

Predictive and Prognostic Value of High-density Lipoprotein Cholesterol in Young Male Patients with Acute Myocardial Infarction

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Abstract

Background: The level of high-density lipoprotein cholesterol (HDL-C) is an important risk indicator and used in risk factor counting and quantitative risk assessment; however, the effect of HDL-C in young male patients with acute myocardial infarction (AMI) is unclear. The aim of this study was to investigate the effect of HDL-C in young male patients.

Methods: We recruited 267 consecutive young male patients (≤ 44 years) diagnosed with AMI. Other 247 participants free from coronary heart disease were enrolled as controls. HDL-C levels of AMI patients and controls were evaluated to analyze the predictive value on AMI. According to the cutoff point of 1.04 mmol/L HDL-C, patients of AMI were divided into two subgroups (normal HDL-C group and low HDL-C group) and were followed up for 2 years. Clinical end points included all major adverse coronary events (MACEs): the main cause of death, nonfatal myocardial infarction, readmissions for acute coronary syndrome, arrhythmias, or revascularization. The prognostic value of HDL-C was evaluated using Cox regression according to MACE.

Results: Patients of AMI had decreased proportion in normal HDL-C group compared to controls (47.2% vs. 57.9%; $P = 0.017$). Logistic regression analysis showed that there was an inverse relationship between HDL-C and AMI in young males. In the low HDL-C subgroup of AMI patients ($n = 141$), 34 (24.1%) patients experienced a MACE during the 2-year follow-up, compared with 15 (11.9%) patients in normal HDL-C subgroup ($n = 126$). The Cox regression analysis showed that HDL-C was an independent predictor of a MACE during the follow-up period (hazard ratio = 0.354, $P = 0.006$).

Conclusion: HDL-C was an important parameter for predicting the risk and the clinical outcomes of AMI in young male patients.

Key words: Acute Myocardial Infarction; High-density Lipoprotein Cholesterol; Male; Prognosis

INTRODUCTION

Acute myocardial infarction (AMI) is unusual among young people. With an upward trend in changing to unhealthy lifestyle, an increased incidence of juvenescence with AMI is getting more concerns from clinical research recently. Various issued studies showed that premature myocardial infarction (MI) individuals were predominantly males, characterized by smoking, obesity, and dyslipidemia (an essential key contributing to atherosclerosis).^[1-4] As a component of lipid metabolism disorders, the abnormal of level of high-density lipoprotein cholesterol (HDL-C) has been gradually being valued recently. Decreased HDL-C levels are often associated with increased atherosclerotic cardiovascular disease (ASCVD) risk. However, in human studies,

low HDL-C levels are not consistently associated with premature ASCVD.^[5] In this study, we aimed to evaluate the role of HDL-C in young AMI males compared to other risk factors of coronary heart disease (CHD), including the predictive effect at the onset of AMI in a case-control study and the prognostic effect assessed in a cohort study with a follow-up period of two years.

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Received: 14-09-2016 **Edited by:** Yi Cui

How to cite this article: Li Z, Huang J, Li N. Predictive and Prognostic Value of High-density Lipoprotein Cholesterol in Young Male Patients with Acute Myocardial Infarction. Chin Med J 2017;130:77-82.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.196581

METHODS

According to the World Health Organization's definition of youth, we recruited male patients aged from 18 to 44 years. All patients were admitted to the Department of Cardiology at Beijing Anzhen Hospital and hospitalized for the treatment of AMI from January 2013 to January 2014. The diagnosis of AMI was based on the following criteria: elevated myocardial enzyme levels (cardiac troponin I [cTnI], creatine kinase [CK], and CK-MB), typical electrocardiogram changes, and typical chest pain >30 min. There were 299 patients altogether from January 2013 to January 2014, and we excluded 32 patients from this study. Patients were excluded if they presented with the following clinical conditions: history of prior MI and history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting, valvular heart disease, acute stroke, serious liver or kidney disease, chronic consumption disease, thyroid dysfunction, or cancer. Patients taking lipid-lowering drug therapy recently were also excluded from the study.

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 three coronary arteries or their primary branches.

Other 247 males as controls, also undergoing coronary angiography and diagnosed free from CHD (diagnosed as esophagitis, pneumonia, cholecystitis, cervical spine disease before discharge), were recruited and matched on age at the same period. In addition, all individuals in the study were divided into two subgroups, according to the cutoff point of 1.04 mmol/L HDL-C.^[5] The normal HDL-C group had a level ≥ 1.04 mmol/L and the low HDL-C group with a level <1.04 mmol/L.

All participants were interviewed during hospitalization, and information about family history of premature CHD (<55 years of age in a male first-degree relative or <65 years in a female), hypertension (a cuff blood pressure $\geq 140/90$ mmHg and/or the current use of anti-hypertensive medication), diabetes (a fasting plasma glucose was ≥ 7.0 mmol/L or 2 h postprandial glucose was >11.1 mmol/L or the current use of anti-diabetic medication), and smoking (cigarettes within one month of the index admission) were recorded. The body mass index (BMI) was calculated as weight divided by height squared (kg/m^2).

All patients consented to this study. The study was approved by the Ethics Committee of Beijing Anzhen hospital of the Capital University of Medical Sciences and complies with the *Declaration of Helsinki* (No. 2016004X).

Venous blood samples were collected from the individuals after an overnight fast within 12 h after incident of AMI. Blood was drawn from the median cubital vein into ethylenediaminetetraacetic acid-containing vials. Plasma was separated within 2 h after collection. Total cholesterol

(TC), HDL-C, and triglycerides (TGs) were measured enzymatically using Beckman Coulter AU5400 Clinical Chemistry analyzer. Moreover, low-density lipoprotein cholesterol (LDL-C) was measured with a homogeneous direct assay. Urea nitrogen, creatinine (Cr), uric acid (UA), and hemoglobin (Hb) were measured according to the standard procedure of Anzhen hospital laboratory.

Follow-up of the acute myocardial infarction patients

After discharge, AMI patients were followed up at every 2-month intervals for 2 years by a trained interviewer at Beijing Anzhen hospital. The evaluated follow-up information was feedback for all 267 AMI patients (100% completed). Data were obtained either from face-to-face appointment or telephone interview. End points were defined as major adverse cardiovascular events (MACEs) as the main cause of death, nonfatal MI, arrhythmias (ventricular tachycardia or ventricular fibrillation), readmissions for acute coronary syndrome, or revascularization (coronary angioplasty or coronary artery bypass graft).

Statistical analysis

Analyses were performed using SPSS version 22.0 software (IBM Corp., USA). Continuous data are expressed as the mean and standard deviations, and differences between groups were determined using the Student's *t*-test. Variables with a skewed normal distribution are presented as medians (interquartile range), and the between-group differences for these variables were determined using the Rank-Sum test. Categorical variables are presented as percentages, and the differences between groups were valued using the Chi-square test. The logistic model was used to evaluate the associations between AMI and clinical parameters. For all of the odds ratios, we calculated 95% confidence intervals (CI). MACE rate estimates were generated with the Kaplan–Meier method. Cox proportional hazards modeling was used to assess the relative importance of the baseline risk factors to the end points. Hazard ratios (HRs) are presented with 95% CIs to show the risk of an event when the factor is present. Significance was defined at the 5% level using a two-tailed test.

RESULTS

In the case-control study, detailed baseline characteristics of the two groups are summarized in Table 1. The prevalence of the risk factors (e.g., hypertension, diabetes, smoking, and family history of premature CHD) was higher in AMI group than control group ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively). The AMI patients also had higher levels of LDL-C, TC, TG, and increased BMI ($P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively). At the time of incident AMI, AMI patients had decreased proportion in normal HDL-C subgroup (47.2%) compared to controls (57.9%, $P = 0.017$).

In the logistic regression analysis, which considered the occurrence of AMI as the binary dependent variable, age, BMI, Hb, blood urea nitrogen (BUN), Cr, UA, LDL-C,

TG, TC, normal HDL-C, hypertension, diabetes, smoking, alcohol, and family history of premature CHD were considered independent variables. It was found that AMI in young males was significantly and positively associated with family history of premature CHD, smoking, diabetes, hypertension, LDL-C, and TG while inversely associated with HDL-C and Hb. The regression coefficient of HDL-C was -0.754 [Table 2].

The baseline characteristics of prognostic study groups (normal and low HDL-C groups) are summarized in Table 3. There were no significant differences between the low HDL-C and normal HDL-C group, with regard to age, non-ST segment elevated MI, PCI, BMI, Hb, BUN, Cr, TC,

LDL-C, ejection fraction of left ventricular, hypertension, smoking, and family history of premature CHD. The patients of normal HDL-C group had higher level of TG, decreased proportion of single-vessel lesion and alcohol, and increased proportion of alcohol.

All of AMI patients were followed up for up to two years. The Kaplan-Meier analyses for MACE showed that there were significant differences between the low and normal HDL-C groups after AMI [Figure 1]. MACEs during the study period occurred in 49 patients. There were 34 (24.1%) patients in low HDL-C group which was more than 2-fold increase compared with 15 (11.9%) in normal HDL-C group ($P < 0.05$). Among these patients, 31 developed ACS (20 in low HDL-C group and 11 in normal HDL-C group), 16 had a revascularization procedure (11 in low HDL-C group and 5 in normal HDL-C group), 2 had arrhythmic events (2 in low HDL-C group), and no death occurred.

Multivariate Cox regression analysis showed that hypertension, diabetes, LDL-C, family history of premature CHD, single-vessel lesion, and normal HDL-C predicted the occurrence of MACE in the study participants. The regression coefficient was -1.014 , with HR 0.354 (95% $CI = 0.181-0.726$, $P = 0.006$) [Table 4].

Table 1: Comparison of baseline clinical characteristics between AMI and controls

Characteristics	AMI (n = 267)	Control (n = 247)	P
Age (years)	38.68 ± 4.44	38.27 ± 4.48	0.255
BMI (kg/m ²)	26.93 ± 2.34	26.05 ± 3.85	0.002
Hb (g/L)	148.00 ± 12.52	153.83 ± 10.89	<0.001
BUN (mmol/L)	4.75 ± 1.41	5.64 ± 1.42	<0.001
Cr (mmol/L)	83.82 ± 17.70	86.57 ± 13.79	0.061
UA (mmol/L)	372.21 ± 98.94	398.95 ± 86.23	0.001
LDL-C (mmol/L)	3.05 ± 0.87	2.66 ± 0.63	<0.001
TG (mmol/L)	2.76 ± 2.17	2.01 ± 1.34	<0.001
TC (mmol/L)	5.00 ± 1.46	4.37 ± 0.85	<0.001
HDL-C (mmol/L)	1.01 ± 0.28	1.05 ± 0.21	0.062
Normal HDL-C	126 (47.2)	143 (57.9)	0.017
Hypertension	123 (46.1)	44 (17.8)	<0.001
Diabetes	91 (34.1)	4 (1.6)	<0.001
Smoking	221 (82.8)	165 (66.8)	<0.001
Alcohol	86 (32.2)	74 (30.0)	0.634
Family history of premature CHD	87 (32.6)	28 (11.3)	<0.001

Data were presented as mean ± SD or n (%). BMI: Body mass index; Hb: Hemoglobin; BUN: Blood urea nitrogen; Cr: Creatinine; UA: Uric acid; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; CHD: Coronary heart disease; AMI: Acute myocardial infarction; SD: Standard deviation.

Table 2: Predictive value of HDL-C using logistic regression analysis

Items	B	Exp(B)	95% CI for Exp(B)		P
			Lower	Upper	
Normal HDL-C	-0.754	0.471	0.297	0.746	0.001
Family history of premature CHD	1.119	3.062	1.755	5.340	0.000
Smoking	0.693	1.999	1.200	3.329	0.008
Diabetes	2.988	19.848	6.805	57.899	0.000
Hypertension	1.277	3.586	2.227	5.774	0.000
LDL-C	0.529	1.697	1.246	2.312	0.001
Hb	-0.035	0.966	0.948	0.984	0.000
TG	0.232	1.261	1.076	1.477	0.004

CI: Confidence interval; HDL-C: High-density lipoprotein cholesterol; CHD: Coronary heart disease; LDL-C: Low-density lipoprotein cholesterol; Hb: Hemoglobin; TG: Triglyceride.

DISCUSSION

In this study, we investigated two relevant researches to evaluate the effect of HDL-C for predicting the risk of developing AMI and the outcomes of AMI after discharge. The results indicated a strong relationship between HDL-C level and both the beginning and 2-year prognosis of AMI in young males.

A reduced HDL-C level is an ASCVD risk factor used in ASCVD risk factor counting and quantitative risk assessment.^[5] Epidemiologically, HDL-C is an independent cardiovascular risk factor^[6] and has an inverse relationship with ASCVD

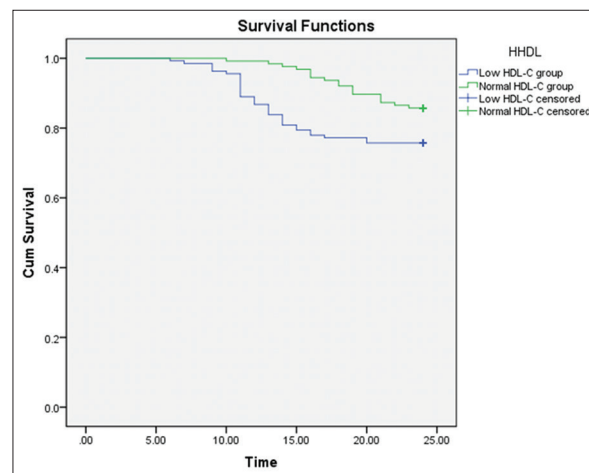


Figure 1: The Kaplan-Meier survival curves of the two groups of acute myocardial infarction patients: Cumulative occurrence of major adverse coronary event. Patients were divided into normal and low high-density lipoprotein cholesterol subgroups using the cutoff level of 1.04 mmol/L ($P = 0.006$) (Log Rank, $\chi^2 = 7.610$).

Table 3: Baseline characteristics of prognostic study groups (normal and low HDL-C groups)

Characteristics	Low HDL-C (n = 141)	Normal HDL-C (n = 126)	P
MACE	34 (24.1)	15 (11.9)	0.011
NSTEMI	13 (10.6)	12 (9.5)	0.548
PCI	130 (92.2)	118 (93.7)	0.414
Age (years)	38.72 ± 3.89	38.63 ± 5.01	0.871
BMI (kg/m ²)	26.96 ± 2.68	26.89 ± 1.89	0.819
Hb (g/L)	146.60 ± 12.28	149.57 ± 12.65	0.054
BUN (mmol/L)	4.90 ± 1.47	4.57 ± 1.30	0.061
Cr (mmol/L)	82.83 ± 16.34	84.92 ± 19.10	0.338
UA (mmol/L)	384.01 ± 106.55	359.00 ± 88.22	0.039
TG (mmol/L)	3.37 ± 2.78	2.07 ± 0.70	0.000
TC (mmol/L)	5.04 ± 1.72	4.96 ± 1.11	0.661
LDL-C (mmol/L)	3.03 ± 0.81	3.06 ± 0.93	0.787
HDL-C (mmol/L)	0.84 ± 0.16	1.26 ± 0.19	0.000
EF (%)	57.00 ± 9.47	56.25 ± 8.81	0.507
Hypertension	69 (48.9)	54 (42.9)	0.328
Diabetes	61 (43.3)	30 (23.8)	0.001
Smoking	117 (83.0)	104 (82.5)	1.000
Single-vessel lesion	60 (42.6)	90 (71.4)	0.000
Alcohol	32 (22.7)	54 (42.9)	0.001
Family history of premature CHD	51 (36.2)	36 (28.6)	0.194
Drug therapy of during follow-up period			
Dual antiplatelet treatment	133 (94.3)	120 (95.2)	0.479
Lipid-lowering medication	119 (84.4)	105 (83.3)	0.472
β-blockers	108 (76.6)	92 (73.0)	0.297
ACE inhibitors or AT1 blockers	91 (64.5)	83 (65.9)	0.461

Data were presented as mean ± SD or n (%). MACE: Major adverse cardiovascular event; NSTEMI: Non-ST segment elevated myocardial infarction; PCI: Percutaneous coronary intervention; BMI: Body mass index; Hb: Hemoglobin; BUN: Blood urea nitrogen; Cr: Creatinine; UA: Uric acid; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; EF: Ejection fraction; CHD: Coronary heart disease; SD: Standard deviation; ACE: Angiotensin-converting enzyme; AT1: Angiotensin II Type 1.

Table 4: Prognostic value of HDL-C using multivariate Cox regression analysis

Items	B	Exp(B)	95% CI for Exp(B)		P
			Lower	Upper	
Hypertension	0.696	2.006	1.026	3.923	0.042
Diabetes	2.120	8.334	4.087	16.995	0.000
Single-vessel lesion	-1.888	0.151	0.066	0.347	0.000
LDL-C	1.282	3.605	2.488	5.222	0.000
Family history of premature CHD	0.747	2.111	1.143	3.898	0.017
Normal HDL-C	-1.014	0.354	0.181	0.726	0.006

HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; CHD: Coronary heart disease; CI: Confidence interval.

risk, irrespective of gender, race, and ethnicity.^[5] HDL-C has been known to be protective against atherosclerosis by several mechanisms. HDL-C takes an anti-atherosclerotic role by the reverse transport of cholesterol from the peripheral tissues.^[7] Moreover, HDL-C may possess antioxidant and anti-inflammatory actions^[8] and inhibit the cytokine-induced expression of endothelial cell adhesion molecules, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1.^[9] In addition, HDL can inhibit thrombus formation.^[10] HDL-C particles include many surface proteins and lipids that influence

the function of HDL and may provide atheroprotection via favorable effects upon atherosclerotic mechanisms, including modulation of inflammation, oxidation, endothelial function, and insulin secretory capacity.

We found that the blood lipids of young males with AMI were different from controls, which have a high level of TC, TG, LDL-C ($P < 0.05$), and HDL-C (1.01 ± 0.28 vs. 1.05 ± 0.21 , $P > 0.05$). The levels of HDL-C of the two groups have not yet reached statistical significance, but there have been changes in the results. Moreover, when using the cutoff point of 1.04 mmol/L HDL-C, AMI patients had decreased proportion in normal HDL-C group (47.2%) compared to controls (57.9%). This result suggested that dyslipidemia in young AMI males was prevalent and closely associated to the development of AMI. In addition, the characteristics of this particular patients were more closely aligned with metabolic syndrome diagnostic criteria of Adult Treatment Panel III,^[11] including increased BMI and abnormal level of TG, HDL-C. The decrease in HDL-C and hypertriglyceridemia as important features of the metabolic syndrome play an important role in the development of atherosclerotic CHD.

According to the results, it was estimated that 82.8% of AMI young males smoked, even though 66.8% in controls, as in other series that have reported that the proportion of smokers

among premature patients was between 76% and 92%.^[12-15] Smoking can decrease in serum antioxidant activity, which further promotes the composition of blood lipids (lowering HDL-C and aggravating LDL-C).^[16]

Based on the comparisons of two groups, we can see that when risk factors such as BMI, smoking, family history of premature CHD, hypertension, and diabetes mellitus accumulated together, these risk factors formed in a positive way of interaction and coordination. Hence, nonlipid ASCVD risk factors should also be managed appropriately, particularly hypertension, smoking, and diabetes mellitus in young males.

In the logistic regression analysis, traditional risk factors (hypertension, diabetes mellitus, family history of premature CHD, and smoking) still play a pivotal role in young males with AMI and should be controlled as the elderly. HDL-C has been showed an inverse correlation in MI, which suggested that the change of HDL-C level was closely related to AMI in young men, and normal level of HDL-C was a protective factor from AMI.

As using the cutoff point of 1.04 mmol/L level of HDL-C, there were differences in the two subgroups. The proportion of the single-vessel lesions and alcohol consumption reduced in low HDL-C with the increase of diabetes, which indicated that coronary artery lesions are correlated with level of HDL-C. When young males have lower levels of HDL-C, it was not only indicated that the incidence of MI will be increased but also indicated that the degree of coronary artery lesions will be more serious. It was also suggested that patients with diabetes have lower level of HDL-C, and appropriate alcohol intake can increase the level of HDL-C.^[5] As reported, HDL-C levels increase with increasing intake of alcohol for both sexes in agreement with the established role of HDL-C as a biomarker of alcohol intake.^[17] According to Rimm *et al.*,^[18] HDL-C concentrations will increase by 0.133 mg/dl, i.e., 0.0035 mmol·L⁻¹·g⁻¹ of alcohol consumed a day.

We found that hypertension, diabetes, LDL-C, family history of premature CHD, single-vessel lesion, and HDL-C were independent predictors of MACE after AMI. All of the first four factors are well-known predictors of long-term mortality in middle-aged or elderly patients with CAD.^[19-21] However, there are few data regarding their prognostic impact in young males of AMI. The impressive finding of our study was that HDL-C was the protective predictor for recurrent cardiac events in young males with AMI. Patients with low HDL-C were associated with 2-fold increase for MACE compared to patients with normal HDL-C (24.1% vs. 11.9%, $P < 0.05$) during the follow-up period. The HDL-C level at the onset of AMI in young males was closely related to the prognosis of this particular people. Qun Lu also reported that the HDL-C level was an independent predictor of a major cardiovascular event in PCI patients with a follow-up of 120 weeks. It is plausible to speculate that young males might have more benefits from high level of HDL-C at the onset of AMI.

Therefore, it is important to evaluate the HDL-C level of young males who may benefit from an increased HDL-C level for the prevention of AMI and prediction in prognosis.

Our study has some potential limitations needed to be considered. First, all patients enrolled were hospitalized in one center. The sample sizes were relatively small. Second, the study objectives were selected from patients completing coronary angiography during hospitalization. We might lost few AMI patients who could not undergo angiography before discharge for contraindications. Third, the time of follow-up was not long enough for this specific population. Although MACEs occurred in 49 patients, mortality rate in our study (0.0%) is discordant to other studies in young coronary patients for long-term study (one 15-year mortality rate was 25.5% among 108 patients aged ≤ 40 years with AMI;^[22] another 15-year mortality of 30% in 843 patients diagnosed as having CAD under the age of 40 years, of whom 55% had a history of AMI^[23]). However, these studies were performed 30–40 years ago, and the perfusion treatment of AMI and drugs (i.e., ACE inhibitors, statins, and clopidogrel) were not widely applied. Therefore, the low mortality rate in our study is mainly due to the improved pattern of treatment during the acute phase of MI and after patients' hospital discharge.

In conclusion, we found that the levels of HDL-C were the lipid parameter strongly associated with premature AMI. In addition, the HDL-C levels at the onset of AMI could predict the cardiovascular events of 2-year follow-up in young males. This study suggests that more attention is needed to evaluate HDL-C levels in young males, and it might serve as a powerful risk predictor in young males (≤ 44 years).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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