Diagnostic Utility of Combined 2D Ultrasonography and Contrast-Enhanced Ultrasonography in Evaluation of Carotid Plaque Vulnerability for Predicting Recurrent Ischemic Strokes

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Research Article

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Abstract

Objective: To evaluate the sensitivity and specificity of combined 2D ultrasonography (USG) and contrast-enhanced ultrasonography (CEUS) in analyzing the carotid plaque vulnerability for predicting the recurrent ischemic strokes (IS).

Methods: One hundred and fifteen patients with first IS were studied by 2D USG and CEUS. The carotid plaques were then classified on the basis of echogenicity (2D USG) and neovascularization (CEUS). The presence or absence of recurrent IS was considered as the dependent variable. Age, gender, body mass index (BMI), hypertension, hyperglycemia, hyperlipidemia, history of smoking and drinking, type of plaque echogenicity, and grade of plaque neovascularization were considered as independent variables. The risk factors of recurrent IS were analyzed by both univariate and multivariate logistic regression analysis. Finally, the sensitivity and specificity of combined 2D USG and CEUS in the diagnosis of recurrent IS was evaluated by receiver operating characteristic curve.

Results: Univariate logistic regression analysis revealed that hypertension, echogenicity type, and grade of plaque neovascularization were predictors of recurrent IS. Further, multivariate logistic regression analysis revealed that the echogenicity type ($OR=0.282$, $P=0.012$) and grade of plaque neovascularization ($OR=7.408$, $P<0.0001$) were independent risk factors for recurrent IS. The sensitivity, specificity, and area under the curve of combined method were 0.865, 0.769, and 0.817, respectively (95%CI: 0.733-0.902, $P<0.0001$), which were higher than both 2D USG and CEUS.

Conclusions: The echogenicity type and grade of plaque neovascularization are independent risk factors for recurrent IS. The combination of two methods has high sensitivity and specificity in predicting the recurrent IS.

1 | Introduction

Amongst strokes, ischemic type is most frequently observed and accounts for 70–80% of the total cases [1]. Ischemic stroke (IS) is characterized by high rates of incidence, disability, and recurrence. Previous studies evaluating cerebral infarcts have demonstrated a one-year recurrence rate of 32% [2]. Thus, the prognosis of patients with IS can be significantly improved by effective prevention of recurrent cerebral infarcts.

Carotid atherosclerotic plaque has been identified as an independent risk factor for IS [3]. Histopathological studies have demonstrated that plaque neovascularization is a marker of plaque vulnerability [4]. Moreover, several researchers have reported that plaque neovascularization is linked to high risk characteristics of plaque [5, 6]. Therefore, early identification of plaque neovascularization and evaluation of its vulnerability are of great value in clinical prevention of recurrent strokes.

Conventional ultrasonography (CUS) is the most commonly employed imaging method for examination of carotid plaques and can evaluate plaque stability on the basis of echogenicity, shape, size, and integrity of fibrous cap. However, it cannot detect neovascularization in plaques. Contrast enhanced ultrasonography (CEUS) is a novel method to evaluate the stability of carotid plaques. It not only identifies the plaque neovascularization in real time, but can also quantitatively evaluate its density [7].

In the past, CUS or CEUS was used to evaluate the vulnerability of plaque. However, their combined ability to improve the predictive value of recurrent cerebral infarcts has not been clarified. Thus, the aim of the present study was to assess the combined sensitivity and specificity of two dimensional (2D) ultrasonography (USG) and CEUS for evaluation of carotid plaques in predicting the recurrence of IS.

2 | Materials And Methods

2.1 | Patients

One hundred and fifteen cases, including 76 males and 39 females, with acute stroke, hospitalized in the Department of Neurology, Gaozhou People's Hospital between January 2020 and March 2021 were included in the study. The age of the study population ranged from 47 to 91 years, with a mean age of 70.0±10.1 years. In all the patients, computed tomography (CT) or magnetic resonance imaging (MRI) was used to arrive at the diagnosis of atherosclerotic cerebral infarcts. In a calm state, the systolic (SBP) and diastolic (DBP) blood pressure of brachial artery were assessed thrice and the mean values were calculated. In the morning, fasting state venous blood sample (3ml) was collected to evaluate the fasting blood glucose, and lipid profile.

The cases belonging to an age group of 18 years or more, with an initial stroke involving carotid artery territory confirmed by MRI or CT, an ultrasonography demonstrating plaques in carotid artery with a size of 2 mm or more, and those willing to follow-up for 15 months were included in the study. While, cases allergic to sulfur hexafluoride, and with contraindication to CEUS were excluded [8, 9]. Moreover, to exclude the influence of stenosis, patients with severe stenosis (70% or more, according to NASCET) of carotid artery were not included. The present study focused on the vulnerability of carotid plaques and the recurrence of cerebral infarct was the end point of the study.

The study protocol was reviewed and approved by the Ethics Review Committee, Gaozhou People's Hospital. As per the requirements of the National Legislation and Institutions, the written informed consent from the patients was not required.

2.2 Instruments and Methods

2.2.1 Instruments CEUS of the carotid plaque was performed with Esaote MyLab Class C scanner (MyLabClassC Advanced, Esaote, Genova, Italy), equipped with a 12-18 MHz linear transducer.

2.2.2 Ultrasonographic examination The common carotid, internal carotid, external carotid, and vertebral arteries were examined by 2D USG. The stenosis of carotid artery, and the number and distribution of carotid plaques were noted. The thickest carotid plaque was identified and evaluated. The same plaque was studied by both 2D USG and CEUS. The CEUS examination was performed following a bolus injection of SonoVue (Bracco, Milan, Italy). Dynamic images were continuously collected for further offline analysis.

2.2.3 Grading of plaques The plaque echogenicity was interpreted by visual analysis on 2D USG and classified into following 5 types: Type 1 (Uniformly anechoic plaque), Type 2 (Predominantly hypoechoic or anechoic plaque), Type 3 (Predominantly echoic or isoechoic plaque), Type 4 (Uniformly isoechoic or uniformly hyperechoic), and Type 5 (Unclassified calcified plaque) [8, 10]. Obvious hyperechoic (part of Type 4) and calcified plaques (Type 5) which didn`t show contrast were excluded from the present study.

CEUS was used to grade the neovascularization of carotid artery plaques and included four grades as follows: Grade 0 (no enhancement of plaques, denoting absence of plaque neovascularization), Grade 1 (Several punctate enhancements within adventitia or tissue surrounding the plaque suggesting limited presence of plaque neovascularization), Grade 2 (Adventitia or shoulder of the plaque was enhanced, suggesting moderate neovascularization, less neovascularization than Grade 3 but more than Grade 1), and Grade 3 (Diffuse enhancement within the plaque suggesting the presence of a pulsatile artery within the plaque) [11].

2.3 Statistical analysis

The continuous data with normal distribution was represented in terms of as mean ± standard deviation (SD), while categorical data was represented in terms of frequency (percentage). The continuous and categorical data were compared with Student's t-test and Chi-Square or Fisher’s exact test, respectively. Univariate and multivariate logistic regression analysis was used to determine the independent risk factors of recurrent cerebral infarcts. Presence or absence of recurrent cerebral infarct was used as a binary dependent variable. The receiver operating characteristic (ROC) curve was used to evaluate the sensitivity and specificity of independent risk factors in predicting the recurrent cerebral infarcts. The data was analysed with SPSS (IBM, Armonk, NY, USA) version 23.0 for windows. A probability (P) of less than 0.05 was considered as statistically significant.

3 | Results

The present study involved 115 cases with acute IS, of which 37 (32.2%) had recurrent IS during the study period.

Comparison of characteristics between recurrent (n = 37) and non-recurrent (n = 78) groups revealed no significant difference between them in terms of mean age, gender, body mass index (BMI), DBP, fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), and high density lipoprotein-cholesterol (HDL-C) (all P>0.05), except SBP (P = 0.039) (Table 1).

Univariate logistic regression analysis revealed that hypertension (Odd’s ratio (OR) = 0.371, 95% confidence interval (CI): 0.163 – 0.843; P = 0.018), type of echogenicity on 2D USG (OR = 0.247, 95%CI: 0.143 – 0.427; P < 0.0001), and grade of carotid artery plaque neovascularization on CEUS (OR = 10.346, 95%CI: 4.335 – 24.692) were predictors of recurrent IS (Table 2). Further analysis by multivariate logistic regression analysis revealed that type of echogenicity (OR = 0.282, 95%CI: 0.105 – 0.756; P = 0.012) and the grade of carotid artery plaque neovascularization (OR = 7.408, 95%CI: 2.952 – 18.593; P < 0.0001) were markers of recurrent cerebral infarcts (Table 3).

Analysis by ROC curve demonstrated that the sensitivity, specificity, and area under the curve (AUC) for predicting the recurrent cerebral infarcts with Type 1 and 2 echogenicity (maximum Youden index: 0.409) were 0.730, 0.679, and 0.705 (95% CI: 0.602-0.807; P < 0.0001), respectively. The corresponding values for CEUS Grade 2 or more (maximum Youden index: 0.474) were 0.730, 0.744, and 0.737 (95% CI: 0.636-0.837, P < 0.0001), respectively. Similarly, the corresponding values for the combination of 2D USG and CEUS (maximum Youden index 0.634) were 0.865, 0.769, and 0.817 (95% CI: 0.733-0.902, P < 0.0001), respectively (Images 1, 2).

4 | Discussion

The present study suggest that the type of echogenicity and grade of carotid artery plaque neovascularization were independent risk factors for recurrent IS. The combination of 2D USG and CEUS was found to have a good sensitivity and specificity for predicting the recurrent cerebral infarcts.

At present, there are many known risk factors of recurrent cerebral infarcts. Amongst them, age, gender, hypertension, diabetes, hyperlipidemia, and history of smoking have been confirmed to be closely associated with recurrent cerebral infarcts [12, 13]. Previous studies have demonstrated that this association is mainly due to the fact that these risk factors have the ability to cause the progression of atherosclerosis and further lead to recurrent cerebral infarcts [14].

Contrarily, the present study demonstrated no significant difference between the recurrent and non-recurrent groups in terms of mean age, gender, BMI, diabetes, and hyperlipidemia. Thus, it may be suggested that the above risk factors have little value in predicting the recurrent cerebral infarcts. Moreover, these risk factors may be of value in increasing the chances and triggering the events leading to cerebral infarcts. However, they may not have any role in promoting their recurrence. The only risk factor with significant difference between the groups was systolic hypertension. Thus, poorly controlled SBP might have resulted in altered structure of carotid artery wall and induced recurrent IS [13].

In the present study, univariate and multivariate logistic regression analysis demonstrated that grade of carotid plaque echogenicity was an independent predictor of recurrent cerebral infarcts. In ROC curve analysis, the AUC was 0.705 (95%CI: 0.602–0.807; P = 0.000) for predicting recurrent cerebral infarcts with Type 1 and 2 echogenicity. This finding is consistent with the previous study [15].

The echogenicity of carotid plaques on 2D USG is an indirect parameter reflecting their vulnerability. Previous studies have confirmed that the echogenicity of carotid plaque is closely associated with the recurrent cerebral infarcts [16]. The highly vulnerable plaques rich in lipid or those having internal bleeding are mostly hypoechoic, while the less vulnerable plaques rich in fibrous tissue are more hyperechoic [16]. However, the degree of plaque vulnerability cannot be accurately reflected. Intraplaque neovascularization is closely related to intraplaque hemorrhage, which is the main cause of IS [16–19]. CEUS can accurately reflect the neovascularization in carotid plaques and is an effective parameter to directly reflect their vulnerability [4, 20]. CEUS can not only result in significantly improved imaging of blood flow and vascular wall, but also depict microvasculature. Moreover, even a single microbubble can be displayed at the capillary level [21]. For homogeneous fibrous tissue and mixed plaques, CEUS can also accurately evaluate their vulnerability [22]. The guidelines and recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) have clearly proposed that CEUS can evaluate the stability of carotid plaques by detecting neovascularization [7].

In addition to the plaque neovascularization, CEUS can also detect ulceration on the surface of carotid plaques, and accurately display the shape, size, depth, and other characteristics of ulceration [23, 24].

In the present study, CEUS had better sensitivity and specificity than 2D USG in predicting recurrent cerebral infarcts. It was found to be an independent risk predictor and closely associated with the recurrent cerebral infarcts. In multivariate logistic regression analysis, the OR of ECUS in predicting recurrent IS was much higher than that of 2D USG (7.408 vs 0.282). This could be due to the exclusion of hyperechoic and calcified plaques.

However, in some cases, such as those with fresh thrombosis-associated carotid plaque, or vulnerable plaques without neovascularization, the reference value of 2D USG was greater than that of CEUS. The combination and cross reference of the both the methods can greatly improve the accuracy of diagnosis. The present study combined the two techniques to evaluate the carotid plaques, and provided a more reliable basis for judging their stability. The ROC curve analysis of the combined method resulted in an AUC of 0.817 (95%CI: 0.733–0.902; $P < 0.0001$), which was larger than that of 2D USG (AUC = 0.705; 95%CI: 0.602–0.807; $P = 0.000$) and CEUS (AUC = 0.737; 95%CI: 0.636–0.837; $P < 0.0001$).

5 | Limitations

In the present study, the thickest plaque rather than plaque which caused the recurrence of IS was evaluated. However, previous studies have reported that the stability of the largest plaque is significantly related to the occurrence of cerebral infarcts [25, 26]. Moreover, the present study was retrospective in nature and whether the conclusions drawn hold the same significance in the prospective study needs to be evaluated further.

6 | Conclusion

The 2D USG-based echogenicity classification and CEUS-based grade of carotid plaque neovascularization were found to be the independent risk factors for recurrence of IS. The combination of the two methods had high sensitivity and specificity in predicting the recurrence of IS, which has clinical importance.

Declarations

Availability of data and materials

The regarding raw data and material of this manuscript can be available through the corresponding author by drleaf@sina.com if required.

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Contributions

Fuyong Ye and Yuwen Yang enrolled patients, directed the researches, carried out statistical analysis, and wrote the manuscript. Xiaofang Li, Fei Lin and Yinting Liang acquired and analyzed echocardiographic images. Jianhua Liu conceived, instructed, reviewed, and revised the manuscript. All authors read and approved the final manuscript.

Ethics declarations

The study protocol was approved by the ethics committee of Gaozhou People's Hospital (Guangdong, China). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

None.

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Tables

Table 1. Characteristics of Two Groups

Characteristic	Recurrent group (n=37)	Non- recurrent group (n=78)	t/X^2 value	p value
Age(y)	69.5±10.4	70.2±10.0	-0.303	0.762
Male gender	26 (70.3%)	50 (64.1%)	0.426	0.514
BMI (KG/M2)	23.9±2.5	23.0±3.0	0.301	0.764
SBP (mmHg)	138.6±17.5	133.8±15.6	2.084	0.039
DBP (mmHg)	84.4±9.6	82.1±8.9	-0.445	0.657
FPG (mmol/L)	6.55±1.77	6.07±1.60	1.650	0.102
TC (mmol/L)	4.66±1.30	4.29±1.03	1.469	0.145
TG (mmol/L)	1.62±0.88	1.39±1.01	-1.008	0.316
HDL-C (mmol/L)	1.12±0.69	1.24±0.71	-0.482	0.631

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol.

Table 2. Univariate Logistic Regression Analysis of Predictors of Recurrence Risk of Ischemic Stroke

Parameter	B	SE.	Wals	*P*	OR (95% CI)
Age	-0.006	0.020	0.093	0.760	0.994 (0.956~1.033)
Gender	-0.280	0.430	0.425	0.515	0.755 (0.325~1.756)
BMI	0.020	0.067	0.092	0.762	1.021 (0.895~1.164)
Hypertension	-0.992	0.419	5.606	0.018	0.371 (0.163~0.843)
Hyperglycemia	-0.727	0.419	3.012	0.083	0.484 (0.213~1.099)
Hyperlipidemia	-0.323	0.402	0.647	0.421	0.724 (0.329~1.591)
History of drinking	0.735	0.435	2.859	0.091	2.086 (0.890~4.893)
History of smoking	-0.148	0.402	0.135	0.713	0.863 (0.393~1.896)
2D ultrasound	-1.398	0.279	25.071	0.000	0.247 (0.143~0.427)
CEUS	2.337	0.444	27.713	0.000	10.346 (4.335~24.692)

2D, two dimension; CEUS, contrast enhanced ultrasound

Table 3. Multivariate Logistic Regression Analysis of Predictors of Recurrence Risk of Ischemic Stroke

Parameter	B	SE.	Wals	*P*	OR (95% CI)
Hypertension	-0.278	0.542	0.262	0.609	0.758 (0.262~2.192)
2D ultrasound	-1.266	0.503	6.336	0.012	0.282 (0.105~0.756)
CEUS	2.003	0.469	18.196	0.000	7.408 (2.952~18.593)
Constant	-1.752	1.135	2.384	0.123	0.173

Figures

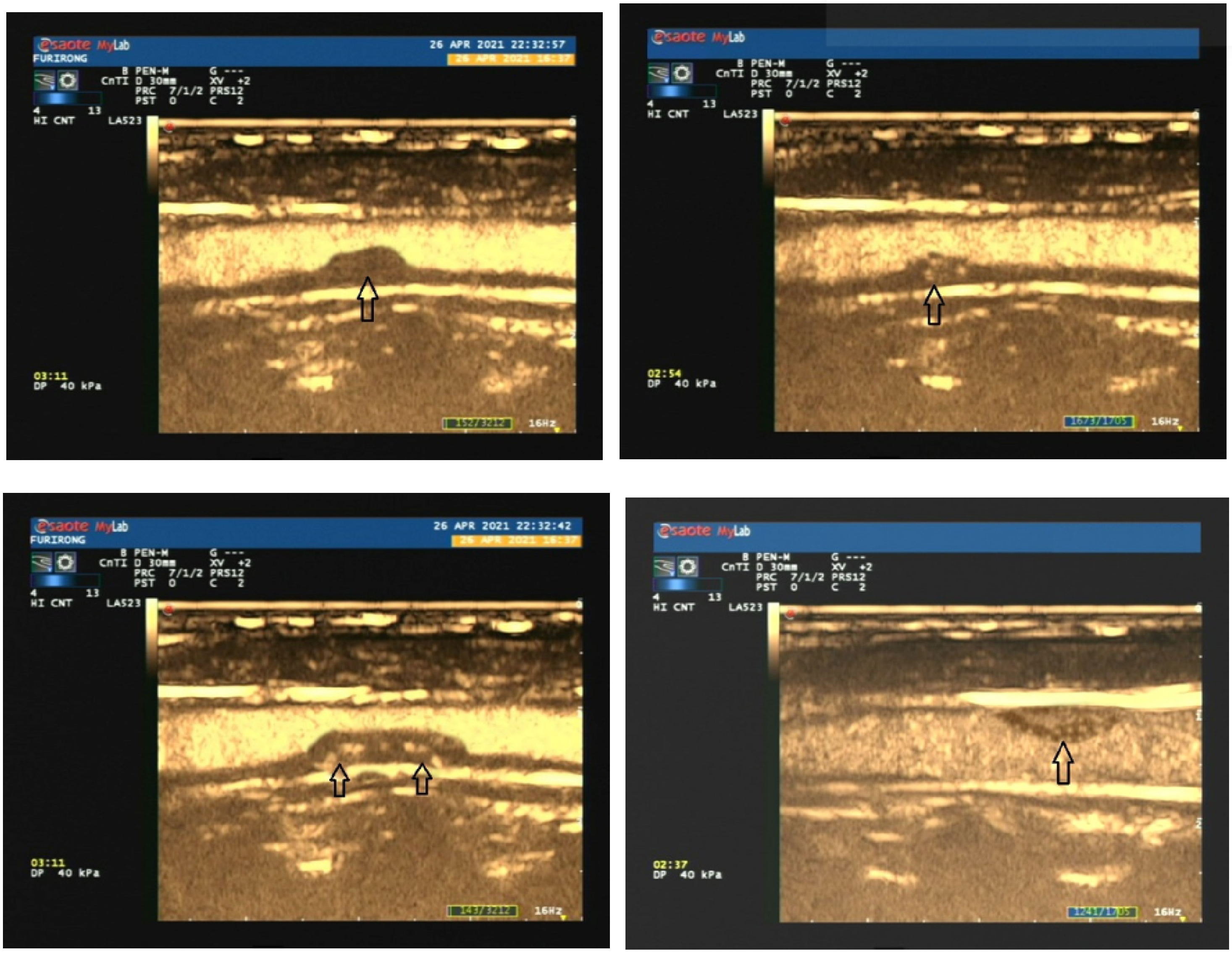

Figure 1

A~D. The carotid artery plaque neovascularization was graded from 0 to 3 by CEUS. A: Grade 0; B: Grade 1; C: Grade 2; D: Grade 3.

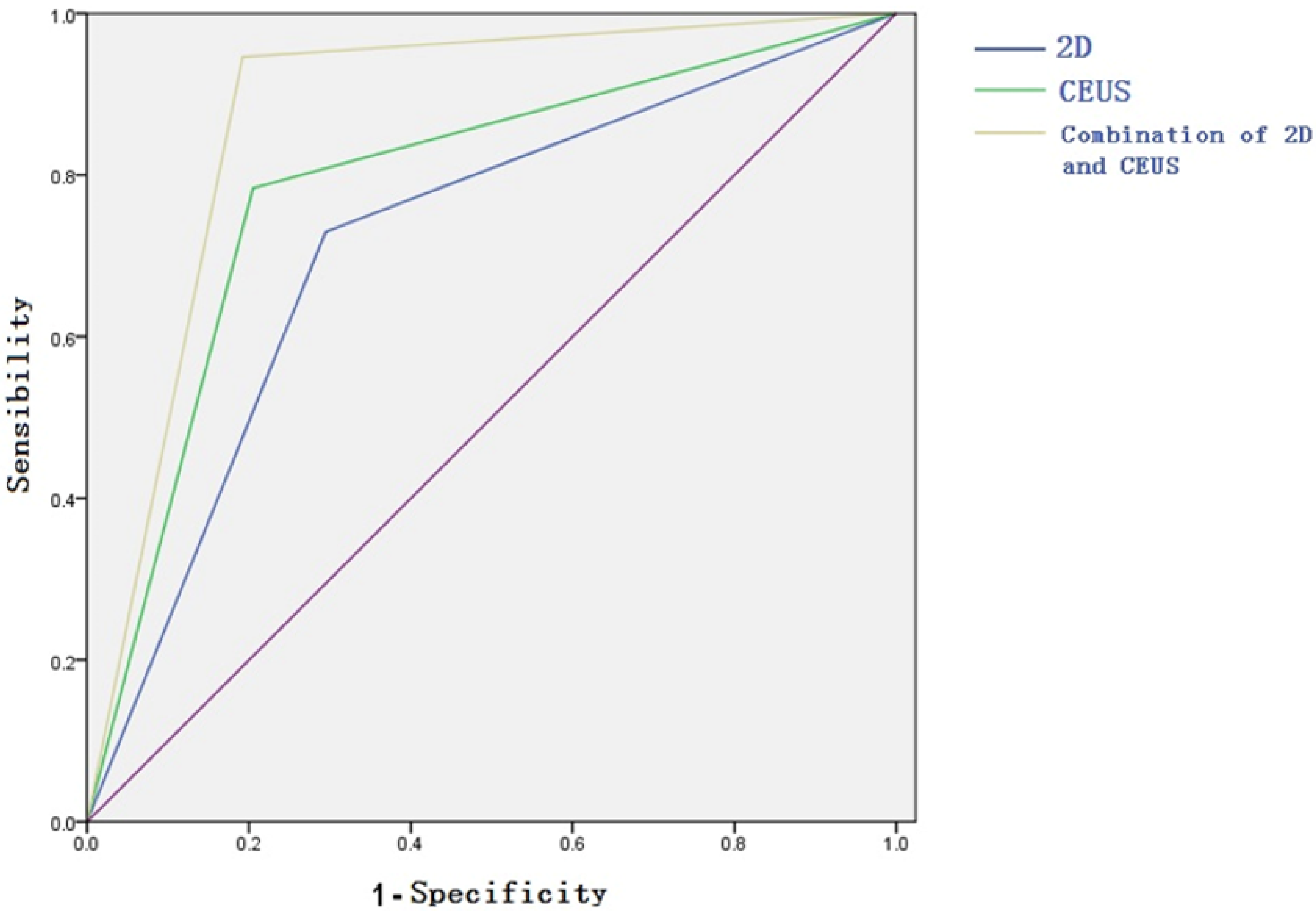

Figure 2

The ROC curve of 2D ultrasound, CEUS and combination of two methods in predicting recurrence of ischemic stroke