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
Although diabetic patients with ACS have high mortality, the relationship between TG/HDLC ratio and death risk in patients with DM and new-onset ACS is unclear. Nowadays, the number of research on the TG/HDLC ratio increases gradually, and this lipid indicator is closely related to many diseases. Several previous studies have indicated a positive correlation between TG/HDLC ratio and hypertension [3, 4], insulin resistance [5, 6], metabolic syndrome [7, 8], and fatty liver [9, 10]. In addition, elevated TG/HDLC 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/HDLC 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/HDLC ratio, patients were divided into the following two groups: Median1 (n=880, TG/HDLC ≤ 1.522), Median 2 (n=618, TG/HDLC > 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 (HDLc), low-density lipoprotein cholesterol (LDLc), 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-HDLc level was obtained by subtracting HDLc 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 ± 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
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/HDL 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/HDL ratio (P<0.001), TC (P<0.001), TG (P<0.001), HDLC (P<0.05), 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 Clopidorgrel/Ticagrelor (P<0.05). Moreover, TG and LDLC increased with the growing TG/HDL 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 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

| Endpoint                  | Median1       | Median2       | Crude HR | 95% CI | Crude P-value | Adjusted HR | 95% CI | Adjusted P-value |
|---------------------------|---------------|---------------|----------|--------|---------------|-------------|--------|------------------|
| All-cause mortality       | 165/1760 (9.3%) | 86/980 (9.5%) | 1.00     | 0.92-1.74 | 0.152         | 1.00        | 0.92-1.74 | <0.001          |
| Cardiac death             | 295/1760 (16.5%) | 84/980 (9.5%) | 1.00     | 0.92-1.74 | 0.088         | 1.00        | 0.92-1.74 | <0.001          |
| Non-fatal MI              | 77/1760 (4.4%)  | 84/980 (9.5%) | 0.714    | 0.55-1.46 | 0.074         | 1.00        | 0.55-1.46 | 0.384           |
| Non-fatal stroke          | 435/1760 (24.7%) | 84/980 (9.5%) | 0.498    | 0.36-1.08 | 0.074         | 1.00        | 0.36-1.08 | 0.994           |
| Non-fatal MI or nonfatal stroke | 502/1760 (28.3%) | 262/980 (27.3%) | 0.471    | 0.26-0.82 | 0.074         | 1.00        | 0.26-0.82 | 0.592           |

Table 2 displays the results of COX regression analysis. The TG/HDL-C 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-C 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-C ratio groups in the adjusted Cox regression model. The hazard ratio was higher in the group with a higher TG/HDL-C 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-C 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 an 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/HDLC ratio assessment is clinically significant in risk stratification for patients receiving statin therapy.

The predictive value of the TG/HDLC 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 HDLC 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 (sdLDLC) particles[32]; (2) In the presence of IR and high secretion of VLDL particles, these sdLDLC particles are usually present in high concentrations[33]; (3) Whereas sdLDLC 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/HDLC 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/HDLC 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/HDLC ratio and the death risk in patients with DM and new-onset ACS: (1) Elevated TG level and reduced HDLC play a vital role in the progression of atherosclerosis, which may be related to the TG/HDLC ratio as a marker of LDL particle size[34]. Previous studies have reported that a high TG/HDLC ratio was strongly associated with elevated levels of small, dense LDLC, which was considered very atherogenic[35-37]. (2) TG/HDLC 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/HDLC ratio is related to the severity of atherosclerosis because the total plaque area is positively correlated with TG/HDLC 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, hemoglobin A1c; 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 LDLC; 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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Figures

**Figure 1**

(A) All-cause mortality

(B) Cardiac death

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

**Figure 2**

Hazard ratio significantly increased with higher TG/HDL-C level for all-cause mortality and cardiac death
Please See image above for figure legend.

Figure 3

Please See image above for figure legend.