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Predictive Value of White Matter Hyperintensities for Early Neurological Deterioration in Patients with Embolic Stroke of Undetermined Source

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Objective: To explore the role of white matter hyperintensities (WMH) in predicting early neurological deterioration (END) in patients with embolic stroke of undetermined source (ESUS) without reperfusion therapy.

Methods: In a retrospective analysis, 111 acute ESUS patients not treated with reperfusion therapy were enrolled. WMH severity was evaluated using the Fazekas scale, with patients categorized into mild (Fazekas score ≤ 2) or moderate-to-severe (Fazekas score ≥ 3) WMH groups. Clinical data were compared between the groups, and END was monitored within 72 hours of hospital admission. The association between WMH and END was assessed using binary logistic regression.

Results: Patients with moderate-to-severe WMH were significantly older (p = 0.001) and more likely to have a history of stroke (28.6% vs 10.5%, p = 0.017) compared to the mild WMH group. The END group (n=16) presented with higher baseline NIHSS scores and a greater prevalence of moderate-to-severe WMH (p < 0.05). Binary logistic regression identified moderate-to-severe WMH (OR = 4.012, 95% CI: 1.080–14.906, p = 0.038), smoking (OR = 4.368, 95% CI: 1.171–16.293, p = 0.028), and diabetes mellitus (OR = 3.986, 95% CI: 1.007–15.789, p = 0.049) as independent predictors of END in ESUS patients.

Conclusion: Moderate-to-severe WMH is an independent risk factor for END in ESUS patients not receiving reperfusion therapy, highlighting the importance of considering WMH in the clinical evaluation and management of stroke patients.

Keywords: white matter hyperintensities, early neurological deterioration, embolic stroke of undetermined source, risk factors

Introduction

White matter hyperintensities (WMH) are a prominent neuroimaging finding associated with cerebral small vessel disease, typically appearing as bilateral and symmetrical hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences.[1] These WMH are not only a hallmark of microvascular pathology but also have been implicated in the pathogenesis of early neurological deterioration (END), a sudden exacerbation of neurological deficits in the acute phase of stroke that often foreshadows poor outcomes.[2–6]

END is a complex phenomenon that has been linked to several underlying mechanisms, including hemodynamic abnormalities and inflammation.[7,8] These factors may contribute to the disruption of cerebral microcirculation, which is further reflected by the presence of WMH. The association between WMH and END in stroke patients underscores the importance of considering microvascular health in the overall management of stroke.

Embolic stroke of undetermined source (ESUS) is a subtype of ischemic stroke that remains cryptogenic even after thorough diagnostic evaluation.[9] Characterized by an embolic pattern on neuroimaging, ESUS constitutes a significant proportion of all ischemic strokes and is associated with a relatively high annual recurrence rate despite the use of antithrombotic therapy.[10,11] This highlights the need for a better understanding of the underlying causes and risk factors for ESUS, particularly in relation to END.

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Given the limited research on the incidence and risk factors for END in ESUS patients, this study was designed to investigate the potential impact of WMH on the development of END in this specific patient population, excluding those who received reperfusion therapy. By exploring this relationship, the study aims to contribute to the body of knowledge on stroke outcomes and inform future therapeutic strategies that may mitigate the risk of END in patients with ESUS.

Methods

Data for this study were retrieved from the stroke center database of Changzhou NO.2 People's Hospital, Jiangsu Province, China. This study was approved by the Clinical Research Ethics Committee of the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University (2021KY312-01). A written informed consent was obtained from the patients or their legally authorized representatives. All methods were carried out in accordance with relevant guidelines and regulations. This study was conducted in accordance with the Declaration of Helsinki.

Participants

Consecutive ischemic stroke patients with ESUS from January 2020 to January 2022 were retrospectively enrolled. All stroke events occurred within 48 hours before admission and were confirmed by magnetic resonance imaging, specifically, diffusion weighted imaging (MRI-DWI). Other inclusion criteria were: (1) $18 \leq$ age ≤ 80 years, (2) anterior circulation infarction, and (3) the modified Rankin scale (mRS) ≤ 1 if patients had a stroke history. Patients were excluded if they (1) had other neurological diseases, (2) had severe systemic diseases that could affect the judgment of outcome, (3) had reperfusion therapy or (4) had no brain magnetic resonance angiography (MRA) or computerized tomography angiography (CTA) which would be essential to assess the stroke subtype.

Clinical Data Collection and Evaluation

Clinical data covering demography, risk factors, and clinical characteristics, were collected. Baseline neurological deficit was assessed with the National Institutes of Health Stroke Scale (NIHSS) score. Smoking was defined as self-reported daily smoking. END was defined as any persisting increase of at least 2 points in the total NIHSS score and at least 1 point on the level of consciousness or motor item score within 72 h of arrival at the hospital without another identified cause.

Diagnosis of Embolic Stroke of Undetermined Source

Essential tests like ≥24h dynamic electrocardiogram, transthoracic echocardiography, hematologic screening, cervical vascular ultrasound and cranial CTA/MRA were routinely performed. Exactly, ESUS was identified as:[10] (1) stroke detected by MRI that is not lacunar, (2) absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischemia, (3) no major-risk cardioembolic source of embolism, and (4) no other identified specific cause of stroke.

Grading of White Matter Hyperintensities

White matter hyperintensities (WMH) were rated on the FLAIR images using the Fazekas scale of 0–3, separately for periventricular and deep locations.[3] Scored characteristics were as follows. Briefly, for periventricular WMH: 0=absence, 1=caps or pencil-thin lining, 2=smooth halo, and 3=irregular periventricular hyperintensities extending into the deep white matter. For deep WMH: 0=absence, 1=punctuate foci, 2=beginning confluence of foci, and 3=large confluent areas. A total Fazekas WMH score (0–6) was acquired by combining periventricular and deep Fazekas scores. Mild WMH was defined as the total Fazekas score ≤ 2, and moderate to severe WMH as the total Fazekas score ≥ 3. A neurologist and a radiologist evaluated the WMH separately. If there were inconsistency, a consensus was reached through discussion. Limited intra-rater reliability testing (40 scans) showed a good reliability with a kappa value of 0.90 for the Fazekas scale scores.

Statistical Analysis

All statistical analysis was performed on SPSS 22.0. Continuous variables were given as mean ± standard deviation (SD) or median (interquartile range, IQR), and categorical variables were presented as frequency and percentage. For

continuous variables, pairwise comparisons were performed by the Student's *t*-test or Mann–Whitney test, and for categorical variables, the Chi-square test was used to assess the differences.

To further investigate the relationship between white matter hyperintensities (WMH) and early neurological deterioration (END), we performed binary logistic regression analysis. This analysis was adjusted for variables that demonstrated a p-value less than 0.1 in the univariate comparisons, ensuring a robust model. The enter method was used for variable entry, allowing for a comprehensive assessment of the predictors. The outcomes of the logistic regression analysis were expressed as odds ratio (OR) with 95% confidence intervals (CI). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline Information

A total of 111 patients were analyzed in this study, with 63 (56.8%) being male. The median age of the participants was 65 years (IQR 56, 72), and the median admission National Institutes of Health Stroke Scale (NIHSS) score was 3 (IQR 1, 6). Among these patients, 35 (31.5%) exhibited moderate to severe WMH, and 16 (14.4%) experienced END, as depicted in Figure 1 and detailed in Table 1.

Comparison of Variables Between WMH Groups

The cohort was stratified into two groups based on the severity of WMH: a mild WMH group and a moderate to severe WMH group, consisting of 76 and 35 patients, respectively. Patients in the moderate to severe WMH group were significantly older (p=0.001) and more likely to have a history of stroke (28.6% vs 10.5%, p=0.017). However, there was no significant difference in the prevalence of hypertension and diabetes mellitus between the two groups, as shown in Table 1.

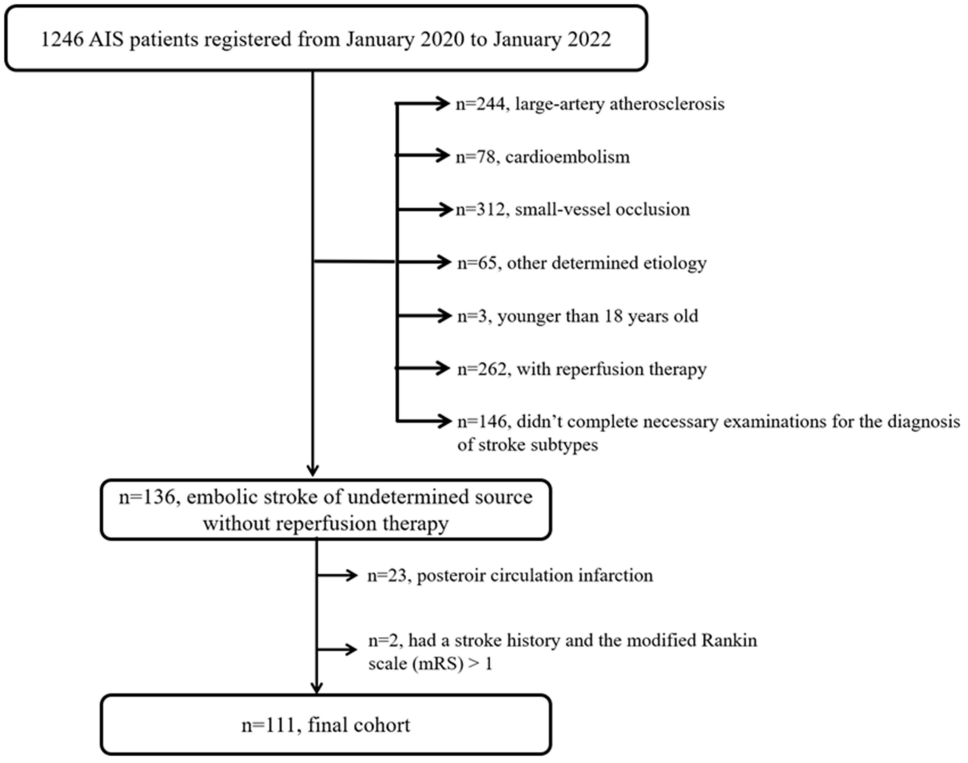

Figure 1 The participant flow chart of the study recruitment.

Table 1 Differences in Variables Between Moderate-to-Severe WMH and Mild WMH Groups

Variable	Moderate-to-Severe WMH (n=35)	Mild WMH (n=76)	*P*-Value
Age, y, median (IQR)	70 (60, 75)	63 (54, 69)	0.001
Male, n (%)	19 (54.3)	44 (57.9)	0.721
Smoking, n (%)	9 (25.7)	24 (31.6)	0.53
Alcoholic Abuse, n (%)	4 (11.4)	14 (18.4)	0.353
Hypertension, n (%)	28 (80.0)	64 (84.2)	0.584
Diabetes Mellitus, n (%)	13 (37.4)	33 (43.4)	0.533
Baseline NIHSS Score, median (IQR)	3 (1, 7)	3 (1, 5)	0.424
Stroke History, n (%)	10 (28.6)	8 (10.5)	0.017
Antithrombotic Therapy, n (%)	33 (94.3)	70 (92.1)	0.986
DAPT Within First 21 days, n (%)	24 (68.6)	57 (75)	0.479
Statin Therapy, n (%)	35 (100)	75 (98.7)	0.690
Laboratory Findings, $(\bar{x}\pm s)$			
Total Cholesterol (mmol/l)	4.5±1.0	4.1±0.9	0.061
Triglyceride (mmol/l)	1.8±1.2	1.6±0.8	0.377
LDL-C (mmol/l)	2.7±0.8	2.5±0.8	0.079
Fasting Glucose (mmol/l)	7.2±2.9	6.5±2.3	0.230
Homocysteine (μmol/l)	10.9±4.7	10.6±3.9	0.784
Fibrinogen (g/l)	3.3±1.2	2.7±0.6	0.005
D-Dimer (mg/l)	0.8±1.0	0.4±0.6	0.032

Abbreviations: WMH, White Matter Hyperintensities; END, Early Neurological Deterioration; NIHSS, National Institutes of Health Stroke Scale; DAPT, Dual Antiplatelet Therapy; LDL-C, Low-Density Lipoprotein Cholesterol; IQR, Interquartile Range.

Clinical Differences Between END and Non-END Groups

END was identified in 16 patients (14.4%), while the remaining 95 patients (85.6%) did not develop END. Those with END had a higher baseline NIHSS score (p=0.015) and a greater proportion of severe WMH (56.3% with moderate to severe WMH vs 27.4% in the non-END group, p=0.021). Additionally, a significantly higher rate of diabetes mellitus was observed among patients with END (68.8% vs 36.8% in the non-END group, p=0.017), as detailed in Table 2.

Impact of Moderate to Severe WMH on END in Regression Analysis

A multivariate binary logistic regression model was constructed to identify independent risk factors for END, including all variables with a p-value < 0.10 in the univariate analysis. The model revealed that moderate to severe WMH (Odds Ratio [OR] = 4.012, 95% Confidence Interval [CI] = 1.080–14.906, p=0.038), smoking (OR = 4.368, 95% CI = 1.171–16.293, p=0.028), and diabetes mellitus (OR = 3.986, 95% CI = 1.007–15.789, p=0.049) were significantly associated with an increased risk of END in patients with ESUS, as presented in Table 3.

Table 2 Differences in Risk Factors and Clinical Findings Between END and Non-END Groups

Variable	END (n=16)	Non-END (n=95)	*P*-Value
Age, y, median (IQR)	67 (57, 74)	64 (55, 72)	0.437
Male, n (%)	9 (56.3)	54 (56.8)	0.965
Smoking, n (%)	8 (50.0)	25 (26.3)	0.065
Alcoholic Abuse, n (%)	3 (18.8)	15 (15.8)	0.770
Hypertension, n (%)	15 (83.0)	77 (74.8)	0.168
Diabetes Mellitus, n (%)	11 (68.8)	35 (36.8)	0.017

(*Continued*)

Table 2 (Continued).

Variable	END (n=16)	Non-END (n=95)	*P*-Value
Baseline NIHSS Score, median (IQR)	5 (3, 7)	3 (1, 5)	0.015
Moderate-to-Severe WMH, n (%)	9 (56.3)	26 (27.4)	0.021
Stroke History, n (%)	4 (25.0)	14 (14.7)	0.327
Antithrombotic Therapy, n (%)	15 (93.8)	88 (92.6)	0.717
DAPT Within First 21 days, n (%)	11 (68.6)	70 (73.7)	0.681
Statin Therapy, n (%)	16 (100)	94 (98.9)	0.309
Laboratory Findings, $(\bar{x}\pm s)$			
Total Cholesterol (mmol/l)	4.8±1.2	4.1±0.9	0.060
Triglyceride (mmol/l)	2.3±1.4	1.5±0.8	0.056
LDL-C (mmol/l)	2.9±0.8	2.5±0.8	0.066
Fasting Glucose (mmol/l)	8.1±3.6	6.5±2.3	0.103
Homocysteine (μmol/l)	10.6±5.4	10.7±3.8	0.918
Fibrinogen (g/l)	2.9±0.9	2.9±0.9	0.968
D-Dimer (mg/l)	0.5±0.5	0.6±0.8	0.817

Abbreviations: WMH, White Matter Hyperintensities; END, Early Neurological Deterioration; NIHSS, National Institutes of Health Stroke Scale; DAPT, Dual Antiplatelet Therapy; LDL-C, Low-Density Lipoprotein Cholesterol; IQR, Interquartile Range.

Table 3 Influence of Moderate-to-Severe WMH on END in ESUS Patients

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	*P*-Value
Moderate-to-Severe WMH	4.012	1.080–14.906	0.038
Smoking	4.368	1.171–16.293	0.028
Diabetes Mellitus	3.986	1.007–15.789	0.049
Baseline NIHSS Score	1.136	0.928–1.391	0.216
LDL-C	1.373	0.185–10.211	0.757
Triglyceride	1.388	0.610–3.160	0.435
Total Cholesterol	0.982	0.156–6.172	0.985

Abbreviations: WMH, White Matter Hyperintensities; NIHSS, National Institutes of Health Stroke Scale; LDL-C, Low-Density Lipoprotein Cholesterol.

Discussion

Our study's findings underscore the significant association between moderate-to-severe white matter hyperintensities (WMH) and the risk of early neurological deterioration (END) in patients with embolic stroke of undetermined source (ESUS). These results align with the growing body of evidence implicating WMH as a marker of microvascular pathology in stroke patients.[3] The presence of WMH, particularly when severe, reflects widespread cerebral small vessel disease, which is increasingly recognized as a critical factor in post-stroke outcomes.[12]

The mechanisms underlying early neurological deterioration (END) in the context of acute ischemic stroke are complex and multifactorial. One such mechanism that has garnered significant attention is the failure of collateral circulation. The role of collaterals in maintaining cerebral perfusion during ischemic events is critical, and their effectiveness can significantly influence clinical outcomes. Huang et al utilized perfusion magnetic resonance imaging (MRI) to assess hemodynamic changes and collaterals in patients with acute small subcortical infarction. Their findings revealed that collateral circulation plays a pivotal role in preserving cerebral perfusion and that patients with focal hypoperfusion and a lower rate of collaterals experienced a higher rate of END.[13] This association between perfusion defects and END, as well as adverse outcomes at three months, has been corroborated by other perfusion MRI-based studies.[14] Furthermore, investigations into collateral circulation in patients with large vessel occlusion have yielded

similar results, emphasizing the importance of collaterals in determining stroke outcomes.[15–17] In addition to these findings, research has indicated that WMH can disrupt the compensation provided by collateral circulation and reduce regional cerebral blood flow.[18] Concurrently, the severity of WMH was found to be inversely associated with the rating of leptomeningeal collateral circulation in patients with acute large artery occlusion.[19] These collective findings suggest that a greater burden of WMH is indicative of worse microcirculation, thereby increasing the likelihood of END. In our study, a significantly higher rate of moderate to severe WMH was observed in patients with END (56.3% vs 27.4%, p=0.021). Our results align with the existing body of research and suggest that WMH may precipitate END by compromising collateral circulation in patients with ESUS.

Our findings also emphasize the importance of considering smoking and diabetes mellitus as modifiable risk factors in stroke management. Smoking is associated with endothelial dysfunction and atherosclerosis, contributing to stroke risk,[20] while diabetes mellitus significantly impacts microvascular disease.[21] Addressing these risk factors through targeted interventions may reduce the incidence of END in ESUS patients.

Our study has limitations, including its retrospective design and single-center setting, which may affect generalizability. The lack of longitudinal data limits our understanding of long-term outcomes. Future research should address these gaps with prospective, multicenter studies and long-term follow-up to better understand the chronic sequelae of END in ESUS patients. Investigating the impact of interventions aimed at improving microvascular health and collateral circulation could provide insights into preventive strategies.

In conclusion, our study adds to the literature by identifying moderate-to-severe WMH as an independent risk factor for END in ESUS patients. This highlights the need for a nuanced approach to stroke management, focusing on microvascular aspects of the disease. The potential benefits of early identification and management of WMH in stroke patients warrant further exploration.

Abbreviations

CI, confidence intervals; CTA, computerized tomography angiography; END, early neurological deterioration; ESUS, Embolic stroke of undetermined source; FLAIR, fluid attenuated inversion recovery; IQR, interquartile range; M(IQR), median (interquartile range); MRA, magnetic resonance angiography; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SD, standard deviation; WMH, white matter hyperintensities.

Ethics Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee of the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University (2021KY312-01). A written informed consent was obtained from the patients or their legally authorized representatives. All methods were carried out in accordance with relevant guidelines and regulations.

Data Sharing Statement

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Consent for Publication

A written informed consent to publish this study result was obtained from the patients or their legally authorized representatives. All patient data were de-identified.

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Disclosure

The authors declare that there is no conflict of interest.

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