Association between pre admission low-density lipoprotein cholesterol concentration and risk of large intracerebral hemorrhage: Results from the Kailuan study

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Abstract

Background: To examine the association between low-density lipoprotein cholesterol (LDL-C) concentrations and the risk of a large hematoma volume after intracerebral hemorrhage (ICH).

Methods: Patients from the Kailuan study (Tangshan, China) who were hospitalized with ICH during 2006 and 2020 were included in this study. The concentration of lipid concentrations, hematoma volume and other clinical characteristics were retrospectively collected and analyzed. Hematoma volumes were measured on the first available brain scan using the ABC/2 method. LDL-C concentrations were obtained from the last physical examination before the occurrence of ICH. LDL-C concentration was categorized into four groups in accordance with the quartiles. Logistic regression was used to assess the association between LDL-C concentrations and the risk of a large hematoma volume of ≥30 ml. A generalized linear regression model was used to analyze the dose–response relationship between LDL-C concentration and hematoma volume.

Results: A total of 836 patients with ICH were evaluated. In the Multivariate logistic regression, compared to the second quartile of LDL-C, the first quartile of LDL-C had a significantly higher risk of a large hematoma volume (OR 2.49 [95% CI 1.54–4.01]), and the higher quartile of LDL-C is not associated with higher odds of large hematoma volume. In the generalized linear regression model, the adjusted β for the association between LDL-C concentration and hematoma volume was 9.46 (95% confidence interval 2.87–16.04), whereas higher LDL-C concentration was not associated with a large hematoma volume.

Conclusions: This study confirmed that low LDL-C concentrations prior to ICH are associated with a higher risk of a large hematoma volume.
1 | INTRODUCTION

Intracerebral hemorrhage (ICH) is the second-most common cerebrovascular disease after ischemic stroke. Although ICH accounts for only 10%-20% of all strokes, it causes much higher mortality and disability rates than ischemic stroke.1–3 The prognosis of ICH depends mainly on the location and volume of the hematoma. Previous studies have shown that neurological recovery tends to be better when the hematoma volume is less than 30 ml,5 with a 30-day mortality rate of 93% when the hematoma volume is >60 ml.6 The risk factors affecting hematoma volume are abnormal lipid metabolism in addition to hypertension,7 diabetes mellitus,8 advanced age,9 warfarin use,10,11 body mass index (BMI), and alcohol consumption.12

High LDL-C concentration is an established risk factor for ischemic cardiovascular disease. Lowering the LDL-C concentration reduces the risk of ischemic cardiovascular disease, and various guidelines have proposed that it is ideal to have as low a LDL-C concentration as possible.13,14 However, although low LDL-C concentrations have been found to reduce the risk of ischemic cardiovascular events, they may increase the risk of ICH and induce a larger hematoma volume.12,15,16 While previous studies have evaluated the association between LDL-C concentrations and hematoma volume after hospital admission, the post-admission LDL-C concentration does not truly reflect the pre-admission LDL-C concentration. Therefore, we analyzed the association between the pre-admission LDL-C concentration and the hematoma volume using data from the Kailuan study.

2 | METHODS

2.1 | Participants

The Kailuan study was a community-based multicenter study including 101,510 participants (81,110 men and 20,400 women, aged 18–98 years) designed to investigate the risk factors for chronic diseases, including cerebrovascular disease.17 The Kailuan study started in 2006. All participants were followed biennially to obtain lipid concentrations, including LDL-C, and to update information on potential risk factors and newly diagnosed diseases, including ICH. The Kailuan study participants have made seven follow-up visits to date. The Kailuan study followed the ethical standards set out in the Declaration of Helsinki and was approved by the Ethics Committee of Kailuan General Hospital.

Inclusion criteria were participation in the Kailuan study (including baseline assessment and follow-up) and development of spontaneous ICH.

Exclusion criteria were trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, simple ventricular hemorrhage or subarachnoid hemorrhage, vascular malformation, or any other suspected cause of secondary ICH. We also excluded participants for whom all LDL-C data were missing, and those with a history of cancer or oral anticoagulant therapy before baseline assessment.

2.2 | Assessment of incident ICH

The outcome of interest was the first occurrence of ICH. All Kailuan study participants were included in the Municipal Social Insurance Institution database and Hospital Discharge Register, which were searched to identify potential cases of incident ICH. ICH cases were identified by International Classification of Diseases, 10th revision codes (I61.0–I61.9). These ICH cases were then reviewed by two neurosurgeons and a radiologist. The diagnosis of ICH was based on the World Health Organization criteria and confirmed by CT or MRI of the brain.

2.3 | Imaging analysis

Initial head CT images were acquired within 24 h of the onset of ICH. Hematoma volume was measured by the ABC/2 method.18 All patients with ICH were divided into those with a large hematoma volume of ≥30 ml (large group) and those with a small hematoma volume of <30 ml (small group).19 For all patients with ICH, there was clear information on the location of the ICH, which was reviewed by an experienced radiologist and a specialized neurosurgeon. Patients with ICH were categorized based on hematoma location into those with non-lobe hematoma (i.e., hemorrhage originating in the thalamus, basal ganglia, cerebellum, or brainstem) and those with lobar hematoma (i.e., cerebral hemorrhage originating in the cortex or corticosubcortical junction).

2.4 | Assessment of serum biochemical indicators

Biochemical data were obtained from the last physical examination before the occurrence of ICH. For example, for a patient who developed ICH in 2009, we used the physical examination data from 2008; if the physical examination data from 2008 were missing, we...
used the physical examination data from 2006; if these data were no longer available, they were defined as missing values.

Blood samples were collected in the morning after overnight fasting. Concentrations of LDL-C, high-density lipoprotein cholesterol, triglycerides, and total cholesterol were measured with the enzymatic colorimetric method (Mind Bloengineering Co. Ltd.). The interassay coefficient of variation for each measurement was <10% with the use of an autoanalyzer (Hitachi 747, Hitachi, Tokyo, Japan) at the central laboratory of Kaite General Hospital.

Fasting blood samples were collected in the morning after an 8- to 12-h overnight fast and transferred into vacuum tubes containing EDTA. An autoanalyzer (Hitachi 747; Hitachi, Tokyo) was used to measure the fasting blood glucose concentration with the hexokinase/glucose-6-phosphate dehydrogenase method. The coefficient of variation for blind quality control specimens was <2.0%.

2.5 | Assessment of potential covariates

Information on age, sex, smoking status, alcohol intake, and medical history (e.g., hypertension, diabetes mellitus, coronary heart disease, ischemic stroke, and active treatment with hypoglycemic, antihypertensive, or lipid-lowering agents) was collected via questionnaires. Weight and height were measured by trained fieldworkers. BMI was calculated as the body weight (kg) divided by the height squared (m²). Systolic and diastolic blood pressures were measured twice with a mercury sphygmomanometer with the patient in the seated position.

Hypertension was defined as a systolic blood pressure of ≥140 mmHg, diastolic blood pressure of ≥90 mmHg, or use of antihypertensive medications in the last 2 weeks (regardless of blood pressure readings). Diabetes mellitus was defined as a fasting blood glucose concentration of 7.0 mmol/L, use of an oral hypoglycemic agent, or active treatment with insulin.

2.6 | Statistical analyses

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Formal hypothesis testing was two-sided with a significance level of 0.05. Discrete variables were expressed as number (percentage), while continuous variables were expressed as mean (standard deviation) or median (interquartile range), as appropriate. We compared the characteristics of the large and small groups using either the t test or Mann–Whitney test for continuous variables, and either the χ² or Fisher test for categorical variables.

LDL-C concentration was categorized into four groups in accordance with the quartiles (Q1–Q4). The LDL-C Q2 concentration was used as the reference group in all models. Multivariable logistic regression was used to assess the association between LDL-C concentrations and the risk of a large hematoma volume. Multivariable analyses were expressed using the odds ratio (OR) and 95% confidence interval (CI). Multiple regression models were run as follows. Model 1 was adjusted for age and sex. Model 2 was adjusted for the variables in model 1 plus smoking status, alcohol consumption. Model 3 was further adjusted for history of ischemic stroke, history of coronary artery disease, administration of antihypertensive drugs, lipid regulators, or hypoglycemic drugs, high-density lipoprotein cholesterol concentration, total cholesterol concentration, fasting blood glucose concentration, systolic blood pressure, and BMI.

Because the hematoma volume is influenced by the location of the hematoma, we also used a multivariate logistic regression model stratified by different hematoma locations.

To investigate whether the effect of LDL-C concentration on hematoma volume interacted with the factors of age, hypertension, or BMI, we performed an interaction analysis and repeated the multivariate logistic regression model stratified by age, hypertension, and BMI.

To analyze whether the relationship between LDL-C concentration and hematoma volume was affected by the administration of lipid-lowering drugs, we conducted a sensitivity analysis by excluding patients who used lipid-lowering agents. Because anticoagulants would increase the hematoma volume, we excluded patients with ischemic stroke or coronary artery disease, which are major indications for anticoagulant therapy, as these patients may have been using anticoagulants. We excluded patients with diabetes mellitus because blood glucose concentration may affect the hematoma volume. The multivariate logistic regression analysis was repeated after excluding patients with the above mentioned factors separately.

The median number of years from the time of the last examination to the occurrence of ICH was 1.76 years; therefore, we excluded patients who developed ICH at ≥2 years after the last examination and repeated the multivariate logistic regression model.

To determine the dose–response relationship between LDL-C concentration and hematoma volume, we used a generalized linear regression model to analyze the effect of LDL-C concentration on hematoma volume. In the unadjusted model, only the LDL-C quartile group was used as an independent variable; the adjusted model included the same covariates as the logistic model analysis.

3 | RESULTS

There were 910 cases of incident ICH identified during the 14-year follow-up period (2006–2020). After the exclusion of three patients with malignancy, eight patients taking oral anticoagulant drugs, 17 patients with missing data and 46 patients with simple ventricular hemorrhage, there were 836 patients with ICH included in the analysis. The mean patient age was 61.55 ± 10.95 years, 90.79% of the study cohort were men, and the median hematoma volume was 9.00 ml (interquartile range: 3.59–25.98). There were 668 patients with a hematoma volume of <30 ml and 168 with a hematoma volume of ≥30 ml. Compared with the large group, the small group had significantly higher prevalence of previous ischemic stroke and lobar hemorrhage, and tended to have higher prevalence of hypertension, diabetes mellitus, and previous coronary heart disease.
The proportion of patients in the LDL-C Q1 group was significantly higher in the large group than the small group (Table 1).

Multivariate logistic regression showed that patients in the LDL-C Q1 group had a significantly higher risk of developing a large hematoma volume than those in the LDL-C Q2 group (OR 2.49 [95% CI 1.54–4.01]) (Table 2).

The median hematoma volume was significantly larger for lobar hemorrhage (17.76 ml) compared with non-lobar hemorrhage (7.67 ml) (not listed in the table). In the LDL-C Q1 group, the risk of a large hematoma volume was not increased among patients with lobar hemorrhage, but was increased among patients with non-lobar hemorrhage (OR 3.17 [95% CI 1.78–5.65]) (Table 3).

The association between LDL-C concentration and hematoma volume was modified by age, hypertension status, and BMI (p <.1 for all interactions). After further stratification, repeated multivariate logistic regression found that being in the LDL-C Q1 group significantly increased the risk of a hematoma volume of >30 ml in patients ≥60 years (OR 2.78 [95% CI 1.39–5.57]), patients with hypertension (OR 2.25 [95% CI 1.29–3.92]), and patients with a BMI of <28 kg/m² (OR 3.12 [95% CI 1.75–5.55]) (Table 4).

The sensitivity analyses showed that the results were unchanged by the exclusion of patients with a history of ischemic stroke, diabetes mellitus, or coronary heart disease; patients who used lipid-lowering drugs during follow-up; or patients with an interval of more than 2 years between the last physical examination and the onset of ICH (Table 5).

The multivariable generalized linear model is presented in Table 6. Compared with the LDL-C Q2 group, the LDL-C Q1 group had a larger hematoma volume (j = 9.46 [95% CI 2.87–16.04]) (Table 6).

4 | DISCUSSION

The main finding of the present study was that the lowest LDL-C concentration (<1.95 mmol/L) was a risk factor for a hematoma

### TABLE 1 Characteristics of the study participants according to hematoma volume

| Characteristics                          | Volume (ml) | p-value |
|------------------------------------------|-------------|---------|
|                                         | Total (n = 836) | Small (<30 ml (n = 668) | Large (≥30 ml (n = 168) | |
| ICH volume (cm³, median, IQR)            | 9.00 (3.59–25.98) | 6.41 (2.66–13.15) | 50.22 (36.00–72.22) | <.0001 |
| Male, n (%)                              | 759 (90.79) | 606 (90.72) | 153 (91.07) | .89 |
| Age (years, mean ± SD)                   | 61.55 ± 10.95 | 61.71 ± 11.11 | 60.89 ± 10.32 | .38 |
| Current drinker, n (%)                   | 277 (33.13) | 224 (33.53) | 53 (31.55) | .63 |
| Current smoker, n (%)                    | 335 (40.07) | 268 (40.12) | 67 (39.88) | .96 |
| Diabetes, n (%)                          | 143 (17.11) | 107 (16.02) | 36 (21.43) | .096 |
| Hypertension, n (%)                      | 666 (79.67) | 530 (79.34) | 136 (80.95) | .64 |
| History of coronary heart disease, n (%) | 24 (2.87) | 18 (2.69) | 6 (3.57) | .54 |
| History of ischemic stroke, n (%)        | 37 (4.43) | 24 (3.59) | 13 (7.74) | .02 |
| ICH location, lobar, n (%)               | 149 (18.72) | 94 (14.07) | 55 (32.74) | <.0001 |
| Use of lipid-lowering agents, n%         | 43 (5.14) | 35 (5.24) | 8 (4.76) | .80 |
| Use of antihypertensive agents, n%       | 240 (28.71) | 194 (29.04) | 46 (27.38) | .67 |
| Use of hypoglycemic agents, n%           | 29 (3.47) | 22 (3.29) | 7 (4.17) | .58 |
| LDL_C (mmol/L, mean ± SD)                | 2.52 ± 0.91 | 2.58 ± 0.91 | 2.30 ± 0.87 | .0004 |
| LDL_C category, n (%)                    | <.0001 |
| Q1 (<1.95 mmol/L), n (%)                 | 207 (24.76) | 140 (20.96) | 67 (39.88) | |
| Q2 (1.95–2.51 mmol/L), n (%)             | 211 (25.24) | 177 (26.50) | 34 (20.24) | |
| Q3 (≥2.51–<3.10 mmol/L), n (%)           | 207 (24.76) | 170 (25.45) | 37 (22.02) | |
| Q4 (≥3.10 mmol/L), n (%)                 | 211 (25.24) | 181 (27.10) | 30 (17.86) | |
| HDL_C (mmol/L, mean ± SD)                | 1.49 ± 0.44 | 1.50 ± 0.45 | 1.48 ± 0.41 | .67 |
| TC (mmol/L, mean ± SD)                   | 5.02 ± 1.16 | 5.05 ± 1.19 | 4.89 ± 1.05 | .13 |
| TG (mmol/L, median, IQR)                 | 1.34 (0.96–1.98) | 1.33 (0.94–1.98) | 1.40 (1.00–2.04) | .72 |
| SBP (mmHg, mean ± SD)                    | 149.38 ± 23.40 | 149.91 ± 23.56 | 147.29 ± 22.69 | .20 |
| DBP (mmHg, mean ± SD)                    | 91.12 ± 13.19 | 91.54 ± 13.22 | 89.42 ± 12.99 | .06 |
| FBG (mmol/L, mean ± SD)                  | 6.07 ± 2.29 | 6.07 ± 2.32 | 6.05 ± 2.19 | .92 |
| BMI (kg/m², mean ± SD)                   | 25.50 ± 3.40 | 25.46 ± 3.37 | 25.46 ± 3.49 | .55 |

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL_C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.
active correlation between the LDL-C concentration within 24 h of admission and the cube root of the initial hematoma volume (linear quartile of LDL-C concentration compared with the second quartile. A prospective cohort study of 672 patients with ICH found an increase in the hematoma volume of 9.46 ml in the lowest quartile of LDL-C concentration compared with the second quartile.

In contrast, Jose et al. found no relationship between the LDL-C concentration at admission and the hematoma volume (r = 0.140; p = .192). Compared with these previous studies, our study included a larger population and was the first to use the pre-admission LDL-C concentration in the analysis, making our results more reliable.

Our study not only found that low LDL-C concentrations were a risk factor for a hematoma volume of ≥30 ml, but also found an age-dependent increase in this risk. In the ≥60-year age group, the OR value was 1.93 but the 95% CI was 0.90–4.17; in the <60-year age group, the OR value was 2.78 and the 95% CI was 1.39–5.57. Although no previous studies have evaluated the effects of different LDL-C concentrations on hematoma volume in different age groups, studies from the Kaiser Permanente Medical Care Program found that cholesterol concentrations in the lowest decile increased the risk of ICH only in those aged ≥65 years (OR 2.7 [95% CI 1.40–5.0]).

### TABLE 2 Multivariate logistic regression analyses evaluating the association of different quartiles of LDL-C with the likelihood of large hematoma volume

|        | Q1 | Q2          | Q3          | Q4          |
|--------|----|-------------|-------------|-------------|
|        | <1.95 mmol/L | >=1.95–<2.51 mmol/L | >=2.51–<3.10 mmol/L | >=3.10 mmol/L |
| Cases/population, n | 67/207 | 34/211 | 37/207 | 30/211 |
| Model 1 (OR, 95% CI) | 2.48 (1.55–3.97) | 1 (Referent) | 1.13 (0.68–1.88) | 0.86 (0.50–1.47) |
| p-value | 0.0001 | 1 (Referent) | 0.65 | 0.58 |
| Model 2 (OR, 95% CI) | 2.49 (1.56–3.98) | 1 (Referent) | 1.13 (0.68–1.89) | 0.86 (0.51–1.47) |
| p-value | 0.0001 | 1 (Referent) | 0.63 | 0.59 |
| Model 3 (OR, 95% CI) | 2.49(1.54–4.01) | 1 (Referent) | 1.16(0.69–1.96) | 0.84(0.49–1.45) |
| p-value | 0.0002 | 1 (Referent) | 0.57 | 0.53 |

Note: Model 1 adjusted for age, gender.
Note: Model 2 adjusted for all variables in Model 1 and additionally adjusted for smoking status (never, current smoker), drinking status (never, current drinker).
Note: Model 3 adjusted for all variables in Model 2 and additionally adjusted for history of coronary heart disease (no, yes), history of ischemic stroke (no, yes), use of lipid-lowering agents (no, yes), use of antihypertensive agents (no, yes), use of hypoglycemic agents (no, yes), HDL_C (mmol/L), TG (mmol/L), Sbp (mmHg), BMI (kg/m²).

### TABLE 3 Adjusteda ORs and 95% CIs for risk of the large hematoma volume according to the quartiles of LDL-C in different ICH location

|        | Lobar | Non-lobar |
|--------|-------|-----------|
|        | <1.78 mmol/L | >=1.78–<2.40 mmol/L | >=2.40–<2.99 mmol/L | >=2.99 mmol/L |
| Cases/population | 20/42 | 14/36 | 10/32 | 11/39 |
| hematoma volume, median (IQR) | 24.00 (7.88–49.34) | 16.89 (4.13–45.26) | 18.01 (7.01–36.80) | 13.20 (7.14–35.44) |
| OR (95% CI) | 1.79 (0.62–5.21) | 1 (Referent) | 0.51 (0.15–1.71) | 0.32 (0.09–1.21) |
| p-value | 0.29 | 1 (Referent) | 0.28 | 0.09 |
| Cases/population | 55/153 | 36/173 | 30/167 | 16/174 |
| hematoma volume, median (IQR) | 13.55 (5.25–32.4) | 6.96 (2.88–18.00) | 6.46 (2.95–20.79) | 6.92 (2.88–16.10) |
| OR (95% CI) | 3.17 (1.78–5.65) | 1 (Referent) | 1.45 (0.78–2.70) | 0.98 (0.50–1.91) |
| p-value | <0.0001 | 1 (Referent) | 0.24 | 0.95 |

Abbreviations: CI = confidence interval; OR = Odds Ratio.
a: All models were adjusted for age, gender, smoking status (never, current smoker), drinking status (never, current drinker), Diabetes (no, yes), Hypertension (no, yes), Snore (no, yes), History of coronary heart disease (no, yes), history of ischemic stroke (no, yes), use of lipid-lowering agents (no, yes), use of antihypertensive agents (no, yes), use of hypoglycemic agents (no, yes), HDL_C (mmol/L), TG (mmol/L), Sbp (mmHg), BMI (kg/m²).

volume of ≥30 ml, and this risk was independent of traditional risk factors for large hematoma volumes. The risk of a large hematoma volume due to a low LDL-C concentration is likely to be more pronounced in patients ≥60 years of age, patients with hypertension, patients without obesity, and patients with non-lobar hemorrhage.

Our findings further confirm the findings of previous studies. A prospective cohort study of 672 patients with ICH found a negative correlation between the LDL-C concentration within 24 h of admission and the cube root of the initial hematoma volume (linear regression coefficient: −0.021, 95% CI: −0.042, −0.001; p = .049). Another study showed a correlation between the LDL-C concentration at admission and the hematoma volume at 24 h after admission (r = 0.23; p = .033). Our generalized linear regression analysis found an increase in the hematoma volume of 9.46 ml in the lowest quartile of LDL-C concentration compared with the second quartile.
11% reduction in the risk of ICH for each 1 mmol/L increase in serum cholesterol concentration (hazard ratio 0.89; 95% CI 0.84–0.94) in patients older than 60 years.

Abbreviations: CI = confidence interval; OR = Odds Ratio.

In the China Kadoorie Biobank project, Cox regression was used to estimate the adjusted relative risks (RRs) and 95% CIs for the risk of ICH per 1 mmol/L increase in the usual LDL-C concentration; the RR (95% CI) was 1.04 (0.9–1.2) in the 30–54-year age group, 0.82 (0.72–0.93) in the 55–60-year age group, and 0.83 (0.75–0.92) in the 65–89-year age group, indicating a significant age dependence. Combined with the findings of our study, we suggest that the influence of LDL-C concentration on the risk of ICH and the hematoma volume increase as the patient age increases, and are especially evident in patients older than 60 years.

We found that low LDL-C concentrations increased the risk of a large hematoma volume only in hypertensive patients (OR 2.25; 95% CI 1.29–3.92), suggesting that hypertension may mediate the effect of low LDL-C concentrations on hematoma volume. A 6-year follow-up study of 350,977 middle-aged American men found that the inverse association between low LDL-C concentrations and the risk of ICH was limited to hypertensive patients. Combined with the results of these previous studies, we suggest that hypertension may mediate the increased risk of a large hematoma volume caused by a low LDL-C concentration.

Our study also found that a low LDL-C concentration increased the risk of a large hematoma volume in patients without obesity (OR 3.12 [95% CI 1.75–5.55]); in contrast, the OR for patients with obesity was 1.85 (95% CI 0.66–5.22). A previous study of 1039 patients with supratentorial deep ICH found that the mean hematoma volume in the lowest BMI quartile was increased by approximately 31% compared with the highest BMI quartile ($p = 0.305$; $p < 0.001$). Alessandro et al. also found that a low BMI (<18.5 kg/m^2) increased the risk of deep ICH (OR 1.76; $p = .011$). Because of the coexistence of low body weight and low LDL-C concentration, it was not possible to determine whether low body weight or low LDL-C concentration increased the risk of a large hematoma volume; this issue needs to be investigated in further cohort studies.

In our study, the association between low LDL-C concentration and the risk of a large hematoma volume was only found in patients with non-lobar ICH (OR 3.17 [95% CI 1.78–5.65]). Similarly, previous

| TABLE 4 | Adjusted ORs and 95% CIs for risk of the large hematoma volume according to the quartiles of LDL-C, stratified by age, hypertension, BMI |
|---------|---------------------------------------------------------------|
|         | Q1 | Q2 | Q3 | Q4 | P Interaction |
| Age     |     |     |     |     |               |
| Cases/population | 27/97 | 16/94 | 18/96 | 15/94 | 0.0001 |
| <60 years | 1.93 (0.90,4.17) | 1 (Referent) | 1.28 (0.57,2.87) | 0.96 (0.41,2.20) |     |
| p-value | 0.09 | 0.09 | 0.55 | 0.91 |     |
| Cases/population | 40/110 | 18/117 | 19/111 | 15/117 |     |
| ≥60 years | 2.78 (1.39,5.57) | 1 (Referent) | 1.01 (0.47,2.17) | 0.74 (0.33,1.66) |     |
| p-value | 0.0038 | 0.98 | 0.47 |     |     |
| Hypertension |     |     |     |     | 0.0003 |
| Cases/population | 57/174 | 28/159 | 29/164 | 22/169 |     |
| Yes | 2.25 (1.29–3.92) | 1 (Referent) | 0.99 (0.54–1.81) | 0.65 (0.34–1.24) |     |
| p-value | 0.0043 | 0.98 | 0.19 |     |     |
| Cases/population | 10/33 | 6/52 | 8/43 | 8/42 |     |
| No | 4.17 (0.86–20.2) | 1 (Referent) | 2.49 (0.57–10.94) | 3.02 (0.36–25.54) |     |
| p-value | 0.08 | 0.22 | 0.31 |     |     |
| BMI |     |     |     |     | 0.018 |
| Cases/population | 53/154 | 21/55 | 26/164 | 25/172 |     |
| <28kg/m^2 | 3.12 (1.75–5.55) | 1 (Referent) | 1.19 (0.63–2.24) | 1.06 (0.56–2.00) |     |
| p-value | 0.0001 | 0.58 | 0.86 |     |     |
| Cases/population | 14/53 | 13/56 | 11/43 | 5/39 |     |
| ≥28 kg/m^2 | 1.85 (0.66–5.22) | 1 (Referent) | 1.11 (0.39–3.16) | 0.36 (0.10–1.33) |     |
| p-value | 0.24 | 0.85 | 0.12 |     |     |

Abbreviations: CI = confidence interval; OR = Odds Ratio.

*All models were adjusted for age, gender, ICH location (lobar, non-lobar), smoking status (never, current smoker), drinking status (never, current drinker), Diabetes (no, yes), Hypertension (no, yes), Snore (no, yes), History of coronary heart disease (no, yes), history of ischemic stroke (no, yes), use of lipid-lowering agents (no, yes), use of antihypertensive agents (no, yes), use of hypoglycemic agents (no, yes), HDL_C (mmol/L), TG (mmol/L), Sbp (mmHg), BMI (kg/m^2).
studies have found that hypercholesterolemia was only associated with non-lobar bleeding (OR 0.46 [95% CI 0.34–0.62]), and that elevated LDL concentrations were only significantly associated with a reduced risk of non-lobar hemorrhage recurrence (hazard ratio 0.88, 95% CI 0.78–0.98 for every 10 mg/dl increase). This may be related to the site-specific pathogenesis of ICH.

We found an association between LDL-C concentration and hematoma volume in elderly patients, hypertensive patients, patients without obesity, and patients with non-lobar hemorrhage; however, the specific mechanism remains unclear. Elderly and hypertensive patients have more severe arteriolar sclerosis, are more likely to form cerebral microaneurysms, and are at higher risk of ICH. Ooneda et al. showed that a low LDL-C concentration promotes necrosis

| Table 5 | Adjusted ORs and 95% CIs for risk of the large hematoma volume according to the quartiles of LDL-C in the sensitivity analysis |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Excluding history of ischemic stroke | Excluding Lipid-lowering drugs use | Excluding history of coronary heart disease | Excluding diabetes |
| Cases/population | Multivariate-adjusted (OR, CI) | p-value | Cases/population | Multivariate-adjusted (OR, CI) | p-value | Cases/population | Multivariate-adjusted (OR, CI) | p-value |
| Q1 <1.95 mmol/L | Q2 >= 1.95–<2.51 mmol/L | Q3 >= 2.51–<3.10 mmol/L | Q4 >= 3.10 mmol/L | Q1 <1.95 mmol/L | Q2 >= 1.95–<2.51 mmol/L | Q3 >= 2.51–<3.10 mmol/L | Q4 >= 3.10 mmol/L |
| 59/192 | 34/205 | 34/197 | 28/205 | 64/198 | 32/197 | 35/201 | 29/197 | 64/201 | 34/208 | 35/200 | 29/203 | 58/173 | 25/184 | 29/169 | 20/167 |
| 2.21 (1.36–3.61) | 1 (Referent) | 1.06 (0.62–1.79) | 0.78 (0.45–1.34) | 2.43 (1.49–3.98) | 1 (Referent) | 1.10 (0.64–1.87) | 0.85 (0.49–1.48) | 2.40 (1.48–3.88) | 1 (Referent) | 1.11 (0.66–1.89) | 0.83 (0.48–1.43) | 3.06 (1.79–5.23) | 1 (Referent) | 1.31 (0.72–2.35) | 0.82 (0.43–1.55) | 0.0004 | 1 (Referent) | 0.74 | 0.57 |
| <0.004 | 0.0004 | 0.0001 | 0.0000 | 3.6 (1.79–5.23) | 1 (Referent) | 1.11 (0.66–1.89) | 0.83 (0.48–1.43) | 58/173 | 25/184 | 29/169 | 20/167 |
| 2.54 (1.31–4.94) | 1 (Referent) | 1.16 (0.56–2.40) | 0.90 (0.42–1.90) | 64/201 | 34/208 | 35/200 | 29/203 | 64/201 | 34/208 | 35/200 | 29/203 | 36/116 | 17/114 | 19/117 | 16/123 |
| 0.0004 | 1 (Referent) | 0.69 | 0.50 | 0.89 | 0.77 |

Abbreviations: CI = confidence interval; OR = Odds Ratio.

All models were adjusted for age, gender, ICH location (lobar, non-lobar), smoking status (never, current smoker), drinking status (never, current drinker), Diabetes (no, yes), Hypertension (no, yes), Snore (no, yes), History of coronary heart disease (no, yes), history of ischemic stroke (no, yes), use of lipid-lowering agents (no, yes), use of antihypertensive agents (no, yes), use of hypoglycemic agents (no, yes), HDL_C (mmol/L), TG (mmol/L), Sbp (mmHg), BMI (kg/m²).

The time between the physical exam and the cerebral hemorrhage.

| Table 6 | Generalized linear model of the hematoma volume with the different quartiles of LDL-C |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Hematoma volume, median (IQR) | Unadjusted (β, 95% CI) | p-value | Adjusted* (β, 95% CI) | p-value |
| Q1 <1.95 mmol/L | Q2 >= 1.95–<2.51 mmol/L | Q3 >= 2.51–<3.10 mmol/L | Q4 >= 3.10 mmol/L |
| 14.52 (5.85–35.96) | 7.92 (2.90–20.81) | 7.56 (2.30–23.40) | 7.83 (3.45–18.24) |
| 8.81 (3.63, 13.99) | 1 (Referent) | 0.63 (−4.55, 5.81) | −1.58 (−6.73, 3.58) |
| 0.0009 | 1 (Referent) | 0.06 | 0.0045 |
| 9.46 (2.87, 16.04) | 1 (Referent) | 0.36 (−4.81, 5.53) | −2.23 (−7.41, −2.94) |
| 0.0004 | 1 (Referent) | 0.89 | 0.40 |

All models were adjusted for age, gender, ICH location (lobar, non-lobar), smoking status (never, current smoker), drinking status (never, current drinker), Diabetes (no, yes), Hypertension (no, yes), Snore (no, yes), History of coronary heart disease (no, yes), history of ischemic stroke (no, yes), use of lipid-lowering agents (no, yes), use of antihypertensive agents (no, yes), use of hypoglycemic agents (no, yes), HDL_C (mmol/L), TG (mmol/L), Sbp (mmHg), BMI (kg/m²).
of arterial smooth muscle cells. Therefore, a low LDL-C concentration may make elderly and hypertensive patients more likely to form brain microaneurysms that rupture and bleed. From the perspective of nutrition, LDL-C concentrations decreased as the BMI decreased. A meta-analysis showed that low body weight is an independent risk factor for non-lobar hemorrhage.\textsuperscript{30} The mechanism may be that a low LDL-C concentration promotes the progression of white matter osteoporosis,\textsuperscript{26} which increases the risk of a large hematoma volume.\textsuperscript{31} Furthermore, a low LDL-C concentration may also induce hematoma expansion by affecting platelet adhesion and aggregation.\textsuperscript{32} Overall, these findings suggest that low LDL-C concentrations may only play a role in chronic injury of small blood vessels in the deep brain, resulting in a larger volume of deep brain hemorrhage in these specific populations.

Our results have significant clinical and public health implications. Regarding the management of blood lipid concentrations in populations at high risk of cardiovascular disease, the current recommendation is to reduce the LDL-C concentration to below 1.8 mmol/L,\textsuperscript{33} whereas our findings show that the risk of a large hematoma volume was higher when the LDL-C concentration was <1.95 mmol/L. Therefore, clinicians should consider not only the LDL-C concentration, but also the age, blood pressure, and BMI when deciding whether to prescribe lipid-lowering treatment or intensive lipid-lowering treatment; individualized treatment should be recommended on the basis of current guidelines.

The main strengths of our study are its large sample size and complete information on hematoma volume and location, as well as the fact that we only included Chinese adults living in the Kailuan community, which greatly reduces the potential confounding factors because of racial and healthcare disparities. However, our study also has several limitations. First, because we used a single LDL-C measurement, we could not analyze the influence of changes in LDL-C concentration over time on the hematoma volume. However, Phuah et al.\textsuperscript{34} found that the average LDL-C concentration began to decline 24 months before the occurrence of ICH. In our study, the median number of years from physical examination to ICH was 1.76 years, and the results did not change in our sensitivity analysis that excluded patients with an interval of >2 years between the last examination and onset of ICH, suggesting that our results are reliable. Second, our study cohort included only a small number of women (n = 77), which may be due to the low incidence of ICH in women. In addition, the study participants were mainly the mining employees of the Kailuan group, which has a significantly higher proportion of men (80%) than women (20%) and differs to the general Chinese population. Therefore, the present results require careful interpretation in the non-professional population and female population.

In conclusion, our study confirmed that low LDL-C concentrations prior to hospitalization significantly increased the risk of a larger hematoma volume in patients with ICH. A large hematoma volume predicts higher mortality and disability rates. Therefore, it may be useful to reduce the risk of a larger hematoma volume by regulating the LDL-C concentration in populations at high risk of ICH. Further studies are needed to confirm these preliminary findings and characterize the underlying biological mechanisms.

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CONFLICT OF INTEREST
No competing (financial interest) interest exits.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author.

PATIENT CONSENT STATEMENT
All persons gave their informed consent prior to their inclusion in the study.

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