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.

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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[2]

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 2016/75

Every patient or his/her legal representative signed a written informed consent at inclusion.

Imaging analysis and outcome assessment have been previously reported.[2]

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 χ^2 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 as the response variable and a characteristic of interest as the explanatory variable. Then, two multivariate models were made: one with the baseline characteristics, and one with baseline characteristics plus HT at 24 hours. No selection method was implemented to find the best model; the choice was to keep all the characteristics in the models.

All tests were two-sided and considered significant at an α level of 0.05. All statistical analyses were conducted using SAS Software version 9.4.

RESULTS

Baseline characteristics

Overall, 218 patients were enrolled in FRAME. A flow chart of the study is provided in the study main paper.[2] Among these, 187 (86%) achieved reperfusion and were included in this substudy. Reperfusion was achieved after a median delay of 259 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 volumeand 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).

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.[2] 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.[6] 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.[7] Second, the severity of the

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

	Total		No.	Final mRS ≤2		Final mRS >2		
	N	%	Missing	N	%	N	%	P value*
	187	100	Data	106	100	81	100	
Patient characteristics								
Median age, years (IQR)	73.3 (64.5–82.0)		0	71.3 (61.8–79.2)		76.4 (70.3–83.8)		0.004
Male sex, n (%)	95	50.8	0	55	51.9	40	49.4	0.73
Hypertension, n (%)	111	59.4	0	63	59.4	48	59.3	0.98
Atrial fibrillation, n (%)	45	24.1	0	22	20.8	23	28.4	0.23
Diabetes mellitus, n (%)	30	16.0	0	14	13.2	16	19.8	0.23
Previous ischemic stroke, n (%)	25	13.4	0	18	17.0	7	8.6	0.10
Median NIHSS total score at baseline (IQR)	17.0 (12.0–21.0)		0	13.0 (9.0–18.0)		20.0 (17.0–24.0)		<0.0001
Median baseline SBP, mmHg (IQR)	150.0 (130.0–162.5)		19	150.0 (130.0–160.0)		150.0 (135.0–170.0)		0.11
Stroke presentation								
Median time from stroke onset to imaging, min (IQR)	150.0 (105.0–227.0)		1	148.0 (101.0–225.0)		156.0 (110.0–232.0)		0.57
Initial occlusion site on Initial Imaging, n (%)			0					0.0008
ICA	48	25.7		16	15.1	32	39.5	0.0002
M1	94	50.3		61	57.5	33	40.7	0.02
M2	45	24.1		29	27.4	16	19.8	0.23
Right hemisphere stroke, n (%)	89	47.6	0	57	53.8	32	39.5	0.05
Median baseline core volume, mL (IQR)	16.3 (6.8–55.3)		0	12.1 (5.3–24.9)		32.7 (13.3–102.4)		<0.0001
Median baseline Tmax >6 s volume, mL (IQR)	100.4 (68.7–139.2)		6	89.7 (58.4–126.6)		117.0 (87.9–164.2)		0.0003
Median hypoperfusion intensity ratio (IQR)	0.46 (0.33–0.61)		6	0.42 (0.31–0.54)		0.51 (0.36–0.67)		0.02
No mismatch, n (%)	26	13.9	6	9	8.5	17	21.0	0.01
Treated with IV-tPA, n (%)	128	68.4	0	80	75.5	48	59.3	0.02
Median time from stroke onset to IV-tPA, min (IQR)	154 (113–210)		60	153 (108–215)		155 (124–187)		0.98
ASPECTS score ≤5, n (%)	42	22.5	1	12	11.3	30	37.0	<0.0001
Thrombectomy treatment								
General anesthesia, n (%)	74	39.6	2	26	24.5	48	59.3	<0.0001
Median SBP at arrival in the cath lab, mmHg (IQR)	150 (135–170)		11	145 (130–160)		155 (140–180)		0.002
Median time from stroke onset to femoral puncture, min (IQR)	220 (175–288)		1	219 (165–293)		221 (184–285)		0.55
Median time from stroke onset to end of procedure, min (IQR)	259 (209–340)		1	248 (198–328)		265 (221–340)		0.25
Median duration of the procedure, min (IQR)	34 (23–54)		0	29 (22–50)		40 (25–57)		0.03
Final TICI score, n (%)			0					0.93
2b	99	52.9		55	51.9	44	54.3	0.74
2c	68	36.4		39	36.8	29	35.8	0.89
3	20	10.7		12	11.3	8	9.9	0.75
Imaging and clinical outcomes								
Hemorrhagic transformation at 24 hours, n (%)			0					<0.0001
0=No	83	44		65	61.3	18	22.2	<0.0001
1=HI1	23	12.3		13	12.3	10	12.3	0.99
2=HI2	21	11.2		10	9.4	11	13.6	0.37
3=PH1	31	16.6		11	10.4	20	24.7	0.009
4=PH2	29	15.5		7	6.6	22	27.2	0.0001
Symptomatic intracranial hemorrhage, n (%)	6	3.2	1	0	0	6	7.4	0.006
Infarction volume at 24 hours (mL), median (IQR)	23.3 (9.6–75.5)		0	13.9 (6.7–38.8)		61.2 (21.3–142.1)		<0.0001

*χ^2 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, modifed 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 Coeficient 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.[2] 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

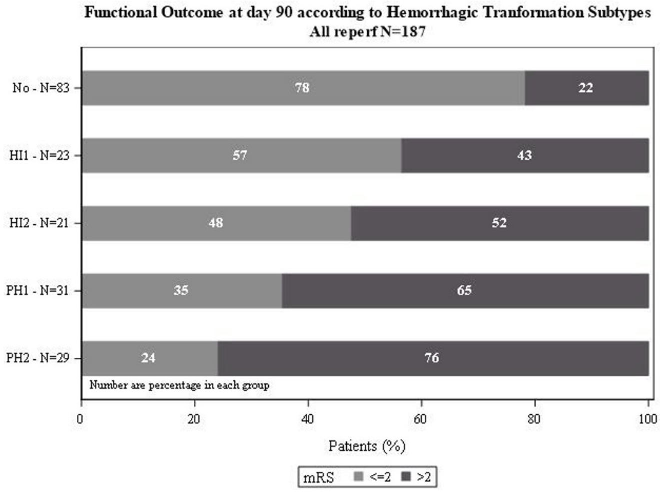

Figure 1 Functional outcome at day 90 according to hemorrhagic transformation subtypes: 83 had no reperfusion hemorrhage; 23 HI1; 21 HI2; 31 PH1; and 29 PH2. The proportion of patients who experienced a poor outcome increased with the severity of reperfusion hemorrhage (Cochran Armitage test p<0.001). HI, hemorrhagic infarction mRS, modified Rankin Scale; PH, parenchymal hemorrhage.

LVO-related AIS, and—when this is not feasible—develop strategies aiming to 'freeze' the penumbra.

Concurring with DEFUSE 3 results,[4] we confirm that HT has a critical impact on patient outcome after reperfusion. Several strategies have been tested, such as MT without iIV-tPA or blood pressure control during MT, aiming to reduce the occurrence of HT, but have yet to demonstrate their efficacy in improving outcomes.[10 11]

Our study suffers from several limitations, which might account for the differences observed with prior studies. First, in our dataset TICI 3 was achieved in 10% and TICI 2c in 35% of the participants. Those rates were similar in both groups, suggesting that, as previously reported in the DEFUSE 3 sub-study, we might have been underpowered to confirm the relationship described between the degree of reperfusion and outcome.[12] In FRAME, more than 90% of the enrolled patients were evaluated with MRI rather than CT perfusion. Direct comparisons have demonstrated that both CT perfusion and MRI processed with RAPID software can identify regions of ischemic core and critical hypoperfusion with good accuracy.[13] However, a study from the HERMES group found MRI to be associated with superior clinical outcomes, which might partially explain differences in our study and those of the DEFUSE 3 study.[14] In FRAME, the median delay from door to the end of procedure was 132 min. This delay was similar to the delay reported in the MR CLEAN registry, in which patients were selected by CT in a well-organized stroke network.[15] Finally, FRAME was performed in two large comprehensive stroke centers in which investigators agreed to acquire perfusion imaging and treat patients blinded to their output. This specific setting limited to the study duration was unique. It allowed us to estimate an objective prevalence of unfavorable profile by comparison with previous trials which used unblinded advanced imaging output to select patients for MT.[14] 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 while others consider that acquiring perfusion imaging is futile and delays treatment.

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

	Description*			Models with event: Final mRS >2						
	Total	Final mRS ≤2	Final mRS >2		Univariate models		Multivariate model 1		Multivariate model 2	
	169 (100%)	99 (100%)	70 (100%)	Reference or unit	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	74.4 (64.5–82.4)	71.3 (61.2–79.2)	77.7 (72.3–84.7)	5	1.23 (1.08 to 1.41)	0.0023	1.257 (1.065 to 1.501)	0.0087	1.254 (1.050 to 1.516)	0.0151
NIHSS total score at baseline	17(12–21)	13(9–18)	20.5 (17–24)	1	1.19 (1.12 to 1.28)	<0.0001	1.149 (1.063 to 1.250)	0.0007	1.121 (1.032 to 1.224)	0.0083
Initial occlusion site on initial imaging, ICA	41 (24%)	15 (15%)	26 (67%)	No ICA	3.31 (1.61 to 7.02)	0.0014	3.027 (1.195 to 7.998)	0.0214	2.789 (1.068 to 7.608)	0.0392
Baseline core volume, mL	16.2 (6.8–54.3)	11.7 (5.7–25.1)	28.1 (12.7–97.6)	10	1.15 (1.07 to 1.24)	0.0002	1.040 (0.936 to 1.163)	0.4736	1.011 (0.904 to 1.135)	0.8480
Baseline Tmax >6s volume, mL	99 (67.9–138.2)	88.6 (56.3–119.6)	116.6 (88.2–164.2)	10	1.11 (1.05 to 1.18)	0.0003	x		x	
HIR	0.46 (0.33–0.6)	0.41 (0.3–0.56)	0.51 (0.36–0.68)	0.1	1.14 (1.00 to 1.31)	0.0615	x		x	
No Mismatch	23 (14%)	8 (8%)	15 (21%)	Mismatch	3.10 (1.26 to 8.15)	0.0160	4.873 (1.096 to 22.806)	0.0384	4.988 (1.049 to 25.409)	0.0457
Treated with IV-tPA	118 70%)	76 (77%)	42 (60%)	No	0.45 (0.23 to 0.88)	0.0205	0.739 (0.310 to 1.769)	0.4925	0.698 (0.286 to 1.702)	0.4254
SBP at arrival in the cath lab, mmHg	150 (135–170)	145 (130–160)	153.5 (140–180)	10	1.24 (1.09 to 1.41)	0.0012	1.128 (0.957 to 1.336)	0.1541	1.118 (0.940 to 1.337)	0.2111
General anesthesia	67 (40%)	2 (26%)	41 (59%)	No	3.97 (2.09 to 7.72)	<0.0001	2.227 (0.970 to 5.171)	0.0593	2.710 (1.135 to 6.649)	0.0261
Duration of the procedure, min	35 (23–54)	30 (22–51)	40 (25–56)	5	1.02 (0.97 to 1.08)	0.3544	1.051 (0.979 to 1.124)	0.1472	1.053 (0.979 to 1.128)	0.1419
Hemorrhagic Transformation at 24 hours	95 (56%)	39 (39%)	56 (80%)	No	6.15 (3.09 to 12.90)	<0.0001	x		3.640 (1.523 to 9.096)	0.0043

*Effective with percentage (N (%)) for qualitative variables and median with IQR for quantitative variable.
cath lab, catheterization laboratory; HIR, hypoperfusion intensity ratio; ICA, internal carotid artery; IV-tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure.

In many regions of the world, the transfer of an LVO-related AIS to the angiosuite 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 collaterals 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 after reperfusion. Strategies aiming to preserve the penumbra before treatment may be encouraged to improve the outcome of patients treated by MT.

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