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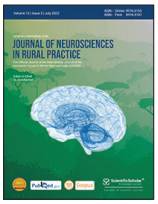

Original Article

Research on the association between non-traditional lipid parameters and intracranial-extracranial artery stenosis in stroke patients

Shanping Wang[1], Hangyan Zhong[1], Rongqi Lin[1], Qinghui Fu[1], Luping Zou[1], Suhua Liu[1], Yangui Chen[2], Yisheng Chen[1]

[1]Department of Neurology, Shanghang County General Hospital, [2]Department of Neurology, Longyan First Hospital Affiliated to Fujian Medical University, Longyan City, Fujian Province, China.

ABSTRACT

Objectives: Study the association between non-traditional lipid parameters and intracranial and extracranial arterial stenosis in stroke patients.

Materials and Methods: Exploring the predictive ability of non-traditional lipid parameters for cerebral arterial stenosis (CAS) using different statistical methods.

Results: Compared to controls, CAS patients exhibited significantly lower levels of triglycerides, atherogenic coefficient, Castelli's Risk Index I, and remnant cholesterol (RC) ($P < 0.001$), while total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and non-HDL-C levels were elevated ($P < 0.001$). Significant subgroup differences were observed for non-HDL-C and RC within the CAS group ($P < 0.001$), whereas conventional lipid parameters did not show such variations. Strong correlations were identified among various lipid markers ($P < 0.001$). Logistic regression analysis confirmed a significant association between lipid parameters and CAS. A restricted cubic spline model demonstrated a non-linear relationship between RC levels and CAS risk. Receiver operating characteristic curve analysis revealed that non-HDL-C had the highest predictive accuracy (area under the curve = 0.655, 95% confidence interval: 0.606–0.703), indicating its strong potential as a biomarker for CAS.

Conclusion: Non-traditional lipid parameters, particularly non-HDL-C and RC, exhibit significant differences across intracranial, extracranial, and combined intracranial-extracranial arterial stenosis. Moreover, non-HDL-C shows the strongest predictive value for CAS risk, suggesting its potential role in routine clinical assessments. Incorporating non-traditional lipid parameters into standard lipid profiling may enhance early detection and risk stratification of CAS.

Keywords: Lipoprotein cholesterol, Receiver operating characteristic curve, Retrospective studies, Stroke

INTRODUCTION

Stroke is the second leading cause of death worldwide,[1] and data from China in 2019 indicate that it ranks as the leading cause of mortality.[2,3] With intracranial and extracranial arterial stenosis being major contributors to both its occurrence and recurrence.[4] Investigating the risk factors associated with these arterial stenoses is crucial for the prevention and management of ischemic stroke, with lipid metabolism abnormalities playing a pivotal role.[5] Traditional lipid parameters are widely applied because they are easy to collect and relatively low-cost. Conventional lipid parameters are widely recognized for their strong association with intracranial and extracranial artery stenosis. However, lowering traditional lipid parameters cannot prevent the onset and progression of arterial stenosis.[6] Non-traditional lipid parameters differ from conventional single lipid markers as they are derived from combinations of two or more traditional lipid indices. Numerous studies suggest a strong correlation between non-traditional lipid parameters and the risk of cardiovascular and cerebrovascular diseases, with some evidence indicating their predictive value may surpass that of traditional lipid parameters.[7] This study aims to explore their correlation, assess their predictive value, and provide direction for early diagnosis of cerebral arterial stenosis (CAS) clinical diagnosis.

MATERIALS AND METHODS

Study participants

A total of 472 CAS patients who underwent head and neck arterial digital subtraction angiography from January 2020 to January 2022 were included as research subjects.

***Corresponding author:** Yisheng Chen, Department of Neurology, Shanghang County General Hospital, Longyan City, Fujian Province, China. chenyisheng2025@163.com

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Inclusion criteria

Inclusion criteria: Age 40–80 years; diagnosed as cerebral infarction.[8]

Exclusion criteria

1. Patients with malignant anemia, moderate-to-severe renal dysfunction, thyroid disorders, chronic inflammatory diseases, malignancies, or autoimmune diseases.
2. Individuals with arterial developmental anomalies, fibromuscular dysplasia, arteritis, moyamoya disease, arterial dissection, intracranial infections, substance abuse, or other related conditions.
3. Those with congenital heart disease, atrial fibrillation, myocardial infarction, cardiomyopathy, heart failure, or valvular heart disease.

Categorization of intracranial and extracranial arterial stenotic lesions

A total of 472 patients were included in the study. Participants were categorized into two primary groups: Group 1, comprising patients with non-cerebral artery stenosis (NCAS) and CAS; CAS was further subdivided into intracranial artery stenosis (ICAS), extracranial artery stenosis (ECAS), and combined intracranial and extracranial artery stenosis (COMS) [Supplementary Figure S1]. Group 2 was stratified based on lipid parameter levels into three tertiles: Low, medium, and high.

Covariates information

Based on previous studies and directed acyclic graphs [Supplementary Figure S2], we selected covariates related to stroke. Covariates included age, sex, alcohol drinking, smoking history, body mass index (BMI), hypertension (HT), and diabetes.

Calculation of non-traditional lipid parameters

(1) Atherogenic coefficient (AC) = Non-high-density lipoprotein cholesterol (HDL-C)/HDL-C[9]

(2) Castelli's Risk Index I (CRI-I) = Total cholesterol (TC)/HDL-C[9]

(3) Non-HDL-C = TC−HDL-C[9]

(4) Remnant cholesterol (RC) = TC−HDL-C−low-density lipoprotein cholesterol (LDL-C).[10]

Statistical analysis

Continuous variables are presented as median and interquartile range (M [P25-P75]), and categorical data are presented as frequencies (percentages); continuous variables were tested for normality and homogeneity of variance using the Kolmogorov–Smirnov test. Variables that were normally distributed were analyzed using an independent samples *t*-test, and those that were non-normally distributed were analyzed using a non-parametric two-sample rank sum test; categorical variables were tested using the Chi-square test; and the study participants were categorized into low, medium, and high groups based on the tertiles of different lipid parameters. The first tertile of lipid parameters was set as a dummy variable, and variables with $P < 0.1$ or clinically relevant variables from univariate analysis were included in the logistic regression model; the restricted cubic spline function was applied to select the optimal knots based on the Akaike Information Criterion, to further evaluate the non-linear association between non-lipid parameters and the risk of intracranial/extracranial stenosis. Receiver operating characteristic (ROC) curve analysis was subsequently conducted to assess the predictive ability of non-lipid parameters for intracranial/extracranial arterial stenosis. Data management was conducted using Microsoft Excel 2019, while statistical analyses were performed with IBM Statistical Package for the Social Sciences Statistics 26.0, R software (version 4.4.1). Graphs were generated using GraphPad Prism 8.0.2 and R software (version 4.1.3). $P < 0.05$ was considered statistically significant, while $P < 0.001$ indicated high statistical significance.

RESULTS

Comparison between the stenosis subgroup and control group

Four hundred and seventy-two patients were included in this study, with 216 in the NCAS group and 256 in the CAS group (114 with ICAS, 85 with ECAS, and 57 with COMS). Compared to the control group, the stenosis group showed significant differences in gender ($P < 0.05$), and in age, smoking history, HT history, diabetes history, BMI, TC, triglycerides, HDL-C, LDL-C, AC, CRI-I, non-HDL-C, and RC ($P < 0.001$). There were significant differences between non-HDL-C and RC, non-traditional lipid parameters, in the stenosis subgroups ($P < 0.001$), but no differences were found between subgroups for traditional lipid parameters. For details, refer to Table 1.

Correlation analysis among lipid parameters

Spearman correlation analysis revealed that all lipid parameters were significantly correlated with each other. The correlation matrix is illustrated in Figure 1. TC showed strong correlations with non-HDL-C, AC, CRI-I, RC, with correlation coefficients of 0.95 ($P < 0.001$), 0.76 ($P < 0.001$), 0.76 ($P < 0.001$), and 0.55 ($P < 0.001$), respectively [Figure 1].

Subgroup analysis

Variables with $P < 0.1$ were included in the binary logistic regression model. Three logistic regression models were constructed: Model 1 (unadjusted for any covariates), Model 2 (adjusted for age and sex), and Model 3 (further adjusted for age, sex, smoking history, HT, diabetes, and BMI). Across all three models, both traditional lipid parameters and non-traditional lipid parameters demonstrated significant associations with intracranial-extracranial arterial stenosis. The results are illustrated in Figures 2-4.

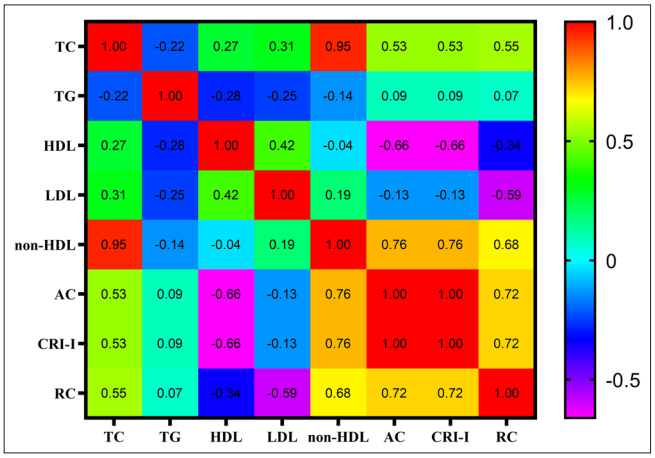

Figure 1: Spearman correlation analysis among different lipid parameters. TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, AC: Atherogenic coefficient, CRI-I: Castelli's risk index I, RC: Remnant cholesterol.

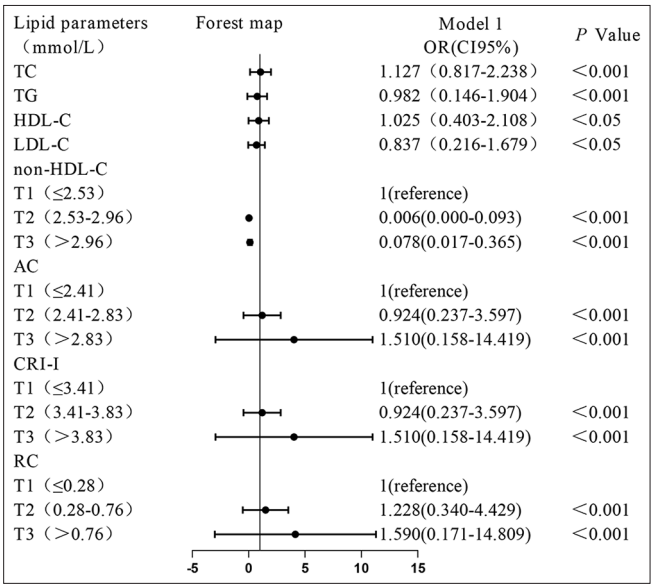

Figure 2: Correlation between lipid parameters and the risk of intracranial and extracranial artery stenosis (Model 1). TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AC: Atherogenic coefficient, CRI-I: Castelli's risk index I, OR: Odds ratio, RC: Remnant cholesterol, CI: Confidence interval, T1: First tertile, T2: Second tertile, T3: Third tertile.

Table 1: Clinical baseline characteristics and lipid parameters of the control and stenosis subgroups.

Variable	NCAS *n*=216	ICAS *n*=114	ECAS *n*=85	COMS *n*=57	*P*-value
Age	52 (33, 56)	63 (52, 70)*	66 (57, 73)*	65 (56, 78)*	<0.001
Gender (Male)	144 (66.7%)	81 (71.1%)	71 (83.5%)#	45 (78.9%)	<0.05
Smoking History	48 (22.2%)	56 (49.1%)*	48 (56.5%)*	24 (42.1%)*	<0.001
Hypertension	48 (22.2%)	90 (78.9%)*	70 (82.4%)*	42 (73.7%)*	<0.001
History of Diabetes	25 (11.57%)	39 (34.2%)*	38 (44.7%)*	15 (26.3%)*	<0.001
Alcohol History	24 (11.1%)	11 (9.6%)	18 (21.2%)	0 (0%)	>0.05
BMI	22.3 (20.7, 23.0)	24.5 (22.7, 26.2)*	24.9 (23.2, 26.0)*	26.0 (24.0, 26.9)*	<0.001
TC	3.58 (3.33, 3.85)	3.97 (3.70, 4.28)*	4.01 (3.69, 4.33)*	3.98 (3.62, 4.38)*	<0.001
TG	0.95 (0.81, 1.16)	0.82 (0.70, 0.99)*	0.94 (0.71, 1.06)*	0.84 (0.71, 1.02)*	<0.001
HDL-C	0.95 (0.88, 1.03)	1.13 (1.03, 1.22)*	1.08 (1.02, 1.18)*	1.14 (1.04, 1.21)*	<0.001
LDL-C	1.93 (1.74, 2.13)	2.50 (2.23, 2.76)*	2.42 (2.13, 2.75)*	2.42 (2.17, 2.55)*	<0.001
AC	2.79 (2.44, 3.10)	2.58 (2.20, 2.95)*	2.67 (2.31, 3.00)*	2.43 (2.16, 2.80)*	<0.001
CRI-Ⅰ	3.79 (3.44, 4.19)	3.58 (3.20, 3.95)*	3.67 (3.31, 4.00)*	3.43 (3.16, 3.80)*	<0.001
non-HDL-C	2.63 (2.37, 2.89)	2.89 (2.57, 3.21)*▲	2.92 (2.65, 3.23)*▲	2.79 (2.49, 3.19)*▲	<0.001
RC	0.74 (0.42, 0.98)	0.40 (0.00, 0.72)*▲	0.44 (0.13, 0.92)*▲	0.39 (0.11, 0.90)*	<0.001

"#" indicates that there is a significant difference between the stenosis subgroup and the control group (P<0.05), "*" indicates that there is a significant difference between the stenosis subgroup and the control group (P<0.001), "▲" indicates that there is a significant difference between the stenosis subgroups (P<0.001). NCAS: Non-cerebral artery stenosis, ICAS: Intracranial artery stenosis, ECAS: Extracranial artery stenosis, COMS: Combined intracranial and extracranial artery stenosis, BMI: Body mass index, TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AC: Atherogenic coefficient, CRI-I: Castelli's risk index I, RC: Remnant cholesterol.

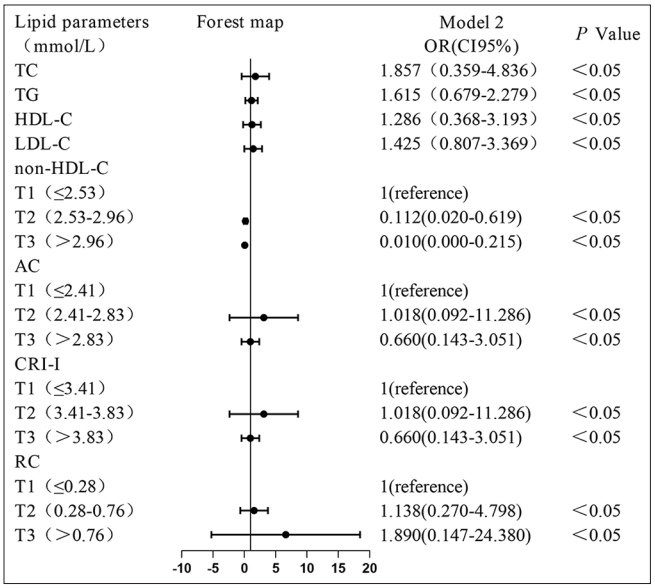

Figure 3: The correlation between lipid parameters and the risk of intracranial and extracranial arterial stenosis (Model 2). TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AC: Atherogenic coefficient, CRI-I: Castelli's risk index I, OR: Odds ratio, RC: Remnant cholesterol, CI: Confidence interval, T1: First tertile, T2: Second tertile, T3: Third tertile.

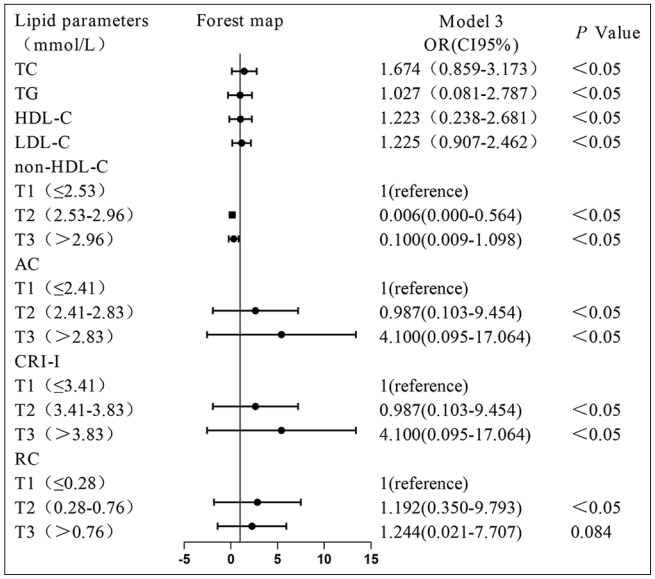

Figure 4: The correlation between lipid parameters and the risk of intracranial and extracranial arterial stenosis (Model 3). TC: Total cholesterol, TG: Triglycerides, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, AC: Atherogenic coefficient, CRI-I: Castelli's risk index I, OR: Odds ratio, RC: Remnant cholesterol, CI: Confidence interval, T1: First tertile, T2: Second tertile, T3: Third tertile.

Exploration of nonlinear relationships

The median values were used as references. The adjusted variables were identical to those in Model 3. RC exhibited a significant nonlinear association with the risk of intracranial and extracranial artery stenosis (P = 0.02) [Figure 5]. Figure 5a illustrates that when RC levels are below the median of 0.57 mmoL, the risk of intracranial and extracranial artery stenosis increases rapidly with decreasing RC levels. However, when RC levels exceed 0.57 mmoL, no significant statistical correlation is observed between RC levels and stenosis risk. Figures 5b and c indicate that when AC and CRI-I levels are below the median values of 2.66 and 3.66, the risk of intracranial-extracranial stenosis is negatively correlated with AC and CRI-I levels. Below this threshold, there are still risk factors for stenosis (odds ratio [OR] >1). When AC and CRI-I levels exceed the median values of 2.66 and 3.66, further increases in AC and CRI-I levels are linked to a reduced risk of stenosis, and thus, AC and CRI-I become protective factors for stenosis risk (OR <1).

Explore predictive ability

The ROC curve analysis of non-traditional lipid parameters and intracranial/extracranial arterial stenosis characteristics showed that non-HDL-C had the largest area under the curve (AUC) of 0.655 (0.606, 0.703), suggesting that non-HDL-C is an effective predictive marker for intracranial and extracranial arterial stenosis, as shown in Table 2 and Figure 6.

DISCUSSION

This study indicates that high levels of non-HDL-C and low levels of AC, CRI-I, and RC are linked to an increased risk of intracranial and extracranial artery stenosis, and non-HDL-C and RC showed significant differences between subgroups of the stenosis group. RC exhibited a nonlinear relationship with the risk of artery stenosis, and non-HDL-C had the strongest predictive capacity for intracranial and extracranial artery stenosis.

Non-HDL-C is easily measurable and does not require fasting for assessment. It effectively predicts the residual risk of atherosclerotic cardiovascular disease in patients undergoing statin therapy, as well as in individuals with obesity, diabetes, or metabolic disorders. Furthermore, it is considered a more reliable indicator of coronary artery disease (CAD) risk.[11,12] As a result, most international guidelines have recognized non-HDL-C as a secondary target for dyslipidemia management and advocate for its inclusion in routine lipid screening to enhance CAD risk assessment.[13,14]

Several studies have indicated that RC is a pathogenic factor for CAD.[15] In terms of treatment, normalizing the traditional lipid parameter LDL-C reduces the risk of

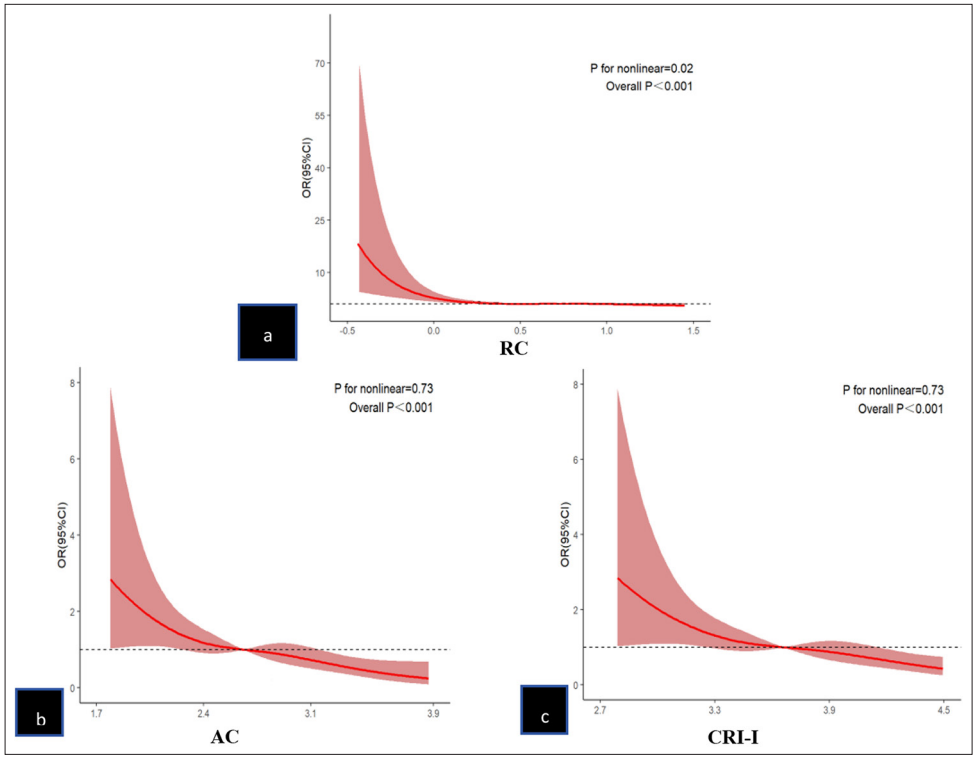

Figure 5: Restricted cubic spline curves for remnant cholesterol (RC), atherogenic coefficient (AC), Castelli's Risk Index-I (CRI-I), and the risk of intracranial and extracranial artery stenosis. Note: The red shaded area represents the 95% confidence interval (CI), and the red solid line represents the odds ratio (OR). The adjusted variables are gender, age, smoking history, hypertension, body mass index, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein, and non-HDL. The reference values are set to the median of each lipid parameter. (a) The reference value is set to 0.57; (b) the reference value is set to 2.66; and (c) the reference value is set to 3.66.

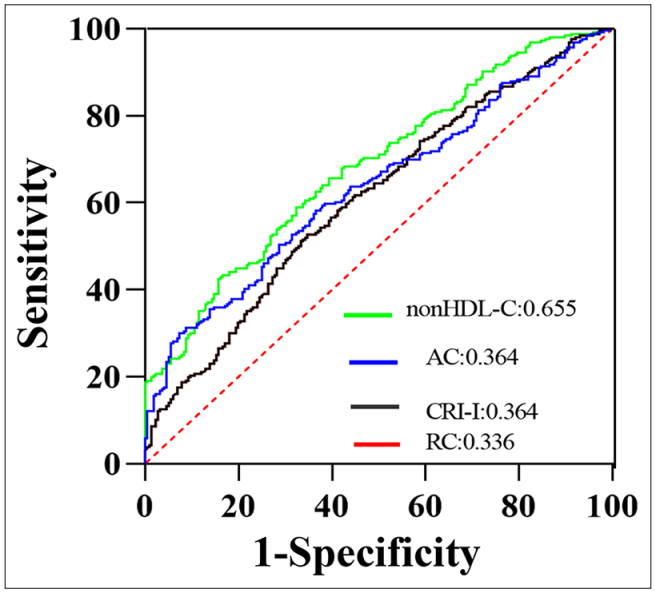

Figure 6: Receiver operating characteristic curves of atherogenic coefficient (AC), Castelli's Risk Index-I (CRI-I), non-high-density lipoprotein cholesterol (nonHDL), remnant cholesterol (RC), and intracranial and extracranial artery stenosis.

cardiovascular and cerebrovascular events. RC may enter the subendothelial space through scavenger receptors, promote foam cell formation, increase smooth muscle toxicity, and contribute to the formation of atherosclerotic plaques. Furthermore, RC may trigger the release of cytokines and adhesion molecules from white blood cells due to vascular wall inflammation, leading to the adhesion of white blood cells to the vascular endothelium and intima, exacerbating vascular wall damage.[16] RC is a potential biomarker for assessing carotid plaque vulnerability in patients with acute ischemic stroke (AIS).[17] It serves as a reliable predictor of both intracranial and extracranial atherosclerotic stenosis[18] and is independently associated with an increased risk of restenosis following treatment.[19]

AC and CRI-I reflect the relationship between atherosclerosis and anti-atherosclerotic lipoproteins. This study observed that CRI-I differs by 1 from AC and shows the same correlation with intracranial and extracranial artery stenosis, with identical AUC values. This implies that in clinical or research work, only one of the two parameters needs to be analyzed. Multiple studies have demonstrated that AC or CRI-I is closely associated with carotid intima-

Table 2: ROC curve parameters for non-traditional lipid parameters and intracranial and extracranial arterial stenosis.

Non-traditional lipid parameters	AUC and 95% CI	Optimal threshold	Sensitivity	Specificity	*P*-value
non-HDL-C	0.655 (0.606, 0.703)	0.928	1	0	0.000
AC	0.364 (0.315, 0.414)	0.629	1	0	0.000
CRI-I	0.364 (0.315, 0.414)	0.629	1	0	0.000
RC	0.336 (0.288, 0.385)	-1.883	1	0	0.000

ROC: Receiver operating characteristic, AUC: Area under the curve, CI: Confidence interval, HDL-C: High-density lipoprotein cholesterol, CRI-I: Castelli's risk index I, RC: Remnant cholesterol, AC: Atherogenic coefficient.

media thickness, carotid plaques,[20-22] and intracranial atherosclerotic stenosis.[9] A study found that CRI-I is negatively correlated with the risk of HT,[23] which aligns with the findings of this study. AIS patients with higher CRI-I levels have a significantly lower 3-month mortality rate, likely due to early intervention. This highlights the clinical importance of CRI-I in treating ischemic stroke.[24]

Non-traditional lipid parameters extend the conventional lipid profile and play a crucial role in predicting intracranial and extracranial artery stenosis. This study is a single-center case-control study and does not consider other non-traditional lipid parameters. Moreover, it does not consider whether patients had used lipid-lowering medications before the acute onset. Future research should involve multicenter case collections, assess a broader range of non-traditional lipid parameters, and account for pre-onset lipid-lowering therapy. Further studies are essential to evaluate the clinical utility of non-traditional lipid parameters, providing more precise guidance for the early detection and management of intracranial and extracranial artery stenosis.

CONCLUSION

Traditional lipid parameters do not effectively differentiate between intracranial, extracranial, or combined intracranial-extracranial artery stenosis. However, non-HDL-C and RC show significant variations across these conditions. Notably, non-HDL-C serves as a stronger predictor of stenosis risk and provides greater clinical utility. Integrating non-traditional lipid parameters into routine assessments is recommended to enhance diagnostic precision and risk stratification.

Ethical approval: The research/study approved by the Institutional Review Board at First Affiliated Hospital of Longyan City, Fujian Medical University, number 2022036, dated January 4, 2022.
Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.
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Conflicts of interest: There are no conflicts of interest.
Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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