Association of Remnant Cholesterol Level with Risk of Recurrent Ischemic Stroke and Its Predictive Value: A Postprint Study

Authors: Liu Xingyu, Du Huijie, Mo Jiali, XU Minghuan, Liu Zuting, Yang Xuezhi, Zhang Huiqin, Yi Yingping, Kuang Jie, Kuang Jie

Date: 2024-05-14T00:00:00+00:00

Abstract

Background Serum remnant cholesterol (RC) is associated with the onset of ischemic stroke; however, studies on the correlation between RC levels and ischemic stroke recurrence are limited, and few have investigated the predictive value of RC for stroke recurrence in ischemic stroke patients.

Objective To investigate the correlation between RC levels and stroke recurrence and its predictive value by detecting serum RC levels in ischemic stroke patients.

Methods Hospitalized patients diagnosed with ischemic stroke at the First Affiliated Hospital of Nanchang University, Second Affiliated Hospital of Nanchang University, Nanchang Second Hospital, and Nanchang Third Hospital from March 2019 to March 2021 were enrolled. Relevant clinical information within 48 hours of admission was collected, and patients were followed up for 12 months to determine stroke recurrence status. COX proportional hazards regression model and restricted cubic spline (RCS) were used to analyze the correlation between RC levels and ischemic stroke recurrence. The predictive value of RC levels for ischemic stroke recurrence was analyzed using receiver operating characteristic (ROC) curve.

Results A total of 1,023 patients were included, of whom 107 (10.46%) experienced recurrence within one year. Multivariate COX proportional hazards regression analysis revealed that RC level was an independent risk factor for ischemic stroke recurrence (HR=2.709, 95%CI=1.150~6.382, P<0.05). There was a non-linear positive dose-response relationship between RC levels and recurrence risk in ischemic stroke patients (P-Nonlinear=0.0193). The area under the ROC curve for RC in predicting one-year recurrence in ischemic stroke patients was 0.687 (95%CI=0.631~0.743), with an optimal cutoff value of 0.58 mmol/L. The area under the ROC curve for RC combined with the Essen Stroke Risk

Score (ESRS) was significantly different from that of ESRS alone in predicting one-year recurrence in ischemic stroke patients (Z=2.3562, P<0.05).

Conclusion RC level is an independent risk factor for recurrence in ischemic stroke patients and possesses certain predictive value for ischemic stroke recurrence.

Full Text

Correlation between Remnant Cholesterol and the Risk of Ischemic Stroke Recurrence and Its Predictive Value

LIU Xingyu[1], DU Huijie[1], MO Jiali[1], XU Minghuan[1], LIU Zuting[1], YANG Xuezhi[1], ZHANG Huiqin[1], YI Yingping[2], KUANG Jie[1]*

[1]Department of Epidemiology, School of Public Health, Nanchang University/Jiangxi Provincial Key Laboratory of Preventive Medicine, Nanchang 330006, China
[2]Big Data Center, the Second Affiliated Hospital of Nanchang University, Nanchang 330006, China
*Corresponding author: KUANG Jie, Associate professor; E-mail: kuangjie@ncu.edu.cn

Abstract

Background Serum remnant cholesterol (RC) is associated with the onset of ischemic stroke (IS). However, studies on the correlation between RC levels and recurrent IS are limited, and the predictive value of RC in recurrent IS has not been analyzed. **Objective** To investigate the correlation between serum RC and the recurrence of IS, and to evaluate the predictive value of RC levels in recurrent IS by detecting serum RC levels in patients with IS. **Methods** Patients diagnosed as IS and hospitalized in the First Affiliated Hospital of Nanchang University, the Second Affiliated Hospital of Nanchang University, the Second Hospital of Nanchang, and the Third Hospital of Nanchang from March 2019 to March 2021 were included in the study. Relevant clinical information within 48 hours of admission was collected. All patients were followed up for 12 months to record the cases of recurrent IS. COX regression and Restricted Cubic Spline (RCS) were performed to identify the correlation between RC levels and recurrent IS. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive value of RC levels in recurrent IS. **Results** A total of 1,023 eligible patients were included in the study, and 107 (10.46%) of them experienced IS recurrence within 1 year. Multivariable Cox regression analysis showed that RC was an independent risk factor for recurrent IS (HR=2.709, 95%CI=1.150-6.382; P<0.05). There was a nonlinear positive dose-response relationship between RC levels and the risk of recurrent IS (P-Nonlinear=0.0193). The area under the curve (AUC) of RC in discriminating 1-year recurrence of IS was 0.687 (95%CI: 0.631-0.743), with the optimal cutoff of 0.58 mmol/L. There was a significant difference in the AUC between the combination detection of RC and the Essen

Stroke Risk Score (ESRS) versus ESRS alone in discriminating 1-year recurrence of IS (Z=2.3562, P<0.05). **Conclusion** RC is an independent risk factor for recurrent IS, showing a predictive value in the recurrence of IS.

Keywords: Ischemic stroke; Remnant cholesterol; Recurrence; Cox proportional hazards regression model; Prognosis

Introduction

Ischemic stroke (IS) is the most common type of stroke, accounting for approximately 80% of all stroke cases [1]. While advances in medical care have improved acute-phase mortality rates for IS, the recurrence rate remains difficult to control [2]. According to the National Stroke Prevention and Treatment Report, the recurrence rate of IS in China is 13.2%, and 60% of first-time stroke patients have a high risk of recurrence [3]. Among preventable risk factors, cholesterol levels play a crucial role in the progression of IS recurrence [4].

Remnant cholesterol (RC), also known as cholesterol in triglyceride-rich lipoproteins (TRLs), includes very low-density lipoprotein cholesterol and intermediate-density lipoprotein cholesterol in the fasting state, as well as cholesterol carried in chylomicron remnants in the non-fasting state [5]. In recent years, low-density lipoprotein cholesterol (LDL-C) has been the primary lipid target for cardiovascular disease prevention [6]. However, residual cardiovascular risk persists even after LDL-C is reduced to recommended targets [7], which may be related to RC [8].

Currently, the Essen Stroke Risk Score (ESRS) can predict the risk of stroke or composite cardiovascular events in both stable-phase and acute-phase patients and is widely used in clinical practice [9]. Given that research on the correlation between RC levels and IS recurrence is scarce, and the predictive value of RC in IS recurrence has not been explored, this study aims to analyze the correlation between RC levels and IS recurrence and to examine whether combining RC with ESRS improves the predictive ability for recurrence risk in IS patients. This could provide a scientific basis for more accurate identification and management of high-risk patients and for developing more personalized lipid-lowering strategies to reduce recurrence risk.

Methods

1.1 Study Population

This study was based on a multicenter, single-blind, randomized controlled clinical trial [10]. The analysis included patients hospitalized and diagnosed with IS at the First Affiliated Hospital of Nanchang University, the Second Affiliated Hospital of Nanchang University, the Second Hospital of Nanchang, and the Third Hospital of Nanchang between March 2019 and March 2021.

Inclusion criteria: (1) Confirmed diagnosis of IS (atherosclerotic IS) or transient ischemic attack (meeting the diagnostic criteria of the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke and confirmed by cranial CT or MRI); (2) Age 18 years or older; (3) Within the acute phase of onset (2 weeks); (4) National Institutes of Health Stroke Scale (NIHSS) score $\leq$ 15; (5) Voluntary participation with signed informed consent.

Exclusion criteria: (1) Cancer patients; (2) Cardiogenic infarction, small vessel disease cerebral infarction, cerebral infarction of other or undetermined causes; (3) Hemorrhagic stroke, mixed stroke, tumor stroke, and transient ischemic attack patients; (4) Comorbid severe cardiac, pulmonary, or hepatic system diseases; (5) Patients judged by researchers to have poor compliance or inability to complete long-term follow-up.

This study was approved by the Institutional Review Board of the Second Affiliated Hospital of Nanchang University [2018 Medical Research Ethics Review (04) No.].

1.2 Baseline Data Collection

A standardized case report form was used to collect baseline data and clinical examination data within 48 hours of admission. Baseline data included sociodemographic information (gender, age, education level, marital status), physical examination data (height, weight, BMI, etc.), and disease-related information (drinking history, smoking history, family history of stroke, previous stroke type, stroke type). Fasting blood samples were collected on the morning after admission to measure total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), LDL-C, apolipoprotein A (ApoA), apolipoprotein B (ApoB), apolipoprotein E (ApoE), lipoprotein a (Lp(a)), non-HDL-C, RC, C-reactive protein (CRP), uric acid (UC), and homocysteine (HCY). RC was calculated as RC = TC - LDL-C - HDL-C [11].

1.3 Follow-up and Endpoint Assessment

Researchers received unified training before follow-up, and an investigation manual was developed. Patients were followed up regularly by telephone after discharge to collect recurrence information. Clinical physicians conducted telephone or outpatient follow-ups for 12 months after discharge to record recurrence during the follow-up period.

The diagnostic criteria for IS recurrence were: a clear diagnosis of IS at first onset, with new neurological deficit symptoms and signs emerging on the basis of stable or improved initial IS symptoms and signs, and confirmation of new ischemic lesions by imaging examinations such as cranial CT or magnetic resonance imaging. Patients were divided into recurrence and non-recurrence groups based on whether they had recurrence within 1 year to analyze risk factors for recurrence in IS patients.

1.4 Statistical Analysis

Statistical analysis was performed using Medcalc 19.0.4 and R 4.2.3 software. The missForest package was used to impute missing information. Measurement data were expressed as ($\bar{x}\pm s$), and count data were expressed as relative frequencies. Cox proportional hazards regression models were used to explore risk factors for recurrence within 1 year in IS patients. Cox regression and restricted cubic spline (RCS) were applied to explore the relationship between RC levels and recurrence risk in IS patients. ROC curves were plotted to evaluate the predictive value of serum RC levels, and the optimal cutoff value was determined. ROC curves were used to assess the predictive performance of ESRS alone versus RC combined with ESRS for 1-year recurrence in IS patients, and the Delong test was used to compare differences between the two models. $P<0.05$ was considered statistically significant.

Results

2.1 General Characteristics and Univariate Analysis

A total of 1,023 IS patients were included, comprising 686 males (67.06%) and 337 females (32.94%). The mean age of the study population was $(63.6\$\pm\$11.1)years.After12monthsoffollow-up,107patients(10.46\pm\$11.5)$ years, 1 case (0.93%) was obese, 38 cases (35.51%) had a smoking history, 22 cases (20.56%) had a drinking history, 3 cases (2.80%) had a family history of stroke, 37 cases (34.58%) had previous stroke, 79 cases (73.83%) had hypertension, and 44 cases (41.12%) had diabetes. Additionally, 5 cases (4.67%) had sleep apnea syndrome, 3 cases (2.80%) had atrial fibrillation, and 5 cases (4.67%) had carotid stenosis.

In the non-recurrence group, the mean age was $(63.36\$\pm\$11.02)$ years, 2 cases (0.22%) were obese, 323 cases (35.26%) had a smoking history, 208 cases (22.71%) had a drinking history, 10 cases (1.09%) had a family history of stroke, 202 cases (22.05%) had previous stroke, 691 cases (75.44%) had hypertension, and 314 cases (34.28%) had diabetes. Additionally, 21 cases (2.29%) had sleep apnea syndrome, 9 cases (0.98%) had atrial fibrillation, and 38 cases (4.15%) had carotid stenosis.

Using recurrence (yes=1, no=0) as the dependent variable and combining literature review with clinically relevant factors that might affect stroke recurrence, univariate Cox proportional hazards regression analysis was performed with age (actual value), previous stroke (yes=1, no=0), CRP (actual value), UC (actual value), HCY (actual value), TC (actual value), TG (actual value), HDL-C (actual value), LDL-C (actual value), ApoA (actual value), ApoB (actual value), ApoE (actual value), Lp(a) (actual value), non-HDL-C (actual value), and RC (actual value) as independent variables. The results showed that age, previous stroke, CRP, UC, TC, ApoA, ApoB, non-HDL-C, and RC affected IS recurrence ($P<0.05$), as shown in Table 1 .

2.2 Multivariate Cox Proportional Hazards Regression Analysis of RC and IS Recurrence

Using 1-year recurrence in IS patients as the dependent variable and RC level as the independent variable, multivariate Cox proportional hazards regression analyses were performed controlling for different sets of confounders. The results showed that without adjusting for any factors (Model 1), RC level had an effect of 2.457 (1.819-3.320) on 1-year recurrence in IS patients. After adjusting for demographic characteristics such as age and gender (Model 2), RC level had an effect of 2.888 (2.096-3.980). Based on Model 2, after further adjusting for medical history including previous stroke, diabetes, hypertension, carotid stenosis, and atrial fibrillation (Model 3), RC level had an effect of 2.804 (2.008-3.916). Based on Model 3, after adjusting for biochemical indicators including CRP, TC, ApoA, ApoB, and LDL-C (Model 4), RC level had an effect of 2.709 (1.150-6.382) ($P<0.05$), indicating that RC is an independent risk factor for IS recurrence, as shown in Table 2 .

2.3 Dose-Response Relationship Between RC Level and IS Recurrence Risk

There was a positive dose-response relationship between RC level and IS recurrence risk (P-Nonlinear=0.0193), as shown in Figure 1 [Figure 1: see original paper].

2.4 Predictive Value of RC Levels for IS Recurrence

ROC curve analysis was performed to evaluate RC level for predicting 1-year recurrence in IS patients. The results showed that the area under the ROC curve (AUC) was 0.687, with an optimal cutoff value of 0.580 mmol/L, corresponding to a sensitivity of 0.713 and specificity of 0.558.

ESRS alone and RC combined with ESRS were included in ROC curve analysis. The AUC for ESRS alone in predicting 1-year recurrence was 0.571, while the AUC for RC combined with ESRS was 0.610. The Delong test showed a statistically significant difference between the AUCs of ESRS alone versus RC combined with ESRS ($Z=2.3562$, $P<0.05$), indicating that adding RC level to the ESRS recurrence assessment scale improved predictive performance for IS recurrence, as shown in Table 3 and Figure 2 [Figure 2: see original paper].

Discussion

This study found that RC is an independent risk factor for stroke recurrence in IS patients, exhibits a positive dose-response relationship with recurrence risk, and serves as an independent predictor of stroke recurrence. Adding RC level to the ESRS recurrence assessment scale improved the model' s predictive ability for IS recurrence.

Our study demonstrates that RC is a risk factor for stroke recurrence in IS patients. Several studies have reached similar conclusions. In the general population, increased RC variability is associated with a higher risk of ischemic stroke [12]. LI et al. [13] reported that high RC increases the risk of first-ever stroke in Chinese populations and suggested that RC may be a potential target for primary stroke prevention. In a prospective cohort study by VARBO et al. [14] that included 112,512 individuals from the general population, elevated RC was associated with increased risk of ischemic stroke, with individuals having RC concentrations $ $1.5 mmol/L (58 mg/dL) showing higher risk compared to those with RC <0.5 mmol/L (19 mg/dL).

RC has been increasingly recognized as an important atherogenic risk factor that can accumulate in the subendothelium, causing various vascular injuries including endothelial dysfunction, inflammation, and ultimately atherosclerosis [15-16]. Multiple clinical studies have confirmed that characteristics of vulnerable carotid atherosclerotic plaques are potential risk factors for most ischemic events and are significantly associated with recurrence of ischemic events [17]. Furthermore, RC can upregulate the expression of pro-inflammatory cytokines, with each 1 mmol/L increase in RC associated with an approximately 3-fold increase in CRP [18], and high RC concentrations show a strong positive correlation with low-grade inflammation [19]. Studies have indicated that low-grade inflammation is associated with higher risk of IS recurrence [20]. In an animal experimental study by ROTH et al. [21], mice that had experienced stroke showed increased plaque formation and susceptibility, as well as accumulation of pro-inflammatory CD11b+ monocytes in the aorta, which may promote IS recurrence. These mechanisms may explain the association between RC and IS recurrence.

This study has several limitations. First, the study population consisted of patients with mild to moderate stroke in Nanchang city, so whether the results can be generalized to stroke patients of different severities in broader populations remains to be determined. Second, this study only collected relevant indicator data at admission, while indicators such RC change over time; therefore, further studies are needed to examine time-varying effects. Finally, this study only adjusted for factors in the dataset that might affect the results, but residual confounding may still exist.

In summary, RC level is associated with IS recurrence and has certain predictive value for stroke recurrence. This study can provide reference for lipid control in secondary stroke prevention. For patients whose recurrence risk cannot be controlled by lowering LDL-C levels, the target of lipid-lowering therapy may shift toward RC.

References

[1] WANG Y J, LI Z X, GU H Q, et al. China stroke statistics 2019: a report from the national center for healthcare quality management in neurological diseases,

China national clinical research center for neurological diseases, the Chinese stroke association, national center for chronic and non-communicable disease control and prevention, Chinese center for disease control and prevention and institute for global neuroscience and stroke collaborations[J]. Stroke Vasc Neurol, 2020, 5(3): 211-239. DOI: 10.1136/svn-2020-000457.

[2] OZA R, RUNDELL K, GARCELLANO M. Recurrent ischemic stroke: strategies for prevention[J]. Am Fam Physician, 2017, 96(7): 436-440.

[3] WANG L D, LIU J M, YANG Y, et al. Summary of the "China Stroke Prevention and Treatment Report 2017" [J]. Chin J Cerebrovasc Dis, 2018, 15(11): 611-616, Feng 3. DOI: 10.3969/j.issn.1672-5921.2018.11.010.

[4] MA R, XU H Y, WANG G M. Research progress on hematological markers of ischemic stroke[J]. Lab Med Clin, 2019, 16(6): 853-856.

[5] VARBO A, NORDESTGAARD B G. Remnant lipoproteins[J]. Curr Opin Lipidol, 2017, 28(4): 300-307. DOI: 10.1097/MOL.0000000000000429.

[6] FERENCE B A, GINSBERG H N, GRAHAM I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel[J]. Eur Heart J, 2017, 38(32): 2459-2472. DOI: 10.1093/eurheartj/ehx144.

[7] JEPSEN A M, LANGSTED A, VARBO A, et al. Increased remnant cholesterol explains part of residual risk of all-cause mortality in 5414 patients with ischemic heart disease[J]. Clin Chem, 2016, 62(4): 593-604. DOI: 10.1373/clinchem.2015.253757.

[8] WU W Q, CHEN G Z, WU K Y, et al. Cumulative exposure to high remnant-cholesterol concentrations increases the risk of cardiovascular disease in patients with hypertension: a prospective cohort study[J]. Cardiovasc Diabetol, 2023, 22(1): 258. DOI: 10.1186/s12933-023-01984-4.

[9] REN K X, JIANG H Y, LI T T, et al. Predictive value of the combination between the intracranial arterial culprit plaque characteristics and the Essen Stroke Risk Score for short-term stroke recurrence[J]. J Stroke Cerebrovasc Dis, 2022, 31(9): 106624. DOI: 10.1016/j.jstrokecerebrovasdis.2022.106624.

[10] WANG J J, HAN M Q, KUANG J, et al. Personalized antiplatelet therapy based on clopidogrel/aspirin resistance tests in acute ischemic stroke and transient ischemic attack: study protocol of a multi-center, single-blinded and randomized controlled trial[J]. Contemp Clin Trials, 2021, 108: 106507. DOI: 10.1016/j.cct.2021.106507.

[11] NORDESTGAARD B G, VARBO A. Triglycerides and cardiovascular disease[J]. Lancet, 2014, 384(9943): 626-635. DOI: 10.1016/S0140-6736(14)61177-6.

[12] LI W J, HUANG Z G, FANG W, et al. Remnant cholesterol variability and

ischemic stroke risk in the general population[J]. Stroke, 2022, 53(6): 1934-1941. DOI: 10.1161/STROKEAHA.121.037756.

[13] LI H, MIAO S, CHEN L, et al. Association and mediating mechanism between remnant cholesterol and first-ever stroke among the Chinese general population[J]. Front Neurosci, 2023, 17: 1161367. DOI: 10.3389/fnins.2023.1161367.

[14] VARBO A, NORDESTGAARD B G. Remnant cholesterol and risk of ischemic stroke in 112,512 individuals from the general population[J]. Ann Neurol, 2019, 85(4): 550-559. DOI: 10.1002/ana.25432.

[15] ZENG N M, SHEN Y E, LI Y, et al. Association between remnant cholesterol and subclinical carotid atherosclerosis among Chinese general population in health examination[J]. J Stroke Cerebrovasc Dis, 2023, 32(8): 107234. DOI: 10.1016/j.jstrokecerebrovasdis.2023.107234.

[16] VARBO A, BENN M, NORDESTGAARD B G. Remnant cholesterol as a cause of ischemic heart disease: evidence, definition, measurement, atherogenicity, high risk patients, and present and future treatment[J]. Pharmacol Ther, 2014, 141(3): 358-367. DOI: 10.1016/j.pharmthera.2013.11.008.

[17] SCHINDLER A, SCHINNER R, ALTAF N, et al. Prediction of stroke risk by detection of hemorrhage in carotid plaques: meta-analysis of individual patient data[J]. JACC Cardiovasc Imaging, 2020, 13(2 Pt 1): 395-406. DOI: 10.1016/j.jcmg.2019.03.028.

[18] DOI H, KUGIYAMA K, OKA H, et al. Remnant lipoproteins induce proatherothrombogenic molecules in endothelial cells through a redox-sensitive mechanism[J]. Circulation, 2000, 102(6): 670-676. DOI: 10.1161/01.cir.102.6.670.

[19] VARBO A, BENN M, TYBJÆRG-HANSEN A, et al. Elevated remnant cholesterol causes both low-grade inflammation and ischemic heart disease, whereas elevated low-density lipoprotein cholesterol causes ischemic heart disease without inflammation[J]. Circulation, 2013, 128(12): 1298-1309. DOI: 10.1161/CIRCULATIONAHA.113.003008.

[20] WU M, ZHANG X H, CHEN J J, et al. A score of low-grade inflammation for predicting stroke recurrence in patients with ischemic stroke[J]. J Inflamm Res, 2021, 14: 4605-4614. DOI: 10.2147/JIR.S328383.

[21] ROTH S, SINGH V, TIEDT S, et al. Brain-released alarmins and stress response synergize in accelerating atherosclerosis progression after stroke[J]. Sci Transl Med, 2018, 10(432): eaao1313. DOI: 10.1126/scitranslmed.aao1313.

Author Contributions: KUANG Jie proposed the research direction, designed the study, and revised the manuscript; LIU Xingyu performed statistical analysis and drafted the manuscript; DU Huijie, MO Jiali, XU Minghuan, and LIU Zuting processed data and assisted with statistical methods; YANG Xuezhi

and ZHANG Huiqin collected and organized data; YI Yingping analyzed feasibility and controlled article quality. All authors approved the final manuscript.

Conflict of Interest Statement: The authors declare no conflict of interest.

Note: Figure translations are in progress. See original paper for figures.