

Comparative Evaluation of Imaging Modalities for Eligibility in Endovascular Treatment of Delayed Onset Acute Anterior Circulation Ischemic Stroke in Siriraj Hospital: A Retrospective Analysis

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ABSTRACT

Objective: The goal of this study is to evaluate the consistency between computed tomographic perfusion (CTP) according to the endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE-3) criteria and other standard computed tomography (CT) imaging modalities, such as multi-phase CT angiography (MCTA) and unenhanced computed tomography (UECT), in assessing patient eligibility for EVT as determined by neurointerventionists evaluations.

Materials and Methods: This retrospective analysis included 64 patients with anterior circulation stroke and onset between 6 to 12 hours or unknown onset. Two neuro-interventionalists independently reviewed images and assessed eligibility for EVT based on the Alberta stroke program early CT score (ASPECTS) derived from UECT and collateral score obtained from MCTA. The results were then compared to CTP, utilizing the DEFUSE-3 criteria.

Results: Out of the 64 cases analyzed (mean age: 69 years \pm 13.9 [SD]), 61 met DEFUSE-3 criteria for EVT by CTP, while 54 were deemed eligible based on an ASPECTS \geq 6 and collateral score \geq 3. Agreement between the modalities was moderate (Kappa coefficient score 0.4). When patients with ASPECTS score $<$ 6 were excluded, concordance improved to perfect (Kappa coefficient score 1.0). Hence, concordance was significantly associated with ASPECTS scores \geq 6 ($P < 0.001$).

Conclusion: In patients experiencing anterior circulation stroke with onset between 6 to 12 hours or unknown onset, excluding an ASPECTS score of 6 or higher, MCTA and UECT proved to be reliable for assessing endovascular treatment eligibility. These modalities may serve as substitutes for CTP and offer support in the clinical decision-making process.

Keywords: Endovascular thrombectomy; acute ischemic stroke; computed tomography; computed tomographic perfusion (Siriraj Med J 2024; 76: 573-580)

INTRODUCTION

Ischemic stroke is currently one of the leading causes of permanent disability in Thailand, especially when attributed to large vessel occlusion. Consequently, timely initiation of treatment during the acute phase is

imperative to optimize the likelihood of complete or near-complete recovery.¹⁻³ Various therapeutic approaches are currently used to manage acute ischemic stroke, including intravenous thrombolysis, intra-arterial or combined thrombolysis, and mechanical recanalization techniques

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which involve various devices for thrombectomy and/or stent placement. Choosing the most suitable treatment approach often requires a customized combination of interventions based on each patient's individual factors.^{4,5}

In recent years, notable strides in both technical and procedural aspects of endovascular therapy (EVT) for stroke have established it as an effective treatment modality.⁵⁻⁷ Numerous studies have highlighted EVT's benefits which extend to patients treated in delayed time windows helping to amplify its therapeutic impact.⁸ The development of imaging techniques has played a pivotal role in improving the selection process for EVT candidates, incorporating tools such as unenhanced computed tomography (UECT), single-phase CT angiography, multiple-phase CT angiography (MCTA), and magnetic resonance imaging (MRI).^{9,10} These advancements have collectively contributed to enhancing the precision and efficacy of endovascular interventions in stroke management.

The standard protocol for assessing patients diagnosed with acute onset ischemic stroke due to large vessel occlusion within a timeframe of less than six hours involves using MCTA and UECT. This evaluation is conducted using the Alberta Stroke Program Early CT Score (ASPECTS) and collateral scoring.^{9,11-13} However, for patients with unknown onset times or onset ≥ 6 hours, the ASPECTS and collateral scores are considered unreliable for evaluation. Numerous studies show that perfusion imaging outperforms conventional imaging in predicting excellent recanalization outcomes and favorable functional recovery.¹⁴⁻²⁰ Therefore, the incorporation of perfusion imaging into the diagnostic process is pivotal for enhancing the accuracy and reliability of assessments, particularly in scenarios involving uncertain onset times or delayed presentations.

The endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE-3) clinical trials conducted by *G.W. Albers et al* in 2018 evaluated patients with occlusions in the proximal middle cerebral artery and internal carotid artery whose onset of symptoms occurred between 6 and 24 hours prior. In this study, computed tomographic perfusion (CTP) using RapidAI (iSchema View, Menlo Park, CA) software was utilized to determine the areas of penumbra and core infarction. Patients identified as suitable candidates proceeded with endovascular surgery, and clinical outcomes of this group showed a greater degree of favorability compared to cases treated solely with medical intervention.¹⁴ This underscores the pivotal role of advanced imaging techniques, such as CTP, in extending the treatment window for endovascular interventions and improving clinical outcomes in specific patient populations.

At Siriraj Hospital, Mahidol University, Bangkok, Thailand, recent updates to stroke management guidelines include the use of UECT, MCTA and CTP with RapidAI software. These updates are in line with the guidelines from the DEFUSE-3 trials for making decisions about EVT, but with some minor modifications. The determination of EVT for delayed-onset strokes in the anterior circulation at Siriraj Hospital is based on the interventionist's assessment using CTP alongside other CT imaging modalities. While the American Heart Association's 2018 guidelines for acute ischemic stroke management recommend CTP criteria from the DEFUSE-3 trial for selecting delayed-onset patients for thrombectomy, certain patients who meet favorable CTP criteria may not undergo the procedure due to other factors, such as a low ASPECT score observed on UECT.² However, the widespread availability of advanced CTP with artificial intelligence (AI) remains limited across many primary, secondary, and tertiary hospitals. Consequently, this study seeks to evaluate the consistency between CTP and other conventional CT imaging modalities, namely MCTA and UECT, in assessing patient eligibility for EVT. The evaluation criteria adhere to the CTP criteria based on DEFUSE-3 and the clinical judgment of neuro-interventionists. The primary objective is to investigate whether the necessity for CTP in routine clinical practice can be minimized by comparing its results with those from more readily available imaging modalities. This comparative analysis seeks to enhance and streamline the decision-making process for EVT eligibility, particularly in environments where advanced CTP with AI technology is less accessible.

MATERIALS AND METHODS

This study aims to assess the agreement between CTP (DEFUSE-3 criteria) and other conventional CT imaging modalities (MCTA and UECT) in determining patients' eligibility for EVT based on the clinical judgement of neurointerventionists.

This study is designed as a single-center retrospective cohort study, involving a review of electronic medical records of patients with anterior circulation acute ischemic stroke with large vessel occlusion, including the M1 segment of middle cerebral artery (MCA), internal carotid artery (ICA) and common carotid artery (CCA), with symptom onset between 6-12 hours or of unknown onset. The review period spans from January 2018 to September 2022 at the Department of Interventional Neuroradiology, Siriraj Hospital.

Inclusion criteria

- 1) Patients diagnosed with anterior circulation

- acute ischemic stroke with large vessel occlusion (CCA, ICA, M1 segment of MCA)
- 2) Age \geq 18 years old
 - 3) Onset between 6-12 hours or unknown onset²¹
 - 4) Received evaluation with UECT, MCTA and CTP in same event.

Exclusion criteria

- 1) Poor image quality
- 2) mRS (modified Rankin Scale) \geq 3
- 3) Inadequate clinical information or incomplete image study
- 4) Patient's National Institutes of Health Stroke Scale (NIHSS) score $<$ 6
- 5) M2 segment of MCA occlusion

MCTA and UECT images for each patient were systematically collected and organized for review. Two neuro-interventionists, each certified by the Thai board of interventional neuroradiology for more than 10 years and with over a decade of experience in diagnostic imaging and neuro-interventional procedures, were recruited to independently assess the cases. Their task was to determine the eligibility of each case for endovascular treatment, guided by specific criteria — such as an ASPECTS score \geq 6 and collateral score of \geq 3.⁹ To maintain objectivity, demographic details, and clinical history were concealed, with the evaluators having access only to information about the occlusion's location. Case reviews were conducted separately to avoid potential bias. The outcomes of these evaluations were subsequently compared to findings from CTP, where the ischemic core and penumbral regions were measured using the RapidAI software, which is an automated image postprocessing system. Eligibility for endovascular treatment was determined according to the DEFUSE-3 criteria. The goal of this comparative analysis was to measure the agreement between the neuro-interventionalists' clinical judgments based on conventional imaging and the results derived from advanced CTP enhanced by AI technology.

DEFUSE-3 criteria:^{9,14}

- 1) infarct core volume $<$ 70 mL
- 2) penumbra volume \geq 15 mL
- 3) penumbra/infarct core ratio \geq 1.8

Statistical analysis was conducted using PASW (Predictive Analytics Software) Statistics 18 software. Quantitative data were presented as means, while qualitative data were expressed as frequencies with percentages. The Fisher Exact test was employed to explore the significant associations between risk factors and endovascular treatment. The agreement between CTP by RapidAI

software and Multiple-phase CT angiography/UECT images, as well as interobserver variability regarding endovascular thrombectomy eligibility was assessed using Kappa correlation coefficients. A p-value $<$ 0.05 was considered statistically significant.

Given that this study was a retrospective analysis of existing medical records, the Institutional Review Board (IRB) of Siriraj Hospital, Mahidol University (Certificate of Approval number: Si 865/2022), granted exemption from the requirement to obtain individual patient consent. However, it is important to note that all patients included in this study had previously consented to their data being included in the hospital's institutional database and for research purposes during their initial clinical consultation. This consent was secured through a standard process, ensuring patients were informed about the potential use of their medical data for research purposes. The retrospective nature of the study ensured stringent adherence to patient privacy and confidentiality. There were no direct patient interventions or interactions, and all patient data were anonymized to safeguard protect patient identities. The study adhered to the principles set in the Declaration of Helsinki, the Belmont Report, the Council for International Organizations of Medical Sciences (CIOMS) Guidelines and the International Conference on Harmonization in Good Clinical Practice (ICH-GCP).

RESULTS

From January 2018 to September 2022, data of 64 patients was collected and reviewed. Baseline characteristics are shown in [Table 1](#). At baseline, the median age was 68.9 years and an analysis of baseline characteristics and risk factors showed no significant relationship with endovascular thrombectomy according to DEFUSE-3 criteria.

Within the original group, 61 patients met the DEFUSE-3 criteria for endovascular treatment based on CTP analysis, while a joint evaluation using MCTA and UECT, identified 52 patients as suitable candidates. Of these, 52 patients received endovascular treatment. Follow-up data was available for 33 patients.

Among the 33 patients for whom follow-up data was available, 16 (48.5%) exhibited functional independence by day 90, as defined by a mRS score of 0 to 2. The collection of comprehensive follow-up information encountered obstacles due to the referral system, resulting in some incomplete records.

A subgroup analysis was carried out, excluding 15 patients with ASPECTS scores $<$ 6. In this refined group of 49 patients, all met the DEFUSE-3 criteria for

TABLE 1. Baseline characteristic and demographic data.

	All	Endovascular treatment by DEFUSE3	P-Value
Age (years), Mean±SD	69±13.9		
Sex (Female, Male) n, (%)	30, 34 (46, 54)		
Demographic Data			
DM n, (%)	20 (31)	19 (29)	.628
HT n, (%)	39 (90)	38 (59)	.414
DLP n, (%)	22 (34)	19 (29)	.393
AF n, (%)	15 (23)	13 (20)	.361
CAD n, (%)	8 (12)	7 (12)	.604
Smoking n, (%)	13 (20)	12 (19)	.484
Previous Stroke n, (%)	13 (20)	12 (19)	.432

Abbreviations: DM = Diabetes Mellitus, HT = Hypertension, DLP = Dyslipidemia, AF = Atrial fibrillation, CAD = coronary arterial disease, mRS = modified Rankin Scale

endovascular treatment, and 48 were considered eligible based on their ASPECTS and Collateral score (>2) as assessed through MCTA and UECT imaging.

The comparison of consistency between CTP and other standard imaging modalities, as assessed by neuro-interventionalists, revealed a Kappa coefficient score of 0.4. According to Landis & Koch's (1977) interpretation of Kappa values, this score is in moderate agreement, with a total concordance of 57 out of 64 cases and 7 discordant cases.²² The interobserver agreement between the two neuro-interventionalists was deemed substantial, with a Kappa coefficient score of 0.7.

After a detailed consensus discussion, the consistency between CT perfusion and other standard imaging modalities improved from slight to fair agreement. A subgroup analysis was also conducted, which excluded patients with ASPECTS scores <6. In this refined subgroup, consistency between the modalities reached perfect agreement, as indicated by a Kappa coefficient score of 1.0. Additionally, it was observed that cases with concordant agreement were significantly associated with ASPECTS scores ≥6, and vice versa, with a p-value less than 0.001. (Diagram 1)

DISCUSSION

Recent stroke guidelines recommend mechanical thrombectomy in patients who present anterior circulation ischemic stroke within 6 to 16 or 24 hours of symptom onset with large vessel occlusion, according to the

diffusion weighted image or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with Trevo trial (DAWN) or DEFUSE-3 trial criteria.⁴ The DAWN trial¹⁵ identified candidates with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy through a clinical-core mismatch based on the NIHSS score and imaging findings from CTP or diffusion-weighted MRI. Meanwhile, the DEFUSE-3 trial selected patients using perfusion-core mismatch and maximum core size as imaging criteria (infarct volume <70 mL, penumbra volume ≥15 mL and a penumbra/infarct core ratio ≥1.8^{9,14}) to select patients with large anterior circulation occlusion 6 to 16 hours from onset for mechanical thrombectomy, which required CTP for patient selection. Despite its advantages, CTP is not universally available. CT has many practical advantages over other cerebral perfusion imaging methods, including its wide availability. Thus, in prior studies²³⁻³² other modalities, such as UECT and MCTA, were used instead of advanced imaging to evaluate acute stroke patients with a late window period, with some questioning the need of perfusion imaging.³³ The recently published MR CLEAN LATE³⁴ demonstrated that patient selection in the late time window could be based on collateral circulation, making ASPECT score and CTP less critical. Studies by Wang et al.²⁴ and Dhillon et al. have suggested that MCTA can match CTP in predicting outcomes and that endovascular treatment is viable and safe without the

need for advance neuroimaging in acute ischemic stroke patients with delayed stroke onset.²⁸ However, conflicting findings persist, as some studies indicate that CTP can lower mortality, even though functional independence after late-window endovascular therapy appear similar to patients selected by UECT.³⁰ The evolving landscape of stroke management underscores the ongoing exploration of diverse imaging modalities and patient selection criteria in the extended time window, acknowledging the practical considerations and limitations of available technologies in different clinical settings.

In this study, our primary objective was to assess the consistency among different imaging modalities in establishing EVT eligibility. This involved comparisons between CT perfusion (utilizing the DEFUSE-3 criteria) and the combined use of multiple-phase CT angiography and unenhanced computed tomography. It should be noted that the guidelines at Siriraj Hospital are predominantly based on DEFUSE 3 trial criteria, with slight adjustments to the time window, which has been narrowed to 6-12 hours or of unknown onset.

Our study's findings indicate a slight agreement between CTP analyzed by RapidAI software and conventional imaging methods. Notably, discordance was noted in 7 out of 64 cases, predominantly due to two factors. In 6 out of the 7 cases, discordance was linked to an overestimation of the core infarction area during ASPECTS evaluation (Fig 1). This overestimation of the core infarction area is a significant concern when relying on UECT as it lacks the ability to differentiate between the penumbral and core infarction areas. A previous study conducted by Siegler et al.²⁶ also highlighted this issue, revealing that while nearly three-quarters of thrombectomy patients showed ischemic changes on UECT, about one-third of these cases had normal core volumes on CTP. This finding underscores the necessity of incorporating both perfusion and non-contrast scans to achieve a thorough and precise determination of endovascular treatment eligibility.

Moreover, the subjectivity in evaluating ASPECTS scores present another challenge. This subjectivity stems from the wide range of cerebral hypodensity attenuation

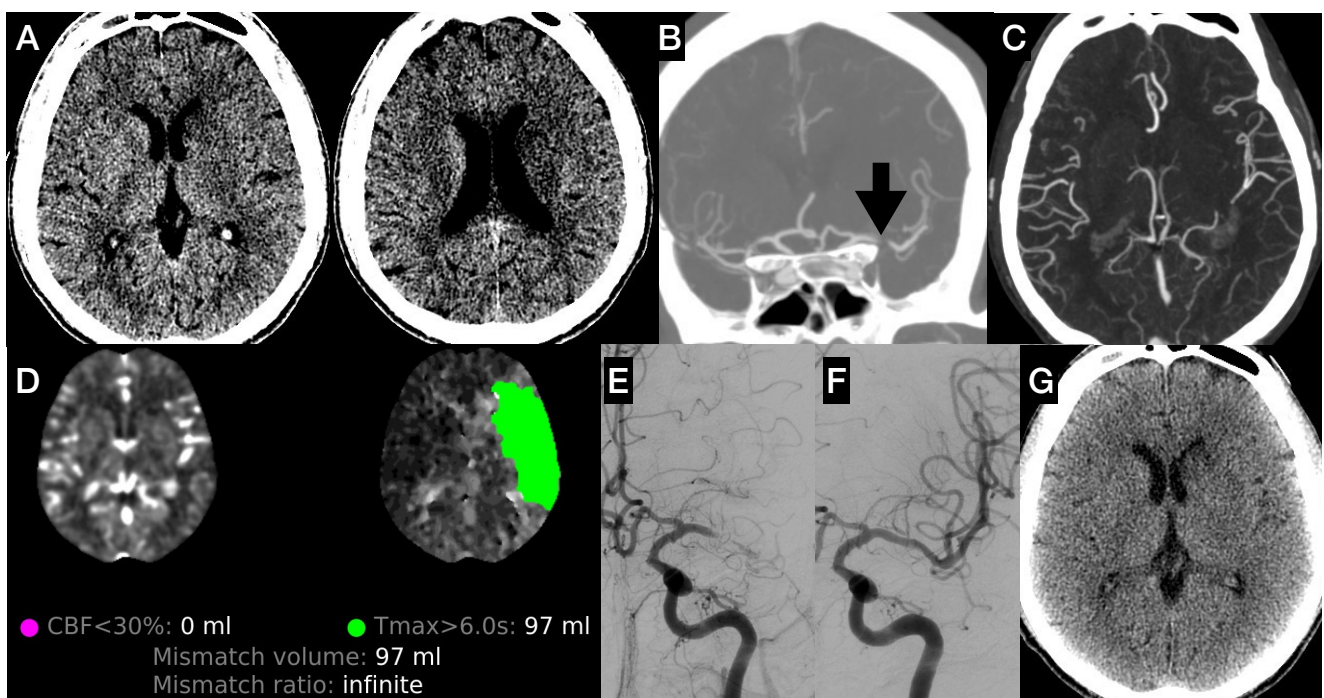


Fig 1. A 47 years old patient presented right-sided weakness for 6 hours, NIHSS = 11 A: NECT of the brain showed a hypodense area in the head of the left caudate nucleus, left internal capsule and left lentiform nucleus, with an ASPECTS score = 7. B: CTA source image shows total occlusion of the M1 segment of left MCA (black arrow). C: Multi-phase CTA during the 1st phase shows a collateral score = 5. D: CT perfusion shows no core infarct with a ischemic penumbra area about 97 ml, resulting in a mismatch ratio = infinite. Based on the DEFUSE-3 criteria from CT perfusion, the patient underwent MT E: Left ICA angiogram shows nearly total occlusion of the M1 segment of the left MCA. F: Post-MT left ICA angiogram shows recanalization of the left MCA. G: Brain CT, 24 hours post-MT shows subacute infarction in the head of left caudate nucleus but no hemorrhagic transformation. The patient exhibited improvement in weakness, NIHSS = 3. At the 3-month follow-up, the patient showed mRS = 0.

Abbreviations: NIHSS = National Institutes of Health Stroke Scale, NECT = Non-enhanced computed tomography, ASPECTS = Alberta Stroke Program Early CT Score, CTA = Computed Tomography Angiography, MCA = middle cerebral artery, CT = computed tomography, MT = mechanical thrombectomy, ICA = internal carotid artery, mRS = modified Rankin Scale

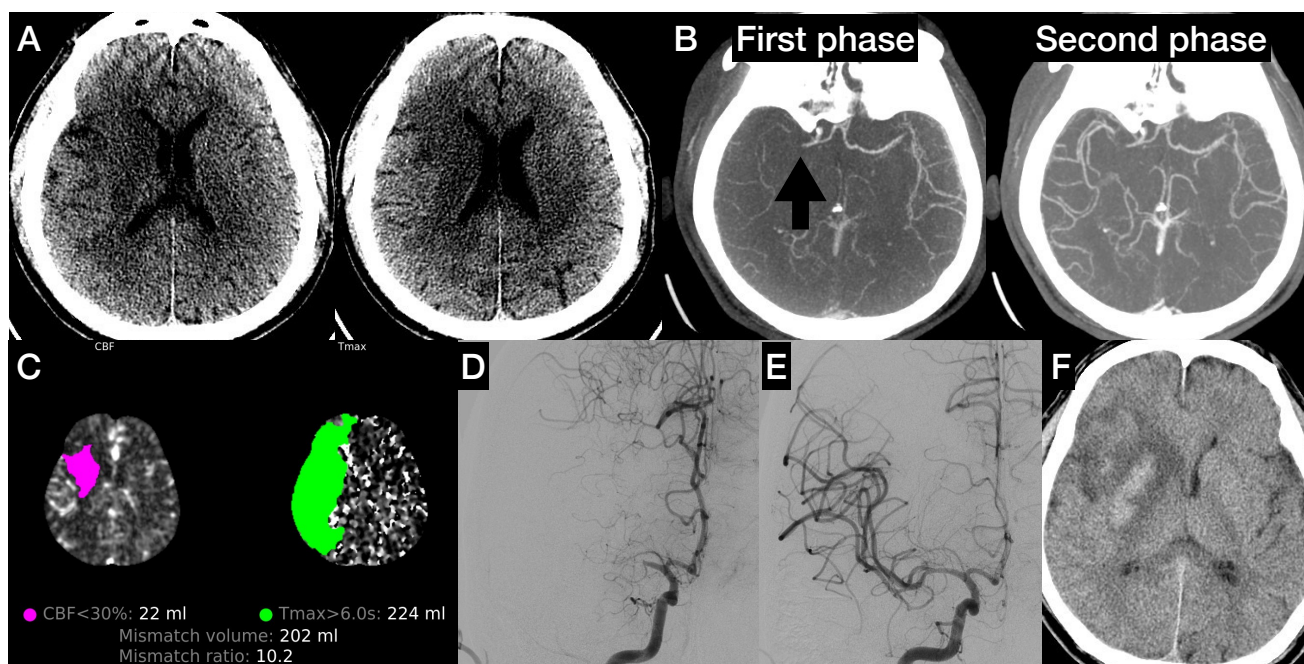


Fig 2. A 55 years old patient presenting left-sided weakness upon waking up, NIHSS = 10. A: NECT of the brain shows a hypodense area in the right caudate nucleus, lentiform nucleus, internal capsule, insular cortex, M1 and M4 areas, and an ASPECTS score = 4. B: Multi-phase CTA in the 1st and 2nd phases shows total occlusion at M1 segment of the right MCA (black arrow) with collateral score = 4. C: CT perfusion shows a small area of core infarct, 22 ml, with a large ischemic penumbra area, mismatch ratio = 10.2. Based on the DEFUSE-3 criteria from CT perfusion, the patient was sent for MT. D: Right ICA angiogram shows total occlusion of the M1 segment of the right MCA. E: Post-MT right ICA angiogram shows recanalization of the right MCA. F: CT of the brain 24 hours after MT showed hemorrhagic transformation in the right basal ganglia. However, the patient improved in weakness, NIHSS = 2. At the 3-month follow-up, the patient showed mRS = 2.

Abbreviations: NIHSS = National Institutes of Health Stroke Scale, NECT = Non-enhanced computed tomography, ASPECTS = Alberta Stroke Program Early CT Score, CTA = Computed Tomography Angiography, MCA = middle cerebral artery, CT = computed tomography, MT = mechanical thrombectomy, ICA = internal carotid artery, mRS = modified Rankin Scale

values, measured in Hounsfield units (HU) on UECT, which can vary significantly when compared to MRI. ASPECTS scoring is predominantly utilized for assessing occlusions in the M1 segment of the MCA.

Furthermore, in one specific case, the complexity was further compounded by the presence of a concurrent posterior circulation occlusion, which was included in the penumbra volume calculation. This inclusion of additional pathology introduces challenges in accurately assessing the extent of ischemic damage and complicates the determination of treatment eligibility. These findings underscore the multifaceted nature of decision-making regarding EVT eligibility and emphasizes the importance of a comprehensive understanding of each patient's unique anatomy and pathology.

In this study, it was found that discordant cases (15 out of 64) were significantly associated with ASPECTS less than 6 (p -value < 0.001). Consequently, by excluding cases with ASPECTS scores below 6 revealed perfect concordance between imaging modalities.

This outcome suggests that by removing cases prone to overestimation of core infarction, UECT and MCTA

could be emerged as reliable tools in the evaluation of delayed-onset acute anterior circulation stroke. The high level of agreement in this refined subgroup implies that these modalities, which are more readily available and less complex than advanced imaging techniques, could potentially serve as dependable alternatives in specific clinical scenarios.

Several limitations of this study should be acknowledged. First, the study's relatively small population was the result of the recent incorporation of CTP using RapidAI software into the institution's guidelines. This limited sample size may affect the broad applicability of our findings. Additionally, the lack of follow-up data for 20 out of 59 patients who underwent endovascular treatment posed additional constraints, potentially impacting the assessment of long-term outcomes and functional recovery.

Additionally, the study's reliance on quantification software from a single vendor could limit the generalizability of the results as the availability of quantitative core infarction/penumbra volume could be influenced by the specific characteristics and algorithms of the chosen software. The exclusive use of a single software may not

account for potential variations that may arise with different software solutions, potentially limiting the broader applicability of the study's results.

These limitations underscore the importance of cautious interpretation of the study's results. There is a clear need for future studies with larger and more diverse populations, alongside comprehensive follow-up data, to strengthen the robustness and generalizability of conclusion drawn from this research.

CONCLUSION

In conclusion, our study indicates that the highest level of agreement between CTP and other standard imaging modalities, including MCTA and UECT, occurs in patients with anterior circulation occlusion with onset between 6 to 12 hours or unknown onset, excluding cases with ASPECTS scores below 6. In cases where patients met these criteria, MCTA and UECT are dependable in assessments and can effectively act as alternative options to CTP analyzed by RapidAI software.

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Conflicts of interest

All authors declare that there are no conflicts of interest related to any aspect of this research.

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Author Contributions

BS and PW: Conceptualization.: RC, BS, EC, TA, AC and PW: Data curation.: RC and PW: Formal analysis.: RC, BS and PW: Methodology.: AC, BS and PW: Supervision.: RC and PW: Writing – original draft.: PW: Writing – review & editing.

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