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Letter to the Editor

Discrepancy Between Ischemic Changes Observed on Non-Enhanced Computed Tomography and Perfusion Imaging: Implications for Decision-Making in Treatment

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Dear Sir:

Recent clinical trials have demonstrated that mechanical thrombectomy (MT) is beneficial for patients with ischemic stroke and a large ischemic core or evidence of extensive early ischemic changes on non-enhanced computed tomography (NECT).[1] These recent trials employed various inclusion criteria, including differences in modality magnetic resonance imaging versus computed tomography (CT) or intervals between onset and imaging. The SELECT-2 (Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke) study was the sole trial to include patients across the entire range of Alberta Stroke Program Early CT Scores (ASPECTS; range, 0–10). Thus, regardless of the initial ASPECTS, patients with a CT-perfusion (CTP) based cerebral blood flow-defined volume >50 mL were considered to have a large core and were subsequently included in this trial.[2] Regarding functional independence on day 90, MT was significantly associated with better outcomes (>80%) in patients with ASPECTS of 3–5 and large core CTP volumes (>50 mL). However, no advantage of MT was observed in patients with higher scores (ASPECTS>5) outside this range. The randomization of the subgroup with high ASPECTS scores has been intensively discussed and criticized in the past.[3] However, insufficient data exists on the effect of MT in patients exhibiting inconsistent patterns of NECT and CTP. Even among patients with an ASPECTS of 6–10, the SELECT (Optimizing Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke) study indicated a correlation between a large ischemic core of >50 mL and unfavorable outcomes, increased mortality, and a higher incidence of symptomatic intracerebral hemorrhage.[4] A large ischemic CTP core and relatively minor ischemic alterations on NECT may indicate a lesion progressing slowly, a broad region of at-risk tissue, or an unfavorable CTP imaging time point when collaterals have not yet been activated. Regardless of the cause, there is a high probability of saving brain tissue in these patients, referred to as "ghost core."

In this exploratory study, the consecutive analysis involved patients with ischemic stroke and acute large vessel occlusion in the anterior circulation admitted to the local university hospital between March 2017 and August 2020. Patients had multiparametric baseline CT, ASPECTS of 6–10 rated on NECT, a known symptom onset, and MT procedures performed per established standards. The clinical endpoint was functional independence, evaluated by a medical professional or a qualified study nurse with neurology training. It was defined as a modified Rankin Scale (mRS) score of 0–2 at 90 days. The imaging time point involved core overestimation, defined as a negative mismatch of CTP-derived core and final infarct volume (final infarct volume minus CTP-derived core volume ≤-1 mL) on follow-up imaging. The local ethics committee (Ethikkommission der Ärztekammer Hamburg) waived the requirement for informed consent after reviewing the retrospective nature of the study and the analysis of the fully anonymized data. Data analysis was *a priori* approved by the ethics committee.

A total of 400 patients with ASPECTS of 6–10 met the inclusion criteria and were analyzed, among whom 61 showed a large ischemic core of >50 mL. The median age of the patients was 73 years (interquartile range [IQR]: 60–80), with a median National Institutes of Health Stroke Scale (NIHSS) score of 15 (IQR: 11–18) and a median ASPECTS score of 8 (IQR: 7–9). The median ischemic core volume was 72 mL (IQR: 59–98). The rates of intravenous thrombolysis and successful vessel recanalization, defined as an extended Thrombolysis in Cerebral Infarction scale score of 2b-3 were 51% and 68%, respectively. The rate of parenchymal hemorrhage type 2 was 4.0% (Table 1).

The multivariable logistic regression analysis depicted the impact of recanalization based on the baseline core volume adjusted for age and NIHSS score (Figure 1). Recanalization was significantly associated with better functional outcomes for the entire core volume range (adjusted odds ratio [aOR]: 2.43, 95% confidence interval [CI]: 1.64–3.61, *P*<0.001). Further independent predictors of outcome were core volume (aOR: 0.97, 95% CI: 0.96–0.98, *P*<0.001), age (aOR: 0.96, 95% CI: 0.95–0.97, *P*<0.001), and NIHSS (aOR: 0.87, 95% CI: 0.84–0.90, *P*<0.001). A significant interaction term between baseline ischemic core volume and recanalization (aOR: 1.04, 95% CI: 1.00–1.08, *P*=0.031) suggested that the effect of vessel recanalization on functional outcome heightened with increasing baseline core volume.

The overall rate of core overestimation in patients with ASPECTS 6–10 and a core volume >50 mL was 40% (n=24), significantly higher than the proportion of patients with core overestimation in those with an ASPECTS 6–10 but a core volume <50 mL (8.2%, *P*<0.001).

Table 1. Patients' baseline, procedural, and outcome characteristics

Baseline characteristics	eTICI 2b-3 (n=286)	eTICI 0-2a (n=114)	*P*
Age (yr)	75 (64–83)	77 (65–83)	0.361
Female sex	137 (48)	59 (52)	0.221
Diabetes mellitus	44 (15.4)	21 (18.4)	0.484
Arterial hypertension	179 (62.6)	115 (67.7)	0.642
Atrial fibrillation	102 (35.5)	30 (26.3)	0.233
Time window (h)	2.8 (1.4–5.8)	2.9 (1.7–5.6)	0.443
Time window >6 h	128 (44.7)	59 (51.5)	0.231
ASPECTS	8 (7–9)	8 (7–9)	0.240
NIHSS on admission	14 (8–18)	15 (10–19)	0.111
Baseline core volume (mL)	8 (0–25)	8 (0–34)	0.271
Follow-up			
Follow-up lesion volume (mL)	19 (7–47)	41 (12–96)	<0.001
NIHSS at 24 h	10 (3–17)	14 (8–19)	0.011
mRS at day 90	3 (1–5)	4 (2–6)	<0.001
Parenchymal hemorrhage type 2	12 (4.2)	4 (3.2)	0.392

Values are presented as median (interquartile range) or n (%).
eTICI, extended Thrombolysis in Cerebral Infarction; ASPECTS, Alberta Stroke Program Early CT Score; mRS, modified Rankin Scale.

Multivariable logistic regression analysis demonstrated an independent association between recanalization and core overestimation (aOR: 2.71, 95% CI: 1.59–4.61, *P*<0.001). A significant interaction with core volumes (aOR: 1.02, 95% CI: 1.01–1.04, *P*=0.002) indicated an increased likelihood of core overestimation by recanalization with higher core volumes.

The key findings of this study are as follows: (1) successful vessel recanalization improved outcomes across the entire core volume range, especially in patients with higher core volumes; and (2) a direct association was observed between high ASPECTS, core volumes, and vessel recanalization indicating an overestimation of the ischemic core. This suggests a subgroup that could particularly benefit from MT. Treatment decision-making in daily clinical practice can be complicated in cases of inconsistent patterns of neuroimaging. A notable limitation of CTP is its potential for overestimating the extent of permanent tissue damage, potentially leading to treatment exclusion, even in cases where level 1 evidence supports MT within this subgroup.[5,6]

To prevent excluding patients who may benefit from the therapy, it is crucial to anticipate core overestimation. A shorter interval between symptom onset and imaging is known to elevate the risk of core overestimation. Patients with large ischemic cores are particularly affected by this condition because the precise moment of onset is sometimes uncertain or may not be well reported, particularly in the event of more severe acute focal neurological impairment.[7,8]

From a physiological perspective, a lesion exhibiting reduced blood flow can still be biologically viable, making it potentially salvageable through the restoration of blood flow. Additionally,

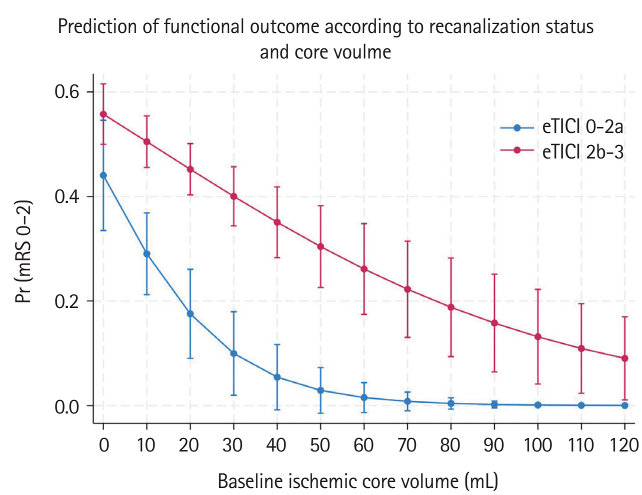

Figure 1. Association of baseline core volume and recanalization on functional outcome in patients with ASPECTS of 6–10. Impact of successful recanalization on functional outcome (y-axis) according to the baseline ischemic core volume (x-axis). eTICI, extended Thrombolysis in Cerebral Infarction; ASPECTS, Alberta Stroke Program Early CT Score; mRS, modified Rankin Scale.

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the imaging timing may be unfavorable, as the collateral activation may not be captured and only one-time point is represented, especially in the early phase after onset. Conversely, lesions with clearly visible hypodensity have advanced, as hypodensity is the imaging correlate of the net uptake of water, a specific indication and prediction tool for infarction with a high likelihood of irreversible tissue damage.[5,9,10] The limitations of this study include its retrospective design. Different thresholds may be suitable for the definition of an ischemic core. Nevertheless, we defined a large ischemic core as >50 mL based on a recently published SELECT-2 trial.[2] Further studies are required to investigate a patient cohort with an unknown onset of stroke, considering that this study only included patients within a known time window.

In conclusion, this pilot study indicates that recanalization is independently associated with improved functional outcomes and overestimation of the ischemic core. This observation may provide insights into the treatment effect of MT for patients with a large ischemic core but high ASPECTS on NECT.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: GB, LM. Study design: GB, LM. Methodology: GB, LM. Data collection: GB, LM. Investigation: all authors. Statistical analysis: GB, LM. Writing—original draft: GB, LM. Writing—review & editing: GB, LM. Approval of final manuscript: all authors.

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