Stroke

ORIGINAL CONTRIBUTION

Salvageable Time Window: Tissue Clock After Acute Ischemic Stroke Onset

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BACKGROUND: Salvageable ischemic tissue has become the treatment target of endovascular therapy (EVT). This study proposed a new concept of salvageable time window that measures the dynamic process of salvageable tissue. We hypothesized that patients who received EVT beyond the salvageable time window would have limited benefits.

METHODS: This was a retrospective multicenter study based on the INSPIRE (International Stroke Perfusion Imaging Registry), enrolling patients with acute ischemic stroke due to large vessel occlusion within 6 hours of stroke onset (August 2011–April 2022, 22 sites). Patients were divided into 3 groups: EVT delivered within the salvageable time window, EVT delivered outside the salvageable time window, and a historical no EVT control. Salvageable time window was calculated by salvageable tissue volume divided by core growth rate, which estimates the time for infarction expanding to the whole ischemic region. Patients were considered outside the window if EVT was initiated after their estimated salvageable window. The primary outcome was a good functional outcome defined by 3-month modified Rankin Scale score of 0 to 2. Propensity score matching was applied to reduce selection bias among groups.

RESULTS: Overall, 1291 patients (mean age 70.3 years, 43.6% female) were included in the study, with 456 in the no EVT group, 727 in the EVT within salvageable time window group, and 108 in the EVT outside salvageable time window group. After propensity score matching (n=62 per group), patients received EVT within the salvageable time window had higher odds of good functional outcome compared with those with no EVT (48% versus 29%, odds ratio, 2.29 [95% CI, 1.09–4.81]; *P*=0.028), without increased risk of bleeding (type 2 parenchymal hematoma of 2% versus 3%, odds ratio, 0.49 [95% CI, 0.04–5.57]; *P*=0.566). In contrast, patients received EVT outside the salvageable time window did not show improved 3-month functional outcomes (32% versus 29%, odds ratio, 1.16 [95% CI, 0.54–2.50]; *P*=0.697) and demonstrated an increased bleeding risk (type 2 parenchymal hematoma of 17% versus 3%, odds ratio, 5.83 [95% CI, 1.22, 27.9]; *P*=0.027).

CONCLUSIONS: This study indicates the importance of estimating the salvageable time window within 6 hours of stroke onset, as initiating endovascular treatment beyond salvageable time window may not benefit.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: hematoma ■ intracranial hemorrhages ■ ischemic stroke ■ perfusion ■ tomography

Endovascular therapy (EVT) has become the primary treatment for acute ischemic stroke caused by large vessel occlusion (LVO).[1,2] The success of the EVT procedure is measured by the recanalization of occluded arteries that restore blood supply to ischemic brain issues. Despite a high recanalization rate achieved with improved endovascular devices over the past decade, over half of the patients who received EVT failed to achieve good

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Nonstandard Abbreviations and Acronyms

CT	computed tomography
CTP	computed tomography perfusion
ESCAPE	Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke
EVT	Endovascular thrombectomy
EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial
INSPIRE	International Stroke Perfusion Imaging Registry
LVO	large vessel occlusion
NIHSS	National Institutes of Health Stroke Scale
PH2	type 2 parenchymal hematoma
sICH	symptomatic intracranial hemorrhage

clinical outcomes.[3] Such futile recanalization might be caused by the lack of salvageable brain tissues.

The existence of salvageable brain tissue is now being recommended for select patients most likely to benefit from endovascular treatment.[1,2] The salvageable brain tissues refer to tissues experiencing mild ischemia but are reversible with the restoration of blood supply. They are known as ischemic penumbra, which surrounds the irreversibly damaged infarction core. Acute perfusion imaging can quantify the salvageable tissues at hospital admission and help select patients for good functional outcomes from EVT.[4–7] In the EXTEND-IA trial (Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial) that used perfusion imaging to select patients with salvageable brain tissues, 71% of patients who received EVT had good functional outcomes.[8] However, EVT commenced 2 hours after perfusion imaging in 25% of the patients in the EXTEND-IA trial.[8] The efficacy of EVT may still be compromised by the delay of the EVT procedure, which could enable further development of infarction and lead to limited ischemic tissues being salvaged by the EVT procedure.

Stroke is a dynamic process with ischemic penumbral tissues progressing to infarction every minute. One strategy to capture the dynamic progress is measuring infarction growth.[9–11] It measures the rate of infarction expansion from stroke onset. For patients with fast core growth, infarction might expand to the whole ischemic region with no salvageable tissues left before the commencement of the EVT procedure. In this study, we proposed a new concept, the salvageable time window, for the first time. It was defined by salvageable tissue volume divided by core growth rate. It predicted the time left before the salvageable tissues disappeared (the infarct core expanding to the whole ischemic region) for each stroke patient. We hypothesize that patients who received EVT beyond the salvageable time window have limited therapeutic benefits.

METHODS

Data Availability

Deidentified participant data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

This was a retrospective cohort study. Patients who received EVT were divided into 2 treatment groups: (1) EVT delivered within the salvageable time window, and (2) EVT delivered beyond the salvageable time window. This study also included a historical control arm consisting of patients who did not receive EVT.

The historical control group selected patients with LVO who had no access to EVT before 2015, when the procedure was not routinely performed; patients in the control group received intravenous thrombolysis or no reperfusion treatment. The EVT groups selected patients who received EVT after 2015, either direct EVT or EVT bridging with intravenous thrombolysis. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. The Strengthening the Reporting of Observational Studies in Epidemiology checklist is provided in the Supplemental Material.

Patients

This study identified patients from the INSPIRE (International Stroke Perfusion Imaging Registry). The INSPIRE was a multicenter database recruiting patients with acute ischemic stroke who underwent baseline multimodal computed tomography (CT), including noncontrast CT, CT perfusion (CTP), and CT angiography between August 2011 and April 2022 from 22 sites (9 Australian, 1 Canadian, and 12 Chinese). The INSPIRE was established in 2011, and it included 2 stages: (1) stage 1, from August 2011 to December 2015, limiting the data collection to patients who were screened for intravenous thrombolysis; (2) stage 2, from January 2016 onward, expanding the data collection to patients who were screened for EVT. The INSPIRE study received central ethics approval from the Hunter New England Human Research Ethics Committee (11/08/17/4.01), and written informed consent was obtained for each participant.

The following clinical data were collected in the INSPIRE: (1) baseline clinical information, including demographics, medical history, times of onset, and the baseline National Institutes of Health Stroke Scale (NIHSS) score; (2) treatment information, including intravenous thrombolysis, or EVT; (3) 24 to 72 hours NIHSS score; (4) the modified Rankin Scale score at 3 months follow-up.

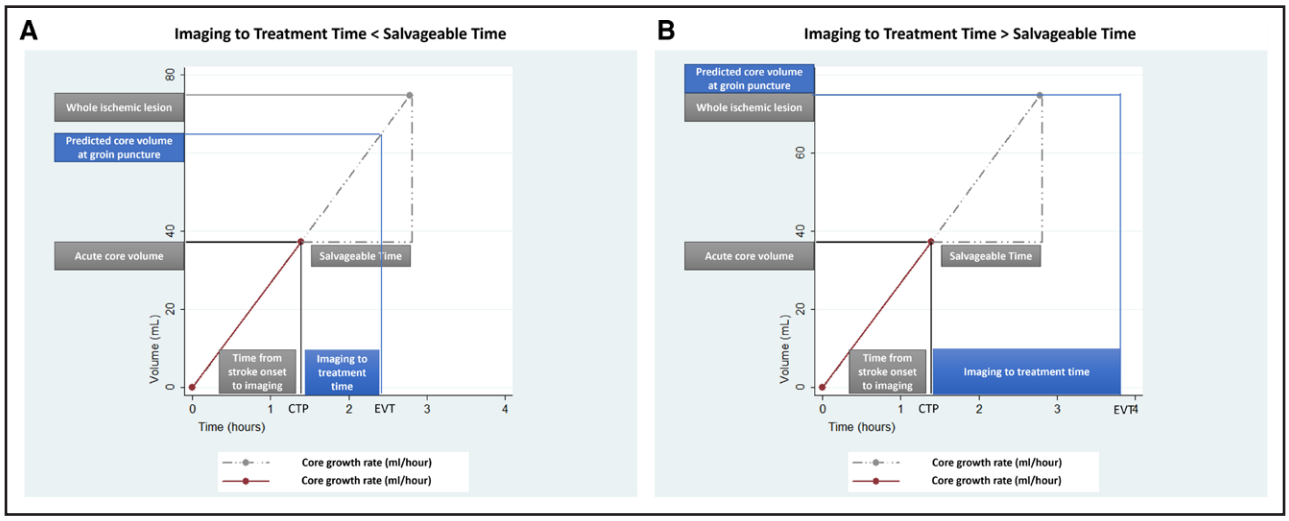

Figure 1. Illustration of salvageable time calculation and its relationship with imaging to treatment time.
CTP indicates computed tomography perfusion; and EVT, endovascular therapy.

Inclusion and Exclusion Criteria

The following inclusion criteria were applied to select patients for this study: (1) patients with acute ischemic stroke with anterior circulation LVO, internal carotid artery, or M1 or M2 segment of middle cerebral artery; (2) baseline CTP scanned within 6 hours of stroke onset. We limited the inclusion of patients within 6 hours of stroke onset to ensure comparability of EVT patients to patients in the historical control group, who were screened for thrombolysis within 6 hours of stroke onset according to the INSPIRE protocol. Exclusion criteria included (1) onset time to scan >6 hours, (2) no LVO occlusion or posterior LVO occlusion, (3) no baseline CTP performed or CTP core volume of 0 mL; (4) unknown symptoms onset time, or unknown groin puncture time of EVT, (5) missing key baseline clinical data, such as age or NIHSS score, and (6) lost to follow-up at 3 months.

Imaging Acquisition and Postprocessing

The imaging acquisition and postprocessing protocol followed the methods described in previous INSPIRE studies.[9–11] Baseline CTP data were processed by commercial software (MIStar; Apollo Medical Imaging Technology, Melbourne, Australia). All imaging was centrally evaluated by a core imaging center to standardize image interpretation across sites. Infarct core volume and ischemic lesion were defined as relative cerebral blood flow <30% and delay time >3 s, respectively.[4,12] The salvageable volume of penumbra was calculated as the ischemic lesion volume minus the infarct core volume.

Ischemic Core Growth Rate and Salvageable Time Window

The ischemic core growth rate was calculated as the baseline infarct core volume divided by the time from stroke onset to CTP scan.[9–11] The calculation of core growth rate was based on the assumption that the infarct core would grow into the whole ischemic lesion in a linear pattern without recanalization of the occluded artery. A previous study demonstrated a near-linear pattern of core growth within 24 hours of stroke onset.[13] Patients were classified into those with fast core growth (>25 mL/h) and slow core growth (≤25 mL/h) according to our previous study.[10]

The salvageable time window was calculated based on individual core growth rate and salvageable tissue volume of each patient, as illustrated in Figure 1: salvageable time window=(total ischemic lesion volume−acute infarct core volume)/core growth rate. As illustrated in Figure 1, EVT delivered outside the salvageable time window would in theory have no salvageable tissue at the time of EVT, as the infarct core had already expanded to the whole ischemic region.

Outcomes

The primary outcome was a good functional outcome, defined as a modified Rankin Scale score of 0 to 2 at 3 months. Secondary outcomes included poor outcome at 3 months (modified Rankin Scale score of 5–6) and mortality rate at 3 months.

Safety outcomes were hemorrhagic transformation measurements at 24 to 72 hours, including any intracranial hemorrhage, type 2 parenchymal hematoma (PH2), and symptomatic intracranial hemorrhage (sICH) according to the European Cooperative Acute Stroke Study II classification criteria.

Statistical analysis

All statistical analysis was done using STATA 13.0 (StataCorp, College Station, TX) or R program (R: A language and environment for statistical computing, Vienna, Austria), with CI set at 95% and a significance level set at 0.05.

Continuous data were summarized as median and interquartile range, and differences across the 3 groups were compared using the Kruskal-Wallis test. Categorical variables were described as proportions and compared using the Pearson χ^2 test or Fisher exact test when cell sizes were small. Multivariable logistic regression was performed to assess the predictive power of EVT delivered within or outside the salvageable time window on patient outcomes compared with the no EVT group.

Covariates included in the model were selected based on their statistically significant between-group differences ($P<0.05$). These covariates included age, baseline NIHSS score, proportion of patients receiving intravenous thrombolysis, internal carotid artery occlusion rates, onset-to-scan time, infarct core volume, and penumbra volume. Core growth rate was excluded from the regression model and propensity score matching due to its high collinearity with infarct core volume and onset-to-scan time. To further reduce selection bias, a propensity score matching approach was applied using the same set of covariates. Patients with missing data of the selected covariates or primary outcome were excluded in propensity score estimation.

The propensity score matching was performed by the TriMatch package of R program (R: A language and environment for statistical computing, Vienna, Austria).[14] The *trips* and *trimatch* functions were used to estimate the propensity scores and find the best-matched triplets, respectively.

1. Propensity scores were estimated for 3 models using logistic regression.
   $PS1=e(x_{T1C}) = Pr(z=1|X_{T1C})$
   $PS2=e(x_{T1C}) = Pr(z=1|X_{T1C})$
   $PS3=e(x_{T2T1}) = Pr(z=1|X_{T2T1})$
2. Match order was determined, starting with the larger of the 2 treatments, followed by the second treatment, and lastly the control group.
3. Three distance matrices were calculated, D1, D2, and D3 corresponding to the propensity scores estimated in step a. That is, D1 is a $n_{Tr1} \times n_{Tr2}$ matrix where D1[*x*, *y*] is the standardized distance between PS1[*x*] and PS1[*y*].
4. Distances greater than the caliper of 0.25 were eliminated.
5. For the remaining units, all possible combinations of matched triplets were formed, and a total standardized distance was calculated.
6. The result of the above procedure was the equivalent of caliper matching in the 2-group case. We then applied The *OneToN* match function to retain a 1-to-1-to-1 match. This was analogous to 1-to-1 matching without replacement in the 2-group case.

After propensity matching, the balance of the 3 groups was assessed by a multiple covariate balance plot that plots the absolute effect size of each covariate before and after adjustment. Simple logistic regression was used to compare outcomes across the matches. No further adjustment was made after propensity score matching.

RESULTS

Patients

A total of 4219 acute ischemic patients from the INSPIRE database were screened. Of these, 1250 were excluded due to symptoms onset-to-CTP scan time exceeding 6 hours, 1108 were excluded for no LVO or LVO on posterior circulation, 85 were excluded due to no CTP performed or CTP showed an infarct volume of 0, 358 were excluded due to unknown stroke onset or groin puncture time, 57 were excluded for missing age or baseline NIHSS score data, and 70 were excluded due to lost follow-up at 3 months. Finally, a total of 1291 patients (mean age, 70.3±12.8 years; 43.6% female) were included in the study, with 456 in the no EVT group, and 835 received EVT. Among the 835 EVT patients, 727 patients had the EVT delivered within the estimated salvageable time window, and 108 patients had EVT delivered outside the estimated salvageable time window. The patient selection process is detailed in Figure 2.

Baseline Characteristics

Table 1 outlines the baseline characteristics of the 3 groups. There were significant differences among the 3 groups, no EVT versus EVT within salvageable time window versus EVT outside salvageable time, in terms of age, baseline NIHSS score, proportion of patients receiving intravenous thrombolysis, internal carotid artery occlusion rates, stroke onset-to-scan time, and the volumes of the infarct core and penumbra (all $P<0.05$, see Table 1 for details). The proportion of patients with fast core growth also differed significantly among the 3 groups (25%, 15%, and 76%, respectively; $P<0.001$).

Patient Outcomes Before Propensity Score Matching

Patient outcomes before propensity score matching were summarized in Table 2. Compared to patients with no treatment EVT, patients who received EVT within salvageable time window had significantly higher odds of achieving 3-month good functional outcome (50% versus 38%, adjusted odds ratio, 1.98 [95% CI, 1.48–2.66]; $P<0.001$). On the contrary, patients who received EVT beyond the salvageable time window showed no difference to no EVT patients in 3-month functional outcome (29% versus 38%, adjusted odds ratio, 1.35 [95% CI, 0.78–2.35]; $P=0.284$). For the safety outcomes, patients delivered EVT within the salvageable time window had similar bleeding risk compared with patients with no EVT, with PH2 rate of 7% versus 6% (adjusted odds ratio, 1.15 [95% CI, 0.66–2.01]; $P=0.610$), and sICH rate of 7% versus 9% (adjusted odds ratio, 0.95 [95% CI, 0.59–1.54]; $P=0.850$). In contrast, patients delivered EVT outside the salvageable time window had a significantly higher risk of PH2 (19% versus 6%, adjusted odds ratio, 3.42 [95% CI, 1.70–6.85]; $P=0.001$), and sICH (22% versus 9%, adjusted odds ratio, 2.00 [95% CI, 1.07–3.74]; $P=0.030$) compared with the no EVT group.

Patient Outcomes After Propensity Score Matching

The propensity score matching was performed based on age, baseline NIHSS score, proportion of patients

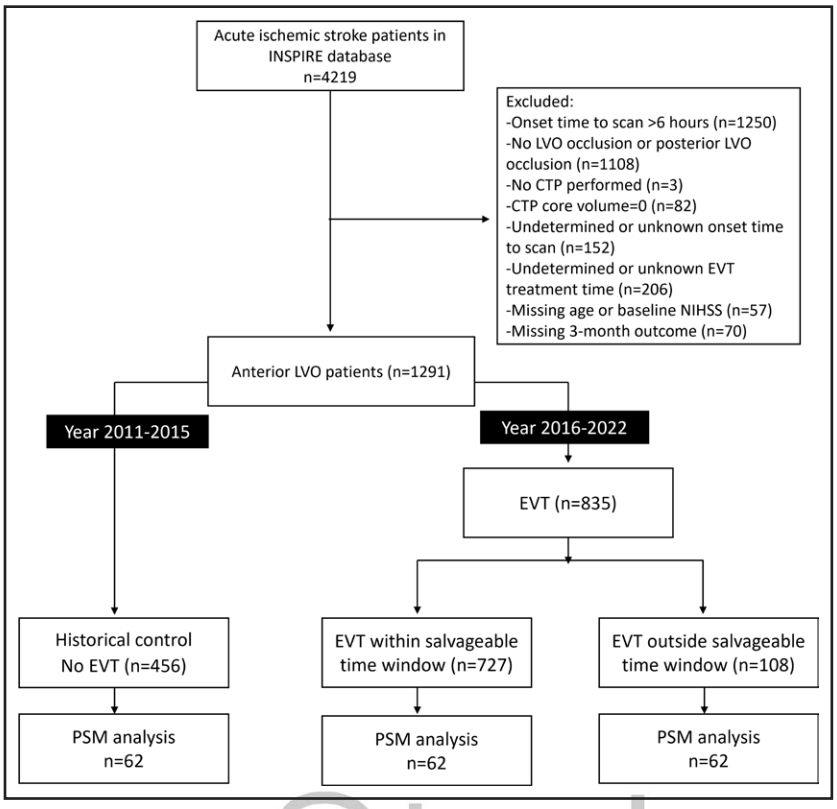

Figure 2. Flowchart of the included patients.
CTP indicates computed tomography perfusion; EVT, endovascular therapy; INSPIRE, International Stroke Perfusion Imaging Registry; LVO, large vessel occlusion; NIHSS, National Institutes of Health Stroke Scale; and PSM, propensity score matching.

receiving intravenous thrombolysis, internal carotid artery occlusion rates, onset-to-scan time, infarct core volume, and penumbra volume, resulting in 62 patients in each group with well-balanced characteristics across the 3 groups (no EVT, EVT within salvageable time window, EVT outside salvageable time; Figure 3; Table S1).

Results of propensity matching were consistent with results of the multivariable regression (Tables 2 and 3). After propensity matching, the 3-month good outcome rate was 29% for patients with no EVT treatment, 48% for patients who received EVT within salvageable time window, and 32% for patients who received EVT beyond salvageable time window. The distribution of 3-month modified Rankin Scale score is displayed in Figure S1. Compared to the no EVT group, patients receiving EVT within salvageable time window increased the odds of achieving 3-month good functional outcome over 2-folds (48% versus 29%, odds ratio, 2.29 [95% CI, 1.09–4.81]; *P*=0.028) without increasing the risk of hemorrhagic transformation (PH2, 2% versus 3%, odds ratio, 0.49 [95% CI, 0.04–5.57]; *P*=0.566). On the other hand, patients receiving EVT outside salvageable time window showed no therapeutic benefit in terms of 3-month good outcome (32% versus 29%, odds ratio, 1.16 [95% CI, 0.54–2.50]; *P*=0.697) but increased risk of PH2 (17% versus 3%, odds ratio, 5.83 [95% CI, 1.22–27.9]; *P*=0.027).

After propensity matching, the 3 groups showed no significant difference in the proportion of patients with fast core growth (42% for patients with no treatment EVT, 48% for patients who received EVT within the salvageable time window, and 60% for patients who received EVT beyond the salvageable time window; *P*=0.135). When further adjusting for the fast core growth rate in the regression model after propensity matching, patients receiving EVT within salvageable time window still showed an increased odds of 3-month good outcome compared with the no EVT group (adjusted odds ratio, 2.57 [95% CI, 1.19–5.53]; *P*=0.016), whereas patients receiving EVT outside salvageable time window showed no improvement in 3-month good outcome compared with the no EVT group (adjusted odds ratio, 1.41 [95% CI, 0.64–3.12]; *P*=0.399).

DISCUSSION

This study validated that a stroke patient would receive no clinical benefit from endovascular treatment within the early time window if the patient was predicted to have no salvageable brain tissue left when the endovascular procedure commenced. The endovascular procedure might even be harmful in those patients, increasing the risk of intracranial hemorrhage. Moreover, this study provides a novel approach to measure the "tissue clock" after ischemic stroke onset. The salvageable time window predicts how much time is left for the individual patient before their salvageable brain tissues progress to irreversible infarction that cannot be restored with blood reperfusion.

Table 1. Patient Characteristics Before Propensity Score Matching

	No EVT (n=456)	EVT within salvageable time window (n=727)	EVT outside salvageable time window (n=108)	*P* value
Age, y, median (IQR)	74 (64–81)	71 (62–79)	71 (61–77)	0.003
Age ≥70 y, % (n)	62% (382/456)	54% (392/727)	54% (58/108)	0.022
Baseline NIHSS score, median (IQR)	16 (12–19)	16 (12–20)	18 (13–21)	0.002
Intravenous thrombolysis, % (n)	79% (361/456)	52% (376/727)	52% (56/108)	<0.001
Onset to imaging scan, h, median (IQR)	1.98 (1.52–2.90)	3.01 (1.71–4.21)	1.24 (0.67–2.14)	<0.001
Scan to groin puncture, h, median (IQR)	…	1.39 (1.01–1.94)	2.33 (1.54–3.71)	<0.001
AF, % (n)	47% (213/451)	46% (335/725)	54% (58/108)	0.346
Hypertension, % (n)	64% (289/453)	63% (457/725)	70% (76/108)	0.333
Diabetes, % (n)	21% (195/450)	18% (129/721)	24% (26/107)	0.175
Smoking, % (n)	31% (134/435)	27% (181/676)	27% (27/100)	0.335
ICA occlusion, % (n)	31% (143/456)	27% (199/727)	40% (43/108)	0.021
Acute core volume, mL, median (IQR)	21.5 (9.0–54.5)	23 (9.0–44)	61 (30.5–96.5)	<0.001
Acute penumbra volume, mL, median (IQR)	73.5 (44–105.5)	89 (65–122)	67 (37.5–107)	<0.001
Core growth rate, mL/h, median (IQR)	10.8 (3.9–25.8)	8.2 (3.2–18.1)	52.3 (27.0–82.9)	<0.001
Fast core growth >25 mL/h, % (n)	25% (116/456)	15% (112/727)	76% (82/108)	<0.001

Ischemic penumbra and core volume are measured by delay time >3 s and cerebral blood flow <30% on CT perfusion imaging. AF indicates atrial fibrillation; CT, computed tomography; EVT, endovascular therapy; ICA, internal carotid artery; IQR, interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

The findings of this study provide direct evidence to support the importance of early delivery of EVT. This is consistent with a meta-analysis report from the HERMES collaboration that earlier treatment with endovascular thrombectomy was associated with improved functional outcomes at 3 months.[15] The ESCAPE trial (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke) reported that every 30-minute delay from imaging to EVT reduced the probability of a functional independent outcome by 8.3% and proposed an optimal imaging to groin puncture time of 60 minutes.[16] However, this 1-hour threshold might not be generalizable to all stroke populations, given the heterogeneity in infarct core growth rates.

This study introduces the concept of an individualized salvageable time window, offering a more personalized approach to stroke management. For example, a stroke patient presenting with a core growth rate of 40 mL/h and salvageable tissue of 20 mL would have a salvageable time window of only 30 minutes. In such cases, extremely prompt response by the stroke team and efficient in-hospital workflows are essential to ensure EVT is initiated within that critical window. Beyond in-hospital management, this concept may also guide interhospital transfer decisions from primary to comprehensive stroke center for an endovascular procedure.[17] Patients might not be able to benefit from EVT if the transfer time is estimated to exceed the salvageable time window.

Findings of this study add evidence to the importance of estimating the core growth rate for acute stroke management. Our previous research demonstrated that core growth rate can help clinicians make treatment decisions on EVT. EVT, compared with medical treatment alone, benefited patients the most if they had a fast core growth rate of >25 mL/h.[10,11] One possible explanation was that EVT could achieve recanalization much faster compared with medical therapy. This study used core growth rate to further predict the salvageable time window and provides an individualized optimal window to deliver EVT. Early delivery of EVT would be particularly important for patients with fast core growth, because they tend to have a much narrower salvageable time window than patients with slow core growth. However, this time window is not solely determined by the core growth rate. It also depends on the volume of salvageable tissue present at hospital arrival. Notably, the assessment of core growth rate and salvageable time window is based on the assumption of a linear development of infarction from stroke onset to treatment. This assumption is supported by an early study showing that infarction develops in a pattern that is close to linear within 24 hours of stroke onset.[13] In our previous studies, we also observed good agreement between the infarct volume predicted by linear growth and the actual infarct volume measured by MR diffusion-weighted imaging.[9] However, a more complex core growth may need to be developed to improve the accuracy of calculating salvageable tissue time in future studies.

One particularly intriguing finding was that patients who underwent EVT within the salvageable time window did not demonstrate an increased risk of hemorrhagic

Table 2. Patient Outcomes Before Propensity Score Match

	No EVT (n=456)	EVT within salvageable time window (n=727)	EVT outside salvageable time window (n=108)	EVT within salvageable time window vs no EVT				EVT outside salvageable time window vs no EVT			
				cOR (95% CI)	*P* value	aOR (95% CI)	Adjusted *P* value	cOR (95% CI)	*P* value	aOR (95% CI)	Adjusted *P* value
3-mo good outcome (mRS score 0–2)	38% (174/456)	50% (360/727)	29% (31/108)	1.59 (1.25–2.02)	<0.001	1.98 (1.48–2.66)	<0.001	0.65 (0.42–1.03)	0.068	1.35 (0.78–2.35)	0.284
3-mo poor outcome (mRS score 5–6)	37% (169/456)	26% (190/727)	52% (56/108)	0.60 (0.47–077)	<0.001	0.56 (0.41–076)	<0.001	1.83 (1.20–2.79)	0.005	1.03 (0.61–1.71)	0.916
3-mo death	23% (106/456)	16% (113/727)	36% (39/108)	0.61 (0.45–0.82)	0.001	0.59 (0.41–0.84)	0.004	1.87 (1.19–2.92)	0.006	1.08 (0.64–1.84)	0.768
ICH	25% (110/446)	31% (222/724)	52% (56/107)	1.35 (1.03–1.76)	0.027	1.29 (0.95–1.74)	0.100	3.35 (2.17–5.19)	<0.001	3.32 (2.05–5.37)	<0.001
PH2	6% (25/446)	7% (48/724)	19% (20/107)	1.20 (0.73–1.97)	0.482	1.15 (0.66–2.01)	0.610	3.87 (2.06–7.28)	<0.001	3.42 (1.70–6.85)	0.001
sICH	9% (41/446)	7% (54/724)	22% (23/107)	0.80 (0.52–1.22)	0.292	0.95 (0.59–1.54)	0.850	2.70 (1.54–4.74)	<0.001	2.00 (1.07–3.74)	0.030

aOR: adjusting for baseline core volume, penumbra volume, onset-to-scan time, ICA occlusion site, baseline NIHSS score, intravenous thrombolysis, and patient age in multivariate logistic regression. aOR indicates adjusted odds ratio; cOR, crude odds ratio; EVT, endovascular therapy; ICA, internal carotid artery; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH2, type 2 parenchymal hematoma; and sICH, symptomatic intracranial hemorrhage.

transformation compared with those who did not receive EVT. This aligns with the HERMES collaboration's pooled analysis of 5 thrombectomy trials published in 2015, which demonstrated that thrombectomy does not significantly increase the risk of sICH compared with medical therapy (4.4% versus 4.3%).[3] However, there have been studies reporting increased sICH after EVT.[18,19] The conflicting findings might be explained by whether patients were treated within or beyond the salvageable window. According to this study, EVT delivered beyond the salvageable time window would increase the risk of sICH significantly.

The increased risk of hemorrhagic transformation may be explained by the extent of blood-brain barrier disruption at the time of recanalization. When recanalization occurs beyond the salvageable time window, the ischemic tissue often exhibits severe blood-brain barrier breakdown due to the accumulation of reactive oxygen species, activation of inflammatory pathways, and upregulation of remodeling factors, rendering it more susceptible to hemorrhagic injury.[20,21] In contrast, timely recanalization within the salvageable window can restore blood flow before irreversible blood-brain barrier damage occurs, without increasing the risk of sICH.[20] Moreover, delayed recanalization can lead to larger infarct volumes, which are associated with a higher risk of sICH.[22]

The findings of this study are applicable to patients with large core volumes. In this study, half of the patients had a large core volume >50 mL after propensity matching. For patients with large core, it is often challenging for clinicians to make treatment decisions due to concerns about bleeding risk. Although recent randomized controlled trials support EVT in large core patients,[23–27] a meta-analysis of the randomized controlled trials reported increased sICH risk with EVT compared with medical treatment.[28] The increased hemorrhagic risk may be caused by delayed EVT delivery. This study has demonstrated that if patients received EVT beyond the salvageable time window, they would have an increased risk of sICH by 2- to 3-fold compared with patients who did not receive EVT. Early delivery of EVT might help to avoid the increased bleeding risk of large core patients. Initiating EVT early may be particularly crucial for patients with a large ischemic core,[29] because they often present with an ultrafast core growth rate, a narrow salvageable tissue time window, even with large penumbra at administration. The relationship between the salvageable time window and EVT delivery time on large core patients needs to be further studied. Notably, different definitions of large core have been used in previous trials, including ASPECT 3 to 5 on noncontrast CT or core volume>50 mL on perfusion imaging.

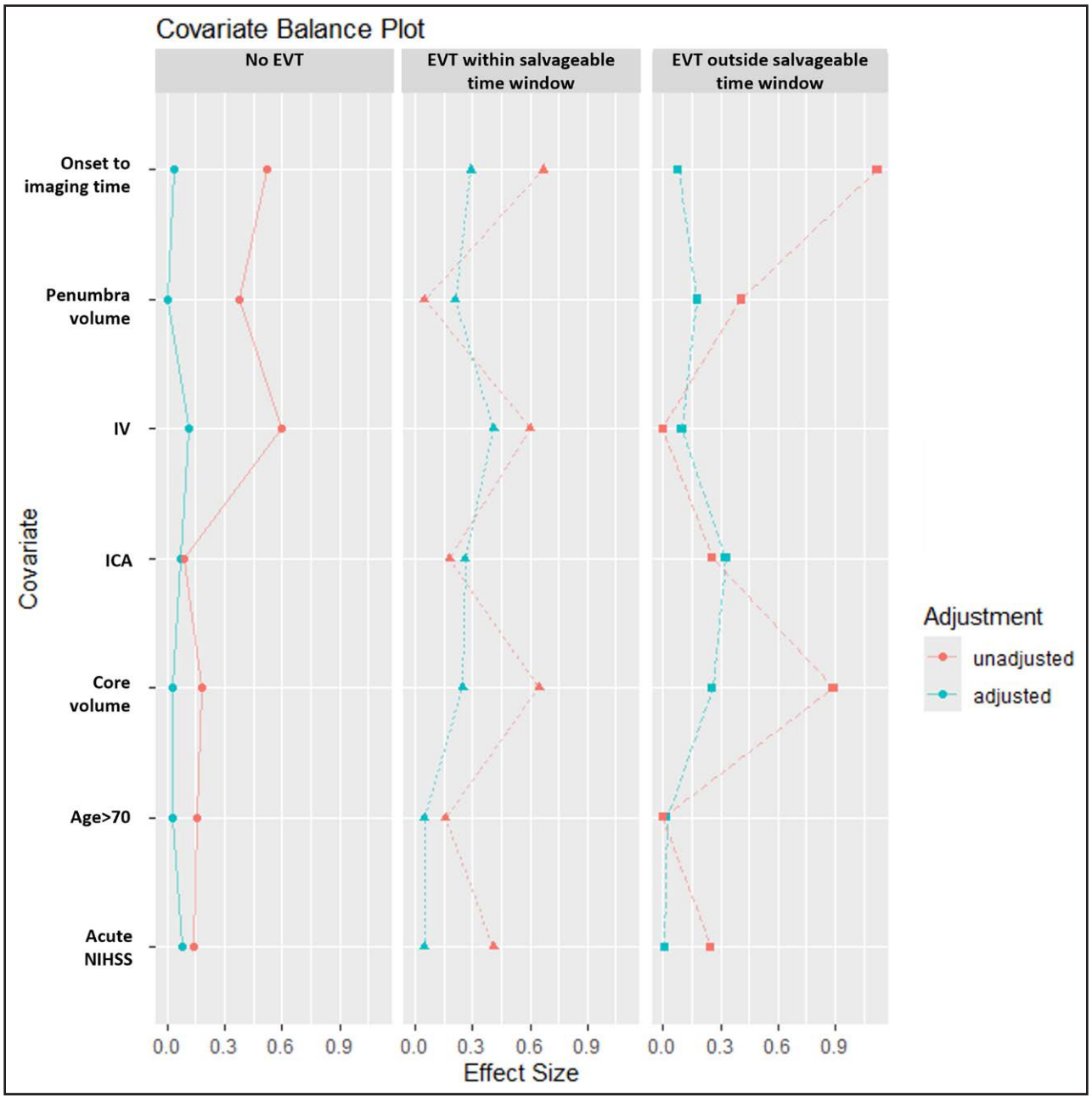

Figure 3. Covariate balance plot with and without propensity score adjustment.
Penumbra and core volume are measured by delay time >3 s and cerebral blood flow <30% on computed tomography perfusion imaging. EVT indicates endovascular therapy; ICA, internal carotid artery; IV, intravenous thrombolysis; and NIHSS, National Institutes of Health Stroke Scale.

This study is not a randomized controlled trial. To reduce the selection bias, we included a historical control arm in which patients with LVO did not receive endovascular procedure because the procedure was not standard care. To further reduce the confounding effect of imbalanced baseline characteristics, we used the statistical approach of propensity score matching. However, there might still be residual selection bias or confounding factors. Another limitation of this study is that the estimations of core growth rate and salvageable time window are based on acute CT perfusion imaging and a clearly defined stroke onset time. Therefore, the results of this study cannot be applied to patients with acute noncontrast CT only, wake-up stroke, or unknown onset time. The application of this study is also limited to patients presenting early, within 6 hours of stroke, and with anterior circulation LVO. As growing evidence supports the efficacy of EVT within extended time windows (6–24 hours), particularly when guided by advanced imaging techniques for patient selection, further studies are required to validate the application of salvageable time window concept to later-presenting patients.

Table 3. Patient Outcomes After Propensity Score Match

	No EVT (n=62)	EVT within salvageable time window (n=62)	EVT outside salvageable time window (n=62)	EVT within salvageable time window vs no EVT		EVT outside salvageable time window vs no EVT	
				cOR (95% CI)	*P* value	cOR (95% CI)	*P* value
3-mo good outcome (mRS score 0–2)	29% (18/62)	48% (30/62)	32% (20/62)	2.29 (1.09–4.81)	0.028	1.16 (0.54–2.50)	0.697
3-mo poor outcome (mRS score 5–6)	40% (25/62)	31% (19/62)	44% (27/62)	0.65 (0.31–1.37)	0.261	1.14 (0.56–2.33)	0.716
3-mo death	24% (15/62)	16% (10/62)	32% (20/62)	0.60 (0.25–1.47)	0.266	1.49 (0.68–3.28)	0.320
ICH	28% (16/58)	28% (16/58)	50% (29/58)	1.00 (0.44–2.26)	1.000	2.62 (1.21–5.68)	0.014
PH2	3% (2/58)	2% (1/58)	17% (10/58)	0.49 (0.04–5.57)	0.566	5.83 (1.22–27.9)	0.027
sICH	7% (4/58)	5% (3/58)	17% (10/58)	0.74 (0.16–3.45)	0.698	2.81 (0.83–9.55)	0.097

cOR indicates crude odds ratio; EVT, endovascular therapy; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; PH2, type 2 parenchymal hematoma; and sICH, symptomatic intracranial hemorrhage.

CONCLUSIONS

In summary, this study provides a simple approach to measure the salvageable time window for individual stroke patients with LVO within 6 hours of stroke onset. Patients may not receive therapeutic benefit from endovascular treatment if the treatment is delivered beyond the salvageable tissue window.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1
Figure S1
The STROBE Statement Checklist

APPENDIX

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