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RESEARCH PAPER

Low-density lipoprotein cholesterol in oldest old with acute myocardial infarction: Is lower the better?

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Abstract

Background: the relationship between low-density lipoprotein cholesterol (LDL-C) and adverse outcomes among the older people remains controversial.
Objective: to further clarify the association between admission LDL-C levels and cardiovascular mortality (CVM) among oldest old individuals (≥80 years) with acute myocardial infarction (AMI).
Design: a prospective cohort study.
Setting: two-centre.
Subjects: a consecutive sample of 1,224 oldest old individuals with AMI admitted to Beijing FuWai and Shenzhen FuWai hospitals.
Methods: all individuals were subdivided according to baseline LDL-C levels (<1.8, 1.8–2.6 and ≥ 2.6 mmol/l) and further stratified by high-sensitivity C-reactive protein (hsCRP) concentrations (<10 and ≥10 mg/l). The primary outcome was CVM. The time from admission to the occurrence of CVM or the last follow-up was analysed in Kaplan–Meier and Cox analyses.
Results: the median age of the overall population was 82 years. During an average of 24.5 months' follow-up, 299 cardiovascular deaths occurred. Kaplan–Meier analysis showed that LDL-C < 1.8 mmol/l group had the highest CVM among oldest old individuals with AMI. Multivariate Cox regression analysis further revealed that compared with those with LDL-C levels <1.8 mmol/l, subjects with LDL-C levels ≥2.6 mmol/l (hazard ratio: 0.67, 95% confidence interval: 0.46–0.98) had significantly lower risk of CVM, especially in those with high hsCRP levels. Moreover, when categorising according to LDL-C and hsCRP together, data showed that individuals with low LDL-C and high hsCRP levels had the highest CVM.
Conclusions: LDL-C < 1.8 mmol/l was associated with a high CVM after AMI in oldest old individuals, especially when combined with high hsCRP levels, which may need to be confirmed by randomised controlled trials.

Keywords: oldest, lipoprotein, inflammation, cardiovascular, mortality, older people

Key Points

- Low admission LDL-C level could predict CVM in oldest old individuals with AMI.
- The relationship between LDL-C and outcomes among the older people remains controversial.
- The paradox phenomenon between LDL-C and CVM mainly existed in patients with high hsCRP levels.
- Admission LDL-C and hsCRP levels were helpful for risk stratification among oldest old individuals with AMI.

- Associations between LDL-C and outcomes in oldest old individuals with AMI need to be confirmed by RCTs.

Introduction

It is well known that elevated low-density lipoprotein cholesterol (LDL-C) is an important risk factor for coronary artery disease (CAD) [1]. Randomised controlled trials (RCTs) of statins in chronic CAD suggest a strong linear relationship between the extent of LDL-C reduction and decreased risk of recurrent events [2, 3]. It has been estimated that per 1 mmol/l reduction in LDL-C resulted in a similar decrease, 25% and 21% respectively, in major vascular events incidence for primary and secondary prevention [3]. The decrease of LDL-C and lower level of it are considered major determinants of the reduction in risk of CAD [4]. Moreover, the concept of 'LDL-the lower, the better' has been proposed in many statin studies to improve major cardiovascular outcomes and mortality [5].

However, the clinical benefit from LDL-C lowering in older patients, especially oldest old, remains debated because participants aged ≥80 years were not well represented in individual trials [6]. Thus, almost all current recommendations to lower LDL-C levels are formulated for the general adult population or the older people aged >65 years [7, 8], and there have been very few studies that focused on the optimal LDL-C level of the oldest old individuals. For older people, primary or secondary prevention studies have brought about conflicting conclusions on the relationship between LDL-C concentrations and worse outcomes [9]. Some studies showed that high LDL-C levels were associated with higher risk of atherosclerotic cardiovascular disease (ASCVD) and all-cause mortality (ACM) among the older people [10, 11], while others suggested that low LDL-C concentrations were associated with increased risk of ACM [12–15] and non-cardiovascular mortality (non-CVM) [16] in older populations, which has drawn particular attention regarding the necessity for LDL-C lowering in this unique population. However, only few studies regarding the association between LDL-C levels and clinical outcomes among oldest old individuals in the primary prevention setting have been reported [9, 17]. To our knowledge, there have been no studies specifically focusing on the association of LDL-C levels with cardiovascular outcomes among oldest old individuals in secondary prevention.

Besides oldest old individuals, acute myocardial infarction (AMI) is another special population, in which the relationship between baseline LDL-C levels and clinical prognosis remains controversial. Several studies showed that lower admission LDL-C levels were associated with an increased risk of mortality following AMI, referred to as the lipid paradox [18, 19], while some other studies observed no associations of LDL-C levels on admission with worse outcomes after AMI [20–22].

Above all, we conducted this study to explore the relationship between LDL-C levels on admission and CVM in oldest old individuals with AMI. Considering the close association of inflammation with cardiovascular risk [23, 24] and the potential anti-inflammatory role of cholesterol [25, 26], we also investigated the potential interaction of LDL-C and inflammation in predicting CVM.

Methods and Population

Study design and population

This study complied with the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001, and was approved by the hospital's ethical review board (FuWai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Written informed consent for publication of their clinical details was obtained from the patient.

From January 2012 to December 2019, 1,438 consecutive Chinese patients aged ≥80 years with AMI, who were hospitalised at Beijing FuWai and Shenzhen FuWai hospitals, were collected for the present study. A total of 203 patients were excluded due to hospitalised for AMI over 24 hours of onset of symptoms, hospitalised for AMI not the first time, missing detailed information, very high triglyceride levels (≥5.6 mmol/l) [27], serious infectious or systematic inflammatory disease, or malignant disease. During the study, 11 patients were lost to follow-up. Eventually, 1,224 patients aged ≥80 years with AMI were enrolled into the study. According to their LDL-C levels on admission, patients were classified into three groups: low (<1.8 mmol/l, n = 324), medium (1.8–2.6 mmol/l, n = 496) and high (≥2.6 mmol/l, n = 404) (Figure 1). Clinical assessment, biochemical analysis and follow-up are detailed in the Supplementary Data.

Statistical analysis

Continuous variables are expressed as mean ± SD or median (interquartile range) as appropriate. The differences between groups were determined by the Student's *t*-test, analysis of variance or non-parametric test where appropriate. Categorical variables were presented as number (percentage) and analysed by χ^2-test. The event-free survival rates among groups were estimated by the Kaplan–Meier analysis and compared by the log-rank test. Cox proportional hazard models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). Significant variables identified in the univariate analysis and other commonly adjusted factors (empirically derived, such as sex and smoking) were adjusted in the multivariate Cox model in an all-enter way. These covariates included age, sex, body mass index (BMI), current smoking, hypertension,

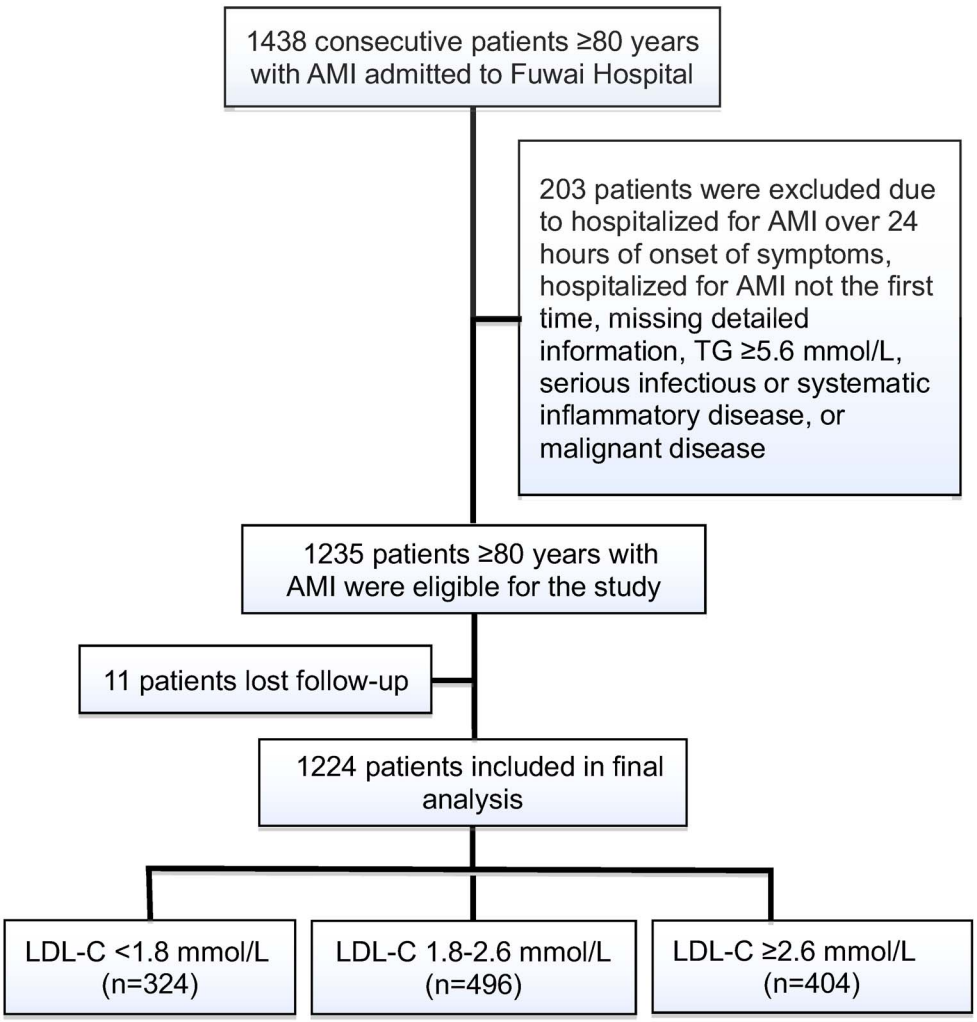


Figure 1. Flowchart illustrating the study population. TG, triglyceride.

diabetes, heart rate, left ventricular ejection fraction (LVEF), creatinine, high-density lipoprotein-cholesterol (HDL-C), high-sensitivity C-reactive protein (hsCRP), nutrition risk index (NRI), anaemia, baseline statin use (Yes or No) and revascularization post-myocardial infarction (MI) (Yes or No). Restricted cubic spline (RCS) adjusted for age and sex was created to assess linearity assumptions of the relationship between LDL-C levels and CVM. Additionally, we tested the influence of hsCRP levels (<10 and ≥ 10 mg/l) [28] on the association between LDL-C and CVM through stratification analysis and subdividing all individuals by LDL-C and hsCRP together. Two-tailed *P*-values <0.05 were considered statistically significant in all analyses. The statistical analyses were performed with SPSS version 24.0 software (SPSS Inc., Chicago, IL, USA) and STATA version 15.1 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

The baseline characteristics of the entire population as well as according to LDL-C levels are detailed in Table 1. Patients with LDL-C ≥ 2.6 mmol/l were less likely to be males and to use clopidogrel and angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARB), and had higher levels of heart rate and cardiac troponin I (cTnI). There was an ascending gradient regarding the proportion of revascularization post-MI, as well as concentrations of fasting plasma glucose (FPG), total cholesterol (TC), HDL-C, triglyceride, apolipoprotein AI (apoAI) and apolipoprotein B (apoB) across LDL-C levels, while the proportions of percutaneous coronary intervention or coronary artery bypass grafting history, anaemia, and aspirin, statins and β-blockers use were negatively correlated with the LDL-C levels.

LDL-C and CVM among oldest old individuals with AMI

During an average of 24.5-month follow-up, 299 cardiovascular deaths (seventy 30-day in-hospital cardiovascular deaths) were recorded, representing 12.3 events per 100 person-years. As shown in Supplementary Table 1, patients with cardiovascular deaths had significantly lower LDL-C levels than those in non-CVM group ($P = 0.003$).

Table 1. Characteristics of the study participants according to LDL-C levels at baseline

Variable	Total subjects (n = 1,224)	LDL-C levels			*P*-value
		<1.8 mmol/l (n = 324)	1.8–2.6 mmol/l (n = 496)	≥2.6 mmol/l (n = 404)	
Age, years	82.9 ± 2.9	82.8 ± 2.7	82.9 ± 2.9	83.1 ± 3.1	0.462
Male, n (%)	728 (59.5)	208 (64.2)	319 (64.3)	201 (49.8)	<0.001
Hypertension, n (%)	892 (72.9)	243 (75.0)	359 (72.4)	290 (71.7)	0.477
Diabetes, n (%)	460 (37.6)	136 (41.9)	176 (35.5)	148 (36.6)	0.125
Current smoking, n (%)	468 (38.2)	127 (39.1)	187 (37.7)	154 (38.2)	0.909
Prior PCI/CABG, n (%)	282 (23.0)	90 (27.7)	118 (23.8)	74 (18.3)	0.003
Revascularization post-MI, n (%)	665 (54.3)	155 (47.8)	268 (54.0)	242 (59.9)	0.002
BMI, kg/m^2	23.85 ± 3.58	24.15 ± 3.63	23.59 ± 3.34	23.92 ± 3.80	0.062
SBP, mmHg	128 ± 21	128 ± 22	128 ± 20	129 ± 21	0.454
DBP, mmHg	70 ± 12	69 ± 12	70 ± 11	71 ± 12	0.193
Heart rate, bpm	70 ± 14	70 ± 14	70 ± 14	71 ± 14	0.047
LVEF, %	52.61 ± 10.18	53.03 ± 10.48	52.74 ± 10.50	52.10 ± 9.51	0.398
NRI	98.87 ± 16.48	97.98 ± 15.14	99.45 ± 15.88	98.91 ± 18.35	0.466
Anaemia, n (%)	392 (32.4)	138 (42.6)	161 (32.5)	93 (23.1)	<0.001
Biochemical parameters					
FPG, mmol/l	6.80 ± 2.93	6.54 ± 2.62	6.69 ± 2.84	7.20 ± 3.25	0.008
HbA1c, %	6.64 ± 1.19	6.59 ± 1.09	6.67 ± 1.23	6.65 ± 1.24	0.651
TC, mmol/l	3.86 ± 0.99	2.89 ± 0.53	3.70 ± 0.40	4.94 ± 0.82	<0.001
HDL-C, mmol/l	1.08 ± 0.31	1.01 ± 0.33	1.07 ± 0.29	1.14 ± 0.31	<0.001
LDL-C, mmol/l	2.35 ± 0.85	1.42 ± 0.30	2.17 ± 0.22	3.30 ± 0.64	<0.001
TG, mmol/l	1.23 (0.93–1.62)	1.06 (0.82–1.42)	1.17 (0.91–1.51)	1.42 (1.11–1.85)	<0.001
apoAI, g/l	1.21 ± 0.28	1.13 ± 0.26	1.19 ± 0.28	1.29 ± 0.29	<0.001
apoB, g/l	0.79 ± 0.25	0.57 ± 0.16	0.77 ± 0.16	1.01 ± 0.22	<0.001
hsCRP, mg/l	6.42 (2.25–11.87)	5.33 (2.02–11.90)	6.69 (2.00–11.85)	6.91 (2.82–11.87)	0.108
Creatinine, μmol/l	104.73 ± 41.42	106.46 ± 41.53	104.68 ± 39.88	103.41 ± 43.16	0.571
cTnI, ng/ml	0.49 (0.06–3.67)	0.31 (0.05–2.63)	0.30 (0.05–3.33)	1.14 (0.12–5.42)	<0.001
Baseline medications					
Aspirin, n (%)	733 (59.9)	213 (65.7)	303 (61.1)	217 (53.7)	0.006
Clopidogrel, n (%)	539 (44.0)	157 (48.5)	236 (47.6)	146 (36.1)	0.001
Statins, n (%)	586 (48.4)	195 (60.2)	257 (51.9)	134 (33.1)	<0.001
ACEI/ARB, n (%)	323 (26.4)	98 (30.1)	145 (29.2)	80 (19.8)	0.002
β-Blockers, n (%)	500 (40.9)	160 (49.4)	224 (45.2)	116 (28.7)	<0.001

Continuous values are summarised as mean ± SD, median (interquartile range) and categorical variables as percentage. CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

Meanwhile, participants with cardiovascular deaths were slightly older, had higher proportions of diabetes and anaemia, and presented higher levels of heart rate, FPG, glycosylated haemoglobin (HbA1c), hsCRP and creatinine, compared with event-free patients. In addition, the CVM group had a lower proportion of revascularizations post-MI and lower levels of BMI, blood pressures, LVEF, NRI and apoAI compared with non-CVM group. However, the baseline uses of antiplatelet drugs, statins, ACEI/ARB and β-blockers had no significant differences between two groups.

The prevalence of CVM in low, medium and high LDL-C groups was 16.9, 11.2 and 10.2 per 100 person-years respectively. As shown in Figure 2A, the Kaplan–Meier analyses showed that subjects with low LDL-C levels had significantly lower cumulative event-free survival rate compared to those with medium or high LDL-C concentrations (both $P < 0.05$), while there was no significant difference between medium and high LDL-C groups. Similarly, LDL-C < 1.8 mmol/l group also had significantly higher risk of 30-day in-hospital CVM than the other two groups (both $P < 0.05$, Figure 2B).

Univariate and multivariate Cox regression analyses of CVM are shown in Table 2. In univariate analysis, lower levels of LDL-C, BMI, LVEF and NRI, and higher levels of heart rate, creatinine, and hsCRP, older age, hypertension, diabetes, non-revascularization post-MI and anaemia were all significant predictors of CVM among oldest old individuals with AMI. In further multivariate analysis, LDL-C, heart rate, LVEF, NRI, creatinine and revascularization post-MI remained significantly associated with CVM (all $P < 0.05$). Compared with subjects with LDL-C < 1.8 mmol/l, patients with LDL-C levels of 1.8–2.6 mmol/l had a 28% lower risk of CVM ($P = 0.052$), while those with LDL-C levels ≥2.6 mmol/l had a 33% lower risk of CVM ($P = 0.039$). Additionally, when 30-day in-hospital CVM was considered specifically, participants with high LDL-C levels also had significantly lower risk of CVM than

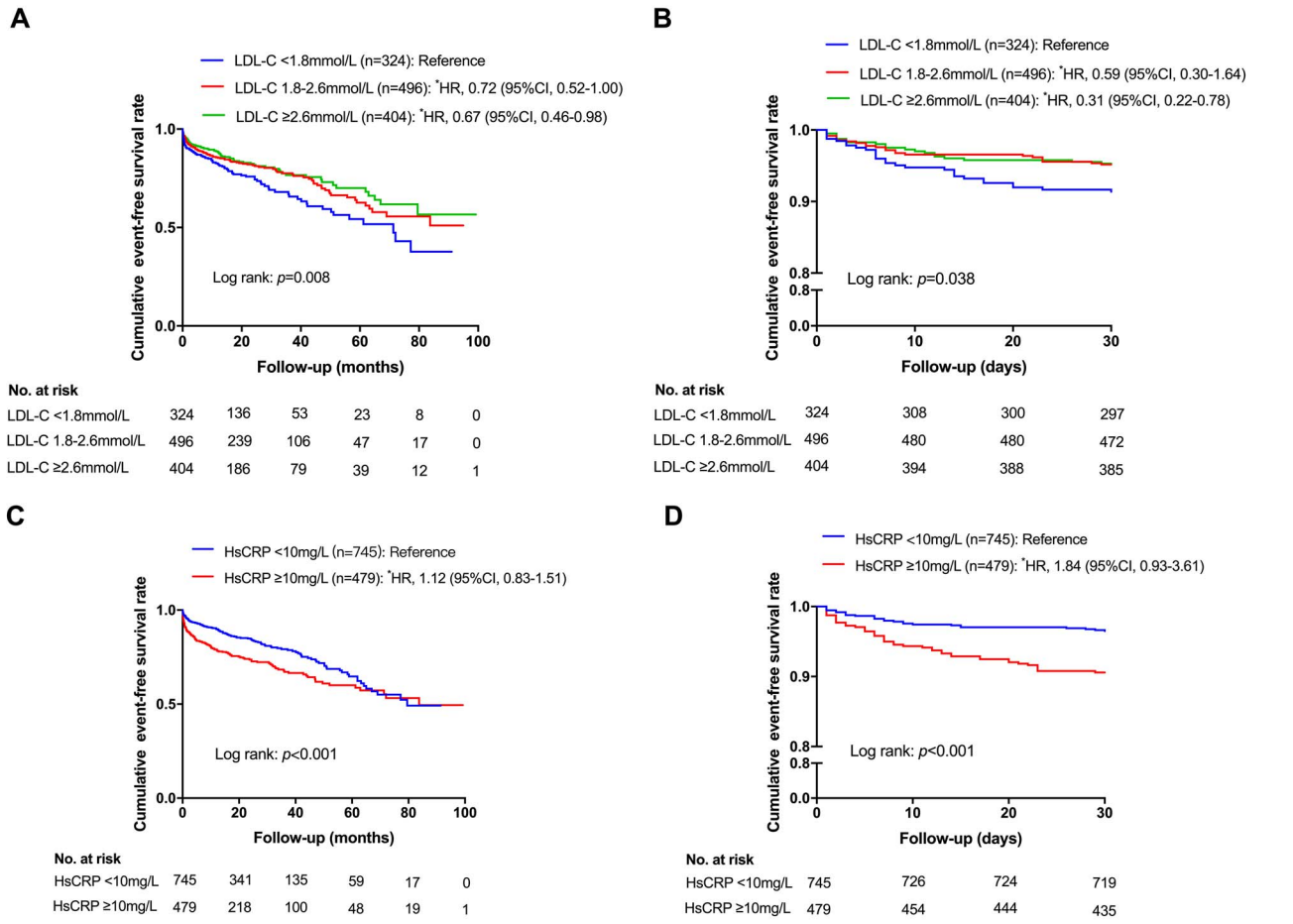


Figure 2. Kaplan–Meier curves of total CVM and 30-day in-hospital CVM stratified by LDL-C or hsCRP levels. (A) Kaplan–Meier curves of total CVM stratified by LDL-C levels; (B) Kaplan–Meier curves of 30-day in-hospital CVM stratified by LDL-C levels; (C) Kaplan–Meier curves of total CVM stratified by hsCRP levels; (D) Kaplan–Meier curves of 30-day in-hospital CVM stratified by hsCRP levels. *Adjusted for age, sex, body mass index, current smoking, hypertension, diabetes, heart rate, left ventricular ejection fraction, nutrition risk index, anaemia, creatinine, high-density lipoprotein-cholesterol, hsCRP, LDL-C, baseline statin use (Yes or No) and revascularization post-MI (Yes or No), other than the parameters being analysed.

those with low LDL-C concentrations, with an adjusted HR of 0.31 (95% CI: 0.22–0.78, $P = 0.012$; Supplementary Figure 1A). Moreover, as shown in Supplementary Figure 2, RCS showed a strong trend towards non-linear positive association of admission LDL-C levels with total CVM and 30-day in-hospital CVM.

Influence of hsCRP on the association between LDL-C and CVM

As shown in Figure 2C and D, patients with high hsCRP levels (≥10 mg/l) had significantly lower cumulative event-free survival rates for both total CVM and 30-day in-hospital CVM, compared to those with low hsCRP levels (<10 mg/l). However, after adjusting for other potential covariates, high level of hsCRP was associated with an increased but non-significant risk of total CVM and 30-day in-hospital CVM (both $P > 0.05$; Table 2 and Supplementary Figure 1B).

Subgroup analysis of the association between LDL-C concentrations and CVM according to hsCRP levels showed that the negative association between LDL-C levels and CVM mainly existed in patients with high hsCRP levels. Compared with subjects with low LDL-C levels, patients with high LDL-C levels had a 55% (95% CI: 0.25–0.83) decrease of total CVM risk and a 76% (95% CI: 0.11–0.95) decrease of 30-day in-hospital CVM risk. Nevertheless, we observed no significant associations of LDL-C levels with either total CVM or 30-day in-hospital CVM in participants with low hsCRP levels (both P for interaction <0.05; Supplementary Figure 3). To further clarify the potential effect of hsCRP on the association of LDL-C levels with CVM, all patients were subdivided according to both LDL-C and hsCRP levels. The Kaplan–Meier analysis showed that patients in LDL-C < 1.8 mmol/l-hsCRP ≥10 mg/l group had the highest risk of total CVM as well as 30-day in-hospital CVM (Figure 3A and B). After adjusting for potential covariates, LDL-C ≥ 2.6 mmol/l-hsCRP ≥10 mg/l

Table 2. Univariate and multivariate Cox regression analyses of total cardiovascular mortality

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	–	–	–	–
80–89 years	1.00 (reference)	–	1.00 (reference)	–
≥90 years	1.92 (1.19–3.09)	0.007	1.38 (0.71–2.67)	0.338
Male	0.91 (0.72–1.14)	0.414	0.80 (0.58–1.11)	0.185
BMI	0.95 (0.91–0.98)	0.002	0.99 (0.93–1.06)	0.719
Heart rate (per 10 bpm increase)	1.14 (1.06–1.23)	<0.001	1.14 (1.00–1.26)	0.009
Current smoking	1.01 (0.80–1.27)	0.969	1.10 (0.81–1.49)	0.535
Hypertension	1.41 (1.08–1.85)	0.013	1.14 (0.82–1.58)	0.432
DM	1.43 (1.14–1.80)	0.002	1.31 (0.98–1.74)	0.065
Baseline aspirin use	0.94 (0.74–1.20)	0.623	–	–
Baseline clopidogrel use	0.94 (0.73–1.20)	0.617	–	–
Baseline statin use	1.00 (0.79–1.28)	0.981	0.99 (0.75–1.32)	0.958
Baseline ACEI/ARB use	1.10 (0.84–1.45)	0.483	–	–
Baseline β-blockers use	1.27 (0.98–1.64)	0.073	–	–
Revascularization post-MI	0.36 (0.29–0.46)	<0.001	0.57 (0.42–0.78)	0.001
LVEF	0.96 (0.95–0.97)	<0.001	0.97 (0.96–0.98)	<0.001
NRI	0.99 (0.98–0.99)	<0.001	0.97 (0.95–0.99)	0.022
Anaemia	1.58 (1.24–2.02)	<0.001	1.14 (0.83–1.57)	0.428
HDL-C	0.71 (0.48–1.05)	0.084	0.82 (0.50–1.35)	0.442
Creatinine	1.01 (1.01–1.01)	<0.001	1.01 (1.00–1.01)	<0.001
cTnI	1.00 (1.00–1.01)	0.189	–	–
hsCRP	–	–	–	–
<10 mg/l	1.00 (reference)	–	1.00 (reference)	–
≥10 mg/l	1.57 (1.24–1.98)	<0.001	1.12 (0.83–1.51)	0.474
LDL-C				
<1.8 mmol/l	1.00 (reference)	–	1.00 (reference)	–
1.8–2.6 mmol/l	0.72 (0.54–0.95)	0.019	0.72 (0.52–1.00)	0.052
≥2.6 mmol/l	0.64 (0.47–0.86)	0.003	0.67 (0.46–0.98)	0.039

DM, diabetes mellitus; MI, myocardial infarction.

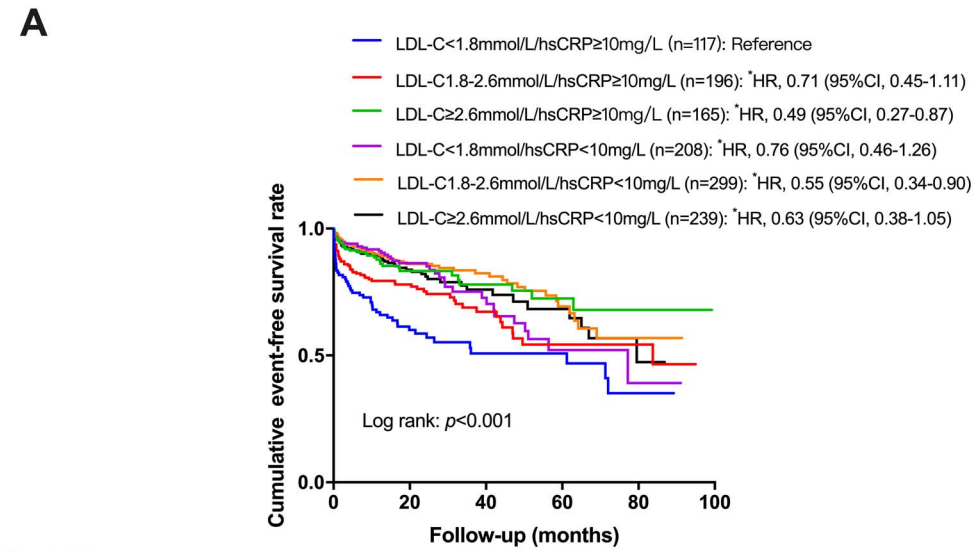
(adjusted HR: 0.49, 95% CI: 0.27–0.87) and LDL-C 1.8–2.6 mmol/l-hsCRP <10 mg/l (adjusted HR: 0.55, 95% CI: 0.34–0.90) groups had significantly lower risk of CVM compared with the reference group (LDL-C < 1.8 mmol/l-hsCRP ≥10 mg/l). Meanwhile, LDL-C 1.8–2.6 mmol/l-hsCRP ≥10 mg/l, LDL-C < 1.8 mmol/l-hsCRP <10 mg/l and LDL-C ≥ 2.6 mmol/l-hsCRP <10 mg/l groups also had a trend towards lower risk of CVM compared with the reference group (Supplementary Figure 4A). When 30-day in-hospital CVM was evaluated, we observed similar phenomena (Supplementary Figure 4B).

Discussion

Under the current situation, the illumination of the association between LDL-C levels and clinical outcomes among oldest old individuals may be clinically essential. In the present study, our data first indicated that LDL-C levels <1.8 mmol/l on admission had a significant predictive role for total CVM and 30-day in-hospital CVM in oldest old individuals with AMI, especially in those with high inflammation status. Moreover, the combination of baseline low LDL-C and high hsCRP levels could better predict worse outcomes among this population.

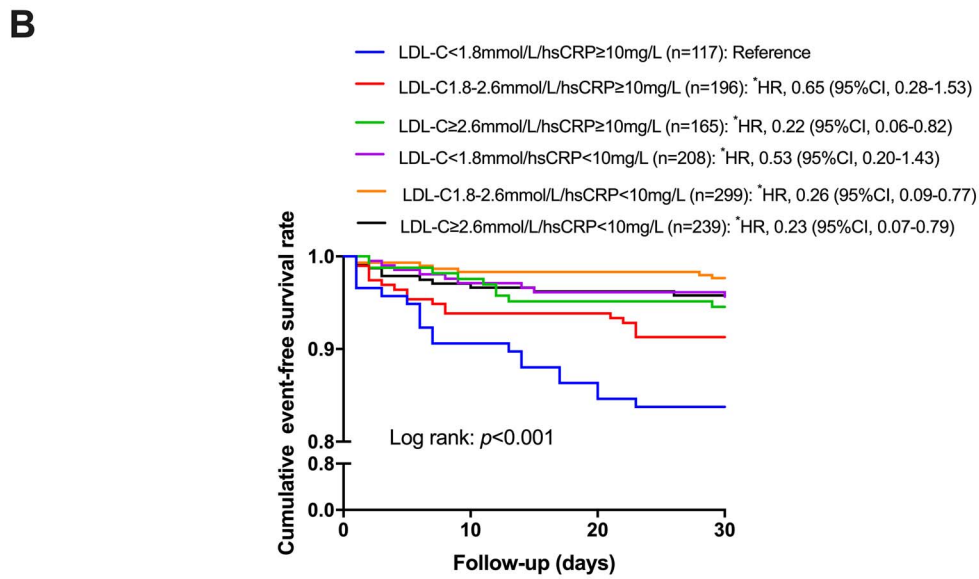
CAD remains the leading cause of death worldwide. Epidemiological studies have shown that the morbidity and mortality of CAD is directly related to circulating levels of atherogenic lipoproteins, in particular LDL-C [29]. Moreover, available RCTs of lipid-lowering drugs have suggested a direct relationship between the change of LDL-C concentrations and a substantial reduction in the risk of CAD in primary prevention populations and the risk of a new ischaemic cardiovascular events (CVE) in patients with established CAD [2, 3]. Currently, the concept of 'the lower the better' has appeared to be widely accepted. Nevertheless, for oldest old individuals, there have been few studies supporting this notion. In fact, the older population have been gradually expanded in recent years and have absolutely higher rates of ASCVD and major CVEs than younger individuals [6], which has aroused great concern in cardiovascular field.

Nowadays, conflicting evidence exists on the relationship between LDL-C and CVEs among the older people [9]. Clinical efficacy of aggressive LDL-C lowering remains less clear in older subjects than that of younger individuals. The previous MRC/BHF Heart Protection Study demonstrated that cholesterol lowering with statins brought about substantial benefit in old age (65–70 or 70–80 years) as well as middle age [11]. In a recent meta-analysis, LDL-C-lowering significantly reduced the risk of major CVEs in



No. at risk

LDL-C<1.8mmol/L/hsCRP≥10mg/L	117	47	23	14	5	0
LDL-C1.8-2.6mmol/L/hsCRP≥10mg/L	196	93	39	16	9	0
LDL-C≥2.6mmol/L/hsCRP≥10mg/L	165	79	40	19	7	1
LDL-C<1.8mmol/L/hsCRP<10mg/L	208	89	31	10	4	0
LDL-C1.8-2.6mmol/L/hsCRP<10mg/L	299	146	66	31	9	0
LDL-C≥2.6mmol/L/hsCRP<10mg/L	239	108	40	20	6	0



No. at risk

LDL-C<1.8mmol/L/hsCRP≥10mg/L	117	108	101	98
LDL-C1.8-2.6mmol/L/hsCRP≥10mg/L	196	186	186	179
LDL-C≥2.6mmol/L/hsCRP≥10mg/L	165	162	158	156
LDL-C<1.8mmol/L/hsCRP<10mg/L	208	202	200	199
LDL-C1.8-2.6mmol/L/hsCRP<10mg/L	299	295	295	292
LDL-C≥2.6mmol/L/hsCRP<10mg/L	239	234	232	230

Figure 3. Kaplan–Meier curves of (A) total CVM and (B) 30-day in-hospital CVM according to both LDL-C and hsCRP levels. CVM, cardiovascular mortality; *Adjusted for age, sex, body mass index, current smoking, hypertension, diabetes, heart rate, left ventricular ejection fraction, nutrition risk index, anaemia, creatinine, high-density lipoprotein-cholesterol, baseline statin use (Yes or No) and revascularization post-MI (Yes or No).

older patients (>75 years), with no significant difference with the risk reduction in patients younger than 75 years [6]. However, a prospective study in France reported that lower LDL-C level was associated with increased risk of ACM among hospitalised older patients (>70 years) [12]. Studies further demonstrated that higher LDL-C was associated with reduced risk of mortality for older people across a wide range of ethnicities [13–15]. In the Cholesterol Treatment Trialists' Collaboration meta-analysis, major CVEs risk reduced by the decrease of LDL-C with statin therapy was attenuated in older patients [30]. Besides the inconsistency, there is also a paucity of data on oldest old individuals regarding the association between LDL-C levels and cardiovascular risk. Except for a few studies suggesting a significant predictive role of low LDL-C levels for ACM among oldest old individuals in primary prevention [9, 17], no data are available regarding the relationship between LDL-C and CVM in oldest old individuals with established CAD.

In addition, the prognostic value of admission LDL-C level has not been established in patients with AMI as well since the available studies showed contradictory results. A previous study by Olsson et al. indicated that baseline LDL-C levels could not predict the risk of recurrent CVEs among patients with ACS [20]. In Sun et al.'s study [31], admission LDL-C concentrations had no significant association with 1-year incidence of CVEs in patients with AMI, but had a negative correlation with the occurrence of CVEs within 1 month. Moreover, the paradox between baseline LDL-C levels and short-term or long-term prognosis after AMI was observed in many studies [18, 19, 22, 32–34], but some of which suggested that this phenomenon was associated with baseline confounding factors related to survival, such as malnutrition [33].

In the present study, we strictly enrolled oldest old patients hospitalised for AMI at first time and admitted within 24 hours of onset of symptoms and excluded those with moderate-to-severe hypertriglyceridemia. Notably, our hospital is the biggest cardiovascular specialist hospital with a large number of patients and standard therapies for patients in China, which may guarantee the relative high-quality of data for the analysis. Purposefully, we tried to further clarify the association between admission LDL-C levels and CVM among oldest old individuals with AMI and firstly observed that low admission LDL-C level was a significant predictor for both total CVM and 30-day in-hospital CVM in this special population after adjusting for potential confounding factors including malnutrition status. Compared with subjects with LDL-C levels <1.8 mmol/l, patients with LDL-C levels ≥2.6 mmol/l had a 33% decrease of total CVM and a 69% decrease of 30-day in-hospital CVM, while those with LDL-C levels of 1.8–2.6 mmol/l had a moderate decrease of the risk of total CVM and 30-day in-hospital CVM. This finding might provide additional information regarding the association between LDL-C and CVM in the older people.

The interaction of cholesterol and inflammation in the pathogenesis of atherosclerosis has drawn much attention in recent years. As is well known, besides LDL-C, inflammation plays a key role in the pathogenesis of atherosclerosis and ACS [35, 36]. HsCRP is one of the best studied inflammatory biomarkers for vascular risk [35, 37]. A meta-analysis by He et al. suggested that hsCRP levels measured within 72 hours following the onset of ACS were related to a higher risk of recurrent CVEs [38]. Furthermore, AMI per se can result in an inflammatory response involved in myocardial repair [39]. HsCRP, as an acute phase reactant, will rise five to eight times in the setting of AMI [35] and has been shown to be correlated with the extent of cardiac injury in the acute phase of MI [40]. More interestingly, it has been reported that plasma lipoprotein might be a buffering factor involved in modifying systemic inflammation in malnourished patients [33]. Higher cholesterol concentrations were suggested to play an anti-inflammatory role in patients with chronic heart failure [25]. Thus, we hypothesised that there may be an interaction effect between hsCRP and LDL-C for predicting the risk of CVM in oldest old individuals with AMI. Indeed, we found that the predictive role of low LDL-C levels for CVM mainly existed in patients with high hsCRP levels. Meanwhile, the combination of low LDL-C and high hsCRP levels could better predict CVM risk.

However, there are several limitations to this study. First, the number of patients might be still insufficient compared with large trials. However, the oldest old individuals with AMI is a unique population and our findings in this cohort may be of great significance in clinical practice. Second, LDL-C value was measured only once at admission, so we could not assess the impact of the variation of LDL-C levels on clinical outcomes during follow-up. Nevertheless, we focused on the clinical significance of initial LDL-C concentrations on clinical outcomes in oldest old individuals with AMI. Third, blood samples for lipid profile were taken at least several hours ('overnight fasting blood') after the onset of AMI, so the LDL-C levels may be influenced by MI. However, a study by Pitt et al. demonstrated that LDL-C concentrations changed relatively little within 4 days following AMI [41]. Finally, given the nature of observational study, we cannot conclude whether low LDL-C and high hsCRP levels were causally related to CVM risk and although we have adjusted for lots of covariates, the association between LDL-C and CVM might be caused by a latent variable not included in the adjusted analysis.

In conclusion, our data showed a significant association between low admission LDL-C levels and a high risk of CVM among oldest old individuals with AMI, especially in those with high hsCRP levels, suggesting that admission LDL-C and hsCRP levels might be helpful for risk stratification in this unique population. RCTs with outcomes stratified by admission LDL and hsCRP levels are needed to further confirm our findings.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Declaration of Conflicts of Interest: None.

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