

Association between triglycerides to high-density lipoprotein cholesterol ratio and death risk in diabetic patients with new-onset acute coronary syndrome—a retrospective cohort study in Han Chinese population

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Research Article

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Abstract

Background and Aims: The incidence of diabetes mellitus has reached an alarming level. Cardiovascular disease (CVD) is the leading cause of mortality in diabetic patients. However, the association between ratio and survival outcomes in patients with diabetes mellitus (DM) and new-onset acute coronary syndrome (ACS) remains unknown. The study aimed to assess the association between TG/HDLC ratio and the death risk in diabetic patients with new-onset acute coronary syndrome in Han Chinese population.

Methods: Data in this study were retrospectively collected from January 2016 to December 2016 from patients with type 2 diabetes mellitus (T2DM) and new-onset ACS in Tianjin Chest Hospital. Patients were classified according to the baseline TG/HDLC ratio. The Kaplan-Meier survival curve showed survival outcomes. Univariate and multivariate Cox proportional risk regression analyses were used to evaluate the hazard ratios and 95% confidence intervals (CIs) of death risk. Subgroup analysis was used to determine whether there was an interaction.

Results: In total, 152 patients died, 98 of them from heart disease. The Kaplan-Meier survival curve showed that the group with a high TG/HDLC ratio has a higher mortality rate than the group with a low TG/HDLC ratio. Multivariate Cox regression analyses revealed that the adjusted hazard ratio increased significantly with increasing TG/HDLC median ($P < 0.05$) for all-cause mortality and cardiac death. The association between TG/HDLC ratio and the risks of all-cause mortality and cardiac death in diabetic patients with new-onset ACS was similar among subgroups (P for interaction > 0.05).

Conclusion: Increased TG/HDLC ratio is significantly associated with higher all-cause and cardiac death risks in diabetic patients with new-onset ACS. Therefore, TG/HDLC ratio may be beneficial to evaluate the prognosis of this high-risk population.

1| Introduction

Diabetes mellitus (DM) is a significant health problem. The prevalence of diabetes has constantly increased over the past few decades and has reached an alarming level[1]. The International Diabetes Federation (IDF) Diabetes Atlas 10th edition revealed more than 500 million people worldwide developed DM, and about one in ten adults was affected. Moreover, the number of diabetic patients has increased by 74 million in the last two years, highlighting the alarming increase in the global prevalence of diabetes[1]. The IDF speculated that this number would reach 783 million by 2045, and the proportion of adults with the disease could reach one in eight. Diabetes is also an important driver of global mortality[1]. The IDF also estimated that approximately 6.7 million adults would die from diabetes or its complications in 2021, accounting for more than one-tenth of the all-cause death worldwide and one end every five seconds due to diabetes[1].

Type 2 diabetes mellitus may affect more than 600 million people worldwide in the next 20 years[1]. It has a significant impact on survival and quality of life, especially in patients diagnosed at a younger

age[1]. Although all complications of diabetes are significant, widespread cardiovascular disease remains the leading cause of morbidity and mortality in this population[2]. These amazing statistics highlight the urgent need for renewed attention to aggressive cardiovascular risk reduction in diabetic patients, especially those already suffering from ACS.

Although diabetic patients with ACS have high mortality, the relationship between TG/HDL ratio and death risk in patients with DM and new-onset ACS is unclear. Nowadays, the number of research on the TG/HDL ratio increases gradually, and this lipid indicator is closely related to many diseases. Several previous studies have indicated a positive correlation between TG/HDL ratio and hypertension [3, 4], insulin resistance[5, 6], metabolic syndrome[7, 8], and fatty liver[9, 10]. In addition, elevated TG/HDL ratio played an important role in periodontal disease and renal insufficiency. Therefore, we carried out a retrospective cohort study to assess the association between TG/HDL ratio and death risk in diabetic patients with new-onset ACS.

2| Methods

2.1 | Study Population

Included in this retrospective cohort study were patients admitted to Tianjin Chest Hospital between January 2016 and December 2016. A total of 1782 diabetic patients with new-onset ACS were enrolled in the study. The acute coronary syndrome can be subdivided into either non-ST-segment elevation myocardial infarction (MI), ST-segment elevation MI, or unstable angina pectoris. Twenty-two patients with incomplete follow-up data were excluded from this study. Based on a median split of TG/HDL ratio, patients were divided into the following two groups: Median1 (n=880, TG/HDL \leq 1.522), Median 2 (n=618, TG/HDL $>$ 1.522). A total of 928 men and 832 women were enrolled in this analysis. The Institutional Review Board of Tianjin Chest Hospital approved this study. The study was a retrospective analysis of clinical data, so informed consent was not required.

2.2| Data Collection and Related Definitions

Clinical data, including sex, age, smoking status, history of hypertension, and duration of diabetes, were collected by trained technicians. Blood tests included total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TG), fasting plasma glucose [FPG], hemoglobinA1c [HbA1c], hypersensitive C-reactive protein (hs-CRP), serum creatinine, and N-terminal pro-brain natriuretic peptide (NT-proBNP). All blood samples were collected through veins and analyzed by the laboratory of Tianjin Chest Hospital using standard automated technologies. Cardiac ultrasound clarified the patient's left ventricular cardiac ejection fraction (LVEF). Furthermore, the ultrasound reports were all from Tianjin Chest Hospital. The glomerular filtration rate was estimated (eGFR) using the MDRD equation. Body mass index (BMI) was calculated as weight/height². The non-HDL level was obtained by subtracting HDL from TC. Major adverse cardiovascular events were

defined as cardiac death, nonfatal MI, or nonfatal stroke. A patient's survival status, alive or dead, was determined on the telephone follow-up on a case-by-case basis. In an incident death, the cause would be confirmed on the phone.

2.3| Endpoints and Mortality Surveillance

The study's endpoints included all-cause mortality and cardiac death. All-cause mortality was defined as death from any cause, including cardiac death and any other cause, such as cancer, stroke. Cardiac death was defined as MI, heart failure, and arrhythmia. Investigators were asked to follow up with patients at least once a year for the duration of the study. Follow up until the end of the study (February 23, 2021), except in the event of the patient's death.

2.4| Statistical analysis

The Kolmogorov–Smirnov test determined whether the continuous variables conform to a normal distribution. If normally distributed, it was expressed as mean \pm standard deviation and tested for significance using ANOVA. If skewed, the distribution was expressed in median and tested for significance using the Kruskal-Wallis test. The Kaplan-Meier survival curve showed survival outcomes. Stepwise backwards Cox proportional hazards regression analysis was estimated hazard ratio (HR) and 95% CIs. The time-dependent Cox regression model was used to test whether the variables met the pH hypothesis, and then these variables were included in the multivariate Cox regression model. Univariable and multivariable analyses were performed by Cox regression analysis. This analysis was evaluated the effects of TG/HDLC ratio on all-cause and cardiac mortality. Subgroup analysis of all-cause and cardiogenic mortality was performed according to age, sex, smoking status, hypertension, LDLC, and HbA1c. Differences between subgroup analyses were also compared using an interaction test. All two-sided P-values <0.05 were considered of statistical significance. All statistical analyses and charts were completed with GraphPad Prism version 8.0.2 and MedCalc version 20.0.4.

3| Results

3.1| Baseline Characteristics

TABLE 1 Baseline characteristics of included patients by a median of TG/HDLC ratio

Variables	Total	Median1	Median2	P-value
No.atrisk	1760	880	880	
Age, years	66.0 ±6.7	66.1 ±6.8	66.0 ±6.7	0.774
Sex				0.390
Female	832 (47.3%)	425 (48.3%)	407 (46.3%)	
Male	928 (52.7%)	455 (51.7%)	473 (53.8%)	
Smoking status				0.173
everorcurrent	706 (40.1%)	339 (38.5%)	513 (58.3%)	
never	1054 (59.9%)	541 (61.5%)	367 (41.7%)	
Hypertension	1354 (76.9%)	681 (77.4%)	673 (76.5%)	0.651
BMI kg/m ²	25.6 ±2.7	25.4 ±2.9	25.6 ±2.7	0.074
Duration of diabetes months	8.0 (3.0-14.0)	8.0 (3.0-14.0)	8.0 (3.0-14.0)	0.540
LVEF,%	60 (56-64)	60 (56-63)	60 (56-64)	0.161
Laboratory findings				
TG/HDLC ratio	2.1 (1.8-2.9)	1.0 (0.8-1.3)	2.1 (1.8-2.9)	<0.001
TC, mmol/L	4.3 (3.5-5.0)	4.5 (3.8-5.3)	4.3 (3.5-5.0)	<0.001
TG, mmol/L	1.5 (1.1-2.1)	1.1 (0.9-1.4)	2.1 (1.7-2.7)	<0.001
HDLC, mmol/L	2.0 (0.9-4.8)	1.2 (1.0-1.3)	0.9 (0.8-1.1)	<0.001
LDLC, mmol/L	2.8 (2.1-3.5)	2.9 (2.3-3.6)	2.8 (2.1-3.5)	0.024
VLDL, mmol/L	0.5 (0.3-0.6)	0.4 (0.2-0.5)	0.5 (0.3-0.6)	<0.001
Lp(a), mmol/L	26.9 (10.7-75.3)	30.1 (12.9-75.5)	26.9 (10.7-75.3)	0.265
HbA1c,%	7.4 (6.1-9.3)	7.3 (6.6-8.3)	7.3 (6.6-8.3)	0.475
FPG, mmol/L	7.3 (6.1-9.3)	7.2 (6.9-9.1)	7.4 (6.1-9.3)	0.103
Hcy, μmol/L	12.7 (10.4-15.9)	12.5 (10.2-15.9)	12.8 (10.6-15.8)	0.142
eGFR, mL/min	92.5 ±24.4	93.1 ±24.0	92.5 ±24.4	0.975
hs-CRP, mg/L	2.0 (0.9-4.8)	1.7 (0.7-4.9)	2.0 (0.9-4.8)	0.007
NT-proBNP, pg/mL	224.5 (99.9-631.6)	204.4 (89.1-612.0)	224.5 (99.9-631.6)	0.049
Treatment Strategies				0.596
Medication only	548 (31.3%)	284 (32.3%)	264 (30.0%)	
PCI	1009 (57.2%)	496 (56.4%)	513 (58.3%)	
CABG	203 (11.5%)	100 (11.4%)	102 (11.6%)	
Medications at discharge				
Aspirin	1697 (96.4%)	845 (96.0%)	852 (96.8%)	0.369
Statin	1667 (94.7%)	836 (95.0%)	831 (94.4%)	0.881
Clopidogrel/Ticagrelor	1386 (78.8%)	676 (76.8%)	710 (80.7%)	0.048
β-blocker	1129 (64.1%)	563 (64.0%)	566 (64.3%)	0.881
ACEI/ARB	1007 (57.2%)	506 (57.5%)	501 (56.9%)	0.810
CCB	491 (27.9%)	218 (24.8%)	254 (28.9%)	0.366
Nitrate	905 (51.4%)	450 (51.1%)	455 (51.7%)	0.812
Insulin	688 (39.1%)	342 (38.9%)	346 (39.3%)	0.845

Note: Continuous data are shown as mean standard deviation or median (interquartile range) and categorical data are shown as frequency (%). Abbreviations: BMI, body mass index; LVEF, left ventricle ejection fraction; TC, total cholesterol; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; TG/HDLC ratio, triglycerides to high-density lipoprotein cholesterol ratio; VLDL, very low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); HbA1c, hemoglobin A1c; Hcy, homocysteine; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro brain natriuretic peptide; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

A total of 1760 diabetic patients with new-onset ACS were selected for analysis. Table 1 summarizes the baseline characteristics of patients in the two groups, which were based on a median split of TG/HDLC ratio. Most variables were not statistically different between groups, including age, sex, smoking status, hypertension, BMI, duration of Diabetes, LVEF, Lipoprotein(a) (Lp(a)), HbA1c, FPG, eGFR, treatment strategies, aspirin, statin, β-blocker, ACEI/ARB, CCB, nitrate, (P>0.05). However, some variables were significant between the two groups, such as TG/HDLC ratio (P<0.001), TC (P<0.001), TG (P<0.001), HDLC (P<0.001), LDLC (P<0.05), very low-density lipoprotein cholesterol (VLDL) (P<0.001), N-terminal pro brain natriuretic peptide (NT-proBNP) (P<0.05), high-sensitivity C-reactive protein (hs-CRP) (P<0.001), and Clopidogrel/Ticagrelor (P<0.05). Moreover, TG and LDLC increased with the growing TG/HDLC ratio.

3.2| Survival curve

Figure 1 shows Kaplan-Meier survival curve for death risk. Time referred to the interval between admission and the last follow-up visit or patient death. This figure suggested that that all-cause mortality and cardiac death increased gradually after 50 months and increased almost vertically at approximately 62.5 months. Moreover, the survival rate was lower in the second group (Median2) than in the first (Median1), whether for all-cause or cardiac mortality.

3.3| Univariate and multivariate Cox regression analysis

TABLE 2 Cox regression models evaluating death risk and cardiovascular events according to TG/HDL ratio

Endpoint	Events,n/total (%)	Crude HR (95% CI)	Crude P-value	Adjusted HR (95% CI)	Adjusted P-value
All-cause mortality	152/1760 (8.6%)		0.152		0.004
Median1	68/880 (7.7%)	1.00 (reference)		1.00 (reference)	
Median2	84/880 (9.5%)	1.26 (0.92-1.74)		1.81 (1.21-2.70)	
Cardiac death	98/1760 (5.6%)		0.088		< 0.001
Median1	41/880 (4.7%)	1.00 (reference)		1.00 (reference)	
Median2	57/880 (6.5%)	1.42 (0.95-2.12)		2.44 (1.45-4.10)	
Nonfatal MI	77/1760 (4.4%)		0.714		0.384
Median1	40/880 (4.5%)	1.00 (reference)		1.00 (reference)	
Median2	37/880 (4.2%)	0.92 (0.58-1.46)		1.32 (0.71-2.44)	
Nonfatal stroke	435/1760 (24.7%)		0.498		0.994
Median1	227/880 (25.8%)	1.00 (reference)		1.00 (reference)	
Median2	208/880 (23.6%)	0.94 (0.78-1.13)		1.00 (0.76-1.31)	
nonfatal MI or nonfatal stroke	502/1760 (28.5%)		0.471		0.592
Median1	262/880 (29.8%)	1.00 (reference)		1.00 (reference)	
Median2	240/880 (27.3%)	0.94 (0.79-1.12)		1.06 (0.85-1.33)	

Note: Abbreviations: HR, hazard ratio; CI, confidence interval

Table 2 displays the results of COX regression analysis. The TG/HDL ratios were statistically significant after adjusting for confounders and whether for all-cause mortality or cardiac death. However, the ratios were not statistically significant in nonfatal MI, nonfatal stroke, and major adverse cardiovascular events before adjusting for confounders. Before adjustment, the risks of all-cause mortality and cardiac death between two groups were similar. After adjusting for confounders, an increase in the TG/HDL ratio was associated with an increasing risk of cardiac death ($P < 0.001$) and all-cause death ($P = 0.004$).

Figure 2 indicates the histogram of hazard ratios for different TG/HDL ratio groups in the adjusted Cox regression model. The hazard ratio was higher in the group with a higher TG/HDL ratio in cardiac and all-cause mortality.

3.4| Subgroup analyses

Figure 3 illustrates the results of the subgroup analysis for all-cause and cardiac mortality. The TG/HDL ratio was not statistically different in evaluating all-cause and cardiac death risks regarding age, sex,

smoking status, hypertension, LDLC, and HbA1c (all of P values >0.05 in subgroups).

4| Discussion

This study systematically analyzed the association between the TG/HDLC ratio and the risks of all-cause mortality and cardiac death in diabetic patients with new-onset ACS. Elevated TG/HDLC ratio was associated with an increased risk of all-cause and cardiac death. As was shown in multivariate Cox regression analysis, TG/HDLC ratio was a risk factor of all-cause and cardiac death risks. In subgroup analysis, there was no statistical difference between TG/HDLC ratio and all-cause and cardiac death risks in terms of age, sex, smoking status, hypertension, LDLC, and HbA1c.

There was an advantage to the TG/HDLC ratio. High TG was a cardiovascular risk factor and was associated with all-cause mortality and the incidence of coronary artery disease (CAD) events[11]. Several epidemiological studies have shown a significant relationship between serum HDLC concentration and CAD risk. The typical lipid profile of diabetes was high TG and low HDLC[11]. TG and HDLC were independent of each other, and in the absence of insulin resistance, a single lipid parameter did not reflect the actual status of plasma atherosclerosis and the risk of CAD. However, TG/HDLC ratio combined them and better evaluated the death risk in diabetic patients with new-onset ACS. It might be a better indicator for primary and secondary prevention of cardiovascular diseases (CVDs)[12-14]. Another study suggested that the TG/HDLC ratio had a better predictive value for mortality than individual lipid parameters[15]. In addition, a high TG/HDLC ratio was a good predictor of the extent of CAD[16, 17]. Elevated TG/HDLC ratio was an independent predictor of long-term all-cause mortality in patients undergoing coronary angiography and was strongly associated with long-term risk of major adverse cardiovascular events[18]. Therefore, the TG/HDLC ratio assessment was of clinical value in diabetic patients with new-onset ACS.

TG/HDLC ratio is associated with a remnant risk of cardiovascular disease. In a certain proportion of patients taking oral statins, however, the incident risk of cardiovascular disease remains despite LDLC compliance. Both remnant lipoprotein particle cholesterol (RLPC) and LDLC are associated with the risk of ischemic heart disease (IHD) and MI[19]. A study showed that residual cholesterol level ≥ 24 mg/dL was associated with an increased risk of atherosclerosis-associated disease regardless of LDLC level[20]. Increased RLPC concentration was associated with all-cause mortality risk under non-fasting[21]. Through intravascular ultrasound, Bayturan et al. found that LDL-C fell to an average of 58.4 mg/dL (1.5 mmol/L) in approximately twenty percent of intensively treated patients, but plaque numbers were still increasing[22]. RLPC explains part of the remnant risk of all-cause mortality in patients with IHD[23]. However, no biological marker can quantify residue level due to its apparent heterogeneity, lack of universally accepted definition, and absence of precise measurement methods. Although statins did not eliminate the remnant risk of CVDs, Renato et al. demonstrated that TG/HDLC was associated with residual cholesterol[24]. Previous studies revealed that TG/HDLC ratio was closely associated with adverse cardiovascular events in patients with CAD[18, 25, 26]. A study indicated that TG/HDLC ratio was a robust independent predictor of CAD, CVD, and all-cause mortality[27]. Elevated TG/HDLC ratio was reported to be a potentially useful predictor of future cardiovascular events in Chinese patients with DM

and stable CAD[28]. Therefore, the TG/HDL ratio assessment is clinically significant in risk stratification for patients receiving statin therapy.

The predictive value of the TG/HDL ratio for cardiovascular events in diabetic patients is controversial. However, insulin resistance (IR) may be the culprit of this controversy because it is a critical condition for cardiovascular events in diabetic patients. One study found that high TG and low HDL levels were significant risk factors for coronary heart disease (CHD) only in the presence of IR[29]. Another study showed that the risk of major cardiovascular events was more significant in the presence of IR, regardless of whether triglyceride and HDL cholesterol levels were high or low[30]. Other studies have shown that IR at any level of obesity exacerbated the risk of developing CHD and T2DM[31]. The mechanisms by which insulin resistance promotes cardiovascular events in diabetic patients are as follows. (1) Triglyceride-enriched VLDL particles are hydrolyzed by lipoprotein lipase or hepatic lipase to produce small dense LDL (sdLDL) particles[32]; (2) In the presence of IR and high secretion of VLDL particles, these sdLDL particles are usually present in high concentrations[33]; (3) Whereas sdLDL particles are highly atherogenic. Compared to normal LDL particles, they are more easily oxidized, have a higher affinity for the extracellular matrix, and have a higher degree of retention in the arterial wall[32]. In addition, the smaller the LDL, the less it binds to the LDL receptor, and the longer it resides in the circulation[32].

Summarizing the findings of previous literatures, we found that the relationship between TG/HDL ratio and death risk in diabetic patients with new-onset ACS was unclear. Clarifying this relationship was extremely important to assess the prognosis of this high-risk population. No papers have revealed this relationship in the published literature. Therefore, to clarify the relationship between the TG/HDL ratio and the death risk in diabetic patients with new-onset ACS, we used COX regression analysis and subgroup analysis to explore this relationship. Eventually, we found that TG/HDL ratio was positively associated with the death risk in diabetic patients with new-onset ACS.

There may be several potential mechanisms for the association between TG/HDL ratio and the death risk in patients with DM and new-onset ACS: (1) Elevated TG level and reduced HDL play a vital role in the progression of atherosclerosis, which may be related to the TG/HDL ratio as a marker of LDL particle size[34]. Previous studies have reported that a high TG/HDL ratio was strongly associated with elevated levels of small, dense LDL, which was considered very atherogenic[35-37]. (2) TG/HDL ratio is significantly associated with insulin resistance in diabetic patients[38-40]. Furthermore, insulin resistance is associated with the vulnerability of atherosclerotic plaques[41]. (3) TG/HDL ratio is related to the severity of atherosclerosis because the total plaque area is positively correlated with TG/HDL ratio[40]. (4) The hyperglycemic environment may lead to systemic macrovascular and microvascular disease in diabetic patients, including diabetic nephropathy, CAD, and ischemic stroke, which may be an additional risk of all-cause and cardiac death[42-44].

However, several limitations of the study should be acknowledged: (1) Follow-up information was collected by telephone or electronic medical record access. This information mainly included survival information. Baseline data after four years of follow-up were not collected. Because blood lipid levels

varied by race, it was unclear whether these findings also apply to other races. (2) The complications and severity of new-onset ACS and DM differed, affecting the risks of all-cause mortality and cardiac death. (3) Because blood lipid levels varied by race, it was unclear whether these findings also applied to other races.

The next step is being under consideration. As a new lipid-lowering drug, the proprotein convertase subtilisin/Kexin type 9 (PCSK9) inhibitor is gaining attention[45]. Therefore, we intend to study whether PCSK9 inhibitor can affect TG/HDLC ratio to increase the risk of all-cause and cardiac death in diabetic patients with new-onset ACS.

5| Conclusion

An elevated TG/HDLC ratio is associated with an increased risk of all-cause and cardiac death in diabetic patients with new-onset ACS. Therefore, TG/HDLC ratio may be beneficial to evaluate the prognosis of this high-risk population.

Abbreviations

ACS, acute coronary syndrome; BMI, Body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; CI, confidence interval; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; EGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobinA1c; HR, hazard ratio; hs-CRP, hypersensitive C-reactive protein; IDF, International Diabetes Federation; IHD, ischemic heart disease; Lp(a), Lipoprotein(a); LVEF, left ventricular cardiac ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal pro brain natriuretic peptide; eGFR, PCSK9, proprotein convertase subtilisin/Kexin type 9; RLPC, remnant lipoprotein particle cholesterol; sdLDLC, small dense LDL;TC, total cholesterol; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein cholesterol; Lp(a), lipoprotein(a);TG/HDLC, triglycerides to high-density lipoprotein cholesterol.

Declarations

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Authors' contributions

Hongliang Cong contributed to the conception and design of the study; Le Wang collected data; Dongdong Shi analyzed data and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data related to the study findings can be requested from the corresponding author for appropriate reasons.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Tianjin Chest Hospital. Consent to participate is not applicable.

Consent for publication

Not applicable.

Conflict of interest

None of the authors declare any conflict of interest.

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References

1. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, et al: IDF diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract* 2021:109119.
2. Cavender MA, Steg PG, Smith SC, Jr., Eagle K, Ohman EM, Goto S, Kuder J, Im K, Wilson PW, Bhatt DL, Investigators RR: Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation* 2015, 132:923-931.
3. Liu D, Guan L, Zhao Y, Liu Y, Sun X, Li H, Yin Z, Li L, Ren Y, Wang B, et al: Association of triglycerides to high-density lipoprotein-cholesterol ratio with risk of incident hypertension. *Hypertens Res* 2020, 43:948-955.

4. Yeom H, Kim HC, Lee JM, Jeon Y, Suh I: Triglyceride to high density lipoprotein cholesterol ratio among adolescents is associated with adult hypertension: the Kangwha study. *Lipids Health Dis* 2018, 17:212.
5. Kim JS, Kang HT, Shim JY, Lee HR: The association between the triglyceride to high-density lipoprotein cholesterol ratio with insulin resistance (HOMA-IR) in the general Korean population: based on the National Health and Nutrition Examination Survey in 2007-2009. *Diabetes Res Clin Pract* 2012, 97:132-138.
6. Gong R, Luo G, Wang M, Ma L, Sun S, Wei X: Associations between TG/HDL ratio and insulin resistance in the US population: a cross-sectional study. *Endocr Connect* 2021, 10:1502-1512.
7. Shin HG, Kim YK, Kim YH, Jung YH, Kang HC: The Relationship between the Triglyceride to High-Density Lipoprotein Cholesterol Ratio and Metabolic Syndrome. *Korean J Fam Med* 2017, 38:352-357.
8. Aslan Cin NN, Yardimci H, Koc N, Ucakurk SA, Akcil Ok M: Triglycerides/high-density lipoprotein cholesterol is a predictor similar to the triglyceride-glucose index for the diagnosis of metabolic syndrome using International Diabetes Federation criteria of insulin resistance in obese adolescents: a cross-sectional study. *J Pediatr Endocrinol Metab* 2020, 33:777-784.
9. Wu KT, Kuo PL, Su SB, Chen YY, Yeh ML, Huang CI, Yang JF, Lin CI, Hsieh MH, Hsieh MY, et al: Nonalcoholic fatty liver disease severity is associated with the ratios of total cholesterol and triglycerides to high-density lipoprotein cholesterol. *J Clin Lipidol* 2016, 10:420-425 e421.
10. Fan N, Peng L, Xia Z, Zhang L, Song Z, Wang Y, Peng Y: Triglycerides to high-density lipoprotein cholesterol ratio as a surrogate for nonalcoholic fatty liver disease: a cross-sectional study. *Lipids Health Dis* 2019, 18:39.
11. Bos G, Dekker JM, Nijpels G, de Vegt F, Diamant M, Stehouwer CD, Bouter LM, Heine RJ, Hoorn S: A combination of high concentrations of serum triglyceride and non-high-density-lipoprotein-cholesterol is a risk factor for cardiovascular disease in subjects with abnormal glucose metabolism- -The Hoorn Study. *Diabetologia* 2003, 46:910-916.
12. Chen Z, Chen G, Qin H, Cai Z, Huang J, Chen H, Wu W, Chen Z, Wu S, Chen Y: Higher triglyceride to high-density lipoprotein cholesterol ratio increases cardiovascular risk: 10-year prospective study in a cohort of Chinese adults. *J Diabetes Investig* 2020, 11:475-481.
13. Matsumoto I, Misaki A, Kurozumi M, Nanba T, Takagi Y: Impact of nonfasting triglycerides/high-density lipoprotein cholesterol ratio on secondary prevention in patients treated with statins. *J Cardiol* 2018, 71:10-15.
14. He S, Wang S, Chen X, Jiang L, Peng Y, Li L, Wan L, Cui K: Higher ratio of triglyceride to high-density lipoprotein cholesterol may predispose to diabetes mellitus: 15-year prospective study in a general population. *Metabolism* 2012, 61:30-36.
15. Edwards MK, Blaha MJ, Loprinzi PD: Atherogenic Index of Plasma and Triglyceride/High-Density Lipoprotein Cholesterol Ratio Predict Mortality Risk Better Than Individual Cholesterol Risk Factors, Among an Older Adult Population. *Mayo Clin Proc* 2017, 92:680-681.

16. da Luz PL, Favarato D, Faria-Neto JR, Jr., Lemos P, Chagas AC: High ratio of triglycerides to HDL-cholesterol predicts extensive coronary disease. *Clinics (Sao Paulo)* 2008, 63:427-432.
17. Yunke Z, Guoping L, Zhenyue C: Triglyceride-to-HDL cholesterol ratio. Predictive value for CHD severity and new-onset heart failure. *Herz* 2014, 39:105-110.
18. Sultani R, Tong DC, Peverelle M, Lee YS, Baradi A, Wilson AM: Elevated Triglycerides to High-Density Lipoprotein Cholesterol (TG/HDL-C) Ratio Predicts Long-Term Mortality in High-Risk Patients. *Heart Lung Circ* 2020, 29:414-421.
19. Varbo A, Benn M, Tybjaerg-Hansen A, Jorgensen AB, Frikke-Schmidt R, Nordestgaard BG: Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol* 2013, 61:427-436.
20. Quispe R, Martin SS, Michos ED, Lamba I, Blumenthal RS, Saeed A, Lima J, Puri R, Nomura S, Tsai M, et al: Remnant cholesterol predicts cardiovascular disease beyond LDL and ApoB: a primary prevention study. *Eur Heart J* 2021, 42:4324-4332.
21. Varbo A, Freiberg JJ, Nordestgaard BG: Extreme nonfasting remnant cholesterol vs extreme LDL cholesterol as contributors to cardiovascular disease and all-cause mortality in 90000 individuals from the general population. *Clin Chem* 2015, 61:533-543.
22. Nicholls SJ, Hsu A, Wolski K, Hu B, Bayturan O, Lavoie A, Uno K, Tuzcu EM, Nissen SE: Intravascular ultrasound-derived measures of coronary atherosclerotic plaque burden and clinical outcome. *J Am Coll Cardiol* 2010, 55:2399-2407.
23. Jepsen AM, Langsted A, Varbo A, Bang LE, Kamstrup PR, Nordestgaard BG: Increased Remnant Cholesterol Explains Part of Residual Risk of All-Cause Mortality in 5414 Patients with Ischemic Heart Disease. *Clin Chem* 2016, 62:593-604.
24. Quispe R, Manalac RJ, Faridi KF, Blaha MJ, Toth PP, Kulkarni KR, Nasir K, Virani SS, Banach M, Blumenthal RS, et al: Relationship of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to the remainder of the lipid profile: The Very Large Database of Lipids-4 (VLDL-4) study. *Atherosclerosis* 2015, 242:243-250.
25. Wan K, Zhao J, Huang H, Zhang Q, Chen X, Zeng Z, Zhang L, Chen Y: The association between triglyceride/high-density lipoprotein cholesterol ratio and all-cause mortality in acute coronary syndrome after coronary revascularization. *PLoS One* 2015, 10:e0123521.
26. Dai XY, Zheng YY, Tang JN, Yang XM, Guo QQ, Zhang JC, Cheng MD, Song FH, Liu ZY, Wang K, et al: Triglyceride to high-density lipoprotein cholesterol ratio as a predictor of long-term mortality in patients with coronary artery disease after undergoing percutaneous coronary intervention: a retrospective cohort study. *Lipids Health Dis* 2019, 18:210.
27. Vega GL, Barlow CE, Grundy SM, Leonard D, DeFina LF: Triglyceride-to-high-density-lipoprotein-cholesterol ratio is an index of heart disease mortality and of incidence of type 2 diabetes mellitus in men. *J Investig Med* 2014, 62:345-349.
28. Yang SH, Du Y, Li XL, Zhang Y, Li S, Xu RX, Zhu CG, Guo YL, Wu NQ, Qing P, et al: Triglyceride to High-Density Lipoprotein Cholesterol Ratio and Cardiovascular Events in Diabetics With Coronary Artery Disease. *Am J Med Sci* 2017, 354:117-124.

29. Robins SJ, Lyass A, Zachariah JP, Massaro JM, Vasan RS: Insulin resistance and the relationship of a dyslipidemia to coronary heart disease: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol* 2011, 31:1208-1214.
30. Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, Faas FH, Anderson JW: Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). *Arch Intern Med* 2002, 162:2597-2604.
31. Abbasi F, Brown BW, Jr., Lamendola C, McLaughlin T, Reaven GM: Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol* 2002, 40:937-943.
32. Packard CJ, Shepherd J: Lipoprotein heterogeneity and apolipoprotein B metabolism. *Arterioscler Thromb Vasc Biol* 1997, 17:3542-3556.
33. St-Pierre AC, Cantin B, Dagenais GR, Mauriege P, Bernard PM, Despres JP, Lamarche B: Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol* 2005, 25:553-559.
34. Yokoyama K, Tani S, Matsuo R, Matsumoto N: Increased triglyceride/high-density lipoprotein cholesterol ratio may be associated with reduction in the low-density lipoprotein particle size: assessment of atherosclerotic cardiovascular disease risk. *Heart Vessels* 2019, 34:227-236.
35. Fan X, Liu EY, Hoffman VP, Potts AJ, Sharma B, Henderson DC: Triglyceride/high-density lipoprotein cholesterol ratio: a surrogate to predict insulin resistance and low-density lipoprotein cholesterol particle size in nondiabetic patients with schizophrenia. *J Clin Psychiatry* 2011, 72:806-812.
36. Tsuruya K, Yoshida H, Nagata M, Kitazono T, Hirakata H, Iseki K, Moriyama T, Yamagata K, Yoshida H, Fujimoto S, et al: Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. *Atherosclerosis* 2014, 233:260-267.
37. Moriyama K: The Association between the Triglyceride to High-density Lipoprotein Cholesterol Ratio and Low-density Lipoprotein Subclasses. *Intern Med* 2020, 59:2661-2669.
38. Gasevic D, Frohlich J, Mancini GB, Lear SA: The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort. *Metabolism* 2012, 61:583-589.
39. Ren X, Chen ZA, Zheng S, Han T, Li Y, Liu W, Hu Y: Association between Triglyceride to HDL-C Ratio (TG/HDL-C) and Insulin Resistance in Chinese Patients with Newly Diagnosed Type 2 Diabetes Mellitus. *PLoS One* 2016, 11:e0154345.
40. Azarpazhooh MR, Najafi F, Darbandi M, Kiarasi S, Oduyemi T, Spence JD: Triglyceride/High-Density Lipoprotein Cholesterol Ratio: A Clue to Metabolic Syndrome, Insulin Resistance, and Severe Atherosclerosis. *Lipids* 2021, 56:405-412.
41. An X, Yu D, Zhang R, Zhu J, Du R, Shi Y, Xiong X: Insulin resistance predicts progression of de novo atherosclerotic plaques in patients with coronary heart disease: a one-year follow-up study. *Cardiovasc Diabetol* 2012, 11:71.

42. DeFronzo RA, Ferrannini E: Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 1991, 14:173-194.
43. Sowers JR, Stump CS: Insights into the biology of diabetic vascular disease: what's new? *Am J Hypertens* 2004, 17:2S-6S; quiz A2-4.
44. Wolf G: New insights into the pathophysiology of diabetic nephropathy: from haemodynamics to molecular pathology. *Eur J Clin Invest* 2004, 34:785-796.
45. Orringer CE: PCSK9 inhibition for acute arterial events: more than LDL lowering. *Eur Heart J* 2021, 42:4830-4832.

Figures

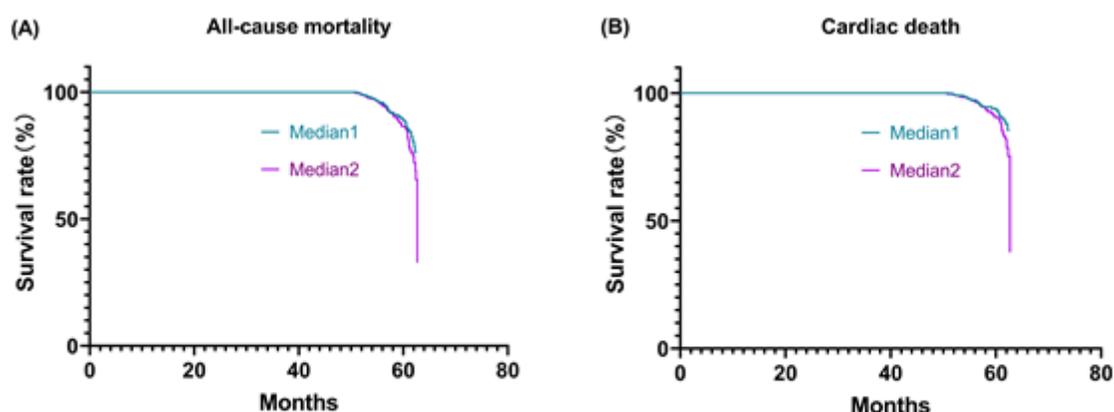


Figure 1. (A) Kaplan-Meier survival curve for all-cause mortality across TG/HDLC ratio median; (B) Kaplan-Meier survival curve for all-cause mortality across TG/HDLC ratio median

Figure 1

Please See image above for figure legend.

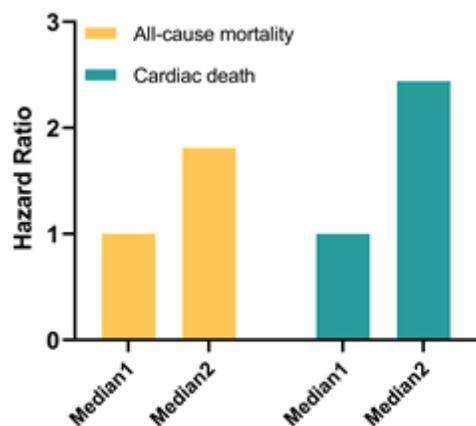


Figure 2. Hazard ratio significantly increased with higher TG/HDLC level for all-cause mortality and cardiac death

Figure 2

Please See image above for figure legend.

Figure 3

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