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ORIGINAL PAPER

PROGRESSION OF INTRACRANIAL ATHEROSCLEROTIC STENOSIS AND RISK OF RECURRENT ISCHEMIC STROKE: A 9-MONTH VIETNAMESE COHORT STUDY

Truong Minh NGO[1], Cuong Chi TRAN[1], Nguyen Thi Tai CAO[2]✉

[1] Can Tho Stroke International Services General Hospital, Can Tho, Vietnam
[2] Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam

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Abstract

Introduction. Recurrent ischemic stroke (RIS) in patients with intracranial atherosclerotic stenosis (ICAS) represents a major clinical challenge. Identification of prognostic factors and evaluation of the role of stenosis progression may improve risk stratification.
The objectives of the study were (1) to identify prognostic factors associated with RIS during 9 months of treatment and (2) to assess the association between progression of ICAS and the risk of RIS .
Material and methods. We conducted a retrospective–prospective cohort study including 143 acute ischemic stroke (AIS) or transient ischemic attack (TIA) patients with intermediate or poor *CYP2C19* metabolizer, who were followed for 9 months. RIS occurred in 21 patients (14.7%). A history of stroke and smoking were independently associated with RIS and were incorporated into the prognostic model. The model demonstrated good discrimination (AUC=0.81; 95% CI: 0.72–0.90), good calibration, and a low Brier score (0.10), indicating a satisfactory overall predictive performance. The progression of ICAS during follow-up was significantly associated with RIS (OR = 3.34; 95% CI: 1.18–9.08; p = 0.019). This association remained

Résumé

Progression de la sténose artérielle intracrânienne et risque de récidive d'accident vasculaire cérébral ischémique: étude de cohorte vietnamienne sur 9 mois

Introduction. La récidive d'accident vasculaire cérébral ischémique (AVCI) chez les patients présentant une sténose artérielle intracrânienne (SAI) constitue un défi clinique majeur. L'identification des facteurs pronostiques et l'évaluation du rôle de la progression de la sténose pourraient améliorer la stratification du risque.
L'objectif de cette étude était: (1) d'identifier les facteurs pronostiques associés à la récidive d'AVCI au cours de 9 mois de traitement et (2) d'évaluer l'association entre la progression de la SAI et le risque de récidive.
Matériel et méthodes. Nous avons réalisé une étude de cohorte rétrospective–prospective incluant 143 patients atteints de SAI présentant un phénotype métaboliseur intermédiaire ou faible du *CYP2C19*, suivis pendant 9 mois. Une récidive d'AVCI est survenue chez 21 patients (14,7%). Les antécédents d'AVCI et le tabagisme étaient indépendamment associés à la récidive et ont été intégrés dans le modèle pronostique.

✉ Address for correspondence: Nguyen Thi Tai CAO
Can Tho University of Medicine and Pharmacy, Vietnam – 179 Nguyen Van Cu street, Tan An Ward, Can Tho city, Vietnam
Email: cttnguyen@ctump.edu.vn

significant after adjustment for stroke history (OR = 4.48; 95% CI: 1.39–15.17; p = 0.012).
Conclusions. Stroke history and smoking are important predictors of RIS during 9 months of treatment. Progression of ICAS is an independent factor associated with RIS, underscoring the clinical value of monitoring stenosis progression in routine clinical practice.

Keywords: intracranial atherosclerotic stenosis, acute ischemic stroke, recurrent ischemic stroke, CYP2C19.

List of abbreviations:
RIS: recurrent ischemic stroke
ICAS: intracranial atherosclerotic stenosis
TIA: transient ischemic attack
AIS: acute ischemic stroke

Ce modèle a montré une bonne capacité discriminante (AUC = 0,81; IC à 95%: 0,72–0,90), une bonne calibration et un faible score de Brier (0,10), indiquant une performance prédictive globale satisfaisante. La progression de la SAI au cours du suivi était significativement associée à la récidive d'AVCI (OR = 3,34; IC à 95%: 1,18–9,08; p = 0,019). Cette association demeurait significative après ajustement sur les antécédents d'AVCI (OR = 4,48; IC à 95%: 1,39–15,17; p = 0,012).
Conclusions. Les antécédents d'AVCI et le tabagisme constituent des facteurs prédictifs importants de récidive d'AVCI au cours d'un suivi de 9 mois. La progression de la SAI est un facteur indépendant associé à la récidive d'AVCI, soulignant l'intérêt clinique du suivi de l'évolution de la sténose en pratique courante.

Mots-clés: sténose artérielle intracrânienne, accident vasculaire cérébral ischémique aigu, accident vasculaire cérébral ischémique récidivant, CYP2C19.

Introduction

Stroke remains a leading cause of mortality and one of the causes of long-term disability worldwide[1]. Despite substantial advances in acute management and secondary prevention, the risk of recurrent ischemic stroke (RIS) remains considerable. Epidemiological studies indicate that the risk of RIS within the first year is approximately 10% to 25%, depending on the underlying stroke mechanism and population characteristics[2–4]. Data from large cohorts further demonstrate that the risk of RIS is particularly high during the first 90 days after the index events, especially among patients with large-artery atherosclerotic stroke[5,6]. Moreover, RIS is associated with significantly increased mortality and worse functional outcomes compared with first-ever stroke[2,7]. RIS substantially increases mortality and disability, underscoring the clinical importance of identifying reliable prognostic factors.

Intracranial atherosclerotic stenosis (ICAS) is a key cause of RIS, particularly in Asian population, where it accounts for a higher proportion of ischemic strokes compared with Western populations[8,9]. The severity of ICAS is classified into four categories: mild (1–49%), moderate (50–69%), severe (70–99%), and complete occlusion (100%)[10]. The WASID study demonstrated that patients with severe ICAS (70–99%) have a significantly higher risk of RIS compared with those with less severe stenosis[11]. Subsequently, the SAMMPRIS trial showed that although aggressive medical therapy improves outcomes, patients with severe ICAS continue to experience a substantial rate of RIS[12]. Long-term follow-up analyses further confirmed that the risk of RIS remains particularly elevated within the first year among patients with high-grade stenosis despite optimized medical treatment[13].

CYP2C19*2 (rs4244285) and CYP2C19*3 (rs4986893) are common loss-of-function polymorphisms in Asian population and are associated with reduced CYP2C19 enzymatic activity, leading to impaired Clopidogrel metabolism. Accumulating clinical evidence suggests that *CYP2C19* loss-of-function alleles are associated with an increased risk of RIS in the setting of antiplatelet therapy. In a Vietnamese cohort, a study demonstrated that *CYP2C19* polymorphisms were associated with adverse cardiovascular outcomes in patients receiving antiplatelet therapy, further supporting the clinical relevance of pharmacogenetic variability in this population[14]. Other study has similarly shown higher rates of RIS or vascular events in patients with intermediate or poor metabolizer phenotypes compared with normal metabolizers[15].

Ticagrelor is a direct P2Y12 receptor inhibitor that does not require metabolic activation by *CYP2C19* and may therefore overcome clopidogrel resistance related to genetic polymorphisms. The CHANCE-2 trial demonstrated that among patients with minor ischemic stroke or transient ischemic attack (TIA) who carry *CYP2C19* loss-of-function alleles, Ticagrelor plus Aspirin significantly reduced the risk of RIS compared with Clopidogrel plus Aspirin[16].

Despite these advances, evidence regarding the independent prognostic value of RIS progression within multivariable prediction models remains limited. Prior studies have reported that progression of middle cerebral artery stenosis is independently

associated with an increased risk of clinically RIS[17]. Similarly, characteristics related to the severity and dynamic changes of intracranial stenosis have been shown to predict ischemic events in the corresponding vascular territory[18].

Moreover, few studies have simultaneously evaluated prognostic model performance using comprehensive metrics such as discrimination, calibration, and internal validation. Prognostic models require rigorous assessment of their reliability before clinical implementation[19]. In this context, clarifying the prognostic value of ICAS progression is crucial for improving risk stratification and guiding follow-up strategies.

The objectives of the study were to: (1) identify prognostic factors and develop a prediction model for RIS during 9 months of treatment in patients with ICAS; and (2) to assess the association between progression of ICAS and the risk of RIS.

Material and methods

Patients

A total of 143 patients diagnosed with AIS or TIA between May 2025 and February 2026 were enrolled at Can Tho Stroke International Services General Hospital, Vietnam. All participants underwent genotyping for *CYP2C19*2 and CYP2C19*3* polymorphisms and were classified as having intermediate metabolizer (IM) or poor metabolizer (PM) phenotypes. The patients were followed for a total of 9 months.

Eligible participants were randomly selected after fulfilling predefined inclusion and exclusion criteria. All enrolled patients received single antiplatelet therapy (Aspirin or Ticagrelor), high-intensity statin therapy, management of concomitant comorbidities, and comprehensive vascular risk factor control. Based on the occurrence of primary endpoint events (RIS or TIA) during follow-up, the patients were divided into two groups: the recurrence (n = 21) and the non-recurrence group (n = 122).

The exclusion criteria were: (1) concomitant intracerebral or subarachnoid hemorrhage; (2) atrial fibrillation, patent foramen ovale, or known coagulation disorders; (3) severe comorbidities likely to affect the disease course or clinical outcomes, including acute myocardial infarction, end-stage malignancy, or major trauma; (4) intolerance to or contraindication to antiplatelet therapy; and (5) prior mechanical thrombectomy or intracranial or extracranial stent placement.

Imaging evaluation of cerebral infarction and intracranial atherosclerotic stenosis

All enrolled patients were diagnosed with AIS or TIA and ICAS were evaluated using MRI and MRA performed on a 3.0-T scanner (MAGNETOM Lumina, Siemens Healthineers, Erlangen, Germany). The stenosis rate was determined by the WASID method[10]. The diameter of the lumen at the narrowest vascular site (Ds) and the lumen diameter at the normal vascular site (Dn) – the diameter of the lumen of the widest segment, running in parallel without winding. The stenosis ratio was calculated according to the formula: (Dn – Ds)/Dn × 100%. Based on the degree of stenosis, the lesions were classified into 4 types: mild (1–49%), moderate (50–69%), severe (70–99%), and total occlusion (100%). All imaging data were independently reviewed by two diagnostic Radiologists at Can Tho Stroke International Services General Hospital. In case of discrepancies, an other expert was involved for final confirmation, and the consensus diagnosis was considered the result.

CYP2C19 polymorphism tests

The test sample was 200 µL of EDTA anticoagulant whole blood that was automatically isolated DNA by the SaMag-12 automatic system and amplified CYP2C19*2 (rs4244285) and CYP2C19*3 (rs4986893) by Real-time PCR technique on the SaCycler-96 machine with a kit from REAL GENE, Italy. From the genotyping results, the *CYP2C19* metabolic phenotype was classified as normal metabolism (*1/*1), intermediate metabolism (*1/*2 or *1/*3) and poor metabolism (*2/*2, *3/*3 or *2/*3). The *CYP2C19* metabolic phenotype was determined based on the combination of two dysfunctional polymorphisms CYP2C19*2 and CYP2C19*3 as recommended by the Clinical Pharmacogenetics Implementation Consortium[20].

The statistical analysis was performed using R software. Qualitative variables were presented as frequencies and percentages; quantitative variables were described in terms of mean and standard or median deviations and quadruple intervals according to the data distribution. Using the Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test to assess the difference. Binary logistic regression analysis was used to identify independent prognostic factors of RIS within 9 months. The variables were selected for inclusion in the multivariate model based on clinical significance and the results of univariate analysis, including history of stroke and smoking. The performance of the prognostic model is evaluated through AUC, 1000 iterations internal bootstrap correction analysis to check the stability of the model, along with calibration graphs and Brier scores to assess the relevance and overall accuracy of the prediction. The statistical significance level was determined when $p < 0.05$.

Table 1. General characteristics of the patients

Characteristics	*Total, N = 143*[1]	*Non-RIS, N=122*[1]	*RIS, N = 21*[1]	*p-value*[2]
Age	63.34 (12.54)	63.24 (12.28)	63.90 (14.26)	0.8
Sex				>0.9
Male	94 (66%)	80 (66%)	14 (67%)	
Female	49 (34%)	42 (34%)	7 (33%)	
NIHSS	3.97 (3.42)	3.93 (3.49)	4.14 (3.07)	0.3
mRS				0.6
Good (0-2)	96 (67.4%)	83 (67.8%)	13 (62.8%)	
Poor (3-6)	47 (32.6%)	39 (32.2%)	8 (37.8%)	
Smoke				0.039
No	96 (67%)	86 (70%)	10 (48%)	
Yes	47 (33%)	36 (30%)	11 (52%)	
Hypertension				>0.9
No	16 (11%)	14 (11%)	2 (9.5%)	
Yes	127 (89%)	108 (89%)	19 (90.5%)	
Diabetes				0.3
No	81 (57%)	71 (59%)	10 (48%)	
Yes	61 (43%)	50 (41%)	11 (52%)	
Stroke				<0.001
No	90 (63%)	86 (70%)	4 (19%)	
Yes	53 (37%)	36 (30%)	17 (81%)	
Acute coronary syndrome				0.6
No	136 (95%)	115 (94%)	21 (100%)	
Yes	7 (5%)	7 (6%)	0 (0%)	
Hyperlipidemia				0.2
No	116 (81%)	101 (83%)	15 (71%)	
Yes	27 (19%)	21 (17%)	6 (29%)	
Drug				0.4
Aspirin	33 (23%)	30 (25%)	3 (14%)	
Ticagrelor	110 (77%)	92 (75%)	18 (86%)	

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

Results

Determination of prognostic factors for RIS in 9 months of treatment

Of the 143 patients studied, there were 21 cases (14.7%) of RIS. Age, gender, initial NIHSS scores, and mRS distribution did not differ statistically significant between groups with and without recurrence ($p > 0.05$). The rates of diabetes mellitus, acute coronary syndrome, hyperlipidemia and platelet aggregation regimens were similar between the two groups. In contrast, stroke history was markedly more common in the RIS group than in the non-recurrent group (81% vs. 30%; $p < 0.001$) (Table 1).

The distribution of *CYP2C19* metabolic phenotypes (IM and PM) did not differ statistically significantly between the group with and without RIS ($p > 0.9$) (Table 2). The results of the univariable analysis recorded in Table 3 show that the history of stroke and smoking are statistically significant.

Of the total 143 patients followed for 9 months of treatment, 21 cases (14.7%) had RIS. Multivariate logistic regression analysis was performed to identify independent prognostic factors of RIS. The results showed that a history of stroke and smoking were two factors independently associated with the risk of RIS. Specifically, patients with a previous stroke history had a 10.9 times higher risk of RIS than patients without a stroke history (OR = 10.9; 95% CI: 3.63–40.7; $p < 0.001$). At the same time, smoking increases the risk of RIS by about 3.01 times (OR = 3.01; 95% CI: 1.07–8.74; $p = 0.038$) (Table 4).

The prognostic model consisted of a history of stroke and smoking with good discrimination

Table 2. Characteristics of *CYP2C19* phenotypes and genotypes

Characteristics of CYP2C19	*Total, N = 143*[1]	*Non-RIS, N=122*[1]	*RIS, N = 21*[1]	*p-value*[2]
Phenotypes				>0.9
Intermediate metabolizer	115 (80%)	98 (80%)	17 (81%)	
Poor metabolizer	28 (20%)	24 (20%)	4 (19%)	
Genotypes				0.3
*1/*2	98 (69%)	82 (67%)	16 (76%)	
*1/*3	17 (12%)	16 (13%)	1 (4.8%)	
*2/*2	6 (4.2%)	4 (3.3%)	2 (9.5%)	
*2/*3	22 (15%)	20 (16%)	2 (9.5%)	
rs4244285				0.2
AA	6 (4.2%)	4 (3.3%)	2 (9.5%)	
GA	120 (84%)	102 (84%)	18 (86%)	
GG	17 (12%)	16 (13%)	1 (4.8%)	
rs4986893				0.15
GA	39 (27%)	36 (30%)	3 (14%)	
GG	104 (73%)	86 (70%)	18 (86%)	

[1]Mean (SD); n (%)

[2]Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test

Table 3. Factors associated with RIS.

Variable	*OR*	*95% CI*	*p*
Age	1.00	0.97 – 1.04	0.821
Sex	0.95	0.34 – 2.48	0.922
NIHSS	1.02	0.88 – 1.15	0.796
mRS	0.98	0.64 – 1.45	0.919
Diabetes	1.56	0.61 – 4.02	0.347
Prior Stroke	10.15	3.48 – 37.19	0.000
Hypertension	1.23	0.31 – 8.24	0.794
Hyperlipidemia	1.92	0.63 – 5.36	0.225
Smoke	2.63	1.02 – 6.85	0.044
CYP2C19 phenotypes	0.96	0.26 – 2.89	0.947

Table 4. Multivariate logistics regression model

Variables	OR	95% CI	p-value
Smoke	3.01	1.07, 8.74	0.038
History of stroke	10.9	3.63, 40.7	<0.001

Table 5. Evaluation of the performance of the model

Variables	Value
AUC	0.81
95% CI AUC	0.72 – 0.9
Bootstrap AUC	0.81
Calibration slope	1
Brier score	0.1

(AUC = 0.81), appropriate correction (calibration slope = 1), and high stability after bootstrap correction, with a low Brier score (0.10), indicating good overall predictive accuracy. Overall, the model of stroke history and smoking demonstrated good discrimination, appropriate correction, and high stability, showing potential value in predicting the risk of RIS at 9 months of treatment in patients with ICAS (Table 5).

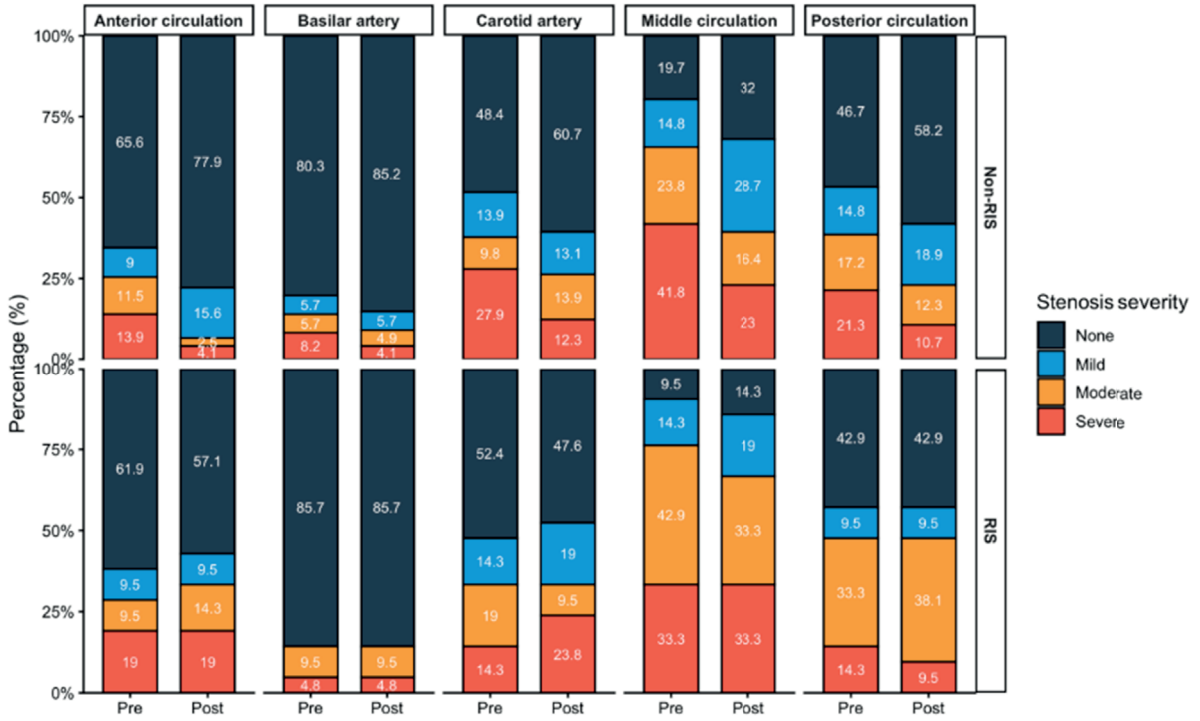

Figure 1. Distribution of the degree of arterial stenosis initially and after 9 months.

Table 6. Results of univariate analysis of intracranial stenosis progression

Variables	OR	95%CI	p
Progression	3.34	1.18 – 9.08	0.019
Progression (Stroke Adjustment)	4.48	1.39 – 15.17	0.012

Evaluation of the association between the progression of ICAS and the risk of RIS

Figure 1 shows the distribution of the degree of arterial stenosis at baseline and after 9 months according to relapse. In the non-recurrent group, most patients did not have stenosis or mild stenosis at most of the survey sites, and this trend was relatively stable after follow-up. In contrast, in the recurrent group, the incidence of moderate and severe stenosis was higher, especially in the middle and posterior cerebral arteries. After 9 months, the relapsed group still maintained a higher ratio of moderate-severe stenosis than the non-relapsed group (Figure 1).

Univariate analysis showed that ICAS progression during the follow-up period was statistically significant with RIS within 9 months of treatment. Patients with progressive stenosis had a 3.34-fold higher risk of recurrence than the non-progressive group (OR = 3.34; 95% CI: 1.18–9.08; p = 0.019). After adjusting for stroke history, this association remained statistically significant and the effect increased (OR = 4.48; 95% CI: 1.39–15.17; p = 0.012), indicating that vascular progression is independently associated with RIS (Table 6).

Discussion

Through a 9-month follow-up of 143 patients with AIS with symptomatic ICAS, all of whom carried the *CYP2C19* gene polymorphism, it was found that 14.7% of patients had RIS. This recurrence rate is consistent with recent study particularly in Asian population with *CYP2C19* gene polymorphism[21], which may reflect the susceptibility of ICAS.

Univariate logistic regression analysis showed that stroke history was the strongest associated factor with the risk of RIS (OR=10.15; 95% CI: 3.48–37.19; p < 0.001). These results show that patients with a history of stroke are many times more likely to have a recurrence than patients who have never had a stroke, reflecting an already existing burden of underlying cerebrovascular disease, including advanced atherosclerosis, chronic endothelial damage, and unstable cerebrovascular pathology. These factors increase the vulnerability of the

cerebral vascular system and promote the risk of recurrence, even if the patient receives secondary prophylaxis according to the standard regimen. Similar findings have been reported in large population-based studies such as the Oxford Vascular Study, which demonstrated that prior stroke or TIA significantly increases the risk of early recurrent ischemic events[4]. Furthermore, Wang et al. also confirmed that patients with a history of cerebrovascular events have a markedly elevated risk of recurrence despite guideline-based secondary prevention[16]. These factors increase the vulnerability of the cerebral vascular system and promote the risk of RIS, even if the patient receives secondary prophylaxis according to the standard regimen.

In addition, smoking behavior also showed a statistically significant association with the risk of RIS (OR=2.63; 95% CI: 1.02–6.85; p = 0.044). Smoking is known to promote endothelial inflammation, increase platelet activation and hypercoagulation, and aggravate the process of atherosclerosis, thereby facilitating thrombosis and RIS associations between smoking and recurrent ischemic events have been reported in large population-based study, which identified active smoking as an independent predictor of recurrent vascular events[4]. This finding underscores the important role of smoking cessation interventions in secondary stroke prevention strategies.

The progression of ICAS is closely related to the risk of RIS[17]. Consistent with findings from the studies that severe intracranial stenosis remains associated with a high recurrence rate despite optimal therapy[11,12]. Progression of ICAS was an independent prognostic factor for RIS at 9 months. Patients with stenosis progression had a 3.34-fold higher risk of recurrence, which remained significant after adjustment for prior stroke (OR=4.48). These findings are consistent with recent high-resolution MRI study showing that progression of plaque burden independently predicts RIS events[22]. Model performance was good (AUC 0.81; bootstrap-corrected AUC 0.80) with adequate calibration (Brier score 0.10), in line with recommendations for prognostic model validation[19].

Limitations of the study

The study has not objectively assessed the level of treatment adherence, so the effect of non-compliance on cerebral infarction recurrence has not been ruled out. The data are mainly based on declarations; some risk factors and voluntary withdrawal of medication have not been strictly controlled.

Conclusions

The rate of RIS was 14.7%. A history of stroke and smoking are important associated factors with RIS. This two-variable model shows good discrimination (AUC = 0.81), proper correction, and high stability. Progression in the degree of ICAS during the follow-up period was independently associated with RIS, even after adjusting for stroke history. The results suggest that a history of stroke, smoking, and monitoring of the progression of cerebrovascular damage may be valuable in risk stratification and management of patients with ICAS.

Author contributions

Conceptualization: T.M.N.; methodology: TM.N. and N.T.T.C.; software: T.M.N., C.C.T. and N.T.T.C.; validation: T.M.N., N.T.T.C. and C.C.T.; formal analysis: T.M.N., C.C.T. and N.T.T.C.; investigation: T.M.N.; resources: T.M.N., C.C.T. and N.T.T.C.; data curation: T.M.N., C.C.T., and N.T.T.C.; writing–original draft preparation: T.M.N.; writing–review and editing: T.M.N., C.C.T., and N.T.T.C.; visualization: T.M.N. and N.T.T.C.; supervision: C.C.T. and N.T.T.C.; project administration: C.C.T. and N.T.T.C. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study. The study was approved by the Medical Ethics Council of Can Tho University of Medicine and Pharmacy, Vietnam, approval number 25.321.HV/PCT-HĐĐĐ, June 30th, 2025."

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