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## INVITED COMMENTARY

# Serum Cholesterol and Outcomes in Intracerebral Hemorrhage: More Smoke, Still no Fire

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Evidence of a paradoxical association between low serum cholesterol and increased risk of intracerebral hemorrhage (ICH) was first described in epidemiologic studies from Japan in the mid-1970s [1, 2]. Nearly 50 years later, the clinical significance and even existence of this association remain unclear despite a large body of research. A possible association between serum cholesterol levels and outcomes after ICH has more recently gained attention, although it, too, is uncertain. Low serum low-density lipoprotein cholesterol (LDL-C) levels have been associated with increased mortality after ICH, although conflicting data exist [3]. Additionally, there is evidence to suggest that higher high-density lipoprotein cholesterol (HDL-C) levels [4] and lower LDL-C/HDL-C ratios [5] may be associated with increased risk of and higher mortality after ICH.

Incentive to settle this issue continues to mount because of discordance between the practice of using statins and other drugs to reach a continually lowering LDL-C goal [6] to prevent atherosclerotic cardiovascular disease [7], with the ongoing growth of ICH as a major worldwide contributor to long-term disability and mortality [8]. In this issue of *Neurocritical Care*, Wu and colleagues [9] add to our knowledge about this topic with their investigation of the association between the LDL-C/HDL-C ratio and functional outcomes after ICH.

The authors performed a retrospective analysis of patients in whom the serum LDL-C/HDL-C ratio was measured on admission as part of routine clinical practice from a prospective cohort of hospitalized patients with ICH drawn from 13 hospitals in Beijing, China, between 2014 and 2016. Of a total cohort of 1,964 patients, 491 were included in the analysis, with half of the exclusions being due to lack of admission LDL-C/HDL-C data. After controlling for confounders using multivariable models, the odds of 90-day poor outcome (modified Rankin Score 3–6) were approximately three times higher in patients in the lowest LDL-C/HDL-C ratio quartile (< 1.74) when compared with those in the highest quartile (≥ 3.16). Although 90-day mortality rates also followed this trend, the differences were not statistically significant. An analysis accounting for the nonlinear relationship between the LDL-C/HDL-C ratio and outcomes using restricted cubic splines corroborated the finding regarding functional outcomes, demonstrating that the lowest risk of poor outcome was associated with a ratio of 3.1–3.5.

The main strengths of this work are the prospective nature of the cohort and outcomes determination; the relatively large number of patients from multiple institutions studied; and the granular nature of the data, which allowed for adjustment for key prognostic factors, such as hematoma location and volume. Several important limitations, acknowledged by the authors, also need to be considered when interpreting this study. The study population has some unique features that significantly limit the generalizability of the results. For example, patients with more severe ICH were excluded from this study because they frequently did not undergo serum cholesterol measurement as part of routine care. Second, a remarkable 48% of the study population had active alcoholism. Third, the study population was disproportionately male (72%). Finally, under 1% of the study

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population was on an anticoagulant medication, and just 10% were taking lipid lowering medications. Next, several key prognostic variables differed significantly between the LDL-C/HDL-C quartile groups. In the lowest quartile/worst outcome group, the patients were older, surgery for ICH and lobar location were more common, and hematoma volume and admission serum glucose concentration were higher, whereas intraventricular hemorrhage was less common. Although these and many other confounders were accounted for in several multivariable models, these differences suggest the possibility that the groups might have been systematically different from each other in ways beyond those accounted for by the authors. Finally, the authors did not test associations of LDL-C and HDL-C alone with outcomes, leaving open the question of which of these variables—if either—was more responsible for their findings.

What can we learn from this study? Its design and limitations render the results hypothesis-generating and should not affect clinical practice, particularly given the clear reduction in risk of atherosclerotic cardiovascular disease associated with lipid lowering therapies [7]. Nonetheless, this study is a valuable addition to the literature regarding the relationship between serum cholesterol levels and ICH. It adds to the small body of evidence indicating that low LDL-C levels are associated with worse outcomes in patients with ICH by showing that this association extends to low LDL-C/HDL-C ratios. Further, this association between low LDL-C/HDL-C ratios and poor functional outcome as opposed to mortality is a unique observation, thus far. Finally, the data from Wu and colleagues [9] demonstrate that the association between LDL-C/HDL-C ratio and poor outcomes may not be linear but rather follows a more complex *U*-shaped curve, with both low and very high ratios conferring a higher risk of poor outcomes compared with ratios in the 3.1–3.5 range. This finding, if replicated in larger and less confounded studies, would add complexity to our understanding of the possible mechanisms underlying the relationship between serum cholesterol levels and ICH.

Yet, in keeping with the larger body of literature on this topic, the results of the study from Wu and colleagues [9] raise more questions than answers: Is the association between low LDL-C and HDL-C ratios real? What are the mechanisms underlying this relationship? Does it represent a modifiable risk factor for poor outcome? Spurring interest in finding definitive answers to these vital questions may be the most important contribution of this study.

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