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Time from Imaging to Endovascular Reperfusion Predicts Outcome in Acute Stroke

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Abstract

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Conflicts-of-Interest / Disclosures
J. P. Tsai, M. Mlynash, S. Kemp, S. Kim, N. Mishra, N. Akhtar, G. Zaharchuk, M. G. Lansberg: None
S. Christensen receives consultant fees from iSchemaView, which produced the software used in this study for post-processing of CT perfusion data.
C. Federau was supported by the Swiss National Science Foundation.
R. G. Nogueira received a research grant from Stryker Neurovascular, and serves on the 3D Separator Trial Executive Committee for Penumbra, on the SWIFT and SWIFT-PRIME Trial Steering Committee for Covidien/Medtronic, on the ARISE-2 Steering Committee for Neuravi, one the Physician Advisory Board for Allin Inc., and as the angiographic Core Lab for the STAR study funded by Covidien/Medtronic. Stryker Neurovascular, Penumbra, and Covidien/Medtronic manufacture reperfusion devices used in this study.
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D. R. Yavagal serves on the trial Steering Committee of Medtronic and Rapid Medical, received consulting fees from Medtronic and Neuralanalytics. Medtronic manufactures reperfusion devices used in this study.
R. Bammer and M. Straka received consulting fees and are shareholders of iSchemaView, which produced the software used in this study for post-processing of CT perfusion data.
M. P. Marks received consulting fees from Covidien/Medtronic, and is a shareholder of ThrombX Medical, which develops reperfusion devices not used in this study.
G. W. Albers received consulting fees and is a shareholder of iSchemaView, which produced the software used in this study for post-processing of CT perfusion data; and received consulting fees from Covidien/Medtronic.
**Background and Purpose**—This study aims to describe the relationship between CT perfusion-to-reperfusion time and clinical and radiological outcomes, in a cohort of patients who achieve successful reperfusion for acute ischemic stroke.

**Methods**—We included data from the CT Perfusion to predict Response in Ischemic Stroke Project (CRISP) in which all patients underwent a baseline CT perfusion (CTP) scan prior to endovascular therapy. Patients were included if they had a mismatch on their baseline CT perfusion scan and achieved successful endovascular reperfusion. Patients with mismatch were categorized into “target mismatch” and “malignant mismatch” profiles, according to the volume of their Tmax>10s lesion volume (target mismatch <100 mL; malignant mismatch >100 mL). We investigated the impact of CTP-to-reperfusion times on probability of achieving functional independence (mRS 0–2) at day 90 and radiographic outcomes at day 5.

**Results**—Of 156 included patients, 108 (59%) had the target mismatch profile, and 48 (26%) had the malignant mismatch profile. In patients with the target mismatch profile, CTP-to-reperfusion time showed no association with functional independence (p=0.84), whereas in patients with malignant mismatch profile, CTP-to-reperfusion time was strongly associated with lower probability of functional independence (OR=0.08, p=0.003). Compared to patients with target mismatch, those with the malignant mismatch profile had significantly more infarct growth (90 [49–166] vs. 43 [18–81] mL, p=0.006) and larger final infarct volumes (110 [61–155 vs. 48 [21–99] mL, p=0.001]).

**Conclusion**—Compared to target mismatch patients, those with the malignant profile experience faster infarct growth and a steeper decline in the odds of functional independence, with longer delays between baseline imaging and reperfusion. However, this does not exclude the possibility of treatment benefit in patients with a malignant profile.

MeSH Key Words

Acute stroke; Perfusion imaging; Cerebral revascularization; Reperfusion; Thrombectomy

AHA Journal Search Terms

Ischemic Stroke; Cerebrovascular Procedures

Reducing the time to reperfusion has become a major focus in the delivery of endovascular therapy for patients with acute ischemic stroke, as time is a recognized predictor of clinical outcome. The HERMES collaboration and ESCAPE trial have reported a decrease in the probability of good clinical outcome with longer time from qualifying neuroimaging to reperfusion. While these data point to a general decrement in good outcome rates with longer imaging-to-reperfusion times, it is possible that patients have variable resilience to time delays and different time windows in which endovascular therapy provides clinical benefit.

In DEFUSE 2, a patient cohort that maintained a high probability of functional independence over time was identifiable by the target perfusion-diffusion mismatch on MRI. These patients have a small ischemic core on DWI, a large volume of critical hypoperfusion (Tmax>6s), and a small volume of brain tissue with very severe delays in

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bolus arrival (Tmax > 10s). In contrast, patients with large Tmax > 10s lesions showed more infarct growth and worse clinical outcomes.5

The aim of this sub-study of the CT Perfusion to predict Response in Ischemic Stroke Project (CRISP) was to explore the relationship between time from imaging to reperfusion, and clinical and radiological outcomes.6 We hypothesized that the association between CTP-to-reperfusion time and the probability of functional independence is modified by the baseline CTP profile. Specifically, we hypothesized that the effect of prolonged CTP-to-reperfusion time is more deleterious among patients with the malignant mismatch (a mismatch and a large Tmax > 10s lesion) than among patients with the target mismatch (a mismatch and a small Tmax > 10s lesion).

**METHODS**

The data that support the findings of this study are available upon reasonable request (Dr. Maarten Lansberg, Lansberg@stanford.edu). CRISP was an NIH-funded, multi-center, prospective cohort study to evaluate the role of CT perfusion (CTP) in patients undergoing endovascular therapy.6 In CRISP, all endovascular treatment and perioperative medical care decisions were at the discretion of the treating physicians. Clinical follow-up included NIH Stroke Scale score (NIHSS) and modified Rankin Scale (mRS) assessments at 24 hours, 30 days, and 90 days after stroke. Two follow-up MRIs were required: Early MRI was acquired within 36 (24±12) hours from the baseline CTP, and included an MR angiogram (MRA) and perfusion-weighted imaging. A second MRI was done at day 5 after the baseline CTP (or on discharge, whichever occurred first), and included diffusion-weighted imaging (DWI), gradient echo/ susceptibility-weighted imaging (GRE/SWI), and fluid-attenuated inversion-recovery (FLAIR) sequences. If any contraindications to MRI existed, a follow-up CTP was performed instead of MRI. Ethics approval was obtained from the institutional review board of all participating centers, and written informed consent was obtained prior to enrollment, from patients or their legally authorized representatives.

**Study Population**

Patients were eligible for CRISP if they had an acute large-vessel occlusion in the anterior circulation, were 18 years or older, had an NIHSS of ≥ 5, and could undergo CT angiography and perfusion imaging within 18 hours of symptom onset and within 90 minutes prior to the start of endovascular therapy. Patients with a baseline mRS greater than 2 and pregnant patients were excluded. In this analysis, we included all patients with successful reperfusion who had evidence of salvageable tissue on baseline CT perfusion imaging, and divided them into two cohorts defined by the type of mismatch profile.

**Definitions**

Time of CTP was defined by the time of completion of the qualifying CT perfusion sequence. Time of reperfusion was defined as the documented endovascular treatment completion time. CTP-to-reperfusion time was the number of hours between time of CTP and time of reperfusion. The ischemic core was defined by a decrease in relative cerebral blood flow (CBF) to less than 30% of normal. Hypoperfused tissue likely to infarct in
absence of reperfusion was defined by a Tmax >6 seconds (Tmax>6s). The CTP mismatch was defined as a CBF core <70 mL and an absolute difference between the Tmax>6s and ischemic core volumes of >15 mL and a volume ratio of > 1.8. CTP mismatch was further divided into two perfusion profiles. “Target mismatch” was defined as a mismatch profile in which the Tmax>10s volume was equal to or less than 100mL, whereas “malignant mismatch” had a Tmax>10s volume greater than 100mL.

**Imaging analysis**

CRISP used the RAPID software (iSchemaView, Menlo Park, CA) at all sites for real time processing of all CT and MR perfusion images. RAPID automatically segmented and quantified the volumes of the ischemic core, Tmax>6s, and Tmax>10s lesion volumes. All digitally-subtracted angiography (DSA) images were reviewed by an experienced neuroradiologist (MPM). A modified Thrombolysis In Cerebral Infarction (mTICI) score was assigned based on the final angiogram of the endovascular procedure. The final infarct volumes were assessed by a neuroradiologist who was blinded to clinical data, baseline imaging and reperfusion status.

Reperfusion status was primarily determined by follow-up MR and CT perfusion data. “Successful reperfusion” was defined as >50% reduction of the Tmax>6s lesion volumes between the baseline and the early follow-up perfusion studies. If neither study was technically adequate (excessive patient movement or failed contrast injection), reperfusion status was defined as an mTICI score of 2b or 3. Final infarct volume was outlined on day 5 FLAIR. Infarct growth was calculated as the difference between the infarct core on baseline CTP and the day 5 FLAIR.

**Outcomes**

The primary outcome for this analysis was independent functional outcome, defined as an mRS of ≤2 at 90 days. If the 90-day mRS was unavailable, the 30-day mRS was carried forward. The NIHSS and mRS were rated by certified study personnel. The 90-day mRS, the primary clinical outcome, was rated blinded to imaging and reperfusion status.

**Statistical Analysis**

The association between CT-to-reperfusion time, as well as other baseline patient characteristics, and the probability of functional independence was determined using univariable logistic regression. Next, to adjust for potential confounders of the association between CT-to-reperfusion time and functional independence, variables significant at the p<0.1 level in univariate analysis were entered into multivariable logistic regression models for patients with target mismatch, malignant mismatch, and for all patients with mismatch. We also adjusted for significant interactions between variables included in the multivariable models and CT-to-reperfusion time. Infarct growth and final infarct volumes were compared between cohorts using Wilcoxon’s rank-sum test. Associations were deemed significant at an α<0.05. All statistical analyses were performed using SAS 9.4.
RESULTS

Between October 2011 and November 2014, 201 patients were enrolled in CRISP, 171 of whom had a mismatch on baseline CTP. Seventeen (10%) patients did not achieve reperfusion and were excluded. Therefore, this study includes 154 patients with mismatch on baseline CTP and successful reperfusion following endovascular thrombectomy: 108 (70%) who met criteria for target mismatch profile, and 46 (30%) for malignant mismatch profile. Other notable patient exclusions from this study are presented in Figure 1. Baseline patient characteristics are presented in Table 1.

Association between CTP-to-reperfusion time and probability of functional independence

In the overall cohort (N=154), age and baseline NIHSS were significantly associated with probability of functional independence. (Table 2). Longer CTP-to-reperfusion time did not show a significant association with functional independence, but there was a strong trend (OR 0.65, 95% CI 0.41–1.03, adjusted p=0.06). (Figure 2)

Among patients with target mismatch profile, median CTP-to-reperfusion time was 1.8 (IQR 1.5–2.4) hours. There was no significant association between CTP-to-reperfusion time and the probability of functional independence in the univariable analysis or after adjustment for age, NIHSS and core volume. (OR 1.06, 95% CI 0.59–1.90, adjusted p=0.84; Figure 3A) Among patients with malignant mismatch profile, median CTP-to-reperfusion time was 1.95 (IQR 1.6–2.5) hours. In these patients, CTP-to-reperfusion time was significantly associated with lower odds of achieving functional independence at 90 days (OR 0.08, 95% CI 0.01–0.42, adjusted p=0.003). The probability of functional independence dropped rapidly from 75% when the patient was reperfused within 30 minutes of CTP, to less than 40% if CTP-to-reperfusion time exceeded two hours. (Figure 3B)

Association between mismatch profile and radiological outcomes

Day 5 FLAIR images were available for 75 (69%) patients with target mismatch, and 24 (50%) patients with the malignant mismatch profile. Patients with malignant mismatch had more infarct growth than those with target mismatch (90 [IQR 49–166] mL vs. 43 [IQR 18–81] mL, p=0.006). Despite similar baseline infarct core volumes and ASPECT scores, patients with malignant mismatch also had larger final infarct volumes (110 [IQR 61–155] mL vs. 48 [IQR 21–99] mL, p=0.001). (Figure 4)

DISCUSSION

This study demonstrates marked heterogeneity in the effect of CTP-to-reperfusion time on functional outcome after endovascular therapy. This analysis failed to detect an association between CTP-to-reperfusion time and the probability of recovering functional independence among patients with target mismatch on baseline CTP. Meanwhile, in patients with malignant mismatch, a longer CTP-to-reperfusion time was strongly associated with lower odds of functional independence.

We explored infarct growth as a physiologically plausible explanation for the discrepant effects of time between patients with target and malignant mismatch profiles. Compared to

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the target mismatch profile cohort, patients in the malignant mismatch cohort had more than double the infarct growth and final infarct volume, despite reperfusion. DEFUSE 2 showed similar findings with MRI perfusion-diffusion mismatch: malignant profiles on PWI were associated with the most rapid infarct growth and less penumbral salvage.\(^7\) Using CT perfusion, d’Esterre et al. demonstrated that severity of perfusion delay is inversely related to the available time window to salvage the hypoperfused lesion from infarction.\(^8\) A Tmax threshold of 10 seconds or more also appeared to be optimal in predicting infarction, especially if reperfusion occurs beyond 90 to 180 minutes after CTP.\(^5\) The malignant mismatch profile thus appears to be a reliable biomarker of rapid progression to irreversible ischemic injury, predicting larger final infarcts and lower odds of regaining functional independence if timely reperfusion does not occur.

The effect of CT-to-reperfusion time on clinical outcome in our study is in keeping with previously published data, which supports the external validity of our study.\(^2\),\(^3\) In our cohort of all patients with successful reperfusion, the association between CTP-to-reperfusion time and functional independence was similar to the one reported in the HERMES meta-analysis.\(^2\) In CRISP and HERMES, the probability of functional independence was greater than 70% when reperfusion occurs within one hour of imaging, then drops to less than 40% at 4 hours.\(^2\) In ESCAPE, this probability showed a more rapid decline, from almost 70% with reperfusion within one hour of imaging, to less than 40% with reperfusion at 2.5 hours.\(^3\) Given the similarity in the overall populations of the ESCAPE trial, the HERMES collaboration, and the CRISP study, we propose that the target and malignant CT perfusion mismatch profiles provide a further refinement in predicting probability of functional independence.\(^9\)

Our results do not imply that patients with a malignant mismatch profile on CTP should not undergo endovascular therapy. It is important to note that the probability of functional independence with short imaging-to-reperfusion time is comparable between patients with the malignant and target mismatch profiles. This suggests that the effect of endovascular treatment may be similar in both populations if imaging-to-reperfusion times are kept short. Also, our results do not imply that patients with target mismatch profile are immune to delays in reperfusion. Infarct growth, albeit at a slower rate, continues in absence of reperfusion. While we were unable to demonstrate an effect of CTP-to-reperfusion time on functional outcome in patients with target mismatch, it is probable that a modest effect does exist which we were underpowered to demonstrate. It is also possible that an effect of time could have been demonstrated if our sample had included target mismatch patients with longer CTP-to-reperfusion times. Therefore, it should be stressed that, while patients with the malignant mismatch appear particularly sensitive to treatment delays, early reperfusion will benefit all patients.

**Limitations**

Our study has limitations. First, in absence of a control group, we can only determine the relationship between CT-to-reperfusion time and functional independence, but not between CT-to-reperfusion time and the effect of endovascular treatment. Second, the relationship between CT-to-reperfusion time and functional independence may be influenced by...
variables other than CTP profile. While we adjusted for potential confounders using multivariable analyses, it is possible that there were unknown confounders that were not adjusted for. Third, final infarct data were only available in a subset of cases, though it unlikely affected the validity of the analysis, as there was no known bias in missing imaging data between the target and malignant mismatch profile cohorts and the imaging analyses remained sufficiently powered to demonstrate differences between the cohorts. Fourth, the infarct core in our study was defined as critically decreased cerebral blood flow, based on previous studies supporting its validity compared with a DWI-based measure. An alternative definition of the ischemic core, such as one based on cerebral blood volume, may have resulted in a slightly different population with mismatch, but this would likely not have affected the overall results of the study. Lastly, day 5 FLAIR likely overestimates the final infarct volume due to the presence of vasogenic edema, but since this effect is present in both groups, it is unlikely to have affected the results of the analyses.

**CONCLUSION**

Time delay between baseline imaging and endovascular reperfusion have discrepant effects depending on patients’ baseline mismatch profile. Patients with a malignant mismatch, characterized by a large territory of severely delayed contrast arrival, have a rapid decline in their chance of functional independence with longer delays, whereas patients with a target mismatch are relatively resilient yet likely not immune to such treatment delays. Our results do not indicate a lack of treatment effect among patients with the malignant profile. However, they suggest that the treatment effect may be greater with shorter imaging-to-reperfusion times, particularly in patients with a malignant mismatch profile.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


Figure 1. Patient cohorts included in this analysis
CTP: CT perfusion
Figure 2. CTP-to-reperfusion time and probability of functional independence in all patients with perfusion mismatch and successful reperfusion

ALL: All patients with mismatch who achieved successful reperfusion within 18 hours from stroke onset. The regression curve estimates the probability of functional independence at 90 days for an average patient in this cohort (mean age 66.5 years, baseline NIHSS score 16.8, and baseline CTP infarct core volume of 15.6 mL). The grey shaded area corresponds to the 95% confidence interval.
Figure 3. CTP-to-reperfusion time and probability of functional independence in patients with target and malignant mismatch profile
The regression curve estimates the probability of functional independence at 90 days for an average patient with mismatch who achieves successful reperfusion (mean age 67 years, baseline NIHSS score 15.5, and baseline CTP infarct core volume of 9.3mL). The shaded area corresponds to the 95% confidence interval.

A. Patients with target mismatch profile reperfused within 18 hours from stroke onset.
B. Patients with malignant mismatch profile reperfused within 18 hours from stroke onset.

For the average patient with mismatch, the probability of functional independence at 90 days rapidly drops below 50% if reperfusion is not achieved within 2.5 hours from CT perfusion.
Figure 4. Infarct growth based on mismatch profile

Despite similar infarct core sizes, patients with malignant perfusion profile demonstrated more than double the infarct growth and final infarct volume measured on day 5 FLAIR, despite successful reperfusion on 24-hour perfusion-weighted imaging. A. Patients with malignant mismatch had larger final infarct volumes (110 [IQR 61–155] vs. 48 [IQR 21–99] mL, p=0.001). B. This subject had an rCBF core of 42mL (pink), a Tmax>6s lesion of 162mL (green), a Tmax>10s lesion of 110mL (red), complete reperfusion at 24 hours, and a final infarct volume of 142mL.
Table 1
Comparison of baseline characteristics and outcomes between the target and malignant mismatch cohorts of patients with reperfusion

TMM: Target mismatch; IQR: Interquartile range; NIHSS: NIH Stroke Scale; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; ICA: Internal carotid artery; MCA: Middle cerebral artery; Tmax: Time-to-maximum; CTP: CT perfusion; mRS: modified Rankin Scale.

<table>
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<tr>
<th>Factors</th>
<th>Patient Subgroups</th>
<th>Median (IQR), or n (%)</th>
<th>P-Values</th>
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<tr>
<td></td>
<td>Target Mismatch N=108</td>
<td>Malignant Mismatch N=46</td>
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<td>Age (years)</td>
<td>68 (60–78)</td>
<td>70 (55–76)</td>
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<td>Baseline NIHSS</td>
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<td>Distal ICA</td>
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<td>MCA-M2</td>
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<td>MCA-M3</td>
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<td>Baseline CTP</td>
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<td>Tmax&gt;6s lesion volume (mL)</td>
<td>105 (74–146)</td>
<td>211 (177–250)</td>
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<td>Tmax&gt;10s lesion volume (mL)</td>
<td>37 (17–65)</td>
<td>127 (113–155)</td>
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<td>Ischemic core volume (mL)</td>
<td>5 (0–13)</td>
<td>20 (3–41)</td>
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<td>Thrombolysis</td>
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<tr>
<td>Intravenous</td>
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<td>Intra-arterial</td>
<td>19 (18)</td>
<td>7 (15)</td>
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<tr>
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<td>Time intervals (hours)</td>
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<td>CTP-to-reperfusion</td>
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<td>Modified Rankin Scale at 90 days</td>
<td>2 (1–3)</td>
<td>3 (1–4)</td>
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<td>Patients with mRS 0–2</td>
<td>72 (67)</td>
<td>23 (50)</td>
<td>0.10</td>
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### Table 2
Factors associated with probability of functional independence

Odds ratio and 95% confidence intervals are presented for significant predictors in each cohort of patients with successful reperfusion. All factors associated with probability of functional independence at 90 days (p<0.05) in the univariable analysis are included in the multivariate model. OR: Odds ratio; NIHSS: NIH Stroke Scale; 95% C.I.: 95% Confidence interval.

<table>
<thead>
<tr>
<th>Factors</th>
<th>OR</th>
<th>95% C.I.</th>
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<td><strong>All patients</strong></td>
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<td>0.77–0.91</td>
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<td>Baseline core volume (5 mL)</td>
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<td>CTP-to-reperfusion time (hour)</td>
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<tr>
<td>Age (years)</td>
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<td>0.94–1.00</td>
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<tr>
<td>Baseline NIHSS score</td>
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<td>0.72–0.89</td>
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<td>Baseline core volume (5 mL)</td>
<td>0.99</td>
<td>0.94–1.03</td>
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<tr>
<td>CTP-to-reperfusion time (hour)</td>
<td>1.06</td>
<td>0.60–1.96</td>
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<td><strong>Malignant mismatch</strong></td>
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<td>Age (5 years)</td>
<td>0.91</td>
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<td>Baseline NIHSS score</td>
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<td>Baseline core volume (5 mL)</td>
<td>0.99</td>
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<td>CTP-to-reperfusion time (hour)</td>
<td>0.08</td>
<td>0.01–0.32</td>
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