Original Article

Intraplaque neovascularization combined with plaque elasticity for predicting ipsilateral stroke in patients with asymptomatic mild carotid stenosis

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Background: Intraplaque neovascularization (IPN) is a biomarker for vulnerable atherosclerotic plaques and can be effectively visualized via contrast-enhanced ultrasound (CEUS). Plaque elasticity is influenced by elements such as lipid core and fibrosis and can be quantitatively assessed on shear wave elastography (SWE). Studies combining the use of CEUS and SWE for the assessment of stroke risk are currently lacking. Our study thus aimed to determine the predictive value of IPN combined with plaque elasticity among patients with asymptomatic carotid plaque.

Methods: Consecutive patients with mild carotid stenosis who underwent CEUS and SWE were retrospectively analyzed. IPN was graded according to the presence and location of microbubbles within the plaque, while plaque elasticity was measured in terms of mean shear wave velocity (SWV). All patients were followed up for 6 months to monitor the development of ischemic stroke. The predictive values of IPN and SWV, individually and in combination, were assessed.

Results: A total of 121 patients were included, of whom 95 (78.5%) were male. The mean age was 63.1±10.7 years. Both grade 2 IPN [hazard ratio (HR) =2.37, 95% confidence interval (CI): 1.58–9.65; P=0.039] and SWV (HR =0.43, 95% CI: 0.20–0.95; P=0.038) were independently associated with future ischemic stroke events. The combined model demonstrated a significantly better predictive performance (HR =3.243, 95% CI: 1.87–6.17; P=0.027).

Conclusions: The combination of IPN and SWV demonstrated significantly better predictive value for the risk of stroke. Our combined model thereby has the potential to guide the clinical stratification and management of patients with asymptomatic mild carotid stenosis.

Keywords: Carotid plaque; neovascularization; elasticity; stroke; ultrasound (US)

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Introduction

Carotid atherosclerosis has been shown to initiate 10–20% of transient ischemic attacks (TIAs) and ischemic strokes (1). The degree of carotid stenosis has long been the only classification criterion for assessing the risk of ischemic events. With the significant development of imaging technology over the past decades, greater attention has been paid to risk stratification based on carotid plaque vulnerability in vascular imaging; however, the identification of vulnerable plaque remains problematic, and the practicable imaging biomarkers for predicting stroke risk need to be explored and validated by clinical trials (2-4).

Ultrasound (US) is considered the first-line imaging modality in the screening of carotid plaques. Contrast-enhanced US (CEUS) and shear wave elastography (SWE) represent novel US techniques for the noninvasive assessment of plaque vulnerability. CEUS has been widely applied in the visualization of intraplaque neovascularization (IPN) (5). Neovascularization with leaky immature neovessels may increase the risk of intraplaque hemorrhage and plaque rupture, consequently leading to clinical events (6,7). SWE, which involves the use of shear wave propagation generated by acoustic radiation force impulses and the Young modulus equation, has been used for the measurement of plaque stiffness (8,9), which, in turn, can be influenced by plaque compositions such as the fibrous cap and the lipid-rich core (10,11). Both IPN and plaque elasticity have been recognized as reliable indicators of carotid plaque vulnerability (7). However, no studies have assessed the combined use of CEUS and SWE for the prediction of future ischemic strokes in patients with mild carotid stenosis, a population known to be at risk for ischemic events (12,13).

Our study thus aimed to evaluate the predictive values of IPN and plaque elasticity, both individually and in combination, for the development of ischemic stroke in patients with asymptomatic mild carotid stenosis. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-202/rc).

Methods

Study design and patient selection

Consecutive patients with asymptomatic carotid plaques who underwent CEUS and SWE between November 2021 and December 2022 were retrospectively included in our study. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the local ethics committee of Shanghai General Hospital (No. [2022]028). Informed consent was obtained from all participants.

The inclusion criteria were as follows: (I) at least one atherosclerotic plaque in the carotid artery, with the longitudinal thickness of carotid plaque ≥2 mm; (II) the absence of ischemic lesions in the ipsilateral carotid territory as confirmed by computed topography (CT) or magnetic resonance imaging (MRI); and (III) mild carotid artery stenosis (lumen stenosis <50%) according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (14,15). Meanwhile, the exclusion criteria were the following: (I) involvement in other thromboembolic sources (e.g., vasculitis, fibrillation, and intracranial embolus), (II) poor image quality due to fragmented and severely calcified plaques and incomplete clinical data, (III) prior neck irradiation or ipsilateral carotid surgery/stenting, and (IV) patients lost to follow-up or with a life expectancy <1 year.

Clinical variables

The following variables were collected: (I) demographic data such as age, gender, and body mass index (BMI); (II) smoking history; (III) medical history, including hypertension, diabetes mellitus, and hyperlipidemia; and (IV) statin use history.

Standard US protocols

All standard US, CEUS, and SWE examinations were performed on an EPIQ Elite scanner (Phillips, Amsterdam, the Netherlands) with an L12–3 and L14–3 linear-array transducer probe. All examinations were performed by radiologists with more than 5 years of experience in vascular ultrasonography who were blinded to the clinical history of patients. The common carotid artery, carotid bifurcation, and internal carotid artery were examined in the longitudinal and transverse planes. All plaques were assessed in the longitudinal view.

Carotid plaques were defined as carotid arterial intima-media thickness ≥1.5 mm. The percent stenosis was calculated based on the NASCET criteria, which divided the residual luminal diameter by the luminal diameter of a distal portion of the same vessel (14,15). If the patient had more than one plaque, the thickest plaque was selected as the target plaque.

CEUS examination and IPN grading

CEUS imaging was initiated with a 1.2-mL bolus injection of SonoVue (Bracco, Milan, Italy) into the median cubital vein, followed by a 5-mL saline flush at a rate of 1–2 mL/s. The mechanical index was adjusted to <0.1, while the settings for depth, gain, and compression rate were adjusted to achieve optimal imaging quality. Cine loops of at least 2 minutes were recorded for subsequent offline analysis.

Carotid IPN was assessed semiquantitatively and was graded according to the presence and location of microbubbles within the plaque. The categories were as follows: grade 0, no visible microbubbles within the plaque; grade 1, microbubbles confined within the shoulder or adventitial side of the plaque; and grade 2, extensive intraplaque enhancement with microbubbles flowing into the plaque core (16). A plaque with the contrast agent flowing from the lumen invading into the plaque was classified as grade 2. Representative SWE images are shown in *Figure 1A-1C*. For subsequent comparative analyses, patients were classified into the grades 0–1 or grade 2 IPN groups according to previous studies (17-19).

SWE examination and quantitative analysis

SWE examination was performed in the longitudinal view for the target plaque, the probe was held with only slight contact to the skin to minimize compression artifacts, and the sampling box was adjusted to cover the target plaque. The region of interest (ROI) for SWE measurement was created using the trace tool to precisely delineate the plaque, and shear wave velocity (SWV) was displayed on the screen, which was quantified using built-in software. The reliability of the reported SWV values were ensured by the radiologists. For each plaque, the ROI was drawn three times continuously, and the mean SWV value was recorded. Representative SWE images are shown in *Figure 1D,1E*.

Primary outcome and follow-up

The primary outcome was a new ischemic anterior circulation lesion ipsilateral to the target carotid plaque confirmed by CT or MRI. Patients were followed up for a period of 12 months or until the development of cerebrovascular events during the follow-up period (20).

Statistical analysis

All statistical analyses were performed using R software version 4.1.3 (The R Foundation for Statistical Computing) and SPSS 26.0 (IBM Corp., Armonk, NY, USA). Categorical and continuous variables are expressed as the mean ± standard deviation (SD) and as the frequency (%), respectively.

The associations of IPN, SWV, and clinical parameters with the primary outcome were identified using univariate and multivariate logistic regression analyses, with outcomes expressed as the odds ratio (OR) and 95% confidence interval (CI). Independent predictors of ischemic stroke were identified using Cox proportional hazards regression modeling, with outcomes expressed as the hazard ratio (HR) and 95% CI. The cumulative incidence of stroke was evaluated using the Kaplan-Meier and log-rank test. The predictive values of IPN and SWV, individually and in combination, were assessed using the receiver operating characteristic (ROC) analysis in terms of the area under the curve (AUC). The AUCs were then compared using the Delong method. For all statistical analyses, a P value <0.05 was considered to indicate statistical significance.

Interobserver consistency in IPN grading and SWV image postprocessing were performed by two independent radiologists (S.G. and L.Z.) who were blinded to each other's interpretation, with any disagreements being resolved by engaging a third expert (C.J.) with more than 10 years of experience in vascular ultrasonography. To evaluate intraobserver consistency, data were reanalyzed by the same radiologist (L.Z.) after an interval of 1 month without reference to the initial results.

Results

Patient characteristics

The patient selection process is shown in *Figure 2*. Among the 152 participants with carotid plaque who underwent CEUS and SWE examinations, 31 were excluded due to plaque <2 mm (n=4), carotid stenosis ≥50% (n=14), poor image quality (n=5), and incomplete clinical data (n=8). A total of 121 participants were eventually enrolled, among whom 95 (78.5%) were male. The mean age was 63.1±10.7 years, and the mean BMI was 24.1±2.8 kg/m^2. In terms of past medical history, 32 (26.4%) had diabetes, 62 (51.2%) had hypertension, and 63 (52.1%) had hyperlipidemia. A history of smoking was observed in 62 (51.2%) patients and a history of statin use in 59 (48.8%) patients. The baseline characteristics of all patients are summarized in *Table 1*.

Carotid IPN grades 0–1 and grade 2 were observed in 79 (65.3%) and 42 (34.7%) patients, respectively. Compared

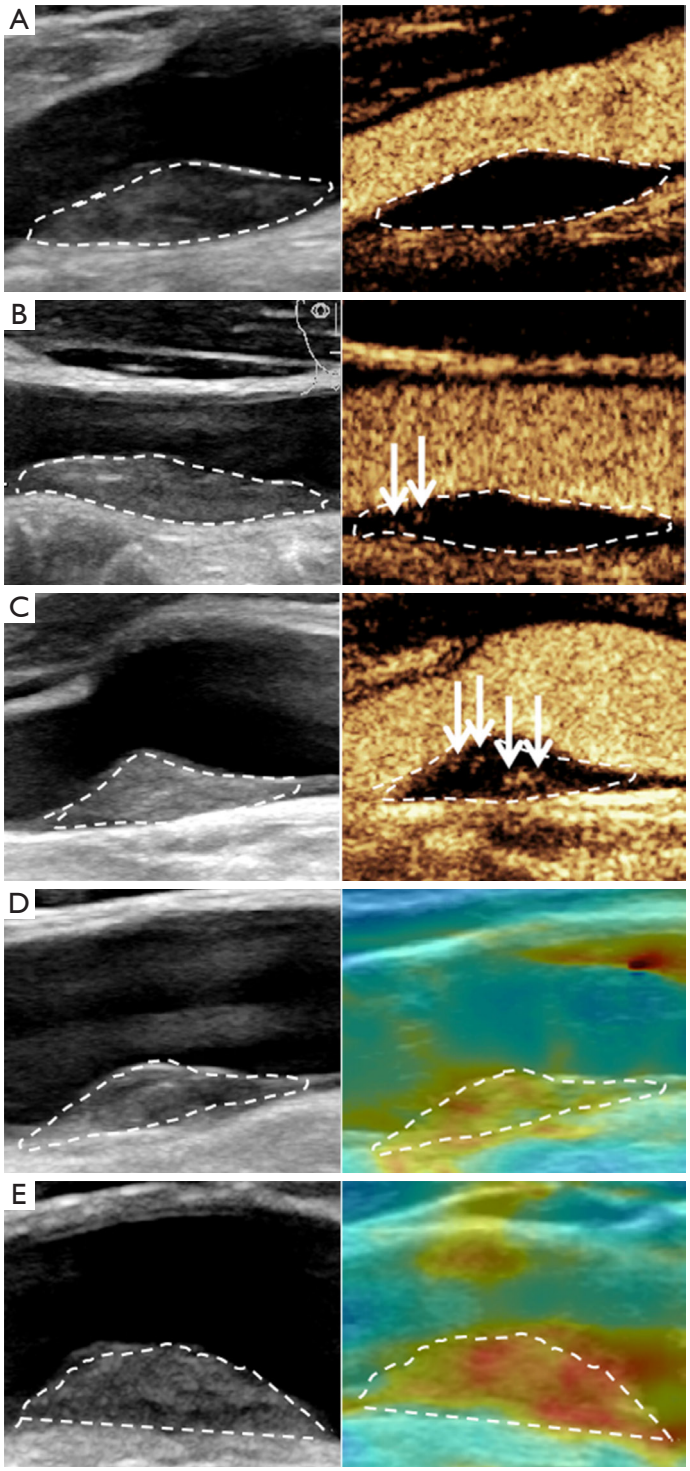

Figure 1 CEUS and SWE images of IPN grades and plaque elasticity. (A) Grade 0 IPN, (B) grade 1 IPN, (C) grade 2 IPN, (D) soft plaque, and (E) hard plaque. The white dotted lines represent the plaque margins. The white arrows represent intraplaque neovascularization. CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography; IPN, intraplaque neovascularization.

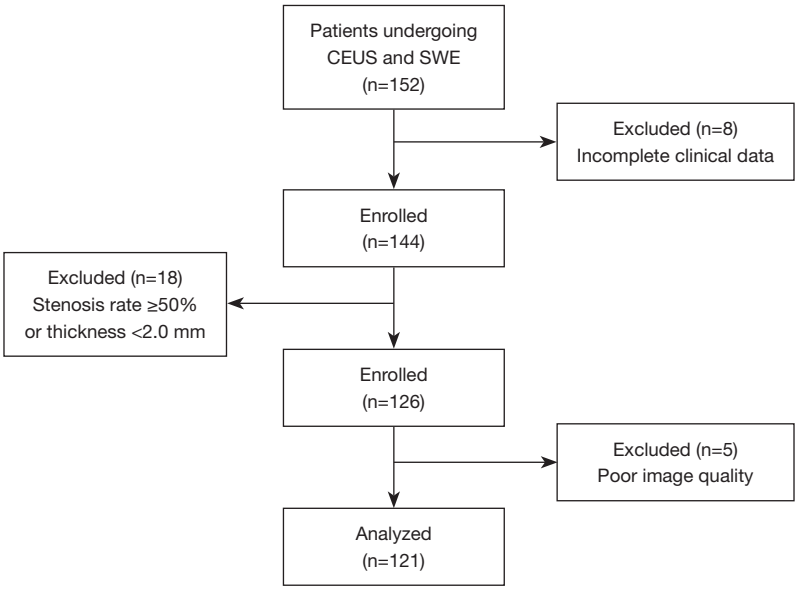

Figure 2 Flowchart of the study population. CEUS, contrast-enhanced ultrasound; SWE, shear wave elastography.

Table 1 Baseline clinical characteristics of patients based on IPN grade

Characteristic	Total (n=121)	IPN		P
		Grades 0–1 (n=79)	Grade 2 (n=42)	
Male, n (%)	95 (78.5)	60 (75.9)	35 (83.3)	0.349
Age (years), mean ± SD	63.1±10.7	61.7±11.1	65.8±9.5	0.001*
BMI (kg/m^2), mean ± SD	24.1±2.8	24.4±2.9	23.7±2.5	0.212
Smoking history, n (%)	62 (51.2)	34 (43.0)	28 (66.7)	0.015*
Medical history, n (%)				
Hypertension	62 (51.2)	41 (51.9)	21 (50.0)	0.842
Diabetes	32 (26.4)	22 (27.8)	10 (23.8)	0.632
Hyperlipidemia	63 (52.1)	41 (51.9)	22 (52.4)	0.960
Statin use, n (%)	59 (48.8)	36 (45.6)	23 (54.8)	0.316

*, P<0.05. IPN, intraplaque neovascularization; SD, standard deviation; BMI, body mass index.

with the grades 0–1 IPN group, the group with grade 2 IPN was significantly older (65.8±9.5 *vs.* 61.7±11.1 years; P=0.001) and had a greater portion of patients with a history of smoking (66.7% *vs.* 43.0%; P=0.015) (*Table 1*). No significant differences in gender, BMI, medical history, or statin use were observed between the two groups (all P values >0.05).

Predictors of ischemic stroke

Ischemic stroke events were reported in 7 patients during the follow-up period. Among them, the rates of grades 0–1 and grade 2 IPN were 1.3% (n=1/79) and 14.3% (n=6/42), respectively.

The univariate and multivariate analysis results are shown in *Table 2*. Among all potential factors included in the univariate analysis, grade 2 carotid IPN and SWV value were significantly associated with the risk of ischemic stroke (P=0.034 and P=0.004, respectively). The association of both grade 2 IPN (HR =2.37, 95% CI: 1.58–9.65; P=0.039) and SWV value (HR =0.43, 95% CI: 0.20–0.95; P=0.038)

Table 2 Predictors of ischemic stroke

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Male	0.29	0.07–1.32	0.111	–	–	–
Age	1.04	0.97–1.13	0.265	–	–	–
BMI	1.02	0.78–1.33	0.895	–	–	–
Hypertension	0.374	0.07–1.93	0.239	–	–	–
Diabetes	0.42	0.05–3.48	0.421	–	–	–
Hyperlipidemia	1.12	0.25–5.00	0.882	–	–	–
Smoking history	1.16	0.26–5.20	0.844	–	–	–
SWV	0.32	0.15–0.69	0.004*	0.43	0.20–0.95	0.038*
Grade 2 IPN	1.83	1.18–8.68	0.034*	2.37	1.58–9.65	0.039*

*, P<0.05. HR, hazard ratio; CI, confidence interval; BMI, body mass index; SWV, shear wave velocity; IPN, intraplaque neovascularization.

Table 3 Multivariable logistic regression analysis results for future stroke

Model	B	OR (95% CI)	P
IPN	1.935	3.93 (1.23–6.58)	0.034*
SWV	–0.937	0.39 (0.16–0.98)	0.045*

*, P<0.05. OR, odds ratio; CI, confidence interval; IPN, intraplaque neovascularization; SWV, shear wave velocity.

with the risk of ischemic stroke remained statistically significant on multivariate analysis.

Prediction of ischemic stroke by IPN, SWV, and the combined model

The multivariate logistic regression analysis results for future stroke are shown in *Table 3*. The risk of stroke was significantly associated with IPN (OR =3.93; 95% CI: 1.23–6.58; P=0.034) and SWV (OR =0.39; 95% CI: 0.16-0.98; P=0.045). The Kaplan-Meier results for grade 2 carotid IPN and the combined model (IPN and SWV) are shown in *Figure 3*. Results of the ROC curve analysis are shown in *Table 4*. AUC values of 0.772, 0.784, and 0.863 were demonstrated for IPN, SWV, and the combined model, respectively. Based on the DeLong test, the combined model demonstrated significantly better predictive performance compared to IPN alone (P=0.036). However, no significant difference was shown between the combined model and SWV alone (P>0.05).

Risk stratification with the combined model

For the combined model, the optimal cutoff value with maximum Youden index on the ROC curve for the prediction of stroke was found to be –3.69. Accordingly, patients with a score of ≤–3.69 and those with a core of >–3.69 were classified as low and high risk, respectively. High-risk patients were found to be significantly associated with the risk of ischemic stroke (HR =3.243, 95% CI: 1.87–6.17; P=0.027). In addition, significant differences in AUC were observed between low- and high-risk patients (P=0.030), as illustrated in *Figure 4*.

Reproducibility of IPN and SWV analyses

Satisfactory reproducibility was observed in our analyses. The intra- and interobserver consistencies for IPN grade were 0.88 (95% CI: 0.80–0.94; P=0.010) and 0.85 (95% CI: 0.79–0.91; P=0.008), respectively, while those for SWV images postprocessing were 0.92 (95% CI: 0.86–0.97; P=0.005) and 0.90 (95% CI: 0.83–0.96; P=0.007), respectively.

Discussion

To our knowledge, our study is the first to assess the combined predictive value of IPN and SWV for the risk of future ischemic stroke. Our findings confirmed that while both parameters were independently associated with future ischemic stroke, their combined use was significantly more predictive. Importantly, our study demonstrated the

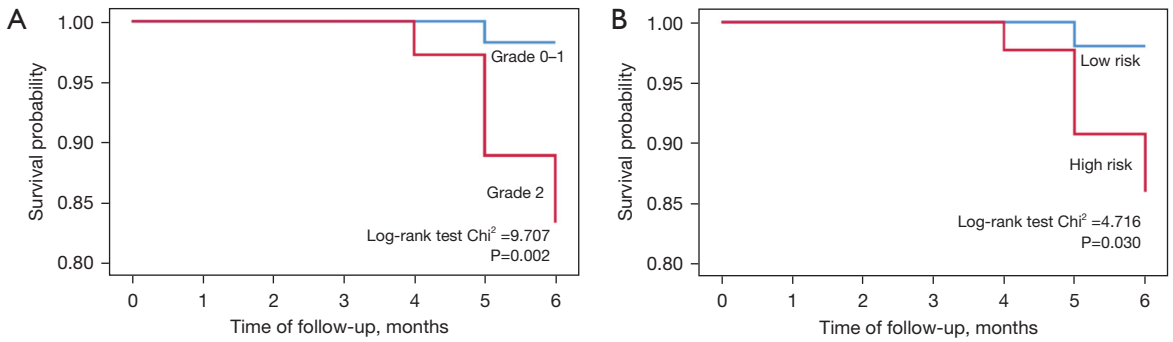

Figure 3 Kaplan-Meier survival curves for IPN grade and the combined model. (A) The Kaplan-Meier results for grade 2 carotid IPN. (B) The Kaplan-Meier results for the combined model (IPN and SWV). IPN, intraplaque neovascularization; SWV, shear wave velocity.

Table 4 ROC analysis results of IPN, SWV, and the combined model

Model	AUC	95% CI	P
IPN	0.772	0.601–0.971	0.036*
SWV	0.784	0.608–0.934	0.365
Combined model	0.863	0.752–0.971	–

*, P<0.05. ROC, receiver operating characteristic; IPN, intraplaque neovascularization; SWV, shear wave velocity; AUC, area under the curve; CI, confidence interval.

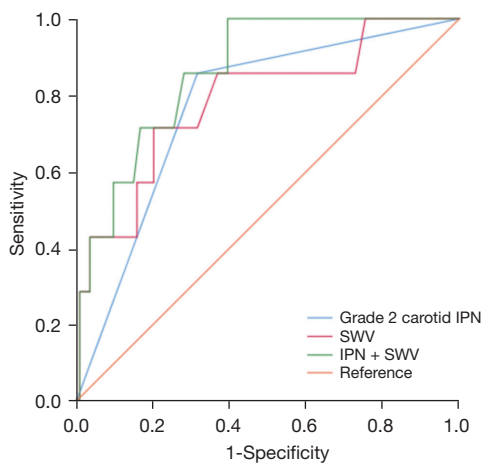

Figure 4 Receiver operating characteristic curves for the predictive performance of IPN, SWV, and the combined model. IPN, intraplaque neovascularization; SWV, shear wave velocity.

feasibility of predicting the development of ischemic stroke events based on CEUS and SWE measurements of carotid plaque neovascularization and elasticity among patients with asymptomatic mild carotid stenosis.

Over the years, IPN has been identified as a marker of vulnerable plaque and is associated with microvascular leakage and thereby potentially contributes to plaque hemorrhage and progression (6). As reported in the literature, in patients with symptomatic carotid stenosis, IPN is an independent risk factor and predictor of ischemic stroke recurrence (18). However, few studies have reported the predictive value of carotid IPN for vascular events in patients with asymptomatic carotid stenosis. In this study, we found that IPN detected by CEUS imaging remained an independent predictor of ischemic stroke among patients with asymptomatic mild carotid stenosis after confounders were adjusted for in the Cox regression multivariate analysis. A previous study of 70 patients with asymptomatic mild-to-severe carotid stenosis also found that the grade 2 carotid IPN group had a higher probability of future vascular events than did the grades 0–1 group (17).

The novel SWE imaging technique involves using shear waves propagating through tissues via impulses of acoustic radiation force to quantitatively measure plaque stiffness using the Young modulus (8,9). The regions with vulnerable compositions demonstrate a lower SWV value; moreover, the SWV value is significantly lower in symptomatic plaque than in asymptomatic plaque (10,11). Our results have extended this knowledge by demonstrating SWV value to be an independent predictor of future stroke events, confirming that SWV measured on SWE examination has the ability to be a noninvasive imaging biomarker for the prediction of ischemic stroke.

Our study is the first to establish a combined prediction model involving IPN and SWV for carotid-related ischemic stroke. Although previous studies reported a negative correlation between IPN grade and plaque elasticity (21,22), we found that the combination of both factors was not

only significantly associated with the risk of stroke but also demonstrated the potential ability to stratify patients. Altogether, our findings suggest that a combined model for plaque vulnerability may be more accurate than a single parameter in predicting future stroke events. Moreover, our proposed risk prediction approach is clinically advantageous due to its ability to provide superior results while necessitating the use of only a single US device despite the involvement of two distinctive imaging techniques.

This was a preliminary observational study that examined a short-term follow up period, and a large-sample cohort study with long-term follow-up will be carried out to explore additional imaging biomarkers from a variety of ultrasound techniques that may be useful for risk stratification. In the future, the assessment of IPN grade and plaque elasticity for identifying vulnerable carotid plaque will not only help predict ischemic stroke and improve the stratification of cardiovascular risk but also measure the benefit of medical treatment.

This study involved several limitations that should be addressed. First, we employed a single-center, single-device design. Second, plaques of <2.0 mm and those with calcifications were excluded from our study due to insufficient resolution of CEUS and SWE images, which limit the generalizability of our results. Third, CEUS and SWE were performed only in the longitudinal view, and this two-dimensional approximation might have resulted in an underestimation of the true vulnerability of the plaques involved in our study. Finally, the technical limitations of SWE need to be considered, as a simple Young modulus equation may not be well-suited for plaques that are anisotropic in nature (23).

Conclusions

The combined assessment of IPN and elasticity of carotid plaques can provide an improved predictive performance of future stroke events and thus holds promise for guiding the clinical management of patients with asymptomatic mild carotid stenosis.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-202/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-202/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the local ethics committee of Shanghai General Hospital (No. [2022]028). Informed consent was obtained from all participants.

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