



# Incomplete reperfusion and the presence of distal emboli in predicting clinical outcome after endovascular thrombectomy

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## ABSTRACT

**Objectives** To explore the relationship between final expanded treatment in cerebral infarction (eTICI) score and the presence or absence of distal emboli on final angiography on clinical outcome after endovascular thrombectomy (EVT) for acute ischaemic stroke (AIS). Persistent distal emboli on angiography are commonly noted, yet not all patients with intermediate eTICI scores demonstrate clear angiographic emboli, raising the possibility that these angiographic differences may correlate with distinct mechanisms of ‘no-reflow’. Therefore, we sought to better understand the potential clinical impact of such angiographic markers in cases of incomplete reperfusion.

**Design** We performed an exploratory retrospective analysis of a prospectively collected group of AIS patients who underwent EVT for M1 occlusions using the ASSIST Registry.

**Setting** 71 sites in 11 countries participated in the registry.

**Participants** A total of 650 patients with M1 occlusions were included.

**Main outcome measures** We compared 90-day modified Rankin scale (mRS) scores based on eTICI score as well as the presence or absence of distal emboli on final angiography.

**Results** Clinical outcome based only on eTICI score revealed a shift in 90-day mRS, with a significant difference across eTICI scores in predicting 90-day mRS 0–2. In the intermediate eTICI grades 2b67 and 2c, there was a trend towards better 90-day mRS when emboli were present on final angiography than when emboli were absent. However, pairwise comparisons between these levels were non-significant.

**Conclusion** In patients with final eTICI 2b67 or 2c, those with persistent emboli trended towards better clinical outcomes. With intermediate eTICI reperfusion, identifying the presence or absence of distal emboli on final angiography may be useful in distinguishing patterns of incomplete reperfusion. These findings should be followed by investigations on correlation between angiography and other markers of microcirculatory ‘no-reflow’.

**Trial registration number** NCT03845491.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Incomplete reperfusion and the ‘no-reflow’ phenomenon have been hypothesised to contribute to suboptimal functional outcomes observed after endovascular thrombectomy (EVT) for large vessel occlusion (LVO) in acute ischaemic stroke (AIS).

## WHAT THIS STUDY ADDS

⇒ This exploratory analysis confirms a stepwise relationship between eTICI reperfusion scores and clinical outcome after EVT in LVO and adds a novel finding that in patients with intermediate eTICI grades, there is a trend towards better outcomes in those with distal emboli present on final angiography than in those without persistent distal emboli.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These preliminary results suggest that the presence or absence of distal emboli on final angiography in patients with intermediate eTICI scores may be of value both in prognostic terms and in providing insights into different pathophysiological patterns of incomplete reperfusion.

## INTRODUCTION

Endovascular thrombectomy (EVT) is the mainstay of large vessel occlusion treatment in acute ischaemic stroke (AIS).<sup>1</sup> Successful recanalisation, conventionally defined as a modified treatment in cerebral ischaemia (mTICI) score of ≥2b (filling of 50% or more of the downstream territory), occurs in greater than 70% of patients.<sup>2</sup> However, despite excellent ‘successful’ recanalisation rates, favourable clinical outcomes occur in only one-third of patients.<sup>3</sup> Importantly, even incremental improvements in ischaemic territory reperfusion have been shown to confer meaningful differences in clinical outcomes.<sup>4</sup> The

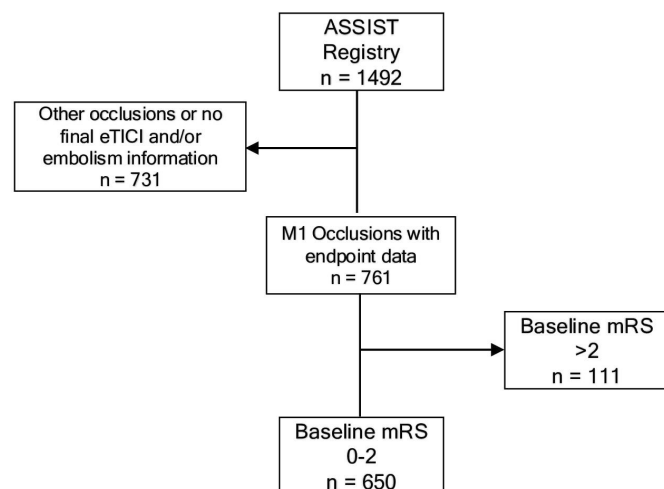


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**Figure 1** Study flowchart.

expanded TICI score (eTICI), which splits the 2b grade into 2b50 (ie, 50–66% reperfusion) and eTICI 2b67 (ie, 67–89% reperfusion), was developed to provide a more granular scale of reperfusion, and each increase in level of reperfusion has been found to predict better clinical outcomes.<sup>4–6</sup> Nevertheless, the extent of territory reperfusion is influenced by factors both on the macrocirculatory level, such as the presence of residual distal emboli, as well as on the microcirculatory level, in the form of microvascular inflammation, constriction or compression from downstream cerebral oedema and venous outflow obstruction.<sup>7–12</sup> The presence of distal emboli is common after EVT and is likely a major contributor to incomplete reperfusion.<sup>7,13</sup> However, some patients with intermediate eTICI scores demonstrate no clear distal emboli on angiography, potentially alluding to alternate, microcirculatory causes of ‘no-reflow’.<sup>14</sup> To our knowledge, studies have yet to explore the clinical impact or prognostic significance of these angiographic differences in ‘successfully’ recanalised cases. In the present study, we sought to investigate whether the presence or absence of distal emboli, as separately regarded from the extent of eTICI reperfusion, influences final clinical outcome.

## METHODS

### Study description

We performed an exploratory, retrospective analysis of prospectively collected clinical and imaging data in AIS patients with proximal or distal M1 occlusions using the ASSIST Registry. The ASSIST Registry is a prospective, global, multicentre registry of anterior circulation AIS patients with an LVO who have undergone EVT using Stryker Neurovascular devices for the first pass in treating a target occlusion. Detailed methodology and inclusion criteria are described elsewhere.<sup>15</sup> For this subgroup analysis, only patients with M1 occlusions were included to ensure homogeneity with regard to reperfusion grading.

Clinical outcomes were compared among five groups of patients with the following final angiographic outcomes

(based on the expanded TICI score (eTICI)), as adjudicated by an independent core lab: (1) eTICI 2b50 with the presence of distal emboli, (2) eTICI 2b67 with *a*) presence or *b*) absence of distal emboli, (3) eTICI 2c with *a*) presence or *b*) absence of distal emboli or (4) eTICI 3 (with absence of distal emboli). The presence of an embolus was defined by the observation of a clear distal meniscus or embolic cut-off on the final macroangiographic run after the final device pass.

The primary outcome of interest was ordinal 90-day modified Rankin scale (mRS). Statistical analyses also included multivariable binary logistic regression models including age, sex, time between last well-known and groin puncture, baseline NIHSS, presence of intravenous thrombolysis, eTICI at first pass (0, 1, 2a, 2b50, 2b67, 2c, 3), final eTICI (0, 1, 2a, 2b50, 2b67, 2c, 3) and collateral status (based on modified American Society of Interventional and Therapeutic Neuroradiology (ASITN) grade) on 90-day mRS  $\leq 2$ . Patients with a baseline mRS of  $>2$  were excluded from all analyses where 90-day mRS was an outcome but are included in the demographic table.

Standard descriptive statistics were presented for categorical variables with continuous data presented as mean and SD. For between-group comparisons,  $\chi^2$  tests and Fisher exact tests were used for categorical variables, whereas t-tests and Wilcoxon rank-sum tests were used for continuous variables. To compare differences in 90-day mRS between eTICI scores, pairwise contrasts were made between adjacent eTICI levels for 90-day mRS of 0–2. To explore the effect of the presence of distal emboli on 90-day mRS values, a GLIMMIX model was used. Specifically, the distal emboli vs no distal emboli comparison was made while holding the final eTICI value constant. This was only possible for final eTICI levels 2b67 and 2c, as final eTICI 2b50 only had a single subject without distal emboli and level 3 had no subjects with distal emboli. These analyses were conducted using both 90-day mRS 0–1 (excluding patients with baseline mRS  $>1$ ) and 90-day mRS 0–2 (excluding patients with baseline mRS  $>2$ ). All parametric analyses were adjusted to account for the clustering of individual patients within treatment centres. A p value of  $<0.05$  was considered to indicate statistical significance. All statistical analyses were performed using the SAS statistical software package.

Ethics approval was obtained by the institutional review board at each centre. The ASSIST Registry Studying Various Operator Techniques is registered at ClinicalTrials.gov (number NCT03845491). The authors wrote this manuscript according to the Strengthening the Reporting of Observational Studies in Epidemiology cohort reporting guidelines. The data supporting the findings of this study are available from the corresponding author on reasonable request.

## RESULTS

786 patients with M1 occlusion were included in the ASSIST Registry. 25 patients did not have information on

**Table 1** Baseline characteristics

Mean age, years (range)	71.1 (19–106)
Female sex, % (n)	54.0% (411/761)
Comorbidities:	
Hyperlipidaemia, % (n)	47.6% (354/744)
Hypertension, % (n)	71.6% (539/753)
Diabetes, % (n)	23.5% (176/750)
Atrial fibrillation/flutter, % (n)	34.1% (256/751)
Coronary artery disease, % (n)	21.0% (155/740)
Prior Stroke, % (n)	13.0% (96/740)
Current Smoker % (n)	19.6% (131/669)
Baseline NIHSS, mean (range)	14.8 (0–36)
Mean LKW to puncture time, hours (range)	7.6 (0.7–148.6)
Baseline total ASPECTS score, mean (range)	7.5 (1–10)
Final eTICI score +/-distal emboli, % (n)	
2b50,+distal emboli	4.2% (32/761)
2b50, - distal emboli	0.3% (2/761)
2b67,+distal emboli	21.0% (160/761)
2b67, - distal emboli	1.8% (14/761)
2c, + distal emboli	17.0% (129/761)
2c, - distal emboli	19.0% (145/761)
3, - distal emboli	36.7% (279/761)
3,+distal emboli	0% (0/761)
Modified ASITN collateral grade (pre-intervention), % (n)	
0	1.2% (7/592)
1	6.4% (38/592)
2L	18.1% (107/592)
2H	35.8% (212/592)
3	36.8% (218/592)
4	1.7% (10/592)

Continuous data are reported as mean±SD and (range). ASITN, American Society of Interventional and Therapeutic Neuroradiology; ASPECTS, Alberta stroke program early CT score; eTICI, expanded treatment in cerebral infarction; “H”, High; IV, Intravenous; “L”, Low; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale.

final eTICI and/or embolism status and were excluded. Among the remaining 761 subjects, there were 650 with a baseline mRS of 0–2 and were included in the analysis (figure 1).

Baseline demographics are represented in table 1. The distribution of scores on the mRS at 90 days based only on eTICI score is presented in figure 2A. The eTICI score predicted mRS 0–2 ( $p=0.011$ ), but not mRS 0–1 ( $p=0.085$ ). Pairwise comparisons were non-significant between 2b50 vs 2b67 (44.0% vs 50.7%,  $p=0.599$ ) or 2b67 vs 2c (50.7% vs 56.6%,  $p=0.225$ ), but significant for eTICI 2c vs 3 (56.6 vs 66.1%,  $p=0.013$ ).

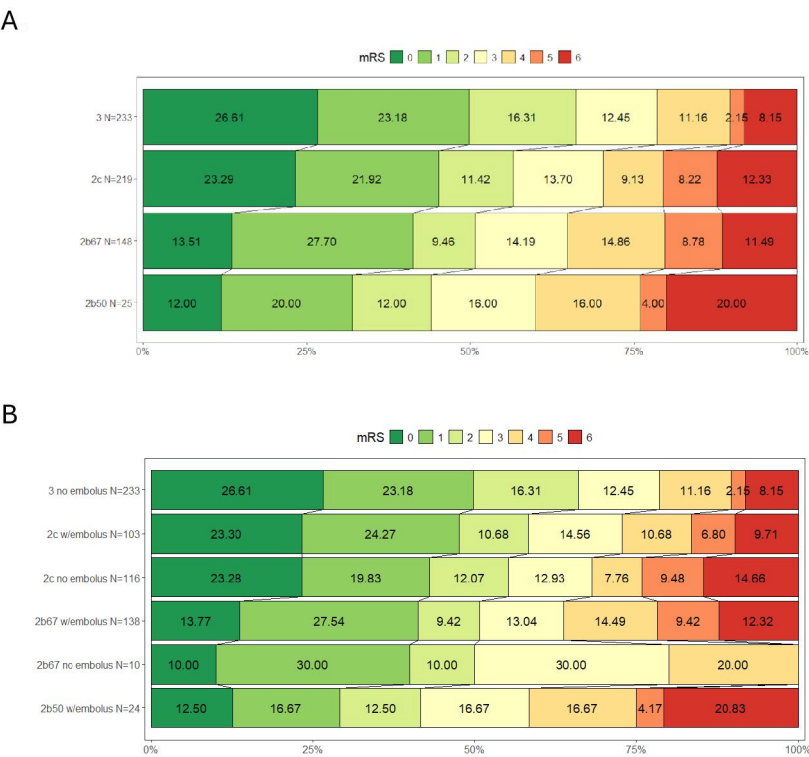
The distribution of 90-day mRS based on reperfusion grade and distal emboli status is presented in figure 2B. No patients with eTICI of 3 were found to have distal emboli; therefore, this category was excluded. Similarly, only one patient with eTICI 2b50 was found to have absence of distal emboli; therefore, this category was also excluded. 138/148 (93.2%) of patients with eTICI 2b67 had distal emboli, and 103/219 (47.0%) of patients with eTICI 2c had distal emboli. Reperfusion grade and distal emboli status predicted mRS 0–2 ( $p=0.024$ ), but not mRS 0–1 ( $p=0.088$ ) (table 2). In the intermediate eTICI grades 2b67 and 2c, there was a shift towards better 90-day mRS when emboli were present on final angiography than when emboli were absent. However, pairwise comparisons between these levels were non-significant ( $p=0.962$  and  $0.647$ , respectively).

The multivariable logistic regression evaluating 90-day mRS of 0–2 as an outcome is shown in table 3. Baseline ASPECTS score was omitted from the equation due to the large number of missing values. Furthermore, since there were only 17 subjects with final eTICI<2b50, the parameter estimation for the binary final eTICI  $\geq 2b50$  was unstable and resulted in an extremely wide CI. To remedy this, the 28 subjects with final eTICI 2b50 were reassigned and grouped with final eTICI 0,1,2a, resulting in a total of 45 subjects in this lower group. eTICI at the first pass remained divided at 0,1,2a vs  $\geq 2b50$ . With these qualifications, the following variables were found to be significant: age ( $p=0.019$ ), eTICI at first pass ( $p=0.004$ ), collateral grade ( $p=0.024$ ) and baseline NIHSS ( $p<0.0001$ ). The administration of IV thrombolysis was not associated with outcome, and there were no significant differences in the rate of intravenous thrombolytic administration across the eTICI/distal emboli groups. The average rate was 37.3%, ranging from 31.8% in the eTICI 2c with distal emboli group to 46.9% in the eTICI 2b50 with distal emboli group ( $p=0.66$ ).

## DISCUSSION

In the present study, we explored the relationship between the presence of persistent distal emboli on final angiography, eTICI score and clinical outcome. We identified that with increasing reperfusion grades, there are proportionally fewer distal emboli observed on angiography at each eTICI level. Furthermore, in patients with intermediate eTICI grades, in whom the presence or absence of emboli is most variable, we found a trend towards better outcomes in those with distal emboli present on final angiography. This surprising result adds a new layer of granularity to the relationship between incomplete reperfusion and clinical outcome and can potentially inform future studies investigating angiographic manifestations of ‘no-reflow’ phenomena.

Successful yet incomplete reperfusion is associated with worse functional outcome and mortality when compared with complete reperfusion in endovascular thrombectomy for LVO in AIS.<sup>16</sup> Even modest changes in the extent



**Figure 2** (A) Clinical outcome based on reperfusion grade alone. (B) Clinical outcome based on reperfusion grade and distal emboli status. (A) Grotta bars illustrating the distribution of 90-day mRS scores based only on eTICI score, demonstrating a shift in improved 90-day mRS with increasing eTICI score and a significant difference across eTICI levels in predicting mRS 0–2. (B) Grotta bars illustrating the relationship between reperfusion grade, distal emboli status and clinical outcome. A similar shift in 90-day mRS is seen. Note that as reperfusion grade increases, there are proportionally less distal emboli observed at each eTICI level. In the intermediate eTICI grades, there was a shift towards better 90-day mRS when emboli were present on final angiography than when emboli were absent. However, pairwise comparisons between these levels were non-significant. eTICI, expanded treatment in cerebral infarction; mRS, modified Rankin scale.

of reperfusion have been linked to improved outcome.<sup>4–6</sup> In the present study, this trend remained apparent with a shift in improved 90-day mRS with increasing eTICI score, and a significant difference across eTICI levels in predicting mRS 0–2 (figure 2A). However, pairwise differences in outcome between patients with 2b50 and 2b67 or 2b67 and 2c reperfusion did not meet significance, possibly due to the small number of patients in these subgroups (eg, only 28 patients with final eTICI 2b50 were included). Nevertheless, understanding incomplete reperfusion goes beyond simply eTICI score and includes consideration of both persistent small distal emboli apparent on final angiography and angiographically

occult microcirculatory ‘no-reflow’ phenomena.<sup>14 17</sup> Operational definitions of this microvascular ‘no-reflow’ phenomenon after EVT have been described in various ways using post-intervention perfusion imaging<sup>17–22</sup> and recently in angiographic terms based on delay or absence of capillary blush despite mTICI scores of 2c or 3.<sup>23 24</sup> In our study, we explored whether patients with incomplete reperfusion due to persistent distal emboli on the macro-circulatory level might be clinically distinguishable from patients with incomplete reperfusion *without* evidence of distal emboli, who may be hypothesised to have micro-vascular impairment as the underlying aetiology of their delayed or incomplete antero-grade filling.

Table 2 Clinical outcome based on reperfusion grade and distal emboli status							
	eTICI 2b50, + distal emboli	eTICI 2b67, + distal emboli	eTICI 2b67, - Distal emboli	eTICI 2c, + distal emboli	eTICI 2c, - Distal emboli	eTICI 3, - Distal emboli	P value
90-day mRS, 0–1, n (%)*	(7/23) 30.4%	(55/126) 43.7%	(3/9) 33.3%	(48/98) 49.0%	(49/107) 45.8%	(116/215) 54.0%	0.088
90-day mRS 0–2, n (%)†	(10/24) 41.7%	(70/138) 50.7%	(5/10) 50.0%	(60/103) 58.3%	(64/116) 55.2%	(154/233) 66.1%	0.024
*Limited to subjects with baseline mRS 0–1.							
†Limited to subjects with baseline mRS 0–2.							
eTICI, expanded treatment in cerebral infarction; mRS, modified Rankin scale.							



**Table 3** Multivariable logistic regression with 90-day modified Rankin score of 0–2 as outcome

Characteristic	OR (95% CI)	P value
Age	0.97 (0.95 to 1.00)	0.019
Female sex	1.13 (0.66 to 1.95)	0.644
History of atrial fibrillation	1.14 (0.75 to 1.73)	0.528
eTICI at first pass (eTICI 2b50, 2b67, 2c, 3, or other)	2.29 (1.31 to 3.98)	0.004
Final eTICI score (eTICI 2b67, 2c, 3, or other)	2.55 (0.90 to 7.23)	0.078
Modified ASITN collateral grade (pre-procedure)	1.34 (1.04 to 1.72)	0.024
Baseline NIHSS	0.92 (0.89 to 0.95)	<0.0001
IV thrombolysis	1.57 (0.81 to 3.05)	0.179
LKW to puncture time	0.94 (0.83 to 1.07)	0.343
ASPECTS score*	OMITTED	OMITTED

\*Baseline Aspects score was omitted from the equation due to the large number of missing values.

ASITN, American Society of Interventional and Therapeutic Neuroradiology; eTICI, expanded treatment in cerebral infarction; LKW, last known well; NIHSS, National Institutes of Health Stroke Scale.

Previous studies have shown that distal embolisation after EVT is seen in up to 50% of patients.<sup>7 13</sup> However, the implications of such occlusions on clinical outcome have yet to be investigated, as separately regarded from reperfusion score. The eTICI score does incorporate the presence of downstream occlusions in so much as percent territory reperfusion is affected. In line with this, we identified a clear relationship between the extent of reperfusion and the frequency of emboli on final angiography: only one subject in our series was graded as having eTICI 2b50 *without* a distal embolism, and no patients with eTICI 3, as expected, had distal emboli. However, at the intermediate stages (ie, eTICI 2b67 and 2c), patients varied most in this regard. We found that among the intermediate eTICI grades, patients had proportionally increased likelihood of emboli on final angiography: 138/148 (93.2%) of patients with eTICI 2b67 had distal emboli, and 103/219 (47.0%) of patients with eTICI 2c had distal emboli (figure 2B). Overall, reperfusion grade and distal emboli status predicted mRS 0–2 (table 2). In comparing the relationship between emboli and outcome in patients within the intermediate grades, we found a surprising result: patients trended towards a better clinical outcome if emboli were present (figure 2B). Notably, these comparisons did not meet statistical significance, which may be due to the lower number of patients in each subset as the groups were progressively subclassified. However, this trend—if confirmed in future studies—may have practical implications regarding both the potential of identifying ‘no-reflow’ pathophysiology angiographically and its associated prognostic value.

In patients with eTICI 2b67 to 2c *with* distal emboli, the aetiology of incomplete reperfusion is likely related at least in part to these angiographically apparent distal emboli causing macrocirculatory obstructions. On the contrary, intermediate eTICI scores *without* distal emboli raise the possibility that the loss of complete and brisk antegrade reperfusion on angiography may reflect angiographically occult microcirculatory flow impairment, such as severe cerebral blood volume compromise in the setting of a completed infarct. This potential mechanism involves increased vascular resistance and diminished arteriolar inflow due to elevated interstitial pressure from tissue ischaemia and cerebral oedema.<sup>25–27</sup> Building on this idea, recent studies have demonstrated that obstructed tissue-level perfusion is seen in association with impaired venous outflow, likely related to cerebral oedema after AIS.<sup>28–31</sup> In the present study, given the large number of missing data points regarding ASPECTS, examining whether a relationship existed between patients in this subgroup and lower ASPECTS was unfortunately not possible, but should be explored in the future. Angiographically, the observation of ‘competitive leptomeningeal flow’ has also been recently described, referring to retrograde contrast clearing of distal leptomeningeal branches from non-contrast opacified collateral inflow.<sup>32</sup> While this mechanism could account for the loss of full antegrade reperfusion seen on angiography, one would expect better outcomes in this population rather than the worse outcomes we observed, given the presumed robustness of collaterals contributing to this phenomenon. Other potential aetiologies for incomplete reperfusion in these patients include microcirculatory dysfunction and ‘no-reflow’ secondary to endothelial, pericyte or immune dysregulation.<sup>14</sup> Confirming the correlation with these microvascular phenomena is inherently difficult but has been explored with dedicated perfusion imaging<sup>17 18</sup> and should be trialled in the future. Nevertheless, potentially distinguishing these macrocirculatory and microcirculatory mechanisms angiographically may be of clinical utility, given the trend we identified towards worse functional outcome in patients without distal emboli.

Importantly, we acknowledge several reservations to these interpretations. First, though the presence and absence of emboli were clearly defined prior to data collection by objective core lab visualisation of frank distal menisci or embolic cutoffs, these determinations are based on macro-angiographic injections rather than selective microcatheter runs, which might be needed to truly confirm the absence of an embolus. Second, as mentioned above, we are unable to connect our angiographic findings with other evidence of underlying ‘no-reflow’ pathophysiology; for example, the limited ASPECTS data in our cohort precluded exploring the relationship to large infarcts or significant oedema. Likewise, data on final infarct volume were not available in the current analysis. These interpretations should therefore be regarded as preliminary and will need to be investigated in future dedicated studies that correlate such patients

with incomplete reperfusion and no distal emboli on angiography to other imaging markers of microcirculatory dysfunction.

The strengths of this study include adjudication of all imaging by an independent core lab. Furthermore, the size and uniformity of the included population lend strengths to the validity of eTICI assessment and outcome consistency. There are several limitations to this study in addition to those mentioned above. First, as a subanalysis of the ASSIST Registry, only data captured in the initial study could be used. Second, though the initial subset of patients analysed was large, once broken down into the studied subgroups, sample sizes diminished substantially, hindering robust statistical comparisons. Larger-scale studies should be assessed by independent imaging core labs to confirm the trends suggested in our study.

## CONCLUSION

In this exploratory analysis of the prospective ASSIST Registry, we found a stepwise relationship between eTICI reperfusion and clinical outcome. Furthermore, we found a trend in the relationship between the presence of persistent distal occlusions on final angiography and clinical outcome in patients with intermediate eTICI scores. These preliminary results suggest this angiographic feature may be of value in clarifying different pathophysiological patterns of incomplete reperfusion and may potentially be of prognostic value. However, these results should be interpreted with caution and followed up with larger studies investigating this relationship with other imaging characteristics, such as ASPECTS score or post-intervention perfusion markers.

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