# Low-density Lipoprotein Cholesterol/High-density Lipoprotein Cholesterol Ratio as Predictor of First Acute Myocardial Infarction and Major Adverse Cardiovascular Event after Intervention in Young Males

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To the Editor: Acute myocardial infarction (AMI) is an unstable ischemic syndrome induced event of myocardial necrosis.[1] Although it is well known that lipid abnormalities are linked to AMI risk, the optimal lipid parameter for risk prediction is unclear. Analyses from the INTERHEART study demonstrated the role of low-density lipoprotein cholesterol (LDL-C)/high-density lipoprotein cholesterol (HDL-C) ratio and triglycerides (TG)/HDL-C ratio in AMI, in addition to that of LDL-C and HDL-C absolute values,[2,3] prompting the search for optimal and reliable markers for AMI. Furthermore, lipid abnormalities are affected by ethnicity, age, and gender.[3,4] However, limited data are available for young Chinese males. The present study aimed to evaluate the characteristics of plasma lipids and their association with the risk and clinical outcome of a first AMI in this population.

Between January 2013 and 2014, this case-control study enrolled 267 male AMI patients aged 18–44 years who were hospitalized in the Department of Cardiology at Beijing Anzhen Hospital, as well as 247 age-matched males who received coronary angiography and were free from coronary heart disease (CHD). Patients were diagnosed as AMI if they met the following criteria: elevated myocardial enzyme levels (cardiac troponin I, creatine kinase [CK], and CK-muscle/brain), typical electrocardiogram changes, and typical chest pain >30 min. During the study, 32 out of 299 consecutive cases were excluded from the study. The exclusion criteria included a history of prior myocardial infarction (MI), history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting, heart valvular disease, acute stroke, serious liver or kidney disease, chronic consumption disease, thyroid dysfunction or cancer. Lipid lowering drug therapy recently was not allowed. All patients underwent coronary angiography using the Judkins or Sones technique during hospitalization. Coronary artery stenosis was defined as >50% reduction in lumen diameter of any of the 3 coronary arteries (left anterior descending artery, left circumflex artery, and right coronary artery) or their primary branches. Multi-vessel lesions were defined as lesions involving more than two coronary arteries. The study was approved by the Ethics Committee of Beijing Anzhen Hospital of the Capital University of Medical Sciences (No. 2016004X) and was conducted in accordance with the *Declaration of Helsinki*. Written informed consent was provided by each participant.

Baseline demographic characteristics and concomitant diseases were collected during hospitalization by interview.[5] All statistical analyses were conducted using SPSS version 22.0 software (IBM Corp., Chicago, IL, USA). Categorical variables were presented as percentages, and the differences between groups were valued using the Chi-square test. Shapiro-Wilk test of normality distribution was performed for quantitative data. Normally distributed continuous data were expressed as mean ± standard deviations (SD), and differences between groups were compared using the Student's *t*-test. Variables with a skewed normal distribution were presented as medians (interquartile range [IQR]), and the intergroup differences were determined using the Mann-Whitney *U*-test. The step-wise multivariable logistic regression analysis was conducted to evaluate the risk factors for AMI and multi-vessel lesions. All of the odds ratios (*OR*s), 95% confidence intervals (*CI*s) were calculated. Receiver operating characteristic (ROC) curve and Youden's index (sensitivity + specificity − 1) were used to determine the optimal cutoff value of the key quantitative risk factor. After discharge, AMI patients were followed up for 2 years by face-to-face appointment or telephone interview, and data including the

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occurrence of major adverse cardiovascular events (MACEs) such as the main cause of death, nonfatal MI, arrhythmia (ventricular tachycardia or ventricular fibrillation), readmission for acute coronary syndrome, or revascularization (coronary angioplasty or coronary artery bypass graft) were collected. The cumulative MACE-free curves of different risk groups were drawn in the Kaplan-Meier manner and compared with the log-rank test. Cox proportional hazards modeling was used to assess the independent prognostic factors for occurrence of MACE. Hazard ratios (*HR*s) were presented with 95% *CI*s to show the risk of an event when the factor was present. Significance was defined at the 5% level using a two-tailed test.

Among the 267 AMI patients, 248 (92.9%) cases received PCI. Lipid data were available for all cases and controls. Our previous study demonstrated a higher level of LDL-C in AMI cases compared with controls.[5] In the present study, we found that AMI patients also showed higher ratios of LDL-C/HDL-C (median [IQR]: 2.95 [2.51, 3.92] vs. 2.60 [2.00, 3.05], $P < 0.001$) and TG/HDL-C (2.11 [1.55, 3.09] vs. 1.61 [1.02, 2.41], $P < 0.001$). To further determine which lipid characteristic was an independent risk factor for AMI, step-wise multivariable logistic regression analysis was conducted. Among 8 potential risk factors (LDL-C/HDL-C, hemoglobin, blood urea nitrogen, uric acid, hypertension, diabetes, smoking, family history of premature, CHD), only LDL-C/HDL-C ratio was strongly associated with the risk of AMI ($P = 0.011$; *OR* = 1.416; 95% *CI*: 1.083–1.851).

According to ROC analysis, LDL-C/HDL-C ratio could be used to predict AMI with an area under the curve (AUC) of 0.646 (95% *CI*: 0.589–0.693; $P < 0.001$). The Youden cutoff point for LDL-C/HDL-C ratio was 3.36, suggesting that an LDL-C/HDL-C ratio higher than 3.36 was associated with increased risk of AMI. We further determined the optimal cutoff value for different age subgroups. The results showed that LDL-C/HDL-C ratio predicted AMI with an AUC of 0.603 (95% *CI*: 0.533–0.673; $P = 0.004$) for the population aged <40 years and 0.699 (95% *CI*: 0.634–0.765; $P < 0.001$) for those aged ≥40 years. Based on the Youden cutoff point, an LDL-C/HDL-C ratio higher than 3.78 and 2.68 predicted high risk of AMI for populations aged <40 and ≥40 years, respectively.

Among the 267 AMI patients, 49 experienced a MACE during the follow-up of 2 years. We further investigated whether LDL-C/HDL-C ratio was a prognostic factor for MACE. The 267 AMI patients were divided into low (*n* = 168) and high (*n* = 99) LDL-C/HDL-C groups, according to the cutoff point of 3.36. Kaplan-Meier analysis showed significant differences between groups [$P < 0.001$; log rank, $\chi^2 = 55.965$; Figure 1].

There were significant differences between the low- and high-LDL-C/HDL-C groups in TG, TC, LDL-C, HDL-C, TG/HDL-C ratio, diabetes, smoking, alcohol, family history of premature CHD, and vessel lesions, which were included in multivariate Cox regression analysis, as well as LDL-C/HDL-C ratio (the categorical variable). Five independent prognostic factors for MACE were identified, among which LDL-C/HDL-C ratio was the strongest ($P < 0.001$; *HR* = 4.381; 95% *CI*: 1.971–9.735).

In addition to the AMI risk, we also evaluated whether and which lipid parameter was associated with disease severity. Based on the results of coronary angiography, AMI patients were divided into single-vessel lesion and multi-vessel lesion groups. The prevalence of potential risk factors was higher in the multi-vessel lesion group than in the single-vessel lesion group, including hypertension ($P < 0.001$), diabetes ($P = 0.003$), and family history
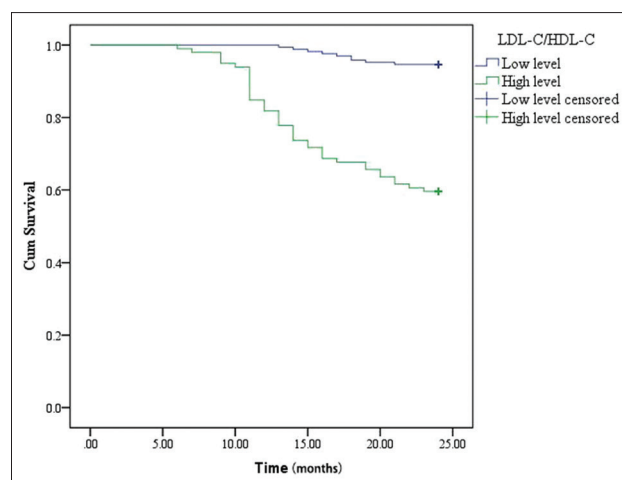


**Figure 1:** Cumulative MACE-free curve for different risk groups based on Kaplan-Meier analysis. Patients were divided into low- and high-LDL-C/HDL-C groups using the cutoff point of 3.36. MACE: Major adverse cardiovascular; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

of premature CHD ($P = 0.041$). Cases in the multi-vessel lesion group also had higher levels of uric acid and TG, and increased body mass index (BMI) ($P = 0.028$, 0.002, and 0.021, respectively). AMI patients with multi-vessel lesions showed lower levels of HDL-C, increased proportion of LDL-C, and higher LDL-C/HDL-C and TG/HDL-C ratios ($P = 0.037$, <0.001, <0.001, and <0.001, respectively). Step-wise multivariable logistic regression analysis indicated that decreased HDL-C ($P < 0.001$; *OR* = 0.049; 95% *CI*: 0.012–0.200) and high LDL-C ($P < 0.001$; *OR* = 5.459; 95% *CI*: 2.828–10.537) were the risk factors indicating multi-vessel lesions.

Thus, this study found that LDL-C/HDL-C ratio was a strong risk factor for AMI and prognostic factor for MACE. Although the association between lipids and cardiovascular disease has been widely investigated, few studies have reported the relationship between lipid abnormalities and AMI. The large global INTERHEART study in 52 countries indicated that smoking, exercise, fruit and vegetable intake, alcohol, hypertension, diabetes, abdominal obesity, psychosocial factors, and high apolipoprotein B100 (ApoB)/apolipoprotein A1 (ApoA1) ratio were associated with AMI.[6,7] In addition to ApoB/ApoA1, Karthikeyan *et al*.[3] investigated the role of other lipid indexes of AMI risk in the Asian population. Although ApoB/ApoA1 showed the strongest association with AMI compared with LDL-C alone and LDL-C/HDL-C ratio, the discrimination was weak (*OR*: 1.38; 95% *CI*, 1.31–1.46 vs. 1.22; 95% *CI*, 1.17–1.28 vs. 1.14; 95% *CI*, 1.09–1.20). Other studies also recognized LDL-C/HDL-C ratio as a stronger predictor of risk and treatment benefit in cardiovascular disease.[8,9] Actually, there is no strong evidence regarding which marker is better for AMI risk in young male AMI patients, i.e. ApoB and ApoA1, their cholesterol counterparts, or the ratios. We found that despite the significant difference in LDL-C levels between AMI cases and controls, LDL-C/HDL-C ratio was independently and strongly associated with the risk of AMI (*OR* = 1.416; 95% *CI*, 1.083–1.851). As the lipid abnormality pattern is affected by ethnicity and gender, a cutoff value for the LDL-C/HDL-C ratio of 3.36 in young Chinese males was determined based on Youden's index. Notably, LDL-C/HDL-C ratio was the strongest prognostic factor for the occurrence of MACE. Patients with an LDL-C/HDL-C ratio over 3.36 had a high risk of MACE. In contrast

to LDL-C or HDL-C alone, the LDL-C/HDL-C ratio that indicates balance between atherogenic and protective lipoproteins is likely to better affect the progression of atherosclerosis and thus influence the outcome of vascular disease prevention and intervention. The National Lipid Association Annual Summary of Clinical Lipidology 2015 reported that Asians are at increased risk for metabolic syndrome, insulin resistance, and adiposopathic dyslipidemia. Asians often have elevated TG and reduced HDL-C levels, which may increase atherosclerotic cardiovascular disease (ASCVD) risk. However, TG/HDL-C was not an independent risk factor for young male AMI patients.

In addition to the differences between AMI and control patients, we found that the involvement of coronary arteries gradually increased with the decrease in HDL-C, and that HDL-C level was an independent protective factor. The multi-vessel lesion group had lower levels of HDL-C than the single-vessel lesion group, indicating that the abnormality of lipid levels was not only related to the occurrence of AMI but also the severity of AMI. Hypertension, diabetes, and increased BMI were also more common in the multi-vessel lesion group compared with the single-vessel lesion group, indicating that HDL-C levels were associated with coronary artery disease in young male patients with AMI, especially those with low HDL-C accompanied by hypertension, diabetes, and overweight. A lower HDL-C level in a young male not only indicated increased risk of myocardial infarction, but also increased severity of coronary artery lesions, suggesting a poor prognosis. In patients with adiposopathic metabolic syndrome or insulin resistance, optimal HDL concentration and function are best achieved by appropriate lifestyle interventions, such as smoking cessation, appropriate nutrition, and increased (vigorous) physical activity.[10]

Based on the comparison between AMI patients and controls as well as between AMI patients with multi- and single-vessel lesions, we found that combined risk factors such as smoking, family history of premature CHD, hypertension, and diabetes mellitus (which differed between the two groups) acted synergistically. Hence, non-lipid ASCVD risk factors should also be managed appropriately, particularly hypertension, smoking, and diabetes mellitus in young males.

Several limitations of this study should be considered. First, this was a single-center study involving a small sample size and therefore the results should be interpreted with caution. Second, some AMI patients may have been omitted from the analysis, as we only included individuals who underwent coronary angiography during hospitalization.

In conclusion, we enrolled 267 young male patients with AMI and 247 age-matched controls and found that LDL-C/HDL-C ratio was the strongest risk factor associated with AMI. With MACE as the endpoint of clinical treatment, LDL-C/HDL-C ratio was also identified as a strong prognostic factor for these AMI patients. Our data indicated that LDL-C/HDL-C ratio should be introduced into clinical practice to serve as a predictor of risk and clinical outcome in young male patients with AMI.

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## Conflicts of interest

There are no conflicts of interest.

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