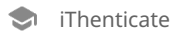


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Remnant cholesterol and early prognosis after acute ischemic stroke: the potential mediating role of maximum carotid plaque thickness

Abstract

Background: Remnant cholesterol (RC) is now widely regarded as a contributor to residual cardiovascular risk, its relationship with early prognosis following acute ischemic stroke (AIS) remains uncertain, and it is still unclear whether carotid plaque burden may act as a mediator. The present study therefore examined the association between RC and two early outcomes after AIS—early neurological deterioration (END) and 3-month poor functional outcome (3M-PFO)—and evaluated whether maximum carotid plaque thickness (cPTmax) could serve as a potential mediator of these relationships.

Methods: This retrospective cohort study enrolled 623 consecutive patients with AIS. Analyses included: (1) restricted cubic splines and multivariable logistic regression for the associations of RC with END and 3M-PFO; (2) subgroup analyses for 3M-PFO by age, diabetes, stroke severity, and TOAST subtype; and (3) mediation analyses of maximum carotid plaque thickness (cPTmax) as a potential mediator.

Results: Restricted cubic spline analysis showed that RC was linearly associated with both END and 3M-PFO ($P < 0.001$; non-linearity test not statistically significant). Each 0.1 mmol/L increase in RC was associated with an OR of 1.182 for END (95% CI: 1.114–1.255) and an OR of 1.188 for 3M-PFO (95% CI: 1.119–1.260). Using Q1 as the reference, the ORs for the two outcomes in Q4 were 3.467 (95% CI: 1.980–6.071) and 2.846 (95% CI: 1.681–4.817), respectively. Subgroup analyses showed consistent associations across age, diabetes, stroke severity, and TOAST subtype, with no significant interactions (interaction $P > 0.05$). In

mediation analyses, cPTmax was consistent with a potential partial mediation of the association between RC and END (indirect effect = 0.144, 95% CI: 0.033–0.256); a similar potential mediating pathway was observed for 3M-PFO (indirect effect = 0.146, 95% CI: 0.030–0.262).

Conclusions:

Higher RC was linked to both END and 3M-PFO after AIS, and cPTmax was consistent with a potential mediating pathway. Monitoring RC and carotid plaque thickness may help identify high-risk patients early. However, based on the observational design of this study, whether targeting RC can improve secondary prevention of stroke remains to be investigated by future randomized controlled trials.

Keywords: Remnant cholesterol; Plaque, Atherosclerotic; Ischemic Stroke; Prognosis; Mediation Analysis

1. Introduction

Acute ischemic stroke (AIS) is one of the leading diseases worldwide that severely endangers human health and causes death and disability [1]. Low-density lipoprotein cholesterol (LDL-C) plays a key role in carotid plaque instability and related cerebrovascular events, and lowering LDL-C levels reduces the risk of ischemic stroke [2]. Although statins effectively lower LDL-C and reduce the risk of stroke recurrence, patients receiving statin therapy still have a residual cardiovascular risk even when LDL-C levels are at target [3, 4]. This phenomenon suggests that, in addition to LDL-C, other lipid components may be involved in the regulation of residual risk. Elevated remnant cholesterol (RC) has been linked to a higher

risk of peripheral artery disease, myocardial infarction, and ischemic stroke [5, 6], as well as to an increased risk of cardiovascular disease, stroke, and all-cause mortality [7, 8]. RC refers to cholesterol in all triglyceride-rich lipoproteins, consisting of chylomicron remnants, very low-density lipoprotein, and intermediate-density lipoprotein [9]. RC readily penetrates the arterial wall and accumulates in the subendothelial space, where it is substantially retained and taken up by macrophages, leading to endothelial dysfunction, inflammatory responses, and promoting atherogenesis [10-13]. The present study aimed to investigate the effect of RC on early prognosis in patients with AIS and to analyze the potential mediating role of maximum carotid plaque thickness (cPTmax) in this relationship. It was hypothesized that elevated RC is associated with an increased risk of early neurological deterioration (END) and 3-month poor functional outcome (3M-PFO) in patients with AIS, and that cPTmax may act as a potential mediator of these associations. Compared with previous studies, the present study additionally evaluates whether cPTmax mediates the association between RC and early prognosis in AIS. Therefore, while focusing on achieving LDL-C targets, assessment of RC levels may provide additional information for risk stratification and warrants investigation as a potential therapeutic target in AIS.

2. Methods

2.1 Study population

Patients with AIS admitted to the Department of Neurology, Anhui No. 2 Provincial People's Hospital, between June 2023 and January 2026, were consecutively enrolled in this retrospective study. The study protocol, research hypotheses, and statistical analysis plan were predefined after data extraction and data cleaning but before any formal statistical analysis,

and the research hypotheses were formulated a priori based on the existing literature. All patients met the diagnostic criteria of the Chinese Guidelines for the Diagnosis and Treatment of AIS 2023 [14]. Inclusion criteria: (1) age ≥ 18 years; (2) receipt of standardized inpatient treatment (hospital stay ≥ 3 days); (3) complete cerebrovascular examination (definitive diagnosis by brain magnetic resonance imaging or computed tomography, and carotid ultrasound); (4) time interval from symptom onset to hospital admission < 48 hours. Exclusion criteria: (1) receipt of intravenous thrombolysis or endovascular intervention; (2) coexistence of malignant tumor, autoimmune disease, epilepsy, severe heart failure, or hepatic/renal insufficiency; (3) failure to complete venous blood sampling for laboratory testing within 24 hours of admission; (4) lack of key examination data such as carotid ultrasound; (5) previous cerebral infarction with significant residual sequelae, defined as a pre-stroke modified Rankin Scale (mRS) score > 1 ; (6) loss to follow-up after discharge; (7) cardioembolic stroke; (8) other determined etiologic subtypes according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification.

This study followed the Declaration of Helsinki and relevant ethical standards. The Medical Ethics Committee of Anhui No. 2 Provincial People's Hospital approved the study protocol on July 24, 2025 (approval No. R2025-095). The approval permitted retrospective review of existing medical records, including those of patients admitted before approval. Given the retrospective design, the use of anonymized data, and the absence of additional risk or intervention, informed consent was waived by the Ethics Committee.

2.2 Data collection for cohort studies

After admission, patients were evaluated by attending neurologists who collected baseline

demographic, clinical, and laboratory data, including age, sex, medical history (smoking history, defined as at least one cigarette per day for six consecutive months [15]; alcohol use, defined as average daily alcohol intake ≥ 15 g over the past year [16]; hypertension, diabetes, coronary artery disease, hyperlipidemia, and stroke); medication history (antiplatelet agents, statins, antihypertensive drugs, and antidiabetic drugs; regular use for ≥ 3 months was considered valid); baseline systolic blood pressure (SBP); baseline diastolic blood pressure; National Institutes of Health Stroke Scale (NIHSS); and TOAST classification. Fasting venous blood was collected on the morning of the day after admission (after an overnight fast of at least 8 hours) to measure total cholesterol, LDL-C, and high-density lipoprotein cholesterol (HDL-C).

2.3 Carotid ultrasound examination and reproducibility assessment

During hospitalization, all participants underwent carotid ultrasound examination performed by two experienced sonographers. Carotid ultrasound was performed using a Philips EPIQ 7C system (Philips Healthcare, Best, the Netherlands) with a 7.5–10 MHz probe in B-mode. Plaque was considered present when focal wall thickening reached at least 50% of the adjacent wall thickness, or a luminal protrusion with a thickness of at least 1.5 mm was observed. For carotid intima-media thickness (cIMT) measurement, the far wall of the common carotid artery was measured 10 mm proximal to the bifurcation, and the average of bilateral measurements was used. Maximum carotid plaque thickness (cPTmax) was defined as the maximum thickness among all visible plaques in either carotid artery, measured on longitudinal or transverse views as the perpendicular distance from the adventitia-media interface to the luminal surface. Plaque echogenicity was determined based on the side with

the larger cPTmax and was categorized as mixed echogenic plaque (mixed plaque), hypoechoic plaque (soft plaque), or hyperechoic plaque (hard plaque).

To assess the inter-reader reproducibility of cPTmax, 52 patients were randomly selected from the 623 included patients, and stored images were re-measured offline by another senior sonographer who was blinded to clinical data, original cPTmax values, and outcomes. Measurements were compared with the original cPTmax values recorded in the database, and intraclass correlation coefficients (ICCs), coefficients of variation (CVs), and Bland-Altman 95% limits of agreement (LoA) were calculated (Supplementary Table S1).

2.4 Treatment

All patients received aspirin 100 mg/day and/or clopidogrel 75 mg/day plus atorvastatin 20 mg/day after admission, consistent with the 2023 Chinese Guidelines for the Diagnosis and Treatment of AIS [14].

2.5 Definitions and outcome assessment

The following formula was used to obtain RC: total cholesterol – HDL-C – LDL-C [17].

Because total cholesterol, LDL-C, HDL-C, and triglycerides are mathematically related to RC, these four lipid parameters were not entered into the regression models at the same time as RC, in order to prevent multicollinearity.

END was defined as an increase of at least 4 points on the NIHSS total score within 72 hours after symptom onset, relative to the score at admission [18].

3M-PFO: mRS score ≥ 3 , assessed by telephone follow-up or outpatient visit at 3 months after discharge.

All neurologists involved in outcome assessment received standardized training prior to study initiation, including NIHSS certification training and a unified mRS interview protocol, to ensure scoring consistency.

2.6 Statistical Analysis

Statistical analyses were conducted in R version 4.5.1. Mediation analysis was performed separately in SPSS 27.0 using the PROCESS macro (Model 4). Categorical variables are summarized as n (%). Continuous variables are summarized as mean $\pm$ SD or median (IQR), as appropriate. Patients were grouped by RC quartile (Q1–Q4). Between-group comparisons used one-way ANOVA, the Kruskal–Wallis test, or the chi-square test.

Restricted cubic splines with four knots were used to assess the dose-response association between RC and END, as well as between RC and 3M-PFO; non-linearity was assessed by the Wald chi-square test. Adjustment variables (age, diabetes, pre-admission statin use, SBP, and baseline NIHSS score) were identified through univariable comparisons across RC quartile groups ($P < 0.1$). With Q1 as the reference, multivariable logistic regression assessed the associations of RC quartile groups with END and with 3M-PFO.

Subgroup and interaction analyses focused on the primary outcome (3M-PFO), according to age (<65 vs. ≥ 65 years), diabetes (present vs. absent), stroke severity (NIHSS <6 vs. ≥ 6), and TOAST classification (large-artery atherosclerosis vs. other subtypes). END was not analyzed in subgroups because it was a secondary outcome, and event numbers within individual strata would have been too small for stable estimates.

Mediation analysis: cPTmax was used as a potential mediator for the relationships between RC and END, and between RC and 3M-PFO. First, a total effect model of RC on END was

established (path c, logistic regression). Then, after including the mediator, the effect of RC on cPTmax (path a, linear regression) and the effect of cPTmax on END (path b, logistic regression) were analyzed, and the direct effect of RC on END after accounting for the mediation (path c', logistic regression) was calculated. All regression coefficients were reported as unstandardized regression coefficients (β). Bias-corrected bootstrap methods (5,000 resamples) were used to obtain 95% CIs. Mediation analysis was performed using the product-of-coefficients method, which has been validated as an effective approach for mediation analysis with binary outcomes [19]. In a sensitivity analysis, cIMT was also used as an alternative mediator to cPTmax, with the same model specifications and covariate adjustments.

Model diagnostics: Collinearity was assessed using the variance inflation factor (VIF); all VIFs remained below 2, indicating no substantial collinearity. The Hosmer–Lemeshow test was applied to assess calibration, with $P > 0.05$ considered to indicate adequate fit. The area under the receiver operating characteristic curve (AUC) was used to evaluate discrimination. In all models, the events per variable ratio exceeded the minimum requirement of 10 events per variable. To assess the robustness of the effect estimates, internal validation was carried out using the Bootstrap method (1,000 resamples with a fixed random seed) to derive Bootstrap-corrected 95% CIs for the ORs of the RC quartile groups (with Q1 as the reference). All variables involved in the primary analyses had complete data ($n = 623$), and no imputation was performed.

Statistical significance was set at $P < 0.05$.

3 Results

3.1 Patient Screening Results

Initially, 1,347 patients with AIS who had been admitted to the Department of Neurology between June 2023 and January 2026 were screened (Figure 1). Exclusions: 305 patients who received intravenous thrombolysis or endovascular intervention; 45 patients with malignant tumors, autoimmune diseases, epilepsy, severe heart failure, or liver/kidney dysfunction; 18 patients who did not undergo venous blood collection within 24 hours of admission; 15 patients lacking key examination data such as carotid ultrasound; 55 patients with significant residual deficits from previous cerebral infarction (pre-stroke mRS >1); 18 patients lost to follow-up after discharge; 223 patients with cardioembolic stroke; and 45 patients with other determined etiologies according to the TOAST classification. A total of 623 patients with non-cardiogenic AIS were ultimately included, with the majority being the large artery atherosclerosis subtype (302 cases, 48.5%) and small vessel occlusion subtype (250 cases, 40.1%), while the remaining 71 cases (11.4%) were of undetermined etiology (Table 1).

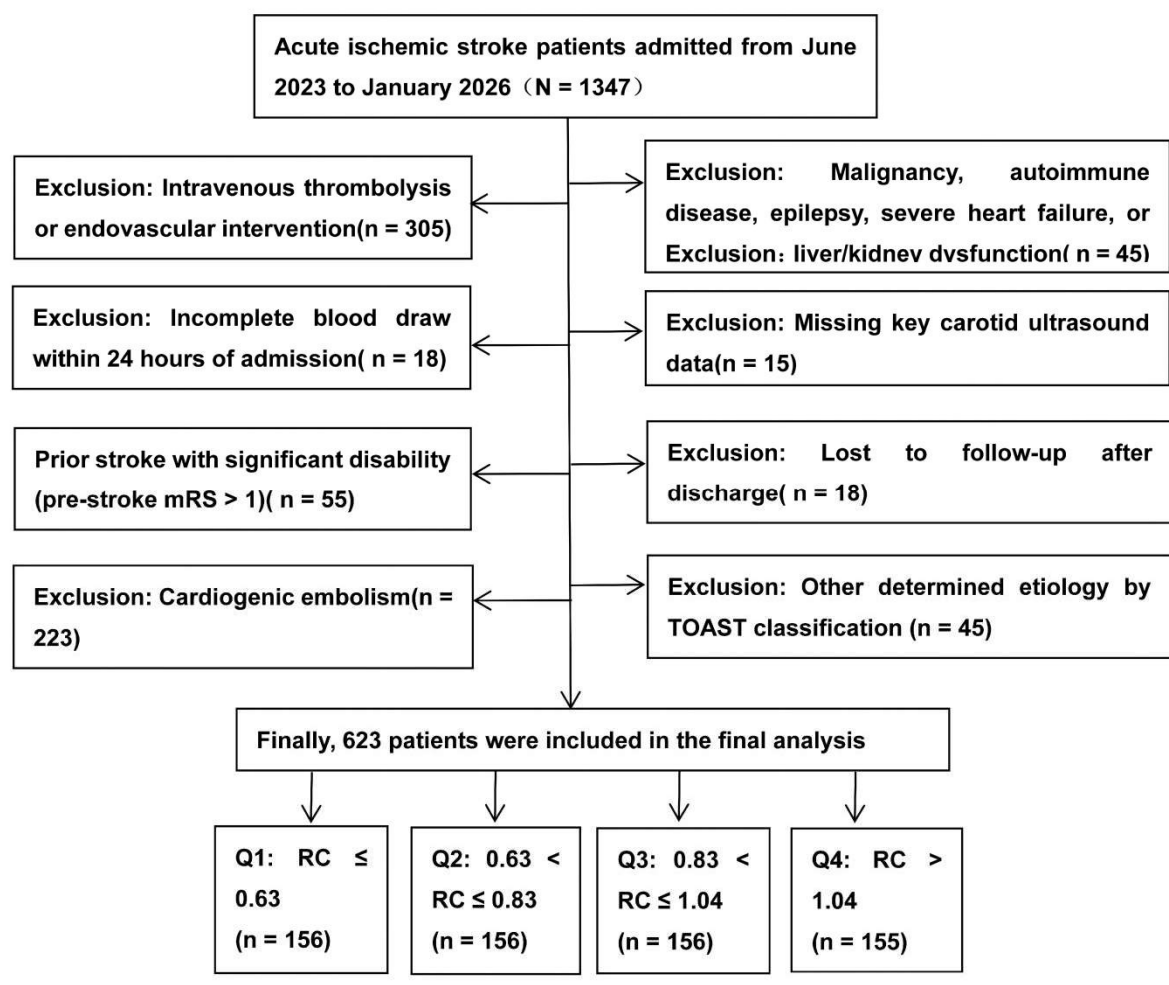


Figure 1. Patient flow diagram. Abbreviations: mRS, modified Rankin Scale; RC, remnant cholesterol; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

3.2 Baseline Characteristics

RC quartile was used to classify patients into four groups (n = 156 or 155 per group). Comparisons across the four groups revealed significant differences in age, cIMT, and cPTmax (all $P < 0.05$). Plaque echogenicity also differed significantly across the groups ($P = 0.006$): as RC levels increased, the proportion of mixed echogenic plaques gradually increased (from 28.85% to 43.87%), the proportion of hyperechoic plaques gradually decreased (from 33.33% to 15.48%), while the proportion of hypoechoic plaques remained relatively stable across groups (37.82%–40.65%). Prevalence of diabetes, statin use, SBP, and

baseline NIHSS score showed borderline significant differences among the four groups ($P = 0.062, 0.091, 0.078, \text{ and } 0.070$, respectively). Other demographic features, vascular risk factors, comorbidities, and medication use did not differ significantly across the four groups (all $P > 0.05$) (Table 1). By contrast, both END and 3M-PFO differed significantly across the groups (both $P < 0.001$), suggesting that RC grouping is closely related to clinical outcomes (Table 2).

Table 1. Patient characteristics according to RC quartile.

Variable, n (%) unless stated	Q1, n=156	Q2, n=156	Q3, n=156	Q4, n=155	Statistic	P
RC, mmol/L, median (IQR)	0.53 (0.42 - 0.63)	0.78 (0.74 - 0.83)	0.98 (0.94 - 1.04)	1.27 (1.18 - 1.39)	583.11	<0.001
Age, years, median (IQR)	64.00 (57.75 - 69.00)	65.00 (60.00 - 70.00)	66.00 (59.00 - 71.00)	68.00 (61.00 - 72.00)	10.009	0.018
Male, n (%)	97 (62.18%)	82 (52.56%)	88 (56.41%)	95 (61.29%)	3.861	0.277
Smoking, n (%)	57 (36.54%)	62 (39.74%)	53 (33.97%)	61 (39.35%)	1.45	0.694
Alcohol use, n (%)	43 (27.56%)	44 (28.21%)	48 (30.77%)	46 (29.68%)	0.474	0.924
Hypertension, n (%)	91 (58.33%)	82 (52.56%)	87 (55.77%)	88 (56.77%)	1.127	0.77
Diabetes, n (%)	42 (26.92%)	45 (28.85%)	58 (37.18%)	60 (38.71%)	7.349	0.062
Coronary Artery Disease, n (%)	45 (28.85%)	42 (26.92%)	50 (32.05%)	44 (28.39%)	1.06	0.787
Hyperlipidemia, n (%)	88 (56.41%)	78 (50.00%)	91 (58.33%)	90 (58.06%)	2.876	0.411
Stroke, n (%)	29 (18.59%)	28 (17.95%)	35 (22.44%)	34 (21.94%)	1.513	0.679
Medical history						
Antiplatelet agents, n (%)	54 (34.62%)	47 (30.13%)	51 (32.69%)	48 (30.97%)	0.847	0.838
Statin use, n (%)	58 (37.18%)	56 (35.90%)	45 (28.85%)	40 (25.81%)	6.463	0.091
Antihypertensive agents, n (%)	79 (50.64%)	67 (42.95%)	74 (47.44%)	78 (50.32%)	2.379	0.498
Antidiabetic agents, n (%)	31 (19.87%)	27 (17.31%)	39 (25.00%)	33 (21.29%)	2.921	0.404
SBP, mmHg, median (IQR)	155.00 (148.00 - 162.00)	153.00 (147.00 - 158.25)	153.00 (147.00 - 160.25)	152.00 (145.50 - 160.00)	6.815	0.078
DBP, mmHg, mean $\pm$ SD	90.19 $\pm$ 6.63	90.60 $\pm$ 7.25	89.60 $\pm$ 7.59	90.52 $\pm$ 7.44	0.607	0.611
NIHSS, median (IQR)	6 (4 - 7)	6 (4 - 7)	6 (4 - 7)	6 (4 - 8)	7.063	0.070
TOAST, n (%)					7.684	0.262
Large artery atherosclerosis	81 (51.92%)	69 (44.23%)	82 (52.56%)	70 (45.16%)		
Small vessel occlusion	58 (37.18%)	69 (44.23%)	52 (33.33%)	71 (45.81%)		
Undetermined	17 (10.90%)	18 (11.54%)	22 (14.10%)	14 (9.03%)		
Plaque echo, n (%)					18.238	0.006
Mixed Echogenic Plaque	45 (28.85%)	57 (36.54%)	65 (41.67%)	68 (43.87%)		
Hypoechoic Plaque	59 (37.82%)	63 (40.38%)	62 (39.74%)	63 (40.65%)		
Hyperechoic Plaque	52 (33.33%)	36 (23.08%)	29 (18.59%)	24 (15.48%)		
cIMT, mm, median (IQR)	1.10 (1.00 - 1.20)	1.20 (1.10 - 1.30)	1.20 (1.10 - 1.30)	1.30 (1.20 - 1.30)	57.99	<0.001
cPTmax, mm, median (IQR)	2.40 (1.89 - 2.92)	2.61 (2.21 - 3.13)	2.86 (2.52 - 3.50)	3.14 (2.72 - 3.79)	88.85	<0.001

RC quartile groups: Q1: RC ≤ 0.63 ; Q2: $0.63 < \text{RC} \leq 0.83$; Q3: $0.83 < \text{RC} \leq 1.04$; Q4: RC > 1.04 ;

Abbreviations: cIMT, carotid intima-media thickness; cPTmax, maximum carotid plaque thickness; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; RC, remnant cholesterol; SBP, systolic blood pressure; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Table 2. Outcomes across RC quartiles.

Variable	Q1, n=156	Q2, n=156	Q3, n=156	Q4, n=155	Statistic	P
END, n (%)	23 (14.74%)	28 (17.95%)	46 (29.49%)	60 (38.71%)	29.929	<0.001
3M-PFO, n (%)	28 (17.95%)	30 (19.23%)	43 (27.56%)	69 (44.52%)	35.154	<0.001

Abbreviations: END, early neurological deterioration; RC, remnant cholesterol; 3M-PFO, 3-month poor functional outcome

3.3 Relationship of RC with END and 3M-PFO assessed by restricted cubic splines and logistic regression

Restricted cubic spline analysis demonstrated a significant linear dose-response pattern linking RC to both END and 3M-PFO (overall $P < 0.001$ for each), and the tests for non-linearity were not significant (END: $P = 0.192$; 3M-PFO: $P = 0.250$). As RC levels increased, the risk of END and 3M-PFO gradually rose, with no obvious inflection point (Figure 2).

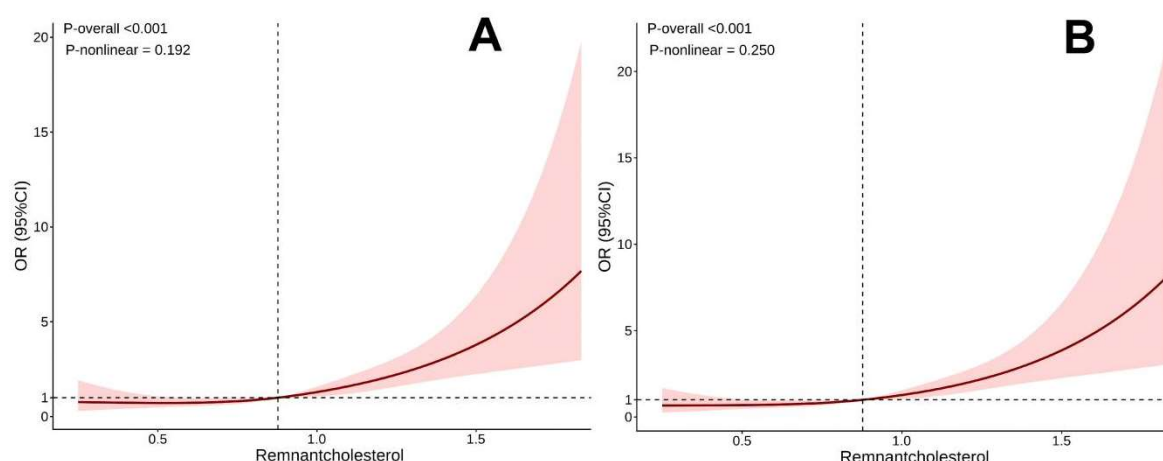


Figure 2. Restricted cubic spline curves for the association of RC with END (A) and 3M-PFO (B). The solid curve represents the OR; the shaded band represents the 95% CI. P -overall < 0.001 for both; P -nonlinear = 0.192 (A) and 0.250 (B). Models were adjusted for age, diabetes, statin use, SBP, and baseline NIHSS score.

Abbreviations: RC, remnant cholesterol; END, early neurological deterioration; 3M-PFO, 3-month poor functional outcome; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

RC was entered into multivariable logistic regression as a continuous variable, adjusted for age, diabetes, pre-admission statin use, SBP, and baseline NIHSS score. To improve clinical interpretability, RC was scaled by a factor of 10, so that a 1-unit change corresponds to a 0.1 mmol/L change. Each 0.1 mmol/L increment in RC was associated with an OR of 1.182 for END (95% CI: 1.114–1.255, $P < 0.001$) and an OR of 1.188 for 3M-PFO (95% CI: 1.119–

1.260, $P < 0.001$). In the quartile analysis using Q1 as reference and the same adjustment, RC remained independently associated with both outcomes (overall $P < 0.001$ for both). Compared with Q1, Q3 and Q4 had ORs of 2.366 (95% CI: 1.339–4.181) and 3.467 (95% CI: 1.980–6.071) for END, and ORs of 1.867 (95% CI: 1.094–3.185) and 2.846 (95% CI: 1.681–4.817) for 3M-PFO (both $P < 0.05$) (Table 3).

Bootstrap internal validation (1,000 resamples) was performed to validate the OR estimates for RC quartile groups in the multivariable logistic regression models. The bootstrap-corrected 95% CIs were highly consistent with the conventional regression results, indicating that the effect estimates for RC quartile grouping were not significantly influenced by sample specificity and were robust (Supplementary Table S2).

Supplementary Table S3 summarizes the model diagnostics, showing that each model had >10 events per variable, no significant multicollinearity (VIF range: 1.015–1.052; overall condition number $\kappa = 1.273$), good calibration (Hosmer-Lemeshow test $P > 0.05$), and acceptable discrimination (AUC for the END model: 0.655, 95% CI: 0.618–0.711; AUC for the 3M-PFO model: 0.650, 95% CI: 0.610–0.705). Given that the primary objective of the present study was effect estimation (OR values) rather than prediction model development, the AUC values are provided only as a reference evaluation of model discrimination and are not used as primary evidence for the conclusions.

Table 3. Multivariable logistic regression for outcomes across RC quartiles.

RC quartile	END (OR, 95% CI)	<i>P</i> (END)	3M-PFO (OR, 95% CI)	<i>P</i> (3M-PFO)
per 0.1 mmol/L increase	1.182(1.114 - 1.255)	<0.001	1.188(1.119 - 1.260)	<0.001
Q1	Reference		Reference	
Q2	1.248(0.679-2.295)	0.475	0.929(0.522-1.655)	0.803
Q3	2.366(1.339-4.181)	0.003	1.867(1.094-3.185)	0.022
Q4	3.467(1.980-6.071)	<0.001	2.846(1.681-4.817)	<0.001

Models were adjusted for age, diabetes, statin use, systolic blood pressure, and baseline NIHSS score.

Abbreviations: END, early neurological deterioration; RC, remnant cholesterol; 3M-PFO, 3-month poor functional outcome

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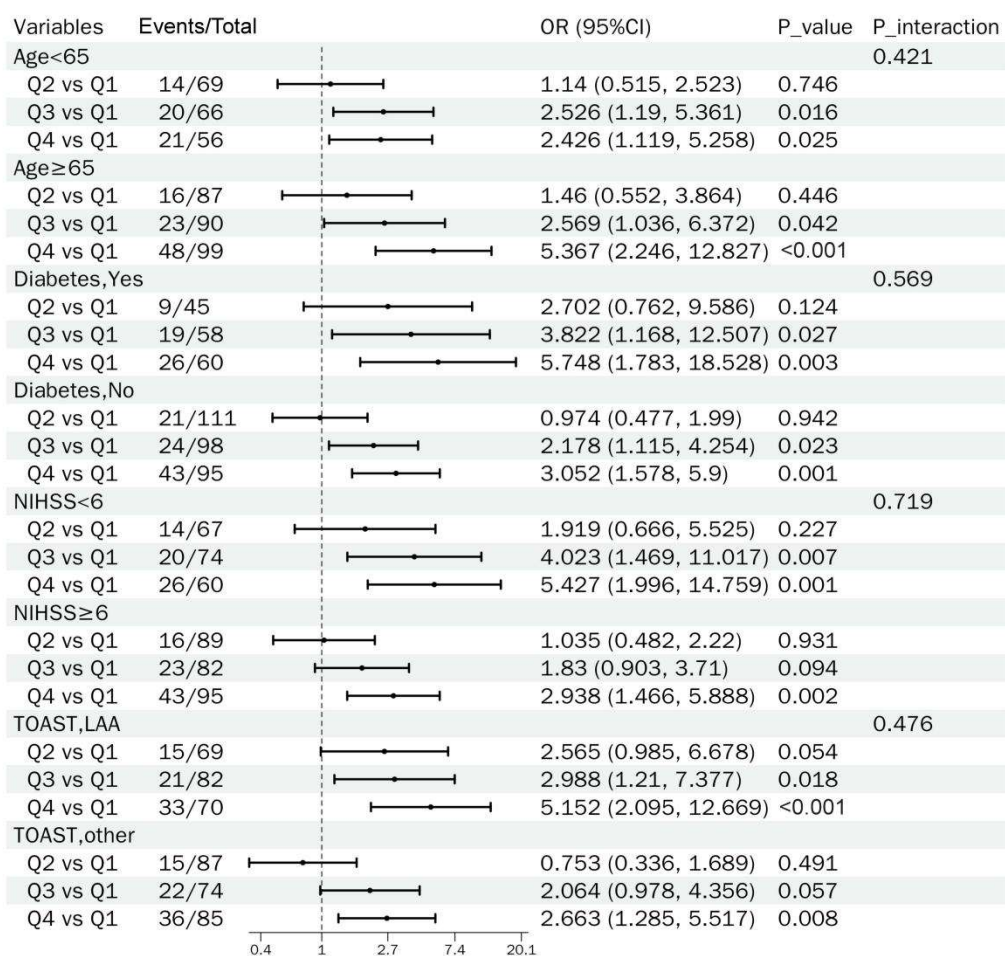
260 3.4 Subgroup Analysis

261 Subgroup analysis was restricted to the primary outcome (3M-PFO), with Q1 as the reference

262 and stratification by age, diabetes, NIHSS score, and TOAST subtype (Figure 3). Across all

263 subgroups, higher RC levels—particularly in Q3 and Q4—were linked to a greater likelihood

264 of 3M-PFO, with no significant interaction across subgroups (all interaction $P > 0.05$).



265

266 Figure 3. Subgroup analyses of RC quartiles (Q2 – Q4 vs. Q1) for 3M-PFO. Models were adjusted for age, diabetes, statin

267 use, SBP, and NIHSS score, with the stratifying variable excluded. Interaction P values were obtained from interaction terms

268 between RC quartiles and each stratifying variable.

269 Abbreviations: RC, remnant cholesterol; 3M-PFO, 3-month poor functional outcome; SBP, systolic blood pressure; NIHSS,

270 National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; TOAST, Trial of Org 10172 in Acute Stroke

271 Treatment.

272

273 3.5 Exploratory mediation analysis

274 In exploratory mediation analyses with cPTmax as the mediating variable, the RC → cPTmax
275 path was identical for both outcomes (path a: $\beta = 0.401$, 95% CI: 0.339–0.464, $P < 0.001$).
276 For END, cPTmax was significantly associated with END (path b: $\beta = 0.359$, 95% CI: 0.090–
277 0.628, $P = 0.009$), the direct effect of RC on END was significant (path c': $\beta = 0.161$, 95% CI:
278 0.010–0.318, $P = 0.044$), and the indirect effect through cPTmax was 0.144 (95% CI: 0.033–
279 0.256, $P = 0.011$), with a total effect of 0.306 (95% CI: 0.200–0.411, $P < 0.001$) and a
280 proportion mediated of 47.2% (95% CI: 6.5%–87.8%, $P = 0.023$) (Figure 4A). For 3M-PFO,
281 the corresponding path b was $\beta = 0.364$ (95% CI: 0.083–0.645, $P = 0.011$), the direct effect
282 was $\beta = 0.171$ (95% CI: 0.018–0.325, $P = 0.029$), the indirect effect was 0.146 (95% CI:
283 0.030–0.262, $P = 0.014$), the total effect was 0.318 (95% CI: 0.213–0.422, $P < 0.001$), and the
284 proportion mediated was 46.0% (95% CI: 6.9%–85.1%, $P = 0.021$) (Figure 4B). All mediation
285 effects were estimated on the logit scale. The relatively wide 95% CIs for the mediating effect
286 of cPTmax suggest limited precision of the point estimates.

287 In a sensitivity analysis using cIMT instead of cPTmax as the mediator, the indirect effects
288 were 0.042 (95% CI: –0.007 to 0.091, $P = 0.092$) for END and 0.044 (95% CI: –0.009 to
289 0.098, $P = 0.102$) for 3M-PFO, providing no evidence of a statistically significant indirect
290 effect through cIMT. Given the limited statistical power, this null finding should not be
291 interpreted as excluding a potential mediating role of cIMT (Supplementary Table S4).
292 Neither interaction term between plaque echogenicity and RC or cPTmax was statistically
293 significant (Supplementary Table S5).

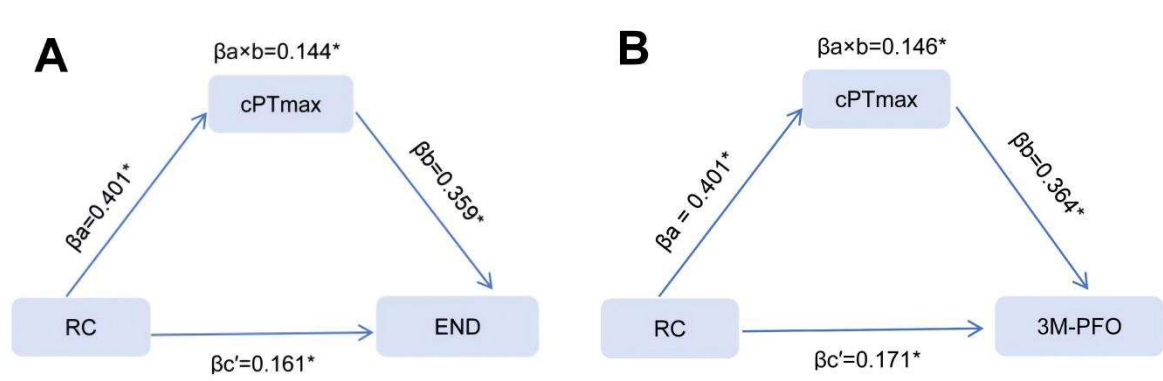


Figure 4. Mediation analysis. (A) Unstandardized coefficients (β): a (RC $\rightarrow$ cPTmax), b (cPTmax $\rightarrow$ END), c' (direct effect of RC on END). Indirect effect ($a \times b$) is indicated. Adjusted for age, diabetes, statin use, SBP, and NIHSS. (B) Unstandardized coefficients (β): a (RC $\rightarrow$ cPTmax), b (cPTmax $\rightarrow$ 3M-PFO), c' (direct effect of RC on 3M-PFO). Indirect effect ($a \times b$) is indicated. Adjusted for age, diabetes, statin use, SBP, and NIHSS. * $P < 0.05$ for the indicated paths in both (A) and (B).

Abbreviations: RC, remnant cholesterol; cPTmax, maximum carotid plaque thickness; END, early neurological deterioration; 3M-PFO, 3-month poor functional outcome.

Discussion

RC showed a significant association with both END and 3M-PFO after AIS, with a linear relationship observed between RC and both outcomes in restricted cubic spline analysis. The findings for cPTmax were consistent with a potential mediating pathway linking RC to both outcomes. However, given the wide bootstrap confidence intervals for the mediated proportions, these estimates should be interpreted with caution. These results suggest that in the management of AIS, attention should be directed not only toward achieving LDL-C targets but also toward RC levels.

Higher RC levels have been linked to 3M-PFO after AIS. Tan et al. [20] reported findings consistent with ours and, in their subgroup analysis, the association was more pronounced among individuals with higher NIHSS scores. Using restricted cubic splines, they found that once RC rose above 0.38 mmol/L, the likelihood of poor 90-day outcome increased progressively. Similarly, Zhu et al. [21] reported that higher RC was linked to poor 90-day outcome among AIS patients who received intravenous thrombolysis. In contrast, Yu et al. [22]

317 reported that RC was not an independent correlate of 3-month outcome among AIS patients.
318 Instead, the residual cholesterol inflammatory index served as an independent predictor, and
319 combining RC with inflammatory markers improved predictive performance.

320 Beyond its association with 3M-PFO in AIS, RC has also been implicated in the development
321 of AIS. A Danish prospective study published in 2019 [6], with follow-up extending to 14
322 years, showed a clear dose-dependent association of RC with AIS risk.

12 323 A large prospective cohort from China in 2024 [23] provided further evidence that elevated
324 RC increased the likelihood of ischemic stroke. In that cohort, discordance analyses further
10 325 showed that participants with low LDL-C but high RC had a higher risk of stroke, whereas
326 those with high LDL-C but low RC did not show a significant increase in risk, suggesting that
10 327 the association between RC and stroke may be independent of LDL-C levels. Long-term
328 dynamic changes in RC also carry independent predictive value. Li et al. [24] reported that in
329 the general population, greater RC variability—beyond a single elevated measurement—was
330 linked to a higher ischemic stroke risk. Wang et al. [25] followed 62,443 participants without
54 331 prior stroke for a median of 10.3 years and found that those with increasing RC levels had a
332 12% higher stroke risk.

45 333 RC levels correlate positively with carotid plaque thickness. In 1,496 patients with ischemic
1 334 stroke, Qian et al. [26] used carotid ultrasound to measure cIMT and found that RC was
335 independently and positively associated with abnormal cIMT in a linear dose-response
336 manner. Notably, this association persisted even when LDL-C had reached optimal levels. Yu
60 337 et al. [27] reported that elevated RC was significantly associated with intracranial artery
338 stenosis, extracranial artery stenosis, and mixed stenosis. RC contributes not only to

atherosclerotic stenosis but is also directly linked to carotid plaque instability. In a cross-sectional study of 1,100 participants without prior stroke, Li et al. [28] found that a high RC level was independently associated with unstable carotid plaques, whereas other lipid parameters showed no such association. Li et al. [29] further showed that among patients with carotid stenosis, RC was independently associated with plaque instability, with a stronger association in those with severe stenosis. Using contrast-enhanced ultrasound in 110 patients with ischemic stroke, Song et al. [30] found that RC was positively correlated with the grade of intraplaque neovascularization, suggesting that RC may promote plaque vulnerability by enhancing intraplaque neovascularization, thereby precipitating stroke events. Servadei et al. [31] examined endarterectomy specimens and reported a higher proportion of unstable plaques in patients with elevated RC, providing direct histological evidence linking RC to carotid plaque vulnerability. Beyond carotid atherosclerosis, elevated RC is also independently associated with intracranial atherosclerosis [32], and it remains an independent risk factor for atherosclerotic vascular disease even when LDL-C is well controlled. Carotid plaque burden is also associated with 3M-PFO in AIS. In a study of 951 patients with AIS, Jin et al. [33] found that cPTmax was positively associated with poor 90-day outcome, and that inflammatory markers—monocytes, lymphocyte-to-monocyte ratio, and monocyte-to-HDL ratio—played a positive mediating role in this relationship. In 205 AIS patients with carotid plaques, Fan et al. [34] showed that maximum carotid plaque area was the strongest predictor of poor 90-day outcome. Genkel et al. [35], studying a larger population, demonstrated that a baseline total carotid plaque area above 42.0 mm² corresponded to a 3.10-fold elevation in the risk of major adverse cardiac and cerebrovascular events (95% CI: 1.54–6.26), reinforcing the

independent prognostic value of baseline plaque burden.

RC may also affect stroke prognosis through the following mechanisms: (1) promoting intraplaque neovascularization [30], leading to plaque instability and increasing the risk of artery-to-artery embolism; (2) inducing systemic inflammatory responses [36]; (3) impairing endothelial function and disrupting blood-brain barrier integrity [37], thereby promoting cerebral edema and neurological deterioration. These mechanisms together explain the "direct effect" of RC.

Although the findings were consistent with a potential mediating pathway, the bootstrap confidence intervals were relatively wide, indicating limited precision of the point estimates; therefore, the interpretation of the mediated proportions should be approached with caution.

In a sensitivity analysis using cIMT as an alternative mediator, the analysis did not provide evidence of a statistically significant indirect effect through cIMT. However, because this analysis had limited statistical power, the non-significant result should not be interpreted as excluding a potential mediating role of cIMT.

RC tended to promote focal plaque formation (reflected by increased cPTmax) rather than diffuse vessel wall thickening (reflected by increased cIMT), which is consistent with the pathological evidence that triglyceride-rich lipoprotein particles preferentially deposit in focal lesion areas of the arterial wall.

Plaque echogenicity was not included as a covariate in the main mediation model because RC can promote intraplaque neovascularization and inflammatory responses, altering plaque composition (from stable to vulnerable) [30, 31]. Other unmeasured features of carotid atherosclerosis—such as intraplaque neovascularization, fibrous cap thickness, or plaque

inflammatory activity—may also participate in mediating the association between RC and prognosis. Future work applying more advanced plaque imaging methods—for example, high-resolution magnetic resonance imaging—would help further elucidate the complete pathway through which RC affects stroke prognosis.

Because cPTmax was assessed at only one time point on admission in the present study, the influence of long-term changes in cPTmax on stroke prognosis could not be evaluated. In a study by Gacoń et al. [38], repeated cIMT measurements showed that sustained cIMT regression was linked to a 68%–75% lower risk of major adverse cardiac and cerebrovascular events (hazard ratio = 0.25, 95% CI: 0.15–0.42), whereas cIMT progression predicted elevated risk. Future studies combining longitudinal RC measurements with serial carotid plaque assessments hold promise for refining risk stratification tools in stroke secondary prevention.

Strengths and Limitations

Strengths: Consecutive enrollment of 623 patients with AIS; assessment of both END and 3M-PFO; exploratory evaluation of cPTmax as a potential mediator; use of restricted cubic spline analysis and bootstrap internal validation; and exclusion of patients receiving reperfusion therapy or with cardioembolic stroke to enhance pathophysiological homogeneity.

Limitations: First, the data came from a single center in a retrospective design, and the sample size was moderate (623 patients), and the number of events for the mediation analysis (157 for END and 170 for 3M-PFO) was relatively small, resulting in wide bootstrap confidence intervals for the indirect effects and limited precision of the point estimates. Second, all participants were of Chinese Han ethnicity; whether the conclusions apply to other ethnic or

405 regional populations remains to be validated. Third, to control for treatment-related
406 confounding and to ensure pathophysiological homogeneity, patients who received
407 reperfusion therapy (intravenous thrombolysis/endovascular thrombectomy) and those with
408 cardioembolic stroke were excluded. Although this approach enhanced internal validity, it
409 inevitably introduced selection bias, making the conclusions primarily applicable to AIS
410 patients with non-cardiogenic ischemic stroke receiving standard medical therapy, and not
411 directly generalizable to the entire AIS population. Fourth, both RC and cPTmax were
412 measured at a single time point upon admission, which limits causal inference of the
413 mediation results. Fifth, although the models were adjusted for major confounders, including
414 age, diabetes, statin use, SBP, and baseline NIHSS score, potential confounding variables such
415 as inflammatory markers, detailed infarct characteristics (e.g., lesion volume and location), or
416 precise degree of carotid stenosis were not systematically collected. These could not be
417 included in the regression models; therefore, residual confounding cannot be completely
418 excluded. Sixth, the mediating variable was limited to cPTmax; other vulnerability features
419 such as intraplaque neovascularization, fibrous cap thickness, intraplaque hemorrhage, or
420 inflammatory activity were not assessed. This may have underestimated the full mediating
421 pathway of carotid plaque burden between RC and prognosis. Future studies should
422 incorporate more refined plaque assessment techniques, and standardize the collection of
423 inflammatory and neuroimaging parameters to comprehensively elucidate the mechanisms by
424 which RC affects stroke prognosis. Seventh, the mediation analysis used in this study has
425 statistical methodological limitations. Because the outcome variables were binary, the
426 product-of-coefficients method estimated effects on the logit scale, and the mediated

proportions on the logit scale cannot be directly equated to proportions on the probability scale; therefore, overinterpretation should be avoided.

Conclusion

In this study, higher RC levels were associated with END and 3M-PFO among patients with AIS, with linear dose-response relationships for both outcomes. In the mediation analysis, cPTmax was consistent with a potential mediating pathway. From a clinical perspective, RC and cPTmax may serve as readily available markers for early identification of high-risk patients, potentially informing closer monitoring and more intensive secondary prevention. Future studies should evaluate whether early assessment of RC and cPTmax can guide risk-adapted management and whether targeting RC improves clinical outcomes.

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