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Association between low-density lipoprotein cholesterol level and mortality in patients with cardiogenic shock: a retrospective cohort study

Jiali Jin,[1] Zhewei Shi,[1] Xiaomin Pang [ID] [2]

[1]Department of Cardiology, Zhuji People's Hospital of Zhejiang Province, Zhuji, China
[2]Department of Emergency, People's Hospital of Tiantai County, Taizhou, Zhejiang, China

Correspondence to
Dr Xiaomin Pang;
congcong1035@163.com

ABSTRACT

Aims Inflammation plays a key role in the pathophysiology of cardiogenic shock (CS). Low-density lipoprotein cholesterol (LDL-C) is a biomarker of inflammation and is used to predict prognostic outcomes of several diseases. The primary purpose of this study was to evaluate if LDL-C can be used as a biomarker to predict the mortality of CS.

Methods and results Records of critically ill patients with CS were identified from the Medical Information Mart for Intensive Care III database. A multivariate Cox regression model was employed to adjust for imbalances by incorporating parameters and potential confounders. A total of 551 critically ill patients with CS were enrolled for this analysis, including 207 with LDL-C <1.8 mmol/L and 344 with LDL-C ≥1.8 mmol/L. Results of multivariate Cox regression models found that higher concentration of LDL-C (LDL-C ≥1.8mmol/L) was associated with a reduced risk of in-hospital mortality (HR 0.66, 95% CI 0.50 to 0.87; p=0.003) and 28-day mortality (HR 0.61, 95% CI 0.46 to 0.80; p=0.002) LDL-C in patients with CS. Patients with LDL-C ≥1.8 mmol/L were independently associated with improved in-hospital survival (HR 0.32, 95% CI 0.20 to 0.52, p<0.001) and 28-day survival (HR 0.51, 95% CI 0.33 to 0.73, p=0.002) compared with patients with LDL-C <1.8 mmol/L. The impact of LDL-C on in-hospital mortality and 28-day mortality persisted in patients with acute coronary syndrome (ACS) and was not statistically significant in the non-ACS subgroup.

Conclusions Our study observed that increased LDL-C level was related with improved survival in patients with CS, but not with improved outcomes in patients with uncomplicated ACS. The results need to be verified in randomised controlled trials.

Strengths and limitations of this study

► This was the first study to explore the prognostic value of low-density lipoprotein cholesterol (LDL-C) level in patients with cardiogenic shock.
► A multivariate Cox proportional hazards model and Kaplan-Meier model were used in the study.
► This was a retrospective observational study in a single centre.
► The sample size of patients selected was small.
► The level of LDL-C was measured only when patients were first admitted to the intensive care unit.

of patients with CS,[8 9] however, these inflammatory factors are not commonly measured in clinical practice.

Low-density lipoprotein cholesterol (LDL-C) is an important risk factor for ACS[10 11] and plays a key role in the inflammatory procedure.[12] Recent studies have found that initial LDL-C level was inversely associated with mortality in patients with ACS.[13–16] Meanwhile, data from large observational studies revealed that LDL-C may function as an inflammatory biomarker and is predictive of poor outcome in those with rheumatoid arthritis, heart failure, stroke and atrial fibrillation.[17–23]

Thus, we hypothesised that LDL-C may affect the prognosis of CS. However, the association between LDL-C and mortality in patients with CS remains unknown, and this study aimed to clarify the association.

INTRODUCTION

Cardiogenic shock (CS) continues to be associated with poor prognosis and acute coronary syndrome (ACS) remains the most common cause of CS.[1–3] Despite advances in pharmacological and mechanical circulatory support (MCS), short-term mortality remains as high as 35%–40% in recent studies.[4–7] Inflammatory markers and cytokines have demonstrated predictive power for mortality

METHODS
Data source

We extracted data from the Medical Information Mart for Intensive Care III V.1.4 (MIMIC-III, V.1.4), a publicly available and freely accessible intensive care unit (ICU) database.[24] The MIMIC-III database contains comprehensive, time-stamped information

for more than 60 000 ICU patients (medical, surgical, coronary care and neonatal) admitted to Beth Israel Deaconess Medical Centre (Boston, Massachusetts, USA) from 1 June 2001 to 31 October 2012 (single centre), representing more than 46 000 patients.

Study subjects

Patients in our study were selected from persons in MIMIC-III aged ≥18 years at ICU admission with CS (ICD-9-CM (International Classification of Diseases-9-Clinical Modification) diagnosis codes 785.51 or 998.01), plus any of the following criteria: minimum systolic blood pressure <90 mm Hg, or need for vasopressors therapy (any of dopamine, epinephrine, norepinephrine, phenylephrine, vasopressin), or with signs of hypoperfusion (first 24 hours of urine output <400 mL or maximum blood lactate >2 mmol/L). Patients with LDL-C measurement at the initial 48 hours of ICU entry were included. Of these patients, we excluded patients with ≤0 days or ≥100 days between ICU admission and discharge, defined as the earliest documented ICU discharge, hospital discharge or time of death. If patients who had multiple admissions to ICU, only the first ICU admission was included for analysis. Patients were also excluded as follows: 1. With more than 10% individual data missing; 2. Individual data values exceeded the mean ±3 times the SD

Data extraction

The following variables were extracted from the MIMIC-III database for the first day of ICU admission: age at the time of hospital admission, gender, ACS, LDL-C level, Acute Physiology Score III (APS III), Simplified Acute Physiology Score II, use of MCS, maximum lactate, maximum creatinine, maximum bilirubin, maximum international normalised ratio (INR), mean heart rate, mean of mean blood pressure, urine output first day after ICU entry, using milrinone, dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, vasopressin, mechanical ventilation and renal replacement therapy (RRT). If a variable was measured more than once in the first 24 hours, the maximum value was used.

The primary end point was the in-hospital mortality and 28-day mortality, which were defined as the survival status of patients at discharge and at day 28.

Statistical analysis

According to the target level of LDL-C in current guidelines,[10 11] the study population was categorised into low LDL-C (LDL-C <1.8 mmol/L) and high LDL-C (LDL-C ≥1.8 mmol/L) groups. Categorical variables were expressed as the number of percentages. They were compared between the low LDL-C and high LDL-C groups with χ^2 test or Fisher's exact test, as appropriate. Continuous variables were expressed as mean (SD) or median (IQR) with variance analysis or the Wilcoxon test, as appropriate.

We selected these potential confounders on the basis of their associations with the outcomes of interest or a
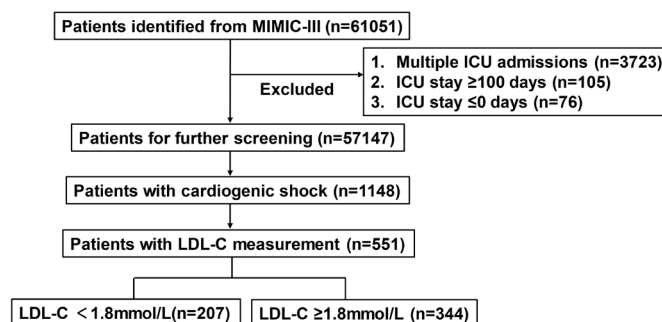

Figure 1 Flow chart of patient selection. ICU, intensive care unit; LDL-C, low-density lipoprotein cholesterol; MIMIC-III, Medical Information Mart forIntensive Care III,

change in effect estimate of >10% or values of p<0.1 in univariable analyses, as well as on strong clinical judgement. The multivariate Cox proportional hazards model and Kaplan-Meier model were used for survival analysis to adjust for imbalance by including parameters and potential confounders judged by clinical expertise.

A two-tailed value of p<0.05 was considered to be statistically significant. EmpowerStats V.2.17.8 (http://www.empowerstats.com/) and R software V.3.42 were used for all statistical analysis.

RESULTS
Subject characteristics

A total of 551 critically ill patients with CS were eligible for this analysis (figure 1). Table 1 shows the baseline characteristics of the low LDL-C (LDL-C <1.8 mmol/L) and high LDL-C (LDL-C ≥1.8 mmol/L) groups. There were higher baseline measures in the low LDL-C group, including age, maximum lactate, maximum creatinine and maximum INR. Patients in the low LDL-C group were more complicated with ACS, with more use of MCS, milrinone, dopamine and vasopressin. In the low LDL-C group, patients were less likely to be female, had lower APS III scores, mean blood pressure, mean heart rate, maximum bilirubin, and less use of dopamine, while having higher in-hospital and 28-day mortality.

Association between LDL-C level and mortality

The Kaplan-Meier survival estimate is shown in figure 2. During the in-hospital and 28-day follow-up periods, patients with LDL-C ≥1.8 mmol/L were associated with improved survival (p<0.001), as compared with patients with LDL-C <1.8 mmol/L.

Multivariate Cox regression model results demonstrated that higher level of LDL-C was associated with decreased risk of in-hospital mortality (HR 0.66, 95% CI 0.50 to 0.87; p=0.003) and 28-day mortality (HR 0.61, 95% CI 0.46 to 0.80; p=0.002) in patients with CS, after adjusting for age, gender, APS III, ASPS II, use of MCS, mechanical ventilation, RRT, milrinone, dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine and vasopressin.

Table 1 Baseline Characteristics*

Characteristics	LDL-C <1.8 mmol/L (n=207)	LDL-C ≥1.8 mmol/L (n=344)	P value
Age, years	70.58±11.05	61.45±11.76	<0.001
Gender, female (%)	66 (31.88)	155 (45.06)	0.002
ACS, n (%)	142 (68.60)	129 (37.50)	<0.001
APS III	47.68±19.72	51.18±17.07	0.028
SAPS II	40.14±13.08	39.82±10.91	0.761
MCS, n (%)	83 (40.10)	80 (23.26)	<0.001
IABP, n (%)	82 (39.61)	80 (23.26)	<0.001
ECMO, n (%)	3 (1.45)	0 (0.00)	0.025
Maximum lactate, mmol/L	4.83±4.41	3.10±2.61	<0.001
Maximum creatinine, mg/dL	2.13±1.67	1.60±0.89	<0.001
Maximum bilirubin, mg/dL	0.91±1.21	1.36±1.21	<0.001
Maximum INR	2.13±1.74	1.83±1.19	0.017
Mean heart rate, beats/minute	85.51±14.29	92.05±15.11	<0.001
Mean of mean BP, mm Hg	72.55±8.54	76.30±7.38	<0.001
Urine output first day, mL	1712.67±1261.28	1773.21±1083.08	0.564
LDL-C, mmol/L	1.11±0.38	2.30±0.67	<0.001
Mechanical ventilation, n (%)	92 (44.44)	170 (49.42)	0.258
RRT, n (%)	2 (0.97)	5 (1.45)	0.621
Milrinone, n (%)	37 (17.87)	23 (6.69)	<0.001
Dobutamine, n (%)	40 (19.32)	134 (38.95)	<0.001
Dopamine, n (%)	72 (34.78)	80 (23.26)	0.003
Epinephrine, n (%)	15 (7.25)	14 (4.07)	0.106
Norepinephrine, n (%)	63 (30.43)	126 (36.63)	0.138
Phenylephrine, n (%)	48 (23.19)	106 (30.81)	0.053
Vasopressin, n (%)	21 (10.14)	13 (3.78)	0.003
In-hospital mortality, n (%)	76 (36.71)	39 (11.34)	<0.001
28-day mortality, n (%)	70 (33.82)	36 (10.47)	<0.001

*plus–minus values are means±SD.
ACS, acute coronary syndrome; APS III, Acute Physiology Score III; BP, blood pressure; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; INR, international normalised ratio; LDL-C, Low-density lipoprotein cholesterol; MCS, mechanical circulatory support; RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score II.
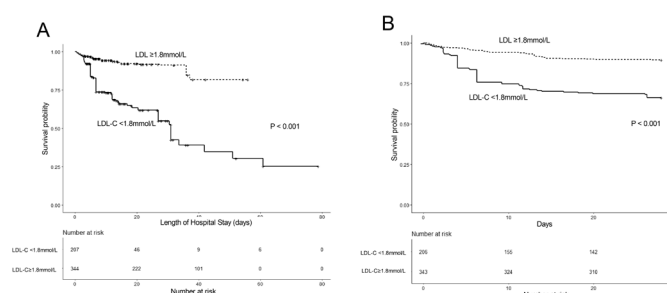

Figure 2 Kaplan-Meier survival from in-hospital mortality and 28-day mortality for patients with LDL-C <1.8 mmol/L and LDL-C ≥1.8 mmol/L. LDL-C, low-density lipoprotein cholesterol.

Compared with patients in the reference group (LDL-C <1.8 mmol/L), patients with CS with LDL-C ≥1.8 mmol/L were still independently related with improved in-hospital survival (HR 0.32, 95% CI 0.20 to 0.52, p<0.001) and 28-day survival (HR 0.51, 95% CI 0.33 to 0.73, p=0.002), adjusting for these potential confounders (table 2).

Subgroup analysis for patients with or without ACS in CS

There were 49.73% patients in CS complicated with ACS. Subgroup analysis was conducted among patients with ACS and non-ACS, as shown in figure 3. The relationship of LDL-C with in-hospital mortality (HR 0.36, 95% CI 0.21 to 0.60, p<0.001) as well as 28-day mortality (HR 0.53, 95% CI 0.34 to 0.83, p=0.002), remained in patients with ACS but was not statistically significant in the non-ACS subgroup.

Table 2 Association of LDL-C and in-hospital mortality and 28-day mortality by Cox regression after the multivariable model

	Death, n (%)	HR (95% CI)	P value
In-hospital mortality			
Multivariable model			
LDL-C per mmol/L		0.66 (0.50 to 0.87)	0.003
Multivariable model			
LDL-C <1.8 mmol/L	76 (36.71)	1	
LDL-C ≥1.8 mmol/L	39 (11.34)	0.32 (0.20 to 0.52)	<0.001
28-day mortality			
Multivariable model			
LDL-C per mmol/L		0.61 (0.46 to 0.80)	<0.001
Multivariable model			
LDL-C <1.8 mmol/L	70 (33.82)	1	
LDL-C ≥1.8 mmol/L	36 (10.47)	0.51 (0.33 to 0.78)	0.002

LDL-C, low-density lipoprotein cholesterol.

DISCUSSION

In the present retrospective study, data on survival end points showed that initially a higher level of LDL-C conferred a significantly lower risk of in-hospital mortality with an HR of 0.66 and 28-day mortality HR of 0.61. This inverse relationship was only statistically significant in patients of the ACS subgroup.

Previous randomised clinical studies, in addition to biological and experimental evidence, have provided convincing evidence that LDL-C is causally associated with the risk of coronary artery disease.[10 11] However, a number of studies have reported a protective association between higher concentrations of LDL-C and ACS.[13–15] In the Global Registry of Acute Coronary Events mortality model, lower in-hospital mortality was associated with hypercholesterolaemia in patients with ACS.[16] Meanwhile, an increased level of LDL-C was also associated with a lower risk of 30-day mortality, 1 year mortality and even 5-year mortality in patients with ACS,[13–16] respectively. To our knowledge, this 'lipid paradox' has not been reported in critically ill patients with CS. Indeed, we explored this paradox in the current study of patients

with CS and found a significant protective effect of LDL-C on hospitalisation and 28-day mortality after adjustment.

In our study, subgroup analysis showed that this lipid paradox was only statistically significant in patients with ACS. This should be mainly due to the inflammatory procedure for the underlying pathophysiology of patients with CS complicated with ACS.[8 9] Data from observational studies reported lower lipid levels in patients with active rheumatoid arthritis and postulated that this may be due to inflammatory processes.[23] An inflammatory biomarker release is also observed in acute pancreatitis in which the lipid paradox has been observed.[25] This inflammatory hypothesis has recently been reinforced in the Canakinumab Anti-inflammatory Thrombosis Outcome Study Trial, which studied the use of the orphan drug canakinumab to reduce the risk of developing cardiovascular events, using anti-inflammatory therapy with interleukin-1β inhibition.[26]

There are several limitations worth mentioning. Above all, there is a lack of randomisation and data from a single US centre were used, which may lead to selection bias. Second, in-hospital mortality and 28-day mortality were used, which may affect the assessment of long-term prognosis. In addition, it is to be noted that the nature of our study was observational, and this paradox relationship between lower LDL-C levels and mortality should be further tested in a randomised controlled study.

Figure 3 Subgroup analyses of in-hospital mortality and 28-day mortality among patients with ACS and non-ACS for patients in the LDL-C <1.8 mmol/L and LDL-C ≥1.8 mmol/L groups. ACS, acutecoronary syndrome.

CONCLUSIONS

In conclusion, in this study cohort of patients with CS, patients with high LDL-C levels were associated with lower in-hospital mortality and 28-day mortality compared with patients with low LDL-C levels. However, this relationship was only statistically significant in patients complicated with ACS. These findings should be prospectively evaluated by randomised controlled trials.
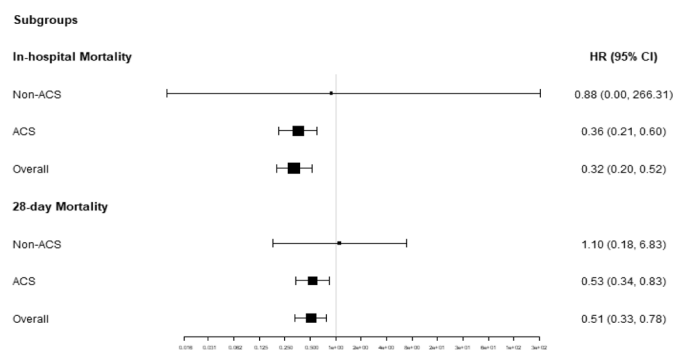
ORCID iD
Xiaomin Pang http://orcid.org/0000-0002-8918-4277

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