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Late time window endovascular treatment for acute ischemic stroke: rethinking the role of simplified imaging

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Abstract

Objective To assess safety and efficacy of endovascular treatment (EVT) in acute ischemic stroke (AIS)patients selected by ASPECTS within 6–24 h after onset.

Methods Patients were divided into early and late time window groups. Primary outcome was 90-day mRS 0–2, safety outcomes were 90-day any intracranial hemorrhage (ICH) and mortality. Univariate and multivariate analyses were conducted for the prediction of good outcome.

Results Of the 296 patients screened, 242 patients fulfilled the study criteria. Patients in the late time window group were younger, had lower baseline NIHSS scores and ASPECTS, a lower proportion of atrial fibrillation, a higher proportion of large-artery atherosclerosis, less received intravenous thrombolysis, and had a longer time from symptom onset to treatment. No difference in primary and safety outcomes: good outcome (42% vs. 50.5%, $p=0.188$), ICH (26.1% vs. 20.6%, $p=0.311$), and mortality (18% vs. 9.9%, $p=0.067$). Multivariate analysis showed that age (OR = 0.977, 95%CI 0.955–0.999, $p=0.039$), NIHSS score (OR = 0.905, 95%CI 0.858–0.953, $p=0.001$), ASPECTS (OR = 1.242, 95%CI 1.004–1.538, $p=0.046$), glucose (OR = 0.817, 95%CI 0.720–0.926, $p=0.002$), platelet (OR = 1.005, 95% CI 1.000 -1.010, $p=0.031$) and successful recanalization (OR = 5.037, 95%CI 1.137–22.318, $p=0.033$) were independent predictors of good outcomes.

Conclusions For late-window acute anterior-circulation LVO patients, those selected based on the ASPECTS exhibited comparable 90-day good outcomes and safety profiles to those in the early time window. This finding implies that ASPECTS could serve as a screening tool for patients in the late time window when undergoing EVT.

Clinical trial This is a clinical retrospective study. However, at the time when the study was initiated, clinical trial registration was not a mandatory requirement. Therefore, this trial was not registered.

Keywords Acute ischemic stroke, ASPECTS, Large vessel occlusion, Endovascular treatment

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Introduction

Endovascular therapy (EVT) has emerged as an advanced and effective therapeutic strategy for patients with acute ischemic stroke (AIS) caused by large-vessel occlusion (LVO), even in the context of late time window strokes. The DAWN and DEFUSE-3 trials are widely regarded as the gold standard of clinical evidence for patients with AIS within the late time window. However, the practical application of their results in routine clinical practice may be somewhat restricted by the overly narrow inclusion criteria [1, 2]. Advanced imaging modalities may lead to the exclusion of certain patients who could potentially gain benefit from EVT. Additionally, perfusion imaging may not be readily available in primary stroke centers, especially in developing countries. In conjunction with the risks of increased radiation exposure, contrast-induced kidney injury, and lengthened treatment time, it is of crucial importance to identify and validate simpler imaging-based selection criteria.

The Alberta Stroke Program Early CT Score (ASPECTS) offers a relatively reliable approach for evaluating the infarct core in AIS. Additionally, as the time from symptom onset elapses, the infarct core becomes more prominent on non-contrast computed tomography (NCCT), and the precision of ASPECTS may be further enhanced. Consequently, many centers consistently choose endovascular treatment patients based on fundamental imaging techniques, such as the combination of NCCT and CT perfusion (CTP), often integrating ASPECTS. The selection paradigm based on ASPECTS for late-presenting and wake-up stroke patients undergoing EVT has been shown to exhibit similar patient eligibility rates and comparable 90-day functional outcomes to those using the DAWN and DEFUSE-3 criteria. MR CLEAN-LATE trial has indicated that patient selection for EVT in the extended time window can be mainly based on the assessment of collateral flow using CT angiography (CTA) [3].

The aim of this study was to conduct a comprehensive evaluation of the safety and efficacy of endovascular treatment in patients with acute anterior circulation large vessel occlusion stroke within a treatment time window ranging from 6 to 24 h, using ASPECTS as the screening criterion.

Patients and methods

Patients

This study retrospectively analyzed patients who underwent endovascular treatment for acute ischemic stroke (AIS) resulting from large vessel occlusion in the anterior circulation between January 2019 and December 2022. The inclusion of consecutive patients was predicated on the following criteria: (1) age ≥ 18 years; (2) a modified Rankin Scale (mRS) score of ≤ 2 prior to the stroke; (3) an Alberta Stroke Program Early CT Score (ASPECTS) of ≥ 6; (4) occlusion of the proximal internal carotid artery or middle cerebral artery (M1/M2 segments); and (5) groin puncture executed within 24 h following stroke onset. Demographic characteristics, medical history, clinical features, neuroimaging findings, and endovascular treatment procedures were prospectively documented.

Patients were divided into early and late time window groups.

Imaging evaluation

Imaging assessment was carried out by two trained neuroradiologists. The imaging protocol mandated a non-contrast-enhanced CT (NCCT) scan, CT angiography (CTA), and CT perfusion (CTP), which were performed at baseline. The assessment of ischemic changes was conducted using the Alberta Stroke Program Early CT Score (ASPECTS) scale, where a score of 10 denotes normal and 1 point is subtracted for each abnormal area [4].

Outcome assessment

The modified Rankin Scale(mRS) scores were used to assess functional outcomes, ranging from 0 (no disability) to 6 (death) and mRS ≤ 2 was indicated a good outcome [5]. Safety outcomes included mortality (mRS = 6) and any intracranial hemorrhage (ICH). Successful recanalization was defined as a eTICI score ≥ 2b [6].

Statistical analysis

Patients were subsequently divided into two groups based on stroke onset time, including the early time window (within 6 h of stroke onset) group and the late time window (within 6–24 h of stroke onset) group. Nominal variables were described in terms of frequencies, ordinal variables as the median (interquartile range, IQR), and continuous variables as the mean ± SD. Differences between the groups were evaluated using Fisher's exact test, χ^2 test, Mann - Whitney test, or t - test as appropriate, and a p - value < 0.05 was deemed statistically significant. Univariate and multivariate analyses for the primary endpoint of 'good outcome' were conducted. Data analysis was performed using SPSS 29.0 (SPSS, USA).

Results

In total, 296 patients received an EVT for acute anterior circulation LVO within 24 h were included during the study. Of 242 patients (excluded: ASPECTS<6, $n = 38$;loss the 90- day mRS, $n = 12$; absence of postoperative NCCT images, $n = 4$)fulfilled eligible criteria, 111 patients and 131 patients were assigned to the early time window and late time window groups, respectively.

This study demonstrated that the median ASPECTS score was 9 (8–10), the median infarct volume was 18

(6–38) ml, and the median penumbra volume was 90 (57–128) ml. A Spearman correlation analysis was performed between the ASPECTS score and the infarct core volume. The results indicated a correlation coefficient r was −0.189 ($p = 0.004$), suggesting an inverse correlation between the ASPECTS score and the infarct core volume.

This study has demonstrated that regardless of the treatment time, there were no differences in the primary endpoint and safety outcomes between the two groups. The proportions of 90-day good outcome in the early time window group and the late time window group were 50.5% and 42%, respectively (Fig. 1). Moreover, the incidences of ICH (26.1% vs. 20.6%, $p = 0.311$) and mortality (18% vs. 9.9%, $p = 0.067$) were also comparable in the two groups. Compared to the early time window group, patients in the late time window group were younger, with lower baseline NIHSS scores, lower ASPECTS, a lower proportion of atrial fibrillation, and a higher proportion of large - artery atherosclerosis. Additionally, they were less frequently treated with intravenous thrombolytic therapy and the time from symptom onset to treatment was longer. The proportion of successful recanalization was comparable between the two groups (96.4% vs. 90.8%, $p = 0.083$) (Table 1).

In the univariate analysis, the factors significantly associated with a good outcome included age, NIHSS score, ASPECTS, glucose, platelet count, smoking, and successful recanalization. After conducting multivariate regression analysis, the independent predictors of a good outcome were as follows: age (OR = 0.977, with a 95% CI 0.955–0.999, $p = 0.039$), NIHSS score (OR = 0.905, 95% CI 0.858–0.953, $p = 0.001$), ASPECTS (OR = 1.242, 95% CI 1.004–1.538, $p = 0.046$), glucose (OR = 0.817, 95% CI 0.720–0.926, $p = 0.002$), platelet (OR = 1.005, 95% CI 1.000–1.010, $p = 0.031$), and successful recanalization (OR = 5.037, 95% CI 1.0137–22.318, $p = 0.033$) (Table 2).

Discussion

Our study shown that patients with AIS caused by anterior circulation LVO in the late time window, those selected based on the ASPECTS exhibited comparable 90-day good outcomes and safety profiles to those in the early time window. The functional outcomes were consistent with the results of the HERMES meta-analysis, as well as the DAWN and the DEFUSE 3 study. These results suggest that a baseline ASPECTS score of ≥6 on non - contrast computed tomography (NCCT) might serve as an alternative to the selection paradigms based on computed tomography perfusion (CTP) or magnetic resonance imaging (MRI) in the late time window.

Multiple large randomized controlled trials have confirmed the efficacy and safety of endovascular treatment for acute anterior circulation LVO stroke within 6 h after onset. The guideline gives the highest level of evidence and recommendation for endovascular treatment within 6 h after onset [7–11]. Subsequently, a subgroup analysis of the HERMES collaboration (a pooled database of 5 randomized controlled trials) showed that in stroke patients receiving EVT within 6 h time window, the clinical outcomes was comparable with or without perfusion imaging, and the value of advanced imaging in improving functional outcomes may be limited [12]. The guideline recommends that patients receiving EVT within the 6 h time window do not need advanced imaging assessment. In 2018, the DAWN and DEFUSE 3 studies expanded the time window for the benefit of EVT to 24 h by screening patients with acute anterior circulation LVO stroke with clinical-imaging mismatch or significant penumbra using advanced imaging assessment [1, 2]. A meta-analysis of 10 clinical trials conducted by Tsivgoulis, et al. showed that compared with traditional imaging, endovascular treatment using advanced imaging assessment was associated with better clinical outcomes [13]. Based on the best and strict CT perfusion parameters to select patients may improve the proportion of good outcomes. For patients with acute anterior circulation LVO within the 6–24 h, the guideline recommends that only those who meet the DAWN and DEFUSE 3 study criteria after advanced imaging assessment can receive EVT. However, CTP imaging may overestimate the infarct core and may exclude a certain proportion of patients who could have benefited from endovascular treatment.

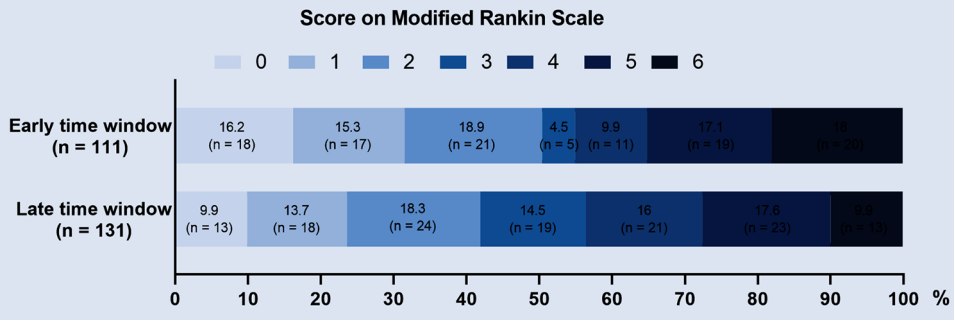

Fig. 1 Clinical outcome after 90 days on the modified Rankin Scale (mRS) in early time window and late time window patients

Table 1 Characteristics of patients in early window and late window

Variable	Early time window (*n* = 111)	Late time window (*n* = 131)	*P* values
Clinical baseline data			
Age, median (IQR), y	71(60–79)	68(56–75)	0.036
Male, n (%)	69(62.2)	81(61.8)	0.958
NIHSS score, median (IQR)	17(14–21)	15(11–19)	0.008
ASPECTS, median (IQR)	9(8–10)	8(7–10)	0.008
Risk factors			
Hypertension, n (%)	77(69.4)	84(64.1)	0.389
Diabetes, n (%)	22(19.8)	21(16)	0.442
Atrial fibrillation, n (%)	62(55.9)	43(32.8)	0.001
Smoking, n (%)	28(25.2)	26(19.8)	0.317
Baseline measurements			
SBP, median (IQR), mm Hg	152(132–170)	153(135–170)	0.690
Platelet, mean (IQR), 10^9/L	172(143–205)	182(143–212)	0.330
Glucose, median (IQR), mmol/L	6.8(6.2–8.6)	7.1(6.1–8.3)	0.937
Occlusion site, n (%)			0.249
ICA	38(34.2)	54(41.2)	
MCA-M1	68(61.3)	75(57.3)	
MCA-M2	5(4.5)	2(1.5)	
Stroke cause, n (%)			0.002
LAA	32(29.1)	66(51.6)	
Cardioembolic	60(54.5)	47(36.7)	
Others	18(16.4)	15(11.7)	
Procedural data			
Intravenous thrombolysis, n (%)	65(58.6)	34(26)	0.001
OTP, median (IQR), min	240(167–293)	590(457–836)	0.001
OTR, median (IQR), min	299(227–370)	647(529–909)	0.001
eTICI, 2b or 3, n (%)	107(96.4)	119(90.8)	0.083
Outcome			
mRS score 0–2 (%)	56(50.5)	55(42)	0.188
mRS score 6 (%)	20(18)	13(9.9)	0.067
ICH (%)	29(26.1)	27(20.6)	0.311

IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; SBP, systolic blood pressure; ICA, Internal Carotid Artery; MCA-M1, Middle Cerebral Artery-M1 Segment; LAA, large-artery atherosclerosis; eTICI, expanded Thrombolysis in Cerebral Infarction; OTP, symptoms onset to groin puncture time; OTR, symptoms onset to recanalization time; mRS, modified Rankin Scale; ICH, intracranial hemorrhage

Whether advanced imaging assessment is a necessary prerequisite for endovascular treatment in patients in the late time window remains controversial. An increasing amount of evidence suggests that using the ASPECTS on NCCT to select patients in the late time window for endovascular treatment may be safe and effective. Recently, Santos et al. found that the clinical outcome of patients in the late time window selected by the clinical - ASPECTS mismatch pattern was similar to that of patients within 6 h of onset receiving endovascular treatment [14]. Nagel et al. also did not find any difference in the clinical outcome of patients with and without CT or MRI perfusion imaging [15]. Studies have shown that there is a moderate correlation between the infarct core assessed by ASPECTS on NCCT and the infarct core volume assessed by CT perfusion, and this correlation is more significant in patients in the late time window [16]. In an international cohort study of patients with acute anterior circulation LVO within the 6–24 h time window, compared with patients receiving only medical treatment, patients selected by NCCT and CT angiography for endovascular treatment had a better clinical outcome and lower disability and mortality at 90-day [17]. The RESCUE BT trial selected patients in the late time window with ASPECTS ≥ 6 on NCCT for endovascular treatment, and the clinical outcomes was comparable to the DAWN and DEFUSE – 3 trials. CT or MRI perfusion imaging assessment led to a delay in the in-hospital treatment process (longer time from admission to puncture), suggesting that advanced imaging assessment may be redundant [18]. In addition, evidence suggests that in the late time window, NCCT may be more sensitive and accurate than relative cerebral blood flow in showing irreversible brain tissue damage [19–21]. Recently published trials have demonstrated that patients with large - core infarction within 0–24 h of onset or last normal

Table 2 Multivariate analysis of predictors of good outcome after EVT in unadjusted and adjusted analysis

Variable	Unadjusted OR (95% CI)	*P* values	Adjusted OR (95% CI)	*P* values
Age	0.962(0.943–0.981)	0.001	0.977(0.955–0.999)	0.039
NIHSS score	0.895(0.854–0.937)	0.001	0.905(0.858–0.953)	0.001
ASPECTS	1.227(1.018–1.480)	0.032	1.242(1.004–1.538)	0.046
Glucose	0.848(0.755–0.952)	0.005	0.817(0.720–0.926)	0.002
Platelet	1.006(1.001–1.010)	0.011	1.005(1.000-1.010)	0.031
Smoking	2.216 (1.193–4.117)	0.012	1.702(0.843–3.436)	0.138
eTICI, 2b or 3	3.966 (1.100-14.296)	0.035	5.037(1.137–22.318)	0.033

NIHSS, National Institute of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; eTICI, expanded Thrombolysis in Cerebral Infarction

time and having an ASPECTS score of 3–5 on NCCT can derive benefits from endovascular treatment [22, 23, 24]. Therefore, we have sufficient reasons to believe that the necessity of using advanced imaging assessment in selecting endovascular treatment in the late time window is gradually decreasing. NCCT assessment has the advantages of wider popularity, faster examination time, lower radiation exposure and cost. ASPECTS imaging assessment may be a reasonable alternative for screening patients for endovascular treatment in the late time window. ASPECTS is a practical semi-quantitative tool for assessing the infarct core in clinical practice. Although the overall consistency of ASPECTS is good, the absolute inter-rater consistency is low. Through scientific and systematic training and with the help of computer-aided software, the problem of scoring consistency may be solved to achieve accurate and rapid screening of acute stroke patients.

In addition, this study revealed that the proportion of intracranial atherosclerosis was higher in the late time window group. This might be attributed to the better collateral circulation in patients with atherosclerosis. Owing to the existence of collateral circulation, the brain tissue in the lesioned vascular area of the patient may survive for a longer period before transforming from the ischemic state to core infarction. Consequently, the patient can receive endovascular treatment within a late time window and achieve a favorable clinical outcome. This implies that collateral circulation assessment may assist in selecting stroke patients in the late time window who are eligible for endovascular treatment. The recent MR CLEAN LATE trial has confirmed that for patients with anterior - circulation LVO ischemic stroke within 6–24 h after onset or the last known good health condition and with collateral blood flow screened by CTA, endovascular treatment is both effective and safe [3]. This trial uses a simpler imaging screening method to expand the eligibility of patients in the late time window for endovascular treatment, which may help expand the current guideline recommendations for the indication of endovascular treatment.

In addition, this study confirmed that the important factors affecting the clinical outcomes of EVT are still traditional factors such as age, baseline NIHSS score, blood glucose and successful recanalization. Despite the exciting results of a series of clinical trials, patient selection continues to be a complex problem that demands a comprehensive assessment of clinical symptoms, imaging characteristics, and individual patient factors (including age, underlying comorbidities, etc.). The precise identification of patients suitable for endovascular treatment remains an area that requires further exploration. Nevertheless, in the context of a large and increasingly needy stroke population, simplifying preoperative evaluation methods and reducing treatment delay will be an effective strategy to expand the population that can benefit from such interventions.

This study has some limitations: First, the lack of random allocation and retrospective design has the inherent risk of selection bias. Second, our study did not measure CTA collateral circulation. Therefore, our study may support the use of non-contrast computed tomography alone in patients with good non-contrast computed tomography without considering the presence or degree of collateral circulation. Thirdly, our study was confined to patients with anterior circulation large - vessel occlusion, and thus our findings might not be applicable to patients with posterior circulation occlusion.

Conclusions

In this large patient cohort study, we have successfully verified the efficacy and safety of simple imaging criteria (that is, ASPECTS score ≥ 6 and confirmation of large vessel occlusion by CT angiography) in the selection of patients for endovascular treatment in the late time window. The clinical outcomes and safety profiles obtained by applying these criteria show no significant differences compared with those of patients receiving endovascular treatment in the early time window. This research finding indicates that ASPECTS imaging assessment may potentially serve as a reasonable alternative approach for screening patients for endovascular treatment in the late time window.

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No.

Author contributions
Zongjie shi (ZJS): Conceived the study, designed the experiments, analyzed the data, and wrote the manuscript. Sujie zheng (SJZ): Performed the experiments, contributed to data analysis, and helped with manuscript preparation. Xinzhao jiang (XJJ): Assisted with data interpretation, and reviewed the manuscript. Xu wang (XW): Helped with data collection and organization, and provided feedback on the manuscript. Yu geng (YG): Conceptualized the research idea, designed the overall study framework, and was responsible for project administration, ensuring the smooth progress of the entire research.

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No.

Data availability
The data and materials presented in this study are not publicly available due to privacy and ethical restrictions. However, they can be made available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (approval number: 2017KY021) and adhered to the principles of the Declaration of Helsinki. All patients or their legal representatives provided signed informed consent prior to endovascular treatment.

Consent for publication
All participants provided written informed consent for their personal or clinical details along with any identifying images to be published in this study.

Competing interests
The authors declare no competing interests.

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