Low-Density Lipoprotein Cholesterol and Mortality in Patients With Intracerebral Hemorrhage in Taiwan

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Objective: Lower serum low-density lipoprotein cholesterol (LDL-C) levels are associated with increased intracerebral hemorrhage (ICH) risk. However, reverse causality and residual confounding has not attracted public attention. Therefore, we assessed whether people with LDL-C have increased risk of mortality adjusting for potential confounders using two large Taiwan cohorts.

Methods: The Mei-Jhao (MJ) cohort has 414,372 adults participating in a medical screening program with 378 ICH deaths within 15 years of follow-up (1994–2008). Cox proportional hazards regressions estimated hazard death ratios according to LDL-C levels. We identified 4,606 ICH patients from the Taiwan Stroke Registry (TSR) and analyzed the impact of LDL-C on 3-month mortality.

Results: Low cholesterol (LDL-C <100 mg/dL), found in 1/4 of the MJ cohort, was highly prevalent (36%) among young adults (age 20–39). There was a graded relationship between cholesterol and mortality for ICH [Hazard ratio, 1.56; 95% confidence interval (CI), 1.13–2.16]. Compared with patients with an LDL-C of 110–129 mg/dL in TSR, the risk for mortality was 1.84 (95% CI, 1.28–2.63) with an LDL-C of <100 mg/dL.
Conclusion: Lower serum LDL-C level independently predicts higher mortality after acute ICH. While its causative role may vary, low cholesterol may pose potential harms in Taiwan.

Keywords: stroke, ICH, LDL, Taiwan Stroke Registry, mortality, proportional hazards regression analysis

INTRODUCTION

Stroke is the second commonest cause of death worldwide after ischemic heart disease, accounting for 6 million deaths in 2016 (1). Strokes can be broadly classified as hemorrhagic or ischemic. Intracerebral hemorrhage (ICH) accounts for only 10–15% of all strokes. ICH occurs following the rupture of cerebral vessels, usually manifesting as a rapidly expanding hematoma arising within the brain parenchyma. It is significantly associated with a worse functional outcome and higher mortality compared with ischemic stroke (2). Given the increasing burden and costs associated with stroke care, there is a pressing need to identify potential modifiable risk factors (3, 4).

Low-density lipoprotein cholesterol (LDL-C) transfers lipids around the body in the extracellular fluid, making them available to the body’s cells for receptor-mediated endocytosis. LDL-C can contribute to atherosclerosis if it is oxidized within the walls of arteries. Therefore, LDL-C has long been associated with the risk for ischemic stroke, and myocardial infarction (5). A reduction in LDL-C level has been demonstrated to reduce cardiovascular disease risk significantly.

Some studies have shown a relationship between low cholesterol levels and hemorrhagic stroke (6). However, those observational studies were pretreated with statins (7, 8). Neurologists are aware that statins may increase the risk for future ICH but have focused mainly on statins safety (7, 8). However, the link between LDL-C levels, ICH mortality, and clinical deterioration in patients with acute ICH remains largely unknown.

We assessed the mortality rates of low low-density lipoprotein cholesterol (LDL-C) and cross-tabulated their overlapping effects in a large cohort sample. To gain a clearer picture of ICH developments, we have included an additional prospective Taiwan Stroke Registry (TSR) cohort. This cohort has accumulated >100,000 stroke cases (and counting) and has records of hospital stay and follow-up information on mortality. With these two large data sets, we examined the impact of lower LDL on ICH mortality by analyzing stroke and healthy adult data together.

METHODS

Mei-Jhao Health Survey Data

Study Population and Data Collection

The MJ cohort consisted of adults aged 20 years or older who participated in a self-paying health surveillance program between 1994 and 2008. A description of this cohort has been reported previously (9, 10). The data used in this research were authorized by and received from MJ Health Research Foundation (Authorization Code: MJHRFB2014001C). Any interpretation or conclusion described in this paper does not represent the views of MJ Health Research Foundation. All participants in the research have given written informed consent before the health examination to authorize the data analysis. Personal identification data was removed in the MJ Health Research Foundation, so the participants remained anonymous during the whole research process. The detail of the study population and data collection is described and reported elsewhere (http://www.mjhrf.org/main/page/resource/en/#resource04). The study protocol conformed to the ethical standards established by the Declaration of Helsinki (1964), which do not require written or verbal consent for data-linkage studies.

Main Outcome Measures

This study consisted of 414,372 adults with a median follow-up of 8.62 years. Those with cancer history were excluded. Each participant went through a standard panel of medical screening with fasting blood analyzed by a Hitachi 7150 Autoanalyzer, and a self-administered history and lifestyle questionnaire. LDL-C was measured directly in the laboratory. Vital status was identified by matching with the Taiwan death file: a total of 11,787 deaths were identified. Taiwan death file were categorized as per the diagnosis codes assigned by the International Classification of Diseases, 10th Revision Clinical Modification (ICD-10-CM); All-cause mortality (A00-Y98), Coronary heart disease (I01-I10.0, I05-I09, I20-I25, I27, I30-I52), Intracerebral hemorrhage (I60-I62), and Ischemic stroke (I63-I69) were used in the study.

Statistical Analysis

Cox proportional hazards models were used to assess LDL-C and TC associations with all-cause and cause-specific mortality. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated for mortality risk using LDL-C and TC as categorical variables. LDL-C and TC also were regarded as continuous variables to estimate the effect per 1 mg/dL decrease in level among those with an LDL-C level lower than 110 mg/dL or TC level lower than 180 mg/dL. Low cholesterol was defined as LDL-C <100 mg/dL or TC <160 mg/dL, and very low cholesterol as LDL-C <70 mg/dL or TC <130 mg/dL. HRs were adjusted for 9 variables: age, gender, body mass index (BMI), systolic blood pressure (SBP), fasting glucose level, smoking status, alcohol consumption, physical activity, and anemia status. Sensitivity analyses were conducted by excluding participants who: died within the first 5 or 9 years of follow-up; were enrolled for <1 year, were carriers of hepatitis B virus (HBV) or hepatitis C virus...
(HCV), had liver diseases (liver cancer and liver cirrhosis), had abnormal liver functions [alanine aminotransferase (ALT) >40 U/L or aspartate aminotransferase (AST) >40 U/L], or had a history of cardiovascular disease (CVD), diabetes, liver cirrhosis, or kidney disease at enrollment. In addition, stratifying analysis of all-cause mortality risk by demographic, behavioral, and medical characteristics was performed. We used Markov chain Monte Carlo multiple imputation with 10 iterations to account for missing observations. We assumed that the imputation model had a joint multivariate normal distribution, and imputed data calculations were only performed on sensitivity analysis in hepatitis virus infection. Life expectancy was calculated using the Chiang's life table method. All analyses were performed with Stata (College Station, TX), and 2-sided p < 0.05 was considered statistically significant.

**Taiwan Stroke Registry Data, Analytic Methods, and Research Materials Transparency**

The Taiwan Stroke Registry (TSR) is a nationwide hospital-based prospective study with 56 participating stroke centers. The study was established in 2006 and is sponsored by the Taiwan Department of Health (11). Ethical approval for the study was obtained from China Medical University and the Institutional Review Boards (IRB) of the collaborating hospitals (CMUH104-REC2-115). Details on the database’s generation, monitoring, and maintenance are published by the Taiwan Stroke Society (12, 13). All participants provided informed consent. The TSR provides a structured record of demographics, including stroke types, imaging, in-hospital management, other known vascular risk factors, and long-term functional outcomes at follow-up.

### TABLE 1 | Distribution of characteristics by LDL-C levels in MJ cohort.

| LDL-C levels (mg/dL), %* | <100 | <70 | 70–99 | 100–109 | 110–129 | 130–159 | 160–179 | ≥180 |
|--------------------------|------|-----|-------|--------|--------|--------|--------|------|
| **Age, years** | | | | | | | | | |
| 20–39 | 54.5 | 35.7 | 5.7 | 30.0 | 14.0 | 24.5 | 19.1 | 4.2 |
| 40–64 | 38.5 | 19.5 | 2.7 | 16.8 | 10.7 | 24.6 | 28.9 | 9.4 |
| ≥65 | 7.0 | 17.1 | 2.3 | 14.7 | 9.6 | 23.9 | 30.1 | 10.7 |
| **Gender** | | | | | | | | | |
| Men | 47.8 | 23.6 | 3.4 | 20.2 | 11.7 | 25.3 | 26.6 | 7.7 |
| Women | 52.2 | 32.3 | 5.2 | 27.1 | 13.1 | 23.7 | 20.9 | 5.7 |
| **Smoking status** | | | | | | | | | |
| Non-smoker | 70.7 | 29.8 | 4.6 | 25.2 | 12.8 | 24.4 | 22.6 | 6.2 |
| Ex-smoker | 6.1 | 22.2 | 3.0 | 19.2 | 11.0 | 24.7 | 27.5 | 8.5 |
| Current-smoker | 23.2 | 25.8 | 4.2 | 21.6 | 12.0 | 24.6 | 25.3 | 7.4 |
| **Drinking** | | | | | | | | | |
| Non-drinker | 78.2 | 29.3 | 4.4 | 24.9 | 12.7 | 24.4 | 22.8 | 6.3 |
| Occasional drinker | 3.0 | 25.3 | 3.7 | 21.5 | 11.3 | 23.9 | 25.4 | 7.9 |
| Regular drinker | 18.8 | 25.0 | 4.2 | 20.8 | 11.6 | 24.7 | 26.0 | 7.6 |
| **Physical activity** | | | | | | | | | |
| Inactive | 52.9 | 29.6 | 4.7 | 24.9 | 12.6 | 24.3 | 22.7 | 6.3 |
| Low active | 22.0 | 28.5 | 4.3 | 24.2 | 12.7 | 24.9 | 23.2 | 6.5 |
| Fully active | 25.1 | 24.7 | 3.6 | 21.1 | 11.8 | 24.6 | 25.9 | 7.7 |
| BMI (kg/m²) | | | | | | | | | |
| <18.5 | 8.3 | 49.2 | 9.9 | 39.3 | 14.8 | 20.0 | 12.2 | 2.4 |
| 18.5–24.9 | 65.0 | 29.4 | 4.4 | 25.0 | 13.0 | 24.8 | 22.7 | 6.0 |
| 25–29.9 | 22.9 | 18.5 | 2.4 | 16.1 | 10.4 | 25.0 | 29.5 | 9.6 |
| ≥30 | 3.8 | 18.6 | 2.8 | 15.8 | 10.6 | 24.9 | 29.8 | 9.3 |
| **SBP (mmHg)** | | | | | | | | | |
| <120 | 50.7 | 34.0 | 5.5 | 28.6 | 13.7 | 24.4 | 20.0 | 4.8 |
| 120–139 | 29.9 | 24.5 | 3.5 | 21.1 | 12.0 | 25.1 | 25.8 | 7.4 |
| ≥140 or HTN | 19.5 | 18.1 | 2.7 | 15.5 | 9.9 | 23.7 | 29.8 | 10.3 |
| **Fasting glucose (mg/dL)** | | | | | | | | | |
| <110 | 89.3 | 29.2 | 4.5 | 24.8 | 12.8 | 24.8 | 23.0 | 6.2 |
| 110–125 | 5.6 | 17.7 | 2.9 | 14.8 | 9.6 | 23.4 | 30.3 | 10.7 |
| ≥126 or DM | 5.1 | 20.2 | 3.5 | 16.7 | 9.5 | 22.7 | 28.1 | 10.4 |
| **Anemia** | | | | | | | | | |
| No | 92.5 | 27.1 | 4.0 | 23.1 | 12.3 | 24.7 | 24.2 | 6.9 |
| Yes | 7.5 | 41.4 | 8.1 | 33.3 | 14.0 | 21.9 | 16.2 | 3.9 |
| **Hepatitis virus infection** | | | | | | | | | |
| HBV(–) & HCV(–) | 62.6 | 27.3 | 4.0 | 23.2 | 12.5 | 24.7 | 24.2 | 6.8 |
| HBV(+) or HCV(+) | 37.4 | 27.4 | 3.9 | 23.6 | 13.0 | 25.5 | 23.8 | 6.3 |

LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; BMI, body mass index; SBP, systolic blood pressure; HTN, hypertension; DM, diabetes; HBV, hepatitis B virus; HCV, hepatitis C virus. To convert mg/dL to mmol/L, multiply by 0.0259.

*Percentages by column. †Percentages by row. ‡Anemia is defined as hemoglobin level <13 g/dL for men and <12 g/dL for women. §Missing for 257,498 (62.1%) participants.
Lower LDL-C Predicts Higher Mortality

between August 1st, 2006 and May 20th, 2016. Patients were included in the present study if they met the following criteria: (1) had suffered from a stroke and presented at the hospital within 10 days of symptom onset, and (2) were diagnosed with stroke as confirmed by a neurologist or neurosurgeon.

Main Outcome Measures
ICH patients with missing LDL-C data were excluded from the study. Patients were categorized into six groups based on their baseline levels: <70, 70–99, 100–129, 130–159, and ≥160 mg/dL of LDL-C. The primary factors considered in the present study were the potential confounding factors. For each case, stroke severity was determined using the National Institutes of Health Stroke Scale (NIHSS) scores. Modified Rankin Scales (mRS) were used to assess functional outcomes. A mRS score of 3 or higher was considered an unfavorable outcome. Vascular risk factors were defined in accordance with the consensus TSR criteria. Serum LDL-C were obtained within the first 24 h from symptom onset after a minimum of 12 h fasting. All registered follow-up data were collected from patients at 3-month after stroke. This data was collected either in the clinic or via telephone interview for those who could not be present at the clinic. Follow-up data included assessment of functional status, stroke recurrence, and survival.

Statistical Analysis
Data analysis first compared distributions of age, sex, stroke risk factors, medications, and laboratory data. A Cox proportional hazard regression was used to estimate the risk of mortality. Univariate and multivariate logistic regression analyses were used to determine crude odds ratios (OR) and adjusted odds ratios (aOR), by several variables: Age, gender, past history, medication, NIHSS score, hematoma condition, and surgery. Patients with LDL-C 100–129 mg/dL was used as the reference group. The threshold for statistical significance was set at a two-sided p-value of ≤0.05.

RESULTS
Low LDL Increase ICH Mortality in MJ Cohort
The MJ cohort consisted of 414,372 adults with a median follow-up of 8.62 years. The vital status was identified by matching with the Taiwan death file. A total of 11,787 deaths were identified (378 deaths were ICH related). One-quarter of the cohort (28%) and one-third of younger people (age 20–39) (37%) had low LDL-C (<100 mg/dL). Nearly half of the underweight patients (BMI <18.5 kg/m²) had low cholesterol (49%) (Table 1). After controlling for 9 confounding factors, a U-shaped association was found between LDL levels and all-cause mortality (Figure 1). Compared to their counterpart in the range of 110–129 mg/dL (LDL-C), participants with low LDL-C (<100 mg/dL) had a 30% increase in all-cause mortality (Table 2). Furthermore, among low cholesterol participants we found a significant increase of mortality (~56%) for ICH, contributing to increases in cardiovascular disease (CVD) mortality. Coronary
heart disease did not increase at low cholesterol, with a J-shaped association, confirming an HR at 2.54 for high LDL-C ≥180 mg/dL.

**Low LDL Had Higher Mortality in TSR**

We excluded 9,037 patients without fasting TC and 581 patients without 3 months follow up records from the TSR. Hence, in this study we included 4,606 spontaneous ICH patients with baseline fasting LDL levels measured immediately after stroke. The mean (SD) age was 61.7 (51.9–72.8) years, and 1,519 (33.0%) were female (Table 3, Supplementary Table 1). Patients with LDL <70 mg/dL were older and mainly male (Table 3, Supplementary Table 2). However, there were no obvious differences in pre-ICH medications (Supplementary Table 3). Patients on admission presented with a median GCS score of 15 [interquartile range (IQR), 11 ± 15] and a median NIHSS score of 9 (IQR, 3 ± 18). The overall case-mortality rate of ICH at 3-month was 7.56%. At 3-month, most patients (70%) had a mRS of >2. Patients with LDL <70 mg/dL were more likely to have hematoma enlargement, and a higher 3-month mortality (Table 4). Finally, compared to patients with LDL 110–129 mg/dL, those with LDL <100 mg/dL had higher 3-month mortality (aOR, 1.84; 95% CI, 1.28–2.63) and initial NIHSS >15 (aOR, 1.35 95% CI, 1.13–1.62) (Table 5, Figure 2).

As reported in Table 6, the Cox proportional hazards models showed that several independent variables were related to 3 months mortality. These included age (OR, 1.01; 95% CI: 1.00–1.02), warfarin (OR, 3.53; 95% CI: 1.31–9.53), glucose (OR, 1.004; 95% CI: 1.001–1.02), warfarin (OR, 3.53; 95% CI: 1.31–9.53), glucose (OR, 1.004; 95% CI: 1.001–1.01), GCS (OR, 0.72; 95% CI: 0.68–0.75), hematoma enlargement (OR, 5.37; 95% CI: 2.73–10.6), and surgery for ICH (OR, 0.52; 95% CI: 0.33–0.83).

**DISCUSSION**

Low cholesterol, commonly encountered among Taiwaneses, has been overlooked as a health risk or a warning sign. In the present study, we described the association between serum LDL-C levels, and ICH mortality by using of 2 data sets. The main finding of our study was that low levels of LDL-C are independently associated with an increased risk of death in patients with ICH (aHR, 1.56; 95% CI, 1.13–2.16), especially in LDL-C levels lower than 70 mg/dL (aHR, 2.53; 95% CI, 1.50–4.26). Compared to patients with LDL 110–129 mg/dL, those with LDL <100 mg/dL had higher 3-month mortality (aOR, 1.84; 95% CI, 1.28–2.63). They were more likely to have hematoma enlargement, and initial NIHSS >15. The effects of lipid-lowering drugs were negligible since only a small percentage of the ICH population was taking them at per-ICH stage.

Many epidemiological studies including the Framingham Heart Study (14), the Multiple Risk Factor Intervention Trial (15), the Coronary Primary Prevention Study (16), and the Helsinki Heart Study (17), have suggested that high cholesterol levels are associated with myocardial infarction and ischemic stroke. The 2013 guidelines for managing blood cholesterol from the American College of Cardiology and the

**TABLE 2** | Multivariable adjusted hazard ratios for all-cause and cause-specific mortality by LDL-C levels in MJ cohort.

| LDL-C levels (mg/dL) | No. of cases | All-cause mortality | CVD | CHD | Ischemic stroke | ICH |
|----------------------|-------------|---------------------|-----|-----|----------------|-----|
| <70                  | 1,178       | 1.39                | 1.24*| 1.09*| 0.94           | 1.05*|
| 70–99                | 2,521       | 1.24                | 1.37| 1.28| 1.02           | 1.24*|
| 100–109              | 1,178       | 1.24                | 1.37| 1.28| 1.02           | 1.24*|
| ≥110–129             | 1,178       | 1.24                | 1.37| 1.28| 1.02           | 1.24*|
| ≥130–159             | 1,178       | 1.24                | 1.37| 1.28| 1.02           | 1.24*|
| ≥160–179             | 1,178       | 1.24                | 1.37| 1.28| 1.02           | 1.24*|
| ≥180                 | 1,178       | 1.24                | 1.37| 1.28| 1.02           | 1.24*|

LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; CHD, coronary heart disease; ICH, intracerebral hemorrhage; HR, hazard ratio; CI, confidence interval. To convert mg/dl to mmol/L, multiply by 0.0259.

*Indicates a significant (p < 0.05) death rate compared to LDL-C levels between 110 and 129 mg/dL. Hazard ratio adjusted for age, gender, body mass index, smoking status, alcohol consumption, physical activity, systolic blood pressure, fasting glucose level, and anemia.
American Heart Association state that lowering cholesterol levels reduces cardiovascular events. This establishes a central, causal role of atherogenic cholesterol-containing lipoprotein particles, particularly LDL-C, in cardiovascular events (18). The most recent 2018 guidelines advocate for a “lower is better” approach to LDL-C. They suggest that an optimal LDL-C level at or below 100 mg/dL lowers the rate of heart disease and stroke (19). This emphasis on low LDL-C is mainly to prevent heart disease.

As Taiwan have fewer deaths due to cardiovascular disease, the benefits of low LDL are far less than in Western countries (20). In 2000, coronary heart disease accounted for 29.6% of the total death rate in the United States while in Taiwan, it accounted for 8.5% (21, 22). The prevalence of LDL with 160 mg/dL or higher was 33% in the United States and only 12.8% in Taiwan (23). The overall difference in proportion was >3 times, showing that Taiwanese have a lower coronary heart disease mortality rate compared to Westerners and a low prevalence of high cholesterol. On average, the Taiwan population has lower cholesterol and LDL than the Western population, therefore high LDL is not as
TABLE 5 | Association between initial stroke severity and 3 months outcome by LDL-C levels and pre-ICH lipid-lowering drugs use in TSR.

| OR (95% CI) | All ICH patients (n = 4,606) | Age/sex-adjusted | Multivariate adjusted |
|-------------|-----------------------------|------------------|-----------------------|
| **3-month mortality** | | | |
| <100 | 1.39 (0.91, 2.16) | 1.33 (0.86, 2.05) | 1.26 (1.18, 2.63) |
| <70 | 1.82 (1.36, 2.42) | 1.75 (1.31, 2.34) | 1.31 (1.09, 2.43) |
| 70–99 | 1.13 (0.71, 1.80) | 1.10 (0.69, 1.76) | 1.21 (0.68, 2.14) |
| 100–109 | 0.74 (0.38, 1.45) | 0.74 (0.38, 1.44) | 0.71 (0.31, 1.63) |
| 110–129 | 1 | 1 | 1 |
| 130–159 | 0.43 (0.21, 0.88) | 0.42 (0.20, 0.87) | 0.38 (0.15, 0.95) |
| 160–179 | 0.62 (0.21, 1.81) | 0.64 (0.22, 1.89) | 0.57 (0.13, 2.55) |
| ≥180 | 0.94 (0.32, 2.80) | 1.04 (0.35, 3.08) | 1.15 (0.32, 4.14) |
| Pre-ICH lipid-lowering drugs use | 0.74 (0.41, 1.34) | 0.70 (0.38, 1.29) | 0.84 (0.43, 1.66) |
| **3-month mRS > 2** | | | |
| <100 | 1.04 (0.90, 1.20) | 0.97 (0.84, 1.13) | 0.96 (0.81, 1.13) |
| <70 | 1.02 (0.81, 1.28) | 0.97 (0.77, 1.22) | 0.98 (0.75, 1.29) |
| 70–99 | 1.30 (1.00, 1.68) | 1.26 (0.97, 1.64) | 1.27 (0.94, 1.73) |
| 100–109 | 1.26 (0.90, 1.77) | 1.26 (0.89, 1.77) | 1.37 (0.92, 2.04) |
| 110–129 | 1 | 1 | 1 |
| 130–159 | 0.93 (0.69, 1.26) | 0.95 (0.70, 1.29) | 1 |
| 160–179 | 1.12 (0.68, 1.82) | 1.24 (0.76, 2.04) | 1.01 (0.71, 1.44) |
| ≥180 | 1.01 (0.57, 1.79) | 1.21 (0.68, 2.16) | 1.24 (0.70, 2.19) |
| Pre-ICH lipid-lowering drugs use | 0.94 (0.70, 1.27) | 0.85 (0.63, 1.16) | 1.03 (0.54, 1.97) |
| **Initial NIHSS score > 15** | | | |
| <100 | 1.36 (1.06, 1.75) | 1.35 (1.05, 1.73) | 1.35 (1.13, 1.62) |
| <70 | 1.65 (1.26, 2.16) | 1.64 (1.25, 2.15) | 1.53 (1.12, 2.09) |
| 70–99 | 1.34 (1.16, 1.56) | 1.32 (1.14, 1.54) | 1.99 (1.42, 2.79) |
| 100–109 | 1.15 (0.80, 1.64) | 1.15 (0.80, 1.63) | 1.20 (0.78, 1.86) |
| 110–129 | 1 | 1 | 1 |
| 130–159 | 1.06 (0.75, 1.47) | 1.06 (0.76, 1.48) | 1.38 (0.93, 2.06) |
| 160–179 | 1.24 (0.74, 2.05) | 1.26 (0.76, 1.48) | 1.61 (0.86, 3.00) |
| ≥180 | 1.02 (0.55, 1.90) | 1.06 (0.57, 1.98) | 1.17 (0.56, 2.46) |
| Pre-ICH lipid-lowering drugs use | 0.87 (0.63, 1.20) | 0.85 (0.61, 1.16) | 0.95 (0.65, 1.38) |

An accumulation of LDL-C in the tunica intima is an important step in the initiation of atherosclerosis (6). Serum cholesterol levels can help maintain the integrity of vascular vessels. Lower cholesterol levels may modify platelet aggregability and decrease the resistance of the vascular wall (25). These effects can lead vessels to rupture and cause ICH. In addition, low LDL-C is associated with a higher risk of some cancers, especially liver cancer, where cholesterol is synthesized. However, the causative direction of this association is not clear, with some arguing that cancer patients had lower cholesterol and not the other way around. Therefore, the “lower the better” approach toward LDL may not be suitable for Taiwanese.

A link between ICH, but not ischemic stroke, and low cholesterol or LDL is well known (26–38). Higher levels of LDL-C seem to be associated with a lower risk of ICH. A previous study by Sturgeon et al. also showed that lower LDL-C and lower triglycerides were risk factors for ICH (26). In a meta-analysis by Wang et al., total cholesterol levels were inversely associated with the risk of ICH (27). Therefore, low LDL-C has been proposed as a risk factor for ICH.

Other studies have suggested that hypertension are bigger risk factors for ICH, more so than low LDL-C (29–32). However, care must be taken in extrapolating from these results because they lack defined LDL-C levels.

Although these results suggest that lower LDL-C at admission is an independent predictor of higher mortality, this evidence should be interpreted with caution because cohorts are Taiwanese (Han Chinese). Taiwanese has lower cholesterol than the Western population, and do not really reflect all East Asian race/ethnicities. Therefore, further research in this area is necessary to determine the best target range of LDL-C levels, especially in patients with atherosclerotic disease who might be at a higher baseline risk of ICH.

Unlike our current study, previous studies have only reported a trend between low LDL-C concentrations and high ICH incidence or mortality (6, 32–36). For example, higher levels of LDL-C at admission were independently (p < 0.001) associated with a lower likelihood of in-hospital mortality (OR per 10 mg/dL increase 0.68, 95% CI: 0.57–0.80) in multivariable logistic regression models (6). In another cohort study, LDL-C levels
TABLE 6 | Univariate and multivariate logistic regression analyses evaluating the association of baseline characteristics with the likelihood of 3-month mortality.

| Variable               | Univariate logistic regression analysis | Multivariate logistic regression analysis |
|------------------------|----------------------------------------|------------------------------------------|
|                        | OR (95% CI)                            | P-value                                  | OR (95% CI)                            | P-value                                  |
| Age (years)            | 1.01 (1.00, 1.01)                      | < 0.001                                  | 1.01 (1.00, 1.02)                      | 0.049                                    |
| Sex (%), female        | 1.09 (0.99, 1.21)                      | 0.06                                     | 1.02 (0.65, 1.60)                      | 0.93                                     |
| Hypertension           | 0.61 (0.55, 0.67)                      | < 0.001                                  | 0.63 (0.37, 1.07)                      | 0.09                                     |
| Diabetes               | 1.25 (1.13, 1.39)                      | < 0.001                                  | 0.81 (0.48, 1.36)                      | 0.43                                     |
| Heart disease          | 1.54 (1.37, 1.73)                      | < 0.001                                  | 1.50 (0.94, 2.37)                      | 0.09                                     |
| Previous stroke        | 1.09 (0.97, 1.23)                      | 0.16                                     | 1.14 (0.74, 1.77)                      | 0.55                                     |
| Uremia                 | 3.89 (2.35, 4.65)                      | < 0.001                                  | 1.06 (0.39, 2.86)                      | 0.92                                     |
| Alcoholism             | 0.91 (0.81, 1.03)                      | 0.13                                     | 1.57 (0.97, 2.55)                      | 0.07                                     |
| Smoking                | 0.89 (0.80, 0.98)                      | 0.02                                     | 0.83 (0.53, 1.30)                      | 0.41                                     |
| Aspirin                | 1.00 (0.83, 1.20)                      | 0.99                                     | 0.73 (0.34, 1.60)                      | 0.44                                     |
| Aggrenox               | 0.51 (0.16, 1.68)                      | 0.27                                     | 0.84 (0.09, 8.34)                      | 0.88                                     |
| Ticlopidine            | 1.17 (0.52, 2.64)                      | 0.71                                     | -                                       | -                                       |
| Clopidogrel            | 2.04 (1.43, 2.92)                      | < 0.001                                  | 0.54 (0.10, 3.12)                      | 0.49                                     |
| Warfarin               | 1.89 (1.43, 2.49)                      | < 0.001                                  | 3.53 (1.31, 9.53)                      | 0.01                                     |
| Anti H/T drug          | 0.95 (0.86, 1.04)                      | 0.26                                     | 0.87 (0.56, 1.34)                      | 0.52                                     |
| Anti DM drug           | 1.17 (1.03, 1.33)                      | 0.02                                     | 0.53 (0.27, 1.05)                      | 0.07                                     |
| Lipid lowering drug    | 0.79 (0.60, 1.05)                      | 0.10                                     | 0.81 (0.30, 2.19)                      | 0.68                                     |
| Admission SBP          | 1.00 (1.003, 1.005)                     | < 0.001                                  | 1.01 (1.00, 1.01)                      | 0.15                                     |
| Admission DBP          | 1.00 (0.99, 1.00)                      | 0.17                                     | 1.00 (0.99, 1.01)                      | 0.81                                     |
| Admission glucose      | 1.01 (1.01, 1.01)                      | < 0.001                                  | 1.004 (1.001,1.006)                    | 0.001                                    |
| Admission platelets    | 1.00 (0.99, 1.00)                      | < 0.001                                  | 1.00 (0.99, 1.00)                      | 0.17                                     |
| Admission LDL-C        | 0.99 (0.99, 0.996)                     | < 0.001                                  | 0.99 (0.99, 0.996)                     | 0.001                                    |
| Admission HDL          | 0.99 (0.993, 0.999)                    | 0.008                                    | 0.99 (0.99, 1.00)                      | 0.11                                     |
| Admission hemoglobin A1c| 0.84 (0.82, 0.86)                     | < 0.001                                  | 0.98 (0.89, 1.08)                      | 0.66                                     |
| Admission creatinine   | 1.19 (1.17, 1.22)                      | < 0.001                                  | 1.14 (1.02, 1.28)                      | 0.02                                     |
| NIHSS score            | 1.02 (1.017, 1.019)                    | < 0.001                                  | 1.01 (1.01, 1.02)                      | < 0.001                                  |
| Initial GCS            | 0.70 (0.68, 0.72)                      | < 0.001                                  | 0.72 (0.68, 0.75)                      | < 0.001                                  |
| Hematoma enlargement   | 4.22 (2.91, 6.14)                      | < 0.001                                  | 5.37 (2.73, 10.6)                      | < 0.001                                  |
| Surgery for ICH        | 2.06 (1.58, 2.66)                      | < 0.001                                  | 0.52 (0.33, 0.83)                      | 0.006                                    |

< 95 mg/dL emerged as an independent predictor of 3-month mortality (OR, 6.34; 95% CI, 1.29 to –31.3; P = 0.023) (29). In our study, we showed that LDL-C levels were independently associated with an increased risk of mortality in patients with ICH, especially when LDL-C was lower than 70 mg/dL. A large study from Korea and extensive analyses from Japan essentially support our conclusion (39, 40). Researchers from one study determined the harms of low cholesterol so robust that “their data cast doubt on the scientific justification for lowering cholesterol to very low levels in elderly people” (41). Our results, and other similar findings from previous studies, would suggest the “lower is better” view of LDL-C is not always correct. LDL-C and triglyceride levels drop at the onset of acute illness and return to normal during recovery. More importantly, hypcholesterolemia is not only a marker for the disease severity, but it may also predispose critically ill patients to sepsis and adrenal failure, and may carry a significantly increased risk of mortality (42). While the causal role of cholesterol in mortality may vary, our findings reveal that a high prevalence of low cholesterol is not a cause for celebration, but it could actually be a strong risk factor for mortality. This study suggests that the efforts to keep cholesterol as low as possible may not improve life expectancy but may cause harm.

However, the present study has several limitations. First, it was based on a single LDL-C measurement upon admission. LDL and HDL showed a significant diurnal variation: lowest values were seen early in the morning followed by an increase before breakfast, with the highest levels during the afternoon in most cases. Fluctuations in LDL-C following admission could have a significant impact on the mortality rate, but information on this important aspect was not available within the MJ or TSR dataset. Furthermore, we included all patients that presented at the hospital within 10 days of symptom onset. Thus, the latency period from ICH onset to LDL-C sampling could vary from minutes to 10 days. Secondly, ICH may cause a severe disability but not death most of the time. In this case, the higher risk of death may contribute from other factors, i.e., baseline health condition, complication of ICH and the socioeconomic status.
Therefore, ICH mortality maybe underestimation. Thirdly, factors independently associated with mortality were the Glasgow Coma Scale score, age > 80 years, infratentorial origin of ICH, and ICH volume. If hematoma expansion happened in patients with ICH, we noticed a higher neurologic impairment and mortality rate. Our result hint low LDL was associated with the development of hematoma expansion in the setting of spontaneous ICH. We have controlled for several important confounders, but unknown confounders or misclassification of confounders by self-reporting instruments may have resulted in residual confounding. These include the volume and the location of blood clots. Thus, it was not taken in account in the analysis. Fourthly, low LDL-C due to genetics or a marker of an underlying nutritional is unclear. Acute high-fat feeding increased the level of total and LDL cholesterol, significantly reduced HDL cholesterol, and worsened the outcome following ischemic stroke. Healthy low-carbohydrate-diet and low-fat-diet were associated with lower total mortality (43, 44). Those were not adjusted in the analysis. Finally, MJ cohort is a private fee-for-service company offering comprehensive health screening programs. All participants are membership based and may have slightly higher socioeconomic status than the general Taiwan population.

CONCLUSION

In conclusion, our study suggests that lower serum LDL-C level independently predicts higher mortality after ICH in Taiwanese Cohorts, especially when LDL-C levels were <100 mg/dL. Although these results suggest that lower LDL-C at admission is an independent predictor of higher mortality, this evidence should be interpreted with caution because cohorts are Taiwanese (Han Chinese). Taiwanese has lower cholesterol than the Western population, and do not really reflect all East Asian race/ethnicities. Therefore, further research in this area is necessary to determine the best target range of LDL-C levels, especially in patients with atherosclerotic disease who might be at a higher baseline risk of ICH.

DATA AVAILABILITY STATEMENT

The data analyzed in this study were obtained from two independent data sets, the Mei-Jhao (MJ) Health Survey Data and Taiwan Stroke Registry (TSR). The MJ Cohort is available to the worldwide research community and offers collaboration (Authorization Code: MJHRFB2014001C). Applicants for data access should contact the MJ Health Research Foundation (http://www.mjhrf.org/main/page/release2/en/#release01). The TSR data that support the findings of this study are available from Taiwan Stroke Registry, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Taiwan Stroke Registry (taiwanstrokeregistry@gmail.com).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by China Medical University and the Institutional Review Boards (IRB) of the collaborating hospitals (CMUH104-REC2-115). The patients/participants provided their written informed consent to participate in this study.

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C-PW, Y-CL, H-KW, and CH: designed and conceptualized study, analyzed the data, data acquisition, and drafted the manuscript for intellectual content. Y-TS and C-YH: designed and conceptualized study and analyzed the data. C-HT, P-LC, W-LC, P-YY, C-YW, and M-JT: collection and analysis of data and editing of the manuscript. YS, C-ML, J-TL, T-CL, L-ML, M-CL, C-LL, and J-HL: conception and design of the study and drafting of the manuscript and preparation of figures. All authors contributed to the article and approved the submitted version.

**FUNDING**

This study was supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-114004), Ministry of Science and Technology (MOST 110-2321B-039-003), MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-039-003), and Tseng-Lien Lin Foundation, Taichung, Taiwan.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.793471/full#supplementary-material

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