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Postprint of a Study on the Risk Threshold for Carotid Plaque Development in Postmenopausal Middle-aged and Elderly Women with Normal Homocysteine Levels

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Abstract

Background: Carotid plaque represents an important early predictive indicator of clinical carotid atherosclerosis. While the association between homocysteine (Hcy) and carotid plaque has been well established, no definitive conclusion has been reached regarding the correlation between Hcy and carotid plaque in postmenopausal middle-aged and elderly women.

Objective: To analyze the impact of Hcy within the normal reference range on the risk of carotid plaque development in postmenopausal middle-aged and elderly women, and to determine the risk threshold.

Methods: A total of 1,465 postmenopausal middle-aged and elderly women who underwent health check-ups at the Physical Examination Center of the Affiliated Hospital of Guizhou Medical University between January 2020 and June 2023 were enrolled. General information, blood biochemical parameters, and carotid ultrasound indicators were collected. Multivariate Logistic regression analysis was employed to investigate the association between Hcy and carotid plaque. Receiver operating characteristic (ROC) curve analysis was utilized to determine the Hcy cutoff value for predicting carotid plaque risk in postmenopausal middle-aged and elderly women with normal homocysteine levels.

Results: Among the 1,465 participants, 644 (43.96%) exhibited carotid plaque. The plaque group demonstrated higher age, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, and Hcy compared with the non-plaque group, while high-density lipoprotein cholesterol was lower ($P<0.05$). Multivariate Logistic regression analysis revealed that age (OR=1.097, 95%CI=1.059~1.135), systolic blood

pressure (OR=1.021, 95%CI=1.010~1.033), low-density lipoprotein cholesterol (OR=1.871, 95%CI=1.066~3.281), high-density lipoprotein cholesterol (OR=0.568, 95%CI=0.387~0.835), and Hcy (OR=1.153, 95%CI=1.075~1.236) were independent influencing factors for carotid plaque in postmenopausal middle-aged and elderly women (P<0.05). ROC curve analysis indicated that Hcy $\geq$ 11.87 mol/L is the optimal cutoff value for predicting carotid plaque in postmenopausal middle-aged and elderly women with normal Hcy levels, with an area under the ROC curve of 0.605, specificity of 75.8%, and sensitivity of 40.4%.

Conclusion: Hcy is an independent influencing factor for carotid plaque in postmenopausal middle-aged and elderly women, and Hcy $\geq$ 11.87 mol/L is the optimal cutoff value for predicting carotid plaque in this population within the normal range. This threshold can provide an important reference for clinical assessment of carotid plaque risk in postmenopausal middle-aged and elderly women.

Full Text

A Threshold Study of Carotid Plaque Risk in Postmenopausal Middle-Aged Women with Normal Homocysteine

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Abstract

Background Carotid plaque is an important early predictive signal of clinical carotid atherosclerosis. The association between homocysteine (Hcy) and carotid plaque is well recognized; however, the correlation between Hcy and carotid plaque in postmenopausal middle-aged women is not clearly established. **Objective** To analyze the impact of Hcy within the normal reference range on the risk of carotid plaque in postmenopausal middle-aged women and determine the risk threshold. **Methods** A total of 1,465 postmenopausal women who underwent health examinations at the Affiliated Hospital of Guizhou Medical University between January 2020 and June 2023 were randomly selected.

General information, blood biochemical indicators, and carotid ultrasound indicators were collected, and multivariate Logistic regression analysis was used to explore the association between Hcy and carotid plaque. The cutoff value of Hcy for predicting carotid plaque risk in postmenopausal middle-aged women with normal Hcy range was determined by plotting receiver operating characteristic (ROC) curve. **Results** Six hundred and forty-four (43.96%) out of 1,465 study subjects had carotid artery plaques. Age, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triacylglycerol (TG), and Hcy were higher in the plaque group than in the non-plaque group, while high-density lipoprotein cholesterol (HDL-C) was lower ($P<0.05$). Logistic regression analysis showed that age (OR=1.097, 95%CI=1.059-1.135), SBP (OR=1.021, 95%CI=1.010-1.033), LDL-C (OR=1.871, 95%CI=1.066-3.281), HDL-C (OR=0.568, 95%CI=0.387-0.835), and Hcy (OR=1.153, 95%CI=1.075-1.236) were independent risk factors for carotid plaque in postmenopausal middle-aged women ($P<0.05$). ROC curve analysis indicated that Hcy $\geq$ 11.87 mol/L was the optimal cutoff value for predicting carotid plaque in postmenopausal middle-aged women within normal Hcy range, with area under curve (AUC) of 0.605, specificity of 75.8%, and sensitivity of 40.4%. **Conclusion** Hcy is an independent risk factor for carotid plaque in postmenopausal middle-aged women, and Hcy $\geq$ 11.87 mol/L is the optimal cutoff value for predicting carotid plaque in postmenopausal middle-aged women with normal Hcy. This threshold may provide an important reference for clinical assessment of carotid plaque risk in postmenopausal middle-aged women.

Key words Carotid plaques; Carotid Stenosis; Postmenopause; Homocysteine; Threshold

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Introduction

Carotid intima-media thickness and carotid plaque formation are reliable markers for the presence and progression of carotid atherosclerosis (CAS) [1]. Homocysteine (Hcy) is a sulfur-containing amino acid derived from dietary protein methionine [2]. Elevated Hcy can cause carotid intima-media thickening and plaque formation, leading to luminal stenosis and increasing the risk of cardiovascular and cerebrovascular diseases [3]. Studies show that after menopause, estrogen levels in middle-aged and elderly women drop sharply, affecting metabolic function and significantly increasing Hcy levels and the prevalence of hyperhomocysteinemia (HHcy) [4].

Numerous epidemiological studies have demonstrated that HHcy is an important independent risk factor for atherosclerosis and related diseases in middle-aged and elderly populations, dramatically increasing postmenopausal women's cardiovascular disease risk [5-9]. Research indicates that the risk of carotid plaque in postmenopausal women is more than 1.9 times higher than in premenopausal women [10]. However, few studies have examined the impact of normal-range

Hcy on carotid plaque in postmenopausal middle-aged women. Therefore, this study used carotid ultrasound to detect plaque occurrence and investigate the relationship between normal-range Hcy and carotid plaque in postmenopausal middle-aged women, providing evidence for cardiovascular disease prevention and risk screening in this population.

Methods

1.1 Study Population A total of 1,465 postmenopausal middle-aged women who underwent health examinations at the Health Management Center of the Affiliated Hospital of Guizhou Medical University between January 2020 and June 2023 were randomly selected. Inclusion criteria were: (1) age 45-65 years; (2) amenorrhea for 12 months or more; (3) complete physical examination data with simultaneous serum Hcy testing and carotid ultrasound examination; (4) Hcy < 15 mol/L. Exclusion criteria were: (1) history of stroke or transient ischemic attack; (2) history of coronary atherosclerosis; (3) hepatic or renal insufficiency, dyslipidemia, anemia, or malignant tumor history; (4) diabetes or hypertension history; (5) use of hormone therapy (MHT), folic acid, vitamin B6, vitamin B12, or related health supplements within the past six months. This study was approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University (2023170K), and all subjects signed informed consent forms.

1.2 Detection Methods **1.2.1 Biochemical Indicators:** After 12 hours of overnight fasting, professional technicians collected 3-5 mL of elbow venous blood from subjects in EDTA anticoagulant tubes. Samples were stored at 4°C and centrifuged within 1 hour to obtain plasma specimens. Hcy was detected using enzymatic cycling method (kit: Meikang Bio-Technology Co., Ltd.). Serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triacylglycerol (TG) were detected using enzymatic colorimetric method (kit: Roche Diagnostics Shanghai Co., Ltd.), strictly following the instructions. All specimens were measured using the Cobas c702 automatic biochemical analyzer by the same group of professional laboratory technicians. Hcy levels ≥ 15 mol/L were defined as HHcy [11]. According to the "Chinese Adult Dyslipidemia Prevention and Treatment Guidelines (2016 Revised Edition)" [12], TC ≥ 6.2 mmol/L was defined as hypercholesterolemia, TG ≥ 2.3 mmol/L as hypertriglyceridemia, LDL-C ≥ 4.1 mmol/L as high LDL-C, and HDL-C < 1.0 mmol/L as low HDL-C.

1.2.2 Carotid Plaque Examination: A Mindray DC-8EXP Doppler ultrasound machine with a variable frequency probe (3-12 MHz) was used. Before examination, subjects were instructed to lie supine and rest for 10 minutes, fully exposing the neck examination area. The left and right common carotid arteries and carotid bifurcations were scanned sequentially. The vertical distance between the intima and adventitia within the lumen 1 cm before and after the carotid bifurcation was measured, repeated three times, with the average value

taken as the intima-media thickness (IMT). Carotid plaque was defined as local protrusion into the arterial lumen >0.5 mm or exceeding 50% of the surrounding IMT value, or IMT > 1.5 mm [13].

1.2.3 Anthropometric Measurements: Before height and weight measurement, the electronic height-weight scale (Shenzhen Shuangjia Electronic Technology Co., Ltd.) was calibrated. Subjects were instructed to be fasting in the morning, empty bowels and bladder, wear light clothing, and remove shoes and hats before standing upright on the measuring instrument. For height measurement, subjects were instructed to look straight ahead with both upper limbs hanging naturally. The error range was below 0.1%. Readings were recorded in cm for height and kg for weight, precise to 0.1. BMI was calculated as weight (kg)/height^2 (m^2). Blood pressure was measured using an Omron blood pressure monitor (Omron Healthcare Co., Ltd., BP-203RVIIIC). The instrument was checked for proper function before measurement. Subjects rested in a quiet environment with suitable temperature and humidity for 5-10 minutes before measurement, recorded in mmHg.

1.3 Statistical Methods SPSS 25.0 statistical software was used for data analysis. Quantitative data were expressed as ($\bar{x}\pm s$) and compared between groups using independent t-tests. Multivariate Logistic regression analysis was used to explore the effect of Hcy on carotid plaque. Receiver operating characteristic (ROC) curve was plotted to analyze the predictive value of Hcy for carotid plaque. The bilateral test level was α=0.05.

Results

2.1 General Data Analysis Among the 1,465 subjects, the average age was (58.5$±$4.6) years, with 644 cases (43.96%) having carotid artery plaques. There was no significant difference in BMI between the plaque and non-plaque groups (P>0.05). However, the plaque group had significantly higher age, SBP, DBP, TC, TG, LDL-C, and Hcy, and lower HDL-C compared to the non-plaque group (P<0.05), as shown in Table 1 .

Table 1 Comparison of general information between plaque patients and non-plaque patients ($\bar{x}\pm s$)

Variable	Non-plaque (n=821)	Plaque (n=644)	P-value
Age (years)	57.4$±4.7|59.9±4.2| <	<0.001	
	0.001||$BMI(kg/m\hat{}\{2\})$|23.3±7.1|23.7±3.1| >		
	0.05||$SBP(mmHg)$|120±17|128±17| <		
	0.001||$DBP(mmHg)$|72±10|75±10| <		
	0.001||$TC(mmol/L)$|5.07±0.83|5.15±0.94| <		
	0.001||$TG(mmol/L)$|1.58±1.18|1.76±1.14| <		
	0.001||$LDL-C(mmol/L)$|3.16±0.75|3.27±0.90| <		
	0.001||$HDL-C(mmol/L)$|1.49±0.34|1.41±0.30| <		
	0.001||$Hcy(\mu mol/L)$|10.47±2.05|11.21±$1.99		

Note: SBP=systolic blood pressure, DBP=diastolic blood pressure, TC=total cholesterol, TG=triacylglycerol, LDL-C=low-density lipoprotein cholesterol, HDL-C=high-density lipoprotein cholesterol, Hcy=homocysteine.

2.2 Multivariate Logistic Regression Analysis of Carotid Plaque in Postmenopausal Women with Normal Hcy Using carotid plaque occurrence as the dependent variable (assignment: yes=1, no=0), variables with statistically significant differences in univariate analysis were included in multivariate Logistic regression analysis. After controlling for confounding factors including age, SBP, DBP, TG, TC, LDL-C, and HDL-C, the results showed that age, SBP, LDL-C, HDL-C, and Hcy were independent influencing factors for carotid plaque in postmenopausal middle-aged women (P<0.05), as shown in Table 2 .

To further investigate the relationship between Hcy and carotid plaque, the study population was divided into quartile groups based on Hcy levels: Q1 group (<9.4 mol/L, n=354), Q2 group (9.4-10.5 mol/L, n=369), Q3 group (10.7-<12.39 mol/L, n=376), and Q4 group ($ $12.39 mol/L, n=366). Using carotid plaque occurrence as the dependent variable (assignment: yes=1, no=0) and Hcy group (assignment: Q1=1, Q2=2, Q3=3, Q4=4) as the independent variable, multivariate Logistic regression analysis showed that after adjusting for confounding factors (age, BMI, SBP, DBP, TG, TC, HDL-C, LDL-C), the risk of carotid plaque in Q2 group was 1.573 times that of Q1 group, Q3 group was 1.467 times that of Q1 group, and Q4 group was 2.238 times that of Q1 group, as shown in Table 3 .

2.3 ROC Curve of Hcy Predicting Carotid Plaque Risk in Postmenopausal Women ROC curve results showed that Hcy $\geq$ 11.87 mol/L was the optimal cutoff value for predicting carotid plaque in postmenopausal middle-aged women. The area under the ROC curve (AUC) was 0.605 (P<0.001), with sensitivity of 40.4% and specificity of 75.8%, as shown in Figure 1 [Figure 1: see original paper].

Figure 1 ROC curve of Hcy predicting carotid plaque risk in postmenopausal women

Discussion

Numerous epidemiological studies have shown that postmenopausal status is a risk factor for carotid plaque [14-15]. Our results similarly reflect this relationship, with a carotid plaque detection rate of 43.96% in postmenopausal middle-aged women. This rate is lower than that reported by Zuo et al. [16], possibly because our study subjects were healthy individuals undergoing physical examinations with Hcy levels within the normal range. Our results show that Hcy levels were higher in women with carotid plaques than in those without, consistent with other studies [17-18], indicating a close relationship between Hcy and carotid plaque formation.

Research has confirmed that carotid plaque formation is associated with multiple factors including age [19], Hcy [18], SBP [20], and LDL-C [21], which our study also demonstrated. With increasing age, physiological changes in blood vessels and increased exposure to various risk factors lead to carotid intima damage and plaque formation. Additionally, patients with long-term hypertension experience reduced vascular compliance and increased endothelial cell permeability, causing varying degrees of intimal damage [17]. Elevated LDL-C promotes carotid plaque formation by transporting more cholesterol from the liver to peripheral tissues, thereby increasing atherosclerosis risk [22-24]. Furthermore, after excluding the influence of age, SBP, DBP, TG, TC, HDL-C, and LDL-C, our study showed that normal-range Hcy level is an independent risk factor for postmenopausal middle-aged women, similar to previous research [25-26]. Hcy contributes to carotid plaque formation through several mechanisms [27-29]: (1) Hcy causes vascular endothelial cell dysfunction and even apoptosis, promoting cardiovascular and cerebrovascular diseases; (2) Hcy induces vascular smooth muscle cell proliferation and apoptosis, and Hcy oxidation leads to oxygen free radical production, promoting LDL-C oxidation and ultimately causing arterial smooth muscle cell hyperplasia and occlusive vascular disease; (3) Hcy induces oxidative stress, increasing arterial wall thickness and promoting plaque formation; (4) Hcy increases inflammatory factor expression, leading to atherosclerosis formation.

Our ROC curve analysis of Hcy for predicting carotid plaque risk in postmenopausal middle-aged women showed that Hcy $\geq$ 11.87 mol/L could reasonably predict carotid plaque occurrence (AUC=0.605, specificity=75.8%, sensitivity=40.4%). SUN et al. [30] followed 2,009 Chinese subjects without cardiovascular disease at baseline for 12 years and found that subjects with Hcy $>$ 9.47 mol/L had a 2.3-fold increased risk of cardiovascular and cerebrovascular disease (95%CI=1.24-4.18), with an optimal cutoff lower than our study. This difference may be because SUN et al. [30] included both men and women, and male sex is an independent risk factor for carotid plaque with higher cardiovascular disease risk than females [31], while our study focused on postmenopausal

women. Additionally, based on the physiological characteristics of our subjects, postmenopausal middle-aged women experience sharp declines in estrogen levels due to endocrine system disorders. Estrogen plays a regulatory role in Hcy metabolism, and decreased estradiol levels may cause Hcy elevation [32-34]. Without estrogen protection, postmenopausal middle-aged women experience endocrine disorders and reduced neurological function, affecting Hcy metabolism and increasing the risk of carotid plaque even within the normal Hcy range. Therefore, our results suggest that normal-range Hcy is also a risk factor for carotid plaque in postmenopausal middle-aged women, and monitoring Hcy levels and increasing carotid plaque screening in this population should be strengthened. However, current research on normal Hcy and carotid plaque remains limited, and more large-sample studies are needed to clarify this issue.

This study has several limitations. First, it is a cross-sectional study that cannot establish causality, and the sample size is relatively small. Future studies with larger sample sizes are needed to further investigate the relationship between normal Hcy levels and carotid plaque. Second, this study only analyzed physical examination data and general conditions; future research should include lifestyle factors such as smoking, alcohol consumption, and physical activity. Finally, this study only explored the risk prediction of carotid plaque in postmenopausal middle-aged women with normal Hcy levels; future studies could investigate the risk in middle-aged and elderly men with normal Hcy.

In summary, this study demonstrates that age, SBP, LDL-C, and Hcy are independent influencing factors for carotid plaque in postmenopausal middle-aged women with normal Hcy levels. Hcy $\geq$ 11.87 mol/L is an independent predictor of carotid plaque formation within the normal range in postmenopausal middle-aged women. These findings suggest that Hcy monitoring should be strengthened in clinical practice for postmenopausal middle-aged women, with timely screening and early prevention to help reduce the adverse effects of carotid plaque and provide reference for cardiovascular disease prevention, ultimately improving quality of life and reducing cardiovascular disease risk in postmenopausal middle-aged women.

Author Contributions

LU Ran and RAN Limei designed and conceptualized the study. LU Ran and WU Chunyan implemented the research, analyzed data, interpreted results, and drafted the manuscript. LU Ran, WU Chunyan, AN Miaomiao, XU Haina, WU Baoqin, and LAI Jun collected data. WU Baoqin and LAI Jun provided technical or material support. RAN Limei supervised quality control and review, secured funding, guided manuscript writing, and took overall responsibility for the article.

This article has no conflicts of interest.

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