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Is elevated triglyceride/high-density lipoprotein cholesterol ratio associated with poor prognosis of coronary heart disease? A meta-analysis of prospective studies

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Abstract

Background: Elevated triglycerides (TG) and reduced high-density lipoprotein cholesterol (HDL-C) are recognized as essential and independent hazard factors for total death and major adverse cardiovascular events (MACE) in patients with coronary heart disease (CHD). However, whether the increased TG/HDL-C forecasted the prognosis of CHD is still unknown. Therefore, we performed a meta-analysis to investigate the relationship between the elevated TG/HDL-C ratio and poor prognosis of CHD.

Methods: A systematic literature search was conducted in PubMed, Web of Science, EMBASE, and The Cochrane Library, until August 30, 2021. Prospective observational studies regarding the association between TG/HDL-C and long-term mortality/MACEs in CHD patients were included.

Results: In total, 6 independent prospective studies of 10,222 participants with CHD were enrolled in the systematic and meta-analysis. Our outcomes of the meta-analysis indicated that the elevated TG/HDL-C group had a significantly increased risk of long-term all-cause mortality (hazard ratio [HR] = 2.92, 95% confidence interval [CI]: 1.75–4.86, $P < .05$) and long-term MACEs (HR = 1.56, 95%CI 1.11–2.18, $P < .05$).

Conclusion: In patients with CHD, the present study showed that the high TG/HDL-C was associated with increased risk of long-term all-cause mortality and MACE.

Abbreviations: CHD = coronary heart disease, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, MACE = major adverse cardiovascular events, NOS = Newcastle-Ottawa scale, TG = triglycerides.

Keywords: coronary heart disease, major adverse cardiac events, meta-analysis, mortality, triglyceride to high-density lipoprotein cholesterol ratio

1. Introduction

Coronary heart disease (CHD) is the principal cause of death worldwide and a growing global public health problem.[1] Early risk stratification is particularly significant for the prevention and management of CHD. Some biomarkers, such as troponin I, NT-proBNP, and dyslipidemia were reported to be interrelated with the prognosis of CHD.[2–4] Previous studies[5,6] also indicated that elevated triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C) had been regarded as independent predictors of total mortality and major adverse cardiovascular events (MACE) in CHD patients.

High TG promoted the formation of atherosclerosis by producing small and dense low-density lipoprotein, reducing HDL, promoting blood coagulation and strengthening oxidized modified lipoprotein.[7] HDL-C has a negative correlation with the incidence of CHD. It mainly promotes the reverse cholesterol transport, antioxidant, anti-inflammatory and other mechanisms to achieve anti-atherosclerosis, and low HDL-C is significantly associate with severity of coronary atherosclerosis.[8]

CLG and HTL contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are publicly available.

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The increased TG/HDL-C was considered as an easily available marker of the severity of coronary atherosclerosis.[9–12]

Gaziano reported that the elevated TG/HDL-C ratio strongly predicted the risk of myocardial infarction in a case-control study.[13] A growing body of studies also showed that the high TG/HDL-C ratio was a powerful independent predictor of mortality/MACE in cardiovascular disease.[14–21] However, the predictive values of TG/HDL-C were various in different studies. Therefore, we performed a meta-analysis of published researches to explore the predictive value of TG/HDL-C in CHD patients.

2. Methods

The present meta-analysis was conducted and reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Our data is based on published articles, so there is no need for ethical approval.

2.1. Search strategy

A systematic literature search through August 30, 2021 was performed using the following databases from two independent authors: PubMed, Web of Science, EMBASE, and The Cochrane Library. The following text words and MESH terms were used in different ways of combination to determine studies examining the association between serum TG/HDL-C and the prognosis of CHD: triglyceride to high-density lipoprotein cholesterol, acute coronary syndrome, acute myocardial infarction, and coronary heart disease, non-high-density lipoprotein cholesterol, triglyceride. Manual scanning was conducted for the reference lists of all pertinent studies to capture additional eligible articles.

2.2. Inclusion and exclusion criteria

Studies meeting the following requirements were enrolled: prospective study enrolling CHD patients; clear the calculation the ratio of TG/HDL-C for human participants; at least one of the following cardiovascular outcomes of follow-up were reported: mortality, major adverse cardiovascular events, nonfatal myocardial infarction, heart failure, cardiogenic shock, stroke, recurrent MI and repeated percutaneous coronary intervention or coronary artery bypass grafting; multivariate-adjusted hazard ratio (HR) with corresponding 95% confidence interval (CI) of CHD connected with the highest versus lowest categories of TG/HDL-C was reported.

All retrospective studies, reviews, conference abstracts, animal studies, case-control studies, and other irrelevant clinical trials were excluded. For studies of the same crowd, we included articles with larger sample sizes or more accurate data.

2.3. Data extraction and quality assessment

Two authors collected the following basic information: the surname of author, publication data, geographical location, sample size, follow up time (≥12 months), type of CHD, HR and 95% CI, quality scores, and end-point events. The primary cardiovascular events were included: all-cause mortality or MACE (including acute or old nonfatal MI, stroke, acute heart failure, and cardiogenic shock and revascularization).

The methodological quality of each research was estimated by the Newcastle-Ottawa Scale (NOS) of cohort studies.[22] The NOS ranges from 0 to 9 stars. Score 7 to 9 is high quality, score 4 to 6 is medium quality and score <4 is low quality. By using the "9-star system", we thought studies as higher quality if its score >7 stars.

2.4. Ethics

In this meta-analysis, ethical approval was not necessary, because of no original clinical data was collected or utilized in previously published articles.

2.5. Statistical analysis

STATA version 15.0 statistical software was performed for all data. To assess the relationship between the TG/HDL ratio and clinical outcomes. HR with 95% CI was presented as the standardized risk estimates. I^2 statistic was applied to assess heterogeneity among studies. An I^2 value of <25% represents low level of heterogeneity; 25%–50% moderate level of heterogeneity, and >50% high level of heterogeneity. A value of $I^2 < 50\%$ was considered to be indicative of no significant heterogeneity, and a fixed-effect model was applied. Otherwise, the random effect model was applied.

3. Results

3.1. Literature search and include studies

In the primary literature search, a total of 880 relevant records were included. All retrospective studies, reviews, conference abstracts, animal studies, case-control studies, and other irrelevant clinical trials were excluded after the title and abstract screening. The remaining 10 articles were included. Of these, 4 articles were excluded for the following reasons: no follow-up results; reporting CHD with other diseases; and not reporting all-cause mortality or MACE. Finally, 6 studies were included in the meta-analysis. The detailed selection process was shown in the flow chart (Fig. 1).

3.2. Study characteristics

We identified 6 prospective articles[16–21] reported that the association TG/HDL-C and the prognosis of CHD. The 6 included studies were recorded from 2009 to 2021 and included 10,222 participants. Of 6 studies, 4[17–20] in Asia, 1[16] in America, and 1[21] conducted in Australia.

Table 1 summarizes the main characteristics of enrolled articles regarding the impact of TG/HDL-C ratio on clinical prognosis in CHD participants. The sample size of the 6 included articles ranged from 416 to 7016. The follow-up duration of enrolled CHD participants rated on a scale of 12 to 72 months. Among 6 enrolled studies, 5 articles[16–18,20,21] reported the outcomes of MAC, 4 articles[16,17,19,21] reported all-cause mortality. Based on geographical locations, study population, sample size, and the average age, further subgroup analyses were made to assess the association between prognosis of CHD and TG/HDL-C (Table 2). Moreover, the quality score assessing of the NOS ranged from eight to nine, which was regarded as a relatively high score in all included studies (Table 3).

3.3. Association of the serum TG/HDL-c ratio and long-term mortality/mace

In general, the joint analysis of 6 prospective studies including 10,222 participants describes the relationship between the TG/HDL-C ratio and prognosis of CHD. Comparing the low TG/HDL-C group, the elevated TG/HDL-C ratio was significantly associated with all-cause mortality (HR 2.92, 95%CI 1.75–4.86, $P < .05$) in patients with CHD. The increasing TG/HDL-C was more likely to have high incidence of long-term MACE (HR 1.56, 95%CI 1.11–2.18, $P < .05$), compared the high TG/HDL-C group (Fig. 2).

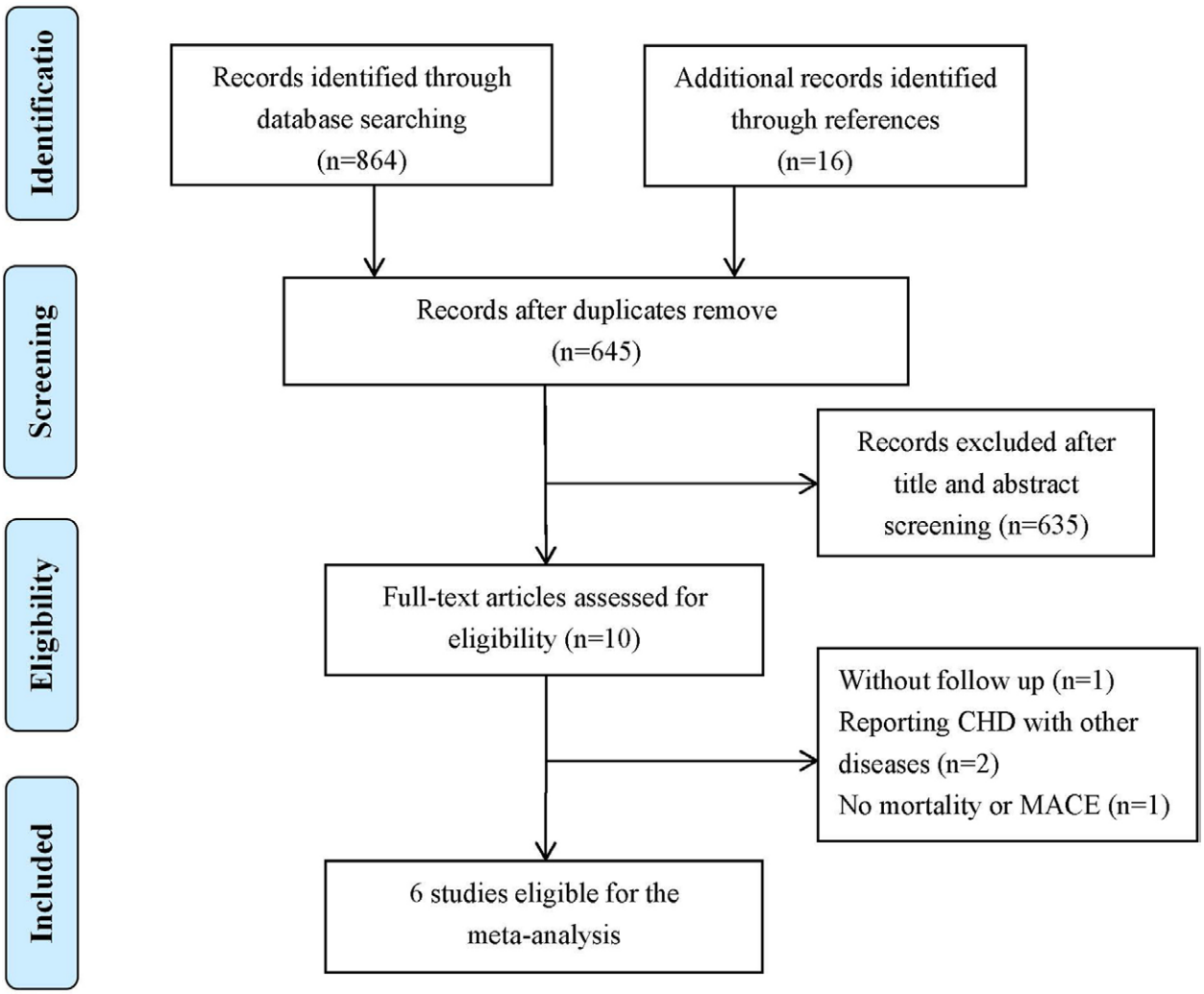

Figure 1. Flow chart outlining selection process for these articles included in the meta-analysis.

Table 1

Main characteristics of the included studies.

Author, yr	Country	Duration	Sample	Mean age (yr)	Study population	Cutoff value	End-point	Follow up (mo)
Bittner V (2009)[16]	America	1996–2000	554	57 ± 11	CHD	3.66	All-cause mortality, cardiovascular events	72
Wan K (2015)[17]	China	2006–2010	416	64 ± 11	ACS	5.32	Death of any cause, MACEs	36
Kim J (2016)[18]	Korea	2005.11–2008.07	7016	62.3 ± 12.3	AMI	3.35	MACEs	12
Matsumoto I(2018)[20]	Japan	2005.01–2015.12	1170	67 ± 10.8	CHD	5.60	MACE	47
Sultani R (2019)[21]	Australia	2009.10–2013.05	482	63.4 ± 11.0	CHD	2.5	All-cause mortality, MACEs	61
Chen HC (2020)[19]	China	2005.01–2014.12	584	62.8 ± 11.5	AMI	3.5	All-cause mortality	12

ACS = acute coronary syndrome, AMI = acute myocardial infarction, CHD = coronary heart disease, MACEs = major adverse cardiac events.

3.4. Subgroup analysis

We conducted four subgroup analyses based on region (Asian and non-Asian), clinical classification of the study population (ACS and CHD), sample size (2000 and <2000) and mean ages (63 and <63). All results of the subgroup analysis were shown in Table 2. Interestingly, compared with the patients of ≥63 years (HR = 1.70, 95%CI 0.93–3.12, P = .085), the elevated TG/HDL-C ratio was better in the patients of <63 years (HR = 1.50, 95%CI 1.12–2.01, P < .05). In the subgroup of CHD patients, I^2 increased to 78.7%. Based on the change of I^2, the sources of heterogeneity might be study population and mean age of enrolled patients.

4. Discussion

As the leading cause of non-infection disease deaths worldwide, CHD has become an increasing and un-negligible public health problem.[1,23,24] Preliminary risk stratification can provide better prevention and management of CHD. Novel biomarkers, such as elevated TG/HDL-C ratio, were reported to be associated with a higher risk of atherosclerotic CHD.[25–27] However, the connection between elevated TG/HDL-C ratio and poor prognosis of CHD remains in dispute. Our meta-analysis showed that a significant positive correlation between the elevated TG/HDL-C and poor prognosis of CHD.

Table 2

The association between the TG/HDL-C ratio and MACE according to different subgroups.

Subgroup		Study (No.)	I^2 (%)	*P* (I^2)	OR	*P* (OR)
Geographic locations	Asia[17,18,20]	3	74.5	<.05	1.50 (0.93, 2.44)	.098
	Non-Asia[16,21]	2	38.3	.203	1.68 (1.15, 2.44)	<.05
Study population	ACS and AMI[17,18]	2	24.8	.249	1.94 (1.16, 3.24)	<.05
	CHD[16,20,21]	3	78.7	<.05	1.40 (0.96, 2.03)	.079
Sample size	<2000[16,17,20,21]	4	78.8	<.05	1.55 (1.05, 2.31)	<.05
	≥2000[18]	1	-	-	1.84 (1.04, 2.59)	<.05
Mean age	<63[16,18]	2	0	.620	1.50 (1.12, 2.01)	<.05
	≥63[17,20,21]	3	84.1	<.05	1.70 (0.93, 3.12)	.085

OR = odds ratio, CHD = coronary heart disease, CI = confidence interval.

Table 3

Newcastle-Ottawa Scale.

	Selection				Comparability		Exposure			
Study	Case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability: basic factors	Comparability: additional actors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate: same rate for both groups	Quality
Bittner V[16]	★	★	★	★		★	★	★	★	8
Wan K[17]	★	★	★	★		★	★	★	★	8
Kim J[18]	★	★	★	★	★	★	★	★	★	9
Chen HC[19]	★	★	★	★		★	★	★	★	8
Matsumoto I[20]	★	★	★	★		★	★	★	★	8
Sultani R[21]	★	★	★	★		★	★	★	★	8

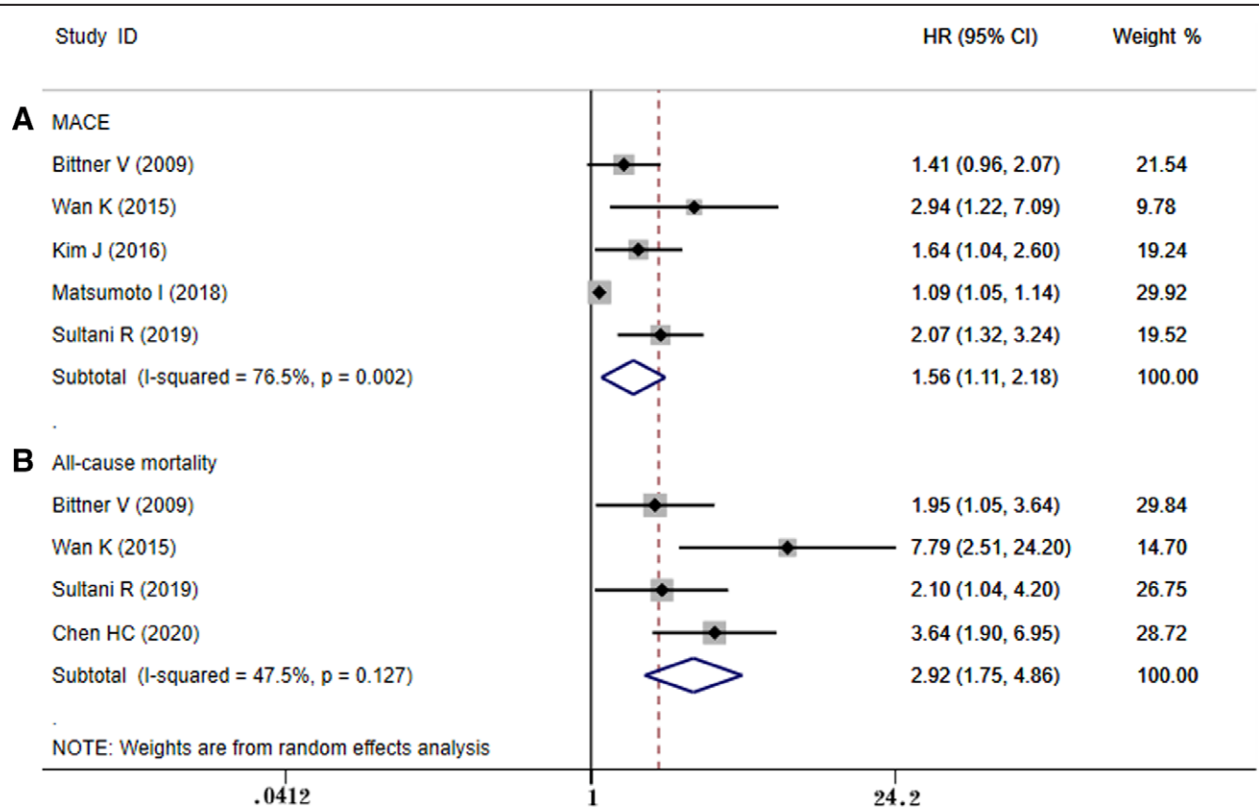

Figure 2. Forest plot of the association between TG/HDL-C and outcomes in patients with CHD. (A) High TG/HDL-C predicted MACE. (B) High TG/HDL-C predicted all-cause mortality. CHD coronary heart disease, TG/HDL-C triglyceride to high-density lipoprotein cholesterol ratio, CI = confidence interval, HR = hazard ratio, MACE = major adverse cardiac events, TG = triglycerides.

High TG could promote the course of CHD by affecting inflammation and atherosclerosis.[28] HDL-C plays its protective effect on the heart mainly through its function in reverse cholesterol transport, which prevents atherosclerosis by transporting cholesterols from peripheral cells to the liver for recycling.[29] In the context of high TG level, the larger very-low-density lipoprotein (VLDL) particle pool conducted to the greater cholesteryl ester transfer protein (CETP) mediated exchange from HDL to VLDL in exchange for TG.[30–33] So the risk of atherosclerotic disease was high when HDL-C increased in the setting of TG-enriched.[26,34]

TG/HDL-C ratio was positively correlated with the degree of coronary atherosclerosis. Jeppesen et al[35] previously showed the TG/HDL-C ratio to be an independent predictor of cardiovascular mortality and the risk of CHD. Other prior reports indicated that the ratio of TG/HDL-C has been considered as an effective marker of powerful risk factors for metabolic syndrome,[36] vascular change and insulin resistance.[37,38]

Our meta-analysis enrolled 6 prospective cohort studies[16–21] to assess the association between the TG/HDL-C ratio and long-term mortality/MACE in patients with CHD. We found that the elevated ratio of TG/HDL-C was correlated with an increased long-term mortality/MACE risk. Among them, five studies checked the effect of TG/HDL-C on long-term MACE, four studies tested the effect of TG/HDL-C on long-term mortality. More relevant studies are needed to explore the prognostic value of TG/HDL-C ratio. Meanwhile, we performed subgroup analysis to corroborate this conclusion. Some factors such as geographic locations of participants, study population, sample size and mean age were analyzed in the subgroup analysis. In the subgroup with mean age <63 and enrolled patients with ACS and AMI, there was no significant heterogeneity among these studies (Table 2). Consequently, the study population and the mean age were possibly the origins of the significant heterogeneity in this meta analysis.

To the best of our knowledge, this is the first meta-analysis to assess the possible relevance between TG/HDL-C and clinical prognosis in participants with CHD. However, several limitations of the current meta-analysis may be considered. Firstly, subgroup analysis based on length of follow-up, geographical location, and the study population had a connection with the between-sample heterogeneity. Secondly, the HR and 95%CI of all-cause mortality was too high, due to the large difference in the sample size of enrolled studies. Further more, the study population and the mean age were possibly the origins of the significant heterogeneity in this meta analysis. Finally, relevance between the elevated TG/HDL-C and adverse prognosis of CHD may be overestimated, due to the lack of adjustment for confounding factors.

5. Conclusion

Our findings of the meta-analysis indicate that the elevated TG/HDL-C ratio was potentially connected with clinical outcomes of CHD participants at increased risk of long-term mortality and long-term MACE. The high TG/HDL-C value stemming from the ratio between TG and HDL-C could be associated with poor prognosis of CHD. Further well-designed researches providing more evidence on TG/HDL-C should be performed to make the findings more convincing and trustworthy.

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Author contributions

Chun-li Guan and Hong-Tao Liu: Design of the study; acquisition and interpretation of data; manuscript preparation and the initial draft; accountable for all aspects of the work. Dong-Hui Chen and Xiao-Qing Quan: Statistical analysis, analysis and interpretation of data; accountable for all aspects of the work. Xue-Yan Duan and Wei-Liang Gao: design of the study; critical review of the draft and contribution to the writing of the manuscript; final approval of the version to be published and accountable to the accuracy or integrity of the work.

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Writing – review & editing: Chun-Li Guan, Hong-Tao Liu, Xue-Yan Duan.

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