

Original Article

Association of multimodal computed tomography imaging and early modified Rankin Scale score with prognosis in patients with wake-up stroke and stroke while awake: an exploratory study

Jun Cao^{1,2}, Ming Sun^{1,2}, Yaodong Li^{1,2}, Kai Qin^{1,2}, Leiming Xu³, Xiaodong Ma^{4,5}

¹Department of Radiology, Affiliated Haiyan Hospital of Jiaxing University, Jiaxing 314300, Zhejiang, China;

²Department of Radiology, Haiyan People's Hospital, Jiaxing 314300, Zhejiang, China; ³Department of Radiology, Second Affiliated Hospital of Zhejiang University, Hangzhou 310058, Zhejiang, China; ⁴Department of Neurology, Affiliated Haiyan Hospital of Jiaxing University, Jiaxing 314300, Zhejiang, China; ⁵Department of Neurology, Haiyan People's Hospital, Jiaxing 314300, Zhejiang, China

Received May 12, 2026; Accepted July 10, 2026; Epub September 15, 2026; Published September 30, 2026

Abstract: Objective: To evaluate the prognostic value of multimodal computed tomography (CT) imaging and early modified Rankin Scale (mRS) score in patients with wake-up stroke (WUS) and stroke while awake (SWA). Methods: This retrospective study included 108 patients with acute ischemic stroke, including 40 WUS and 68 SWA patients. All patients underwent multimodal CT imaging, including non-contrast CT, CT angiography, and CT perfusion. Early mRS was assessed within 24 hours after admission, and functional outcome was evaluated at 90 days. Firth penalized logistic regression was used to identify factors associated with poor functional outcome. Hierarchical models were constructed to evaluate the incremental value of early mRS and CTP-derived mismatch ratio beyond admission NIHSS. ROC analysis and nomogram construction were performed. Results: Compared with SWA patients, WUS patients showed higher admission NIHSS scores, longer onset-to-admission intervals, and worse perfusion profiles, including lower CBF, higher MTT and TTP, and lower mismatch ratio (all $P < 0.05$). Early mRS and CTP-derived mismatch ratio were independently associated with poor 90-day functional outcome in the Firth logistic regression model. The final model showed good discrimination (AUC = 0.964, 95% CI: 0.929-0.999). Adding early mRS significantly improved discrimination beyond admission NIHSS (AUC: 0.612 vs. 0.925, $P < 0.001$), and further addition of mismatch ratio provided additional improvement (AUC: 0.925 vs. 0.964, $P = 0.041$). Conclusion: Early mRS provides substantial prognostic information beyond admission NIHSS, and CTP-derived mismatch ratio offers additional value for 90-day functional outcome assessment. The combined model may assist individualized risk stratification in patients with WUS and SWA.

Keywords: Multimodal computed tomography imaging, wake-up stroke, stroke while awake, early modified Rankin Scale, prognostic evaluation, exploratory study

Introduction

Wake-up stroke (WUS) and stroke while awake (SWA) account for approximately 20%-30% of all ischemic strokes. These two subtypes are characterized by differences in the certainty of symptom onset timing, which significantly affects therapeutic decision-making [1]. Conventional treatment paradigms based on "last known well (LKW)" often exclude these patients from reperfusion therapy, thereby increasing the risk of poor outcomes [2]. With recent advances in imaging technology, multimodal com-

puted tomography (CT), including non-contrast CT (NCCT), CT perfusion (CTP), and CT angiography (CTA), has become instrumental in identifying stroke etiology, evaluating the ischemic penumbra (IP), and guiding treatment strategies in patients with WUS and SWA [3]. In addition, early assessment using the modified Rankin Scale (mRS), a key measure of post-stroke functional outcomes, may offer dynamic and individualized prognostic insights. However, few systematic studies have investigated the combined prognostic value of multimodal CT and early mRS assessment in patients with WUS

and SWA. Moreover, the heterogeneity between these two groups remains underexplored.

Currently, the clinical management of WUS and SWA remains a subject of ongoing debate. While landmark trials such as DAWN and DEFUSE-3 have demonstrated the benefit of imaging-guided extended-window reperfusion therapies [4], studies specifically investigating the imaging-clinical correlation in WUS and SWA patients remain limited. In terms of imaging assessment, multimodal CT can help identify patients likely to benefit from therapy by quantifying hemodynamic parameters such as infarct core volume, hypoperfused volume, and perfusion mismatch ratio [5]. However, it is still unclear whether these imaging biomarkers outperform traditional clinical scales in prognostic prediction for the WUS/SWA populations. Furthermore, early neurological deterioration is relatively common in both WUS and SWA [6], and early changes in mRS assessed within 24 hours after hospital admission may provide additional prognostic information - an aspect that has often been overlooked in favor of focusing on 90-day outcomes.

In this context, we performed a retrospective study of 108 patients with acute ischemic stroke (AIS) admitted to Haiyan County People's Hospital between January 2024 and March 2025, to explore the clinical value of multimodal CT imaging combined with early mRS assessment in prognostic prediction in patients with WUS and SWA.

Materials and methods

Study subjects

This retrospective study included 108 patients with AIS admitted to Haiyan County People's Hospital between January 2024 and March 2025. All patients underwent multimodal CT imaging upon admission.

Patients were included if they: (1) presented with sudden-onset hemiplegia, speech impairment, or altered consciousness consistent with a diagnosis of AIS; (2) experienced their first-ever stroke; (3) were admitted to the hospital within 24 hours of their LKW; (4) underwent multimodal CT imaging (NCCT, CTA, and CTP) with sufficient image quality for post-processing; (5) had complete follow-up data and mRS

scores; and (6) received standardized scanning protocols and treatments according to relevant clinical guidelines.

Patients were excluded if they: (1) had a history of prior stroke or other neurological disorders; (2) had imaging findings indicative of hemorrhagic stroke, brain tumors, or other non-ischemic lesions; (3) were diagnosed with severe cardiac, hepatic, or renal dysfunction, or concomitant malignant tumors; (4) failed to complete mRS scoring or had incomplete follow-up within 90 days post-stroke; or (5) had multimodal CT images with severe artifacts or poor quality precluding accurate post-processing and analysis.

The hospital's ethics committee approved this study (approval No. 2023-05), which was conducted in accordance with the ethical standards of the Declaration of Helsinki. Based on onset time characteristics, patients were categorized into the WUS group (patients who woke up with stroke symptoms and had an unknown onset time) and the SWA group (patients who developed stroke symptoms while awake with a clearly defined onset time).

The sample size was calculated using PASS software (version 15.0, NCSS, LLC, USA) based on the comparison of two independent proportions. The required sample size was estimated using the following formula:

$$n = \frac{(Z_{\alpha/2} \sqrt{2\bar{p}(1-\bar{p})} + Z_{\beta} \sqrt{p_1(1-p_1) + p_2(1-p_2)})^2}{(p_1 - p_2)^2}$$

Where p_1 and p_2 represent the assumed poor outcome rates in the WUS and SWA groups, respectively. With $p_1=0.60$, $p_2=0.35$, $\alpha = 0.05$, and power = 80%, the calculated minimum sample size was 39 patients per group (total 78). Accounting for a 10% loss to follow-up and a 5% imaging quality exclusion rate, we enrolled 108 patients (WUS: 40, SWA: 68). The final sample met the minimum requirement for the WUS group, while the SWA group was oversampled due to its higher prevalence in our clinical population.

Data collection

Clinical data collected included sex, age, medical history, low-density lipoprotein cholesterol level, mRS scores at 24 hours post-admission

and 90-day post-stroke outcome, National Institutes of Health Stroke Scale (NIHSS) scores at admission, 24 hours post-admission, and 7 days post-admission, stroke vascular territory (anterior or posterior circulation), and multimodal CT imaging parameters. All patients received standard stroke management according to clinical guidelines, including intravenous thrombolysis (IVT), endovascular thrombectomy (EVT), or conservative medical therapy (e.g., antiplatelet or anticoagulant agents), at the discretion of the treating physicians based on clinical presentation and imaging findings. For patients with WUS, the onset-to-admission interval was estimated using the LKW time. For SWA patients, the onset time was defined as the time of symptom onset as reported by the patient or witnesses. Follow-up was conducted via telephone or face-to-face visits, during which 90-day mRS scores were assessed. Repeat cranial CT or magnetic resonance imaging (MRI) was performed when clinically indicated.

Imaging methods

NCCT was primarily used to exclude intracranial hemorrhage and other non-ischemic lesions, and to evaluate early ischemic changes before further perfusion and vascular imaging assessment. The NCCT findings were reviewed by experienced radiologists.

CTP data were imported into the uAI-CT workstation (United Imaging Intelligence Co., Ltd., Shanghai, China) for post-processing using dedicated stroke protocol software. The software automatically generated color-coded perfusion maps, which were evaluated at the axial slice showing the maximal lesion extent. Regions of interest (ROIs) included the infarct core and ischemic penumbra (IP), which were automatically generated by the uAI-CT stroke analysis software based on predefined perfusion thresholds. The generated ROIs were reviewed and confirmed by two experienced radiologists, and any discrepancies were resolved by consensus. The software paired these regions of interest with mirrored contralateral brain regions to derive perfusion parameters, including cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), time to peak (TTP), and time to maximum (Tmax). The IP was defined based on the mismatch between the hypoperfused area and the infarct core. These

parameters were used to assess cerebral perfusion status, identify and quantify hypoperfused areas and infarct core, and perform mismatch analysis. Infarct core was defined as tissue with relative CBF < 30%, and hypoperfused tissue was defined as Tmax > 6 seconds, consistent with commonly used thresholds in CTP studies.

Head and neck CTA data were post-processed using uAI-CT vascular software (United Imaging Intelligence, Shanghai, China) to reconstruct the cervical and intracranial vasculature. The software automatically reconstructed head and neck arteries with bone removal, and enabled detection of vascular variants, atherosclerotic plaques, and aneurysms. It provided information on vessel stenosis degree and plaque type. Maximum intensity projection, volume rendering, and multiplanar reconstruction images were generated for evaluation of the cervical and intracranial arteries. Image quality was independently assessed by two senior physicians who were blinded to clinical data. Disagreements were resolved by consensus.

Image quality evaluation

Head and neck CTA image quality was scored according to published criteria [7] as follows: 3 points - clear vessels with good contrast, smooth vessel walls, and no obvious background noise; 2 points - clear vessels with good contrast, but with slight vessel wall irregularity or mild background noise that did not affect diagnostic interpretation; 1 point - poor vessel contrast, obvious vessel wall irregularity, or significant background noise. Images scoring 2-3 were considered diagnostically acceptable; a score of 1 was deemed insufficient for diagnosis. CTP image quality was evaluated using a three-level scoring system based on four factors: (1) color-scale differences between gray and white matter perfusion; (2) color-scale differences between ischemic lesions and normal tissue perfusion; (3) image uniformity; and (4) presence or absence of artifacts [8]. Each factor was scored as good (2 points), moderate (1 point), or poor (0 points), with a maximum total score of 8 points. A total score > 6 indicated high image quality (7-8 points) with good diagnostic value. Scores of 4-6 indicated moderate image quality sufficient for basic diagnostic purposes. Scores ≤ 3 indicated poor image

quality, precluding accurate diagnosis. Image quality was independently assessed by two senior radiologists using the above-mentioned criteria [7, 8]. Any discrepancies between the two assessments were resolved through consensus.

Neurological function and prognostic evaluation

At 90 days after stroke onset, follow-up was conducted by neurologists from the study team via telephone or face-to-face interviews. The primary outcome was the 90-day mRS score, with scores of 0-2 defined as favorable functional outcome and scores ≥ 3 as poor functional outcome [9, 10]. Secondary outcome measures included NIHSS scores at 24 hours and 7 days post-admission. NIHSS scores were categorized as follows: 0 = normal neurological function; 1-4 = mild stroke; 5-15 = moderate stroke; 16-20 = moderate-to-severe stroke; and 21-42 = severe stroke [11].

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 and R software version 4.3.1. Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range), and categorical variables were expressed as numbers and percentages. Between-group comparisons were performed using the independent-samples t test, Mann-Whitney U test, chi-square test, or Fisher's exact test, as appropriate. Point-biserial correlation analysis was used to assess the associations between multimodal CT parameters, early mRS score, and 90-day functional outcome. Due to the limited number of outcome events, Firth penalized logistic regression was applied to reduce small-sample bias and identify factors associated with poor functional outcome. Candidate variables were selected according to clinical relevance and correlation analysis. The final model included age, admission NIHSS, early mRS score, and CTP-derived mismatch ratio. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Three hierarchical Firth logistic regression models were constructed to evaluate incremental prognostic value. Model 1 included admission NIHSS alone, Model 2 added early mRS, and Model 3 further added mismatch ratio. Model performance was assessed using the area under the

receiver operating characteristic curve (AUC), and differences between models were compared using DeLong's test. ROC analysis was performed using predicted probabilities from the final model, with 1,000 bootstrap resampling iterations to estimate 95% CIs. A nomogram was developed based on the final Firth logistic regression model to visualize the estimated probability of poor 90-day functional outcome. A two-sided P value < 0.05 was considered statistically significant.

Results

Comparison of basic clinical characteristics between WUS and SWA groups

Compared with the SWA group, the WUS group were older, had higher admission NIHSS scores, and had significantly longer onset-to-admission intervals (all $P < 0.05$). No significant differences were observed between the two groups in sex, history of hypertension or diabetes, stroke vascular territory, or treatment variables, including reperfusion therapies (intravenous thrombolysis [IVT] and endovascular thrombectomy [EVT]) and subsequent medical therapies (antiplatelet or anticoagulant therapy) (all $P > 0.05$; **Table 1**).

Differences in multimodal CT imaging parameters and image quality assessment between WUS and SWA groups

The WUS group had significantly lower CBF and higher MTT and TTP than the SWA group (all $P < 0.05$), whereas CBV did not differ significantly between the two groups ($P > 0.05$). Furthermore, the volume of tissue with $T_{max} > 6$ s was larger, and the mismatch ratio (defined as the ratio of IP to infarct core volume) was lower in the WUS group than in the SWA group (both $P < 0.05$). CTA and CTP image quality scores did not differ significantly between the two groups (both $P > 0.05$). Detailed imaging parameters and image quality scores are presented in **Table 2**.

Representative imaging findings from the two groups are presented in **Figures 1** and **2**. Case 1 (WUS group) was a 65-year-old male patient who presented with right limb weakness and aphasia at 6 hours after symptom onset. CTA three-dimensional reconstruction images (**Figure 1A, 1B**) demonstrated vascular abnormalities in the right middle cerebral artery (MCA)

Table 1. Baseline characteristics of the WUS and SWA groups

Variables	WUS group (n = 40)	SWA group (n = 68)	Statistical value	P
Age (years)	68.93 ± 8.26	59.93 ± 7.66	5.726	0.000
Sex (male/female, n, %)	17 (42.5%)/23 (57.5%)	33/35	0.368	0.544
History of hypertension (n, %)	28 (70.0%)	37 (54.4%)	2.554	0.110
History of diabetes mellitus (n, %)	10 (25.0%)	18 (26.5%)	0.028	0.866
LDL-C (mmol/L)	2.92 ± 0.56	3.13 ± 0.60	-1.850	0.067
Vascular territory (anterior circulation, n, %)	25 (62.5%)	53 (77.9%)	2.993	0.084
Admission NIHSS score	12.10 ± 3.64	6.79 ± 2.39	9.135	< 0.001
Onset-to-admission interval (hours)	14.80 ± 5.21	7.53 ± 3.35	8.822	< 0.001
mRS score at 24 h post-admission	3.08 ± 1.27	2.13 ± 0.99	4.295	< 0.001
IVT (n, %)	6 (15.0%)	17 (25.0%)	1.503	0.220
EVT (n, %)	3 (7.5%)	6 (8.8%)	0.058	0.810
Antiplatelet therapy (n, %)	30 (75.0%)	52 (76.5%)	0.030	0.863
Anticoagulant therapy (n, %)	4 (10.0%)	8 (11.8%)	0.079	0.778

Note: Data are presented as mean ± SD for normally distributed continuous variables or n (%) for categorical variables. Group comparisons were performed using the independent samples t-test for continuous variables and the χ^2 test for categorical variables, as appropriate. Abbreviations: WUS, wake-up stroke; SWA, stroke while awake; SD, standard deviation; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; IVT, intravenous thrombolysis; EVT, endovascular thrombectomy; LDL-C, low-density lipoprotein cholesterol.

Table 2. Differences in multimodal CT imaging parameters and image quality evaluation between WUS and SWA groups

Parameters		WUS group (n = 40)	SWA group (n = 68)	Statistical value	<i>P</i>
Perfusion parameters	CBF (mL/100 g/min)	30.46 ± 4.78	39.79 ± 5.28	-9.173	< 0.001
	CBV (mL/100 g)	2.05 ± 0.39	1.99 ± 0.27	1.013	0.313
	MTT (s)	6.55 ± 1.15	5.01 ± 0.94	7.306	< 0.001
	TTP (s)	8.48 ± 0.99	6.96 ± 1.04	7.694	< 0.001
	Tmax > 6 s volume (mL)	9.53 ± 1.09	7.47 ± 1.03	10.327	< 0.001
	Mismatch ratio (penumbra/core infarct)	1.95 ± 1.22	2.31 ± 0.47	-9.702	< 0.001
CTA image quality, n (%)	Excellent (3 points)	10 (25%)	20 (29%)	0.497	0.483
	Good (2 points)	24 (60%)	37 (54%)		
	Poor (1 point)	6 (15%)	11 (16%)		
CTP image evaluation, n (%)	High quality (> 6 points)	28 (70%)	51 (75%)	0.613	0.435
	Moderate (4-6 points)	10 (25%)	14 (21%)		
	Poor (≤ 3 points)	2 (5%)	3 (4%)		

Note: Data are presented as mean ± SD for continuous variables or n (%) for categorical/ordinal variables. Group comparisons were performed using the independent samples t-test or Mann-Whitney U test for continuous variables, and the χ^2 test or Mann-Whitney U test for categorical/ordinal variables, as appropriate. Abbreviations: CT, computed tomography; WUS, wake-up stroke; SWA, stroke while awake; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; TTP, time to peak; Tmax, time to maximum; CTA, computed tomography angiography; CTP, CT perfusion; SD, standard deviation.

territory. Head and neck CTA (**Figure 1C-F**) revealed severe stenosis of the left internal carotid artery (ICA) at the C1 segment and of the M2 segment of the MCA, with sparse distal collateral vessels. Head NCCT (**Figure 1G**) showed preserved gray-white matter differentiation without obvious abnormal density. Whole-brain CTP imaging (**Figure 1H, 1I**) demonstrated prolonged TTP and MTT in the left

temporal lobe compared with the contralateral side, with mildly decreased CBV and significantly reduced CBF. The infarct core volume was 15.4 mL, the hypoperfused volume (Tmax > 6 s) was 159.0 mL, the penumbra volume was 143.6 mL, and the mismatch ratio was 10.3, which is substantially higher than the group mean (1.95 ± 1.22), illustrating the heterogeneity within the WUS group.

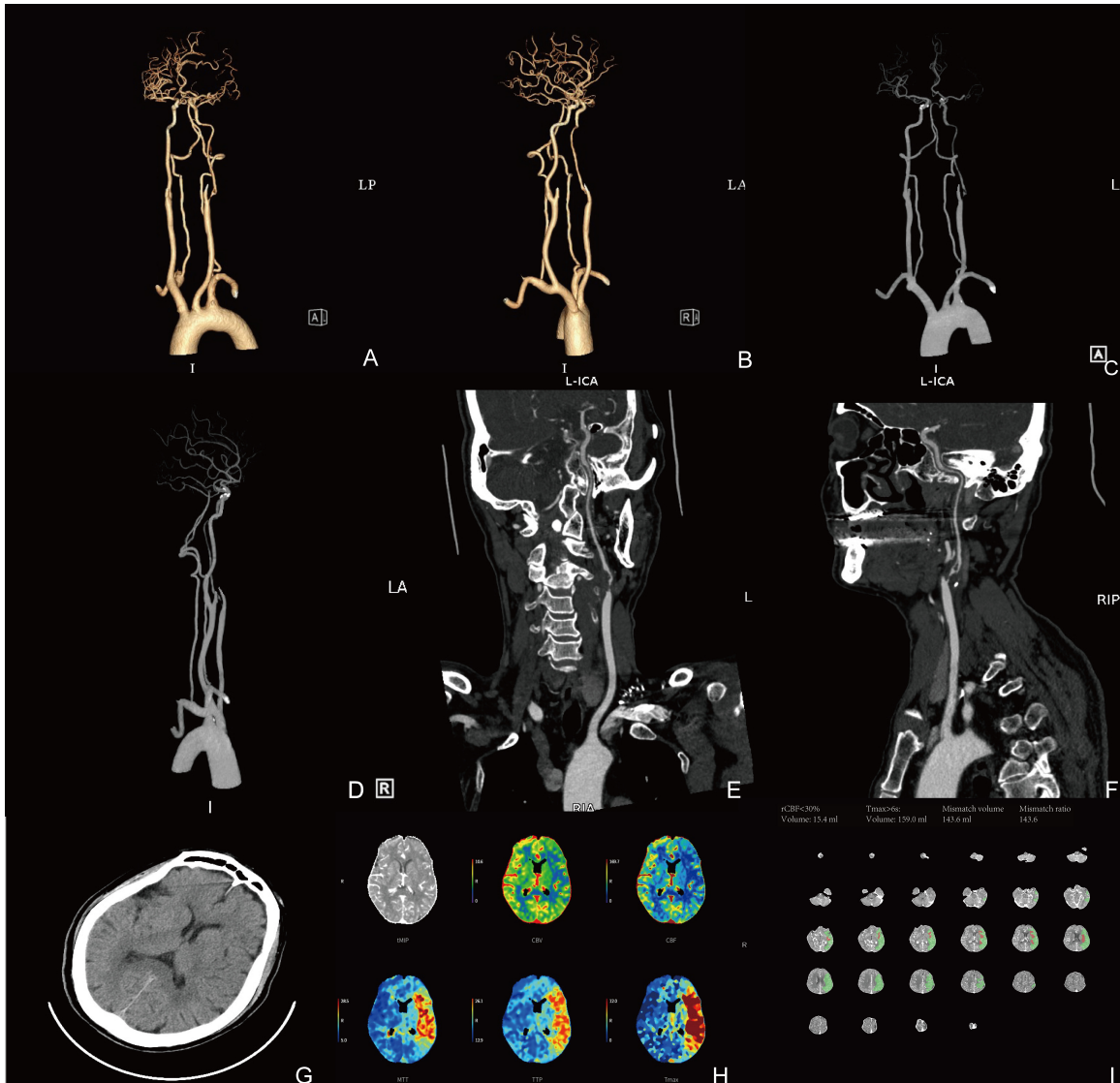


Figure 1. Representative multimodal CT imaging findings in a WUS patient with left ICA and MCA stenosis. Note: A, B. 3D reconstruction images showing vascular abnormalities in the right MCA territory; C-F. Head and neck CTA images revealing severe stenosis of the left ICA at the C1 segment and of the M2 segment of the MCA, with sparse distal collateral vessels; G. Head NCCT showing preserved gray-white matter differentiation without obvious abnormal density; H, I. Whole-brain CTP images demonstrating prolonged TTP and MTT in the left temporal lobe compared with the contralateral side, with mildly decreased CBV and significantly reduced CBF. The infarct core volume was 15.4 mL, the hypoperfused volume ($T_{max} > 6$ s) was 159.0 mL, the penumbra volume was 143.6 mL, and the mismatch ratio was 10.3. Abbreviations: CT, computed tomography; WUS, wake-up stroke; 3D, three-dimensional; CBF, cerebral blood flow; CBV, cerebral blood volume; CTA, computed tomography angiography; ICA, internal carotid artery; MCA, middle cerebral artery; MTT, mean transit time; NCCT, non-contrast computed tomography; TTP, time to peak; CTP, computed tomography perfusion; L-ICA, left internal carotid artery; tMIP, thin-slab maximum intensity projection; rCBF, relative cerebral blood flow; T_{max} , time to maximum of the residue function; LIP, left ischemic penumbra; RIP, right ischemic penumbra. “R” indicates the right side of the patient.

Case 2 (SWA group) was a 91-year-old female patient who presented with left-sided limb weakness and aphasia at 2.5 hours after symptom onset. CTA three-dimensional reconstruction images (**Figure 2A, 2B**) demonstrated vas-

cular occlusion in the right MCA territory. Head and neck CTA (**Figure 2C-F**) showed occlusion of the right ICA at the C2 segment and in the MCA territory, with delayed opacification of the distal ICA. Head NCCT (**Figure 2G**) revealed

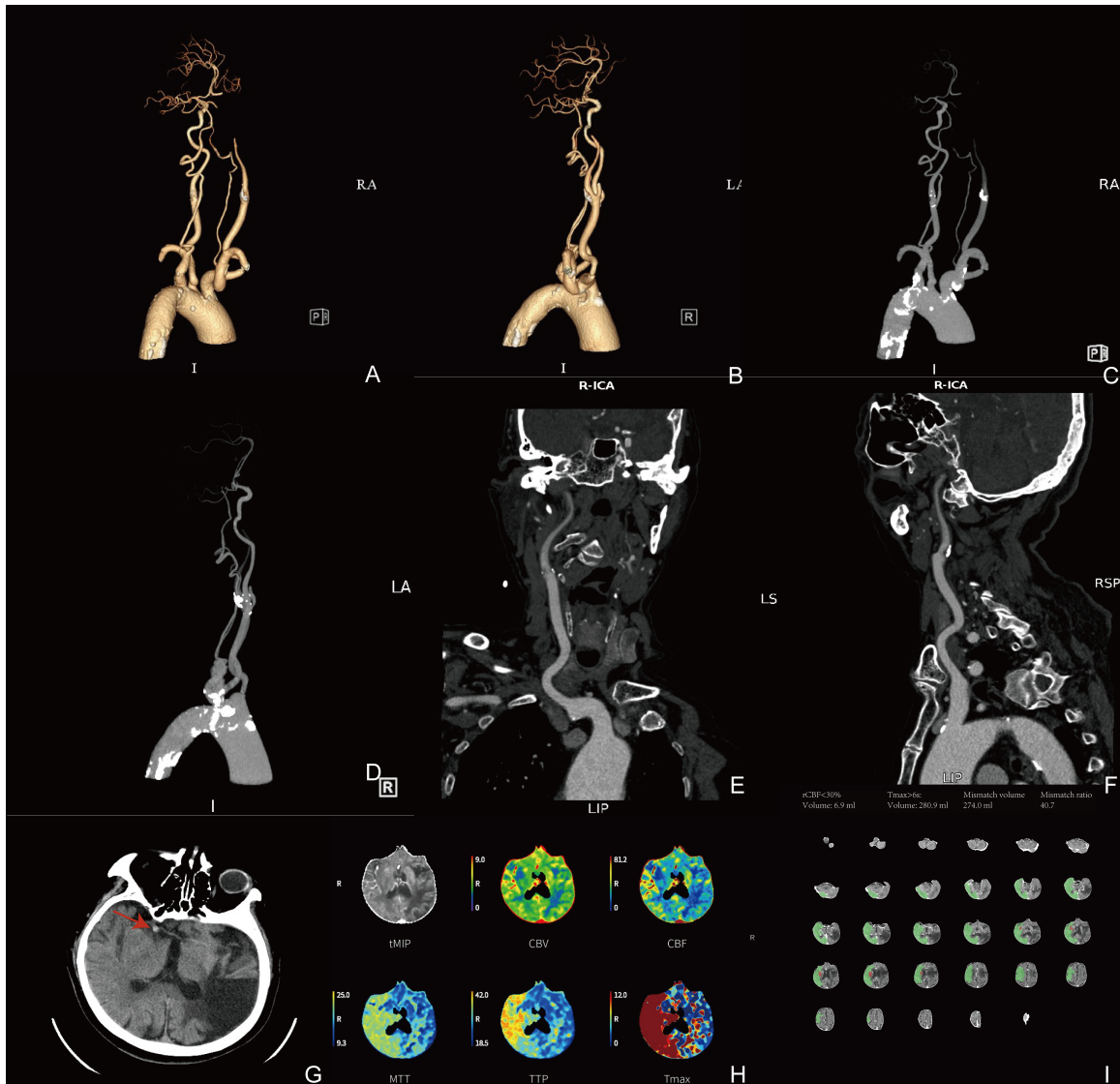


Figure 2. Multimodal CT imaging findings in an SWA patient with right MCA territory occlusion. Note: A, B. 3D reconstruction images demonstrating vascular occlusion in the right MCA territory; C-F. Head and neck CTA images showing occlusion of the right ICA at the C2 segment and in the MCA territory, with delayed opacification of the distal ICA; G. Head NCCT revealing a hyperdense artery sign in the right MCA territory (arrow) and an old infarct in the left cerebral hemisphere, suggestive of a prior ischemic stroke; H, I. Whole-brain CTP images including CBV, CBF, MTT, TTP, and Tmax maps, demonstrating prolonged TTP and MTT in the right frontal, parietal, temporal, and occipital lobes, as well as the basal ganglia, compared with the contralateral side. CBV and CBF were both reduced. The infarct core volume was 6.9 mL, the hypoperfused volume (Tmax > 6 s) was 280.9 mL, the penumbra volume was 274.0 mL, and the mismatch ratio was 40.7. Abbreviations: SWA, stroke while awake; 3D, three-dimensional; CTA, computed tomography angiography; ICA, internal carotid artery; MCA, middle cerebral artery; MIP, maximum intensity projection; MTT, mean transit time; NCCT, non-contrast computed tomography; CTP, computed tomography perfusion; Tmax, time to maximum; TTP, time to peak; tMIP, thin-slab maximum intensity projection; rCBF, relative cerebral blood flow; LIP, left ischemic penumbra. "R" indicates the right side of the patient.

a hyperdense artery sign in the right MCA territory (arrow) and an old infarct in the left cerebral hemisphere, suggestive of a prior ischemic stroke. Whole-brain CTP imaging (**Figure 2H, 2I**)

demonstrated prolonged TTP and MTT in the right frontal, parietal, temporal, and occipital lobes, as well as the basal ganglia, compared with the contralateral side. CBV and CBF were

Table 3. Comparison of early neurological function changes between WUS and SWA groups

Time point	WUS group (n = 40)	SWA group (n = 68)	t value	P
At admission	12.10 ± 3.64	6.79 ± 2.39	9.135	< 0.001
24 h post-admission	10.30 ± 3.69	3.84 ± 2.62	10.613	< 0.001
7 d post-admission	9.35 ± 3.81	3.18 ± 2.46	10.247	< 0.001

Note: Data are presented as mean ± SD. Group comparisons at each time point were performed using the independent samples t-test. Abbreviations: WUS, wake-up stroke; SWA, stroke while awake; SD, standard deviation.

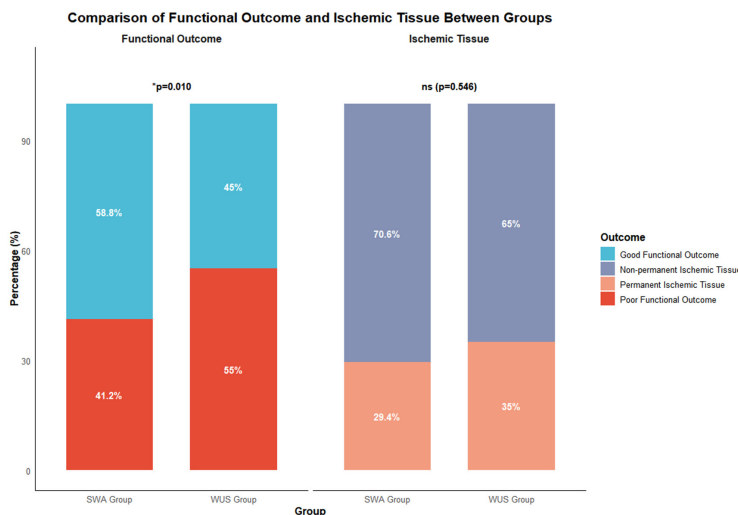


Figure 3. Comparison of 90-day functional outcomes and follow-up imaging findings between WUS and SWA groups. Note: Data are presented as percentages, with the number of patients shown on each bar. Group comparisons were performed using the χ^2 test. *P* values for group comparisons are shown above the corresponding bars. ns, not significant. Color coding: Blue bars, favorable functional outcome (mRS 0-2); red bars, poor functional outcome (mRS ≥ 3); light blue bars, non-permanent ischemic tissue; light red bars, permanent ischemic tissue. Abbreviations: WUS, wake-up stroke; SWA, stroke while awake; mRS, modified Rankin Scale.

both reduced. The infarct core volume was 6.9 mL, the hypoperfused volume (Tmax > 6 s) was 280.9 mL, the penumbra volume was 274.0 mL, and the mismatch ratio was 40.7.

Comparison of early neurological function changes between WUS and SWA groups

Compared with the SWA group, the WUS group had significantly higher NIHSS scores at admission, 24 hours post-admission, and 7 days post-admission (all *P* < 0.05; **Table 3**).

Analysis of 90-day post-stroke outcome between WUS and SWA groups

At 90 days after stroke onset, the rate of poor functional outcome (mRS ≥ 3) was higher in the

WUS group (62.5%, 25/40) than in the SWA group (36.8%, 25/68; *P* < 0.05) (**Figure 3**).

Point-biserial correlation analysis between CTP-derived parameters, early mRS score, and 90-day functional outcome

Point-biserial correlation analysis was performed to assess the correlations between continuous variables, including CTP-derived parameters and early mRS score at 24 hours after admission, and 90-day functional outcome (0 = favorable outcome, 1 = poor functional outcome). Among the CTP-derived parameters, CBF showed a significant negative correlation with 90-day poor functional outcome (*r* = -0.672, *P* < 0.001). CBV was not significantly correlated with functional outcome (*r* = -0.027, *P* = 0.779). MTT (*r* = 0.678, *P* < 0.001), TTP (*r* = 0.639, *P* < 0.001), and Tmax (*r* = 0.651, *P* < 0.001) showed significant positive correlations with poor functional outcome. Mismatch ratio was negatively correlated with poor functional outcome (*r* = -0.350, *P* < 0.001). Early mRS score at 24 hours after admission showed a significant positive correlation with 90-day poor functional outcome

(*r* = 0.768, *P* < 0.001). The correlation matrix of CTP-derived parameters, early mRS score, and 90-day functional outcome is presented in **Figure 4**.

Firth penalized logistic regression and ROC curve analysis

To address potential separation and small-sample bias associated with conventional logistic regression, Firth's penalized logistic regression was performed to identify factors independently associated with poor functional outcome at 90 days. The model included age, admission NIHSS, early mRS score at 24 hours after admission, and CTP-derived mismatch ratio. In the Firth logistic regression model, early mRS score remained independently associated with

Multimodal CT and early mRS in WUS and SWA

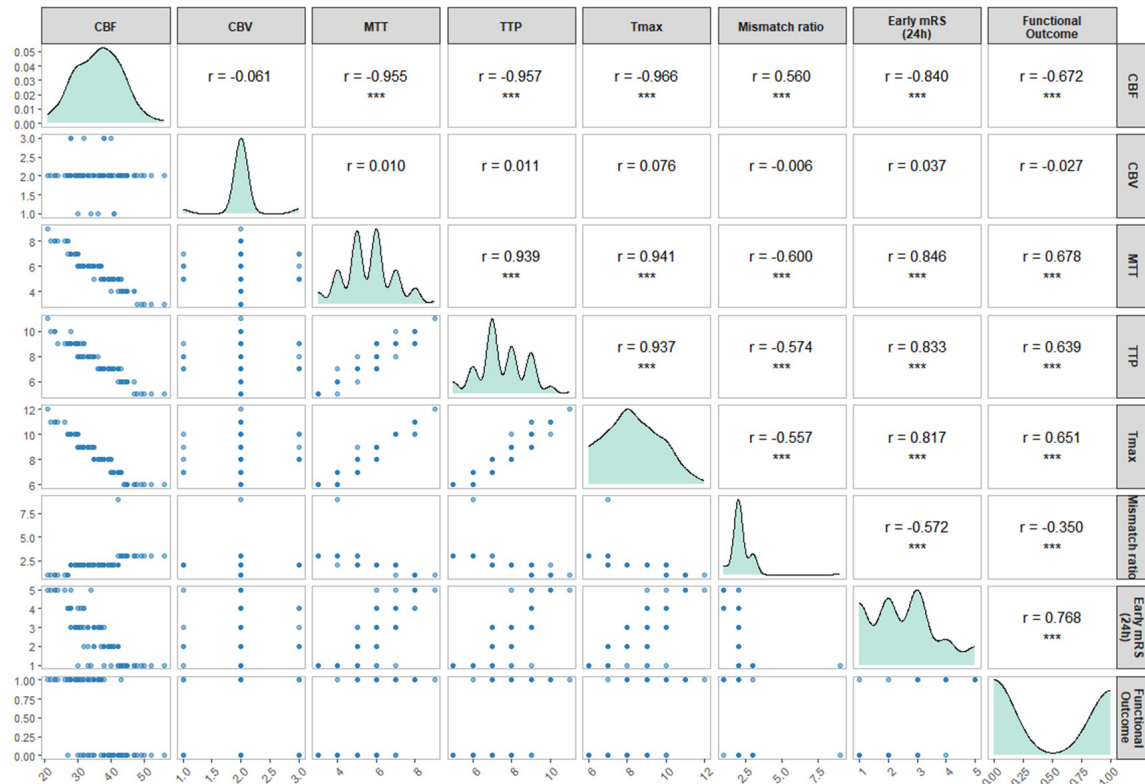


Figure 4. Correlation matrix between CTP-derived parameters, early mRS score, and 90-day functional outcome. Note: Statistical method: point-biserial correlation. Positive and negative correlations are indicated by color intensity. *** $P < 0.001$. Abbreviations: CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transit time; TTP, time to peak; Tmax, time to maximum; mRS, modified Rankin Scale; CT, computed tomography.

Table 4. Firth penalized logistic regression analysis of factors associated with poor functional outcome at 90 days

Variable	β coefficient	SE	z value	P value	OR (95% CI)
Age	-0.059	0.044	-1.354	0.176	0.942 (0.865-1.027)
Admission NIHSS	-0.105	0.089	-1.184	0.236	0.900 (0.757-1.071)
Early mRS (24 h)	3.951	0.770	5.131	< 0.001	51.990 (11.490-235.160)
CTP-derived mismatch ratio	0.839	0.356	2.359	0.018	2.310 (1.150-4.650)

Note: Data are presented as coefficients, standard errors, z values, P values, and ORs with 95% CIs. VIF analysis revealed severe multicollinearity among perfusion parameters ($VIF > 10$), and thus coefficients should be interpreted with caution. Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; CTP, computed tomography perfusion; OR, odds ratio; CI, confidence interval.

poor functional outcome at 90 days, and CTP-derived mismatch ratio provided additional prognostic information after adjustment (**Table 4**). ROC curve analysis based on the predicted probabilities from the Firth logistic regression model showed excellent discrimination for 90-day poor functional outcome, with an AUC of 0.964 (95% CI: 0.929-0.999) (**Figure 5**).

Incremental prognostic value of early mRS and CTP-derived mismatch ratio

To evaluate the incremental value of early neurological status and CTP-derived mismatch ratio beyond admission NIHSS, three hierarchical Firth penalized logistic regression models were constructed. Model 1 included admission

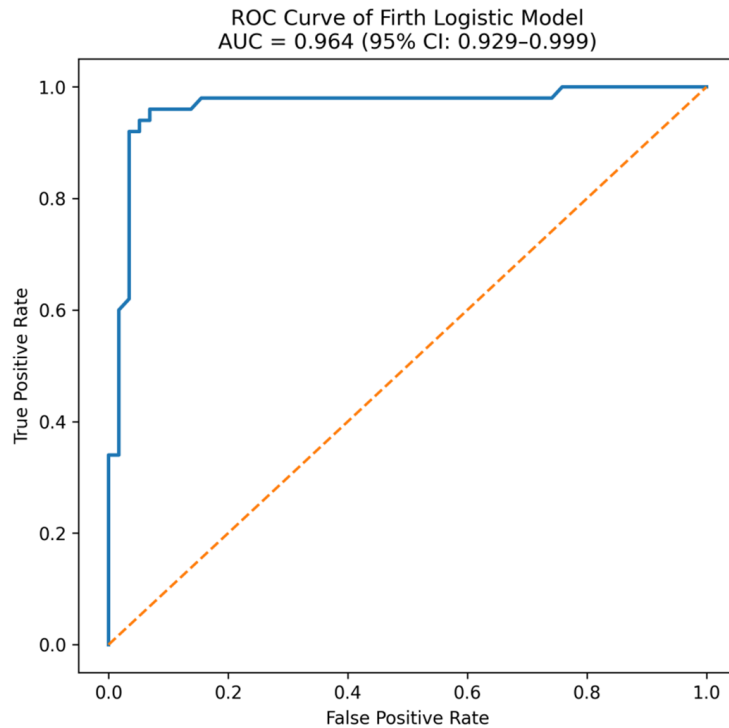


Figure 5. Receiver operating characteristic curve of the Firth penalized logistic regression model for 90-day functional outcome. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

NIHSS alone, Model 2 added early mRS score at 24 hours after admission, and Model 3 further incorporated CTP-derived mismatch ratio.

Model discrimination progressively improved with the addition of early mRS and mismatch ratio. Compared with Model 1, Model 2 showed a significant increase in discriminative performance (AUC: 0.612 vs. 0.925, $P < 0.001$). The further addition of mismatch ratio in Model 3 resulted in a modest but significant improvement compared with Model 2 (AUC: 0.925 vs. 0.964, $P = 0.041$). These findings indicate that early mRS provides substantial prognostic information beyond admission NIHSS, while CTP-derived mismatch ratio offers additional incremental value for functional outcome stratification (**Table 5**).

Nomogram construction based on the Firth penalized logistic regression model

Based on the final Firth penalized logistic regression model, a nomogram was developed to estimate the probability of poor functional outcome at 90 days after stroke (**Figure 6**). The

nomogram incorporated admission NIHSS, early mRS score at 24 hours after admission, and CTP-derived mismatch ratio. Each variable was assigned a corresponding score, and the total score was converted into an estimated probability of poor functional outcome.

Discussion

Acute ischemic stroke (AIS) remains a major cause of mortality and long-term disability worldwide [12]. Accurate assessment of disease severity and early outcome stratification are essential for individualized management. However, prognostic evaluation remains challenging in patients with uncertain stroke onset, particularly in those with wake-up stroke (WUS). Because the exact onset time is unavailable, WUS patients may experience delayed hospital presentation and treatment opportunities compared with patients with

clearly witnessed stroke onset [13]. Stroke while awake (SWA) patients, in contrast, usually have a definite onset time, which may facilitate earlier clinical assessment. Therefore, identifying clinical and imaging factors associated with functional outcomes in WUS and SWA patients remains clinically relevant.

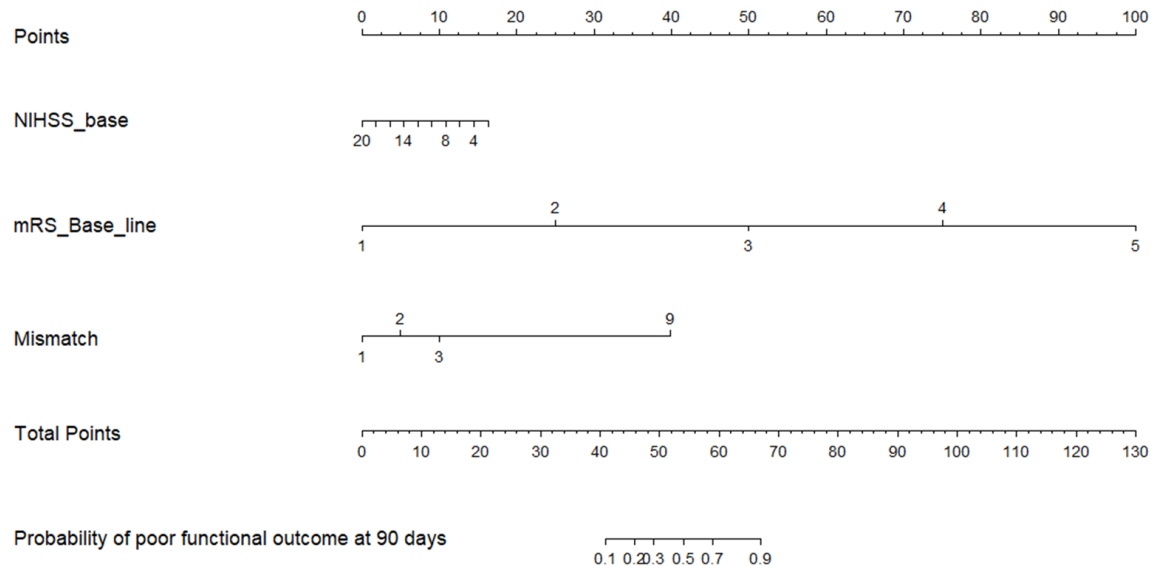
Multimodal computed tomography (CT), including non-contrast CT (NCCT), CT angiography (CTA), and CT perfusion (CTP), has been widely incorporated into acute stroke workflows for evaluating vascular status and cerebral perfusion characteristics [14]. Previous clinical trials, including DAWN and DEFUSE-3, demonstrated the value of imaging-based tissue assessment for selecting patients who may benefit from reperfusion therapy beyond conventional time windows. However, whether multimodal CT parameters provide additional prognostic information beyond early neurological assessment in WUS and SWA patients remains insufficiently explored.

In the present study, WUS patients showed higher admission NIHSS scores, longer onset-

Table 5. Incremental value of early mRS and CTP-derived mismatch ratio for 90-day functional outcome

Model	Variables	AUC (95% CI)	Compared model	P value
Model 1	Admission NIHSS	0.612 (0.507-0.717)	-	-
Model 2	Admission NIHSS + Early mRS (24 h)	0.925 (0.875-0.975)	Model 2 vs. Model 1	< 0.001
Model 3	Admission NIHSS + Early mRS (24 h) + CTP mismatch ratio	0.964 (0.929-0.999)	Model 3 vs. Model 2	0.041

Note: Data are presented as AUC with 95% bootstrap confidence intervals. Model 1 included admission NIHSS alone; Model 2 added early mRS to Model 1; Model 3 further added the CTP-derived mismatch ratio. Comparisons of AUC values between models were performed using DeLong's test. Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; CTP, computed tomography perfusion.

**Figure 6.** Nomogram based on the Firth penalized logistic regression model for estimating the probability of poor functional outcome at 90 days after stroke. Abbreviations: CTP, computed tomography perfusion; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

to-admission intervals, and more unfavorable perfusion characteristics compared with SWA patients, including lower CBF, higher MTT and TTP, larger Tmax > 6 s volumes, and lower mismatch ratios. These findings indicate that differences in symptom recognition and admission timing may be associated with different clinical and imaging profiles between the two stroke subtypes. Previous studies have suggested that delayed recognition and uncertain onset time may contribute to more advanced ischemic changes and poorer collateral compensation in WUS patients [15, 16]. In our study, although perfusion characteristics differed between groups, CTA and CTP image quality were comparable, supporting the feasibility of multimodal CT assessment in both WUS and SWA populations. This finding is consistent with previous imaging-based treatment strategies, including DEFUSE-3, which empha-

sized tissue characteristics rather than time alone for patient selection [17].

Correlation analysis showed that several CTP-derived parameters were associated with 90-day functional outcome. Lower CBF and mismatch ratio were correlated with poor outcome, whereas higher MTT, TTP, Tmax, and early mRS scores were associated with unfavorable functional status. These findings are consistent with previous studies indicating that perfusion abnormalities reflect the severity of ischemic injury and tissue vulnerability [18, 19]. A lower mismatch ratio represents a less favorable tissue profile with a smaller proportion of potentially salvageable tissue. This observation is consistent with the target mismatch concept described in the DAWN trial [20]. However, the present study focused on prognostic association rather than treatment

selection, and these findings should not be interpreted as direct evidence of treatment benefit.

Although multiple CTP parameters showed significant correlations with outcome, they demonstrated substantial interrelationships. Therefore, individual perfusion parameters may provide overlapping information, and their independent contribution should be interpreted cautiously. In our study, CBV showed no significant association with functional outcome, which may be related to the limited sample size, measurement variability, or the relatively narrow distribution of CBV values. These findings highlight the importance of considering imaging parameters within an integrated clinical context rather than interpreting individual CTP measurements separately.

Because of the limited sample size and potential small-sample bias, Firth penalized logistic regression was applied in the present study. In the final model, early mRS score at 24 hours after admission and CTP-derived mismatch ratio remained independently associated with poor 90-day functional outcome. Early mRS showed strong prognostic relevance, indicating that early neurological status provides important information beyond baseline stroke severity. The association between delayed presentation and unfavorable recovery has also been reported previously [21]; however, in our study, onset-to-admission interval did not remain independently significant after adjustment, suggesting that its effect may be partly reflected by other clinical and imaging characteristics.

The importance of early neurological assessment was further supported by the hierarchical model analysis. Adding early mRS to admission NIHSS markedly improved model discrimination, demonstrating that early functional assessment provides additional prognostic information beyond initial stroke severity. Further incorporation of mismatch ratio resulted in additional improvement, although the incremental contribution was smaller than that provided by early mRS. These findings suggest that CTP-derived tissue information may complement clinical assessment rather than replace conventional neurological evaluation.

Previous studies have shown that early neurological deterioration is associated with unfavor-

able long-term outcomes after stroke [22]. Consistent with these findings, our study demonstrated a strong association between early mRS score and 90-day functional outcome. Early functional assessment may capture clinically meaningful changes occurring after admission and provide additional information for outcome stratification. Previous research has also suggested that early changes in neurological function are associated with subsequent functional recovery [23]. Therefore, early monitoring of functional status may help identify patients at higher risk of poor recovery.

Based on the final Firth logistic regression model, a nomogram incorporating admission NIHSS, early mRS, and mismatch ratio was developed. The nomogram provides a visual representation of the combined association between clinical characteristics, imaging parameters, and 90-day functional outcome. However, because this was an exploratory single-center study with a limited sample size, the nomogram should be considered a preliminary risk stratification tool. External validation in larger multicenter cohorts is required before clinical application.

Clinical implications and limitations

Clinical implications

From a clinical perspective, our findings suggest that early functional assessment combined with selected CTP-derived imaging information may improve outcome stratification in WUS and SWA patients. Multimodal CT remains valuable for evaluating tissue characteristics in patients with uncertain onset time, while early mRS provides readily available clinical information for functional assessment. A combined clinical-imaging approach may provide additional information for individualized management.

Limitations and future directions

Several limitations of this work should be acknowledged. First, this was a single-center retrospective study with a relatively small sample size, which may limit the generalizability of the findings. Second, although Firth penalized regression was applied to reduce small-sample bias, the model remains exploratory and requires external validation. Third, CTP parameters may be influenced by acquisition protocols

and post-processing methods, which may affect measurement reproducibility. Fourth, despite adjustment for clinically relevant variables, residual confounding factors, including treatment selection and vascular characteristics, could not be completely excluded. Fifth, CTA and CTP image-quality assessment methods were adapted from previously reported CT evaluation approaches rather than stroke-specific validated systems, and further validation is needed. Sixth, sleep-related factors were not evaluated, limiting assessment of their potential influence on WUS prognosis. Finally, long-term outcomes beyond 90 days were not assessed. Future multicenter studies with larger cohorts are needed to validate these findings and further explore the clinical value of combined clinical and imaging assessment.

Conclusion

In conclusion, early mRS provides important prognostic information beyond admission NIHSS, while CTP-derived mismatch ratio offers complementary information for 90-day functional outcome stratification in patients with WUS and SWA. The combination of clinical assessment and multimodal CT imaging may provide a practical approach for individualized outcome assessment, although further validation is required.

Acknowledgements

This study was supported by the Zhejiang Provincial Medical and Health Science and Technology Project (2024XY167) and the Jiaxing Municipal Health Technology Plan Project (JWKJ-25089).

Disclosure of conflict of interest

None.

Address correspondence to: Xiaodong Ma, Department of Neurology, Haiyan People's Hospital, No. 699 Jianfeng Road, Wuyuan Street, Haiyan County, Jiaxing 314300, Zhejiang, China. E-mail: jloveh11-10@163.com

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