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Risk factors for hypoechoic carotid plaque in healthy physical-examination population

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Abstract

Background We studied the characteristics of carotid ultrasound plaque in a healthy physical-examination population and analyzed the risk factors for hypoechoic carotid plaque for early control and prevention of stroke.

Results A total of 1333 healthy physical-examination individuals were included in this study, including 457 females and 876 males. According to the results of carotid artery ultrasound, they were divided into hyperechoic carotid plaque ($n=940$) and hypoechoic carotid plaque ($n=393$). Multivariate logistic analysis showed that male, alcohol consumption, and low-density lipoprotein were risk factors for hypoechoic carotid plaque. SPSS 25.0 software was used to draw the receive operating characteristic curve and calculate the prediction probability of the risk factor indicators obtained by the multifactor model. The area under the curve was also calculated to be 0.623 (95% CI = 0.591–0.655).

Conclusion Male, alcohol consumption, and low-density lipoprotein are risk factors for hypoechoic carotid plaque in a healthy physical-examination population.

Keywords Carotid arteriosclerosis, Hypoechoic carotid plaque, Hyperechoic carotid plaque, Healthy physical-examination population, Risk factors

Background

Since 2015 to date, acute ischemic stroke (AIS) has become the leading cause of death and disability in China. The burden of stroke in China has gradually increased, posing a major threat to the health of Chinese citizens [1]. TOAST typing of AIS includes the following [2, 3]:(1) thrombosis or embolism due to atherosclerosis of large arteries, (2) cardiogenic embolism, (3) occlusion of small blood vessels, (4) other identified causes, and (5) uncertain causes. Atherosclerosis is a progressive disease that is essentially an accumulation of lipid and fibrous components in large arteries [4]. A key component of atherosclerosis leading to clinical events in stroke is the infiltration of inflammatory cells onto the surface of the carotid plaque, which promotes plaque rupture and leads to embolization or carotid occlusion [5]. The assessment of plaque morphological characteristics can predict the risk of ipsilateral stroke in patients with asymptomatic carotid stenosis [6]. Ultrasound is a radiation-free and cost-effective technique that is often considered patient friendly and ideal for immediate diagnosis and follow-up [7]. A meta-study [8] has demonstrated that the assessment of atherosclerotic plaque characteristics by carotid ultrasound accurately predicts the risk of cerebrovascular symptoms in asymptomatic and symptomatic patients. Moreover, the analysis of carotid plaque echogenicity identifies those at high risk of cardiovascular events in asymptomatic

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and symptomatic patients. Hypoechoic carotid plaque is usually considered to be associated with increased cerebrovascular risk [9, 10]. Several studies have shown that hypoechoic carotid plaques are associated with elevated lipid levels, low levels of high-density lipoprotein, and elevated postprandial triglyceride levels [11–13]. The correlation between classical vascular risk factors and carotid plaque development has been extensively studied. However, the risk factors of hypoechoic plaques should elicit more research attention because vulnerable carotid plaques play a decisive role in the link of stroke occurrence. Accordingly, we investigated the carotid ultrasound plaque characteristics of healthy physical-examination population and analyzed the risk factors of hypoechoic plaques for the early control and prevention of stroke.

Methods

This study was a retrospective one. We collected data related to 1,333 healthy physical-examination individuals from the Physical Examination Department from August 1, 2022, to December 31, 2022.

People who met the following criteria were included: healthy physical-examination population aged > 40 years, and carotid ultrasound (brand: Philips, model: Affiniti 70, manufacturer name: Philips Ultrasound, Inc., country of origin: USA) findings suggestive of the presence of carotid plaque in all enrollees. The following populations were excluded from this study: patients with malignant tumors, connective-tissue system diseases, hematologic system diseases, autoimmune system diseases, osteoporosis, severe liver and kidney damage, and mental disorder.

We identified the profile data such as age, gender, fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), creatinine (Cr), blood urea nitrogen (Bun), uric acid (UA), history of smoking, history of alcohol consumption, and carotid artery ultrasound results.

Carotid artery ultrasound was performed by an ultrasound specialist. All subjects were placed in a supine position with the lateral neck fully exposed and head tilted to the opposite side. The common carotid artery and its branches were detected successively, and the intimal thickness of the tube wall was observed. Carotid atherosclerotic plaque was defined as a focal carotid intima–media thickness greater than 1.1 mm with localized protrusion of the arterial wall into the arterial lumen. Based on the carotid ultrasound results, the healthy physical-examination population was divided into hypoechoic and hyperechoic plaque groups.

Statistical analysis

SPSS 25.0 statistical software (IBM Corp., IBM SPSS Statistics for Windows version 25.0, full window menu mode, Armonk, NY, USA) was used to analyze the data. For the comparison of baseline features, normal distribution test was initially performed. The data did not conform to normal distribution. Continuous variables are expressed as medians and interquartile ranges, and nonparametric two independent sample tests were performed. X^2 test was used for categorical variables, and chi-square tests stratified by gender were performed. Univariate analysis was performed first, and then multivariate logistic stepwise regression analysis was performed on data with $P < 0.05$ in univariate analysis. Taking the occurrence of hypoechoic carotid plaque as the gold standard, receiver operating characteristic (ROC) curve was drawn, and the area under the ROC curve (AUC) was calculated. The calibration chart of the prediction model for carotid atherosclerosis was drawn. All tests were two sided, and $P < 0.05$ was considered statistically significant.

Results

A total of 1333 healthy physical-examination people were included in this study. According to the results of carotid artery ultrasound, they were divided into hyperechoic carotid plaque ($n = 940$) and hypoechoic carotid plaque ($n = 393$). The baseline data of the two groups showed that the gender, TC, LDL, HDL, Cr, UA, smoking history, and alcohol consumption history were statistically significant ($P < 0.05$; Table 1).

This study included 457 females and 876 males. We performed a stratified chi-square analysis of carotid plaque data from healthy physical-examination population based on gender differences. Before stratified chi-square analysis, continuous variables such as laboratory indicators need to be converted into binary categorical variables. The study variable assignment is detailed in Table 2. Comparing the data of two groups of categorical variables, we found that the difference in gender, TC, LDL, Cr, UA, smoking history, and alcohol consumption history between the hyperechoic and hypoechoic carotid plaque groups was statistically significant ($P < 0.05$). Refer to Table 3. Stratified chi-square test according to gender showed that the homogeneity test of odds ratio (OR) value between strata of TC was $P < 0.05$. After stratification according to gender, TC was found to be a risk factor for hypoechoic carotid plaque in males (OR = 1.337, 95% CI = 1.007–1.776) and females (OR = 2.646, 95% CI = 1.638–4.276). Stratified chi-square results showed that LDL, TC, alcohol

Table 1 Basic data of hypoechoic and hyperechoic plaque groups in healthy physical-examination population

Risk factors	Hyperechoic carotid plaque (*n* = 940)	Hypoechoic carotid plaque (*n* = 393)	*Z*/X^2 value	*P* value
Age (year)	57 (12)	57 (12)	− 1.142	0.253
Gender			13.224	0.000*
Male	589 (62.7%)	287 (73.0%)		
Female	351 (37.3%)	106 (27.0%)		
VLDL(mmol/L)	0.66 (0.45)	0.70 (0.46)	− 1.393	0.164
TG(mmol/L)	1.45 (0.99)	1.53 (1.01)	− 1.403	0.160
TC(mmol/L)	5.05 (1.49)	5.30 (1.25)	− 3.650	0.000*
LDL(mmol/L)	3.00 (1.15)	3.21 (0.97)	− 4.725	0.000*
HDL(mmol/L)	1.34 (0.42)	1.29(0.43)	− 2.151	0.031*
FBG(mmol/L)	6.69 (1.98)	6.62(1.81)	− 1.206	0.228
Cr(μmol/L)	73.76 (18.90)	77.00 (22.19)	− 3.275	0.001*
Bun(μmol/L)	5.10 (1.90)	4.99 (1.68)	− 1.395	0.163
UA(μmol/L)	343.00 (118.00)	366.00 (135.50)	− 2.863	0.004*
Smoking			7.112	0.008*
Yes	161 (17.1%)	92 (23.4%)		
No	779 (82.9%)	301 (76.6%)		
Alcohol consumption			21.667	0.000*
Yes	280 (29.8%)	169 (43.0%)		
No	660 (70.2%)	224 (57.0%)		

VLDL Very low-density lipoprotein, *TG* Triglycerides, *TC* Total cholesterol, *LDL* Low-density lipoprotein, *HDL* High-density lipoprotein, *FBG* Fasting blood glucose, *Cr* Creatinine, *Bun* Blood urea nitrogen, *UA* Uric acid

*$P < 0.05$

Table 2 Assignment of dichotomous variables

Study variables	Assignment(0)	Assignment(1)
Gender	female	male
FBG	≤ 6.1	> 6.1
TC	≤ 5.2	> 5.2
TG	≤ 1.7	> 1.7
HDL	≥ 1.1	< 1.1
LDL	< 3.4	≥ 3.4
Cr	≤ 73	> 73
UA	≤ 357	> 357
Bun	≤ 7.5	> 7.5
Smoking	No	Yes
Drinking	No	Yes
VLDL	≤ 0.78	> 0.78
Age	≤ 60	> 60

FBG Fasting blood glucose, *TC* Total cholesterol, *TG* Triglycerides, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *Cr* Creatinine, *UA* Uric acid, *Bun* Blood urea nitrogen, *VLDL* Very low-density lipoprotein

consumption, and UA were risk factors for hypoechoic carotid plaque (Table 4).

Gender, age, LDL, TC, history of alcohol consumption and smoking, Cr, and UA were included in multivariate logistic analysis. Results suggested that male, alcohol consumption, and LDL were risk factors for hypoechoic carotid plaque (Table 5).

SPSS 25.0 software was used to draw the ROC curve and calculate the AUC to predict the fitting degree of the model. The AUC was 0.623 (Table 6 and Fig. 1).

A calibration plot of the prediction model for hypoechoic carotid plaque formation was drawn, as shown in Fig. 2. The measured and predicted probabilities are shown in Table 7.

Discussion

The prevalence of carotid plaque is rising, and its global burden is increasing. Early stages of carotid plaques are primarily characterized by carotid intima–media thickening. In later stages, inflammatory cell infiltration and an increased risk of plaque rupture mark an increased risk of cardiovascular events. A meta-analysis study has shown that atherosclerosis may increase the risk of dementia after stroke [14]. Early ultrasonography can detect abnormalities in the carotid arteries [15]. The nature of carotid plaque can be categorized as hypoechoic, mixed echogenic, and strongly echogenic based on ultrasound findings. Hypoechoic and mixed echo plaques are unstable plaques, indicating that the plaque has a vulnerable nature [16, 17]. It is rich in more lipid components and is at risk of rupture. A previous study

Table 3 Comparison of categorical variable data of carotid plaque in healthy physical-examination population

Risk factors	Hyperechoic carotid plaque (*n* = 940)	Hypoechoic carotid plaque (*n* = 393)	X^2 value	*P* value
Age			0.300	0.584
≤ 60	583 (62.0%)	250 (63.6%)		
> 60	357 (38.0%)	143 (36.4%)		
Gender			13.224	0.000*
Male	589 (62.7%)	287 (73.0%)		
Female	351 (37.3%)	106 (27.0%)		
VLDL			2.842	0.092
Normal	601 (63.9%)	232 (59.0%)		
Abnormal	339 (36.1%)	161 (41.0%)		
TG			3.274	0.070
Normal	595 (63.3%)	228 (58.0%)		
Abnormal	345 (36.7%)	165 (42.0%)		
TC			11.498	0.001*
Normal	519 (55.2%)	177 (45.0%)		
Abnormal	421 (44.8%)	216 (55.0%)		
LDL			4.797	0.029*
Normal	642 (68.3%)	244 (62.1%)		
Abnormal	298 (31.7%)	149 (37.9%)		
HDL			2.886	0.089
Normal	752 (80.0%)	298 (75.8%)		
Abnormal	188 (20.0%)	95 (24.2%)		
FBG			0.965	0.326
Normal	311 (33.1%)	141 (35.9%)		
Abnormal	629 (66.9%)	252 (64.1%)		
Cr			7.284	0.007*
Normal	449 (47.8%)	156 (39.7%)		
Abnormal	491 (52.2%)	237 (60.3%)		
Bun			0.952	0.329
Normal	879 (93.5%)	373 (94.9%)		
Abnormal	61 (6.5%)	20 (5.1%)		
UA			9.158	0.002*
Normal	523 (55.6%)	183 (46.6%)		
Abnormal	417 (44.4%)	210 (53.4%)		
Smoking			7.112	0.008*
Yes	161 (17.1%)	92 (23.4%)		
No	779 (82.9%)	301 (76.6%)		
Alcohol consumption			21.667	0.000*
Yes	280 (29.8%)	169 (43.0%)		
No	660 (70.2%)	224 (57.0%)		

VLDL Very low-density lipoprotein, *TG* Triglycerides, *TC* Total cholesterol, *LDL* Low-density lipoprotein, *HDL* High-density lipoprotein, *FBG* Fasting blood glucose, *Cr* Creatinine, *Bun* Blood urea nitrogen, *UA* Uric acid

* $P < 0.05$

[18] has shown that the size of hypoechoic plaques is linearly correlated with the risk of stroke, with an area under the ROC curve of 0.816. Therefore, identifying reliable risk factors for plaque echogenicity is essential for the early prevention of acute cardiovascular and cerebrovascular diseases.

Alcohol consumption, a major risk factor contributing to the global disease burden, was consumed by approximately 47% of adults worldwide by 2017 [19]. A Chinese

Table 4 Stratified chi-square analysis of healthy physical-examination population in the carotid plaque

Index	X^2 value	*P* value	Test of the homogeneity of the OR values (*P* value)	OR value (95%CI)	*P* value
Age	0.300	0.584	0.233	0.933 (0.730–1.192)	0.579
FBG	0.965	0.326	0.709	0.856 (0.668–1.098)	0.221
LDL	4.797	0.029	0.081	1.358 (1.060–1.739)	0.016*
HDL	2.886	0.089	0.228	1.205 (0.907–1.601)	0.199
TC(male)	4.038	0.044	0.016	1.337 (1.007–1.776)	0.000*
TC(female)	16.473	0.000	0.016	2.646 (1.638–4.276)	0.000*
TG	3.274	0.070	0.861	1.223 (0.960–1.557)	0.103
Smoking	7.112	0.008	0.991	1.329 (0.988–1.787)	0.060
Alcohol consumption	21.667	0.000	0.975	1.606 (1.240–2.080)	0.000*
Cr	7.284	0.007	0.219	1.241 (0.964–1.596)	0.093
Bun	0.952	0.329	0.571	0.738 (0.438–1.246)	0.256
UA	9.158	0.002	0.584	1.328 (1.042–1.693)	0.022*
VLDL	2.842	0.092	0.983	1.207 (0.947–1.538)	0.128

FBG Fasting blood glucose, *TC* Total cholesterol, *TG* Triglycerides, *HDL* High-density lipoprotein, *LDL* Low-density lipoprotein, *Cr* Creatinine, *UA* Uric acid, *Bun* Blood urea nitrogen, *VLDL* Very low-density lipoprotein

* $P < 0.05$

Table 5 Multivariate logistic analysis of hypoechoic carotid plaque formation in healthy physical-examination population

Risk factors	*B*	SB	Wald	Freedom	*P* value	OR value	95% CI of OR value	
							Lower limit	Upper limit
Male	0.370	0.142	6.773	1	0.009*	1.448	1.096	1.913
Alcohol consumption	0.492	0.133	13.595	1	0.000*	1.635	1.259	2.123
LDL	0.399	0.079	25.443	1	0.000*	1.490	1.276	1.739
Constant	− 2.532	0.281	80.931	1	0.000	0.079		

LDL Low-density lipoprotein

* $P < 0.05$

Table 6 The AUC value of hypoechoic carotid plaque formation

Hypoechoic carotid plaque formation	
AUC(95% CI)	Hosmer–Lemeshow test(*P* value)
0.623(0.591–0.655)	9.858($P = 0.275$*)

* $P > 0.05$

study [20] investigated the causal relationship of alcohol intake with carotid artery thickness and atherosclerosis in 22,000 adults. The findings suggest that high levels of alcohol intake are associated with higher carotid plaque burden but not with carotid intima–media thickness. Another study [21] has found that alcohol consumption is associated with carotid atherosclerosis. Jiao Y [22] and coworkers found that noninvasive carotid ultrasound combined with serum markers can identify asymptomatic patients with vulnerable carotid plaque early. However, they do not find an association between alcohol consumption and hypoechoic carotid plaque. The results of stratified chi-square analysis in the present study showed that alcohol consumption was a risk factor for hypoechoic carotid plaques (OR = 1.606; 95% CI = 1.240–2.080). Multifactorial logistic analysis similarly showed that alcohol consumption was a risk factor for hypoechoic carotid plaques.

The prevalence and morphology of carotid atherosclerosis have been [23] assessed in 3016 men and 3404 women by ultrasound. The carotid plaques are found to be more likely to be softer in men than in women, and the proportion of soft plaques in men increases with age. Another study [24] has investigated gender differences in atherosclerosis in patients with AIS. In these patients, gender differences have no effect on the prevalence of intracranial atherosclerosis, whereas extracranial atherosclerosis is less prevalent in women than in men. The multifactorial logistic analysis in this

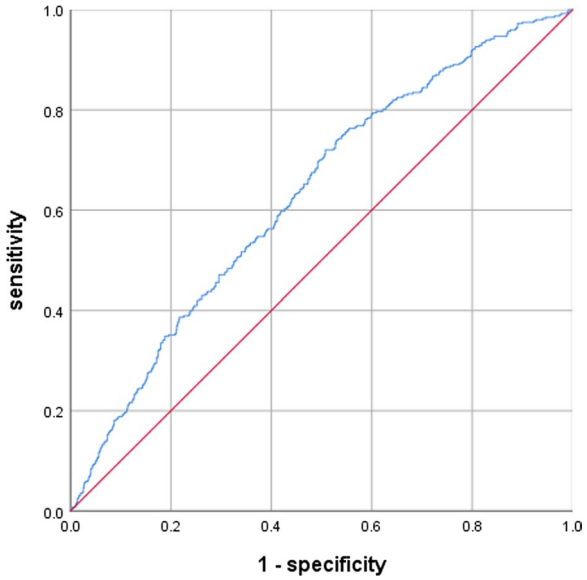

Fig. 1 ROC curve of hypoechoic carotid plaque formation. AUC = 0.623, 95%CI (0.591–0.655)

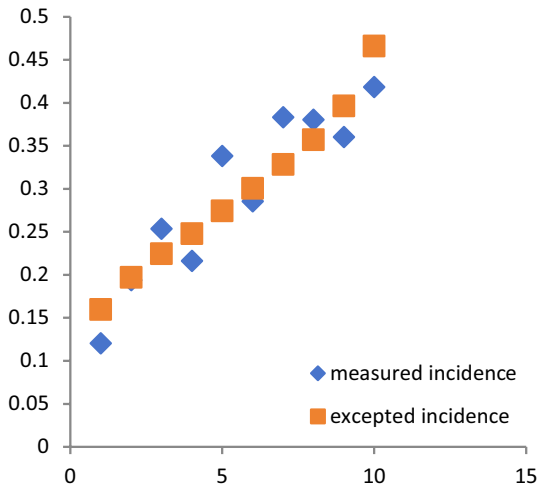

Fig. 2 Calibration of a predictive model for hypoechoic carotid plaque formation

study pointed out that being male is one of the risk factors for the hypoechoic carotid plaque.

LDL is the best lipid predictor of the extent of atherosclerosis and is a determinant of vulnerable plaques. It predicts dangerous, rupture-prone, and lipid-rich plaques in the carotid arteries [25]. LDL is further oxidized in plaques, and high levels of oxidized LDL increase the risk of rupture of atherosclerotic lesions [26]. The target value of LDL for reducing cardiovascular events after stroke has also been explored. The included subjects are treated by intensive lipid-lowering therapy with statins, and the

Table 7 Measured and predicted values of a predictive model for hypoechoic carotid plaque formation

Actual measurement	Anticipation	Total	Measured probability	Prediction probability
16	21.239	133	0.120	0.160
26	26.416	134	0.194	0.197
34	30.111	134	0.254	0.225
29	33.226	134	0.216	0.248
45	36.479	133	0.338	0.274
38	39.980	133	0.286	0.301
51	43.662	133	0.383	0.328
51	47.851	134	0.381	0.357
49	53.922	136	0.360	0.396
54	60.113	129	0.419	0.466

median follow-up is 3.5 years. The primary endpoints of the main cardiovascular events studied include ischemic stroke, myocardial infarction, and death from cardiovascular causes. After ischemic stroke or transient ischemic attack due to atherosclerosis, the risk of subsequent cardiovascular events is lower in patients with a target value of less than 70 mg/dL than that in patients with a target value of 90 mg/dL to 110 mg/dL for LDL cholesterol [27]. Teng Y and coworkers found that in young adults without overt cardiovascular disease, risk factors for increased carotid artery intimal–medial thickness include age, male, body mass index, TG, LDL, homocysteine, UA, and smoking [28]. LDL is found to be correlated with hypoechoic carotid plaques as a risk factor for their formation. LDL levels are closely related to the nature of plaque vulnerability and cardiovascular events. Early control of the risk factors has an important impact on the prevention of stroke events.

In this study, 1333 healthy physical-examination individuals with carotid plaque including 457 females and 876 males were enrolled. Multifactorial logistic analysis suggested that men, alcohol consumption, and LDL were risk factors for hypoechoic carotid plaque formation. The predictive probability of the risk factor indicators derived from the multifactorial model was then plotted as an ROC curve with AUC = 0.623 (95% CI = 0.591–0.655). However, this study had some limitations. First, all study populations were selected from a single center. Second, women were fewer. Therefore, future research design should include the impact of gender differences.

Conclusion

Male, alcohol consumption, and LDL are risk factors for hypoechoic carotid plaque in healthy physical-examination population.

Abbreviations

AIS	Acute ischemic stroke
ROC	Receiver operating characteristic
FBG	Fasting blood glucose
TG	Triglycerides
TC	Total cholesterol
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
VLDL	Very low-density lipoprotein
Cr	Creatinine
Bun	Blood urea nitrogen
UA	Uric acid
ROC	Receiver operating characteristic
AUC	Area under the ROC curve
OR	Odds ratio

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Author contributions
MF processed data and wrote this article. YNF reviewed the literatures and wrote this article. JHW, FFC, and YC assisted in organizing data. YDL, BBZ, and BZ collected and entered data. LLC framed the article and she was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. We confirm that the numbers used are raw numbers.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Tangshan Gongren Hospital. Date: 2023.06.26. Ethics number: [2023] Ethical Review Study No. (097). After review by the ethics committee, it was agreed to conduct this study.

Informed written consent
This study is a retrospective study. The subjects included in this study were the healthy physical-examination population in the medical examination department. We retrospectively collected information from the medical examination department of the healthy physical-examination participants, such as blood glucose, blood lipids, and other laboratory indicators, and the results of carotid artery ultrasound, which did not involve a clinical trial study, and there was no risk to the subjects in this study. There was no written informed consent. This study was approved by the Ethics Committee of Tangshan Gongren Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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