Original research

What predicts poor outcome after successful thrombectomy in early time window?

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ABSTRACT

Background Half of the patients with large vessel occlusion (LVO)-related acute ischemic stroke (AIS) who undergo endovascular reperfusion are dead or dependent at 3 months. We hypothesize that in addition to established prognostic factors, baseline imaging profile predicts outcome among reperfusers.

Methods Consecutive patients receiving endovascular treatment (EVT) within 6 hours after onset with Thrombolysis In Cerebral Infarction (TICI) 2b, 2c and 3 revascularization were included. Poor outcome was defined by a modified Rankin scale (mRS) 3–6 at 90 days. No mismatch (NoMM) profile was defined as a mismatch (MM) ratio ≤1.2 and/or a volume <10 mL on pretreatment imaging.

Results 187 patients were included, and 81 (43%) had a poor outcome. Median delay from stroke onset to the end of EVT was 259 min (IQR 209–340). After multivariable logistic regression analysis, older age (OR 1.26, 95% CI 1.06 to 1.5; p=0.01), higher National Institutes of Health Stroke Scale (NIHSS) (OR 1.15, 95% CI 1.06 to 1.25; p<0.0001), internal carotid artery (ICA) occlusion (OR 3.02, 95% CI 1.2 to 8.0; p=0.021), and NoMM (OR 4.87, 95% CI 1.09 to 22.8; p=0.004) were associated with poor outcome. In addition, post-EVT hemorrhage (OR 3.64, 95% CI 1.5 to 9.1; p=0.04) was also associated with poor outcome.

Conclusions The absence of a penumbra defined by a NoMM profile on baseline imaging appears to be an independent predictor of poor outcome after reperfusion. Strategies aiming to preserve the penumbra may be encouraged to improve these patients’ outcomes.

INTRODUCTION

Endovascular treatment (EVT) dramatically improves the outcome of patients experiencing an acute ischemic stroke (AIS) due to a proximal anterior large vessel occlusion (LVO).1 Nonetheless, despite an endovascular reperfusion rate close to 90%, only half of the patients are functionally independent at 3 months. We have shown in the FRENCH Acute multimodal imaging to select patients for MEchanical thrombectomy (FRAME) study, among patients treated by EVT within 6 hours after onset by physicians blinded to the baseline imaging profile, that 80% of the LVO-treated AIS patients have a substantial penumbra estimated by a mismatch (MM) on baseline imaging. In FRAME these patients with an MM on baseline imaging, independent of infarct core volume, experience a larger response to endovascular reperfusion than those who have no salvageable penumbra.2 EVT is indicated, regardless of baseline imaging profile, for the vast majority of patients experiencing an LVO-related AIS within 6 hours after onset (limited cases such as patients with a large core may be discussed based on clinical judgment). Conversely, advanced imaging selection is mandatory beyond 6 hours.3 Considering the large indication for EVT and its efficacy, research is now focusing on the identification and treatment of modifiable factors that would influence the outcome of patients who experienced an endovascular reperfusion.

In a recent DEFUSE 3 sub-study, several potentially modifiable factors such as post-endovascular reperfusion hemorrhage and delays between stroke onset and reperfusion have been associated with poor outcome among reperfusers.4 The DEFUSE 3 study group consists of a highly selected group of patients with a target mismatch (TMM), defined by an MM and a core lesion volume <70 mL on baseline imaging, treated from 6 to 16 hours after last known well.5 FRAME MM definition was less stringent than the DEFUSE 3 TMM. First FRAME MM was calculated regardless of a maximal core lesion volume. Second FRAME MM used a lower core/critical hypoperfusion volume ratio that was different from DEFUSE 3 TMM (1.2 vs 1.8 mL and 10 vs 15 mL, respectively). Finally, most of the FRAME participants (95%) underwent MRI at baseline, versus 25% in DEFUSE 3.

Hence, the FRAME dataset offers an opportunity to expand this type of analyses in the early time window, in a cohort of unselected LVO-AIS patients treated according to the current guidelines regardless of baseline imaging profile. We aim to evaluate, in addition to established factors, whether the absence of penumbra on baseline imaging is a predictor of poor outcome after endovascular reperfusion.
METHODS
Study and patients
This is a post-hoc analysis of the FRAME study. Briefly, FRAME is a prospective cohort study from two comprehensive French stroke centers (Toulouse and Bordeaux), which investigated the relationships between baseline perfusion imaging profile and functional outcome in LVO-related AIS patients treated by mechanical thrombectomy (MT) within 6 hours from symptom onset. The study design has been previously described.

The trial protocol was approved by the French Ethical Committee (CPP SOOM III) on October 5, 2016, and was authorized by the French Health Authority under the number 2016/7575. Every patient or his/her legal representative signed a written informed consent at inclusion.

Imaging analysis and outcome assessment have been previously reported.

MM and hypoperfusion intensity ratio (HIR) definitions are summarized in the online supplemental data. Clinical outcomes were assessed 90 days after treatment using a dichotomized modified Rankin Scale score (mRS: favorable, mRS 0–2; unfavorable, mRS 3–6) at 90 days. mRS was assessed by independent evaluators blinded to the clinical history and baseline imaging profile. Hemorrhagic transformation (HT) was defined according to the Third European Cooperative Acute Stroke Study (ECASS III) definition.

Statistical analyses
Descriptive analysis was performed for baseline characteristics, stroke presentation, EVT and imaging outcomes. Mean±SD accompanied by range or median with IQR were provided for quantitative variables, and number and percentage for qualitative variables.

Baseline characteristics and stroke presentation were compared between patients with good outcome and those with poor outcomes (mRS 0–2 vs mRS 3–6 at 90 days). Wilcoxon Mann-Whitney test was used for quantitative variables and Chi² test (or Fisher test if inappropriate) for qualitative variables. Then, the Cochran-Armitage test for trend was applied for HT.

To identify factors associated with unfavorable outcome at 90 days, a multivariate logistic regression model was constructed. First, univariate models were performed with mRS at 90 days, and a multivariate logistic regression model was constructed.

Unfavorable outcome after reperfusion was associated with older age and a higher median NIHSS at baseline. On baseline imaging, poor outcome patients had more frequently a NoMM profile, a higher HIR, a larger core infarction volume and an internal carotid artery (ICA) occlusion on vessel imaging.

Patients who had a poor outcome were less likely to receive IV-tPA before MT. At arrival in the angio-suite poor outcome patients had a higher systolic blood pressure (SBP), underwent MT under general anesthesia (GA) more commonly, and the procedure duration was longer. TICI 2b, 2c and 3 rates did not differ between the good and poor outcome patients.

Following EVT, poor outcome patients had a larger infarction volume at 24 hours and higher rates of any HT. There was a relationship between the severity of reperfusion hemorrhage and patient outcome (Cochran Armitage test p<0.001) (figure 1). The rate of parenchymal hemorrhage (PH) 1 and 2 were higher in the subgroup of patients who had a poor outcome. Symptomatic intracranial hemorrhage was observed in six patients (7.4%), all of whom had a poor outcome (figure 1).

Multivariate analysis
In a multivariable analysis, patient demographic and stroke presentation factors were associated with poor outcome: older age (OR 1.26, 95% CI 1.06 to 1.5; p=0.01), higher NIHSS (OR 1.15, 95% CI 1.06 to 1.25; p<0.001), ICA occlusion (OR 3.02, 95% CI 1.2 to 8.0; p=0.021), and NoMM (OR 4.87, 95% CI 1.09 to 22.8; p=0.004) (table 2). HT was also associated with poor outcome (OR 3.64, 95% CI 1.52 to 9.1; p=0.004) when it was introduced into the multivariate model. When baseline core volume was replaced in the model by a dichotomized Alberta Stroke Program Early CT Score (ASPECTS) ≤5 versus >5, NoMM (OR 4.63, 95% CI 1.2 to 18.7; p=0.025) and HT (OR 3.5, 95% CI 1.5 to 8.8; p=0.005) remained significantly associated with poor outcome (online supplemental data).

RESULTS
Baseline characteristics
Overall, 218 patients were enrolled in FRAME. A flow chart of the study is provided in the study main paper. Among these, 187 (86%) achieved reperfusion and were included in this sub-study. Reperfusion was achieved after a median delay of 239 min (IQR 209–340). Mean age was 71.4±13.8 years, 92 (49.2%) were female, median National Institutes of Health Stroke Scale (NIHSS) was 17 (IQR 12–21), and 128 patients (68%) received intravenous tissue plasminogen activator (IV-tPA). Eighty-one (43%) had an unfavorable outcome (table 1).

Unfavorable outcome after reperfusion was associated with older age and a higher median NIHSS at baseline. On baseline imaging, poor outcome patients had more frequently a NoMM profile, a higher HIR, a larger core infarction volume and an internal carotid artery (ICA) occlusion on vessel imaging.

Patients who had a poor outcome were less likely to receive IV-tPA before MT. At arrival in the angio-suite poor outcome patients had a higher systolic blood pressure (SBP), underwent MT under general anesthesia (GA) more commonly, and the procedure duration was longer. TICI 2b, 2c and 3 rates did not differ between the good and poor outcome patients.

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DISCUSSION
In this post-hoc analysis of the FRAME study, we identified two potentially modifiable factors that influence patient outcome after successful EVT: the preservation of the salvageable penumbra before treatment, and the prevention of post-EVT hemorrhage. These findings may inform future neuroprotective studies in LVO-related AIS patients who are treated by EVT. The results of the FRAME study confirmed that the presence of a substantial penumbra on perfusion imaging helps to identify the patients more likely to be improved by the occurrence of endovascular reperfusion. The results of this sub-study demonstrate that among patients with successful reperfusion after EVT, the absence of a penumbra is one of the strongest predictors of poor outcome after adjustment on most common independent predictors including core lesion volume. Also consistent with this result, NoMM and HT were strong independent predictors of poor outcome when baseline core volume was replaced with a dichotomized ASPECTS (ASPECTS ≤5 vs >5), which is a common selection criteria to delineate patients with significant ischemic injury. These findings concur with another study from our group which found that in patients with a large core (>50 mL), MT increased the rate of functional recovery only in the subgroup of patients with MM. Taken together, the results of both studies suggest that in this subgroup of patients, HT and its influence on poor clinical outcome could be overcome by penumbral salvage.

Several factors have been associated with infarct progression. First, the presence of an MM between the critically hypoperfused region and the core of the infarction. Second, the severity of the
Ischemic stroke

Table 1  Characteristics of patients with TICI 2b-3 revascularization dichotomized by clinical outcome

<table>
<thead>
<tr>
<th>Total</th>
<th>No. Missing</th>
<th>Final mRS ≤2</th>
<th>Final mRS &gt;2</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>Data</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>187</td>
<td>100</td>
<td>106</td>
<td>100</td>
<td>81</td>
</tr>
</tbody>
</table>

Patient characteristics
- Median age, years (IQR): 73.3 (64.5–82.0) vs. 71.3 (61.8–79.2) vs. 76.4 (70.3–83.8) (P = 0.004)
- Male sex, n (%): 95 (50.8) vs. 55 (51.9) vs. 40 (49.4) (P = 0.73)
- Hypertension, n (%): 111 (59.4) vs. 63 (59.4) vs. 48 (59.3) (P = 0.98)
- Atrial fibrillation, n (%): 45 (24.1) vs. 22 (20.8) vs. 23 (28.4) (P = 0.23)
- Diabetes mellitus, n (%): 30 (16.0) vs. 14 (13.2) vs. 16 (19.8) (P = 0.23)
- Previous ischemic stroke, n (%): 25 (13.4) vs. 18 (17.0) vs. 7 (8.6) (P = 0.10)
- Median NIHSS total score at baseline (IQR): 17.0 (12.0–21.0) vs. 13.0 (9.0–18.0) vs. 20.0 (17.0–24.0) (<0.0001)
- Median baseline SBP, mmHg (IQR): 150.4 (139.7–179.2) vs. 150.0 (135.0–160.0) vs. 150.0 (135.0–170.0) (0.11)

Table 1  Characteristics of patients with TICI 2b-3 revascularization dichotomized by clinical outcome

Stroke presentation
- Median time from stroke onset to imaging, min (IQR): 150.0 (105.0–227.0) vs. 148.0 (101.0–225.0) vs. 156.0 (110.0–232.0) (P = 0.57)
- Initial occlusion site on imaging, n (%): ICA 48 (25.7) vs. 16 (15.1) vs. 32 (39.5) (P = 0.0002)
- M1 94 (50.3) vs. 61 (57.5) vs. 33 (40.7) (P = 0.02)
- M2 45 (24.1) vs. 29 (27.4) vs. 16 (19.8) (P = 0.23)
- Right hemisphere stroke, n (%): 89 (47.6) vs. 57 (53.8) vs. 32 (39.5) (P = 0.05)
- Median baseline core volume, mL (IQR): 16.3 (6.8–55.3) vs. 12.1 (5.3–24.9) vs. 32.7 (13.3–102.4) (<0.0001)
- Median baseline Tmax >6s volume, mL (IQR): 100.4 (68.7–139.2) vs. 89.7 (58.4–126.6) vs. 117.0 (87.9–146.2) (0.0003)
- Median hypoperfusion intensity ratio (IQR): 0.46 (0.33–0.61) vs. 0.42 (0.31–0.54) vs. 0.51 (0.36–0.67) (P = 0.02)
- No mismatch, n (%): 26 (13.9) vs. 9 (11.3) vs. 17 (21.0) (P = 0.01)
- Treated with IV-tPA, n (%): 128 (68.4) vs. 80 (75.5) vs. 48 (59.3) (P = 0.02)
- Median time from stroke onset to IV-tPA, min (IQR): 154 (113–210) vs. 153 (108–215) vs. 155 (124–187) (0.98)
- ASPECTS score ≤5, n (%): 42 (22.5) vs. 12 (11.3) vs. 30 (37.0) (<0.0001)

Thrombectomy treatment
- General anesthesia, n (%): 74 (39.6) vs. 26 (24.5) vs. 48 (59.3) (P = 0.0001)
- Median SBP at arrival in the cath lab, mmHg (IQR): 150 (135–170) vs. 145 (130–160) vs. 155 (140–180) (0.002)
- Median time from stroke onset to femoral puncture, min (IQR): 220 (175–288) vs. 219 (165–293) vs. 265 (221–340) (0.25)
- Median time from stroke onset to end of procedure, min (IQR): 34 (23–54) vs. 29 (22–50) vs. 40 (25–57) (0.03)
- Final TICI score, n (%): 2b 99 (52.9) vs. 55 (51.9) vs. 44 (54.3) (0.74)
- 2c 68 (36.4) vs. 39 (36.8) vs. 29 (35.8) (0.89)
- 3 20 (10.7) vs. 12 (11.3) vs. 8 (9.9) (0.75)

Imaging and clinical outcomes
- Hemorrhagic transformation at 24 hours, n (%): 0 vs. 55 vs. 44 (54.3) (0.74)
- Symptomatic intracranial hemorrhage, n (%): 6 vs. 7 vs. 6 (7.4) (0.006)
- Infarction volume at 24 hours (mL), median (IQR): 23.3 (9.6–75.5) vs. 13.9 (6.7–38.8) vs. 61.2 (21.3–142.1) (<0.0001)

* χ² test for qualitative variable or Wilcoxon Mann-Whitney test for quantitative variable (missing data are not included in statistical test).

ASPECTS, Alberta Stroke Program Early CT Score; cath lab, catheterization laboratory; HI, Hemorrhagic Inarction; ICA, Internal carotid artery; IV-tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hemorrhage; SBP, systolic blood pressure; TICI, Thrombolysis In Cerebral Infarction.

Critically hypoperfused region estimated by the HIR or collateral index. Hence, HIR correlates with collaterals and predicts the speed of infarct core growth downstream of an LVO.8 Third, the degree of the hypoperfusion of an acute diffusion weighted imaging (DWI) lesion, which in addition to the severity of Apparent Diffusion Coefficient restriction influences the degree of DWI reversal after reperfusion.9 In FRAME, despite a median delay between symptom onset and imaging <3 hours, 20% of the study subjects already had a NoMM profile. We previously showed that this profile was strongly associated with a high (unfavorable) HIR, and its prevalence increased with delay from onset to imaging.9 The NoMM profile was also more frequently observed among transfer patients than those directly admitted to a comprehensive stroke center. These findings confirm that infarct progression can be very fast in some individuals, emphasize the need to expedite the triage of patients with an
outcomes. But have yet to demonstrate their efficacy in improving pressure control during MT, aiming to reduce the occurrence of complications during the procedure. Several strategies have been tested, such as MT without iIV-A or blood pressure control during MT, aiming to reduce the occurrence of HT while minimizing the risk of hemorrhagic transformation.

While others consider that acquiring perfusion imaging is futile, advanced imaging relies on their output for patient management. Specifically, RAPID software can identify regions of ischemic core and critical hypoperfusion with good accuracy. However, a study from the HERMES group found MRI to be associated with superior clinical outcomes, which might partially explain differences in our results compared to prior studies. In our dataset, TICI 3 was achieved in 10% and TICI 2c in 35% of the cases. This specific setting limited to the study duration was unique.

Our study suffers from several limitations, which might have been underpowered to confirm the relationship. First, in our dataset, TICI 3 was achieved in 10% and TICI 2c in 35% of the cases. As a consequence, due to its specific setting replicating such a trial has been proven to be difficult, as most of the centers equipped with advanced imaging rely on their output for patient management. This specific setting limited to the study duration was unique. Finally, FRAME was performed in two large comprehensive stroke centers in which investigators agreed to acquire perfusion imaging in order to select patients for MT. As a consequence, due to its specific setting replicating such a trial has been proven to be difficult, as most of the centers equipped with advanced imaging rely on their output for patient management.

It allowed us to estimate an objective prevalence of unfavorable outcomes, which might partially explain differences in our results compared to prior studies. In our dataset, TICI 3 was achieved in 10% and TICI 2c in 35% of the cases. This specific setting limited to the study duration was unique. Finally, FRAME was performed in two large comprehensive stroke centers in which investigators agreed to acquire perfusion imaging in order to select patients for MT. As a consequence, due to its specific setting replicating such a trial has been proven to be difficult, as most of the centers equipped with advanced imaging rely on their output for patient management.

Table 2: Association between patient characteristics, stroke presentation and clinical outcome by logistic regression models (n=169)

<table>
<thead>
<tr>
<th>Description</th>
<th>Total</th>
<th>Final mRS ≤2</th>
<th>Final mRS &gt;2</th>
<th>Models with event: Final mRS &gt;2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference or unit</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Age, years</td>
<td>74.4 (64.5–82.4)</td>
<td>71.3 (61.2–79.2)</td>
<td>77.7 (72.3–84.7)</td>
<td></td>
</tr>
<tr>
<td>NIHSS total score at baseline</td>
<td>17 (12–21)</td>
<td>13 (9–18)</td>
<td>20.5 (17–24)</td>
<td></td>
</tr>
<tr>
<td>Initial occlusion site on initial imaging, ICA</td>
<td>41 (24%)</td>
<td>15 (15%)</td>
<td>26 (87%)</td>
<td></td>
</tr>
<tr>
<td>Baseline core volume, mL</td>
<td>16.2 (58–54.3)</td>
<td>11.7 (7.7–25.1)</td>
<td>28.1 (17.2–97.6)</td>
<td></td>
</tr>
<tr>
<td>Baseline Tmax &gt;6s volume, mL</td>
<td>99 (67.9–138.2)</td>
<td>88.6 (56.3–119.6)</td>
<td>116.8 (88.2–164.2)</td>
<td></td>
</tr>
<tr>
<td>Treated with IV-A</td>
<td>0.46 (0.33–0.68)</td>
<td>0.41 (0.33–0.68)</td>
<td>0.51 (0.36–0.88)</td>
<td></td>
</tr>
<tr>
<td>No Mismatch</td>
<td>0.23 (14%)</td>
<td>0.8 (8%)</td>
<td>15 (21%)</td>
<td></td>
</tr>
<tr>
<td>SBP at arrival in the cath lab, mmHg</td>
<td>118 (70%)</td>
<td>76 (77%)</td>
<td>42 (80%)</td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>67 (40%)</td>
<td>26 (26%)</td>
<td>41 (59%)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic Transformation at 24 hours</td>
<td>95 (56%)</td>
<td>39 (39%)</td>
<td>56 (80%)</td>
<td></td>
</tr>
</tbody>
</table>

*Effective with percentage (N (%)) for qualitative variables and median with IQR for quantitative variable.
In many regions of the world, the transfer of an LVO-related AIS to the angiosite may take several hours during which infarct progression will result in no salvageable ischemic tissue left on arrival. Advanced imaging appears to be more and more widely available in referring centers, and could even be implemented in a mobile stroke unit. Moreover, the presence of an MM and poor collars can forecast a high risk of progression. Therefore, we can speculate that advanced imaging might help to identify candidate prehospital treatment strategies aiming to prevent infarct progression by, and not exclusively, improving collateral blood flow or oxygen delivery in the ischemic region.16 17 In addition, as our results emphasize the importance of a persistent penumbra even among patients with a low ASPECTS (online supplemental data), future studies investigating the efficacy of MT in patients with a documented large stroke and substantial penumbra are warranted.

CONCLUSION

The absence of penumbra defined by a NoMM profile on baseline imaging appears to be an independent predictor of poor outcome of patients treated by MT.

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