Serum Cholesterol LDL and 90-Day Mortality in Patients With Intracerebral Hemorrhage

José María Ramírez-Moreno, MD; Ignacio Casado-Naranjo, MD; Juan Carlos Portilla, MD; María Luisa Calle, MD; David Tena, MD; Alfonso Falcón, MD; Ana Serrano, MD

**Background and Purpose**—Prognostic significance of low-density lipoprotein cholesterol (LDL-C) in intracranial hemorrhage (ICH) is unclear. The objective of this study was to determine the association between LDL-C and mortality in ICH.

**Methods**—Consecutive patients \((n=88)\) presenting with ICH were included in the study. Lipid profile was obtained during the first hours after admission. We analyzed the impact of LDL-C on 90-day mortality using the Hazard Rate (HR) crude, analysis crude for trend by Mantel–Haenszel Test, Multiple Cox Proportional Hazards model, and analysis of survival curves. Association between LDL-C and severity markers of ICH were explored using Spearman correlation coefficient.

**Results**—Low LDL-C levels were independently associated with death after intracranial hemorrhage \((HR=3.07\, (95\%\, CI:1.04 to 9.02; \(P=0.042\))\) in multivariable analysis after controlling for confounding factors. Analysis for trend showed a significant association \((Xt=-2.144; \(P=0.032\))\) by Mantel-Haenszel Test. Spearman analysis showed no correlation between LDL-C and variables that are markers of ICH severity: NIH score \((r=-0.091; \(P=0.400\))\), GCS score \((r=0.136; \(P=0.207\))\), ICH volume \((r=0.140; \(P=0.192\))\), and length of stay \((r=-0.111; \(P=0.308\))\).

**Conclusions**—Low levels of LDL-C are independently associated with an increased risk of death in patients with brain hemorrhage. We have not found evidences that the levels of LDL-C can act as a biological marker of severity. (Stroke. 2009; 40:1917-1920.)

**Key Words:** cardiovascular disease ■ intracerebral haemorrhage ■ prognosis ■ cholesterol ■ low-density lipoprotein cholesterol

The association between cholesterol and stroke remains uncertain. Epidemiological studies have failed to associate cerebral infarction and cholesterol, but they have found an inverse relation with the incidence of intracerebral hemorrhage (ICH).\(^1\) SPARCL study suggests that statins increase the occurrence of ICH, which enhances the controversy.\(^2\) Moreover, an association between low cholesterol and mortality attributable to ICH has been documented in several large population-based studies.\(^3,4\) Additionally, higher cholesterol levels have been associated with better short-term health outcome after stroke, including ICH.\(^5\) However, most of these studies did not measure cholesterol fractions nor investigate whether HDL-C or LDL-C levels affected mortality or outcome. We studied the association between levels of LDL-C and mortality in ICH.

**Materials and Methods**

We prospectively included 104 consecutive patients over age 18 with ICH. ICH was confirmed by CT within 12 hours after onset. We excluded patients with traumatism, brain tumor, previous ICH, hemorrhagic transformation of ischemic stroke, vascular cerebral malformations, and patients who required neurosurgical procedures. We analyzed the variables: age, sex, hypertension, diabetes, hypercholesterolemia, current smoking, and alcohol overuse. Temperature, systolic and diastolic blood pressure, NIH stroke scale (NIHSS), and Glasgow Coma Scale (GCS) were evaluated at admission. On the initial CT we evaluated the ICH localization, volume (ABC/2 method), ventricular extension, or infratentorial affection. Routine laboratory test was performed in the first hour after arrival. Albumin and lipid profile were taken from fasting patients 12 to 36 hours after admission. We recorded previous use of statin, antihypertensive, antiplatelet, or anticoagulant treatments and length of stay. Primary outcome was 90-day mortality evaluated by visits of follow-up or telephonic interviews.

**Statistical Analysis**

Differences between the groups were compared by \(\chi^2\) test or Fisher exact test; \(t\) test was used for continuous variables. LDL-C levels were classified into \(<100\) and \(\geq100\) mg/dL. To value the crude effect of LDL-C on 90-day mortality we used the incidence rates with 95% CI. We categorized LDL-C in quartiles and realized the analysis crude for trend by Mantel-Haenszel Test. We assessed the effect of LDL-C on survival using a Cox proportional hazard model, controlling potential confounding factors with \(P\leq0.2\) in univariate analysis. We analyzed binary and quartiles LDL-C separately. Association between LDL-C levels and markers of ICH severity and markers of malnutrition were explored using Spearman correlation coefficient. Significance tests were 2-sided, with \(P<0.05\); confidence intervals were set at 95%. Data were analyzed with statistics package SPSS 13.0.
Complete data were available for 88 patients; 50 (56.8%) men. Mean (SD) age was 73.8 (8.9) years. Total mortality of 21 during follow-up (23.9%) and mean follow-up of survivors was 65 days. Mean (SD) serum LDL-C concentration was 128 (48) mg/dL for survivors and 109 (36) for deceased. Demographic, risk factors, clinical scales, radiology, and laboratory data are summarized in Table 1.
Crude hazard rate between dichotomous LDL-C and survival was statistically significant; a LDL-C \( \leq 100 \) mg/dL increases 2.5 times (95% CI: 1.1 to 5.9) the risk of death. The analysis for trend was statistically significant (\( X^2 = 2.1443; P = 0.032 \)) by Mantel-Haenszel Test, reflecting a clear dose-response gradient. Cox proportional hazards model proves that the following independent variables are related to 90-day mortality: LDL-C \( \leq 100 \) mg/dL, HR = 3.067 (95% CI: 1.043 to 9.017); Age, per 1 year increase, HR = 1.085 (95% CI: 1.015 to 1.161) and NIHSS, per 1 point increase, HR = 1.211 (95% CI: 1.094 to 1.340). Cox proportional hazards model was repeated with LDL-C in quartiles. Table 2 resumes these data. The Figure shows accumulative survival curves according LDL-C levels.

Spearman analysis showed no significant correlation between LDL-C and markers of ICH severity: NIHSS (\( r = 0.091; P = 0.400 \)), GCS (\( r = 0.136; P = 0.207 \)), ICH volume (\( r = 0.140; P = 0.192 \)), leukocytes (\( r = 0.192; P = 0.040 \)), fibrinogen (\( r = 0.206; P = 0.054 \)), and length of stay (\( r = 0.111; P = 0.308 \)). There was significant correlation between albumin and lipids: total cholesterol (\( r = 0.414; P = 0.0001 \)), LDL-C (\( r = 0.406; P = 0.0001 \)), HDL-C (\( r = 0.341; P = 0.001 \)), but not for triglycerides (\( r = 0.086; P = 0.428 \)).

### Discussion

Observational studies have evaluated the relationship between lipids and ICH outcome. In these works an inverse association between the level of total cholesterol (TCh) and ICH has been observed, relating highest mortality risk to lowest cholesterol level. However, the majority of studies evaluated TCh levels but not LDL-C, a primary target in hypercholesterolemia treatment. The Multiple Risk Factor Intervention Trial showed higher mortality in men with ICH and TCh \( < 160 \) mg/dL. Moreover, low TCh and triglycerides in the first hours after ICH are strong independent predictors of in-hospital mortality, and surprisingly higher cholesterol levels have been associated with better short-term outcomes after acute strokes, independently of subtype, vascular territory, age, and glycemia.

Studies have reported a U-shaped relation between TCh and mortality from all causes. Indeed, TCh tends to decrease among old persons, probably related to a poor health, confounding the association TCh and long-term mortality. Clinical parameters of malnutrition, alcohol overuse, and markers of inflammation are known independent mortality predictors;

<table>
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<tr>
<th>Categorization</th>
<th>Crude Hazard Rate</th>
<th>Adjusted Analysis*</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Binary</td>
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<tr>
<td>( \leq 100 ) vs &gt;100 mg/dL</td>
<td>2.50 (1.06–5.88)</td>
<td>0.030‡</td>
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<td>Quartiles</td>
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<td>&gt;120 mg/dL</td>
<td>1.00</td>
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<tr>
<td>100–119 mg/dL</td>
<td>0.97 (0.25–3.76)</td>
<td>0.90 (0.15–5.56)</td>
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<tr>
<td>69–99 mg/dL</td>
<td>2.51 (0.91–6.92)</td>
<td>2.58 (0.76–8.79)</td>
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<tr>
<td>&lt;69 mg/dL</td>
<td>4.36 (1.13–16.86)</td>
<td>0.032</td>
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HR indicates hazard rate; LDL-C, low-density lipoprotein cholesterol.

*Cox Proportional Hazard Rate adjusted for age, sex, hypertension, prior antihypertensive treatment, prior anticoagulation, ICH volume, ventricular extension, Glasgow Coma Scale, NIHSS, and glucose.

†Mantel–Haenszel Chi²; ‡Mantel–Haenszel test for trend.
we found a clear correlation between lipid profile and markers of nutritional status, except for triglycerides; however, univariate and multivariate analysis showed that patients who survived did not have higher albumin levels than those who died; ie, mortality in the group of lower LDL-C cannot be explained by a poor nutritional status.

There are numerous prognostic models of mortality and outcome after ICH that include different clinical, biochemical, and neuroimaging criteria. We did not find correlation between lipid profile and known markers of ICH severity, discarding LDL-C levels as biological marker of ICH severity at admission.

Recent investigations have improved the knowledge about the pathophysiology of early hematoma growth, edema, and resultant tissue injury, factors that can cause early neurological deterioration and affect its long-term outcome. However, the relation between cholesterol levels and ICH-growth or perihematoma edema has not been specifically studied. Some authors suggest that higher cholesterol levels are associated with lesser hemorrhage growth. Cholesterol is known to have effects on the vasculature and is essential for normal membrane fluidity, and adequate cholesterol levels may be important for maintaining the integrity of vessels and their resistance to rupture.

Theoretically, statins may increase the risk of cerebral hemorrhage because high cholesterol apparently protects against ICH. Meta-analyses provide evidence that the statins significantly reduce the risk of ischemic stroke, however a recent review suggests that this beneficial effect is partly reduced by increasing ICH. In our study, univariate analysis showed no differences in mortality terms attributable to the use of statins. We believe there is not enough evidence to modify the current management of these patients.

The present results support that LDL-C independently influences survival of patients with ICH; lower LDL-C levels were associated with higher mortality. Results should be interpreted with caution given the limited sample size; nevertheless, they are another proof of the relation between ICH and cholesterol, which remains controversial and should be clarified. Studies that explain role of lipids in early growth and neurological worsening of ICH are necessary because this item may be the clue of the worst outcome of patients with low cholesterol, and it would be interesting to define the safety of an aggressive reduction of cholesterol in these patients.

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Disclosures
None.

References
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