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Research Article

Clinical analysis in older patients with a first-ever, second, third, and recurrent strokes

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Abstract

Introduction: Recently, recurrent ischemic stroke has attracted significant attention in both research and clinical settings.

Aim: A comparative retrospective analysis of risk factors and clinical characteristics in elderly patients (≥65 years) experiencing a first-ever, second, third, and recurrent cerebral infarction.

Materials and methods: This study included 260 patients with acute stroke admitted to the Neurology Clinic. Patients were classified into three groups: Group 1—first-ever stroke (n=212), Group 2—second stroke (n=35), and Group 3—third and subsequent stroke (n=13). A model focused on the most common vascular risk factors, etiological classifications, and assessment scales. Clinical, instrumental, and statistical methods were applied.

Results: Two independent risk factors with strong prognostic relevance were identified: age and dyslipidemia (noted specifically between Group 1 and Group 2). Clinically important comorbidities with moderate impact on vascular risk included arrhythmias and conduction disorders, other cardiovascular diseases, and diabetes mellitus. No statistically significant differences were found among the three groups with respect to sex, arterial hypertension, smoking status, or affected vascular territories. The main TOAST criteria were large-artery atherosclerosis, cardioembolism, and small-vessel disease. Among patients in Groups 2 and 3, phenotypes A1, A2, S3, C1, and C2 (ASCOD) were identified as significant etiological factors. The incidence of subsequent cerebrovascular events was 18.46%.

Conclusion: Recurrence of ischemic stroke is a significant barrier to the development of effective, long-term prognostic models, the implementation of secondary prevention strategies, and the advancement of therapeutic paradigms.

Keywords

ischemic stroke, prognosis, risk factors

Introduction

In recent years, recurrent ischemic stroke has become the focus of growing scientific research and clinical expertise. Modern approaches increasingly use artificial intelligence (AI) systems in conjunction with sophisticated mathematical and statistical algorithms, especially machine learning models, to create individualized patient profiles and produce customized predictions about the likelihood of subsequent cerebrovascular events.[1]

Kolmos et al. identified the most significant independent risk factors for recurrent cerebral infarction, including arterial hypertension, atrial fibrillation and other arrhythmias and conduction disturbances, diabetes mellitus, smoking, prior cerebrovascular events, and complicated clinical presentations during the initial stroke episode.[2]

Current evidence on sex-related differences in recurrent cerebrovascular risk remains inconsistent. The POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) randomized controlled trial, which enrolled 4,881 patients with minor ischemic stroke or high-risk transient ischemic attack (TIA) and followed them for 90 days, found no statistically significant difference in risk between women (5.76%) and men (5.67%). Although a trend toward lower recurrence risk was observed among women under the age of 60, the difference did not reach statistical significance.[3]

According to Fu et al., the most common risk factors included age, male sex, a history of cardiovascular or cerebrovascular events, diabetes mellitus, and coronary artery disease.[4] In a retrospective study involving 787 patients conducted at a single hospital center, Chung et al. identified arterial hypertension and dyslipidemia as the primary predictors of subsequent acute stroke, independent of sex. However, sex-specific associations were observed: diabetes mellitus was a prominent metabolic risk factor in women, while smoking and alcohol consumption were major behavioral risk factors in men.[5]

Aim

The objective of the study was to make a comparative retrospective analysis of non-modifiable and modifiable risk factors and clinical characteristics in elderly patients with a first-ever, second, third and subsequent ischemic stroke.

Materials and methods

This study is part of previous original research.[6,7] A total of 260 patients (aged >65 years) diagnosed with acute stroke and admitted to the Neurology Clinic between January 1, 2023, and March 1, 2024, were included. For the purposes of the analysis, patients were divided into three groups: Group 1—first-ever stroke (n=212), Group 2—second stroke (with a history of prior cerebrovascular event) (n=35), and Group 3—third and recurrent stroke (with a history of at least two previous cerebral infarctions) (n=13). A model incorporated an assessment of the most prevalent vascular risk factors: arterial hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, and smoking

Two etiological classification systems were applied: the Trial of Org 10172 in Acute Stroke Treatment (TOAST)[8] and the ASCOD phenotyping system[9,10]. Stroke severity was assessed using the NIH Stroke Scale (NIHSS)[11], and cognitive impairment was evaluated using the Mini-Mental State Examination (MMSE)[12].

The TOAST classification identified five primary etiological subtypes: 1. Large-artery atherosclerosis (involving the aorta, carotid, and vertebral arteries), 2. Cardioembolism, 3. Small-vessel diseases, 4. Other determined causes (e.g., migraine, vasculitis, vasculopathies, and venous thrombosis), and 5. Stroke of undetermined etiology (cryptogenic).[8]

According to the ASCOD phenotyping system, patients were divided into five etiological profiles: arterial dissection (D), cardioembolic source (C), small-vessel disease (S), atherosclerosis (A), and other causes (O). Each category was further graded according to defined diagnostic criteria and levels of causal likelihood, corresponding to three levels of evidence: A (definite), B (probable), and C (possible). The degree of phenotypic expression was classified as follows: 0 – absence of disease, 1 – presence of a potential factor, 2 – presence of a possible but uncertain factor, 3 – presence of a non-etiological but comorbid factor, and 9 – insufficient clinical and instrumental data to allow interpretation.[9,10]

NIHSS scores were grouped into three severity categories: mild (0–7), moderate (8–15), and severe (>16).[11] The affected vascular territories were defined as the left middle cerebral artery (MCA), right MCA, and vertebrobasilar system. Cognitive impairment was determined by an MMSE score ≤ 27 points.

Statistical analyses included descriptive statistics, recoding of variables, independent-samples t-tests, chi-square tests, one-way analysis of variance (ANOVA), multiple linear regression, multinomial logistic regression, decision tree modeling using Classification and Regression Trees, radial basis function neural networks, and graphical data representations.[13,14] A significance level of 0.05 (*p*-value) was adopted. Data were analyzed using IBM SPSS Statistics, version 26.

Results

Demographic and clinical characteristics

The mean age of patients in Group 1 was 72.75 years (*SD* 5.16), in Group 2, it was 76.63 years (*SD* 4.77), and in Group 3, it was 79.0 years (*SD* 2.27). When the data were compared by sex (male-female), the mean age in Group 1 was 72.20 years (*SD* 5.47) for males and 73.21 years (*SD* 4.66) for females. In Group 2, the mean age was 75.93 years (*SD* 6.07) and 77.10 years (*SD* 3.75), respectively. In Group 3, the mean age was 78.17 years (*SD* 2.64) and 79.71 years (*SD* 1.80). **Table 1** presents the main characteristics of all ischemic strokes, including stroke recurrence, sex, and associated risk factors.

Etiological classifications

According to the TOAST criteria, the most prevalent pathophysiological mechanisms involved large-artery ath-

Table 1. Baseline characteristics of study patients presented as number (n) and percentages (%)

Clinical characteristics, n (%)	First-ever stroke (*n*=212) n (%)	Second stroke (n=35) n (%)	Third and recurrent stroke (n=13) n (%)
Sex, male	102 (48.10%)	14 (40.0%)	6 (46.15%)
Arterial hypertension	189 (89.15%)	35 (100.0%)	13 (100.0%)
Cardiac arrhythmias and conduction disorders	50 (23.59%)	10 (28.57%)	5 (38.46%)
Other cardiovascular diseases	78 (36.79%)	20 (57.14%)	8 (61.54%)
Diabetes mellitus	92 (43.40%)	23 (65.71%)	9 (69.23%)
Dyslipidemia	134 (63.21%)	31 (88.57%)	11 (84.62%)
Never smoker	65 (30.66%)	13 (37.14%)	5 (38.46%)
Formal smoker	96 (45.28%)	18 (51.43%)	7 (53.85%)
Current smoker	51 (24.06%)	4 (11.43%)	1 (7.69%)
Left middle cerebral artery	80 (37.74%)	12 (34.29%)	6 (46.15%)
Right middle cerebral artery	71 (33.49%)	14 (40.0%)	4 (30.77%)
Vertebrobasilar system	61 (28.77%)	9 (25.71%)	3 (23.08%)

erosclerosis, cardioembolism, and small-vessel disease. The leading risk factors were as follows: in Group 1, small-vessel disease was present in 76 (35.85%), and large-artery atherosclerosis in 72 patients (33.96%); in Group 2, large-artery atherosclerosis was present in 13 (37.14%), and small-vessel disease in 11 (31.43%); and in Group 3, large-artery atherosclerosis and cardioembolism were equally represented, each accounting for 5 (38.46%), followed by small-vessel disease in 3 subjects (23.08%).

According to the ASCOD classification system, the most significant etiological phenotypes in the groups with first-ever, second, and recurrent strokes were A, S, C, and O.

Assessment scales

In the group of patients who had first ever stroke, 112 (52.83%) had NIHSS scores ranging from 0 to 7, 91 (42.92%) demonstrated scores between 8 and 15, and 9 (4.25%) registered scores of 16 or higher. In the group with the second stroke, 12 (34.29%) had NIHSS scores of 0–7, 18 (51.43%) had scores of 8–15, and 5 (14.28%) had scores >16. In the group with third and subsequent strokes, 4 (30.77%) scored 0 to 7, 8 (61.54%) scored 8 to 15, and 1 (7.69%) scored >16. Cognitive impairment was identified in 140 cases (66.04%) in Group 1, 30 cases (85.71%) in Group 2, and all 13 cases (100.0%) in Group 3.

Analysis of variance

A one-way ANOVA comparing the three groups revealed statistically significant differences for the following variables: age [$F(2, 257)=12.48$, $p<0.001$], cardiovascular diseases [$F(2, 257)=7.29$, $p=0.001$], diabetes mellitus [$F(2, 257)=5.02$, $p=0.007$], dyslipidemia [$F(2, 257)=5.48$, $p=0.005$], NIHSS scores [$F(2, 257)=4.28$, $p=0.02$], and cognitive impairment [$F(2, 257)=5.86$, $p=0.003$].

The post-hoc Tukey HSD test confirmed significant differences between Groups 1 and 2 and between Groups 1 and 3, while no significant difference was observed between Groups 2 and 3. The results showed a rising pattern—the frequency of accompanying risk factors, clinical severity, and cognitive decline increased with each subsequent stroke, being most prominent in the indicators of age and dyslipidemia.

No statistically significant differences were detected among the groups regarding the indicators of sex [$F(2, 257)=0.40$, $p=0.67$], arterial hypertension [$F(2, 257)=2.89$, $p=0.06$], smoking status [$F(2, 257)=1.59$, $p=0.21$], and the involvement of vascular territories [$F(2, 257)=0.19$, $p=0.83$].

Regression analyses

A multivariate linear regression analysis was performed to assess the linear relationship between age, sex, risk factors, anatomical localization, stroke severity, and stroke subtype. A model of these variables proved statistically significant for prognostic purposes: $F(9, 250)=31.25$, $p<0.001$. The correlation matrix indicated values within acceptable limits for multicollinearity ($r<0.7$), confirming the independence of the variables. The resulting regression coefficients were $R=728$, $R^2=0.529$, and an adjusted $R^2=0.512$.

Three of the independent variables—sex, clinical severity, and affected vascular territories—did not demonstrate statistically significant regression coefficients (β and Beta). After their exclusion, a second regression model was constructed: $F(6, 251)=34.80$, $p<0.001$ with similar regression values: $R=0.725$, $R^2=0.526$, and adjusted $R^2=0.511$. This modified approach accounted for 51.0% of the observed variance and demonstrated a moderate influence of the examined factors on the likelihood of developing a second or subsequent ischemic stroke.

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To evaluate demographic and clinical characteristics associated with the risk of recurrent events and to calculate odds ratios (OR; 95% CI), a multinomial logistic regression analysis was conducted. The dependent variable was defined by the grouping of patients into Group 1, Group 2, and Group 3. The overall model was statistically significant [$\chi^2(22)=61.31$, $p<0.001$] as confirmed by the Goodness-of-Fit test ($p>0.05$). Pseudo R^2 values indicated a weak to moderate relationship: Cox & Snell = 0.210, Nagelkerke = 0.304, and McFadden = 0.201. Among the investigated predictors, age [$\chi^2(2)=12.93$, $p=0.002$] and dyslipidemia [$\chi^2(2)=9.70$, $p=0.008$] were statistically significant. When comparing patients with a first-ever versus second stroke, both variables, age [B=0.095, SE=0.05, $p=0.05$, OR=1.10, 95% CI (1.00-1.21)] and dyslipidemia [B=1.494, SE=0.59, $p=0.01$, OR=4.45, 95% CI (1.39-12.23)], were associated with increased vascular risk. In the comparison between Group 1 and Group 3, age was identified as the leading risk factor [B=0.310, SE=0.12, $p=0.009$, OR=1.36, 95% CI (1.08-1.72)].

Decision trees

To develop a predictive model for recurrent strokes based on ASCOD phenotyping and other independent variables—age, sex, smoking status, and clinical severity—the Classification and Regression Trees (CRT) method was applied. The configuration demonstrated a risk estimate of 0.185 with a standard error (SE) of 0.024 under both resubstitution and cross-validation, confirming the accuracy of the predicted values without evidence of overfitting. In the constructed decision tree, the most significant predictor of cerebrovascular risk was age, serving as the primary splitting factor at the first level, followed by ASCOD-S and ASCOD-A at subsequent levels. A critical age threshold of 75.5 years was identified, beyond which a substantial increase in the frequency of recurrent strokes was observed. Among participants aged ≤75.5 years, first-ever strokes predominated (93.20%), with second strokes accounting for 6.10% and third and subsequent for 0.7%. In contrast, in the >75.5 years age group, there was a significant rise in the incidence of cases in Group 2 (23.0%) and Group 3 (10.60%).

Additional contributions to cerebrovascular risk were associated with phenotypes S (≤75.5 years, Nodes 3 and 4) and A (>75.5 years, Nodes 5 and 6). The incidence of recurrent events among subjects classified as S3 was 11.30%, which is markedly higher compared to those with etiological profiles corresponding to S0, S1, and S2 (4.30%). Within Node 5, 7.70% of the cases were composed of patients that exhibited the A3 phenotype and had experienced a second stroke. In Node 6, phenotypes A1 and A2 were predominant, with observed frequencies of second (25.0%) and subsequent (12.0%) strokes **(Fig. 1)**.

An additional CRT analysis was performed excluding the age factor, resulting in the emergence of a new leading predictor with prognostic value—phenotype C (0.012). Patients classified as C1 and C2 exhibited a higher proportion of second (17.8%) and subsequent (7.1%) strokes. Conversely, phenotypes C0, C3, and C9 were associated with a lower risk of developing second (5.5%) and third (1.1%) ischemic events.

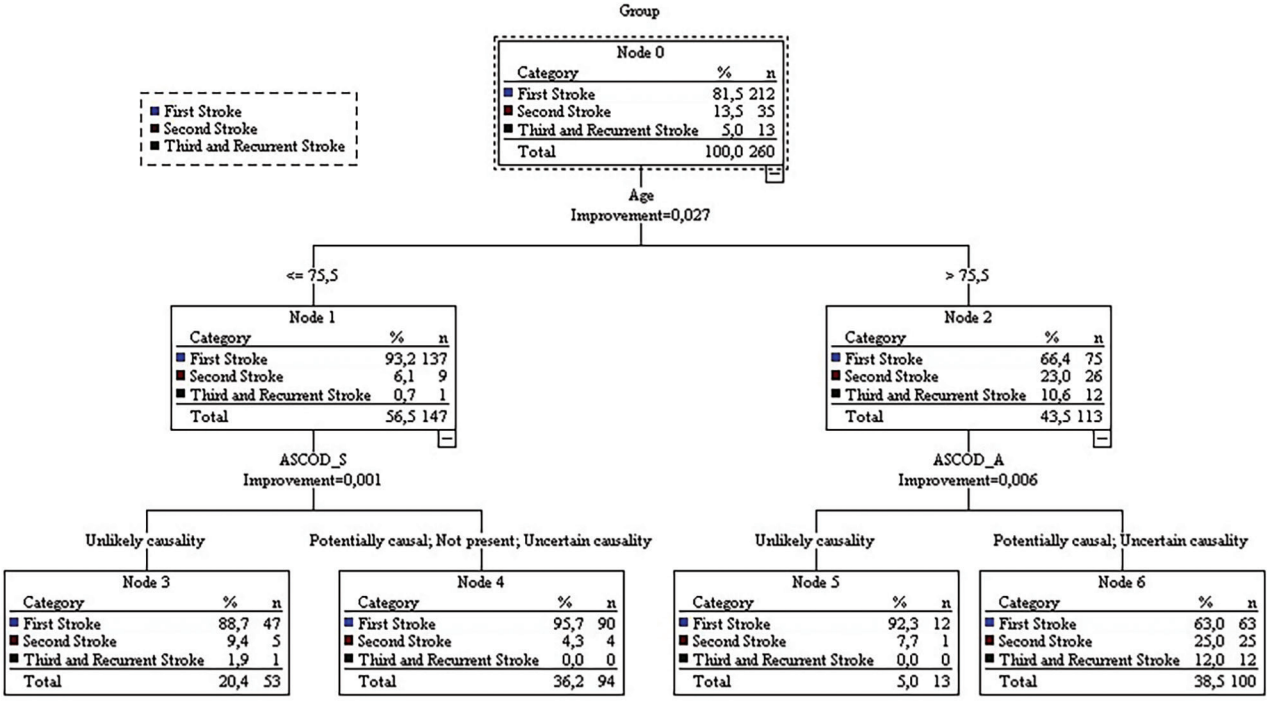

Figure 1. A decision tree for cerebrovascular risk stratification. Age was identified as the primary splitting variable (threshold: 75.5 years, 0.027), followed by the ASCOD-S (0.001) and ASCOD-A (0.006) on the second level.

Radial Basis Function (RBF) Neural Network

To predict patients' probable classification into one of three groups based on sex and the ASCOD system, an artificial neural network was applied. The model consisted of seven input variables (input layer), a single hidden layer with three neurons—H(1), H(2), and H(3)—utilizing a Softmax activation function, and an output layer with an identity activation function and a target variable representing Group (1, 2, 3). Visualization of the neural network indicated that all input variables contributed actively to the training of the hidden neurons. The different predictive factors exhibited selective influence, evidenced by both positive (synaptic weight >0) and negative (synaptic weight <0) synaptic connections. The first and third hidden neurons, H(1) and H(3), demonstrated moderate to strong negative associations with Group 3, suggesting their potential role in distinguishing this group. The second hidden neuron, H(2), exhibited weaker and more specifically directed connections towards Group 1 and Group 2 **(Fig. 2)**.

Discussion

In the studied cohort, the incidence of recurrent cerebrovascular events was 18.46%. Analysis of the age distribution across the three groups revealed a clear progressive trend with the average age increasing from Group 1 to Group 3. When stratified by sex, females in each group exhibited a higher average age compared to males. The regression and classification coefficients confirmed age as an independent vascular risk factor with strong predictive value, in line with findings from numerous previous studies.[15-18]

Significant independent comorbidities exerted a moderate influence on the risk of recurrent stroke, including dyslipidemia, cardiac rhythm and conduction abnormalities, other cardiovascular diseases and diabetes mellitus, corroborating the results of Callaly et al. and Elhefnawy et al.[19,20] Multinomial logistic regression analysis comparing Groups 1 and 2 identified dyslipidemia, in addition to age, as a statistically significant factor associated with an increased risk of recurrent stroke.

No statistically significant differences were found among the three groups with respect to sex, arterial hypertension,

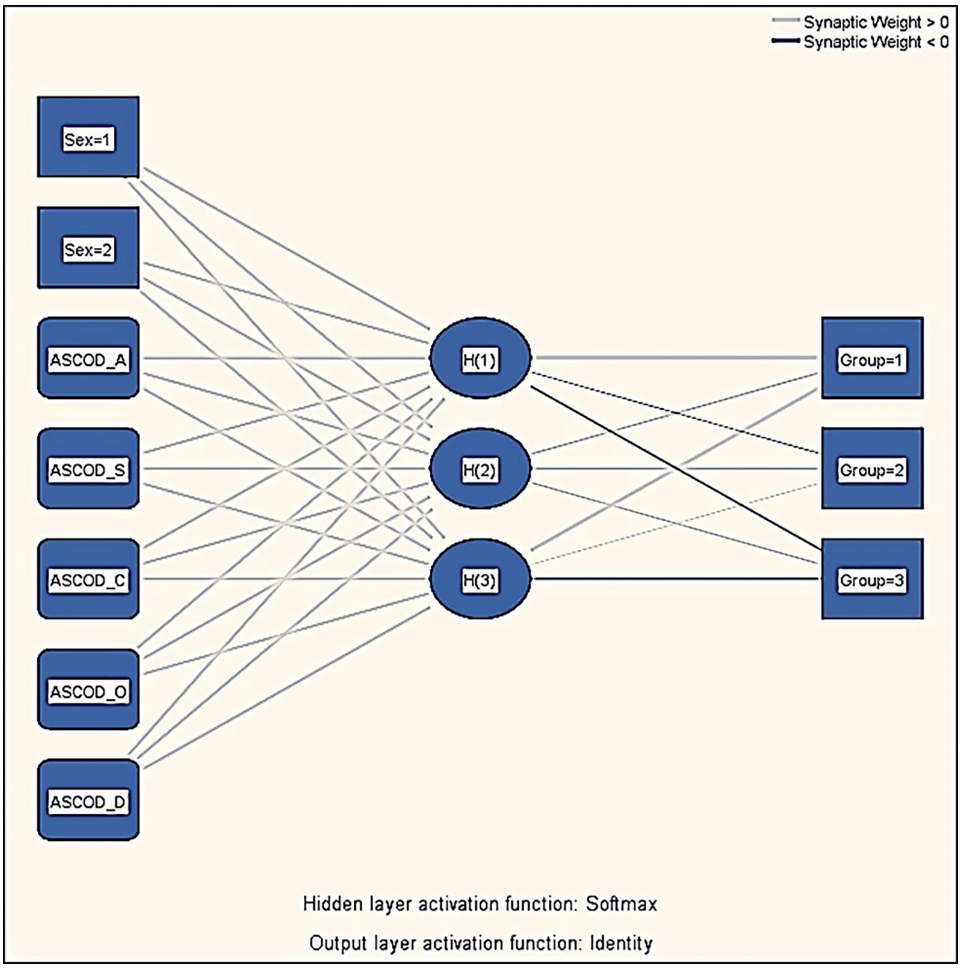

Figure 2. Artificial neural network – Neurons H(1) and H(3) are associated with differentiation of Group 3. Neuron H(2) is linked to Groups 1 and 2.

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smoking status, and affected vascular territories. Clinically, patients with second and subsequent strokes demonstrated more severe residual motor and/or speech impairments and cognitive deficits, correlating with poorer prognostic outcomes.[21]

In a study by Elnady et al., based on the TOAST classification, the cumulative risk of recurrent stroke was found to be highest and occurred earliest (<1 year) in cases of large-artery atherosclerosis and cardioembolism, whereas it was lowest and occurred later (>1 year) in cases attributed to small-vessel disease and cryptogenic stroke.[22] Uzuner and Uzuner analyzed four primary TOAST subtypes in the context of vascular recurrences: cardioembolism, large-artery atherosclerosis, strokes of undetermined etiology, and small-vessel disease.[23] Our results indicated that large-artery atherosclerosis was the primary etiology in Groups 2 and 3, followed by cardioembolism, small-vessel disease, and cryptogenic stroke.

The ASCOD classification eliminated the term 'cryptogenic' and instead evaluated coexisting conditions in cases of possible Embolic Stroke of Undetermined Source (ESUS). It has demonstrated strong predictive value in estimating the risk of subsequent stroke.[9,10,24] Among patients in Groups 2 and 3, phenotypes A, S, and C were identified as significant etiological factors. Categories A1, A2, S3, C1, and C2 correlated with an increased incidence of second, third, and recurrent cerebral infarctions.

The structure of the artificial neural network supports the hypothesis that the inclusion of sex as a variable, along with elements from the ASCOD system, may enhance the accuracy and effectiveness of predictive models.

This study is subject to several limitations, notably the presentation of preliminary data, a short follow-up period, a small number of cases in Groups 2 and 3, and the lack of a comparative analysis of secondary prevention strategies.

Conclusions

Recurrent ischemic stroke is associated with a moderate to high prevalence. Rigorous quantification of both cumulative and individual vascular risk is essential for guiding therapeutic strategies, optimizing secondary prevention efforts, and establishing a robust foundation for long-term prognosis in cerebrovascular disease progression.

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Competing interests

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Author contributions

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