). Furthermore, a TG/HDL-C ratio of ≥2.5 was strongly linked to a heightened risk of long-term MACEs (OR: 2.72, 95% CI: 1.42–5.20, p=0.002) [13]. Zhou et al. conducted a study involving 17643 participants with acute coronary syndrome (ACS) who underwent percutaneous coronary intervention. MACEs were defined as cardiac death, nonfatal MI, stroke, and target vessel revascularization within 12 months after discharge. During the 12-month follow-up, 638 patients, representing 3.9%, experienced MACEs. The TG/HDL-C showed significant positive correlations with the occurrence of MACEs, all-cause mortality, and cardiac death. Patients in the higher quartile of TG/HDL-C ratio exhibited significantly increased risks for MACEs when compared to those in the lower quartile [14]. Weng et al. performed a retrospective cohort study involving 614 adults with newly diagnosed heart failure (HF). MACEs were defined as cardiovascular (CV) death and HF rehospitalizations occurring within 12 months post-discharge. Throughout the 12-month follow-up period, 156 patients experienced MACEs, which included 18 CV deaths and 138 HF rehospitalizations. Individuals in quartile 4 exhibited the highest risk of MACEs in comparison to other groups (p<0.001). High TG/HDL-C ratio was associated with an increased cumulative incidence of MACEs, HF rehospitalization, and CV death (all p<0.001). In addition, RCS analysis demonstrated a positive non-linear correlation between the TG/HDL-C ratio and risk of MACEs (p for non-linear = 0.026) [15].



Nevertheless, Drwiła et al. carried out a study by analyzing 1301 patients of non-ST-segment elevation MI (NSTEMI). MACEs were defined as MI, in-stent restenosis, unstable angina, stroke or transient ischaemic attack, and hospitalisation due to HF. In this investigation, 1301 patients were included, and the relationship between TG/HDL-C ratio and the risk of MACEs was examined. The study found no correlation between TG/HDL-C ratio and the risk of MACEs in either the overall population or in subgroups categorized by the presence of diabetes or coronary artery disease diagnosed before admission [16].

Several reasons may explain these conflicting results. First, different populations were analyzed in these studies: patients who underwent coronary angiography, patients with newly diagnosed HF, patients with ACS, and patients with NSTE-MI. Second, MACEs were defined differently among these studies. In the study conducted by Sultani et al., MACEs were characterized as cardiac death, nonfatal MI, stroke, or coronary revascularization; in Zhou et al.'s research, they were defined as cardiac death, nonfatal MI, stroke, and target vessel revascularization occurring within 12 months following discharge; Weng et al. identified them as cardiovascular death and HF rehospitalizations that took place within 12 months after discharge; while Drwila et al. described them as a composite of MI, in-stent restenosis, unstable angina, stroke or transient ischaemic attack, and hospitalization due to HF.

This study has some limitations. First, we only explored the association between the TG/HDL-C ratio and the risk of MACEs. Other indexes of IR include homeostatic model assessment for IR, anthropometric variables, the visceral adiposity index, and lipid accumulation product. However, since the relevant anthropometric variables were not collected in the Kailuan study, these indexes are unavailable in

the current study. Second, the components of MACEs exhibited significant variability across observational studies. Normally, MACEs encompasses acute MI, stroke, and cardiovascular mortality [17]. Nevertheless, data regarding CV death was not accessible in the Kailaun study. Consequently, only MI and stroke were included in the present study. Lastly, because of the observational nature of the study and the single-center design, cause-and-effect conclusions cannot be made. In addition, considering the impact of unmeasured confounders, the results of a study are not generalizable to some extent.

Conclusions

Higher TG/HDL-C ratios were associated with elevated risks of MACEs in non-diabetic individuals. The TG/HDL-C ratio can serve as a prognostic marker of MACEs in non-diabetic individuals.

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Disclosure statement

The authors report that there are no competing interests.

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No conflict of interest is reported.

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