

ORIGINAL RESEARCH

Perfusion Imaging-Based Triage for Acute Ischemic Stroke: Trends in Use and Impact on Clinical Outcomes

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BACKGROUND: Perfusion imaging (PI) serves as a valuable tool for triaging patients with acute ischemic stroke for endovascular treatment (EVT). This study aims to investigate trends in PI use and its impacts on EVT rates and clinical outcomes, particularly focusing on variations across different time windows.

METHODS: Data from a prospective, nationwide, acute stroke registry in South Korea were analyzed retrospectively. PI was regarded as treatment-decision imaging when conducted either (1) prior to EVT, or (2) within 3 hours from hospital arrival in patients not receiving EVT. The study spanned 3 epochs: 2011–2014, 2015–2017, and 2018–2021. Based on the time from onset to arrival, patients were categorized into 2 time windows: early (0–6 hours) and late (6–24 hours). We evaluated EVT rates and clinical outcomes in patients with anterior large vessel occlusion.

RESULTS: From 2011 to 2021 among 49 449 patients with acute ischemic stroke presenting within 24 hours of onset, PI use rates declined from 36.9% to 30.1%. In the early window, rates dropped from 48.4% to 32.4%, whereas in the late window, they increased from 23.5% to 27.8%. Factors such as older age, atrial fibrillation, anterior large vessel occlusion, and severe stroke were associated with higher rates in the late window. Conversely, younger age and male sex were associated with higher rates in the early window. For patients with anterior large vessel occlusion, PI use increased the likelihood of receiving EVT in the late window and minimized the risk of symptomatic intracranial hemorrhage in the early window. However, 3-month functional outcomes and mortality were unaffected.

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CONCLUSION: The study revealed distinct trends in PI use across early and late time windows, indicating varying roles of PI in these time frames. However, the definitive value and necessity of PI in guiding EVT decision-making remain unclear, underscoring the need for further research

Key Words: acute ischemic stroke ■ endovascular treatment ■ perfusion imaging ■ secular trend

The advent of the perfusion mismatch concept positioned perfusion imaging (PI) as a key element in optimizing the use and effectiveness of endovascular treatment (EVT) for acute ischemic stroke (AIS).¹ Pivotal EVT trials in the early time window (up to 6 hours after stroke onset) employing perfusion mismatch for patient triage^{2,3} showed a potential for larger treatment effects compared with those not using this approach.^{4,5} Furthermore, PI has been instrumental in extending the time window for EVT eligibility. Notably, the DAWN (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3) trials used PI to identify patients with salvageable brain tissue, thereby expanding the treatment window to 6–24 hours poststroke onset.^{6,7}

Despite strong evidence supporting the use of PI in AIS, its practical application remains limited. For instance, in the United States, the use of computed tomography (CT) perfusion for AIS only modestly increased from 1.4% to 4.2% between 2014 and 2017, despite the release of pivotal early window EVT trials in 2015.⁸ During this period, only 14% of hospitals treating patients with stroke were equipped with CT perfusion, in contrast to the widespread availability of noncontrast CT (100%) or magnetic resonance imaging (91%). Following the release of the DAWN and DEFUSE 3 trials in 2018, PI has gained recognition as a critical imaging technique for AIS, particularly in the late time window.⁹ However, there is a lack of comprehensive data detailing trends in PI use for AIS since the publication of these landmark trials.

This study aims to examine temporal trends in PI use for treatment decisions and its impact on both EVT rate and clinical outcomes in the real-world practice of South Korea. We also seek to uncover any disparities in PI use trends and its association with EVT rate and clinical outcomes between the early and late time windows.

METHODS

Data in this study are available from the corresponding author by a reasonable request. The study was

approved by local institutional review boards across all participating centers.

Study Design and Population

This retrospective analysis leverages the CRCS-K-NIH (Clinical Research Collaboration for Stroke in Korea-National Institute of Health) registry, a nationwide, multicenter, prospective stroke registry, initiated in 2008. It includes 20 tertiary or secondary hospitals, of which 17 (8 tertiary and 9 secondary hospitals) participated in this study. The registry operates on a voluntary basis and enrolls consecutive patients admitted with acute stroke or transient ischemic attack. Further information on the CRCS-K-NIH registry is provided elsewhere.¹⁰

Our analysis focused on patients aged 18 and above diagnosed with AIS, presenting within 24 hours of their time last seen well (TLSW) from January 2011 to December 2021. Ineligible participants were those who were transferred post-EVT. Anterior large vessel occlusion (aLVO) was identified as occlusion in the intracranial internal carotid artery or the M1 segment of the middle cerebral artery.⁶ Our cohorts for analysis included (1) all AIS within 24 hours for PI use trend, (2) patients with aLVO for EVT rate, and (3) patients with aLVO excluding those with missing outcomes for clinical outcomes. Additionally, we evaluated patients with AIS and aLVO undergoing EVT for the impact of PI on clinical outcomes in this subgroup.

Data Collection

In the CRCS-K-NIH registry, collection of clinical information and data entry were performed by research coordinators (usually registered nurses). Variable definitions and data collection processes were standardized, and training workshops for registrars were held regularly.¹⁰ Among the collected information, demographics, history of medical illness, history of medications, stroke characteristics including location of occlusion sites in symptomatic artery, initial National Institutes of Health Stroke Scale (NIHSS) score, premonitory modified Rankin Scale (mRS) score, causative stroke mechanism, lab data, reperfusion therapy (intravenous thrombolysis and EVT), transfer status, and workflow time metrics were extracted from the registry database and used for this study.

Study Outcomes

In examining trends in PI use, PI was considered as treatment-decision imaging under 2 conditions: if it was conducted before EVT or within 180 minutes from patient arrival in cases where EVT was not administered. The 180-minute cutoff was established based on an analysis of the time elapsed from patient arrival to PI acquisition for patients with aLVO undergoing EVT. This time frame encompasses the 99th percentile for the early window and the 96th percentile for the late window (Figure S1). PI modalities included both CT perfusion and magnetic resonance perfusion.

To assess the effectiveness of PI use, outcomes were EVT rate and 3-month functional outcomes (the proportion of achieving an mRS score 0–2 and mRS score 0–1, and the distribution of mRS scores). Safety outcomes were 3-month mortality and symptomatic intracranial hemorrhage (ICH) during hospitalization.

Statistical Analysis

Categorical variables were analyzed using Pearson's chi-square test and continuous variables using analysis of variance, Student's *t*-test, or Wilcoxon rank sum test when appropriate. For variables with <5% missing data, imputation was performed using group median and mode values.

To discern trends in PI use, patients with AIS presenting within 24 hours from TLSW were analyzed with the study period being divided into 3 epochs: 2011–2014, 2015–2017, and 2018–2021.^{4,6,7} Further granularity was introduced by categorizing our subjects based on the time elapsed between TLSW and arrival, forming 2 groups: the early (0–6 hours) and the late (6–24 hours) time windows.¹¹ Subsequently, the Cochran–Armitage trend test was applied in each population of the overall, early, and late time window, respectively. To explore potential factors affecting PI use, we used multivariable logistic regression models with a generalized estimating equation method to account for center clustering. Candidate factors were selected based on clinical relevance and prior literature.¹² To evaluate the differential impact of these factors according to the time window, interaction terms between each factor and time window were introduced.

The association of PI use with EVT rate and functional and safety outcomes was assessed in patients with aLVO. We employed modified Poisson regression and ordinal logistic regression models, applying the generalized estimating equation method to account for center clustering. Variables for adjustment include age, sex, hypertension, diabetes, hyperlipidemia, atrial fibrillation, history of stroke or transient ischemic attack and taking statin, previous mRS score, causative stroke mechanism, occlusion site, intravenous thrombolysis,

Nonstandard Abbreviations and Acronyms

AIS	acute ischemic stroke
ALVO	anterior large vessel occlusion
CRC-K-NIH	Clinical Research Collaboration for Stroke in Korea - National Institute of Health
CT	computed tomography
DAWN	Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
EVT	endovascular thrombectomy
ICH	intracranial hemorrhage
PI	perfusion imaging
TLSW	time last known well

CLINICAL PERSPECTIVE

What Is New?

- In the era of endovascular thrombectomy, the trends and clinical impact of perfusion imaging use in the early (0–6 hours) and late time windows (6–24 hours) remain unclear.
- Regarding perfusion imaging use trend, a decrease in the early window and an increase in the late window were observed, in line with recommendations from international acute stroke guidelines.

What Are the Clinical Implications?

- Although perfusion imaging use was associated with higher likelihood of receiving endovascular thrombectomy in the late window and reduced risk of symptomatic hemorrhage in the early window, it did not affect 3-month functional outcomes and mortality.

systolic blood pressure, initial glucose, transfer-in status, epoch, and elapsed time from TLSW to arrival. EVT was not adjusted regarding its mediation effect on the outcomes. An interaction term was introduced to assess the effect modification by the time window on the impact of PI use. In addition to this traditional approach, we applied inverse probability of treatment weighting analysis using propensity scores for further

adjustments of baseline imbalances according to PI use. Variables used to generate propensity scores for PI use were predetermined based on clinical relevance and prior literature.^{11,13–21} In the assessment of functional outcome and mortality at 3 months for patients with aLVO, subjects missing 3-month mRS data were excluded.

Under the assumption that PI-based triage might primarily affect clinical outcomes through EVT, separate analyses regarding functional and safety outcomes were conducted in patients with aLVO who underwent EVT. This analysis aimed to identify any potential augmentation in the effectiveness of PI use.

A value of $P < 0.1$ was considered significant for assessment of interaction. In the other comparisons, a value of $P < 0.05$ with a 2-sided test was considered significant. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC).

RESULTS

We analyzed 49 449 adults with AIS who presented within 24 hours after TLSW from a pool of 97 324 patients in the CRCS-K-NIH database, spanning 2011–2021 (Figure 1). The mean age was 69 ± 13 years. Fifty-nine percent were men, and the median value of the initial NIHSS score was 4 (interquartile range 2–10).

Upon examining the data across different epochs, we observed notable trends in patient characteristics. There was an increase in the mean age, along with decreasing trends in initial NIHSS scores, atrial fibrillation, aLVO, premorbid disabilities, and transfer-in rates (Table 1).

Among the 17 participating centers, the PI use rates exhibited a wide variation ranging from nearly 0% at certain centers to exceeding 60% at others, with a median rate of 15% (Figure S2).

Temporal Changes of PI Use as Treatment-Decision Imaging

Throughout the study period, there was a noticeable decrease in PI use rates by 6.8% points (Figure 2). This decrease was more pronounced in the early window, showing a substantial 16% points reduction. Conversely, in the late window, there was a modest increase of 4.3% points (P 's for trend < 0.001 on Cochran–Armitage trend test).

Determinants Influencing PI Use Across Time Windows

Among all patients with AIS presenting within 24 hours after TLSW ($n = 49\,449$), significant differences in baseline characteristics exist according to PI use (Table

S1). Multivariable analysis identified male sex, aLVO, higher initial NIHSS score, and presentation in the late window as factors increasing the likelihood of PI use (Table 2A). Given the contrasting use trends between the early and late windows, we incorporated an interaction term between each variable and time window. This approach allowed us to highlight the distinct influences of predefined factors on PI use across different time frames (Table 2B). Early window analysis linked younger age and male sex to increased PI use, whereas, in the late window, factors like older age, atrial fibrillation, aLVO, and higher initial NIHSS scores predominated. Consistent with the trend analysis, regarding PI use, a marked decline in the early window and a significant uptick in the late window were observed (P for interaction = 0.004).

Correlation Between PI Use, EVT Rates, and Clinical Outcomes for Patients With aLVO

In our cohort, 10 315 patients were diagnosed with aLVO. Notable disparities in baseline characteristics were observed between patients with and without PI (Table S2). However, these imbalances were neutralized after applying inverse probability of treatment weighting (Figure S3).

Patients with PI demonstrated higher EVT rates in the late window and fewer symptomatic ICHs in the early window compared with those without PI (Table 3). An improvement in 3-month mRS score distributions was also observed in patients with PI in the early window. Multivariable analyses confirmed that the reduction of symptomatic ICH in the early window and the increased likelihood of receiving EVT in the late window were significantly associated with PI use. However, regarding 3-month functional outcomes and mortality, PI use did not show a significant impact in either window (Figure 3).

Association of PI Use With Clinical Outcomes in Patients With aLVO Who Underwent EVT

A total of 4008 patients with aLVO underwent EVT. Baseline characteristics were well balanced after applying inverse probability of treatment weighting (Figure S4 and Table S3). There was no difference in time elapsed from patient arrival to EVT between those with and without PI (98 [78–125] versus 100 [77–130] minutes; median [interquartile range]; $P = 0.30$).

In the early window, an improvement of 3-month mRS distribution ($P = 0.003$) and a lower rate of symptomatic ICH (3.7% versus 5.3%, $P = 0.03$) were observed in the PI group compared with the no PI

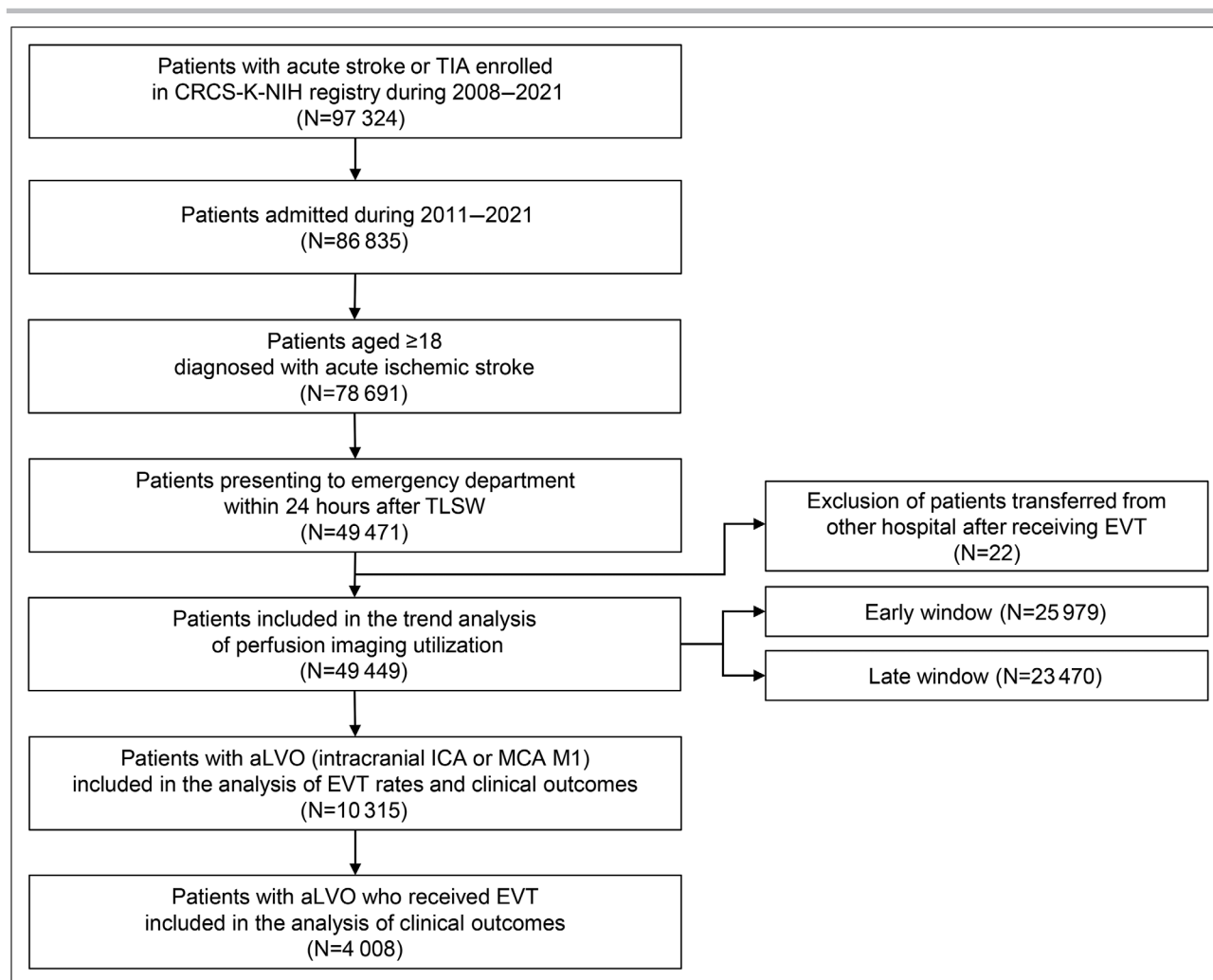


Figure 1. Study flow chart. aLVO indicates anterior large vessel occlusion; CRCS-K-NIH, Clinical Research Center for Stroke-Korea-National Institute of Health; EVT, endovascular treatment; ICA, internal carotid artery; MCA, middle cerebral artery; CRCS-K-NIH, Clinical Research Collaboration for stroke in Korea-National Institute of Health; TIA, transient ischemic attack; and TLSW, time last seen well.

group (Table S4). In the multivariable models, PI use did not affect functional outcomes and mortality at 3 months. Regarding symptomatic ICH, an interaction between the time window and PI use was not statistically significant (P for interaction = 0.70; Figure S5).

DISCUSSION

Our study, covering the years 2011–2021, revealed an overall notable downward trend in PI use among patients with AIS in South Korea presenting within 24 hours after onset. Interestingly, although PI use significantly decreased in the early window, there was a modest increase in the late window. For patients with aLVO, PI use considerably increased the probability of receiving EVT in the late window and reduced the risk of symptomatic ICH in the early window. How-

ever, 3-month functional outcomes and mortality were unaffected in either window. When specifically focusing on patients with aLVO who underwent EVT, the differential influence of PI use on symptomatic ICH between the early and late time windows was not evident.

The distinct trends in PI use between the early and late windows may reflect changes in the stroke guidelines.^{9,22,23} The successful early window EVT trials in 2015, which required only noncontrast CT and the identification of aLVO for EVT eligibility,^{4,24} might have led to uncertainty about the role of PI in the early window. This hypothesis is supported by a substantial 12.2% point decrease from 2011–2014 to 2015–2017 (Figure 2). On the other hand, the adoption of the DAWN and DEFUSE 3 criteria, which included PI for EVT triage in the late window,^{6,7} probably contributed to the increase of PI use in the late window, as evidenced by a 3.2% point rise from 2015–2017 to

Table 1. Baseline Characteristics of Patients With Acute Ischemic Stroke Who Presented Within 24 Hours After Stroke Onset According to Epochs (N=49 449)

	2011–2014 (N = 14824)	2015–2017 (N = 13795)	2018–2021 (N = 20830)	<i>P</i> _{trend} *
Demographic factor				
Age, mean ± SD, y	68.0 ± 12.8	68.6 ± 12.8	69.5 ± 13.2	<0.001
Male sex, n (%)	8694 (58.6)	8143 (59.0)	12425 (59.6)	0.05
History of medical illness				
Hypertension, n (%)	9972 (67.3)	8665 (62.8)	13822 (66.4)	0.30
Diabetes, n (%)	4506 (30.4)	4070 (29.5)	6643 (31.9)	<0.001
Hyperlipidemia, n (%)	4371 (29.5)	3508 (25.4)	6736 (32.3)	<0.001
Smoking, n (%)	5746 (38.8)	4966 (36.0)	6841 (32.8)	<0.001
Stroke or TIA, n (%)	106 (0.7)	66 (0.5)	131 (0.6)	0.42
Coronary artery disease, n (%)	1336 (9.0)	1256 (9.1)	2116 (10.2)	<0.001
Atrial fibrillation, n (%)	3881 (26.2)	3478 (25.2)	5160 (24.8)	<0.001
Stroke characteristics				
Anterior LVO, n (%)	3171 (21.4)	2905 (21.1)	4239 (20.4)	0.01
Initial NIHSS score, median (IQR)	4 (2–11)	4 (2–10)	4 (1–9)	<0.001
0–5, n (%)	8491 (57.3)	8168 (59.2)	13101 (62.9)	
6–15, n (%)	4268 (28.8)	3788 (27.5)	5387 (25.9)	
≥16, n (%)	2065 (13.9)	1839 (13.3)	2342 (11.2)	
Previous mRS				<0.001
0, n (%)	11213 (75.6)	10646 (77.2)	16869 (81.0)	
1, n (%)	1233 (8.3)	1151 (8.3)	1527 (7.3)	
≥2, n (%)	2378 (16.0)	1998 (14.5)	2434 (11.7)	
Causative stroke mechanism				<0.001
LAA, n (%)	4896 (33.1)	4164 (30.2)	6634 (31.9)	
SVO, n (%)	2181 (14.7)	2334 (16.9)	3570 (17.1)	
Cardioembolic, n (%)	3999 (27.0)	3634 (26.4)	5101 (24.5)	
Other determined, n (%)	328 (2.2)	432 (3.1)	837 (4.0)	
Undetermined, n (%)	3403 (23.0)	3226 (23.4)	4686 (22.5)	
Systolic blood pressure, mean ± SD, mmHg	143.2 ± 9.2	143.1 ± 9.3	143.4 ± 9.2	0.01
Initial serum glucose, mean ± SD, mg/dL	133.7 ± 24.3	133.0 ± 23.9	134.0 ± 24.0	0.19
Reperfusion therapy				
IVT, n (%)	3135 (21.1)	2668 (19.3)	3495 (16.8)	<0.001
EVT, n (%)	1413 (9.5)	1712 (12.4)	2956 (14.2)	<0.001
Transfer-in, n (%)	524 (3.5)	439 (3.2)	389 (1.9)	<0.001
Modality of perfusion imaging				<0.001
CT perfusion, n (%)	508 (8.5)	714 (14.3)	1321 (17.5)	
MR perfusion, n (%)	5458 (91.5)	4296 (85.7)	6236 (82.5)	
Workflow metrics				
TLSW to arrival, median (IQR), (h)	5 (2–12)	5 (2–12)	6 (2–13)	<0.001
Early window, n (%)	7967 (53.7)	7352 (53.3)	10660 (51.2)	
Arrival to EVT, median (IQR), (h)	109 (86–139)	98 (78–128)	100 (76–135)	0.47

CT indicates computed tomography; EVT, endovascular treatment; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large artery atherosclerosis; LVO, large vessel occlusion; MR, magnetic resonance; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SVO, small vessel occlusion; TIA, transient ischemic attack; and TLSW, time last seen well.

**P* value by Cochran–Armitage trend test, Cochran–Mantel–Haenszel test and linear contrasts test in analysis of variance.

2018–2021. Additionally, in the late window, PI use significantly increased the likelihood of undergoing EVT in patients with aLVO. However, these effects were not observed in the early window, potentially due to current stroke guidelines emphasizing PI for EVT triage in the late window.⁹

The PI use rate was 32.3% in our study, markedly higher than the 2.5% reported in the United States between 2014 and 2017.⁸ In contrast to the downward trend observed in our study, the US rates showed a slight increase from 1.4% in 2014 to 4.2% in 2017.^{8,25} These differences in both absolute rates and the trend

Table 2. Potential Determinants of PI Use as Treatment-Decision Imaging in Patients Presenting Within 24 Hours After Onset (N = 49 449) Without (A) and With (B) Considering Their Interactions With Time Window

A					
	Adjusted OR (95% CI)			P value	
Demographic factor					
Age, per 10 y	1.01 (0.97–1.06)			0.62	
Male sex	1.07 (1.01–1.13)			0.02	
History of medical illness					
Hypertension	0.97 (0.83–1.14)			0.74	
Diabetes	0.97 (0.90–1.06)			0.51	
Hyperlipidemia	1.16 (0.79–1.70)			0.46	
Stroke or TIA	1.06 (0.68–1.67)			0.79	
Atrial fibrillation	0.95 (0.84–1.07)			0.40	
Stroke characteristics					
Anterior LVO	1.39 (1.05–1.84)			0.02	
Initial NIHSS score, per 1 point	1.02 (1.00–1.04)			0.03	
Previous mRS score					
0	1 (Ref)				
1	1.00 (0.67–1.49)			0.98	
≥2	0.96 (0.66–1.39)			0.83	
Transfer-in	0.89 (0.63–1.26)			0.52	
Epoch					
2011–2014	1 (Ref)				
2015–2017	0.77 (0.40–1.48)			0.42	
2018–2021	0.75 (0.36–1.56)			0.44	
Late window (Early window as a reference)	0.58 (0.47–0.71)			<0.001	
B	Early window		Late window		P for interaction
	Adjusted OR (95% CI)†	P	Adjusted OR (95% CI)†	P	
Demographic factor					
Age, per 10 y	0.99 (0.98–1.00)	0.04	1.04 (1.02–1.06)	<0.001	<0.001
Male sex	1.04 (1.00–1.08)	0.04	0.99 (0.95–1.03)	0.47	0.02
History of medical illness					
Hypertension	1.02 (0.94–1.11)	0.62	0.98 (0.92–1.04)	0.54	0.37
Diabetes	0.99 (0.96–1.03)	0.77	0.99 (0.97–1.02)	0.52	0.94
Hyperlipidemia	0.92 (0.84–1.01)	0.07	0.94 (0.86–1.03)	0.19	0.70
Stroke or TIA	0.88 (0.62–1.25)	0.48	1.08 (0.82–1.40)	0.59	0.04
Atrial fibrillation	0.95 (0.88–1.02)	0.17	1.16 (1.04–1.29)	0.01	<0.001
Stroke characteristics					
Anterior LVO	1.03 (0.94–1.14)	0.51	1.50 (1.19–1.88)	<0.001	0.006
Initial NIHSS score, per 1 point	1.01 (1.00–1.02)	0.07	1.05 (1.01–1.09)	0.02	0.07
Previous mRS score					0.91
0	1 (Ref)		1 (Ref)		
1	0.97 (0.84–1.13)	0.73	0.92 (0.73–1.16)		
≥2	0.99 (0.90–1.08)	0.75	0.97 (0.80–1.18)		
Transfer-in	0.78 (0.52–1.17)	0.23	0.80 (0.58–1.10)		0.84
Epoch					0.004
2011–2014	1 (Ref)		1 (Ref)		
2015–2017	0.61 (0.27–1.36)	0.23	1.08 (0.72–1.62)	0.71	
2018–2021	0.51 (0.21–1.23)	0.14	1.26 (0.75–2.12)	0.38	

The results are presented as *italics* in the variables showing non-significant interaction with time window (P for interaction ≥ 0.1) in Table A and those showing significant interaction with time window (P for interaction < 0.1) in Table B.

LVO indicates large vessel occlusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and TIA, transient ischemic attack.

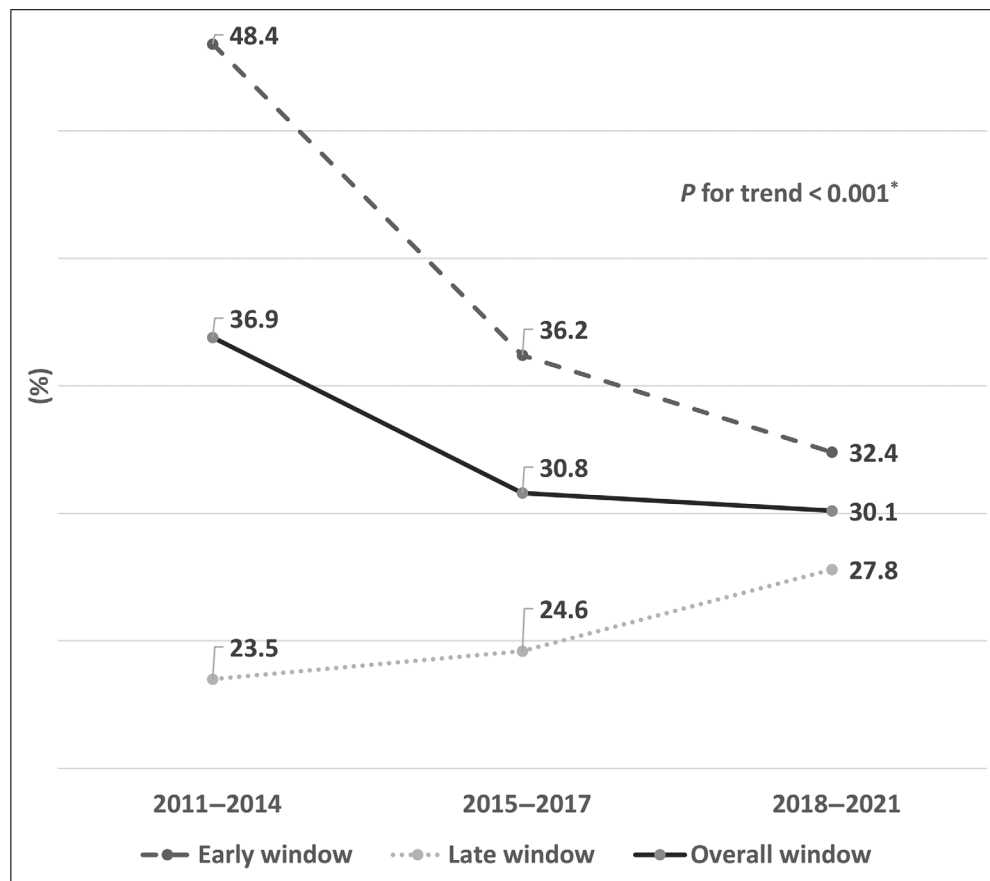


Figure 2. Secular trends of perfusion imaging use in patients with acute ischemic stroke who presented within 24 hours after onset. *Cochran–Armitage trend test was applied, without adjustments for center clustering and other covariates.

Table 3. Comparisons of Outcomes According to PI Use in Patients With Anterior Large Vessel Occlusion (N = 10 315)

	Early window (0–6 hours)			Late window (6–24 hours)		
	PI, n (%) (N = 2804)	No PI, n (%) (N = 3688)	$P^{\dagger}$	PI, n (%) (N = 1441)	No PI, n (%) (N = 2382)	$P^{\dagger}$
EVT rate	1310 (46.7)	1780 (48.3)	0.22	482 (33.4)	436 (18.3)	<0.001
Functional outcomes at 3 mo*						
mRS score 0–2	1192 (43.5)	1517 (42.8)	0.55	467 (33.3)	815 (35.6)	0.16
mRS score 0–1	852 (31.1)	1075 (30.3)	0.49	321 (22.9)	515 (22.5)	0.78
mRS score distribution			0.002			0.70
0	438 (16.0)	504 (14.2)		144 (10.3)	200 (8.7)	
1	414 (15.1)	571 (16.1)		177 (12.6)	315 (13.8)	
2	340 (12.4)	442 (12.5)		146 (10.4)	300 (13.1)	
3	380 (13.9)	376 (10.6)		205 (14.6)	279 (12.2)	
4	445 (16.3)	543 (15.3)		292 (20.8)	468 (20.5)	
5	350 (12.8)	605 (17.1)		219 (15.6)	391 (17.1)	
Safety outcomes						
Deaths at 3 mo*	371 (13.6)	505 (14.2)	0.43	218 (15.6)	335 (14.6)	0.45
Symptomatic ICH	82 (2.9)	158 (4.3)	0.004	38 (2.6)	65 (2.7)	0.87

EVT indicates endovascular treatment; ICH, intracranial hemorrhage; mRS, modified Rankin Scale; and PI, perfusion imaging.

*2738 and 3546 patients with and without PI in the early window and 1401 and 2288 with and without PI in the late window had data of 3-month mRS.

$P^{\dagger}$ value by chi-square test and Cochran–Mantel–Haenszel shift test.

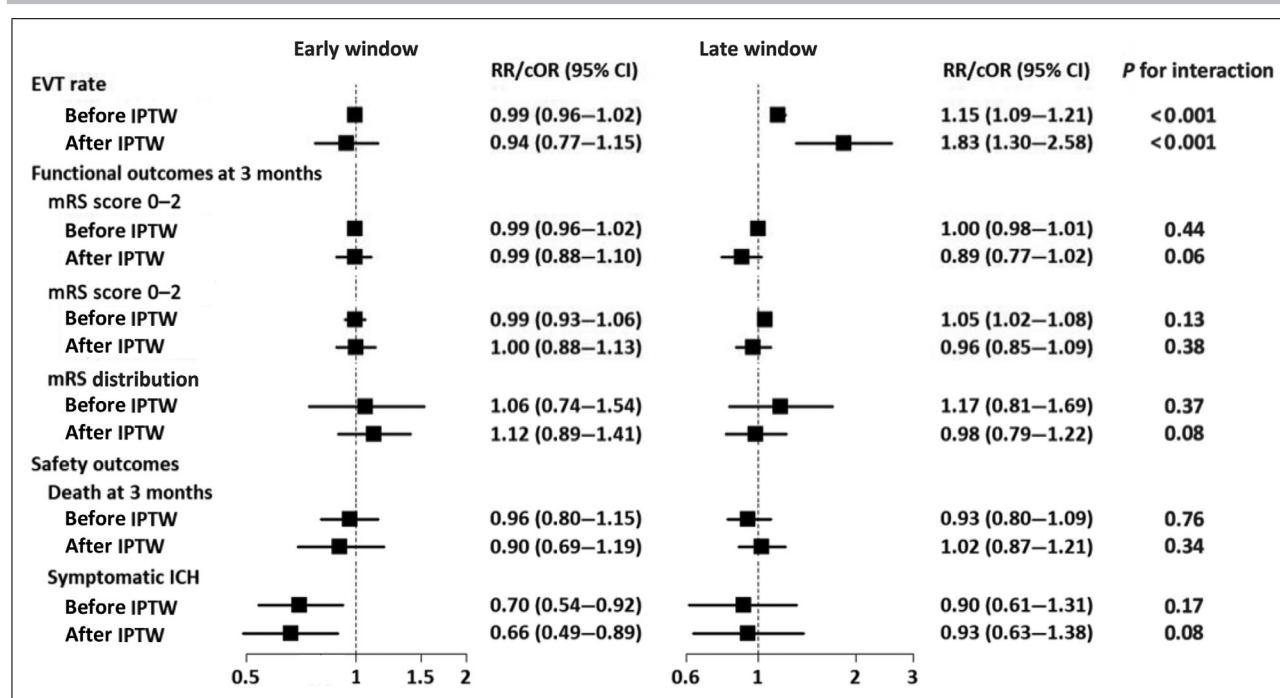


Figure 3. Association between perfusion imaging use and outcomes in patients with anterior large vessel occlusion. RRs and cOR were obtained from modified Poisson regression and ordinal logistic regression models, respectively, before (with adjustments for variables mentioned in the Methods section) and after applying IPTW with propensity scores. cOR indicates common odds ratios; EVT, endovascular treatment; ICH, intracranial hemorrhage; IPTW, inverse probability of treatment weighting; mRS, modified Rankin Scale; and RR, relative risk.

could be due to variations in the types of participating centers. Our data predominantly came from teaching, tertiary, and urban hospitals, whereas the US data primarily included nonteaching hospitals.^{8,25} Notably, even with different methodologies, significant global variations in PI use rates have been reported, such as 63% in the Swiss Stroke Registry and only 1.2% in the United Kingdom's national stroke registry.²⁶

In the late window, aLVO, atrial fibrillation, and higher initial NIHSS scores were associated with an increase in use of PI for treatment decisions. The 3 factors we identified, aLVO, atrial fibrillation, and higher initial NIHSS score, may be associated with larger infarct size or greater severity of stroke deficit.²⁷ Interestingly, these factors did not have a significant impact on PI use in the early window. This suggests that in the late window, clinicians might consider PI as an potential tool for EVT triage, whereas its role seems more uncertain in the early window.^{9,23}

In the early window, we found that younger individuals and males were more likely to undergo PI. This aligns with prior studies that have noted age and sex disparities in access to advanced neuroimaging.^{25,28} Notably, women often have less access to diagnostic evaluations.²⁹ Furthermore, in younger persons PI may serve to help validate the presence of stroke and provide additional evidence to support use of acute stroke therapies especially when a stroke mimic is being con-

sidered in a young person. Conversely, in the late window, older age was associated with PI use. Worse collateral circulation in the elderly³⁰ and more stringent criteria for this population in randomized trials^{5,6} likely necessitate PI use for patient selection and risk stratification in older patients.³¹

It is worth noting that in the early window, even though a higher proportion of patients with aLVO who received PI underwent intravenous thrombolysis (40.1%) compared with those who did not receive PI (30.9%), the rate of symptomatic ICH was lower in those with PI than those without PI. Previous studies have suggested that certain perfusion parameters on PI could predict the risk of symptomatic ICH.^{17,32,33} In the analysis focusing solely on patients with aLVO undergoing EVT, the differential impact of PI use between the early and late time windows might have been alleviated by excluding patients not receiving EVT due to the absence of perfusion mismatch. These patients could have been candidates for EVT if they did not undergo PI.

However, our study indicated that PI use did not significantly improve functional outcomes for patients with aLVO in either time window. Although randomized trials on early window EVT have shown substantial benefits by triaging with perfusion-mismatch imaging,^{2–5} observational studies report conflicting results.^{18,21} Interestingly, the recent MR CLEAN-LATE trial highlighted the

efficacy and safety of late window EVT triage using collateral flow on CT angiography.³⁴ Considering the widespread use of advanced imaging techniques like multiphase CT angiography or magnetic resonance imaging in South Korea,³⁵ it is plausible that patients without PI in our study could have been triaged for EVT using these alternative neuroimaging modalities.

From an economic standpoint, a critical question arises: if PI use does not yield significant improvements in functional outcomes, and considering the additional costs associated with PI contributing to higher EVT rates in the late window, is its integration into EVT triage efforts justified in any time window? Particularly in the late window, there has been an emphasis on identifying EVT-eligible patients without relying on PI to expand the accessibility and applicability of EVT.^{34,36} Although our observations did not reach statistical significance in the multivariable analyses, there was a noticeable trend suggesting that PI use might improve 3-month mRS score distributions in the early time window.

Despite the 2019 guideline from the American Heart Association recommending clinical examination and noncontrast CT with identifying aLVO for early AIS EVT triage without routine PI use,⁹ this study showed that South Korea's clinical practice notably diverges, favoring advanced imaging such as PI to refine EVT patient selection. Moreover, our study counters the potential concern that PI delays EVT, showing no significant impact on the elapsed time from patient arrival to EVT (Table S3). This suggests that efficient integration of advanced imaging, such as PI, into stroke imaging protocols can enhance patient selection without time delays.

The limitations of this study should be noted. First, the impact of PI on physicians' decision-making for EVT remains uncertain. However, our definition based on imaging acquisition time arguably aligns more closely with treatment decisions than previous literature,^{8,25} that relied on billing claims to categorize PI as a decision-making tool if performed on day 1 or day 2. Second, the potential for varying performance across different centers may have affected our findings. Although the generalized estimating equation method was employed to account for center clustering, there is still room for unmeasured confounders. Third, the specific imaging modalities used, particularly CT and magnetic resonance imaging, might have influenced our results. Magnetic resonance imaging-based selection for EVT was reported to be associated not with functional outcomes but with a reduced risk of symptomatic ICH.¹⁶ Notably, 80% of patients with PI received magnetic resonance perfusion in our cohort. Fourth, recent randomized trials for EVT in the late time window and large core infarct aimed to broaden the pool of eligible patients with or without advanced neuroimaging.^{34,37–39}

Our database does not encompass the recent trends since 2022. Last, regarding the representativeness of the CRCS-K-NIH registry, it primarily comprises tertiary or teaching hospitals. Nevertheless, demographics, presentation, and stroke severity in our registry are almost identical to those reported in a national stroke audit.¹⁰

Despite these limitations, our study highlights a noticeable difference in PI use trends between the early and late time windows, suggesting that physicians may perceive the role of PI differently in each time window. Although there was an expansion in EVT eligibility in the late window and a decrease in symptomatic ICH in the early window, PI use did not lead to improved 3-month functional outcomes in patients with aLVO. This raises questions regarding the necessity and effectiveness of PI in EVT triage and underscores the need for additional research.

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Disclosures

None.

Supplemental Materials

Supplemental material

Figure S1. Distribution of the elapsed time from arrival to acquisition of perfusion imaging in patients who underwent endovascular treatment in the early (A) and late windows (B)

Figure S2. Perfusion imaging utilization rates across 17 participating centers in patients with acute ischemic stroke presenting within 24 hours of stroke onset

Figure S3. Absolute standardized differences in covariates used for estimating propensity score in patients with anterior large vessel occlusion before and after applying IPTW

Figure S4. Absolute standardized differences in covariates used for estimating propensity score in patients with anterior large vessel occlusion who underwent endovascular treatment before and after matching

Figure S5. Association between perfusion imaging utilization and outcomes in patients with anterior large vessel occlusion who underwent EVT

Table S1. Comparisons of baseline characteristics according to PI utilization (N = 49,449)

Table S2. Comparisons of baseline characteristics in patients with anterior large vessel occlusion according to PI utilization (N = 10,315)

Table S3. Baseline characteristics of patients with anterior large vessel occlusion who presented within 24 hours after stroke onset and underwent EVT according to PI utilization (N = 4,008)

Table S4. Comparisons of outcomes according to PI utilization in patients with anterior large vessel occlusion who underwent EVT (N = 4,008)

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