The LDL-C/HDL-C ratio and 4-year risk of coronary artery disease: a retrospective study

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Research

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Abstract

Background

Numerous studies have demonstrated that the low-density lipoprotein cholesterol/high-density lipoprotein cholesterol (LDL-C/HDL-C) ratio can reflect the positive correlation index LDL-C and the negative index HDL-C of coronary artery disease (CAD) at the same time, which is increasingly considered as a novel marker to evaluate the risk of CAD. However, whether the short-term evaluation effect of the LDL-C/HDL-C ratio can be maintained during long-term follow-up is unclear. In addition, it is not clear whether the value of LDL-C/HDL-C ratio in the risk assessment of major adverse cardiac events (MACE) varies with different treatments. Our aim of the study was to investigate the link between LDL-C/HDL-C ratio and long-term risk of CAD and find out whether the LDL-C/HDL-C ratio could effectively evaluate the occurrence of MACE in CAD patients under different treatments.

Methods

From May 2013 to November 2015, a total of 2409 patients who underwent coronary angiography (CAG) with or without revascularization therapy were enrolled in this study. They were divided into two groups based on the LDL-C/HDL-C ratio and three groups based on the treatments: medical therapy alone (MTA), percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

Results

In total, 1784 patients (74.1%) were followed for health outcome and 625 patients (25.9%) experienced a MACE event. The median follow-up time was 4.27 years (1560 days). The patients with a higher LDL-C/HDL-C ratio (≥ 2.33) also had a significantly higher incidence of MACE (HR: 1.47, 95% CI: 1.25 to 1.72, $p < 0.001$). The cumulative incidence of rehospitalization for UA (HR: 1.53, 95% CI: 1.27 to 1.84, $p < 0.001$) and rehospitalization for HF (HR: 3.70, 95% CI: 1.22 to 22.25, $p = 0.021$) were significantly higher in high group than in low group. There were no significant differences in MI (HR: 1.25, 95% CI: 0.63 to 2.48, P = 0.521), TLR (HR: 0.98, 95% CI: 0.62 to 1.55, $p = 0.947$), Stroke (HR: 1.65, 95% CI: 0.64 to 4.25, $p = 0.301$) and 4-year all-cause death (HR: 1.45, 95% CI: 0.58 to 3.61, $p = 0.423$). Kaplan-Meier cumulative curve showed that patients with higher LDL-C/HDL-C ratio had a significantly lower MACE-free survival ($p < 0.001$). Multivariate Cox regression analysis demonstrated that LDL-C/HDL-C ratio (HR: 1.34, 95% CI: 1.14 to 1.60, $p < 0.001$) together with age, smoking, hypertension, diabetes mellitus, Syntax score and TG were independent predictors of 4-year MACE in the total CAD population (all $p < 0.05$). Further subgroup analysis showed that age, smoking, Syntax score, TG and LDL-C/HDL-C ratio were the independent predictors of MACE in MAT group (all $p < 0.05$); However, Syntax score and diabetes mellitus were the only independent predictor of MACE in PCI group and the CABG group, respectively (both $p < 0.05$).

Conclusions

In this study, we found that LDL-C/HDL-C ratio was an independent predictor of 4-year MACE in the total CAD population. The value of LDL-C/HDL-C ratio in assessing MACE risk varied among CAD patients with

different treatments.

Background

Coronary artery disease (CAD) resulting from atherosclerosis is one of the major causes of mortality and morbidity worldwide, driven by both environmental and genetic factors [1]. Many studies have shown that lipid concentrations are closely related to the risk of CAD. Blood lipid and lipoprotein constituent are risk factors for coronary atherosclerosis and cardiovascular prognosis in patients with CAD. Numerous evidences have revealed that the decrease of high-density lipoprotein cholesterol (HDL-C) and the increase of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and triglyceride (TG) may contribute to the progression of atherosclerosis [2, 3]. Among them, LDL-C has been considered as one of the main predictors of CAD, and thus in recent decades, LDL-C was recommended as the primary treatment target of lipid management in CAD patients. However, trials have shown that there is still a risk of residual major adverse cardiac events (MACE) in high-risk patients even if the current guideline recommended LDL-C target value (< 70 mg/dl) is reached [4–6]. In contrast, some studies have shown that HDL-C is negatively correlated with the development of CAD [7]. Compared with this single lipid parameter, comprehensive lipid indexes, such as LDL-C/HDL-C, TC/HDL-C, non-HDL-C (TC minus HDL-C), non-HLD-C/HDL-C (atherogenic index, AI), and TC*TG*LDL/HDL-C (lipoprotein combine index, LCI), are considered to be better predictors for CAD [8]. Among these lipid indexes, LDL-C/HDL-C ratio can reflect the positive correlation index LDL-C and the negative index HDL-C of CAD at the same time, which is increasingly considered as a novel marker to evaluate the risk of CAD. However, there is little evidence regarding the predictive value of the LDL-C/HDL-C ratio for detecting adverse cardiovascular events in patients with CAD.

In a recently study by Zhong et al. [9] after an 1-year follow-up of 1937 acute coronary syndromes (ACS) patients with drug-eluting stent (DES) implantation patients after percutaneous coronary intervention (PCI) showed that LDL-C/HDL-C ratio is an independent biomarker for predicting cardiovascular events. However, this study was followed up for only one year and the participants were patients with ACS after DES implantation. Whether the short-term evaluation effect of the LDL-C/HDL-C ratio can be maintained during long-term follow-up is unclear. In addition, it is not clear whether the value of LDL-C/HDL-C ratio in the risk assessment of adverse cardiovascular events varies with different treatments. Therefore, the true value of LDL-C/HDL-C ratio has not been determined in the generalized CAD population. For this reason, we undertook the present study, which aimed at investigating the link between LDL-C/HDL-C ratio and 4-year risk of CAD and finding out whether the LDL-C/HDL-C ratio could effectively evaluate the occurrence of adverse cardiovascular events in CAD patients under different treatments. We now report the 4-year clinical outcomes study to determine the effect of LDL-C/HDL-C ratio on longer-term investigations, treatments and clinical events.

Methods

Study population

This is a retrospective observational study. From May 2013 to November 2015, a total of 2409 patients who underwent coronary angiography (CAG) with or without revascularization therapy were enrolled in this study. In addition, those who with malignant tumours, kidney dysfunction needing dialysis treatment or uncompensated liver cirrhosis were excluded from this study. The primary objective of the study was to assess the predictability of attaining LDL-C/HDL-C ratio on the long-term MACE occurrence in patients with CAD. The secondary objective was to identify whether the value of LDL-C/HDL-C ratio in the risk assessment of adverse cardiovascular events varies with different treatments. The study protocol was approved by the Ethics Committee of Affiliated Hospital of Jining Medical University, Shandong province, China. Because this retrospective observational study was based on data from patient medical records, written informed consent was not obtained from the participants. A flowchart outlining our study was shown in Fig. 1.

Definition

The enrolled patients were divided into two groups based on the LDL-C/HDL-C ratio and three groups based on the treatments: medical therapy alone (MTA), PCI and coronary artery bypass grafting (CABG). CAD was quantitatively defined as a diameter stenosis ≥ 50% in a major epicardial artery, which is consistent with contemporary angiographic guidelines [10]. The CAG examinations were performed using Judkin technique via the radial or femoral artery. Scoring of CAD severity was performed with the Syntax (Synergy Between Percutaneous Coronary Intervention With Taxus) score. The Syntax score (http://www.syntaxscore.com) was developed as an angiographic stratification tool initially used to grade the complexity of coronary lesions and establish evidence-based guidelines for determining the most appropriate revascularization strategy in patients with complex multivessel and left main disease [11]. In patients with left main or multivessel disease, it is recommended that the Syntax score is calculated to assess the anatomical complexity of CAD and the long-term risk of mortality and morbidity after PCI [12–14]. In the current study, it is used to evaluate the anatomical complexity of coronary artery. After the CAG examinations have been confirmed, physicians decided on treatment: medical management or revascularization therapy by means of PCI or CABG. Angiograms were analyzed by two experienced physicians who were blinded to this study.

Essential hypertension (EH) was defined as current or previous therapy for hypertension or systolic blood pressure of at least 140/90 mmHg; Diabetes mellitus (DM) was defined as ongoing oral or insulin therapy or fasting blood glucose (FBG) of at least 7.0 mmol/l and postprandial blood glucose of at least 11.1 mmol/l. Current smokers were subjects who had smoked regularly within the previous 12 months. Body mass index (BMI) was calculated as weight divided by height squared. The cumulative incidence of MACE was investigated during a maximum of 5 years after CAG with or without revascularization therapy. The following events were considered MACE: 1) all-cause death: any death during or after CAG examinations and the followed treatments; 2) non-fatal myocardial infarctions: myocardial infarctions that did not result in death; 3) non-fatal strokes: strokes that did not result in death; 4) target lesion revascularization (TLR): any repeat percutaneous intervention of the target lesion (including 5 mm proximal and 5 mm distal to the target lesion) or surgical bypass of the target vessel performed for

restenosis or other complication involving the target lesion; 5) Rehospitalization for unstable angina (UA) is defined as an event that meets all of the following criteria: (i) Ischemic discomfort ≥ 10 minutes in duration occurring at rest, or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity; (ii) Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms; (iii) New or worsening ST or T wave changes on resting electrocardiogram (ECG), or other definite evidence of inducible myocardial ischemia; 6) Rehospitalization for heart failure (HF) is defined as an event that meets all of the following criteria: (i) The patient is admitted to the hospital with a primary diagnosis of HF; (ii) The patient's length-of-stay in hospital extends for at least 24 hours; (iii) The patient exhibits documented new or worsening symptoms due to HF on presentation; (iv) The patient has objective evidence of new or worsening HF; (v) The patient receives at least one treatment specifically for HF [15]. For those who had ≥ 2 events during the study period, only the first event was included. The study investigators obtained follow-up information at regular intervals via face-to-face or telephone interviews. The follow-up period lasted from the time of recruitment to 31 May 2019 or the date of a MACE.

Data collection

Demographic data from medical record included baseline characteristic, diagnostic data of CAD, cardiovascular risk factors, lipid parameters, in-hospital treatments and MACE outcomes. Lipid parameters used in the data analysis included TC, TG, LDL-C and HDL-C. In addition, the Syntax score was used for assessing the anatomical complexity of coronary artery, and the estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft-Gault formula.

Statistical analysis

All analyses were performed with the use of R software, version 3.5.1 (R Foundation for Statistical Computing). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as percentage. Differences between continuous variables were assessed using an unpaired 2-tailed t test for normally distributed continuous variables and the Mann-Whitney test for skewed variables. Proportions were compared by Chi-square test when appropriate. Univariate Cox regression analyses were performed to explore the entire occurrence of adverse cardiovascular events according to the LDL-C/HDL-C ratio. The adjusted hazard ratio (HR) per 1 SD increase in the corresponding variable and 95% confidence intervals (95% CIs) were calculated. MACE-free survival was estimated and depicted by the Kaplan-Meier method, and differences were assessed by the log-rank test. Multivariate Cox proportional hazard regression analysis using the Stepwise selection (R package "MASS") was performed to evaluate the independent predictors of clinical endpoint. The Stepwise selection is a method of model screening, it includes iteratively adding and deleting predictors to find the subset of variables in the data set, so as to obtain the model with the best performance, that is, the model with reduced prediction error. For all analyses, two-tailed p values < 0.05 were considered statistically significant.

Results

Baseline characteristics

From May, 2013 to November, 2015, a total of 2409 patients who underwent CAG were enrolled in this study. The median LDL-C/HDL-C ratio of all patients was 2.33 and the median follow-up period was 4.27 years (1560 days). The number in low group (lower LDL-C/HDL-C ratio, < 2.33) and high group (higher LDL-C/HDL-C ratio, ≥ 2.33) was 1205 and 1204, respectively. The distribution of various clinical and biological variables is depicted by Table 1. The patients in the low group were older than those in the high group ($p < 0.05$). Compared with the high group, the percentage of diabetes mellitus, STEMI, in-hospital revascularization (PCI & CABG) and β-blocker therapy in the low group was lower (all $p < 0.05$). By contrast, the percentages of coronary stent history, unstable angina, in-hospital MTA were higher in low group (all $p < 0.001$). There were significant differences in the level of BMI, diastolic BP, Syntax score, TC, TG, LDL-C, HDL-C, FBG, Uric acid, eGFR and LDL-C/HDL-C ratio between the two groups (all $p < 0.05$). Otherwise, there were no significant differences in other characteristics between the two groups (Table 1). The characteristics of the in-hospital treatments subgroup are also summarized in Table 1: 1123 in the MTA group, 984 in the PCI group and 302 in the CABG group.

Table 1

Baseline Characteristics of participants

Characteristics	Overall (n = 2409)	Low (n = 1205)	High (n = 1204)	P-value
Age (years)	61.33 ± 9.33	61.74 ± 9.12	60.91 ± 9.53	0.029
Male, n(%)	1476 (61.27)	724 (60.08)	752 (62.46)	0.231
BMI (kg/m^2)	25.44 ± 3.10	25.14 ± 3.02	25.74 ± 3.15	< 0.001
Current smoking, n(%)	1180 (48.98)	575 (47.72)	605 (50.25)	0.214
Systolic BP (mmHg)	136.11 ± 20.45	135.80 ± 20.16	136.42 ± 20.74	0.458
Diastolic BP(mmHg)	80.58 ± 12.97	80.06 ± 12.63	81.10 ± 13.28	0.049
Hypertension, n(%)	1383 (57.41)	692 (57.43)	691 (57.39)	0.986
Diabetes mellitus, n(%)	576 (23.91)	256 (21.25)	320 (26.58)	0.002
History of Heart failure, n(%)	61 (2.53)	28 (2.32)	33 (2.74)	0.515
History of AMI, n(%)	176 (7.31)	78 (6.47)	98 (8.14)	0.116
History of stroke, n(%)	271 (11.25)	135 (11.20)	136 (11.30)	0.943
History of coronary stent, n(%)	266 (11.04)	158 (13.11)	108 (8.97)	0.001
History of CABG, n(%)	7 (0.29)	3 (0.25)	4 (0.33)	0.726
Clinical presentation				
Unstable angina, n (%)	1961 (81.40)	1020 (84.65)	941 (78.16)	< 0.001
NSTEMI, n (%)	79 (3.28)	32 (2.66)	47 (3.90)	0.085
STEMI, n (%)	325 (13.49)	134 (11.12)	191 (15.86)	< 0.001
Syntax score	14.48 ± 9.73	12.97 ± 9.22	16.00 ± 10.00	< 0.001
In-hospital treatments				
MTA, n (%)	1123 (46.62)	616 (51.12)	507 (42.11)	< 0.001
PCI, n (%)	984 (40.85)	468 (38.84)	516 (42.86)	< 0.001

Data are shown as mean ± standard deviation or percentages (n). P values from analysis of the unpaired 2-tailed t test, Mann-Whitney test, or Chi-square tests. Two-tailed $p < 0.05$ was considered statistically significant. BP blood pressure, BMI body mass index, NSTEMI non-ST elevation myocardial infarction, STEMI ST elevation myocardial infarction, MTA medical therapy alone, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, TC total cholesterol, TG triglycerides, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, FBG fasting blood glucose, ALT alanine aminotransferase, eGFR estimated glomerular filtration rate

Characteristics	Overall (n = 2409)	Low (n = 1205)	High (n = 1204)	P-value
CABG, n (%)	302 (12.54)	121 (10.04)	181 (15.033)	< 0.001
Medications				
Aspirin, n(%)	2357 (97.84)	1173 (97.34)	1184 (98.34)	0.093
Clopidogrel, n(%)	2108 (87.51)	1043 (86.56)	1065 (88.46)	0.159
β-blockers, n(%)	1824 (75.72)	877 (72.78)	947 (78.65)	< 0.001
Statins, n(%)	2178 (90.41)	1089 (90.37)	1059 (90.45)	0.950
ACEI/ARB, n(%)	973 (40.39)	498 (41.33)	475 (39.45)	0.348
Calcium blockers, n(%)	814 (33.79)	426 (35.35)	388 (32.23)	0.105
Laboratory parameters				
TC (mmol/L)	4.56 ± 1.04	4.11 ± 0.84	5.00 ± 1.03	< 0.001
TG (mmol/L)	1.62 ± 1.17	1.50 ± 1.27	1.75 ± 1.05	< 0.001
LDL-C (mmol/L)	2.69 ± 0.84	2.19 ± 0.58	3.19 ± 0.75	< 0.001
HDL-C (mmol/L)	1.14 ± 0.28	1.25 ± 0.30	1.04 ± 0.20	< 0.001
FBG (mmol/L)	6.04 ± 2.22	5.83 ± 1.89	6.26 ± 2.48	< 0.001
ALT (U/L)	32.39 ± 39.32	32.62 ± 44.02	32.16 ± 33.99	0.774
Uric acid (mg/dl)	305.76 ± 87.23	299.01 ± 86.20	312.52 ± 87.77	< 0.001
Creatinine (mg/dl)	62.79 ± 17.35	62.52 ± 18.31	63.05 ± 16.33	0.453
eGFR (ml/min/1.73 m^2)	107.32 ± 37.34	105.42 ± 31.27	109.22 ± 42.48	0.013
LDL-C/HDL-C ratio	2.45 ± 0.89	1.79 ± 0.38	3.11 ± 0.74	< 0.001

Data are shown as mean ± standard deviation or percentages (n). P values from analysis of the unpaired 2-tailed t test, Mann-Whitney test, or Chi-square tests. Two-tailed $p < 0.05$ was considered statistically significant. BP blood pressure, BMI body mass index, NSTEMI non-ST elevation myocardial infarction, STEMI ST elevation myocardial infarction, MTA medical therapy alone, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker, TC total cholesterol, TG triglycerides, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, FBG fasting blood glucose, ALT alanine aminotransferase, eGFR estimated glomerular filtration rate

Clinical outcomes

In total, 1784 patients (74.1%) were followed for health outcome and 625 patients (25.9%) experienced a MACE event. The median follow-up time was 4.27 years (1560 days). The univariable Cox regression analysis demonstrated that the patients with a higher LDL-C/HDL-C ratio (≥ 2.33) also had a significantly

higher incidence of MACE (HR: 1.47, 95% CI: 1.25 to 1.72, p < 0.001). The cumulative incidence of rehospitalization for UA (HR: 1.53, 95% CI: 1.27 to 1.84, p < 0.001) and rehospitalization for HF (HR: 3.70, 95% CI: 1.22 to 22.25, p = 0.021) were significantly higher in high group than in low group. There were no significant differences in MI (HR: 1.25, 95% CI: 0.63 to 2.48, P = 0.521), TLR (HR: 0.98, 95% CI: 0.62 to 1.55, p = 0.947), Stroke (HR: 1.65, 95% CI: 0.64 to 4.25, p = 0.301) and 4-year all-cause death (HR: 1.45, 95% CI: 0.58 to 3.61, p = 0.423) (Table 2). As depicted by the Kaplan-Meier cumulative curve, patients with a higher LDL-C/HDL-C ratio (≥ 2.33) showed a significantly lower MACE-free survival (p < 0.001, Fig. 2).

Table 2
Clinical outcome up to 4-year

	Low (n = 1205)	High (n = 1204)	HR (95% CI)	P value
Rehospitalization for UA	189(15.68)	274(22.75)	1.53 (1.27 to 1.84)	< 0.001
Rehospitalization for HF	4(0.33)	14(1.16)	3.70 (1.22 to 11.25)	0.021
MI	15(1.25)	18(1.50)	1.25 (0.63 to 2.48)	0.521
TLR	38(3.15)	36(2.99)	0.98 (0.62 to 1.55)	0.947
Stroke	7(0.58)	11(0.91)	1.65 (0.64 to 4.25)	0.301
All-cause death	8(0.66)	11(0.91)	1.45 (0.58 to 3.61)	0.423
MACE	261(21.66)	364(30.23)	1.47 (1.25 to 1.72)	< 0.001

P values were from univariate Cox regression. Two-tailed p < 0.05 was considered statistically significant. HR hazard ratio, CI confidence interval, UA unstable angina, HF heart failure, MI myocardial infarction, TLR target lesion revascularization, MACE major adverse cardiac events

To determine whether the traditional clinical prognostic factors were associated with MACE, we performed univariate Cox regression analysis. In the univariate analysis, all the traditional factors except eGFR were associated with MACE. LDL-C/HDL-C ratio was also correlated with MACE (HR: 1.47, 95% CI: 1.25 to 1.72, p < 0.001) (Table 3). To further eliminate confounding factors, multivariate Cox regression analysis and stepwise selection were made. In model 1, after adjusting for the traditional clinical prognostic factors, we found that age, smoking, hypertension, diabetes mellitus, Syntax score, TG and LDL-C/HDL-C ratio were independent predictors of 4-year MACE in the total CAD population (all p < 0.05). Further subgroup analysis showed that age, smoking, Syntax score, TG and LDL-C/HDL-C ratio were the independent predictors of MACE in MAT group (all p < 0.05); However, Syntax score and diabetes mellitus were the only independent predictor of MACE in PCI group and the CABG group, respectively (both p < 0.05) (Table 4). The only difference between model 2 and model 1 was that the factor Syntax score was removed. After regression analysis, LDL-C/HDL-C ratio (HR: 1.30, 95% CI: 1.03 to 1.64, p = 0.024) was the only independent risk factor for MACE in PCI group, while diabetes mellitus (HR: 1.91, 95% CI: 1.15 to 3.17, p = 0.013) was the only independent risk factor for MACE in CABG group (Table 5).

Table 3

Univariate Cox regression for the independent predictors of MACE

Variables	HR (95% CI)	P value
Age	1.01 (1.00, 1.02)	0.014
Gender (male)	1.21 (1.03, 1.42)	0.024
BMI	1.04 (1.01, 1.06)	0.005
Smoking	1.23 (1.05, 1.43)	0.011
Hypertension	1.27 (1.08, 1.49)	0.004
Diabetes mellitus	1.34 (1.12, 1.59)	0.001
Syntax score	1.03 (1.02, 1.03)	< 0.001
Uric acid	1.00 (1.00, 1.00)	0.005
eGFR	1.00 (1.00, 1.00)	0.182
TG	1.09 (1.03, 1.15)	0.003
LDL-C/HDL-C (ratio ≥ 2.33)	1.47 (1.25, 1.72)	< 0.001
P values were from Cox proportional hazard regression. Two-tailed p < 0.05 was considered statistically significant. MACE major adverse cardiac events, HR hazard ratio, CI confidence interval, BMI body mass index, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, eGFR estimated glomerular filtration rate, TG triglycerides		
Additional files		

Table 4

Multivariate Cox regression for the independent predictors of MACE (model 1)

Variables	All participants		MTA group		PCI group		CABG group	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (1.00, 1.02)	0.014	1.02 (1.00, 1.03)	0.023	1.00 (0.99, 1.02)	0.298	1.01 (0.98, 1.05)	0.403
Gender (male)	1.10 (0.87, 1.37)	0.458	0.89(0.62, 1.27)	0.515	1.21 (0.87, 1.68)	0.250	1.11 (0.52, 2.38)	0.779
BMI	1.01 (0.99, 1.04)	0.361	1.01 (0.97, 1.05)	0.564	1.01 (0.97, 1.05)	0.543	1.01 (0.91, 1.11)	0.886
Smoking	1.22 (1.03, 1.44)	0.018	1.46 (1.14, 1.86)	0.003	0.85 (0.63, 1.15)	0.291	1.15 (0.57, 2.35)	0.694
Hypertension	1.21 (1.02, 1.42)	0.025	1.18 (0.91, 1.54)	0.203	1.22 (0.97, 1.54)	0.086	1.31 (0.76, 2.27)	0.336
Diabetes mellitus	1.23 (1.03, 1.48)	0.024	1.25 (0.95, 1.65)	0.117	1.02 (0.78, 1.34)	0.886	1.91 (1.15, 3.17)	0.013
Syntax score	1.02 (1.01, 1.03)	< 0.001	1.06 (1.05, 1.07)	< 0.001	1.02 (1.00, 1.03)	0.040	0.98 (0.95, 1.01)	0.291
Uric acid	1.00 (1.00, 1.00)	0.084	1.00 (1.00, 1.00)	0.725	1.00 (1.00, 1.00)	0.479	1.00 (1.00, 1.00)	0.470
TG	1.07 (1.01, 1.14)	0.028	0.16 (1.06, 1.28)	0.002	1.07 (0.96, 1.19)	0.238	0.97 (0.83, 1.13)	0.678
LDL-C/HDL-C (ratio ≥ 2.33)	1.34 (1.14, 1.60)	< 0.001	1.43 (1.12, 1.83)	0.004	1.25 (0.99, 1.58)	0.063	1.47 (0.84, 2.54)	0.174

Model 1 adjusted for: age, gender (male), BMI, smoking, hypertension, diabetes mellitus, Syntax score, uric acid, TG and LDL-C/HDL-C (ratio ≥ 2.33). P values were from Cox proportional hazard regression. Two-tailed $p < 0.05$ was considered statistically significant. MACE major adverse cardiac events, MTA medical therapy alone, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, HR hazard ratio, CI confidence interval, BMI body mass index, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglycerides

Table 5
Multivariate Cox regression for the independent predictors of MACE (model 2)

Variables	PCI group		CABG group	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.01 (1.00, 1.02)	0.163	1.01 (0.98, 1.05)	0.424
Gender (male)	1.23 (0.89, 1.70)	0.219	1.14 (0.53, 2.43)	0.736
BMI	1.02 (0.98, 1.05)	0.460	1.00 (0.91, 1.10)	0.978
Smoking	0.86 (0.64, 1.16)	0.320	1.14 (0.56, 2.32)	0.720
Hypertension	1.18 (0.93, 1.50)	0.164	1.31 (0.75, 2.26)	0.341
Diabetes mellitus	1.03 (0.79, 1.35)	0.817	1.91 (1.15, 3.17)	0.013
Uric acid	1.00 (1.00, 1.00)	0.529	1.00 (1.00, 1.00)	0.448
TG	1.07 (0.96, 1.19)	0.251	0.96 (0.82, 1.12)	0.607
LDL-C/HDL-C (ratio ≥ 2.33)	1.30 (1.03, 1.64)	0.024	1.46 (0.84, 2.55)	0.176

Model 2 adjusted for: age, gender (male), BMI, smoking, hypertension, diabetes mellitus, uric acid, TG and LDL-C/HDL-C (ratio ≥ 2.33). P values were from Cox proportional hazard regression. Two-tailed p < 0.05 was considered statistically significant. MACE major adverse cardiac events, MTA medical therapy alone, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, HR hazard ratio, CI confidence interval, BMI body mass index, LDL-C low-density lipoprotein cholesterol, HDL-C high-density lipoprotein cholesterol, TG triglycerides

Discussion

To the best of our knowledge, this is the first time to observe the independent association between LDL-C/HDL-C ratio and long-term risk of MACE in CAD patients with different treatments. The major findings can be summarized as follows: (1) LDL-C/HDL-C ratio was an independent predictor of 4-year MACE in the total CAD population. A higher LDL-C/HDL-C ratio (≥ 2.33) also had a significantly higher incidence of MACE; Age, smoking, hypertension, diabetes mellitus, Syntax score and TG were also independent predictors in this regard; (2) The value of LDL-C/HDL-C ratio in assessing MACE risk varied among CAD patients with different treatments. (3) The LDL-C/HDL-C ratio was an independent predictor of 4-year MACE for CAD patients in-hospital medical therapy alone, while age, smoking, Syntax score and TG were also independent predictors of MACE in this population; (4) Syntax score was the only independent predictor of MACE in patients receiving PCIs, while diabetes mellitus was the only independent predictor of MACE in patients undergoing CABG.

Numerous epidemiological studies, Mendelian randomization studies, and randomized controlled trials (RCTs) have consistently demonstrated a log-linear relationship between the absolute changes in plasma LDL-C and the risk of CAD. The remarkable consistency among these studies provides compelling

evidence that LDL-C is causally associated with the risk of CAD, and that lowering LDL-C reduces the risk of CAD proportionally to the absolute achieved reduction in LDL-C [16–20]. However, despite the success of LDL-C lowering, it is also clear from the evidence that the persistence of a high CAD risk, as a concept called residual risk, are notable after using lipid-lowering agents. In the 4S trial, patients treated with statin therapy experienced CAD event rates approximating 19% (compared to 28% with placebo) over the 5-year study period [16, 20–23]. The inverse association between plasma HDL-C and the risk of CAD is among the most consistent and reproducible associations in observational epidemiology [20, 24]. LDL-C/HDL-C ratio can reflect the positive correlation index LDL-C and the negative index HDL-C of CAD at the same time, which is increasingly considered as a novel marker to evaluate the risk of CAD. In the previous work, LDL-C/HDL-C has been regarded as an excellent marker for CAD [25]. More recently, Zhong et al. investigate the impact of LDL-C/HDL-C ratio on 1-year prognosis of DES implantation patients after PCI. 1937 patients with ACS were divided into two groups based on the ratio of LDL-C/HDL-C. The cumulative incidence of MACE (HR: 1.54, 95% CI: 1.24 to 1.91, $p < 0.001$) were significantly higher in high group than in low group. Cox regression revealed that age, diabetes mellitus and LDL-C/HDL-C ratio (HR: 1.638, 95% CI: 1.260 to 2.218, $p < 0.001$) were independent predictors of 1-year MACE [9]. This is similar to the regression of our PCI subgroup in the case of the unadjusted variable Syntax score (Table 5, model 2). However, in our PCI subgroup, Cox regression with Syntax score showed that the Syntax score was the only independent predictor, not the LDL-C/HDL-C ratio (Table 4, model 1).

The Syntax score reflects a comprehensive angiographic assessment of the coronary vasculature, with 0 as the lowest score, and higher scores (no upper limit) indicating more complex coronary anatomy [14]. The evaluation of CAD risk should consider anatomic risk criteria in the context of the overall patient risk profile [26]. In current study, it was used in particular to evaluate the anatomical complexity of coronary artery. In 2016, Bettinger et al. Studied 13 819 patients in the ACUITY trial and undergoing CAG. They found In patients with ACS undergoing medical therapy the Syntax score was shown to be a strong predictor of 1-year MACE, including mortality [27]. This is consistent with the results of our MTA subgroup (Table 4). Studies have confirmed that he discriminative capacity of Syntax score on long-term outcomes was relevant in the PCI group but not in the CABG group [28, 29]. The MAIN-COMPARE (Ten-Year Outcomes of Stents Versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease) study recently reported that, in each revascularization group, conventional tertiles of Syntax score had a differential prognostic impact on 10-year clinical outcomes in the PCI arm but not in the CABG arm [30]. Consistent with this, in our study, Syntax score was found to be the only independent predictor of MACE in PCI subgroup, but not in CABG subgroup (Table 4). With CABG treatment, graft vessels usually bypass the entire diseased lesion. Therefore, if there is a disease-free point at the mid to distal site of the coronary artery with a satisfactory anastomosis, Syntax score reflecting lesion length, heavy calcification, or angulations cannot be related to adverse outcomes in the CABG group. In contrast, high baseline Syntax score in PCI treatment is associated with the use of more stents, longer stents, and bifurcation stent techniques, which were usually associated with worse clinical outcomes [30, 31]. We reconfirmed this view by performing regression analysis of the data of the PCI subgroup by model 1 (incorporating Syntax score) and model 2(excluding Syntax score), respectively (Table 4, Table 5). In the case of the

unadjusted variable Syntax score in PCI subgroup (Table 5, model 2), the regression results will be similar to those of Zhong et al. : LDL-C/HDL-C ratio was the independent predictor of MACE in PCI patients [9].

We acknowledge that there are some limitations of the trial. Fist, this is a single-center retrospective observational study and readers should be cautious about generalization of these results to other populations worldwide. Second, although collection of clinical information, invasive data, and laboratory data was comprehensive, this study was retrospective in nature and not all data were collected in all patients. We did not enroll consecutive patients and had some patients lost at follow-up, possibly leading to under recognition of angina and heart failure recurrence. Third, due to the inherent limitations of retrospective study, we could not inform whether all the enrolled patients have received optimal medical treatment (OMT) or not. Well-designed randomized controlled trials are needed to solve these problems. Additionally, because we could not precisely differentiate cardiovascular death in the retrospective cohort, we included all-cause mortality in the composite endpoint. Instead, to minimize the potential influence of non-cardiovascular death, we excluded patients who had malignancy and severe kidney dysfunctions from the analysis.

CAD may develop from the erosion or rupture of obstructive or nonobstructive coronary atherosclerotic plaques. Non-obstructive and obstructive CAD were defined by at least 1 coronary artery with a < 50% or ≥ 50% stenosis, respectively. Large retrospective studies of patients referred for nonurgent angiography demonstrated a prevalence of non-obstructive CAD of between 20% and 60% of all referrals. Furthermore, while classically non-obstructive CAD had not been thought to be associated with increased risk of mortality or cardiovascular events, more recent evidence suggests that certain subpopulations with non-obstructive CAD are at heightened risk [26, 32–35]. In our study, CAD was quantitatively defined as a diameter stenosis ≥ 50% in a major epicardial artery. However, non-obstructive CAD with luminal stenosis < 50% were excluded from this study. The findings of this study cannot be used for these people. Therefore, there is a certain deficiency in the universality and extrapolation of research. A large, multicenter study incorporating the non-obstructive CAD population is needed to validate our findings and reduce selection bias.

Conclusions

In this study, we found that LDL-C/HDL-C ratio was an independent predictor of 4-year MACE in the total CAD population. The value of LDL-C/HDL-C ratio in assessing MACE risk varied among CAD patients with different treatments.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitor; ACS: Acute coronary syndromes; AI: Atherogenic index; ALT: Alanine aminotransferase; AMI: Acute myocardial infarction; ARB: Angiotensin receptor blocker; β-blockers: Beta-receptor blockers; BP: Blood pressure; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CAG: Coronary angiography; CCB: Calcium channel-blocking; CI: Confidence

interval; DES: Drug-eluting stents; DM: Diabetes mellitus; ECG: Electrocardiogram; EH: Essential hypertension; eGFR: estimated glomerular filtration rate; FBG: Fasting blood glucose; HDL-C: High-density lipoprotein cholesterol; HF: Heart failure; HR: Hazard ratio; LCI: Lipoprotein combine index; LDL-C: Low-density lipoprotein cholesterol; MACE: Major adverse cardiac events; MTA: Medical therapy alone; NSTEMI: Non-ST elevation myocardial infarction; OMT: Optimal medical treatment; PCI: Percutaneous coronary intervention; RCTs: Randomized controlled trials; SD: Standard deviation; STEMI: ST elevation myocardial infarction; Syntax: Synergy between percutaneous coronary intervention with Taxus; TC: Total cholesterol; TG: Triglycerides; TLR: Target lesion revascularization; UA: Unstable angina.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Conception and research design: Shaohui Zhang and Qiang Su; Manuscript writing and discussion of results: Shaohui Zhang, Qiang Su and Xueying Chen; Data collection: Shaohui Zhang, Qiang Su, Yongliang Zhao, Xiangting Li, Wen Dai, Guoliang Yang, Lixin Liu, which contributed equally; Statistical analysis: Shaohui Zhang and Xueying Chen. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

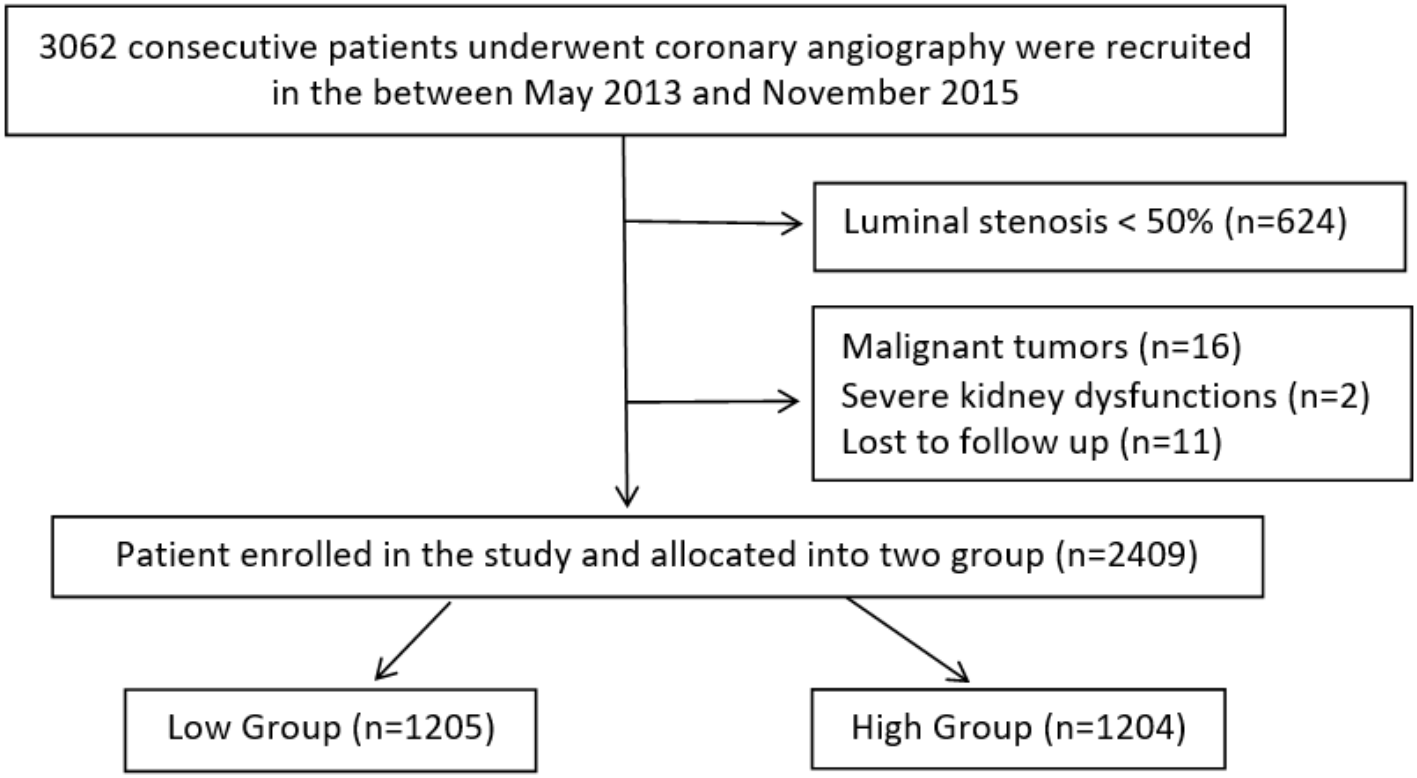

Figure 1

The flow chart of the study

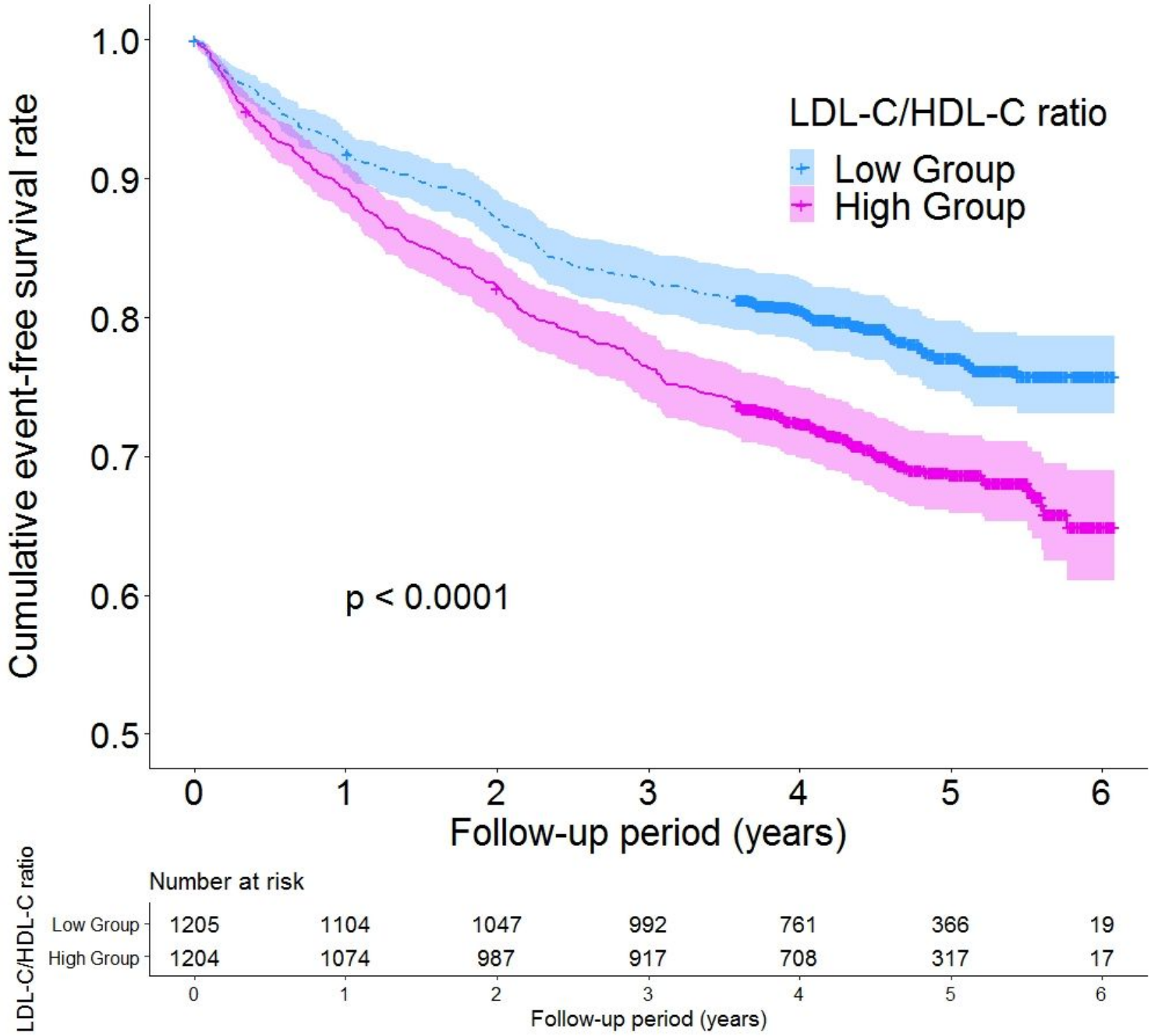

Figure 2

Kaplan-Meier curves displaying the 4-year MACE-free survival related to LDL-C/HDL-C ratio