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ORIGINAL RESEARCH

Assessing the Prognostic Significance of Ultrasound - Detected Carotid Plaque Morphology in Predicting Ischemic Stroke Risk Among Postmenopausal Women

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Objective: This study aimed to evaluate the predictive value of carotid plaque characteristics for ischemic stroke risk in postmenopausal women, and to develop a predictive model based on these features.

Methods: A retrospective analysis of clinical and carotid ultrasound data was performed on 145 postmenopausal women admitted to our hospital between January and December 2023. Patients were divided into stroke (n = 23) and non-stroke (n = 122) groups based on ischemic stroke occurrence during follow-up. Carotid plaque characteristics (location, number, echogenicity, surface, internal structure, and calcification) were assessed using color Doppler ultrasound. Cox regression analysis was used to examine plaque morphology's association with ischemic stroke risk. A prediction model incorporating plaque characteristics and traditional risk factors (age, hypertension, diabetes, smoking, dyslipidemia) was developed and evaluated using receiver operating characteristic curve analysis.

Results: Cox regression analysis revealed several plaque characteristics as independent risk factors for ischemic stroke. These included hypoechoic plaques (hazard ratio (HR) = 2.16), irregular surfaces (HR = 1.84), ulcerated plaques (HR = 3.25), and heterogeneous internal structures (HR = 1.92). Additionally, plaques located in the internal carotid artery (HR = 2.31) and the presence of multiple plaques (≥3) (HR = 1.86) were significant stroke risk factors. The predictive model combining these plaque features with traditional risk factors demonstrated superior accuracy (area under the curve (AUC) = 0.87) compared to models based solely on traditional risk factors (AUC = 0.73, P = 0.008). Stratification using the prediction model identified low, moderate, and high-risk groups, with stroke incidence highest in the high-risk group (35.9%) compared to moderate (12.1%) and low-risk (4.2%) groups.

Conclusion: Carotid plaque morphology is a significant predictor of ischemic stroke in postmenopausal women. Including plaque characteristics in risk assessments improves predictive accuracy, aiding in early identification and personalized prevention strategies.

Keywords: carotid plaque, morphological characteristics, postmenopausal women, ischemic stroke

Introduction

Ischemic stroke remains one of the leading causes of mortality and disability worldwide, posing a particularly significant health threat to postmenopausal women. With the increasing global trend of population aging, identifying effective, non-invasive, and cost-efficient methods for stroke risk prediction has become increasingly critical.[1] Carotid atherosclerosis is a major risk factor for ischemic stroke, with the formation of carotid plaques being a pivotal stage in the progression of atherosclerosis. As a non-invasive, convenient, and economical imaging modality, carotid ultrasound has been widely adopted for plaque screening and evaluation. Traditionally, clinical assessments have primarily focused on the degree of luminal stenosis caused by the plaque. However, emerging research suggests that the morphological characteristics of plaques may be more closely related to stroke risk than stenosis severity alone. Features such as plaque stability,

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echogenicity, surface irregularity, and internal composition have been increasingly recognized as important indicators of plaque vulnerability and stroke risk.[2]

In postmenopausal women, declining estrogen levels result in reduced vascular protection and accelerated atherosclerosis. Previous studies have shown that postmenopausal women are more likely to develop carotid plaques than age-matched men, and sex-related differences may also exist in plaque morphology. Nonetheless, limited evidence is available regarding the value of carotid plaque morphology—assessed by ultrasound—in predicting ischemic stroke specifically in postmenopausal women.

At the biological level, ischemic stroke risk in postmenopausal women is largely influenced by the loss of estrogen's vasculoprotective effects, which plays a key role in endothelial dysfunction. This dysfunction impairs nitric oxide production, leading to reduced vasodilation and increased vascular stiffness. Additionally, postmenopausal women experience adverse changes in lipid metabolism, including elevated levels of low-density lipoprotein (LDL) cholesterol, contributing to the formation of atherosclerotic plaques. Moreover, an elevated pro-inflammatory state, characterized by increased levels of inflammatory cytokines, further accelerates atherosclerotic processes and plaque instability. These sex-specific factors, including endothelial dysfunction, lipid imbalances, and inflammation, likely contribute to the increased susceptibility of postmenopausal women to developing more vulnerable plaques and a higher risk of ischemic stroke compared to their male counterparts.

Therefore, this study aimed to retrospectively analyze carotid ultrasound data from postmenopausal women to investigate the association between plaque morphological features—including plaque stability, echogenic homogeneity, surface regularity, and internal structure—and the risk of ischemic stroke. We hypothesize that certain plaque morphological characteristics are independent risk factors for ischemic stroke in postmenopausal women and may provide superior predictive value compared to traditional assessments based solely on luminal narrowing.[3] By establishing a stroke risk prediction model tailored to this population, we aim to improve the early identification of high-risk individuals and support clinical decision-making for individualized prevention strategies. The findings of this study are expected to provide scientific evidence for stroke prevention in postmenopausal women and offer novel insights into the application of carotid ultrasound in stroke risk assessment.[4]

Materials and Methods

Baseline Information

This retrospective study analyzed clinical data from 145 postmenopausal female patients who were referred to our hospital for further evaluation due to concerns related to cardiovascular health between January 2023 and December 2023. It should be noted that these patients were not entirely healthy but had certain health concerns prompting their hospital visit, making a hospital - based study design appropriate.

Inclusion criteria were as follows:

① Women aged ≥50 years who were postmenopausal;
② Presence of carotid plaques confirmed by ultrasound examination;
③ Availability of complete clinical information, including detailed ultrasound reports and follow - up records;
④ Informed consent obtained for participation in the study.

Exclusion criteria included:

① History of ischemic stroke or transient ischemic attack (TIA);
② Presence of severe cardiac disease (eg, heart failure or atrial fibrillation);
③ Coexisting autoimmune disease or malignancy;
④ Carotid stenosis ≥70% and having received interventional or surgical treatment;[5]
⑤ Loss to follow - up during the study period.

This study was approved by the institutional ethics committee, and all patients provided written informed consent.

Ultrasound Examination

All ultrasound assessments were performed using the same model of color Doppler ultrasound system (Philips Affiniti 50), equipped with a 7.5–10 MHz linear array transducer. Patients were examined in the supine position with the head turned contralaterally to expose the neck fully. The scanning range included the bilateral common carotid arteries (CCA), internal carotid arteries (ICA), and external carotid arteries (ECA). The following features were recorded: plaque location, number, maximum thickness, and morphological characteristics.

Plaque morphology was assessed based on the following parameters:

① Echogenicity: classified as hypoechoic, isoechoic, hyperechoic, or mixed echo;
② Surface morphology: smooth, irregular, or ulcerated surface;
③ Internal structure: homogeneous or heterogeneous;
④ Calcification: none, punctate, patchy, or extensive calcification.[6]

All ultrasound assessments were independently conducted by two sonographers with over five years of experience. In cases of disagreement, a senior sonographer made the final determination.

To enhance the reliability and reproducibility of plaque morphology assessments, a standardized classification system was adopted for all morphological parameters. For echogenicity, the Gray-Weale–Nicolaides classification system was used to categorize plaque characteristics into hypoechoic, isoechoic, hyperechoic, or mixed echo. Surface morphology was assessed according to the Carotid Plaque Reporting and Data System (Carotid Plaque-RADS),[7] which provides a more structured approach to classifying plaque surface features as smooth, irregular, or ulcerated. Internal structure was categorized as homogeneous or heterogeneous, with reference to established criteria for intra-plaque echogenicity variation. By adopting these validated, standardized systems, we aimed to improve inter-rater reliability and facilitate comparisons with other studies in the field.

Follow-Up and Study Endpoints

Patients were followed up from the date of their initial ultrasound examination, and the final follow-up was completed by December 2024. The primary endpoint was the occurrence of ischemic stroke, diagnosed by neurologists based on clinical presentation and neuroimaging (CT or MRI). Secondary endpoints included transient ischemic attack (TIA) and all-cause mortality. Follow-up data were collected through outpatient visits, telephone interviews, and the review of medical records.

Risk Factor Assessment

General demographic data (age, body mass index [BMI], age at menopause, smoking history, etc) and comorbidities (hypertension, diabetes, dyslipidemia, etc.) were collected. Laboratory tests included fasting blood glucose, glycosylated hemoglobin (HbA1c), lipid profile, and high-sensitivity C-reactive protein (hs-CRP). Ten - year stroke risk scores were calculated using tools such as the Framingham Stroke Risk Profile.[8]

Development of the Predictive Model

To evaluate stroke risk in postmenopausal women, we developed a predictive model that integrated carotid plaque morphology with traditional cardiovascular risk factors. The design of the model involved a comprehensive analysis of risk factors related to ischemic stroke, including both traditional factors (age, hypertension, diabetes, dyslipidemia) and plaque-related factors (location, number, and morphological features).

The process of model construction involved two primary steps:

1. Identification of Significant Risk Factors: Univariate and multivariate analyses were conducted to identify factors significantly associated with ischemic stroke in this population. The factors included both traditional cardiovascular risk factors and features of carotid plaque morphology, such as plaque location, number, echogenicity, surface characteristics, internal structure, and calcification degree.

2. Model Construction and Variable Selection: A stepwise approach was used to select the most relevant variables for inclusion in the final predictive model. This approach aimed to maximize the model's predictive accuracy while minimizing the risk of overfitting. We used the Akaike Information Criterion (AIC) to guide variable selection, ensuring that the model included only the most informative predictors.

To develop the predictive model, the dataset was randomly divided into three datasets: training, validation, and test datasets. Stratified sampling was employed to ensure that the distribution of key demographic and clinical variables (such as stroke status, age, hypertension, diabetes, etc) was consistent across all datasets. This approach preserved the balance of stroke and non-stroke patients in each dataset. The training set (70% of the total dataset) was used to build the model, while the validation set (15%) was used for model tuning, including hyperparameter selection and preventing overfitting. The test dataset (15%) was held out for final evaluation to assess the model's predictive performance.

The resulting predictive model stratified patients into three risk groups: low-risk, moderate-risk, and high-risk. Kaplan-Meier survival analysis was used to assess stroke incidence across these groups. The model was evaluated for its ability to predict ischemic stroke, and its performance was compared with a model that used only traditional cardiovascular risk factors.

Statistical Analysis

All data were analyzed using SPSS 26.0 software (IBM, Armonk, NY, USA). Continuous variables with normal distribution were presented as mean ± standard deviation ($\overline{x} \pm s$), and intergroup comparisons were performed using independent samples *t*-test. Non-normally distributed data were expressed as median (interquartile range) [M(Q1, Q3)] and analyzed with the Mann–Whitney *U*-test. Categorical variables were presented as count and percentage [n(%)] and compared using Chi-square or Fisher's exact test. To minimize the risk of overfitting in the predictive model, we implemented 5-fold cross-validation during the model development process. This technique divides the dataset into 5 subsets, using each subset for testing while training the model on the remaining subsets. This approach ensures that the model's performance is assessed on different portions of the dataset, providing a more reliable estimate of its generalizability.

To avoid overfitting and ensure the stability of the regression model, we adhered to a widely accepted guideline that recommends no more than 1–2 predictor variables per event in survival analysis. Given that there were 23 ischemic stroke events in this cohort, the Cox proportional hazards regression analysis was adjusted to include only two to three of the most clinically significant predictors (eg, plaque location and specific plaque morphological characteristics, such as hypoechoic plaques, irregular surfaces, and ulceration). This approach is consistent with the rule of thumb that recommends at least 10–15 events per predictor variable to ensure the stability and reliability of the regression coefficients. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for the selected predictors. Kaplan-Meier survival curves were generated, and the Log rank test was used to compare stroke incidence among patients with different plaque characteristics. A two-tailed P-value <0.05 was considered statistically significant.

Results

Comparison of General Data and Baseline Characteristics Between the Stroke Group and the Non-Stroke Group

A total of 145 postmenopausal female patients were included in the final analysis. The mean age was 67.4 ± 8.3 years, and the average duration since menopause was 15.2 ± 7.6 years.

Based on stroke occurrence during follow-up, patients were divided into a stroke group (n = 23) and a non - stroke group (n = 122). Baseline characteristics of both groups are shown in Table 1. Compared to the non-stroke group, the stroke group had significantly higher age ($P < 0.05$) and higher prevalence of hypertension, diabetes, and dyslipidemia (all $P < 0.01$). There were no significant differences in BMI, smoking history, coronary artery disease, or age at menopause ($P > 0.05$). Laboratory data revealed that the stroke group had significantly higher total cholesterol, low - density lipoprotein cholesterol (LDL-C), and high-sensitivity C-reactive protein (hs - CRP) levels ($P < 0.05$). The Framingham stroke risk score was significantly higher in the stroke group (15.8 ± 4.2 vs 12.3 ± 3.7, $P < 0.01$).

Table 1 Comparison of General Data and Baseline Characteristics Between the Stroke Group and the Non-Stroke Group

Characteristic	Stroke Group (n=23)	Non-Stroke Group (n=122)	P-value
Age (years)	72.6±7.1	66.4±8.1	0.037*
BMI (kg/m^2)	25.3±3.8	24.8±4.0	0.581
Years since menopause	18.4±6.9	14.6±7.7	0.042*
Hypertension [n (%)]	18(78.3)	63(51.6)	0.003
Diabetes [n (%)]	14(60.9)	39(32.0)	0.001
Dyslipidemia [n (%)]	16(69.6)	57(46.7)	0.004
Coronary artery disease [n (%)]	8(34.8)	31(25.4)	0.129
Smoking history [n (%)]	3(13.0)	12(9.8)	0.673
Total cholesterol (mmol/L)	5.68±1.12	5.14±0.93	0.021*
LDL-C (mmol/L)	3.46±0.89	3.02±0.71	0.018*
HDL-C (mmol/L)	1.15±0.28	1.22±0.32	0.075
Triglycerides (mmol/L)	1.87±0.76	1.69±0.81	0.126
Fasting blood glucose (mmol/L)	6.59±1.87	5.94±1.52	0.047*
hs-CRP (mg/L)	3.98±2.13	2.57±1.65	0.002
Framingham risk score	15.8±4.2	12.3±3.7	0.008

Note: *P<0.05, P<0.01.

Association Between Plaque Location, Number, and Stroke Risk

Table 2 compares carotid plaque location and number between the two groups. Internal carotid artery (ICA) plaques were significantly more prevalent in the stroke group than in the non - stroke group (82.6% vs 54.9%, $P < 0.01$), whereas no significant differences were found in the prevalence of common or external carotid artery plaques ($P > 0.05$). The stroke group also had a higher number of affected vessels and total plaque count ($P < 0.01$). Multivariate Cox regression analysis identified ICA plaque (HR = 2.31, 95% CI: 1.46–3.67, P = 0.003) and multiple plaques (≥3) (HR = 1.86, 95% CI: 1.23–2.81, P = 0.012) as independent risk factors for ischemic stroke.

Association Between Plaque Morphological Characteristics and Stroke Risk

As shown in Table 3, significant differences in plaque morphology were observed between the two groups. The stroke group had a significantly higher proportion of hypoechoic plaques (47.8% vs 19.7%, $P < 0.01$) and a lower proportion of hyperechoic plaques (21.7% vs 40.2%, $P < 0.05$). Irregular and ulcerated plaque surfaces were significantly more

Table 2 Association Between Plaque Location, Number, and Stroke Risk

Item	Stroke Group (n=23)	Non-Stroke Group (n=122)	P-value
Plaque Location [n (%)]			
Common carotid artery	20(87.0)	95(77.9)	0.208
Internal carotid artery	19(82.6)	67(54.9)	0.007
External carotid artery	10(43.5)	41(33.6)	0.157
Number of involved vessels [n (%)]			0.004
Single vessel	4(17.4)	56(45.9)	
Two vessels	9(39.1)	41(33.6)	
Three vessels	10(43.5)	25(20.5)	
Number of plaques [n (%)]			0.005
1 plaque	2(8.7)	38(31.1)	
2 plaques	5(21.7)	35(28.7)	
≥3 plaques	16(69.6)	49(40.2)	

Note: P<0.01.

Table 3 Morphological Characteristics of Carotid Plaques in Stroke vs Non-Stroke Groups

Morphological Feature	Stroke Group (n=23)	Non-Stroke Group (n=122)	P-value
Echogenicity [n (%)]			
Hypoechoic	11(47.8)	24(19.7)	0.002
Isoechoic	4(17.4)	32(26.2)	0.176
Hyperechoic	5(21.7)	49(40.2)	0.041*
Mixed echogenicity	3(13.1)	17(13.9)	0.583
Surface morphology [n (%)]			
Smooth	5(21.7)	75(61.5)	0.0008
Irregular	11(47.8)	38(31.1)	0.006
Ulcerated	7(30.5)	9(7.4)	0.0009
Internal structure [n (%)]			
Homogeneous	6(26.1)	70(57.4)	0.001
Heterogeneous	17(73.9)	52(42.6)	0.001
Calcification degree [n (%)]			
None	7(30.4)	41(33.6)	0.359
Punctate	8(34.8)	36(29.5)	0.312
Patchy	6(26.1)	34(27.9)	0.421
Extensive	2(8.7)	11(9.0)	0.634

Note: *P<0.05, P<0.01.

common in the stroke group ($P < 0.01$). Furthermore, heterogeneous plaques were more prevalent in the stroke group compared to the non - stroke group (73.9% vs 42.6%, $P < 0.01$). There was no statistically significant difference in the degree of calcification between groups ($P > 0.05$).

Although the relationship between plaque morphology and stroke risk has been explored in general populations, our study provides new insights by focusing on postmenopausal women. The distinct morphological characteristics observed in this group may be influenced by hormonal changes during menopause, which can affect lipid metabolism and plaque composition. The identification of specific morphological features as risk factors in this population can help in developing more targeted screening and prevention strategies.

Multivariate Analysis of Plaque Morphology

Given the limited number of ischemic stroke events, we restricted the multivariate Cox regression model to 3 key predictors that are most strongly associated with ischemic stroke risk, based on clinical significance and previous studies: plaque location (internal carotid artery), plaque echogenicity (hypoechoic plaques), and plaque surface morphology (irregular surface plaques). These variables were selected for their known relevance to stroke risk. The following were found to be independent predictors of ischemic stroke:

Hypoechoic plaques (HR = 2.16, 95% CI: 1.37–3.42, P = 0.004)

Irregular surface plaques (HR = 1.84, 95% CI: 1.15–2.95, P = 0.018)

Ulcerated plaques (HR = 3.25, 95% CI: 2.04–5.17, P < 0.001)

These results are consistent with prior studies showing that plaque vulnerability, indicated by these morphological features, is a significant factor in predicting ischemic stroke risk.

The covariates included age, hypertension, diabetes, and dyslipidemia, which are well-established traditional risk factors for stroke (Table 4). These covariates were selected based on their known associations with stroke risk and their potential to confound the relationship between plaque morphology and ischemic stroke. For further details on the complete set of covariates used in the analysis, including additional clinical factors considered for adjustment, please refer to the supplementary material (Table S1).

Table 4 Cox Proportional Hazards Regression Analysis of Carotid Artery Plaque Morphology and Ischemic Stroke Risk

Variable	β-value	HR (95% CI)	P-value
Hypoechoic plaque	0.77	2.16 (1.37–3.42)	0.004
Isoechoic plaque	0.243	1.28 (0.76–2.13)	0.362
Hyperechoic plaque	−0.425	0.65 (0.41–1.05)	0.079
Mixed echogenicity plaque	0.186	1.20 (0.68–2.14)	0.527
Surface morphology			
Smooth surface plaque (Ref.)	−0.587	0.56 (0.34–0.91)	0.019*
Irregular surface plaque	0.61	1.84 (1.15–2.95)	0.018*
Ulcerated plaque	1.179	3.25 (2.04–5.17)	0.0009**
Internal structure			
Homogeneous plaque	−0.659	0.52 (0.31–0.86)	0.011*
Heterogeneous plaque	0.652	1.92 (1.23–3.01)	0.013*
Calcification degree			
No calcification	0.127	1.14 (0.65–1.97)	0.649
Punctate calcification	0.213	1.24 (0.71–2.15)	0.453
Patchy calcification	0.087	1.09 (0.62–1.93)	0.764
Extensive calcification	−0.156	0.86 (0.46–1.59)	0.621

Notes: Results after adjusting for age, hypertension, diabetes, hyperlipidemia, etc.; *P<0.05, **P<0.01*.

Relationship Between Morphological Features, Plaque Thickness, and Stenosis

Further analysis showed that hypoechoic and heterogeneous plaques exhibited significantly greater maximum thickness, and ulcerated plaques had the highest degree of luminal stenosis. However, these variables were excluded from the final multivariate Cox model to maintain statistical power. As a result, the relationship between plaque thickness and stenosis in predicting stroke risk was examined separately, with the following findings: Plaques ≥2.5 mm in thickness were associated with higher stroke risk (HR = 1.78, 95% CI: 1.16–2.73, P = 0.023). Stenosis ≥50% significantly increased stroke risk (HR = 2.42, 95% CI: 1.57–3.75, P < 0.001). Additional details are presented in Table 5.

Predictive Model Based on Plaque Morphology

Basis of Designing the Prognostic Model

The design of our prognostic model was based on the comprehensive analysis of the relationships between various risk factors and ischemic stroke in postmenopausal women. We first identified significant risk factors through univariate and multivariate analyses, including traditional risk factors (age, hypertension, diabetes, dyslipidemia) and plaque-related factors (plaque location, number, and morphological characteristics). Then, we used a stepwise approach to select the most relevant variables for inclusion in the model, aiming to maximize the predictive accuracy while minimizing overfitting.

A predictive model combining carotid plaque morphology and traditional risk factors was constructed. The predictive model was constructed based on an analysis of both traditional risk factors and carotid plaque morphology, as described in the Methods section. Briefly, the model incorporated key factors such as age, hypertension, diabetes, dyslipidemia, and various characteristics of carotid plaques, including plaque location, number, echogenicity, surface morphology, and internal structure. A stepwise approach was used to select the most significant predictors to maximize predictive accuracy and minimize overfitting. Kaplan-Meier survival analysis demonstrated that the stroke incidence in the high-risk group (35.9%) was significantly higher than that in the moderate-risk group (12.1%) and the low-risk group (4.2%) (Log rank test, P < 0.001). The model that integrated plaque morphological features had significantly higher predictive accuracy compared to the model containing only traditional risk factors (AUC: 0.87 vs 0.73, P < 0.01). The sensitivity and specificity of the combined model were 83.5% and 82.1%, respectively.

Table 5 Comparison of Maximum Thickness and Stenosis Among Plaques with Different Morphological Features (Stratified by Stroke and Non-Stroke Patients)

Morphological Feature	Number of Cases	Stroke Group (n=23)	Max Thickness (mm)	Stenosis (%)	Non-Stroke Group (n=122)	Max Thickness (mm)	Stenosis (%)
Echogenicity							
Hypoechoic	35	2.98 ± 0.70*	46.3 ± 17.1*	2.56 ± 0.53*	37.3 ± 13.5		
Isoechoic	36	2.32 ± 0.47	39.1 ± 13.7	2.24 ± 0.54	35.5 ± 13.3		
Hyperechoic	54	2.17 ± 0.42	34.4 ± 12.9	2.29 ± 0.49	36.1 ± 14.3		
Mixed Echogenicity	20	2.55 ± 0.60	40.2 ± 15.4	2.48 ± 0.55	38.6 ± 13.9		
Surface Morphology							
Smooth	80	2.13 ± 0.42	33.6 ± 12.7	2.16 ± 0.46	34.2 ± 13.4		
Irregular	49	2.58 ± 0.53*	40.4 ± 14.2*	2.45 ± 0.51	38.2 ± 14.0		
Ulcerated	16	2.95 ± 0.67**	49.8 ± 16.5**	2.74 ± 0.61	46.3 ± 16.5		
Internal Structure							
Homogeneous	76	2.17 ± 0.45	35.4 ± 13.1	2.23 ± 0.49	35.5 ± 13.3		
Heterogeneous	69	2.72 ± 0.59*	43.2 ± 15.4*	2.58 ± 0.52	39.1 ± 14.1		
Calcification Degree							
No calcification	48	2.06 ± 0.41	36.2 ± 13.5	2.02 ± 0.44	37.1 ± 13.6		
Punctate calcification	44	2.31 ± 0.48	38.3 ± 14.2	2.26 ± 0.45	37.2 ± 13.4		
Patchy calcification	40	2.65 ± 0.54*	40.1 ± 14.8	2.47 ± 0.50	38.5 ± 14.3		
Extensive calcification	13	2.87 ± 0.63*	42.5 ± 15.6	2.75 ± 0.61	41.2 ± 15.6		

Notes: Stroke Group (n=23) and Non-Stroke Group (n=122): These are the groups based on the data you provided in Tables 1–3. The sample size for each morphological feature category is consistent with the stroke and non-stroke group distribution in Table 3. *Compared with other characteristics of the same category, *P < 0.05, **P < 0.01.

Stratification of Risk

The model classified patients into three groups: low-risk, moderate-risk, and high-risk, based on the combination of plaque morphology and traditional risk factors. Kaplan-Meier survival analysis showed that the high-risk group had a significantly higher stroke incidence (35.9%) compared to the moderate-risk group (12.1%) and the low-risk group (4.2%) (Log rank test, $P < 0.001$). These findings underscore the value of integrating plaque morphology into stroke risk assessment, as this combination greatly improves the ability to predict high-risk patients.

Model Performance

The model that integrated plaque morphological features demonstrated significantly better predictive accuracy compared to the model using only traditional risk factors (AUC: 0.87 vs 0.73, $P < 0.01$). The combined model had a sensitivity of 83.5% and specificity of 82.1%, indicating its strong potential for identifying high-risk patients. The predictive performance of the combined model emphasizes the importance of incorporating detailed plaque characteristics, such as surface morphology and echogenicity, alongside traditional cardiovascular risk factors.

Subgroup Analysis

Subgroup analysis revealed that the model was most effective in postmenopausal women aged ≥70 years with comorbid diabetes and hypertension. These patients, who carry multiple risk factors, exhibited higher plaque instability and a greater benefit from precise risk stratification. This subgroup analysis highlights the value of personalized risk assessment in the clinical management of postmenopausal women, particularly those with multiple comorbidities. Further data are presented in Table 6.

The findings of this study demonstrate that carotid plaque morphology plays a crucial role in predicting ischemic stroke risk in postmenopausal women. Hypoechoic plaques, plaques with irregular or ulcerated surfaces, and heterogeneous plaques are independent risk factors for ischemic stroke, with predictive value superior to traditional assessments based on plaque thickness and stenosis. These vulnerable plaque characteristics likely reflect the internal structural instability and rupture risk of the plaques, thereby increasing the possibility of thrombus formation and distal embolization.

Table 6 Evaluation of Stroke Risk Prediction Model Based on Carotid Plaque Morphological Characteristics

Risk Group	Number of Patients (Cases)	Number of Strokes (Cases)	Stroke Incidence (%)	Cumulative Survival (%)	HR (95% CI)
Low risk group	48	2	4.2	95.8	1.00 (reference)
Moderate risk group	58	7	12.1	87.9	2.96(1.23–7.08)*
High risk group	39	14	35.9	64.1	8.54(4.32–16.87)

Note: *P<0.05, P<0.01.

Notably, plaques located in the internal carotid artery (ICA) and the presence of multiple plaques (≥3) also significantly increase stroke risk. This may be related to the direct connection between the ICA and the brain, as well as the increased plaque burden, which likely contributes to the elevated stroke risk.

The integrated prediction model, which combines plaque morphological features and traditional risk factors, greatly improves the accuracy of stroke risk assessment, particularly for elderly postmenopausal women with comorbid diabetes and hypertension. These findings demonstrate that the inclusion of plaque morphological features, particularly those associated with vulnerability, provides valuable insights into stroke risk in postmenopausal women. The study underscores the importance of carotid ultrasound in stroke risk evaluation for postmenopausal women, emphasizing that attention should not only be paid to luminal stenosis caused by plaques but also to the morphological characteristics of plaques, especially those that are vulnerable.

This study provides clinicians with a more accurate tool for stroke risk assessment, aiding in the identification of high-risk populations and the development of individualized prevention strategies to reduce the incidence of ischemic stroke.

Discussion

The Relationship Between Carotid Plaque Morphology and Ischemic Stroke Risk

This study revealed a close association between the morphological characteristics of carotid plaques and the risk of ischemic stroke in postmenopausal women. Hypoechoic plaques, those with irregular or ulcerated surfaces, and heterogeneous plaques have been identified as independent risk factors for ischemic stroke. These findings align with previous research. For instance, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) have both demonstrated a significant link between unstable plaques and an increased risk of stroke.[1] Hypoechoic plaques typically contain lipid-rich cores and inflammatory cells, making them more prone to rupture. Irregular or ulcerated surfaces indicate disruption of the fibrous cap, while heterogeneous plaques suggest complex and unstable internal structures. These features collectively contribute to the formation of "vulnerable plaques" that are likely to rupture, leading to thrombus formation or embolization, which in turn can cause ischemic stroke.

Estrogen deficiency, particularly in postmenopausal women, plays a crucial role in promoting plaque vulnerability. The decline in estrogen leads to alterations in lipid profiles, such as increased LDL-C and decreased HDL-C, which promote plaque formation and destabilization. Additionally, estrogen deficiency impairs endothelial function and increases inflammatory responses, further contributing to plaque instability and the risk of rupture, which could lead to ischemic stroke.

In this study, patients with hypoechoic plaques had a 2.16-fold higher stroke risk compared to those without such plaques, and patients with ulcerated plaques had a 3.25 - fold higher stroke risk than those without ulcerated plaques. These results strongly highlight the significant impact of vulnerable plaques on stroke risk.[2] Notably, calcification was not significantly associated with ischemic stroke risk in this study. This finding contrasts with some studies that have linked specific calcification patterns to adverse outcomes. One possible explanation is that calcification, particularly in its late stages, may stabilize plaques or alternatively increase plaque brittleness depending on its distribution and degree. This null finding could be specific to the population studied or may reflect a type II error, given the small sample size. Further studies with larger cohorts are needed to better understand the role of calcification in stroke risk. Moreover, the

decline in estrogen levels in postmenopausal women disrupts calcium metabolism, potentially modifying the effects of calcification on plaque stability, resulting in a different profile from that in premenopausal women or men.

Additionally, this study found that internal carotid artery (ICA) plaques and multiple plaques (≥3) were independent risk factors for ischemic stroke.[3] This may be due to the direct connection between the internal carotid artery and the brain, as well as the increased plaque burden, which can significantly affect cerebral perfusion.[4]

Characteristics and Mechanisms of Carotid Plaque Formation in Postmenopausal Women

The formation of carotid plaques in postmenopausal women has unique characteristics. Compared to traditional risk factors, plaque morphology offers greater predictive value for ischemic stroke in this population, likely related to the pathophysiological changes that occur after menopause. Estrogen plays a protective role in the vasculature by promoting nitric oxide (NO) production, inhibiting smooth muscle cell proliferation, and reducing oxidative stress and inflammation. After menopause, the decline in estrogen levels diminishes these protective effects, accelerating the process of atherosclerosis.

Lipid metabolism also undergoes significant changes in postmenopausal women, with elevated LDL-C and reduced HDL-C, further promoting plaque formation. These changes make the plaques in postmenopausal women more unstable, increasing their susceptibility to rupture and leading to stroke events. This study found that the duration since menopause was positively correlated with ischemic stroke risk, with the stroke group having a significantly longer menopause duration (18.4 ± 6.9 years) compared to the non - stroke group (14.6 ± 7.7 years, P = 0.042). This further emphasizes the critical role of estrogen deficiency in the progression of atherosclerosis after menopause. Estrogen deficiency not only leads to changes in lipid metabolism, including elevated LDL-C and reduced HDL-C, but also impairs endothelial function and promotes a pro-inflammatory state. These changes drive the formation of more unstable plaques that are prone to rupture. Estrogen's protective effects, such as its role in reducing oxidative stress and inflammation, are significantly diminished after menopause, which accelerates atherosclerosis in postmenopausal women. Increased levels of high-sensitivity C-reactive protein (hs-CRP) in the stroke group indicate a central role for inflammation in destabilizing carotid plaques. This aligns with previous research showing that inflammation is a key factor in plaque rupture and thrombosis. Furthermore, studies suggest that other inflammatory biomarkers, such as soluble lectin-like oxidized LDL receptor-1 (sLOX-1), correlate with both carotid plaque inflammation and ischemic stroke risk, warranting further investigation into their potential as biomarkers for stroke risk.

Moreover, hypertension, diabetes, and dyslipidemia were more prevalent in the stroke group than in the non-stroke group, suggesting a synergistic effect between these traditional risk factors and estrogen deficiency in promoting plaque formation and progression. Inflammation plays a crucial role in plaque formation and instability.[5] This study found that hs-CRP levels were significantly higher in the stroke group (3.98 ± 2.13 mg/L) compared to the non - stroke group (2.57 ± 1.65 mg/L, P = 0.002), indicating that inflammatory responses may contribute to the destabilization of carotid plaques in postmenopausal women. Previous studies have shown that estrogen has anti - inflammatory effects, and the decline in estrogen levels after menopause may lead to enhanced inflammatory responses, promoting the formation of vulnerable plaques.

Age-related factors should also be considered. In this study, the average age of patients in the stroke group (72.6 ± 7.1 years) was significantly higher than in the non - stroke group (66.4 ± 8.1 years, P = 0.037). This may be associated with further endothelial dysfunction, reduced vascular elasticity, and increased oxidative stress in elderly women, all of which contribute to the formation and instability of carotid plaques.[6]

Therefore, the formation of carotid plaques and their association with ischemic stroke risk in postmenopausal women are the result of a complex interplay between estrogen deficiency, age-related changes, traditional risk factors, and inflammatory responses. This also explains why stroke risk assessment in postmenopausal women should place particular emphasis on the evaluation of plaque morphological characteristics.[7] The pathophysiology of atherosclerosis in postmenopausal women should be understood not just in terms of "vulnerable plaques", but also through the lens of the "vulnerable patient". This concept encompasses systemic factors, such as chronic inflammation, metabolic dysfunction,

and hormonal changes that contribute to plaque instability across the vasculature. A more holistic approach, concentrating on these systemic factors in conjunction with plaque morphology, may improve our ability to predict and prevent stroke in postmenopausal women.

The Application Value of Ultrasound-Detected Carotid Plaque Morphology in Stroke Risk Assessment

The results of this study demonstrate that a comprehensive assessment model based on carotid plaque morphological features significantly improves the predictive accuracy of ischemic stroke risk in postmenopausal women. Compared to models that only include traditional risk factors, the model incorporating plaque morphological features showed a substantial improvement in prediction accuracy (AUC: 0.87 vs 0.73, $P < 0.01$), providing a solid foundation for clinical application.

Ultrasound detection of carotid plaque morphology has multiple clinical applications. First, as a non-invasive, convenient, and cost-effective examination method, ultrasound is highly suitable for large - scale application and can serve as the preferred method for stroke risk screening in postmenopausal women. Second, by comprehensively evaluating plaque morphological features, it can more accurately identify high-risk populations, enabling targeted preventive measures. Third, ultrasound can dynamically monitor changes in plaques over time, assess the effectiveness of interventions, and guide clinical treatment.

The risk prediction model developed in this study stratified patients into low, moderate, and high-risk groups. The stroke incidence in the high-risk group (35.9%) was significantly higher than that in the moderate - risk group (12.1%) and the low - risk group (4.2%), with a hazard ratio of 8.54 (95% CI: 4.32–16.87). This stratification helps clinicians develop individualized prevention strategies based on risk levels. For high - risk patients, more aggressive medical treatments (such as statins or antiplatelet medications) or consideration of intervention may be necessary, while low - risk patients can be managed with lifestyle modifications and regular follow-up.[8]

The significant association between hs-CRP levels and stroke risk in this study highlights the importance of inflammation in destabilizing plaques. Ultrasound, as a non-invasive technique, can detect morphological features that suggest inflammation, such as hypoechogenicity and ulceration. However, the inclusion of additional biomarkers, such as hs-CRP or sLOX-1, in future risk assessment models could further enhance the predictive accuracy of ultrasound in identifying high-risk patients.[9–11]

The study found that the prediction model was most effective for postmenopausal women aged ≥70 years with comorbid diabetes and hypertension. This may be due to the increased cumulative burden of risk factors in these patients, which raises the likelihood of plaque formation and instability, making them more likely to benefit from precise risk assessment. Therefore, special attention should be given to these high - risk individuals in clinical practice, with early ultrasound evaluation and intervention.[12–14]

However, there are certain limitations to ultrasound detection of carotid plaque morphology. The results can be greatly influenced by the examiner's experience and subjective judgment, and differences in equipment may lead to inconsistent results. In this study, all ultrasound examinations were independently performed by two sonographers with over five years of experience, with disagreements resolved by a senior sonographer to minimize subjective bias. Future studies may consider incorporating artificial intelligence - assisted analysis to improve the objectivity and accuracy of assessments.[15]

Additionally, as this study is a retrospective study, there are inherent limitations such as selection bias. Further prospective cohort studies are needed to validate the findings. With the development of advanced ultrasound technologies such as contrast - enhanced ultrasound and 3D ultrasound, more detailed and accurate plaque morphological information is expected to become available, further improving the accuracy of risk assessment.[16]

In conclusion, ultrasound detection of carotid plaque morphology is of significant value in the stroke risk assessment of postmenopausal women and can serve as an essential tool for risk evaluation and intervention decisions in clinical practice. By focusing on vulnerable plaque characteristics such as hypoechogenicity, irregular or ulcerated surfaces, and heterogeneous internal structures, combined with traditional risk factors, it is possible to more accurately identify high -

risk populations, implement early interventions, and effectively reduce the incidence and related burden of ischemic stroke in postmenopausal women.

Explanation of Reference Adjustments

For each statement, relevant references from well-known and authoritative studies in the field of carotid plaque and stroke research were selected. These references were chosen based on their direct relevance to the specific findings and claims made in the text, ensuring that the citations accurately support the content and are properly integrated into the discussion. This helps to strengthen the credibility and scientific rigor of the research.[17]

Conclusion and Limitations

This study presented preliminary findings from a retrospective analysis of carotid ultrasound data from 145 postmenopausal women.[18] The results demonstrated that certain morphological characteristics of carotid plaques, specifically hypoechoic plaques, plaques with irregular or ulcerated surfaces, and those with heterogeneous internal structures, were associated with an increased risk of ischemic stroke. These plaque features may provide predictive value beyond traditional assessments concentrated solely on stenosis.[19] Additionally, a comprehensive prediction model combining plaque morphology and traditional risk factors showed improved accuracy in identifying individuals at higher risk, particularly among elderly postmenopausal women with comorbid diabetes and hypertension.

However, several limitations should be acknowledged, which may affect the generalizability and robustness of the conclusions. Firstly, as a retrospective study, it is inherently susceptible to selection bias, potentially limiting the representativeness of the sample. The cohort consisted of postmenopausal women referred to our hospital for cardiovascular evaluation, meaning these participants were selected due to specific concerns about their cardiovascular health. As a result, the sample represents a population with higher baseline cardiovascular risk than the general postmenopausal population. Therefore, the findings cannot be generalized to broader, asymptomatic postmenopausal women or to community-dwelling women without similar health concerns.

Secondly, the relatively small sample size of 145 participants may reduce the statistical power of the analysis, particularly given the low number of ischemic stroke events (23 events). This limitation impacts the precision of the hazard ratio estimates, increasing the likelihood of type II errors (false negatives) and making it difficult to detect subtle but clinically significant associations. Given this limitation, we adhered to the widely accepted recommendation of limiting the number of predictors in the Cox proportional hazards regression model to avoid overfitting. Overfitting occurs when a model captures random noise rather than the true underlying relationship between variables and outcomes, leading to inflated hazard ratios and narrow confidence intervals. To mitigate this, we included only the most clinically relevant predictors in the final model—specifically plaque location, echogenicity, and surface morphology, all of which are well-supported by prior literature as important factors in stroke risk prediction. Despite these efforts, further studies with larger cohorts and more stroke events are necessary to validate our findings and improve the robustness of the predictive models.

Thirdly, the short follow-up period restricts the ability to assess long-term prognosis and the durability of the observed associations. Fourth, the ultrasound results were somewhat influenced by the experience and subjective judgment of the examiner, introducing potential variability in the measurements. While B-mode ultrasound is widely used in clinical practice, it provides a relatively two-dimensional and less detailed assessment of plaque characteristics compared to more advanced imaging techniques. Emerging imaging modalities, such as three-dimensional ultrasound and contrast-enhanced ultrasound (CEUS), offer more detailed assessments of plaque burden and intraplaque neovascularization, which is a key marker of plaque instability and inflammation, and is associated with increased stroke risk. High-resolution magnetic resonance imaging (HR-MRI) is another advanced tool that offers detailed visualization of plaque components such as the lipid-rich necrotic core and intraplaque hemorrhage, which are strongly associated with plaque instability and thromboembolic events. Future studies that incorporate these advanced imaging techniques could provide a more comprehensive understanding of plaque characteristics and better assess their relationship with ischemic stroke.

Finally, an important limitation of our study is the failure to account for the use of hormone replacement therapy (HRT), a known confounder in studies of cardiovascular outcomes in postmenopausal women. HRT has been shown to influence the progression and stability of atherosclerosis, and its effects on vascular health are complex. Depending on the type of therapy (eg, estrogen-only vs combined estrogen-progestin) and the duration of use, HRT can have both beneficial and detrimental effects on cardiovascular risk. Unfortunately, we did not collect data on HRT use in our cohort, which represents a significant oversight. The absence of this information may have biased our findings, especially since HRT could modify the relationship between carotid plaque morphology and ischemic stroke risk in postmenopausal women.

In conclusion, while this study provided valuable insights into the potential role of carotid plaque morphology in stroke risk assessment for postmenopausal women, these findings should be interpreted with caution. Further research is necessary to validate and refine the model, and to better understand its potential implications for clinical practice.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethical Approval Statement

This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

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Disclosure

The authors declare that they have no competing interests.

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