Importance of lipid ratios for predicting intracranial atherosclerotic stenosis

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Abstract
Background: We wished to investigate the association of lipid ratios with intracranial atherosclerotic stenosis (ICAS) in a Chinese population.

Methods: We included 658 consecutive patients with ischemic stroke in our cross-sectional study. Intracranial and extracranial arteries were evaluated for atherosclerotic stenosis using digital subtraction angiography or computed tomography angiography. Lipid ratios [total cholesterol (TC)/high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG)/HDL-C, low-density lipoprotein-cholesterol (LDL-C)/HDL-C, non-high-density lipoprotein-cholesterol (non-HDL-C)/HDL-C, remnant cholesterol (RC)/HDL-C, apolipoprotein B (apo B)/apolipoprotein A-I (apo A-I), and apo B/HDL-C] were calculated.

Results: Ratios of TC/HDL-C, LDL-C/HDL-C, RC/HDL-C, non-HDL-C/HDL-C, apo B/HDL-C and apo B/apo A-I were associated significantly with ICAS but not with extracranial atherosclerotic stenosis after adjustment for confounding factors. Analyses of receiver operating characteristic (ROC) curves revealed the apo B/apo A-I ratio have the highest area under the ROC curve (AUC) value for a lipid level alone and for lipid ratios (AUC = 0.588). Lipid ratios had higher AUC values than those for a lipid level alone for identifying ICAS.

Conclusion: The ratios of TC/HDL-C, LDL-C/HDL-C, RC/HDL-C, non-HDL-C/HDL-C apo B/HDL-C and apo B/apo A-I were related significantly to ICAS risk. Compared with the other variables tested, the apo B/apo A-I ratio appeared to be better discriminator for identifying ICAS risk.

Introduction
Intracranial atherosclerotic stenosis (ICAS) is a major cause of ischemic stroke worldwide [1, 2]. The prevalence of ICAS is relatively high in Asians, whereas extracranial atherosclerotic stenosis (ECAS) is more common in Caucasians. The exact causes for this distribution of cerebral atherosclerosis are not clear, but racial differences, socioeconomic status, and risk factors may explain this phenomenon [3]. Because of the detrimental effects of ICAS, better understanding of its risk factors is very important. The role of lipid parameters and lipid ratios in ICAS is controversial. Low-density lipoprotein cholesterol (LDL-C) is associated mainly with ECAS [4]. In Chinese populations, levels of high-density
lipoprotein-cholesterol (HDL-C) [5], non-high-density lipoprotein-cholesterol (non-HDL-C) [6] and total cholesterol (TC) [7] are associated with an increased risk of ICAS. One study based on a Korean population revealed the importance of hypercholesterolemia on ICAS in men [8]. With regard to lipid ratios, Park and colleagues indicated the importance of apolipoprotein B/apolipoprotein A-I (apoB/apo A-I) ratio on ICAS [9]. Levels of HDL-C along with those of remnant cholesterol (RC) and low levels of apo B/apo A-I are related to prevention of the angiographic progression of ICAS [10]. The LDL-C/HDL-C ratio is regarded as a marker for carotid intima-media thickness (CIMT) progression [11]. In addition, some lipid ratios (apo B/apo A-I, TC/HDL-C, LDL-C/HDL-C, and non-HDL-C/HDL-C) have shown clinically important correlations with coronary artery lesions, insulin resistance, and the metabolic syndrome [12-14].

Lipid ratios are considered to be good parameters for identifying vascular diseases. Nevertheless, studies focusing on the association between lipid ratios and cerebral atherosclerosis are lacking. The potential predictive importance of these lipid ratios in Chinese populations is not known. It is important to screen applicable lipid ratios to identify high-risk populations. Therefore, we compared this correlation between lipid ratios (TC/HDL-C, triglycerides (TG)/HDL-C, LDL-C/HDL-C, RC/HDL-C, non-HDL-C/HDL-C, apo B/HDL-C, and apo B/apo A-I) and the risk of cerebral atherosclerosis in patients with ischemic stroke.

Methods

Patients

The study protocol was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University (Chongqing, China). Written informed consent was obtained from all patients. From November 2015 to January 2017, consecutive patients with transient ischemic attack or acute (< 7 days after onset) ischemic stroke admitted to our division within the First Affiliated Hospital of Chongqing Medical University were recruited prospectively into our study. All patients underwent cerebral digital subtraction angiography (DSA) or computed tomography angiography (CTA) to check for atherosclerotic lesions.

The exclusion criteria were patients with: contraindications to, or who refused to undergo, CTA or
DSA; non-atherosclerotic arterial stenosis or totally occlusive stenosis in intracranial and extracranial vessels; incomplete clinical information.

Collection of clinical information
Information of each patient was acquired by completing a detailed questionnaire combined with a standardized interview. The information obtained was on demographics, hypertension, diabetes mellitus (DM), previous stroke, coronary heart disease, medical history, and current smoking. Blood pressure was determined with mercury manometers while the patient was seated after 10 min of rest. The parameter of “current smoking” was self-reported by patients. The diagnosis of hypertension, DM, coronary heart disease and previous stroke was according to that detailed in the International Classification of Diseases (9th revision).

Laboratory measurements
Fasting blood samples were extracted and analyzed in a laboratory department of the First Affiliated Hospital. Lipid levels were measured using a fully automatic biochemistry analyzer (Cobas c701; Roche, Basel, Switzerland) and original reagents in the laboratory department. Levels of TC, TG, HDL-C, and LDL-C were measured using an enzymology assay. Levels of apo A-I and apo B were measured by an immunoturbidimetric assay. The non-HDL-C level was defined as the TC level minus the HDL-C level [15]. The RC level was defined as the non-HDL-C level minus the LDL-C level [16]. Likewise, we calculated the lipid ratios of TC to HDL-C, TG to HDL-C, LDL-C to HDL-C, RC to HDL-C, non-HDL-C to HDL-C, apo B to HDL-C, and apo B to apo A-I.

Assessment of cerebral atherosclerotic stenosis
ICAS was evaluated using the method used in the Warfarin-Aspirin Symptomatic Intracranial Disease Trial [17]. ECAS was evaluated based on the method used in the North American Symptomatic Carotid Endarterectomy Trial [18]. “Intracranial vessels” included anterior, middle, and posterior cerebral arteries, the basilar artery, and intracranial portions of the vertebral and internal carotid artery. “Extracranial vessels” included extracranial segments of the vertebral artery and internal carotid artery. The presence of ICAS or ECAS was defined as stenosis ≥ 50% in large intracranial or extracranial vessels.

Statistical analyses
Data were analyzed using SPSS 18.0 (Chicago, IL, USA) and MedCalc 11.4.2.0 (MedCalc, Ostend, Belgium). Results were compared with the chi-square test for frequency data, Mann–Whitney U-test for skewed data, or t-test for normal data, as appropriate. Results are the mean ± standard deviation for normal data or median and interquartile range for skewed data. Multiple logistic regression was carried out to evaluate the correlation of lipid ratios with ICAS and ECAS. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were obtained. Receiver operating characteristic (ROC) curves were created to assess if variables could predict ICAS, and the results expressed as the area under the curve (AUC). AUC values were compared using the Z-statistic. P < 0.05 was considered significant.

Results
Six hundred and fifty-eight patients (441 men and 217 women; mean age, 65.9 ± 11.2 years) with transient ischemic attack or acute ischemic stroke were included in the final analyses. Of 658 patients analyzed, DSA was done in 24 patients (3.6%) and the remaining 634 patients underwent CTA. Sex-specific characteristics are shown in Table 1.

| Variables | Men (n = 441) | Women (n = 217) | P Value |
|-----------|---------------|-----------------|---------|
| Age, year | 64.6 ± 11.2   | 68.5 ± 10.7     | <0.001  |
| Systolic blood pressure, mmHg | 152.8 ± 23.8 | 154.1 ± 26.0 | 0.522   |
| Diastolic blood pressure, mmHg | 88.7 ± 16.0 | 84.7 ± 14.6 | 0.002   |
| Hypertension, n (%) | 311 (70.5) | 165 (76.0) | 0.137 |
| Diabetes mellitus, n (%) | 144 (32.7) | 74 (34.1) | 0.711 |
| Current smoking, n (%) | 251 (56.9) | 4 (1.8) | <0.001 |
| Previous stroke, n (%) | 131 (29.7) | 56 (25.8) | 0.297 |
| Coronary heart disease, n (%) | 51 (11.6) | 29 (13.4) | 0.507 |
| TC, mmol/L | 4.35 ± 1.06 | 4.67 ± 1.10 | <0.001 |
| TG, mmol/L | 1.66 ± 1.23 | 1.62 ± 1.01 | 0.664 |
| HDL-C, mmol/L | 1.09 (0.94–1.24) | 1.26 (1.09–1.51) | <0.001 |
| LDL-C, mmol/L | 2.82 ± 0.91 | 2.97 ± 0.99 | 0.061 |
| Non-HDL-C, mmol/L | 3.16 (2.48–3.90) | 3.21 (2.53–3.96) | 0.384 |
| apo A-I, mg/L | 0.42 ± 0.40 | 0.37 ± 0.35 | 0.121 |
| Apo A-I, g/L | 1.22 ± 0.35 | 1.40 ± 0.27 | <0.001 |
| Apo B, g/L | 0.99 ± 0.53 | 0.96 ± 0.29 | 0.520 |
| TC/HDL-C | 4.12 ± 1.37 | 3.74 ± 1.22 | 0.001 |
| TG/HDL-C | 1.71 ± 1.77 | 1.45 ± 1.67 | 0.069 |
| LDL-C/HDL-C | 2.68 ± 1.06 | 2.39 ± 0.94 | 0.001 |
| RC/HDL-C | 0.44 ± 0.53 | 0.35 ± 0.55 | 0.036 |
| Non-HDL-C/HDL-C | 3.12 ± 1.37 | 2.73 ± 1.22 | 0.001 |
| Apo B/HDL-C | 2.25 (1.65–2.91) | 1.87 (1.44–2.48) | <0.001 |
| Apo B/apo A-I | 0.78 (0.60–0.98) | 0.69 (0.53–0.86) | <0.001 |

TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; RC, remnant cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A-I, apolipoprotein A-I.

Results are expressed as mean ± standard deviation, median with interquartile range or n (%).
Women were older, had lower diastolic blood pressure, and lower ratios of non-HDL-C/HDL-C, TC/HDL-C, RC/HDL-C, LDL-C/HDL-C, apo B/HDL-C, and apo B/apo A-I than men. A significantly higher proportion of current smokers were men (P < 0.001), and levels of TC, HDL-C, and apo A-I were lower than those in women.

Each lipid ratio was divided based on sex to assess its relationship with the risk of ICAS or ECAS. We compared the lipid ratio in the fourth quartile with that in the first quartile. The corresponding OR and 95% CI of lipid ratios (TC/HDL-C, LDL-C/HDL-C, TG/HDL-C, RC/HDL-C, non-HDL-C/HDL-C, apo B/apo A-I, and apo B/HDL-C) in the first quartile are listed in Fig. 1. Compared with other lipid ratios, apo B/apo A-I showed the most powerful relationship with ICAS after adjustment for potential confounding factors (first quartile vs. fourth quartile; OR, 2.32; 95% CI, 1.44–3.73). Moreover, after adjustment for age, sex, current smoking, hypertension, DM, previous stroke, and coronary heart disease, this significant relationship was also present for other lipid ratios (TC/HDL-C, OR = 2.04, 95% CI = 1.26–3.31; RC/HDL-C, 1.64, 1.01–2.65; non-HDL-C/HDL-C, 2.04, 1.26–3.31; LDL-C/HDL-C, 1.92, 1.19–3.10; apo B/HDL-C, 2.28, 1.41–3.71; fourth quartile vs. first quartile; Fig. 1A). These adjusted logistic regression analyses were repeated for ECAS, but a significant association between lipid ratios and ECAS was not observed (Fig. 1B).

Patients with ICAS had significantly higher ratios of LDL-C/HDL-C (Fig. 2B), apo B/HDL-C (Fig. 2E), and apo B/apo A-I (Fig. 2F) than those without ICAS in both sexes (P < 0.05). However, this difference was not observed for the ratios of TG/HDL-C (Fig. 2A) and RC/HDL-C (Fig. 2C). For the non-HDL-C/HDL-C ratio, a significant difference was observed only in men (Fig. 2D). Due to a similar result with that of non-HDL-C/HDL-C, the ratio of TC/HDL-C is not presented in Fig. 2.

Analyses of ROC curves revealed that the apo B/apo A-I ratio had a peak AUC value (0.588) for ICAS for the lipid level alone and lipid ratios (Table 2). Furthermore, the apo B/apo A-I ratio had the highest AUC value in men but not in women (men: 0.579; women: 0.613). In women, the apo B/HDL-C ratio demonstrated an optimal AUC value (0.617) for predicting ICAS risk. Overall, lipid ratios had higher AUC values than those for the lipid level alone for the identification of ICAS. Also, the AUC in women was higher than that in men for all lipid ratios tested.
Table 2
Comparison of AUC for each evaluated variable in predicting ICAS

| Lipid measures                  | Total AUC(95% CI) | Men AUC(95%CI) | Women AUC(95%CI) |
|---------------------------------|------------------|---------------|------------------|
| TC                              | 0.543 (0.498–0.589) | 0.537 (0.481–0.592) | 0.562 (0.482–0.642) |
| TG                              | 0.525 (0.480–0.570) | 0.499 (0.444–0.554) | 0.576 (0.500–0.652) |
| HDL-C                           | 0.462 (0.417–0.507) | 0.480 (0.426–0.535) | 0.435 (0.356–0.514) |
| LDL-C                           | 0.555 (0.510–0.601) | 0.547 (0.491–0.603) | 0.573 (0.493–0.653) |
| Non-HDL-C                       | 0.559 (0.513–0.604) | 0.543 (0.488–0.599) | 0.590 (0.511–0.669) |
| RC                              | 0.538 (0.493–0.583) | 0.529 (0.475–0.584) | 0.558 (0.481–0.635) |
| Apo A-I                         | 0.456 (0.411–0.501) | 0.465 (0.410–0.520) | 0.424 (0.345–0.504) |
| Apo B                           | 0.576 (0.531–0.622) | 0.561 (0.505–0.617) | 0.605 (0.527–0.683) |
| Lipid ratios                    |                  |               |                  |
| TC/HDL-C                        | 0.566 (0.521–0.611) | 0.546 (0.491–0.601) * | 0.608 (0.531–0.684) |
| TG/HDL-C                        | 0.535 (0.490–0.579) * | 0.511 (0.456–0.566) * | 0.580 (0.503–0.657) |
| LDL-C/HDL-C                     | 0.570 (0.525–0.615) | 0.555 (0.499–0.611) | 0.603 (0.526–0.680) |
| RC/HDL-C                        | 0.544 (0.500–0.589) | 0.530 (0.475–0.584) | 0.575 (0.498–0.652) |
| Non-HDL-C/HDL-C                 | 0.566 (0.521–0.611) | 0.546 (0.491–0.601) * | 0.608 (0.531–0.684) |
| Apo B/HDL-C                     | 0.578 (0.533–0.623) | 0.562 (0.506–0.617) | 0.617 (0.541–0.693) |
| Apo B/apo A-I                   | 0.588 (0.543–0.633) | 0.579 (0.523–0.634) | 0.613 (0.536–0.690) |

TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A-I, apolipoprotein A-I; RC, remnant cholesterol; AUC, area under the curve; 95%CI, 95% confidence interval; ICAS, intracranial atherosclerotic stenosis. * P < 0.05, AUC were compared with apo B/apo A-I ratio in lipid ratios.

Discussion

Our study revealed the ratios of TC/HDL-C, RC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, apo B/HDL-C, and apo B/apo A-I to be correlated significantly with ICAS. Moreover, ROC analyses revealed all lipid ratios to be better than the level of lipid alone for predicting ICAS. The apo B/apo A-I ratio had higher predictive value than that for other variables. This is the first study to present these relationships in a Chinese population.

The correlation of apo B/apo A-I ratio and ICAS was established in a Korean population by Park and colleagues. They demonstrated that a higher apo B/apo A-I ratio could be a discriminator for ICAS rather than ECAS [9]. This ratio has also been shown to be superior to other ratios for the identification of coronary-artery lesions in a Chinese population and coronary disease in a Swedish population [12, 19]. Thus, the apo B/apo A-I ratio has been considered to be an excellent surrogate for prediction of vascular-disease risk. Nevertheless, few studies have focused on the apo B/HDL-C ratio.

Maki and colleagues demonstrated that the apo B/apo A-I ratio can be a predictor of CIMT progression in vascular walls [20]. Biswas et al. [21] demonstrated that this ratio correlated well with the risk of coronary heart disease among Indian populations. Hence, the apo B/HDL-C ratio has been proposed to be a marker of atherosclerosis.

Our study also identified the important predictive abilities of the ratios of apo B/HDL-C and apo B/apo
A-I on ICAS rather than ECAS. A greater effect on antioxidant enzymes in ICAS than in ECAS could be the mechanism that explains this phenomenon [22]. As the crucial lipoprotein in intermediate-density lipoprotein (IDL), very low-density lipoprotein (VLDL), and LDL, apo B can reflect the potential atherogenic lipoprotein particles in lipid metabolism [23]. Conversely, apo A-I is the main component in HDL-C possessing anti-atherogenic and anti-inflammatory potential [24]. HDL-C can reverse cholesterol transport. Valuable antioxidant capacities are present in apo A-I and HDL-C. Therefore, the ratios of apo B/HDL-C and apo B/apo A-I can reflect more comprehensive atherogenicity and lower antioxidant capacity.

Non-HDL-C integrates multiple types of cholesterol, including IDL, LDL, VLDL, and lipoprotein (a). It can be acquired simply by calculation (TC level minus the HDL-C level) [15]. Due to protective role of HDL-C against cardiovascular diseases, non-HDL-C has an atherogenic effect in the circulation. This association between non-HDL-C and ICAS has been confirmed in a Chinese population [6]. However, the diagnostic ability of the non-HDL-C/HDL-C ratio for ICAS has not been investigated. Moreover, the non-HDL-C/HDL-C ratio possesses good predictive ability for some diseases. This ratio has been shown to be more useful than the apo B/apo A-I ratio for identifying the metabolic syndrome in a Korean population. Furthermore, a large retrospective study demonstrated a positive correlation between insulin resistance and the level of C-reactive protein [25]. In addition, for the prediction of risk of cardiovascular diseases, this ratio is similar to that of apo B/apo A-I for DM patients [26]. Compared with traditional lipid variables, this ratio is more suitable for estimation of arterial stiffness in a Chinese population [27]. In our study, the non-HDL-C/HDL-C ratio carried a 2-fold risk of ICAS. Control of this ratio may be important for assessing ICAS risk. Results of the TC/HDL-C ratio were similar to those of the non-HDL-C/HDL-C ratio.

RC comprises the TG-rich lipoproteins IDL, VLDL, and chylomicrons [16]. RC is regarded to be a causal indicator of cardiovascular diseases [28, 29]. The diagnostic values of RC and the RC/HDL-C ratio have been identified simultaneously in Chinese patients with peri-procedural myocardial injury [30]. The RC/HDL-C ratio appears to be a useful tool for ICAS. Compared with other important lipid ratios, only RC/HDL-C showed a slight association with ICAS in our study. The exact mechanism of action is not
clear, but low-grade inflammation caused by RC could be one reason. Subsequently, RC could enter vascular walls by infiltrating the endothelial barrier, and lead to formation of foam cells by upregulating the expression of scavenger receptors [31].

Our study not only verified the data of other studies, it also clarified the specific diagnostic value of lipid ratios upon ICAS. We found that lipid ratios were better than routinely used lipid concentrations for identifying ICAS. Subsequently, ROC curves indicated that the diagnostic ability of apo B/apo A-I surpassed that of all other ratios tested. This ratio was qualified as the best marker for ICAS risk. The lipid ratios indicated the balance between anti-atherogenic and pro-atherogenic mechanisms. The combined effects of lipid ratios could be more valuable than the level of a lipid alone. Our results also suggested that lipid ratios had better predictive values than that of a lipid level alone for identifying ICAS. In addition, sex-based differences were focused on the predictive accuracy of lipid profiles. The apo B/apo A-I ratio had the highest AUC value for men, and the apo B/HDL-C ratio displayed the highest AUC value for women. One interpretation is that estrogen may exert an effect on lipid profiles, but the exact cause is not known and further investigation is needed.

Our study had five main limitations. First, data from a relatively small hospital-based population cannot be generalized to larger populations. Second, given the cross-sectional design and relatively small cohort, a causal relationship between lipid ratios and ICAS could not be ascertained accurately. Third, we focused on a Chinese population, so our conclusions cannot be extrapolated to different ethnic groups. Fourth, cerebral atherosclerotic stenosis was evaluated using DSA and CTA. These methods have a high degree of accuracy for evaluating the severity of stenosis, but less so for cerebral atherosclerotic stenosis. Finally, the absence of data such as insulin resistance, inflammatory indicators, menopausal status, and dietary habits may have affected the outcomes.

In conclusion, the ratios of TC/HDL-C, LDL-C/HDL-C, RC/HDL-C, non-HDL-C/HDL-C and apo B/HDL-C were related significantly to ICAS risk. Compared with the other variables tested, the apo B/apo A-I ratio appeared to be better discriminator for identifying ICAS risk.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethics committee of the First Affiliated Hospital of Chongqing Medical University (Chongqing, China). Written informed consent was obtained from all patients.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All data generated or analysed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests

**Author’s contributions**

Wen-Song Yang, Rui Li, Yi-Qing Shen, Qi Li, Guo-En Yao, and Peng Xie conceived and designed the study. Xing-Chen Wang, Qing-Jun Liu and Hai-Yang Wang coordinated the study. Wen-Song Yang, Rui Li, Yi-Qing Shen, Xing-Chen Wang, Qing-Jun Liu and Hai-Yang Wang did acquisition, analysis, or interpretation of data. Qi Li, Guo-En Yao, and Peng Xie oversaw subjects’ recruitment and monitored gathering of clinical data. Wen-Song Yang, Rui Li and Yi-Qing Shen conducted the statistical analysis and prepared the paper. Qi Li and Peng Xie obtained fundings. Qi Li, Guo-En Yao, and Peng Xie were responsible for the administrative, technical, or material support.

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Figures
Figure 1

Logistic regression analysis of intracranial (A) and extracranial (B) atherosclerotic stenosis, among lipid ratios in the extreme quartiles of each evaluated variable. Adjusted for age, gender, current smoking, hypertension, diabetic mellius, previous stroke and coronary heart disease. OR, odds ratio; 95%CI, 95% confidence interval; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Apo B, apolipoprotein B; Apo A-I, apolipoprotein A-I; ICAS, intracranial atherosclerotic stenosis; ECAS, extracranial atherosclerotic stenosis.
Figure 2

Box-plots of lipid ratios values and their association with ICAS in men and women. TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; Apo B, apolipoprotein B; ApoA-I, apolipoprotein A-I; RC, remnant cholesterol; ICAS, intracranial atherosclerotic stenosis. *Significant difference at P< 0.05