

Received: 2019.05.28

Accepted: 2019.07.08

Published: 2019.08.09

# Association Between Low-Density Lipoprotein Cholesterol (LDL-C) Level and Unfavorable Outcomes in Participants of Ischemic Stroke without Diabetes: A Multi-Center Retrospective Study

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Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Source of support:**

This study was supported by Natural Science Foundation of Liaoning Province (2018225065)

**Background:**

The impact of low-density lipoprotein cholesterol (LDL-C) levels on outcomes in patients with non-diabetic acute ischemic stroke remains uncertain. The objective of this study was to explore whether LDL-C could refine outcomes after acute ischemic stroke in patients with non-diabetic acute ischemic stroke.

**Material/Methods:**

A multi-center, retrospective, clinical-based study was conducted within eight hospitals between January 2015 and August 2016. Adjusted odds ratio (aOR) was used for measurement of unfavorable outcome which was evaluated by the modified Rankin Scale (mRS) score at 6 months after acute ischemic stroke, estimated categorically according to multivariate logistic regression.

**Results:**

A total of 1614 participants with non-diabetic acute ischemic stroke were enrolled, of which 376 patients (23.3%) had unfavorable neurologic outcomes at 6 months. After multivariate analysis comparing 4 LDL-C levels by quartiles (Q), we found that compared to Q1 (LDL-C level  $\leq 2.41$  mmol/L), there was a significant association between the frequency of unfavorable outcomes and levels of LDL-C (Q3: 2.95–3.54 mmol/L) for all participants (adjusted odds ratio [aOR]=0.63; 95% CI: 0.44–0.92,  $P=0.016$ ) and patients with first ever strokes (aOR=0.52; 95% CI: 0.31–0.87,  $P=0.013$ ).

**Conclusions:**


Compared to lower LDL-C levels, non-diabetic patients with LDL-C levels in Q3 (2.95–3.54 mmol/L), were less likely to have unfavorable functional outcomes at 6 months after acute ischemic stroke. Managing HDL-C is one of the most important steps for the recovery of acute ischemic stroke.

**MeSH Keywords:**

**Brain Ischemia • Lipoproteins, LDL • Neurodegenerative Diseases • Retrospective Studies**

**Full-text PDF:**

<https://www.medscimonit.com/abstract/index/idArt/917798>

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## Background

Stroke disease has become the second leading cause of death in the world [1,2]. The proportion of acute ischemic stroke (AIS) is significantly increasing globally. Previously, clinical-based studies have confirmed that the short-term outcomes of patients with AIS are significantly different, and some patients have poor prognosis and high mortality. Therefore, early identification of high-risk patients and regarding factors are important for prognosis. Several predictors for outcomes of AIS have been identified, such as age, cardiac disease, hypertension, and dyslipidemia [3–6]. However, the association between those factors and outcomes of AIS remains controversial. In recent years, some studies have suggested that low-density lipoprotein cholesterol (LDL-C) is a new important factor for AIS onset [5,7–9]. The serum LDL-C levels were reported to be positively correlated with AIS status among diabetes, but clinical research for serum LDL-C levels and short-term prognosis outcomes in non-diabetic patients with AIS were relatively small.

The current study aimed to investigate whether serum LDL-C levels were associated with short-term (6-month) functional outcomes in non-diabetic patients with AIS using a multi-center retrospective study design in China.

## Material and Methods

### Participants

A multi-center, retrospective, and clinical-based observation study was conducted at 8 hospitals in Panjin, Anshan, Liaoyang, and Dandong cities of Liaoning Province from January 2015 to August 2016. A comprehensive investigating process of this study has been published previously [10]. Briefly, participants who were admitted to those hospitals within 24 hours of AIS onset were enrolled, and their medical and radiological records were obtained at baseline. According to the medical records, participants with AIS were divided into 2 groups: first-ever stroke and recurrent stroke onset.

Patients were excluded from the current study if they had any of the following: 1) pre-existing mRS with more than 2 scores, 2) pre-existing any stroke that could hamper interpretation of clinical or radiological data, and 3) neurological or psychiatric disease.

### Clinic data collection

Data on demographics, medical history such as hypertension, diabetes mellitus as well as atrial fibrillation on admission were collected at baseline. Fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C

levels were determined within 24 hours after the onset of AIS at a fasting state.

### Outcomes measures

Functional outcomes at 6 months post-stroke were evaluated by the mRS. A favorable outcome was defined as an mRS score ranging from 0 to 2 points, while unfavorable outcome was considered to be an mRS score of 3 to 6 points at 6 months.

### Definition

AIS was diagnosed according to the World Health Organization recommendations. Recurrent stroke was defined if a period of neurological stability of  $\geq 24$  hours was demonstrated between the index stroke and the new neurological deficit, after excluding other potential causes of neurological deterioration. Current smoking was defined as consumption of  $\geq 1$  cigarette/day, and current drinking was defined as any dose of alcohol  $\geq 1$  time/week.

The current study was approved by the ethics committee of Liaoning Provincial Center for Disease Control and Prevention, and informed written consent was obtained from participants or the appropriate legal guardians.

### Statistical analysis

All analyses statistical procedures were performed using the Statistical Package for Social Scientists (SPSS v. 17.0) software (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared by use of Fisher's exact test. Means of 2 continuous normally distributed variables were compared by independent samples Student's *t* test. Mann-Whitney U test and Kruskal-Wallis test were used, respectively, to compare means of 2 and 3 or more groups of variables not normally distributed. LDL-C levels were divided into tertiles (quartile 1 [Q1],  $< 2.41$  mmol/L; quartile 2 [Q2], 2.41–2.95 mmol/L; quartile 3 [Q3], 2.96–3.54 mmol/L; quartile 4 [Q4],  $> 3.54$  mmol/L), with the lowest tertile being the reference tertile (Q1). Multivariable logistic regression was used to investigate the association between functional outcomes at 6 months (dependent variable) and concentration of LDL-C (independent variable) while adjusting for the confounders (age, gender, current smoking, current drinking, hypertension, transient ischemic attack [TIA], myocardial infarction and atrial fibrillation history) among all participants, participants with first ever strokes and recurrent strokes, respectively. A 2-tailed  $P < 0.05$  was considered statistically significant.

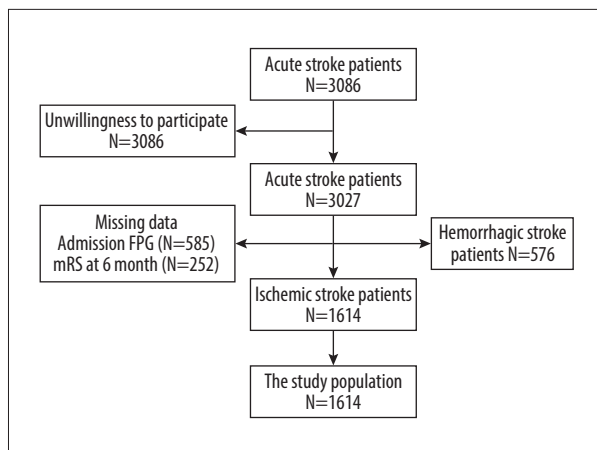


Figure 1. A flow chart for study participants in current study.

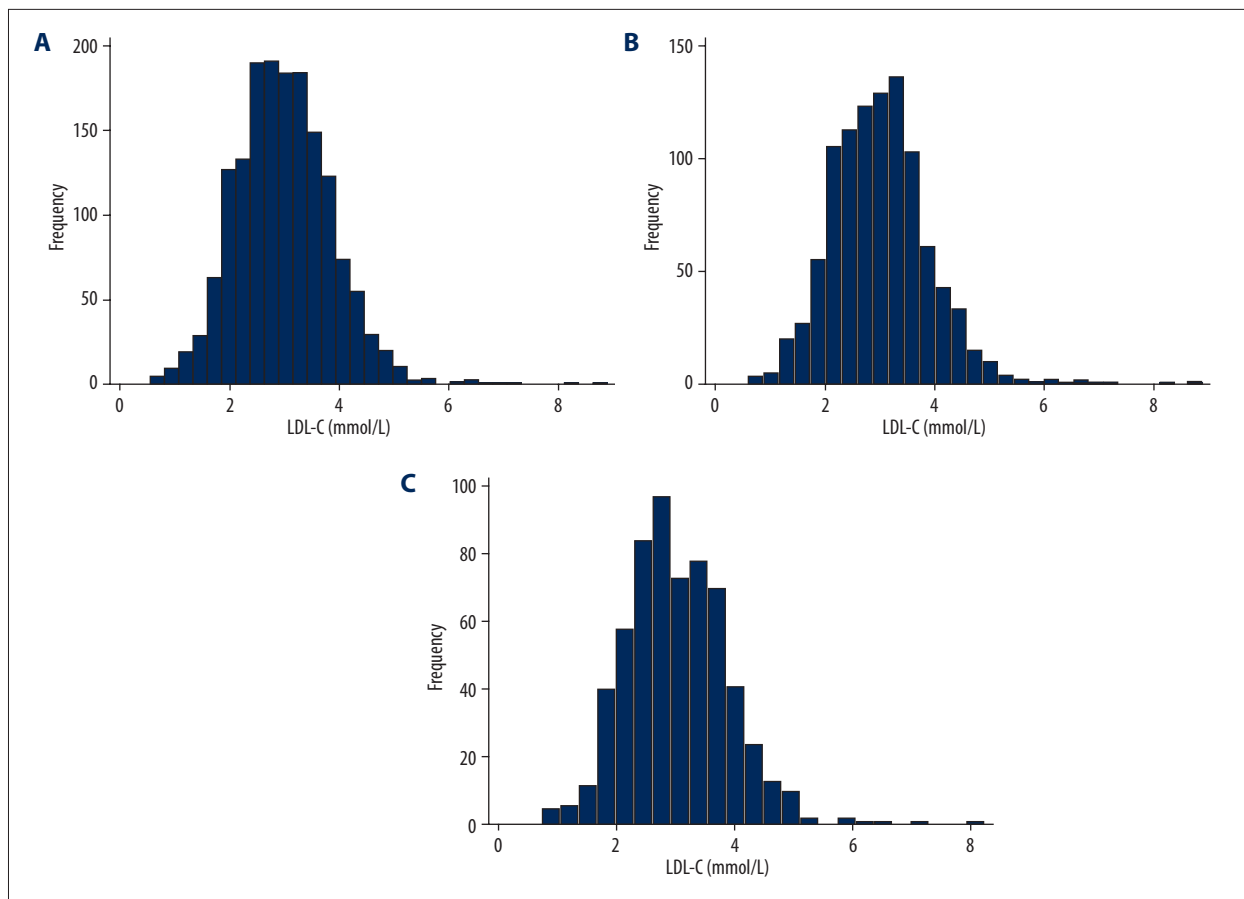
## Results

A total of 3086 patients with any type of stroke presented to 8 hospitals within 24 hours from the onset of AIS. After excluding those patients who were unwilling to participate (n=59), with hemorrhagic stroke (n=57), missing admission FPG level (n=585), and mRS at 6-month (n = 252), there were 1614 participants with non-diabetic AIS included in this study. The study flowchart is shown in Figure 1. Among those 1614 participants with AIS, there were 619 participants (38.4%) who had first ever stroke and 190 participants (11.8%) who had recurrent stroke. At 6-month follow-up, 1238 participants (76.7%) had favorable neurologic outcomes while 376 participants (23.3%) had unfavorable neurologic outcomes. Baseline characteristics of the 1614 participants are shown in Table 1. The participants with favorable neurologic outcomes were more likely

Table 1. Baseline characteristics of participants.

Variables	Unfavorable outcome (n=376)		Favorable outcome (n=1238)		P value
Sex (N, %)					0.038
Males	217	(57.71)	639	(51.62)	
Females	159	(42.29)	599	(48.38)	
Age groups (years, N, %)					<0.001
<60	43	(11.44)	269	(21.73)	
60–69	82	(21.81)	415	(33.52)	
70–79	117	(31.12)	366	(29.56)	
≥80	134	(35.64)	188	(15.19)	
Current smoking (N, %)	86	(22.87)	309	(24.96)	0.410
Current drinking (N, %)	46	(12.23)	160	(12.92)	0.725
Hypertension history (N, %)	230	(61.17)	766	(61.87)	0.806
DM history (N,%)	94	(25.00)	260	(21.00)	0.101
TIA history (N,%)	116	(30.85)	251	(20.27)	<0.001
Myocardial infarction history (N, %)	10	(2.66)	27	(2.18)	0.587
Atrial fibrillation history (N, %)	11	(2.93)	19	(1.53)	0.080
Recurrent stroke history (N, %)	104	(27.66)	86	(6.95)	<0.001
First-ever stroke (N, %)	180	(47.87)	439	(35.46)	<0.001
FPG (mmol/L)	6.40	(5.50–8.78)*	6.20	(5.40–7.83)*	0.012
LDL-C (mmol/L)	2.96±0.93#		3.03±0.88#		0.177
HDL-C (mmol/L)	1.19	(1.00–1.40)*	1.25	(1.02–1.60)*	0.007
TG (mmol/L)	1.36	(0.93–2.00)*	1.41	(1.03–2.07)*	0.019
TC (mmol/L)	4.80	(4.14–5.72)*	4.91	(4.19–5.60)*	0.420

DM – diabetes mellitus; TIA – transient ischemic attack; FPG – fasting plasma glucose; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides, TC – total cholesterol. \* Median and interquartile range; # Mean ± standard deviation.



**Figure 2.** Frequency histogram of the distribution of LDL-C among participants: (A) total participants, (B) first-ever participants, (C) recurrent stroke participants. LDL-C – low-density lipoprotein cholesterol.

to be male, older, and have TIA history, recurrent stroke, and first ever stroke, and had HDL-C and TG levels.

Figure 2 shows the distribution of mean LDL-C among all participants, first-ever stroke participants and recurrent stroke participants. Table 2 shows the characteristics of participants with first ever and recurrent stroke. The LDL-C levels in participants with recurrent stroke was slightly increased but did not reach statistical significance compared with those with first-ever stroke ( $2.99 \pm 0.90$  mmol/L versus  $3.04 \pm 0.88$  mmol/L,  $P=0.256$ ). Furthermore, the mRS score in patients with recurrent stroke was higher than that in patients with first-ever stroke ( $1.71 \pm 1.76$  versus  $1.31 \pm 1.80$ ,  $P<0.001$ ). Figure 3 shows the distributions of patients with scores ranging from 0 to 6. From Figure 4, we found that the incidence of unfavorable neurologic outcomes was a little lower in Q3 of LDL-C levels (18.32%).

In multivariable regression model adjusted for sex, age, current smoking, current drinking, hypertension, diabetes, TIA history, myocardial infarction history, atrial fibrillation history, recurrent stroke history, FPG, TG, and HDL-C levels, we found that participants with higher LDL-C levels (2.95–3.54 mmol/L)

were less likely to have unfavorable outcomes than those with lower LDL-C level ( $<2.41$  mmol/L) at 6-month follow-up (aOR: 0.63; 95% CI: 0.44–0.92,  $P=0.016$ ). Similar results were also seen in participants with first ever strokes (aOR: 0.52; 95% CI: 0.31–0.87,  $P=0.013$ , Table 3).

## Discussion

The current multi-center retrospective survey estimated the impact of baseline LDL-C levels on AIS outcomes in non-diabetic participants. Our findings revealed that non-diabetic participants with levels of LDL-C in the third quartile (2.95–3.54 mmol/L) were less likely to receive unfavorable outcomes at 6-month after AIS. In subgroup analysis, similar results were also found among participants with first ever stroke but this association was not significant among participants with recurrent stroke.

In contrast, previous studies reported that there was a significant association between LDL-C levels and AIS [11]. Epidemiological studies found that LDL-C was significantly

**Table 2.** Characteristics of participants with first ever and recurrent stroke.

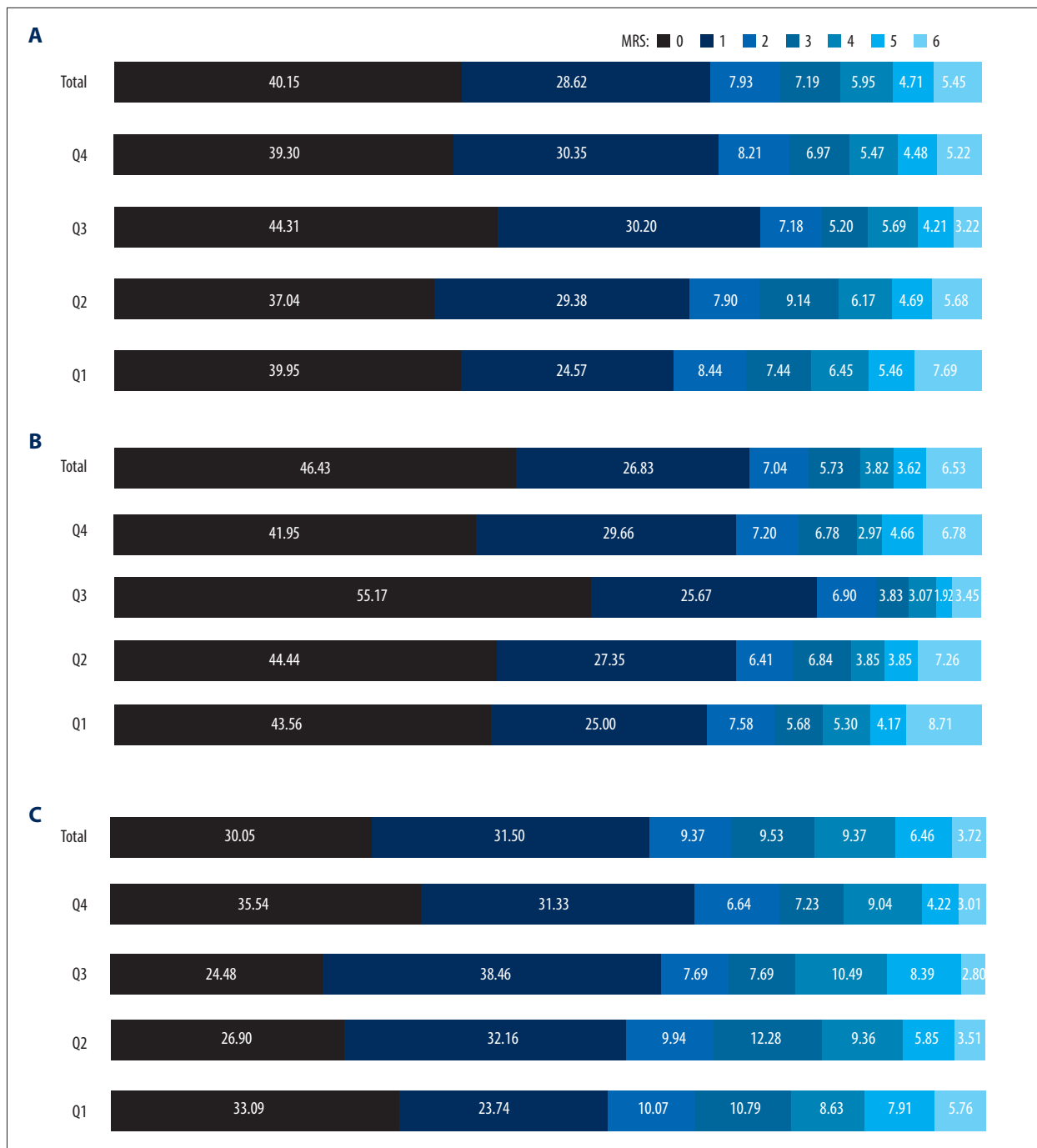
Variables	First ever stroke (n=995)		Recurrent stroke (n=619)		P value
Sex (N,%)					0.006
Males	501	(50.35)	355	(57.35)	
Females	494	(49.65)	264	(42.65)	
Age groups (years, N, %)					0.023
<60	216	(21.71)	96	(15.51)	
60–69	297	(29.85)	200	(32.31)	
70–79	287	(28.84)	196	(31.66)	
≥80	195	(19.60)	127	(20.52)	
Poor outcomes (N, %)	196	(19.70)	180	(29.08)	<0.001
Good outcomes (N, %)	799	(80.30)	439	(70.92)	<0.001
Current smoking (N, %)	249	(25.03)	146	(23.59)	0.513
Current drinking (N, %)	139	(13.97)	67	(10.82)	0.066
Hypertension history (N, %)	573	(57.59)	423	(68.34)	<0.001
DM history (N, %)	212	(21.31)	142	(22.94)	0.441
TIA history (N, %)	102	(10.25)	265	(42.81)	<0.001
Myocardial infarction history (N, %)	19	(1.91)	18	(2.91)	0.193
Atrial fibrillation history (N, %)	17	(1.71)	13	(2.10)	0.571
mRS	1.31±1.80		1.71±1.76		<0.001
FPG (mmol/L)	6.30	(5.40–8.00)*	6.20	(5.40–8.20)*	0.644
LDL-C (mmol/L)	2.99±0.90#		3.04±0.88#		0.256
HDL-C (mmol/L)	1.24	(1.01–1.50)*	1.19	(1.00–1.40)*	0.017
TG (mmol/L)	1.41	(1.00–2.06)*	1.40	(1.01–2.02)*	0.088
TC (mmol/L)	4.91	(4.19–5.68)*	4.86	(4.15–5.51)*	0.914

DM – diabetes mellitus; TIA – transient ischemic attack; Mrs – modified Rankin Scale; FPG – fasting plasma glucose; TC – total cholesterol; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; TG – triglycerides. \* Median and interquartile range; # Mean ± standard deviation.

related to the pathogenesis of cerebral infarction, and several studies confirmed that serum LDL-C level was one of the independent risk factors for ischemic stroke [9]. Moreover, previous studies showed that LDL-C level was positively correlated with carotid stenosis in elderly patients with cerebral infarction, and also positively correlated with the severity of cerebral infarction [12]. This discrepancy could also be explained by differences in study design. All participants in the current study were without diabetes or mRS over 2. Furthermore, the inconsistent correlation between LDL-C levels and outcomes of patients after AIS could be also due to the measurement of lipids levels in different states among these studies. In a study carried

out by Uyttenboogaart et al., serum lipid levels were measured in an acute phase and non-fasting state [13]. However, in our current study, we measured fasting lipid levels after the occurrence of AIS within 24 hours.

Previously studies suggested that LDL-C is an important pro-inflammatory mediator in the oxidative process. After oxidization, LDL-C becomes more pro-inflammatory [14,15]. Furthermore, inflammation has been identified as a crucial mechanism in the development of atherosclerosis as well as the pathogenesis of stroke. However, another report revealed that proper higher LDL-C level was protective for vascular endothelium



**Figure 3.** Bar chart responses as percentage values for LDL-C and mRS: (A) total participants, (B) first-ever participants, (C) recurrent stroke participants. LDL-C – low-density lipoprotein cholesterol; mRS – modified Rankin Scale.

structure and function [16]. Hence, we can deduce that there might be potential alterations that could lead to the observed positive impact of higher LDL-C level to the favorable stroke outcome, but this hypothesis still needed further confirmation.

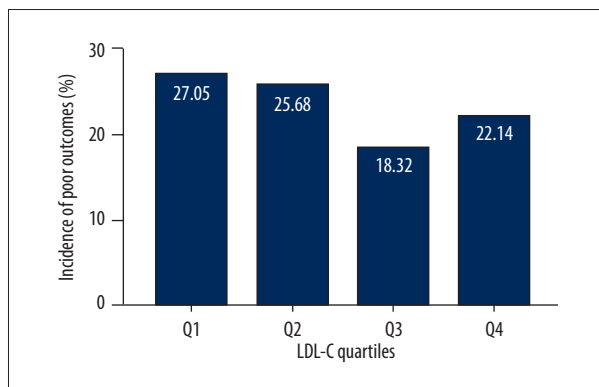
Our results are compatible with those findings in previous studies which revealed that the serum LDL-C level caused poor functional

outcomes after AIS onset [17–21]. In consistent with our results, low HDL-C and TG levels were independently associated with mortality onset, and a higher HDL-C level was correlated with favorable functional outcomes at 3 months. Likewise, our findings noted that lipid levels were not associated to unfavorable outcomes. Rapid decrease of serum lipid levels is considered to be connected with active inflammation in acute illness status [22].

**Table 3.** Multivariable logistic regression for the association between LDL-C levels and outcomes after stroke.

Variables	All participants				First ever stroke participants				Recurrent stroke participants			
	Crude OR (95% CI)	P value	MV adjusted OR (95% CI)*	P value	Crude OR (95% CI)	P value	MV adjusted OR (95% CI) *	P value	Crude OR (95% CI)	P value	MV adjusted OR (95% CI) *	P value
Q1 (<2.41 mmol/L)	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Q2 (2.41–2.95 mmol/L)	0.97 (0.71, 1.33)	0.851	0.98 (0.69, 1.38)	0.892	1.01 (0.67, 1.54)	0.955	0.93 (0.58, 1.48)	0.751	0.92 (0.57, 1.49)	0.746	1.03 (0.61, 1.73)	0.915
Q3 (2.96–3–54 mmol/L)	<b>0.59 (0.42, 0.83)</b>	<b>0.002</b>	<b>0.63 (0.44, 0.92)</b>	<b>0.016</b>	<b>0.45 (0.28, 0.73)</b>	<b>0.001</b>	<b>0.52 (0.31, 0.87)</b>	<b>0.013</b>	0.78 (0.472, 1.31)	0.351	0.86 (0.49, 1.50)	0.601
Q4 (>3.54 mmol/L)	0.78 (0.57, 1.09)	0.144	0.86 (0.59, 1.23)	0.404	0.92 (0.59, 1.40)	0.690	1.03 (0.63, 1.68)	0.901	0.65 (0.39, 1.08)	0.094	0.71 (0.41, 1.24)	0.229

\* Adjusted for sex, age, current smoking, current drinking, hypertension, diabetes, TIA history, myocardial infarction history, atrial fibrillation history, recurrent stroke history, FPG, TG and HDL-C level. LDL-C – low-density lipoprotein cholesterol; Q – quartile; OR – odds ratio; CI – confidence interval; MV – multivariable; TIA – transient ischemic attack; FGP – fasting plasma glucose; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol.



**Figure 4.** Incidence of poor outcomes according to LDL-C quartiles. LDL-C – low-density lipoprotein cholesterol.

Our present study had several strengths, including the large sample size, multicenter, the retrospective study design which could establish the temporal direction of the associations. However, there are still several limitations in current study. Firstly, this hospital-based study included only participants with post-AIS from 8 hospitals located in Liaoning Province, Northern China, thus, this may introduce potential selection bias and diminish the generalizability of our findings. Secondly, we did not collect information on managements about participants

after AIS onset in our study. Therefore, the information provided is limited and it is not possible to determine whether and how the associations between LDL-C levels and outcomes after AIS onset differ by the type of management. Finally, although we have adjusted for potential covariates that relate to LDL-C and outcomes of AIS, residual confounding by unidentified confounders is still possible. Further studies are still needed to understand the mechanisms for the associations of LDL-C levels with outcomes of AIS onset.

### Conclusions

We have identified a protective factor for outcomes of AIS onset that is readily modifiable by LDL-C levels. Increasing the level of LDL-C appropriately was associated with a lower risk of unfavorable outcomes among non-diabetic patients with AIS in China and could have a clinically meaningful effect across the public health spectrum. Further studies are warranted to elucidate the underlying mechanisms.

### Conflict of interests

None.

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